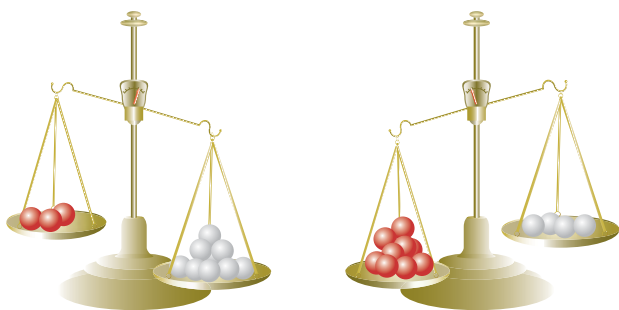


# Angiogenesis and the Tumor Microenvironment

## Malignant Angiogenesis

In normal tissues, the balance of pro-angiogenic and anti-angiogenic growth factors and proteins favors inhibition of angiogenesis, so that as new capillaries are needed, the balance can be adjusted to stimulate vascular growth. This corresponds to the angiogenic switch and the balance hypothesis proposed by Hanahan and Folkman in 1996 (see **Figure 1**).<sup>1</sup> The critical angiogenic activator is vascular endothelial growth factor (VEGF), but several other growth factors participate in the process. Basic fibroblast growth factor (bFGF), matrix metalloproteinases (MMP), transforming growth factor- $\alpha$  (TGF- $\alpha$ ), platelet derived growth factor (PDGF), placenta growth factor (PlGF), angiopoietin-1 (Ang-1), angiopoietin-2 (Ang-2), and hepatocyte growth factor (HGF) are all pro-angiogenic factors. Endogenous angiogenic inhibitors are proteins including endostatin, angiostatin, thrombospondin-1 (Tsp-1), tumstatin, platelet factor 4, and certain interleukins, including IL-12. Some of these proteins, including endostatin, angiostatin, and Tsp-1, are known to promote apoptosis in addition to preventing angiogenesis.

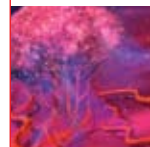


**Figure 1.** The “angiogenic switch” is illustrated as a balance between pro-angiogenic factors (represented by red spheres) and angiogenesis inhibitors (represented by gray spheres). When the level of angiogenic inhibitors predominates (left image), the microenvironment remains angiostatic and the tumor is quiescent. When the level of pro-angiogenic factors increases and overcomes the effects of the angiogenic inhibitors (right image), the process of constructing new vasculature is initiated.

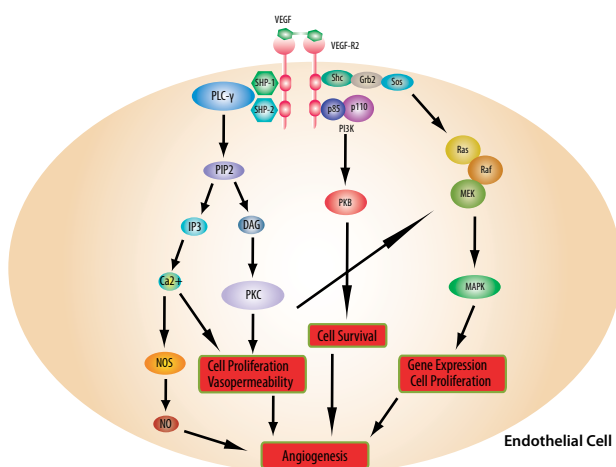
Hypoxia within the tumor microenvironment upregulates many of the angiogenic growth factors, including VEGF, PDGF, PlGF, and HGF.<sup>2</sup> Hypoxia inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ) is considered to be the foundation for the environmental hypoxic-activated response.<sup>2-4</sup> Under normal oxygenation (normoxic) conditions, HIF-1 $\alpha$  is the target of ubiquitination by the von Hippel-Lindan tumor suppressor (pVHL), and the resulting ubiquitinated HIF-1 $\alpha$  undergoes proteasomal degradation, terminating any downstream growth factor expression. Alternatively, under hypoxic conditions HIF-1 $\alpha$  is not ubiquitinated and instead binds to p300 and cAMP responsive element binding protein (CREB). The resulting HIF-1 $\alpha$  protein complex translocates to the nucleus and heterodimerizes with HIF- $\beta$ , whereupon the heterodimer can initiate the transcription of target genes.<sup>5-7</sup> HIF-1 $\alpha$  binds to the hypoxia responsive element (HRE) of *VEGFA*, *PDGF*, and *TGFA* and induces the expression of the protein factors VEGF, PDGF, and TGF- $\alpha$ , respectively.

In addition to HIF-1 $\alpha$  activation, two alternative signaling pathways initiated by hypoxia have been identified. The unfolded protein response (UPR) signaling pathway is initiated by stress of the endoplasmic reticulum (ER). The reader is directed to the article by Wouters and Koritzinsky for further discussion of the mechanisms of hypoxia induced ER stress.<sup>8</sup> Signaling by the kinase mammalian target of rapamycin (mTOR) is also associated with hypoxia.<sup>8,9</sup> Under normal environmental conditions, the mammalian target of rapamycin complex (mTORC1) phosphorylates downstream kinases that affect cell growth and protein synthesis. Signaling by mTOR is inhibited under certain hypoxic conditions and this inhibition occurs through multiple HIF-1 $\alpha$  independent pathways. Under these conditions, hypoxia may act to reduce tumor growth in early tumor development, since several of the negative regulators of mTORC1 signaling also function as tumor suppressors. In advanced malignant tumors, hypoxia regulates mRNA translation and increases gene expression of factors that promote tumor growth. In addition, hypoxic conditions have been found to downregulate the expression of the pro-apoptotic proteins BH-interacting domain death agonist (BID), Bcl-2 antagonist of cell death (BAD), and Bcl-2 associated X protein (BAX). The shift in expression of these proteins reduces the potential for apoptosis and increases the likelihood of cell survival. It has been hypothesized in this case hypoxia aids in the selection of more malignant cell mutants, a concept that will be discussed later in this review. As a result of the relationship between these alternative signaling pathways and hypoxia, cancer therapies are in development that target factors involved in mTOR and UPR signaling pathways.

Since tumors with abnormal mTOR signaling are also highly vascularized, mTOR signaling has been shown to have a direct effect on HIF-mediated transcription in addition to alternative signaling. Land and Tee found that activation of mTOR increased the transcriptional activity of HIF-1 $\alpha$  and VEGF under hypoxic conditions. Overexpression of the Ras homolog enriched in brain (*Rheb*) activated mTOR, while the addition of rapamycin reversed the mTOR activation.<sup>9</sup>



VEGF and its receptors VEGFR-1 and VEGFR-2 are recognized as the primary factors responsible for angiogenesis, and so their mechanisms are of great interest for the development of therapeutic inhibitors. VEGF encourages angiogenesis through multiple functions, including inducing endothelial cells to form capillary-like structures and mediating the secretion of enzymes to degrade extracellular matrix proteins. VEGF enhances cell survival by inducing the expression of anti-apoptotic proteins Bcl-2 and its homolog A1.<sup>10</sup> VEGF receptors (VEGFR) are cell surface tyrosine kinases, and VEGFR dimerization activates tyrosine kinase activity, resulting in the phosphorylation of tyrosine residues and downstream activation of signal transduction molecules (see **Figure 2**).



**Figure 2. Signaling pathways activated by VEGF.** VEGF regulates several endothelial cell functions, including proliferation, differentiation, permeability, vascular tone, and the production of vasoactive molecules. Upon ligand binding, the receptor tyrosines are phosphorylated, allowing the receptor to associate with a range of signaling molecules, including phosphatidylinositol 3-kinase (PI<sub>3</sub>K), Shc, Grb2, and the phosphatases SHP-1 and SHP-2. VEGF receptor activation can induce activation of the MAPK cascade via Raf stimulation leading to gene expression and cell proliferation, activation of PI<sub>3</sub>K leading to PKB activation and cell survival, activation of PLC-γ leading to cell proliferation, vasopermeability, and angiogenesis.

The concentration of angiogenic factors other than VEGF also increases with malignant progression. Early tumor development may primarily use VEGF to support the angiogenic signaling process, while advanced tumors rely on other growth factors, including fibroblast growth factor-1 (FGF-1), TGF-β1 and PlGF.<sup>11</sup> Jain has suggested that inhibitor cocktails used to target multiple pathways may be more efficient than a single VEGF inhibitor to block angiogenesis.<sup>12</sup>

Other pathways upstream can induce VEGF expression by methods other than through hypoxia and HIF-1α signaling. The oncogene *ras* is able to upregulate VEGF expression and downregulate the expression of Tsp-1 and other endogenous angiogenic inhibitors. Conversely, activation of the tumor suppressor genes *p53*, *PTEN*, and *Smad4* increases thrombospondin-1 expression, shifting the balance to prevent angiogenesis. *p53* has been reported to block angiogenesis through regulation of other unidentified inhibitors.<sup>5</sup>

The microtubule cytoskeleton has been cited as another possible target for angiogenesis inhibition. Microtubule targeting agents including 2-methoxyestradiol have been shown to block angiogenesis and inhibit HIF-1α signaling. Albendazole was demonstrated to downregulate VEGF in both *in vitro* experiments and in mouse models.<sup>13</sup>

Gene silencing by microRNAs has been associated with the regulation of multiple genes after hypoxic induction. Kulshreshtha, et al., identified approximately thirty hypoxia-regulated microRNAs (HRM) in breast or colon cancer cells that were consistently regulated in response to hypoxic conditions. Using predictive software, the gene targets of those HRM were predicted. As the HRM could theoretically downregulate multiple genes (between 10 and 200), the specific targets have not been identified. The researchers identified a group of HRM that theoretically target VEGF, implying the VEGF signaling pathway may become even more challenging to construct.<sup>14</sup>

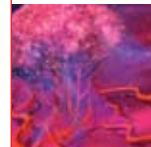
## The Tumor Microenvironment

Several recent reviews underscore the contribution of the microenvironment to tumor development.<sup>12,15-18</sup> While the normal cellular microenvironment can inhibit malignant cell growth, the modifications that occur in the tumor microenvironment synergistically support cell proliferation. Tumors shape their microenvironment and support the development of both tumor cells and non-malignant cells. An extensive review by Polyak, et al., concludes with a cautious summary, noting “although the importance of an altered microenvironment in tumorigenesis is no longer disputed, the nature of the molecular alterations underlying these changes remains unclear.”<sup>15</sup> Cancer treatments are now being considered that focus on the tumor microenvironment as a therapeutic target, as the non-malignant cells are more genetically stable and less likely to evolve into drug resistant phenotypes.

The tumor microenvironment affects angiogenesis by interfering with the signaling pathways required for cell recruitment and vascular construction. Endothelial progenitor cells (EPCs) that are recruited under hypoxic conditions for angiogenesis have been associated as well with metastasis.

The metabolic environment of the tumor is directly affected by lack of vasculature and subsequent oxygen starvation. Hypoxia in the microenvironment results in acidosis, as lactic acid builds up due to anaerobic glycolysis. The acidic environment inhibits the efficacy of more alkaline chemotherapeutic drugs. The absence of normal vasculature also places a physical constraint on the microenvironment. Because lymphatic fluid and waste products are inefficiently transported from the tumor microenvironment, the interstitial pressure in the proximity of the tumor is higher than for typical areas. In the tumor, the low pH of the microenvironment and the high interstitial pressure produce a hostile environment, making drug delivery difficult. An additional contributing factor to this hostile environment is the heterogeneous nature of the tumor and its environment. Not all areas of the tumor are equally hypoxic or acidic, since blood flow within tumors is inconsistent due to abnormal vascularization. The extracellular matrix is altered from normal environmental conditions. Also for solid tumors, the 3-D cellular structure can physically limit drug delivery. Hypoxic conditions also appear to promote tumor survival and growth by creating genomic instability and selecting for more aggressive phenotype cells.<sup>2,16</sup>





Stromal and other non-malignant cells create a supportive microenvironment for tumor growth, angiogenesis, and metastasis.<sup>15</sup> The tumor recruits endothelial cells, fibroblasts, and inflammatory cells, pericytes, and these cells and the components of the extracellular matrix (ECM) secreted by them contribute to the microenvironment composition. Stromal cells generate both tumor enhancing and tumor suppressing signals. In a mouse model of pancreatic cancer, inhibition of the Hedgehog signaling pathway reduced the level of tumor-associated stroma and improved the vascular delivery of gemcitabine.<sup>19</sup> However, while several theories have been proposed regarding the role of stroma in carcinogen induced tumors, the actual relationships are not yet proven. In addition, stromal cells may be a target for carcinogens, to either induce new cancers, or metastatic growths.<sup>15</sup>

Cancer-associated fibroblasts (CAF) and myofibroblasts are stromal cells that are abnormal, but not malignant, and promote angiogenesis and proliferation. These fibroblasts secrete growth factors and cytokines that produce oncogenic signals. In a comparative study which isolated both CAF and normal fibroblasts from six patients with invasive breast cancer, Ormio, et al., demonstrated that CAF were able to promote tumor growth more than normal fibroblasts.<sup>21</sup> These activated fibroblasts were able to promote angiogenesis via expression of stromal cell-derived factor-1 (SDF-1 or CXCL12). SDF-1 produces an endocrine effect by recruiting circulating endothelial progenitor cells (EPC) to the tumor. Tumor cells also contain CXCR4, the receptor for SDF-1, so stromal SDF-1 is able to directly stimulate tumor growth through a paracrine effect. The EPC recruited to the tumor by the cancer-associated fibroblasts are capable of being differentiated into tumor-associated vascular endothelial cells and used to construct new capillaries.<sup>21</sup> Circulating EPC migrate to other tissues and form a "premetastatic niche" for the colonization of circulating tumor cells.<sup>20</sup>

SDF-1 is not the only factor that participates in recruiting cells to the tumor microenvironment. Growth factors secreted by the tumor also control the composition of the microenvironment. Transforming growth factor- $\beta$  (TGF- $\beta$ ) recruits EPC to the microenvironment and is involved in activation of fibroblasts to CAF, while platelet derived growth factor (PDGF) is involved in recruiting fibroblasts and inducing their proliferation. VEGF does not directly recruit fibroblasts, but indirectly supports microenvironmental changes via creation of dysfunctional vascularization that allows plasma leakage, which attracts fibroblasts and other cells.<sup>20</sup> The microenvironment may convert recruited stromal cells to cancer-associated cells through epigenetic changes, including DNA methylation and chromatin remodeling, as changes in histone modification and DNA methylation have been found in tumor cells.

Proteins secreted by the tumor modify the microenvironment by contributing growth factors and proteases that degrade the extracellular matrix, and affect cell motility and adhesion. Stromal cells secrete ECM proteins, cytokines, growth factors, proteases, protease inhibitors, and endoglycosidases such as heparanase. These proteins modify the ECM in what is thought to be a systematic manner. Osteopontin, galectin-3, transforming growth factor- $\beta$  and matrix metalloproteinases (MMP) are important secreted proteins closely associated with cancer development.<sup>22</sup>

MMP are expressed at higher levels by tumor-associated epithelial cells than by normal epithelial cells. These MMP revise the composition of the EMC by degrading the basement membrane and other ECM proteins. This increase in proteolytic activity may also act to support tumor malignancy. Extreme shifts in the inhibition of protease activity by plasminogen activation inhibitor-1 (PAI-1), either by its absence or by excessive levels, demonstrate an anti-angiogenic effect in mouse cells, while physiological levels of PAI-1 support angiogenesis.<sup>23</sup> Tissue inhibitors of metalloproteinases (TIMP) are endogenous inhibitors of MMP and may function to balance the protease activity of MMP to shift the balance from a pro-angiogenic to an inhibitory environment.

## Preventing Angiogenesis and Improving Drug Delivery by Changes to the Microenvironment

Anti-angiogenic therapies have been defined as those that prevent the progression of pathogenic angiogenesis. This is in contrast to anti-vascular therapies, which are defined as those that rapidly block new blood vessels to prevent circulation. Both approaches intend to reverse the tumor progress from a malignant pro-angiogenic state to a quiescent (non-angiogenic) state.<sup>24</sup>

### Angiogenic Signal Inhibition

Direct angiogenesis inhibitors prevent vascular endothelial cells from proliferating or migrating toward the tumor. This class of inhibitors may also reduce the presence of pro-angiogenic factors by protein binding or regulation of gene expression. Since VEGF is the cornerstone of angiogenesis, inhibition of VEGF mediated signaling pathways has been a focus of therapeutic development.<sup>13</sup> Pathway inhibition may be achieved by antibodies against VEGF or VEGFR, synthetic or natural proteins that bind VEGF, and small molecule inhibitors of VEGF and other receptor tyrosine kinases. Bevacizumab (Avastin®), the monoclonal antibody against VEGF, was approved in 2004 by the U.S. F.D.A. for clinical use in treating colorectal cancer and has been shown to be effective against other cancers. Bevacizumab is currently used in combination with chemotherapeutic agents to treat colorectal and lung cancers.

Receptor tyrosine kinase inhibitors, such as sorafenib, sunitinib, and SU6668, are small molecules that prevent angiogenesis by inhibiting VEGF receptors and blocking VEGF signaling. Doxorubicin (**Cat. No. D1515**), cisplatin (**Cat. No. P4394**), and other chemotherapeutic agents previously approved for use in cancer treatment have been investigated and found to repress VEGF production *in vitro*.<sup>13,25</sup> TNP-470 (**Cat. No. T1455**), caplostatin (the water soluble copolymer of TNP-740), and thalidomide (**Cat. Nos. T144, T150**) are other low molecular weight compounds that inhibit angiogenesis. TNP-470 prevents VEGF expression and blocks VEGF-phosphorylation of the VEGFR2 receptor.<sup>26</sup> Thalidomide inhibits angiogenesis mediated by VEGF and bFGF, and increases tissue oxygenation in mouse fibrosarcomas. Roxithromycin (**Cat. No. R4393**) and clarithromycin (**Cat. No. C9742**), macrolide antibiotics that have anti-angiogenic activity, alter VEGF expression, although the mechanism of action is not well-defined.<sup>27</sup>

## Microtubule Inhibitors

Compounds that target microtubule synthesis and tubulin also produce an anti-angiogenic response. Reports by Tsuzuki, et al.,<sup>28</sup> and Escuin, et al.,<sup>29</sup> provide evidence of a relationship between disruption of the microtubule structure and disruption of the hypoxia-induced HIF-1 $\alpha$  pathway. Microtubule targeting agents, including 2-methoxyestradiol<sup>30</sup> (**Cat. No. M6383**) and albendazole<sup>31</sup> (**Cat. No. A4673**) demonstrate anti-angiogenic activity, although their mechanisms of action may differ.<sup>13</sup>

## Indirect Mechanisms of Inhibition

Therapies have also been developed that use indirect mechanisms to inhibit angiogenesis by suppressing angiogenic growth factors or interfering with the signaling pathways of their receptors. This indirect inhibition targets tumor cell proteins that regulate oncogenes, thereby, shifting the balance of the angiogenic switch. For example, tyrosine kinase inhibitors initially developed to target oncogenes have been found to decrease angiogenic activity as well. Trastuzumab (Herceptin<sup>®</sup>), the antibody against HER2/neu receptor tyrosine kinase, was found to downregulate the pro-angiogenic factors TFG- $\alpha$ , Ang-1, and VEGF, and upregulate expression of the angiogenic inhibitor Tsp-1 by gene array.<sup>32</sup> Other signaling pathways affect the expression of pro-angiogenic or anti-angiogenic factors, and produce an indirect effect on angiogenesis. The *ras* oncogene confers resistance to apoptosis and increases proliferation, but *ras* has also been found to upregulate VEGF expression and downregulate expression of angiogenesis inhibiting proteins. In angiogenic tumor cells, Tsp-1 expression is downregulated by PI3K via phosphorylation of cMyc. Other tumor suppressor genes, including *p53*, *PTEN*, and *Smad4*, have been shown to increase Tsp-1 expression.<sup>24</sup>

## Targeting the Tumor Vasculature

Some approaches have focused on the dysfunctional vascular system constructed by tumors as a potential target. As discussed previously, the abnormal constructions of tumor vasculature contributes to a microenvironment that acts as a barrier to chemotherapy. If the microenvironment is normalized, therapy could be more effective.<sup>12</sup> Vasculature normalization might also reduce metastasis and provide greater oxygen levels to the tumor. Successful radiation therapy requires oxygenation of the tissue in order to generate reactive oxygen species (ROS) that damage cellular DNA and drive tumor cells into apoptosis.

Jain and co-authors postulated adjusting the balance of pro-angiogenic and anti-angiogenic factors could shift the angiogenic switch, producing a more normal state of angiogenesis.<sup>2</sup> Jain further hypothesized the judicious application of anti-angiogenic drugs can “normalize” vasculature, making delivery of drugs and oxygen to the tumor more efficient.<sup>12</sup> The resultant improvements in tissue oxygenation and fluid removal may contribute to changes in the microenvironment, shifting it to a less tumorigenic state. This theory was tested in experimental models, which showed both bevacizumab and the antibody against VEGFR2 remodeled abnormal capillaries to produce more normal vasculature. This “normalization” using anti-VEGF agents appears to result in a therapeutic window during which other

treatment methods are more successful. In a series of experiments, therapeutic radiation was found to be more effective when used in conjunction with anti-VEGF treatment.<sup>33,34</sup> However, this therapeutic window appears to have temporal limits. Winkler, et al., found murine gliomal tumors treated with an antibody to VEGFR2 began to revert to a more malignant vasculature eight days after initial treatment.<sup>35</sup> Treatment with anti-VEGFR2 resulted in increased angiopoietin I expression and matrix metalloproteinase activation during this normalization window. In addition to this normalization window, VEGFR tyrosine kinase inhibitors were found to initially inhibit tumor growth, but accelerate tumor growth and metastasis with prolonged use.<sup>36,37</sup> This response may be due to hypoxic selection for more aggressive, malignant cells, or because the therapies improve the release of tumor cells into the circulating vasculature and promote metastasis.

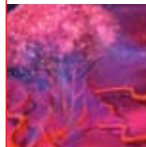
Aspects of this research may support the hypothesis that angiogenesis inhibitors normalize the tumor vasculature by potentially pruning immature structures, resulting in improved drug treatment. However, the test results by Winkler, et al., suggested that a VEGFR2 blockade temporarily facilitates the recruitment of pericytes to tumor vessels and did not selectively prune pericyte-poor capillaries.<sup>35</sup> To further this dichotomy, increasing the tumor vascular system instead of reducing it was shown to increase drug delivery to the tumor in a recent article. Olive, et al., found that by inhibiting the hedgehog signaling pathway in a mouse model of pancreatic ductal adenocarcinoma, the intratumoral vascular density was increased. Pancreatic ductal adenocarcinoma is highly resistant to chemotherapy. This report found treatment with IPI-926, a hedgehog signaling inhibitor, increased the vascular density of the tumor and enhanced delivery of gemcitabine to the tumor. Interestingly, this improved capillary structure was transient in a manner similar to the normalization window, and the improved vascularization reverted after several days of treatment.<sup>19</sup>

Since *Rheb* activation of mTOR increases the activity of HIF-1 $\alpha$  and VEGF, the mammalian target of rapamycin (mTOR) factor is being investigated as a means to inhibit angiogenesis. Rapamycin (**Cat. No. R0395**) and other mTOR inhibitors may prevent angiogenesis by interfering with the mTOR promotion of HIF-1 $\alpha$  activity. Temsirolimus, a rapamycin derivative that targets mTOR, is in clinical trials for the treatment of renal cell carcinoma.

## Inhibition of Epigenetic Modification

Epigenetic modifications in tumor endothelial cells can regulate angiogenesis by silencing tumor suppressor genes. Histone deacetylase (HDAC) and DNA methyltransferase (DNMT) inhibitors are also of current interest for preventing tumor angiogenesis. Histone deacetylation and DNA methylation in cancer cells produce epigenetic suppression that downregulates genes. Hu, et al., analyzed *in situ* and invasive breast cancer cells and identified DNA methylation changes in all cancer cell types as compared to normal tissue.<sup>38</sup> Debby, et al., found that gene silencing in tumor-conditioned endothelial cells was associated with histone modification, but not DNA methylation. Nevertheless, treatment of tumor endothelial cells with either the DNMT inhibitor 5-aza-2'-deoxycytidine (**Cat. No. A3656**) or the HDAC inhibitor trichostatin A (**Cat. No. T8552**) served to reverse the gene





silencing, and inhibit cell growth and tumor angiogenesis.<sup>39</sup> Various HDAC inhibitors have been found to downregulate the expression of VEGF, HIF-1 $\alpha$ , and bFGF, and to upregulate the expression of thrombospondin-1, neurofibromin-2, and other angiogenesis inhibiting factors.<sup>39</sup> A combination of rapamycin with the HDAC inhibitor LBH589 was found to have a synergistic effect and produce greater inhibition of HIF-1 $\alpha$  in human prostate PC3 cells than the individual drugs.<sup>40</sup>

## NF- $\kappa$ B and Copper

NF- $\kappa$ B activity is increased in cancer, and NF- $\kappa$ B activation modulates the expression of over 200 genes, including genes associated with apoptosis, metastasis, and angiogenesis. As a result, NF- $\kappa$ B is known to participate in angiogenesis signaling pathways, but its role is not yet well understood. Some research has been done studying the relationship between NF- $\kappa$ B modulation of angiogenesis and additional factors such as reduced endogenous copper concentration.<sup>41</sup> The participation of copper in angiogenesis was demonstrated by using penicillamine (**Cat. No. P4875**), a copper chelator, to reduce copper plasma levels in rabbits and block a prostaglandin E<sub>1</sub>-induced angiogenic response.<sup>42</sup> Ammonium tetrathiomolybdate (**Cat. No. 323446**), an approved drug that is also a copper chelator, was shown to affect the NF- $\kappa$ B pathway to inhibit angiogenesis and metastasis.<sup>43</sup>

## The Tumor Microenvironment

Indirect anti-angiogenic therapy is also being applied as a means to attack the tumor microenvironment and overcome drug resistance. The tumor microenvironment contributes to drug resistance because of hypoxic and acidic conditions. Several chemotherapeutic drugs, as well as radiation therapy, use oxygen to induce DNA damage to tumor cells. Hypoxia in the microenvironment results in acidosis, as lactic acid builds up due to anaerobic glycolysis. The acidic environment inhibits the efficacy of more alkaline chemotherapeutic drugs.<sup>16</sup> Tumors also develop drug resistance over time through genetic mutation and selection of resistant phenotypes.

In an experiment that focused on endothelial cells, Boehm, et al., reported an anti-angiogenic therapy directed toward tumor-associated endothelial cells, instead of directed toward tumor cells, does not produce drug resistance. The angiogenic inhibitor protein endostatin (**Cat. Nos. E8154, E8279**) was used to reverse angiogenesis in animal models of Lewis lung cancer, fibrosarcoma, and melanoma. The tumors were allowed to grow to a specific size within the animals and then the animals were treated with endostatin until the tumor shrank to an undetectable size. Treatment was stopped and the tumor was allowed to regrow. After repeated cycles of treatment with endostatin, the tumors remained in a dormant state for an extended period.<sup>44</sup>

An alternative to direct or indirect inhibition of the angiogenic signaling pathways regulated by VEGF is therapeutically targeting the tumor microenvironment. Angiogenesis is prevented by interfering with the recruited endothelial cells or blocking the cellular regulatory pathways that are independent of the tumor

cells. Vascular disrupting agents, including tubulin destabilizers that also inhibit HIF-1 $\alpha$  expression, may be used to disrupt tumor blood supply by targeting endothelial cells instead of the tumor.<sup>5</sup> Flavonoids, including DMXAA (**Cat. No. D5817**) and baicalein (**Cat. No. 465119**), induce apoptosis in endothelial cells and disrupt the tumor vasculature.<sup>5,45</sup>

## Angioprevention

Some researchers have suggested a proactive approach to preventing tumor angiogenesis by using antioxidants<sup>18</sup> or anti-inflammatory drugs as preventatives against angiogenesis (called by some authors "angioprevention"). Antioxidants have long been of interest as mediators of oxidative stress and prevention of cancer initiated by DNA damage through reactive oxygen species. However, since angiogenesis may be regulated by free radicals, peroxide, and redox-sensitive factors, including NF- $\kappa$ B, redox signaling may influence the expression of pro-angiogenic proteins.<sup>41</sup> A study of the antioxidants *N*-acetyl-L-cysteine (**Cat. No. A7250**) and epigallocatechin 3-gallate (EGCG) (**Cat. Nos. E4143, E4268**) found that both of the antioxidants reduced the migration and invasion of endothelial cells, and downregulated gene expression of pro-angiogenic factors that control endothelial cell activation and migration.<sup>46,47</sup> Vitamin C (ascorbic acid, **Cat. Nos. A7506, A0278**) demonstrated angiostatic activity *in vivo* that may be due to its function as an antioxidant.<sup>48</sup>

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Other "angiopreventative" compounds that deactivate the angiogenic switch inhibit the recruitment and activation of endothelial cells or interfere with pro-angiogenic signaling. Two triterpenoid compounds based on oleanolic acid demonstrated anti-angiogenic activity against an immortalized Kaposi's sarcoma cell line (KS-Imm). The triterpenoids methyl 2-cyano-3,12-dioxoolean-1,9-dien-28-oate (CDDO-Me) and 2-cyano-3,12-dioxoolean-1,9-dien-28-oic imidazolide (CDDO-Im) prevent the activation of the ERK1/2 pathway after stimulation with VEGF and block NF- $\kappa$ B signaling by inhibiting translocation of NF- $\kappa$ B to the nucleus.<sup>49</sup>

A caveat to these results is the difficulty of moving promising therapies into clinical trials. Research into angiogenesis, the tumor microenvironment, and their relationships to cancer progression has expanded into multiple directions. Transferring the theoretical research to actual clinical results, however, has been a reminder that *in vitro* and animal models cannot completely represent the human condition. The research points toward many interesting and novel directions that intersect with multiple other biological processes and mechanisms, but always the greatest challenge will be to identify those that can truly benefit the patient.

#### References

1. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. Hanahan, D., and Folkman, J., *Cell*, **86**, 353-64 (1996).
2. Tumor microvasculature and microenvironment: targets for anti-angiogenesis and normalization (Review). Fukumura, D. and Jain, R.K., *Microvasc. Res.*, **74**, 72-84 (2007).
3. Inhibiting hypoxia-inducible factor 1 for cancer therapy (Review). Melillo, G., *Mol. Cancer Res.*, **4**, 601-5 (2006).
4. Hypoxia and the hypoxia-inducible-factor pathway in glioma growth and angiogenesis (Review). Kaur, B., et al., *Neuro. Oncol.*, **7**, 134-53 (2005).
5. Novel agents on the horizon for cancer therapy (Review). Ma, W.W. and Adjei, A.A., *CA Cancer*, **59**, 111-137 (2009).
6. Targeting tumor angiogenesis with histone deacetylase inhibitors (Review). Ellis, L., et al., *Cancer Lett.*, **280**, 145-53 (2009).
7. Role of hypoxia-inducible factor-1 $\alpha$  as a cancer therapy target (Review). Patiar, S., and Harris, A.L., *Endocr. Relat. Cancer*, **13**, S61-75 (2006).
8. Hypoxia signalling through mTOR and the unfolded protein response in cancer (Review). Wouters, B.G. and Koritzinsky, M., *Nat. Rev. Cancer*, **8**, 851-864 (2008).
9. Hypoxia-inducible factor 1 $\alpha$  is regulated by the mammalian target of rapamycin (mTOR) via an mTOR signaling motif. Land, S.C. and Tee, A.R., *J. Biol. Chem.*, **282**, 20534-43 (2007).
10. Vascular endothelial growth factor induces expression of the antiapoptotic proteins Bcl-2 and A1 in vascular endothelial cells. Gerber, H.P., et al., *J. Biol. Chem.*, **273**, 13313-6 (1998).
11. Expression of the angiogenic factors vascular endothelial cell growth factor, acidic and basic fibroblast growth factor, tumor growth factor  $\beta$ -1, platelet-derived endothelial cell growth factor, placenta growth factor, and pleiotrophin in human primary breast cancer and its relation to angiogenesis. Relf, M., et al., *Cancer Res.*, **57**, 963-9 (1997).
12. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy (Review). Jain, R.K., *Science*, **307**, 58-62 (2005).
13. Inhibitors of vascular endothelial growth factor in cancer (Review). Pourgholami, M.H. and Morris, D.L., *Cardiovasc. Hematol. Agents Med. Chem.*, **6**, 343-347 (2008).
14. A microRNA component of the hypoxic response (Review). Kulshreshtha, R., et al., *Cell Death Differ.*, **15**, 667-671 (2008).
15. Co-evolution of tumor cells and their microenvironment (Review). Polyak, K., et al., *Trends Genet.*, **25**, 30-38 (2009).
16. Drug resistance and the solid tumor microenvironment (Review). Trédan, O., et al., *J. Natl. Cancer Inst.*, **99**, 1441-1454 (2008).
17. Role of the microenvironment in tumor growth and in refractoriness/resistance to anti-angiogenic therapies (Review). Shojajei, F. and Ferrara, N., *Drug Resist. Updat.*, **11**, 219-30 (2008).
18. Microenvironmental regulation of cancer development (Review). Hu, M. and Polyak, K., *Curr. Opin. Genet. Dev.*, **18**, 27-34 (2008).
19. Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. Olive, K.P., et al., *Science*, **324**, 1457-1461 (2009).
20. Tumor-microenvironment interactions: dangerous liaisons (Review). Witz, I.P., *Adv. Cancer Res.*, **100**, 203-229 (2008).
21. Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion. Orimo, A., et al., *Cell*, **121**, 335-348 (2005).
22. Cancer and the tumor microenvironment: a review of an essential relationship (Review). Mbeunkui, F. and Johann, D.J. Jr., *Cancer Chemother. Pharmacol.*, **63**, 571-582 (2009).
23. The pro- or antiangiogenic effect of plasminogen activator inhibitor 1 is dose dependent. Devy, L., et al., *FASEB J.*, **16**, 147-54 (2002).
24. Tumor-vascular interactions and tumor dormancy (Review). Naumov, G.N., et al., *APMIS*, **116**, 569-585 (2008).
25. Cisplatin and doxorubicin repress vascular endothelial growth factor expression and differentially down-regulate hypoxia-inducible factor I activity in human ovarian cancer cells. Duyndam, M.C., et al., *Biochem. Pharmacol.*, **74**, 191-201 (2007).
26. Inhibition of vessel permeability by TNP-470 and its polymer conjugate, caplostatin. Satchi-Fainaro, R., et al., *Cancer Cell*, **7**, 251-61 (2005).
27. Roxithromycin inhibits angiogenesis of human hepatoma cells *in vivo* by suppressing VEGF production. Aoki, D., et al., *Anticancer Res.*, **25**, 133-8 (2005).
28. Vascular endothelial growth factor (VEGF) modulation by targeting hypoxia-inducible factor-1 $\alpha$   $\rightarrow$  hypoxia response element  $\rightarrow$  VEGF cascade differentially regulates vascular response and growth rate in tumors. Tsuzuki, Y., et al., *Cancer Res.*, **60**, 6248-52 (2000).
29. Both microtubule-stabilizing and microtubule-destabilizing drugs inhibit hypoxia-inducible factor-1 $\alpha$  accumulation and activity by disrupting microtubule function. Escuin, D., et al., *Cancer Res.*, **65**, 9021-8 (2005).
30. 2ME2 inhibits tumor growth and angiogenesis by disrupting microtubules and dysregulating HIF. Mabeesh, N.J., et al., *Cancer Cell*, **3**, 363-75 (2003).
31. Albendazole: a potent inhibitor of vascular endothelial growth factor and malignant ascites formation in OVCAR-3 tumor-bearing nude mice. Pourgholami, M.H., et al., *Clin. Cancer Res.*, **12**, 1928-35 (2006).
32. Tumour biology: hereceptin acts as an anti-angiogenic cocktail. Izumi, Y., et al., *Nature*, **416**, 279-80 (2002).
33. Anti-Vascular endothelial growth factor treatment augments tumor radiation response under normoxic or hypoxic conditions. Lee, C.G., et al., *Cancer Res.*, **60**, 5565-70 (2000).
34. Vascular endothelial growth factor receptor-2-blocking antibody potentiates radiation-induced long-term control of human tumor xenografts. Kozin, S.V., et al., *Cancer Res.*, **61**, 39-44 (2001).
35. Kinetics of vascular normalization by VEGFR2 blockade governs brain tumor response to radiation: role of oxygenation, angiopoietin-1, and matrix metalloproteinases. Winkler, F., et al., *Cancer Cell*, **6**, 553-63 (2004).
36. Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis. Paez-Ribes, M., et al., *Cancer Cell*, **15**, 220-31 (2009).
37. Accelerated metastasis after short-term treatment with a potent inhibitor of tumor angiogenesis. Ebos, J.M., et al., *Cancer Cell*, **15**, 232-9 (2009).
38. Distinct epigenetic changes in the stromal cells of breast cancers. Hu, M., et al., *Nat. Genet.*, **37**, 899-905 (2005).
39. Identification of epigenetically silenced genes in tumor endothelial cells. Debby, M.E.I., et al., *Cancer Res.*, **67**, 4138-48 (2007).
40. Combination strategy targeting the hypoxia inducible factor-1 $\alpha$  with mammalian target of rapamycin and histone deacetylase inhibitors. Verheul, H.M., et al., *Clin. Cancer Res.*, **14**, 3589-97 (2008).
41. Modulation of angiogenesis for cancer prevention: strategies based on antioxidants and copper deficiency (Review). Kahn, G.N. and Merajver, S.D., *Curr. Pharm. Des.*, **13**, 3584-3590 (2007).
42. Role of prostaglandin E<sub>2</sub> and copper in angiogenesis. Ziche, M., et al., *J. Natl. Cancer Inst.*, **69**, 475-82 (1982).
43. Tetrathiomolybdate inhibits angiogenesis and metastasis through suppression of the NF- $\kappa$ B signaling cascade. Pan, Q., et al., *Mol. Cancer Res.*, **1**, 701-6 (2003).
44. Antiangiogenic therapy of experimental cancer does not induce acquired drug resistance. Boehm, T., et al., *Nature*, **390**, 404-7 (1997).
45. Baicalein and baicalin are potent inhibitors of angiogenesis: Inhibition of endothelial cell proliferation, migration and differentiation. Liu, J.J., et al., *Int. J. Cancer*, **106**, 559 (2003).
46. Molecular mechanisms of action of angiopreventive anti-oxidants on endothelial cells: microarray gene expression analyses. Pfeffer, U., et al., *Mutat. Res.*, **591**, 198-211 (2005).
47. Tumor inflammatory angiogenesis and its chemoprevention (Review). Albini, A., et al., *Cancer Res.*, **65**, 10637-41 (2005).
48. Novel function of ascorbic acid as an angiostatic factor. Ashino, H., et al., *Angiogenesis*, **6**, 259-69 (2003).
49. Anti-angiogenic activity of a novel class of chemopreventive compounds: oleanic acid terpenoids (Review). Sogno, I., et al., *Recent Results Cancer Res.*, **181**, 209-212 (2009).



# Angiogenesis Research Products

## VEGF Inhibitors

### Doxorubicin hydrochloride

Adriamycin® hydrochloride; Hydroxydaunorubicin hydrochloride; DOX [25316-40-9] C<sub>27</sub>H<sub>29</sub>NO<sub>11</sub> · HCl FW 579.98

Inhibitor of reverse transcriptase and RNA polymerase; immunosuppressive agent; intercalates in DNA.

Antitumour antibiotic. Effect of adriamycin on heart mitochondrial DNA;<sup>1</sup> Properties.<sup>2,3</sup>

**Lit cited:** 1. C.N. Ellis et al., *Biochem. J.* **245**, 309 (1987); 2. R.J. White et al., *Drugs Pharm. Sci.* **22**, 569 (1984); 3. A. Vigevani, M.J. Williamson, *Anal. Profiles Drug Subst.* **9**, 245 (1980);

#### ▶ ≥98% (TLC)

Naturally fluorescent anthracycline antibiotic, anticancer drug. Doxorubicin is a substrate of MRP1 which was first cloned from a DOX-resistant lung cancer cell line. Fluorescent property has been exploited for the measurement of drug efflux pump activities as well as resolving the important question of intracellular localization of various multidrug resistance proteins and the role of subcellular organelles (Golgi and lysosome) in the sequestration of drugs and its implication in drug resistant phenotypes.

store at: 2-8°C

[D1515-10MG](#) 10 mg

### Honokiol

5,3'-Diallyl-2,4'-dihydroxybiphenyl [35354-74-6] C<sub>18</sub>H<sub>18</sub>O<sub>2</sub> FW 266.33

Honokiol is a natural biphenyl neolignan from magnolia extract. It is antiangiogenic, antitumor, and anxiolytic.

#### ▶ ≥98% (HPLC), powder

store at: 2-8°C

[H4914-10MG](#) 10 mg

[H4914-25MG](#) 25 mg

### SU 4312

3-(4-Dimethylaminobenzylidene)-2-indolinone; 3-[[[4-Dimethylamino phenyl]methylene]-1,3-dihydro-2H-indol-2-one, E/Z mixture [5812-07-7] C<sub>17</sub>H<sub>16</sub>N<sub>2</sub>O FW 264.32

Vascular endothelial growth factor (VEGF) receptor protein tyrosine kinase 1/2 and platelet derived growth factor (PDGF) receptor inhibitor.

This product is a mixture of the cis- and trans- isomers. The ratio is about 55:45 based on HPLC.

#### ▶ ≥98% (HPLC)

store at: 2-8°C

[S8567-5MG](#) 5 mg

[S8567-25MG](#) 25 mg

### Sulochrin

[519-57-3] C<sub>17</sub>H<sub>16</sub>O<sub>7</sub> FW 332.30

Antibiotic from *Aspergillus* and *Penicillium* sp. Fungal metabolite; VEGF inhibitor and anti-angiogenic that inhibits the VEGF-induced tube formation of human umbilical vein endothelial cells.

#### ▶ ≥98% (HPLC), solid

store at: 2-8°C

[S4570-1MG](#) 1 mg

### (-)-Thalidomide

S(-)-2-(2,6-Dioxo-3-piperidinyl)-1H-isindole-1,3(2H)-dione [841-67-8] C<sub>13</sub>H<sub>10</sub>N<sub>2</sub>O<sub>4</sub> FW 258.23

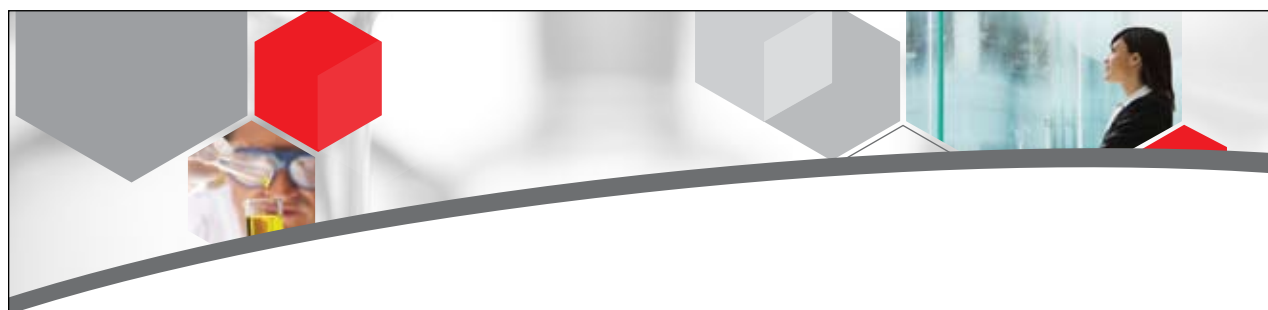
#### ▶ >98%, solid

Selectively inhibits biosynthesis of tumor necrosis factor α (TNF-α); inhibitor of angiogenesis.

[T150-10MG](#) 10 mg

[T150-25MG](#) 25 mg

[T150-100MG](#) 100 mg



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Users of MetaCore and MetaDrug are able to link to Sigma-Aldrich products from molecules displayed in the Drug Detail Pages. This functionality will accelerate productivity for researchers by showing molecule availability during the information gathering process of experiments.

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### (±)-Thalidomide

(±)-2-(2,6-Dioxo-3-piperidinyl)-1H-isoindole-1,3(2H)-dione  
[50-35-1] C<sub>13</sub>H<sub>10</sub>N<sub>2</sub>O<sub>4</sub> FW 258.23

► **>98%, solid**

(±)-Thalidomide selectively inhibits biosynthesis of tumor necrosis factor α (TNF-α); inhibitor of angiogenesis; immunosuppressive; sedative; teratogen.

<a href="#">T144-100MG</a>	100 mg
<a href="#">T144-1G</a>	1 g

### TNP-470

**NEW**

C<sub>19</sub>H<sub>28</sub>ClNO<sub>6</sub> FW 401.88

TNP-470 is a methionine aminopeptidase-2 (MetAP-2) inhibitor, selective for MetAP-2 over MetAP11. TNP-470 is an antiangiogenic.

► **≥98% (HPLC)**

store at: -20°C

<a href="#">T1455-5MG</a>	5 mg
<a href="#">T1455-25MG</a>	25 mg

## VEGFR Inhibitors

### Ki8751 hydrate

**NEW**

1-(2,4-Difluoro-phenyl)-3-[4-(6,7-dimethoxy-quinolin-4-yloxy)-2-fluoro-phenyl]-urea hydrate

C<sub>24</sub>H<sub>18</sub>F<sub>3</sub>N<sub>3</sub>O<sub>4</sub> · xH<sub>2</sub>O FW 469.41 (Anh)

Ki8751 is a potent, selective inhibitor of VEGFR-2 tyrosine kinase (IC<sub>50</sub> = 0.9 nM).

► **≥98% (HPLC), solid**

store at: -20°C

<a href="#">K1265-5MG</a>	5 mg
<a href="#">K1265-25MG</a>	25 mg

### MAZ51

3-(4-Dimethylaminonaphthalen-1-ylmethylene)-1,3-dihydroindol-2-one

[163655-37-6] C<sub>21</sub>H<sub>18</sub>N<sub>2</sub>O FW 314.38

Cell-permeable VEGFR-3 inhibitor. At low concentration ≥ 5 μM, it specifically blocks VEGF-C- and VEGF-D-induced phosphorylation of VEGFR-3, but not VEGFR-2, in PAE cells. It partially blocks VEGFR-2 phosphorylation only at higher concentrations (50 μM).

► **≥98% (HPLC), solid**

store at: 2-8°C

<a href="#">M1695-5MG</a>	5 mg
<a href="#">M1695-25MG</a>	25 mg

### ST638

α-Cyano-(3-ethoxy-4-hydroxy-5-phenylthiomethyl)cinnamide

[107761-24-0] C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>S FW 354.42

Protein tyrosine kinase inhibitor (IC<sub>50</sub> = 370 nM). Also inhibits HGF-induced MAP kinase activation in hepatocytes and inhibits phospholipase D activity in human neutrophils.

Light sensitive and packaged under nitrogen.

► **≥98% (HPLC), solid**

store at: -20°C

<a href="#">S1195-5MG</a>	5 mg
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### SU 5416

1,3-Dihydro-3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-2H-indol-2-one

[204005-46-9] C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>O FW 238.28

SU 5416 is a vascular endothelial growth factor (VEGF) receptor protein tyrosine kinase 1/2 inhibitor.

► **≥98% (HPLC)**

store at: -20°C

<a href="#">S8442-5MG</a>	5 mg
<a href="#">S8442-25MG</a>	25 mg

### Tyrphostin AG 494

Tyrphostin B48; N-Phenyl-3,4-dihydroxybenzylidenecyanoacetamide

C<sub>16</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub> FW 280.28

Inhibitor of EGF-receptor phosphorylation

► **≥98%**

store at: -20°C

<a href="#">T4318-5MG</a>	5 mg
<a href="#">T4318-25MG</a>	25 mg

### Tyrphostin SU 1498

(E)-N-(3''-Phenylpropyl)-α-cyano-3',5'-diisopropyl-4'-hydroxycinnamide

C<sub>25</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub> FW 390.52

Potent and selective inhibitor of the VEGF receptor kinase, Flk-1. Very weak inhibitor of PDGFR-kinase, EGFR-kinase and HER-2 kinase.

► **≥98%**

store at: -20°C

<a href="#">T4192-5MG</a>	5 mg
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## PDGFR Inhibitors

### 2-(3,4-Dimethoxy-benzoylamino)-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylic acid amide

Flt-3 inhibitor

[301305-73-7] C<sub>18</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub>S FW 360.43

Flt-3 (fms-related tyrosine kinase 3) inhibitor

► **≥98% (HPLC), solid**

store at: -20°C

<a href="#">D5943-5MG</a>	5 mg
<a href="#">D5943-25MG</a>	25 mg

### JNJ-10198409

**NEW**

N-(3-fluorophenyl)-2,4-dihydro-6,7-dimethoxy-Indeno[1,2-c]pyrazol-3-amine; 3-Fluoro-N-(6,7-dimethoxy-2,4-dihydroindeno[1,2-c]pyrazol-3-yl)phenylamine; RWJ 540973

[627518-40-5] C<sub>18</sub>H<sub>16</sub>FN<sub>3</sub>O<sub>2</sub> FW 325.34

JNJ-10198409 is a potent ATP-competitive inhibitor of Platelet-Derived Growth Factor receptor tyrosine kinase (PDGF-RTK) with both antiangiogenic and a direct tumor cell antiproliferative activity. It is selective for PDGF-β kinase with IC<sub>50</sub> values of 4.2 nM for PDGF-β and 45 nM for PDGF-α kinase.

► **≥98% (HPLC), solid**

store at: -20°C

<a href="#">J4649-1MG</a>	1 mg
<a href="#">J4649-5MG</a>	5 mg

### Tyrphostin A9

[[3,5-bis(1,1-Dimethylethyl)-4-hydroxyphenyl]methylene]propanedinitrile

[10537-47-0] C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>O FW 282.38

► **solid**

Selective inhibitor of PDGF receptor tyrosine kinase.

<a href="#">T182-5MG</a>	5 mg
<a href="#">T182-25MG</a>	25 mg

### Tyrphostin AG 370

Tyrphostin B7; 2-Amino-4-(1H-indo-5'-yl)-1,1,3-tricyanobuta-1,3-diene

C<sub>15</sub>H<sub>9</sub>N<sub>5</sub> FW 259.27

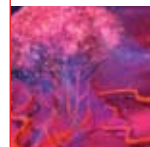
Inhibitor of PDGF-induced cell proliferation.

► **≥98%**

store at: -20°C

<a href="#">T6443-1MG</a>	1 mg
<a href="#">T6443-5MG</a>	5 mg





### Tyrphostin AG 1296

6,7-Dimethoxy-2-phenylquinoxaline  
[146535-11-7] C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> FW 266.29

Selective inhibitor of platelet-derived growth factor (PDGF) receptor protein.

▶ ≥98%

store at: 2-8°C

<a href="#">T4057-1MG</a>	1 mg
<a href="#">T4057-5MG</a>	5 mg

### Tyrphostin AG 1433

2-(3',4'-Dihydroxyphenyl)-6,7-dimethylquinoxaline  
C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> FW 266.29

▶ ≥99%

PDGFB receptor tyrosine kinase inhibitor.

store at: 2-8°C

<a href="#">T5317-5MG</a>	5 mg
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## Non-Receptor Tyrosine Kinase Inhibitors

### Genistein

5,7-Dihydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one;  
4',5,7-Trihydroxyisoflavone

[446-72-0] C<sub>15</sub>H<sub>10</sub>O<sub>5</sub> FW 270.24

Inhibitor of tyrosine protein kinase; competitive inhibitor of ATP in other protein kinase reactions. Antiangiogenic agent, down-regulates the transcription of genes involved in controlling angiogenesis.

▶ synthetic, ≥98% (HPLC), powder

store at: -20°C

<a href="#">G6649-5MG</a>	5 mg
<a href="#">G6649-25MG</a>	25 mg
<a href="#">G6649-100MG</a>	100 mg

▶ from *Glycine max* (soybean), ~98% (HPLC)

store at: -20°C

<a href="#">G6776-5MG</a>	5 mg
<a href="#">G6776-10MG</a>	10 mg

### Herbimycin A from *Streptomyces hygroscopicus*

[70563-58-5] C<sub>30</sub>H<sub>42</sub>N<sub>2</sub>O<sub>9</sub> FW 574.66

An antibiotic that inhibits protein tyrosine kinase. Herbimycin A is a potent inhibitor of angiogenesis.

▶ ≥95% (HPLC), powder

Hygroscopic and photosensitive

store at: -20°C

<a href="#">H6649-1MG</a>	0.1 mg
<a href="#">H6649-1MG</a>	1 mg

### Lavendustin A

5-[[[(2,5-Dihydroxyphenyl)methyl][(2-hydroxyphenyl)methyl]amino]-2-hydroxybenzoic acid

[125697-92-9] C<sub>21</sub>H<sub>19</sub>NO<sub>6</sub> FW 381.38

▶ ~85% (TLC), crystalline

Cell-permeable tyrosine kinase inhibitor with little effect on protein kinase A or C. Inhibits NMDA-stimulated cGMP production. Inhibits VEGF-induced angiogenesis.

Photosensitive

store at: -20°C

<a href="#">L2400-1MG</a>	1 mg
<a href="#">L2400-5MG</a>	5 mg

### Tranilast

2-[[[(3,4-Dimethoxyphenyl)-1-oxo-2-propenyl]amino] benzoic acid;  
SB-252218; 3,4-DAA; N-(3,4-Dimethoxycinnamoyl)anthranilic acid; Rizaben  
[53902-12-8] C<sub>18</sub>H<sub>17</sub>NO<sub>5</sub> FW 327.33

Tranilast is an anti-asthma drug, which inhibits LTC<sub>4</sub> and PGE<sub>2</sub> formation in stimulated monocytes, but does not inhibit cyclooxygenase or lipoxygenase activity; inhibits mast cell degranulation; inhibits VEGF-induced angiogenesis *in vivo* and also inhibits proliferation and tube formation of human endothelial cells *in vitro*. Tranilast may represent a new class of drugs for therapy to treat ongoing T<sub>H</sub>1-mediated autoimmune diseases.

▶ ≥98% (HPLC), solid

store at: 2-8°C

<a href="#">T0318-10MG</a>	10 mg
<a href="#">T0318-50MG</a>	50 mg

## Antibodies to VEGF and other Angiogenic Growth Factors

Product Name	Host	Clone No	Form	Gene Symbol	Species Reactivity	Application	Prestige Antibody	Cat. No.
Anti-Fibroblast Growth Factor-Basic (1-24)	rabbit	-	fractionated antiserum	FGF2, human FGF2, bovine Fgf2, rat	bovine human rat	ELISA (i) IHC (p) WB	-	<a href="#">F3393-1ML</a> <a href="#">F3393-5X.1ML</a>
Anti-Fibroblast Growth Factor-Basic <b>NEW</b>	goat	-	affinity isolated antibody	FGF2, human FGF2, bovine	bovine human	ELISA (i) IHC Neutral WB	-	<a href="#">F5180-100UG</a>
Anti-FIGF <b>NEW</b>	rabbit	-	affinity isolated antibody	FIGF, human	human	IHC (p) PA	✓	<a href="#">HPA027342-100UL</a>
Anti-PDGFB <b>NEW</b>	rabbit	-	affinity isolated antibody	PDGFB, human	human	IHC (p) PA	✓	<a href="#">HPA011972-100UL</a>
Anti-Platelet-Derived Growth Factor	goat	-	IgG fraction of antiserum	PDGFB, human PDGFA, human	human	ELISA (i) Neutral WB	-	<a href="#">P6101-1MG</a>
Anti-Platelet-Derived Growth Factor Receptor α	goat	-	affinity isolated antibody	PDGFRA, human	human	ELISA (i) IHC (p) Neutral WB	-	<a href="#">P2110-1MG</a>
Monoclonal Anti-Platelet-Derived Growth Factor Receptor β	mouse	PDGFR-B2	ascites fluid	PDGFRB, human	human pig	ARR IHC (f) IP WB	-	<a href="#">P7679-2ML</a> <a href="#">P7679-5ML</a>

Product Name	Host	Clone No	Form	Gene Symbol	Species Reactivity	Application	Prestige Antibody	Cat. No.
Anti-Platelet-Derived Growth Factor Soluble Receptor $\beta$	goat	-	affinity isolated antibody	PDGFRB, human	human	ELISA (i) FACS IHC Neutral WB	-	<a href="#">P2229-1MG</a>
Anti-SH2D2A <b>NEW</b>	rabbit	-	affinity isolated antibody	SH2D2A, human	human	IHC (p) PA	✓	<a href="#">HPA019483-100UL</a>
Monoclonal Anti-Vascular Endothelial Growth Factor	mouse	26503	purified immunoglobulin	VEGFC, human VEGFB, human VEGFA, human	human	ELISA (c) IHC Neutral WB	-	<a href="#">V4758-5MG</a>
Anti-Vascular Endothelial Growth Factor Receptor 1	goat	-	affinity isolated antibody	Flt1, mouse	mouse	ELISA (c) FACS Neutral WB	-	<a href="#">V1139-100UG</a>
Monoclonal Anti-Vascular Endothelial Growth Factor Receptor-1	mouse	FLT-11	ascites fluid	FLT1, human	human	ELISA (i) ICC IHC (f) IP WB	-	<a href="#">V4262-2ML</a>
Monoclonal Anti-Vascular Endothelial Growth Factor Receptor-1	mouse	FLT-19	tissue culture supernatant	FLT1, human	human	ARR ELISA (i) IHC (f) IP	-	<a href="#">V4762-5ML</a>
Anti-Vascular Endothelial Growth Factor Receptor 2	goat	-	affinity isolated antibody	Kdr, mouse	mouse	ELISA (i) IHC Neutral WB	-	<a href="#">V1014-100UG</a>
Monoclonal Anti-Vascular Endothelial Growth Factor Receptor-2	mouse	KDR-1	ascites fluid	KDR, human	human	ELISA (i) IHC (f) WB	-	<a href="#">V9134-2ML</a>
Anti-Vascular Endothelial Growth Factor Receptor-3	goat	-	affinity isolated antibody	Flt4, mouse	mouse	ELISA (i) WB	-	<a href="#">V2884-1MG</a>
Anti-Vascular Endothelial Growth Factor Receptor-3	goat	-	affinity isolated antibody	FLT4, human	human	ELISA (i) WB	-	<a href="#">V1135-1MG</a>

### Application Abbreviation Table

Application	Abbreviation
ANA-indirect immunofluorescence	IF (ANA)
Capture ELISA	ELISA (c)
Direct ELISA	ELISA (d)
Direct immunofluorescence	IF (d)
Dot blot	DB
Dot immunobinding	DIBA
Electron microscopy	EM
Enzyme immunoassay	EIA
Flow cytometry	FACS
Immunoblotting	WB
Immunoblotting (chemiluminescent)	WB CL
Immunocytochemistry	ICC
Immuno-electrophoresis	IEP

Application	Abbreviation
Immunohistochemistry	IHC
Immunohistochemistry (formalin-fixed, paraffin-embedded sections)	IHC (p)
Immunohistochemistry (frozen sections)	IHC (f)
Immunoprecipitation	IP
Indirect ELISA	ELISA (i)
Indirect immunofluorescence	IF (i)
Microarray	ARR
Neutralization	Neutral
Ouchterlony double diffusion	ODD
Particle immunofluorescence	PIFA
Quantitative precipitin assay	QPA
Radioimmunoassay	RIA



## Antioxidants and Cytoprotectants

### N-Acetyl-L-cysteine

NAC; LNAC

[616-91-1] HSCH<sub>2</sub>CH(NHCOCH<sub>3</sub>)CO<sub>2</sub>H FW 163.19

Antioxidant and mucolytic agent. Increases cellular pools of free radical scavengers. Reported to prevent apoptosis in neuronal cells but induce apoptosis in smooth muscle cells. Inhibits HIV replication. May serve as a substrate for microsomal glutathione transferase.

► **Sigma Grade, ≥99% (TLC), powder**

store at: 2-8°C

<a href="#">A7250-5G</a>	5 g
<a href="#">A7250-10G</a>	10 g
<a href="#">A7250-25G</a>	25 g
<a href="#">A7250-50G</a>	50 g
<a href="#">A7250-100G</a>	100 g
<a href="#">A7250-500G</a>	500 g
<a href="#">A7250-1KG</a>	1 kg

### L-Ascorbic acid

Antiscorbutic factor; L-Threoascorbic acid; Vitamin C

[50-81-7] C<sub>6</sub>H<sub>8</sub>O<sub>6</sub> FW 176.12

Antioxidant.

► **reagent grade, crystalline, ~325 mesh**

<a href="#">A7506-25G</a>	25 g
<a href="#">A7506-100G</a>	100 g
<a href="#">A7506-500G</a>	500 g
<a href="#">A7506-1KG</a>	1 kg
<a href="#">A7506-5KG</a>	5 kg

► **reagent grade, crystalline, 20-200 mesh**

<a href="#">A0278-25G</a>	25 g
<a href="#">A0278-100G</a>	100 g
<a href="#">A0278-500G</a>	500 g
<a href="#">A0278-1KG</a>	1 kg

### Celastrol

NEW

Tripterin; 10-Hydroxy-2,4a,6a,9,12b,14a-hexamethyl-11-oxo-1,2,3,4,4a,5,6,6a,11,12b,13,14,14a,14b-tetradecahydro-picene-2-carboxylic acid [34157-83-0] C<sub>29</sub>H<sub>38</sub>O<sub>4</sub> FW 450.61

Celastrol is a potent antioxidant, and anti-inflammatory agent. It is a novel HSP90 inhibitor (disrupts Hsp90/Cdc37 complex), that exhibits anticancer (anti-angiogenic - suppresses VEGFR expression); antioxidant (inhibits lipid peroxidation) and anti-inflammatory activity (suppresses iNOS and inflammatory cytokine production).

► **≥98% (HPLC), solid**

store at: -20°C

<a href="#">C0869-10MG</a>	10 mg
<a href="#">C0869-50MG</a>	50 mg

### DL-α-Difluoromethylornithine hydrochloride hydrate

DFMO hydrochloride hydrate; 2-(Difluoromethyl) ornithine hydrochloride hydrate

C<sub>6</sub>H<sub>12</sub>F<sub>2</sub>N<sub>2</sub>O<sub>2</sub> · xHCl · yH<sub>2</sub>O FW 182.17 (FB/Anh)

Inhibits polyamine biosynthesis by the selective, irreversible inhibition of ornithine decarboxylase (ODC). A chemoprotective agent that blocks angiogenesis.

► **solid, ≥97% (NMR)**

<a href="#">D193-25MG</a>	25 mg
<a href="#">D193-100MG</a>	100 mg

## Antiangiogenic Proteins and Peptides

### Angiostatin K1-3 human

A proteolytic fragment of plasminogen containing the first three kringle structures. A specific inhibitor of endothelial cell growth and angiogenesis. More active relative to kringles 1-4.

► **≥90% (HPLC), recombinant, expressed in *Pichia pastoris* (without N-linked glycosylation)**

Supplied as 7.5 mg/ml in 0.15 M sodium chloride.

**Associated gene(s):** PLG (5340)

U.S. Patent Nos. 6,024,688; 5,861,372; 5,639,725; 5,792,845; 5,885,795. Sold under license from Alchemgen and CMCC.

Endotoxin.....	tested
ship: dry ice	store at: -70°C
<a href="#">A1477-250UG</a>	250 µg

### ▼ Endostatin

US Patent 5,854,205. Sold under license from Alchemgen and CMCC.

### Endostatin

Potent inhibitor of angiogenesis and tumor growth *in vitro* and *in vivo*; specifically inhibits endothelial cell proliferation.

► **~4 mg/mL, recombinant, expressed in *Pichia pastoris*, ≥95% (HPLC)**

Solution in 17 mM citric-phosphate buffer, pH 6.2

**Associated gene(s):** COL18A1 (80781)

Endotoxin.....	tested
ship: dry ice	store at: -70°C
<a href="#">E8154-250UG</a>	250 µg

### Endostatin murine

Endostatin is a potent inhibitor of angiogenesis and tumor growth *in vitro* and *in vivo*; specifically inhibits endothelial cell proliferation.

► **4 mg/mL (17 mM citric-phosphate buffer, pH 6.2), recombinant, expressed in *Pichia pastoris*, ≥95% (HPLC)**

17 mM citric-phosphate buffer, pH 6.2.

**Associated gene(s):** Col18a1 (12822)

Endotoxin.....	tested
ship: dry ice	store at: -70°C
<a href="#">E8279-250UG</a>	250 µg
<a href="#">E8279-1MG</a>	1 mg

### Endostatin ▲

### Interleukin-8 human

IL-8

► **≥98% (SDS-PAGE and HPLC), recombinant, expressed in *Escherichia coli*, lyophilized powder, cell culture tested**

Interleukin-8 (IL-8), formerly called monocyte-derived neutrophil chemotactic factor, belongs to the chemokine α or C-X-C family. The mature form of IL-8 has 4 cysteine residues, as do the other members of the chemokine family and the first two cysteine residues are separated by glutamine. Mature human IL-8 consists of 72 amino acids with a molecular mass of 8.4 kDa. IL-8 exhibits chemotactic activity *in vitro* for T cells, basophils, as measured by enzymes including myeloperoxidase, α-mannosidase and β-glucuronidase. IL-8 is an angiogenic factor.

Lyophilized from a 0.2 µm filtered solution with no additives.

**Associated gene(s):** IL8 (3576)

The biological activity is tested in culture by measuring its ability to chemoattract human peripheral blood neutrophils.

Endotoxin.....	tested
store at: -20°C	
<a href="#">I1645-10UG</a>	10 µg

## ▼ Interleukin-12

IL-12

Interleukin-12 (IL-12) was identified as a factor secreted by human Epstein-Barr (EBV)-transformed B cell lines. IL-12, or Natural Killer Cell Stimulatory Factor (NKSF), is a 75 kDa disulfide-linked heterodimer of a 35 kDa subunit and 40 kDa subunit. IL-12 is produced predominantly by monocytes and NK cells and induces T cells and NK cells to produce IFN- $\gamma$ . Human IL-12 is not active on mouse cells, but murine IL-12 is active on both murine and human lymphocytes. The biological activity of recombinant human IL-12 was measured by its ability to stimulate the proliferation of PHA-activated human T lymphoblasts. IL-12 has anti-angiogenic properties.

### Interleukin-12 human

- ▶ **≥97% (SDS-PAGE and N-terminal analysis), recombinant, expressed in Sf21 cells, lyophilized powder, cell culture tested**

Lyophilized from a 0.2  $\mu$ m filtered solution in phosphate buffered saline containing 0.25 mg bovine serum albumin.

**Associated gene(s):** IL12A (3592), IL12B (3593)

glycoprotein mol wt 75 kDa

Endotoxin..... tested  
store at: -20°C

[I2276-5UG](#) 5  $\mu$ g

### Interleukin-12 from mouse

- ▶ **≥97% (SDS-PAGE), recombinant, expressed in Sf21 cells, lyophilized powder, cell culture tested**

Lyophilized from a 0.2  $\mu$ m filtered solution in phosphate buffered saline containing 0.5 mg bovine serum albumin.

**Associated gene(s):** Il12a (16159), Il12b (16160)

glycoprotein mol wt 70 kDa

Endotoxin..... tested  
store at: -20°C

[I8523-10UG](#) 10  $\mu$ g

## Interleukin-12 ▲

### Lactoferricin B, fragment 4-14 trifluoroacetate salt

bLFC (26-36); bovine lactoferricin

Arg-Arg-Trp-Gln-Trp-Arg-Met-Lys-Lys-Leu-Gly  $C_{70}H_{113}N_{25}O_{13}S$  FW 1544.87

Antibiotic peptide in colostrum and milk that protects from bacterial infection at mucosal surfaces.

- ▶ **≥95% (HPLC)**

store at: -20°C

[L1290-1MG](#) 1 mg

### Tissue Inhibitor of Metalloproteinase-1 human

TIMP-1

TIMP-1 has greater binding efficiency to MMP-9, MMP-1, and MMP-3 than the other MMPs.

**Associated gene(s):** TIMP1 (7076)

- ▶ **recombinant, expressed in CHO cells, ~500  $\mu$ g/mL protein, buffered aqueous solution**

Supplied in 0.01 M sodium phosphate buffer pH 7.3, 0.15 M NaCl.

mol wt ~29 kDa

ship: wet ice store at: -20°C

[T8947-5UG](#) 5  $\mu$ g

### Tissue Inhibitor of Metalloproteinase-2 human

NEW

TIMP-2

TIMP-2 has a greater binding efficiency to MMP-2 than the other MMPs. Although TIMP-2 is an inhibitor of MMP-2, it is also required at low concentrations for the activation of MMP-2.

- ▶ **recombinant, expressed in CHO cells, >95% (SDS-PAGE), lyophilized powder**

Lyophilized from a 0.2  $\mu$ m filtered solution in 25 mM Tris, 50 mM sodium chloride, and 0.05% sodium azide, pH 7.5.

**Associated gene(s):** TIMP2 (7077)

apparent mol wt ~20 kDa

The biological activity is measured by the ability to inhibit human MMP-2 hydrolysis of a fluorogenic MMP substrate.

store at: -20°C

[T1077-10UG](#) 10  $\mu$ g

### Tissue Inhibitor of Metalloproteinase-3 human

NEW

TIMP-3

The TIMPs are endogenous inhibitors of the matrix metalloproteinases (MMPs). TIMP-3 inhibits ADAM-17 (TACE) at nanomolar concentrations and also inhibits other metalloproteinases (shedases) that mediate the shedding of soluble receptors and other proteins from the surface of cells.

- ▶ **recombinant, expressed in mouse NSO cells, >95% (SDS-PAGE), buffered aqueous solution**

Lyophilized from a 0.2  $\mu$ m filtered solution in 25 mM Tris and 0.15 M sodium chloride, pH 7.5.

**Associated gene(s):** TIMP3 (7078)

apparent mol wt ~30 kDa

The biological activity is measured by its ability to inhibit human MMP-2 hydrolysis of a peptide substrate.

store at: -20°C

[T1327-10UG](#) 10  $\mu$ g

### Tyr-Ile-Gly-Ser-Arg

Laminin Fragment 929-933

[110590-64-2]  $C_{26}H_{42}N_8O_8$  FW 594.66

- ▶ **≥97% (HPLC)**

Major receptor binding site in laminin; inhibitor of tumor growth and metastasis.

store at: -20°C

[T7154-1MG](#) 1 mg

[T7154-5MG](#) 5 mg

## Microtubule Inhibitors

### Albendazole

Methyl 5-(propylthio)-2-benzimidazolecarbamate

[54965-21-8]  $C_{12}H_{15}N_3O_2S$  FW 265.33

Binds to tubulin and inhibits microtubule assembly.<sup>1</sup>

**Lit cited:** 1. Solana, H.D., et al., *Acta Physiol. Pharmacol. Ther. Latinoam.* **48**, 199 (1998);

[A4673-10G](#) 10 g

### Ansamitocin P-3 from *Actinosynnema pretiosum*

[66547-09-9]  $C_{32}H_{43}ClN_2O_9$  FW 635.14

- ▶ **≥90% (HPLC)**

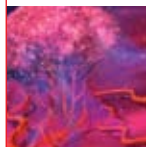
Fungal metabolite with antineoplastic, antimetabolic activity. Binds to tubulin and inhibits vinblastine-induced spiral formation.<sup>1</sup>

**Lit cited:** 1. Correia, J.J., *Pharmacol. Ther.* **52**, 127 (1991);

store at: 2-8°C

[A2836-1MG](#) 1 mg



**CIL-102**

1-[4-(Furo[2,3-*b*]quinolin-4-ylamino)phenyl]ethanone  
[479077-76-4] C<sub>19</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> FW 302.33

Tubulin polymerization inhibitor; apoptosis inducer.

▶ **≥95% (HPLC), solid**

US Patent No. 6,750,223. Sold for non-human research purposes under a non-exclusive license agreement with Kaohsiung Medical University.

ship: wet ice store at: -20°C

[C5492-10MG](#) 10 mg

**Colchicine**

[64-86-8] C<sub>22</sub>H<sub>25</sub>NO<sub>6</sub> FW 399.44

▶ **≥95% (HPLC), powder**

Antimitotic agent that disrupts microtubules by binding to tubulin and preventing its polymerization. Stimulates the intrinsic GTPase activity of tubulin. Induces apoptosis in several normal and tumor cell lines and activates the JNK/SAPK signaling pathway.

[C9754-100MG](#) 100 mg

[C9754-500MG](#) 500 mg

[C9754-1G](#) 1 g

[C9754-5G](#) 5 g

**Demecolcine**

N-Deacetyl-N-methylcolchicine  
[477-30-5] C<sub>21</sub>H<sub>25</sub>NO<sub>5</sub> FW 371.43

Depolymerizes microtubules; blocks mitosis at metaphase.

Often in karyotyping and cell cycle research it is desirable to increase the yield of mitotic cells in a particular phase of the cell cycle. This can be achieved in a variety of ways with the most popular being the use of a cell cycle synchronizing agent such as demecolcine. Demecolcine will arrest cells in metaphase with no remarkable effect on the biochemical events in mitotic cells or in synchronized G<sub>1</sub> and S phase cells. White blood cells are often treated with demecolcine to arrest cells in metaphase.

▶ **≥98% (HPLC)**

store at: 2-8°C

[D7385-5MG](#) 5 mg

[D7385-10MG](#) 10 mg

[D7385-50MG](#) 50 mg

**Dolastatin 15**

(5S)-1-[(2S)-O-(N,N-Val-Val-N-Me-Val-Pro-Pro)-2-hydroxyisovaleryl]-2-oxo-4-methoxy-5-benzyl-3-pyrroline

[123884-00-4] C<sub>45</sub>H<sub>68</sub>N<sub>6</sub>O<sub>9</sub> FW 837.06

An anti-neoplastic pseudopeptide originally isolated from the sea hare *Dolabella auricularia*. Reported to interact with tubulin and induce apoptosis.

Potent inhibitor of the proliferation of murine and cancer cell lines as well as of hematopoietic progenitor cells.

▶ **≥95%**

store at: -20°C

[D5566-1MG](#) 1 mg

**HMBA**

10-[(3-Hydroxy-4-methoxybenzylidene)]-9(10H)-anthracenone  
C<sub>22</sub>H<sub>16</sub>O<sub>3</sub> FW 328.36

Inhibitor of microtubule polymerization<sup>1</sup>; apoptosis inducer.

**Lit cited:** 1. Prinz, H., et al., Novel benzylidene-9(10H)-anthracenones as highly active antimicrotubule agents. Synthesis, antiproliferative activity, and inhibition of tubulin polymerization. *J. Med. Chem.* **46**, 3382-94 (2003);

▶ **≥98% (HPLC), solid**

store at: -20°C

[H4663-10MG](#) 10 mg

[H4663-25MG](#) 25 mg

**5HPP-33**

NEW

5-Hydroxy-(2,6-diisopropylphenyl)-1H-isindole-1,3-dione;  
1H-isindole-1,3(2H)-dione, 2-[2,6-bis(1-methylethyl)phenyl]-5-hydroxy-  
[105624-86-0] C<sub>20</sub>H<sub>21</sub>NO<sub>3</sub> FW 323.39

5HPP-33 is a thalidomide derivative which was reported to be active as anticancer agent through stabilization of the microtubules. 5HPP-33 has shown inhibition of cell proliferation of both estrogen-dependent (MCF-7) and estrogen-independent (MDA-MB-231) breast cancer cells as well as other cell lines. A study in tubulin forming assay reported that 5HPP-33 acts as a microtubule formation inhibitor (IC<sub>50</sub>=810 nM). The compound is a more potent inhibitor of IL-1 induced NF-κB translocation to nucleus than actimid (drug on clinical trial for multiple melanomas).

▶ **≥98% (HPLC), solid**

store at: 2-8°C

[H9415-5MG](#) 5 mg

[H9415-25MG](#) 25 mg

**2-Methoxyestradiol**

2-Hydroxyestradiol 2-methyl ether; 1,3,5(10)-Estratriene-2,3,17-triol 2-methyl ether; 3,17β-Dihydroxy-2-methoxy-1,3,5(10)-estratriene; 2,3,17β-Trihydroxy-1,3,5(10)-estratriene 2-methyl ether

[362-07-2] C<sub>19</sub>H<sub>26</sub>O<sub>3</sub> FW 302.41

▶ **crystalline**

Potent inhibitor of endothelial cell proliferation and angiogenesis.

[M6383-5MG](#) 5 mg

[M6383-10MG](#) 10 mg

[M6383-50MG](#) 50 mg

**Myoseverin B**

2,6-Bis(4-methoxybenzylamino)-9-cyclohexylpurine

[361431-27-8] C<sub>27</sub>H<sub>32</sub>N<sub>6</sub>O<sub>2</sub> FW 472.58

Myoseverin, a new microtubule-binding molecule, acts reversibly on myoblast proliferation without the cytotoxic effects displayed by nonpurine-based microtubule-disrupting molecules, like taxol, vinblastine, nocodazole. Myoseverin can be effectively used for the inhibition of new vessel growth by inhibiting endothelial cell function and differentiation of progenitor cells.

▶ **≥97% (HPLC)**

ship: dry ice store at: -20°C

[M3316-1MG](#) 1 mg

[M3316-5MG](#) 5 mg

**N744 tosylate**

3-(2-Hydroxyethyl)-2-[2-[[[3-(2-hydroxyethyl)-5-methoxy-2-benzothiazolylidene]methyl]-1-butenyl]-5-methoxybenzothiazolium tosylate

[72616-22-9] C<sub>25</sub>H<sub>29</sub>N<sub>3</sub>O<sub>4</sub>S<sub>2</sub> · C<sub>7</sub>H<sub>7</sub>O<sub>3</sub>S FW 656.83

Inhibitor of tau aggregation.

▶ **≥90% (HPLC), solid**

store at: -20°C

[N2287-5MG](#) 5 mg

[N2287-25MG](#) 25 mg

**Nocodazole**

[5-(2-Thienylcarbonyl)-1H-benzimidazol-2-yl]-carbamic acid methyl ester;

Oncodazole; Methyl *N*-(5-thenoyl-2-benzimidazolyl)carbamate; R 17934;

Methyl [5-(2-thienylcarbonyl)-1H-benzimidazol-2-yl]carbamate

[31430-18-9] C<sub>14</sub>H<sub>11</sub>N<sub>3</sub>O<sub>3</sub>S FW 301.32

▶ **≥99% (TLC), powder**

Antimitotic agent that disrupts microtubules by binding to β-tubulin and preventing formation of one of the two interchain disulfide linkages, thus inhibiting microtubule dynamics, disruption of mitotic spindle function, and fragmentation of the Golgi complex. Arrests the cell cycle at G<sub>2</sub>/M phase. Prevents phosphorylation of the T cell antigen receptor and inhibits its activity. Stimulates the intrinsic GTPase activity of tubulin. Activates the JNK/SAPK signaling pathway and induces apoptosis in several normal and tumor cell lines.

store at: 2-8°C

[M1404-2MG](#) 2 mg

[M1404-10MG](#) 10 mg

[M1404-50MG](#) 50 mg

## DNA and RNA Transcription Regulation

### Chetomin

NEW

Chaetomin; NSC 289491  
[1403-36-7] C<sub>31</sub>H<sub>30</sub>N<sub>6</sub>O<sub>6</sub>S<sub>4</sub> FW 710.87

Chaetomin is a natural metabolite produced by several species of the genus *Chaetomium*. Chaetomin is an epidthiodioxopiperazine known to disrupt the hypoxia-inducible factor (HIF) pathway. Chaetomin blocks the interaction of HIF1α and HIF2α with transcriptional co-activators p300 and cAMP response element binding (CREB) binding protein (CBP), thereby attenuating hypoxia-inducible transcription. Disrupting the ability of tumors to adapt to hypoxia leads to decreased tumor growth and can serve as an antitumor strategy. Chaetomin also suppresses the proliferation of LPS-induced mouse spleen lymphocytes.

#### ► from *Chaetomium cochliodes*, ≥98% (HPLC)

store at: -20°C

<a href="#">C9623-1MG</a>	1 mg
<a href="#">C9623-5MG</a>	5 mg

### DMOG

NEW

Dimethylalylglycine; N-(Methoxyoxoacetyl)-glycine methyl ester  
[89464-63-1] C<sub>6</sub>H<sub>9</sub>NO<sub>5</sub> FW 175.14

DMOG is a cell permeable prolyl-4-hydroxylase inhibitor, which upregulates HIF (hypoxia-inducible factor). The protein level of HIF-1α subunit is post-transcriptionally regulated by prolyl and asparaginyl hydroxylase (PAH). Suppression of PAH activity increases endogenous HIF-1α levels. DMOG is a cell permeable, competitive inhibitor of prolyl hydroxylase domain-containing proteins (PHDs and HIF-PHs). It has been discovered that the DMOG possesses neuroprotective effect on NFG deprived cell cultures through preservation of glucose metabolism. DMOG also attenuates myocardial injury in a rabbit ischemia reperfusion model. DMOG is more potent than the older inhibitor 4-Phenylpyridine-2,5-dicarboxylic acid (R395889; Sigma-Aldrich rare chemicals library). The IC<sub>50</sub> is 5.18 μM.

#### ► ≥98% (HPLC)

ship: wet ice store at: -20°C

<a href="#">D3695-10MG</a>	10 mg
<a href="#">D3695-50MG</a>	50 mg

### Xanthohumol from hop (*Humulus lupulus*)

C<sub>21</sub>H<sub>22</sub>O<sub>5</sub> FW 354.40

Prenylated flavonoids such as xanthohumol have antiproliferative and cytotoxic effects in human cancer cell lines<sup>1</sup>. Xanthohumol inhibits diacylglycerol acetyltransferase (DGAT)<sup>2</sup> and human P450 enzymes<sup>3</sup>. It also inhibits the expression of HIF-1α and VEGF under hypoxic conditions<sup>4</sup>.

**Lit cited:** 1. Miranda, C.L. et. al., Antiproliferative and cytotoxic effects of prenylated flavonoids from hops (*Humulus lupulus*) in human cancer cell lines. *Food Chem. Toxicol.* **37**, 271-285 (1999); 2. Tabata, N. et. al., Xanthohumols, diacylglycerol acyltransferase inhibitors, from *Humulus lupulus*. *Phytochemistry* **46**, 683-687 (1997); 3. Henderson, M.C., et. al., *In vitro* inhibition of human P450 enzymes by prenylated flavonoids from hops, *Humulus lupulus*. *Xenobiotica* **30**, 235-251 (2000); 4. Gerhauser, C. et. al., Cancer chemopreventive activity of xanthohumol, a natural product derived from hop. *Mol. Cancer Ther.* **1**, 959-969 (2002);

#### ► ≥96% (HPLC)

store at: 2-8°C

<a href="#">X0379-5MG</a>	5 mg
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## DNA Methyl Transferase (DNMT) Inhibitors

### 5-Azacytidine

Ladakamycin; 4-Amino-1-(β-D-ribofuranosyl)-1,3,5-triazin-2(1H)-one  
[320-67-2] C<sub>8</sub>H<sub>12</sub>N<sub>4</sub>O<sub>5</sub> FW 244.20

A potent growth inhibitor and cytotoxic agent; inhibits DNA methyltransferase, an important regulatory mechanism of gene expression, gene activation and silencing.

#### ► ≥98% (HPLC)

Causes DNA demethylation or hemi-demethylation, creating openings that allow transcription factors to bind to DNA and reactivate tumor suppressor genes.

store at: -20°C

<a href="#">A2385-100MG</a>	100 mg
<a href="#">A2385-250MG</a>	250 mg
<a href="#">A2385-1G</a>	1 g

### 5-Aza-2'-deoxycytidine

2'-Deoxy-5-azacytidine; 4-Amino-1-(2-deoxy-β-D-ribofuranosyl)-1,3,5-triazin-2(1H)-one; Decitabine  
[2353-33-5] C<sub>8</sub>H<sub>12</sub>N<sub>4</sub>O<sub>4</sub> FW 228.21

#### ► ≥97%

5'-Azadeoxycytidine causes DNA demethylation or hemi-demethylation. DNA demethylation can regulate gene expression by "opening" the chromatin structure detectable as increased nuclease sensitivity. This remodeling of chromatin structure allows transcription factors to bind to the promoter regions, assembly of the transcription complex, and gene expression.

<a href="#">A3656-5MG</a>	5 mg
<a href="#">A3656-10MG</a>	10 mg
<a href="#">A3656-50MG</a>	50 mg

### 5-Fluoro-2'-deoxycytidine

NEW

2'-deoxy-5-fluoro-Cytidine; FdCyd; FCDR  
[10356-76-0] C<sub>9</sub>H<sub>12</sub>FN<sub>3</sub>O<sub>4</sub> FW 245.21

5-Fluoro-2'-deoxycytidine is a mechanism based DNMT (DNA cytosine-5 methyltransferase) inhibitor, that forms a covalent link with the cysteine residue in the active site of DNMT.

#### ► ≥98% (HPLC), powder

store at: Room temp

<a href="#">F5307-5MG</a>	5 mg
<a href="#">F5307-25MG</a>	25 mg

### Psammaplin A

NEW

Bisprasin, N,N"-(dithiodi-2,1-ethanediy)bis[3-bromo-4-hydroxy-a-(hydroxyimino)-benzeneprapanamide  
[110659-91-1] C<sub>27</sub>H<sub>24</sub>Br<sub>2</sub>N<sub>4</sub>O<sub>6</sub>S<sub>2</sub> FW 664.39

Psammaplin A is an antibiotic, anti-tumor, DNA methyltransferase inhibitor. It is a bromotyrosine-derived, symmetrical conjugate of cystamine, which was first isolated from the *Psammaplinaplysilla* sponge. Psammaplin A impedes angiogenesis as well as bacterial and tumor cell growth. Psammaplin A inhibits the activities of several key enzymes in prokaryotic and eukaryotic systems including those involved in epigenetic control of gene expression, DNA replication, angiogenesis, and microbial detoxification.

#### ► ≥97% (HPLC), solid

store at: 2-8°C

<a href="#">P8749-1MG</a>	1 mg
<a href="#">P8749-5MG</a>	5 mg

## Histone Deacetylase (HDAC) Inhibitors

### Apicidin

Cyclo[(2S)-2-amino-8-oxodecanoyl-1-methoxy-L-tryptophyl-L-isoleucyl-(2R)-2-piperidinexcarbonyl]  
[183506-66-3] C<sub>34</sub>H<sub>49</sub>N<sub>5</sub>O<sub>6</sub> FW 623.78

Potent (nM) cell permeable inhibitor of histone deacetylase. Also, exhibits antiprotozoal and potential antimalarial properties. Apicidin has antiproliferative activity on HeLa cells accompanied by cell arrest at the G1 phase. In addition, it induces selective changes in the expression of p21 and gelsolin.

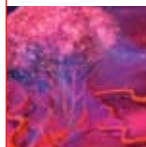
#### ► ≥95%, from microbial, solid

Subject of US Patent No. 5,620,953. Manufactured and sold under license from Merck & Co., Inc.

ship: wet ice store at: -20°C

<a href="#">A8851-1MG</a>	1 mg
<a href="#">A8851-5MG</a>	5 mg



**CI-994**

NEW

4-Acetylamino-N-(2'-aminophenyl)benzamide; Tacedinaline; Acetylinaline [112522-64-2] C<sub>15</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub> FW 269.30

CI-994 is the acetylated derivative form of the original compound Dinaline (PD 104 208). It is an oral cytostatic drug with impressive differential activity against leukemic cells & normal stem-cells. It is used for combination therapy for selected tumors including non-small cell lung, pancreatic, breast, and colorectal cancers. It acts as a histone deacetylase inhibitor. CI-994 blocks cells in the G1-S phase of the cell cycle. The 16 kDa phosphoprotein is confined to the nuclear compartment. Loss of the 16-kDa nuclear phosphoprotein appears to be a direct effect of CI-994 treatment and that the inhibition of this phosphoprotein may play a critical role in the mechanism of action of CI-994.

▶ **≥98% (HPLC), powder**

store at: Room temp

<a href="#">C0621-5MG</a>	5 mg
<a href="#">C0621-25MG</a>	25 mg

**(-)-Depudecin**4,5,8,9-Dianhydro-1,2,6,7,11-pentadeoxy-D-threo-D-ido-undeca-1,6-dienilol [139508-73-9] C<sub>17</sub>H<sub>16</sub>O<sub>4</sub> FW 212.24

Inhibitor of histone deacetylase (HDAC) both *in vivo* and *in vitro*. Alters the spindle shaped morphology of v-Ha-ras-transformed NIH3T3 cells to a flattened shape and induces an intricate actin stress fiber network in these cells and in MG63 osteosarcoma cells. Also exhibits anti-angiogenic activity.

▶ **>95% (HPLC), from microbial**

ship: dry ice store at: -20°C

<a href="#">D5816-1MG</a>	1 mg
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**Scriptaid**6-(1,3-Dioxo-1H,3H-benzo[de]isoquinolin-2-yl)-hexanoic acid hydroxamide C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub> FW 326.35

Histone deacetylase inhibitor with lower toxicity than trichostatin A; used to enhance protein expression.

▶ **≥95% (H-NMR), solid**

Sold under license of U.S. Patent No. 6,544,957.

store at: -20°C

<a href="#">S7817-1MG</a>	1 mg
<a href="#">S7817-5MG</a>	5 mg

**Sodium butyrate**Butyric acid sodium salt [156-54-7] CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>COONa FW 110.09

Decreases Ca<sup>2+</sup> release from intracellular stores. Inhibits histone deacetylase (HDAC). Induces apoptosis in several cell lines.

▶ **≥98.5% (GC)**

<a href="#">B5887-250MG</a>	250 mg
<a href="#">B5887-1G</a>	1 g
<a href="#">B5887-5G</a>	5 g

**Trichostatin A**

[R-(E,E)]-7-[4-(Dimethylamino)phenyl]-N-hydroxy-4,6-dimethyl-7-oxo-2,4-heptadienamides; TSA

[58880-19-6] C<sub>17</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub> FW 302.37

Inhibits histone deacetylase at nanomolar concentrations; resultant histone hyperacetylation leads to chromatin relaxation and modulation of gene expression. May be involved in cell cycle progression of several cell types, inducing cell growth arrest at both G and G/M phases; may induce apoptosis. Enhances the efficacy of anticancer agents that target DNA.

▶ **≥98% (HPLC), from *Streptomyces* sp.**

store at: -20°C

<a href="#">T8552-1MG</a>	1 mg
<a href="#">T8552-5MG</a>	5 mg

**Other Angiogenesis Regulators****Ammonium tetrathiomolybdate**[15060-55-6] (NH<sub>4</sub>)<sub>2</sub>MoS<sub>4</sub> FW 260.28▶ **99.97% trace metals basis**

Acts as a chelator *in vivo* to reduce copper levels. Tetrathiomolybdate interferes with angiogenesis and reduces tumor growth. Its mechanism may involve inhibition of NF-κB and downstream cytokines.<sup>1</sup>

crystalline

Lit cited: 1. Brewer, G.J., *Curr. Cancer Drug Targets* **5**, 195 (2005);

<a href="#">323446-1G</a>	1 g
<a href="#">323446-10G</a>	10 g
<a href="#">323446-50G</a>	50 g

**L-Azetidine-2-carboxylic acid**(S)-Azetidine-2-carboxylic acid [2133-34-8] C<sub>4</sub>H<sub>7</sub>NO<sub>2</sub> FW 101.10

A four-membered ring analog of L-proline that causes protein misconstruction when incorporated instead of proline.<sup>1</sup> Inhibitor of collagen synthesis; anti-angiogenic.

Lit cited: 1. Ingber, D., and Folkman, J., *Lab. Invest.* **59**, 44 (1988);▶ **≥99%**

<a href="#">A0760-50MG</a>	50 mg
<a href="#">A0760-100MG</a>	100 mg
<a href="#">A0760-250MG</a>	250 mg
<a href="#">A0760-1G</a>	1 g

**Baicalein**5,6,7-Trihydroxyflavone [491-67-8] C<sub>15</sub>H<sub>10</sub>O<sub>5</sub> FW 270.24▶ **98%**

The flavonoid component of Nepalese and Sino-Japanese crude drugs.<sup>1,2</sup> Baicalein, a major flavone of *Scutellariae baicalensis*, inhibits the 12-lipoxygenase (12-LOX) pathway of arachidonic acid metabolism, which inhibits cancer cell proliferation and induces apoptosis.

Lit cited: 1. *Chem. Pharm. Bull.* **39**, 1051 (1991); 2. *Chem. Pharm. Bull.* **38**, 3488 (1990);

<a href="#">465119-100MG</a>	100 mg
<a href="#">465119-500MG</a>	500 mg

**Borrelidin**2-(7-Cyano-8,16-dihydroxy-9,11,13,15-tetramethyl-18-oxooxacyclooctadeca-4,6-dien-2-yl)-cyclopentanecarboxylic acid; Cyclopentanecarboxylic acid; Borrelidine; NSC 216128; Treponemycin [7184-60-3] C<sub>28</sub>H<sub>43</sub>NO<sub>6</sub> FW 489.64

Borrelidin, an 18-membered macrolide-polyketide, is a compound with anti-viral, anti-bacterial, anti-malarial, and anti-angiogenic properties. It is a known inhibitor of bacterial and eukaryal threonyl-tRNA synthetases. Borrelidin induces apoptosis in endothelial cells via the caspase 3 and caspase 8 pathway. In addition, borrelidin strongly inhibits capillary tube formation and also disrupts formed capillary tubes by inducing apoptosis of the tube-forming cells in a rat aorta matrix culture model. In *S.cerevisiae*, borrelidin inhibits the cyclin-dependent kinase Cdc28/Cln2 with an IC<sub>50</sub> of 24 μM, causing the arrest of both haploid and diploid cells in G<sub>1</sub> phase and inducing the transcription of amino acid biosynthetic enzymes through a GCN4-dependent pathway.

▶ **from *Streptomyces* sp., ≥95% (HPLC), lyophilized powder**

store at: 2-8°C

<a href="#">B1936-100UG</a>	100 μg
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**Clarithromycin**

NEW

 [81103-11-9] C<sub>38</sub>H<sub>69</sub>NO<sub>13</sub> FW 747.95

Clarithromycin is a macrolide antibiotic. It prevents bacterial growth by interfering with protein synthesis. Clarithromycin is an acid-stable version of erythromycin and is particularly effective against gram-negative bacteria.<sup>1</sup> It has a short half-life<sup>2</sup>, however its metabolite, 14-hydroxy clarithromycin is nearly twice as active as clarithromycin against certain bacteria.<sup>3</sup>

**Lit cited:** 1. Hardy, D.J. et al., *Diagn. Microbiol. Infect. Dis.* **15**, 39-53 (1992); 2. Langtry, H.D., and Brogden, R.N., *Drugs* **53**, 973-1004 (1997); 3. Hardy, D.J., et al., *Antimicrob. Agents Chemother.* **32**, 1710-1719 (1988);

▶ ≥95% (HPLC)

<a href="#">C9742-100MG</a>	100 mg
<a href="#">C9742-250MG</a>	250 mg
<a href="#">C9742-1G</a>	1 g

**Dichloromethylenediphosphonic acid disodium salt**

Clodronic acid disodium salt; Cl<sub>2</sub>MDP; DMDP  
[22560-50-5] CH<sub>2</sub>O<sub>6</sub>Cl<sub>2</sub>Na<sub>2</sub>P<sub>2</sub> FW 288.86

Analog of pyrophosphate ion that inhibits the osteoclastic activity leading to bone resorption and osteoporosis. The compound is used in cancer research, especially in skeletal metastases and breast carcinoma.<sup>1,2</sup> When entrapped in liposomes, it is used for macrophage-selective depletion (macrophage "suicide" technique), especially in spleen and liver.<sup>3</sup> Found also to inhibit collagenase and matrix metalloproteinase.<sup>4</sup>

**Lit cited:** 1. Lipton, A., *Cancer* **80**, 1668 (1997); 2. Fleisch, H.A., *Ann. Med.* **29**, 55 (1997); 3. Van Rooijen, N., *J. Immunol. Methods* **124**, 1 (1989); 4. Teronen, O., et al., *Calcif. Tissue Int.* **61**, 59 (1997);

<a href="#">D4434-1G</a>	1 g
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**DMXAA**

5,6-Dimethylxantheonone-4-acetic Acid  
[117570-53-3] C<sub>17</sub>H<sub>14</sub>O<sub>4</sub> FW 282.29

Apoptosis inducer; anti-vascular.

▶ ≥98% (HPLC), solid

store at: 2-8°C

<a href="#">D5817-5MG</a>	5 mg
<a href="#">D5817-25MG</a>	25 mg

**FK-506 monohydrate**

Tacrolimus  
[109581-93-3] C<sub>44</sub>H<sub>69</sub>NO<sub>12</sub> · xH<sub>2</sub>O FW 804.02 (Anh)

FK-506 is a potent immunosuppressant, neuroprotective and neuroregenerative, and *in vitro* T cell proliferation blocker. FK-506 disrupts calcineurin-mediated signal transduction in T lymphocytes and interacts with its FK-506-binding protein-12 (FKBP12).

▶ ≥98% (HPLC), solid

store at: -20°C

<a href="#">F4679-5MG</a>	5 mg
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**Fumagillin from *Aspergillus fumigatus***

[23110-15-8] C<sub>26</sub>H<sub>34</sub>O<sub>7</sub> FW 458.54

Methionine aminopeptidase-2 (MetAP-2) inhibitor; inhibits endothelial cell proliferation and angiogenesis.

▶ ≥90%, powder

store at: -20°C

<a href="#">F6771-1MG</a>	1 mg
<a href="#">F6771-5MG</a>	5 mg

**IMS2186**

NEW

3-[1-(3-Hydroxy-4-methoxyphenyl)-meth-(E)-ylidene]-6-methyl-chroman-4-one  
[1031206-36-6] C<sub>18</sub>H<sub>16</sub>O<sub>4</sub> FW 296.32

IMS2186 is an anti-proliferative and anti-angiogenic. IMS2186 is a novel synthetic compound developed as an anti-CNV drug. The proposed mechanism action, under investigation, is blocking the cell cycle at G2 and inhibition of the production of PGE2/TNF-α. The latter contributing to antiinflammatory and anti-angiogenic effects. IMS2186 inhibits cell growth *in vitro* in tumor cells, non-transformed fibroblasts, and retinal pigment epithelial cells. IMS2186 inhibits angiogenesis (IC<sub>50</sub> = 0.1 μM) and cell migration, which plays a role in many biological processes: inflammation, angiogenesis, and scar formation. The physicochemical structure of IMS2186 showed also that the free drug concentration in a physiological media (e.g., vitreous or saline) is 8-10 μM above the IC<sub>50</sub> for all these activities (0.1-3.0 μM). Intraocular injection of IMS2186 could be a long-lasting effective treatment for CNV (choroidal neovascularization) in AMD (age-related macular degeneration) with a reduction in scarring and related visual loss.

▶ ≥98% (HPLC), solid

store at: Room temp

<a href="#">I7160-5MG</a>	5 mg
<a href="#">I7160-25MG</a>	25 mg

**Minocycline hydrochloride**

[13614-98-7] C<sub>23</sub>H<sub>27</sub>N<sub>3</sub>O<sub>7</sub> · HCl FW 493.94

▶ crystalline

Inhibits endothelial cell proliferation and angiogenesis.

store at: 2-8°C

<a href="#">M9511-25MG</a>	25 mg
<a href="#">M9511-100MG</a>	100 mg
<a href="#">M9511-250MG</a>	250 mg
<a href="#">M9511-1G</a>	1 g

**Neridronate**

6-Amino-1-hydroxyhexylidene bisphosphonic acid; Neridronic acid; Nerixa  
[79778-41-9] C<sub>9</sub>H<sub>13</sub>NO<sub>7</sub>P<sub>2</sub> FW 277.15

Neridronate is a bone resorption inhibitor. It is used to treat Osteogenesis Imperfecta, an "orphan disease" characterized by a fragility of the bone enough to be named the "illness of bones of crystal".

▶ ≥97% (NMR), solid

may contain <1% (w/w) inorganic salts

store at: 2-8°C

<a href="#">N6037-10MG</a>	10 mg
<a href="#">N6037-100MG</a>	100 mg

**D-Penicillamine**

3,3-Dimethyl-D-cysteine; 3-Mercapto-D-valine; D-(-)-2-Amino-3-mercaptop-3-methylbutanoic acid

[52-67-5] (CH<sub>3</sub>)<sub>2</sub>C(SH)CH(NH<sub>2</sub>)CO<sub>2</sub>H FW 149.21

▶ 98-101%

Characteristic degradation product of penicillin type antibiotics. Active as copper chelating agent and as a disease modifying antirheumatic drug (DMARD).

store at: 2-8°C

<a href="#">P4875-1G</a>	1 g
<a href="#">P4875-5G</a>	5 g
<a href="#">P4875-25G</a>	25 g

**Roxithromycin**

Erythromycin 9-(-O-[2-methoxyethoxy]methyloxime)

[80214-83-1] C<sub>41</sub>H<sub>76</sub>N<sub>2</sub>O<sub>15</sub> FW 837.05

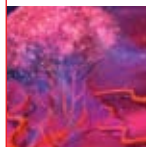
Semisynthetic erythromycin derivative. Impairs NADPH oxidase activation and alters translocation of its cytosolic components to the neutrophil membrane.

▶ ≥90% (HPLC)

store at: 2-8°C

<a href="#">R4393-1G</a>	1 g
<a href="#">R4393-10G</a>	10 g



**RRD-251 hydrochloride**

NEW

Rb/Raf-1 disruptor 251 hydrochloride; S-(2,4-Dichlorobenzyl)-isothiouronium hydrochloride; (2,4-Dichlorophenyl)carbamimidothioic acid methyl ester hydrochloride; 2-(2,4-Dichlorobenzyl)-2-thiopseudourea hydrochloride [72214-67-6] C<sub>8</sub>H<sub>8</sub>Cl<sub>2</sub>N<sub>2</sub>S · HCl FW 271.59

RRD-251 hydrochloride is a reversible, potent, and selective disruptor of Rb/Raf-1 interaction. The retinoblastoma tumor suppressor protein (Rb) controls the G1-S boundary by repressing the transcriptional activity of the E2F family of transcription factors. Raf-1 kinase binds and phosphorylates Rb early in the G1 phase. RRD-251 significantly inhibits angiogenesis and tumor growth *in vivo* in an Rb-dependent manner. RRD-251 does not inhibit the binding of B-Raf to Rb and Raf-1 to Mek1/2. Also, RRD-251 does not affect the kinase activities associated with cyclin D, cyclin E, or Raf-1.

## ▶ ≥98% (HPLC)

store at: Room temp

<a href="#">R7532-5MG</a>	5 mg
<a href="#">R7532-25MG</a>	25 mg

**SB 220025 trihydrochloride**

5-(2-Aminopyrimidin-4-yl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole trihydrochloride

[197446-75-6] C<sub>18</sub>H<sub>19</sub>FN<sub>6</sub> · 3HCl FW 447.76

SB 220025 is a potent, specific inhibitor of human p38 mitogen-activated protein (MAP) kinase, with an IC<sub>50</sub> value of 60 nM and 50- to 1000-fold selectivity. SB 220025 reduces inflammatory cytokine production and inhibits angiogenesis. SB 220025 reduced the lipopolysaccharide-induced production of TNF at an ED<sub>50</sub> value of 7.5 mg/kg. At 30 mg/kg, SB 220025 reduced the expression of TNF and inhibited angiogenesis by ~40%. In a further study, the effects of p38/CSBP MAP kinase inhibition in angiogenesis-dependent chronic inflammatory disease was tested in murine collagen-induced arthritis and SB 220025 was able to prevent the progression of established arthritis.

## ▶ ≥98% (HPLC), solid

<a href="#">S9070-500UG</a>	500 µg
<a href="#">S9070-2MG</a>	2 mg

**Silibinin**

Silybin; 2,3-Dihydro-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-6-(3,5,7-trihydroxy-4-oxobenzopyran-2-yl)benzodioxin  
C<sub>25</sub>H<sub>22</sub>O<sub>10</sub> FW 482.44

## ▶ ≥98% (HPLC)

Principal component of silymarin; flavonolignan that is chemopreventive against prostate and liver cancer.

Contains both A and B diastereomers

store at: -20°C

<a href="#">S0417-1G</a>	1 g
<a href="#">S0417-10G</a>	10 g

**Silymarin**

Silymarin provides cardioprotective activity against ischemia-reperfusion induced myocardial infarction in rats.

Mixture of anti-hepatotoxic flavonolignans from the fruit of *Silybum marianum*.

store at: -20°C

<a href="#">S0292-10G</a>	10 g
<a href="#">S0292-50G</a>	50 g

**▼ Staurosporine**

Antibiotic AM-2282

Potent inhibitor of phospholipid/calcium-dependent protein kinase. Inhibits the upregulation of VEGF expression in tumor cells.

**Staurosporine from *Streptomyces* sp.**[62996-74-1] C<sub>28</sub>H<sub>26</sub>N<sub>4</sub>O<sub>3</sub> FW 466.53

## ▶ ≥95% (HPLC), film

Partially reverses MDR, sensitizing cells with MDR phenotype to cytotoxic agents. Inhibits Pgp phosphorylation. However, functional significance of Pgp phosphorylation is ill defined.

store at: 2-8°C

<a href="#">S4400-1MG</a>	0.1 mg
<a href="#">S4400-5MG</a>	0.5 mg
<a href="#">S4400-1MG</a>	1 mg

**Staurosporine solution from *Streptomyces* sp.**

## ▶ Ready Made Solution, 1 mM in DMSO (100 µg/214 µL), 0.2 µm filtered

Potent cell-permeable inhibitor of protein kinase C. Induces apoptosis in Jurkat cells. cell culture tested

&gt;98% (HPLC)

ship: wet ice store at: -20°C

<a href="#">S6942-200UL</a>	200 µL
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**Staurosporine ▲****L-Sulforaphane**

(R)-1-Isothiocyano-4-(methylsulfinyl)butane; 4-Methylsulfinylbutyl isothiocyanate

[142825-10-3] C<sub>6</sub>H<sub>11</sub>NOS<sub>2</sub> FW 177.29

L-Sulforaphane is a potent, selective inducer of phase II detoxification enzymes with anticarcinogenic properties. L-Sulforaphane occurs naturally in broccoli.

## ▶ ≥95% (GC), oil

store at: -20°C

<a href="#">S6317-5MG</a>	5 mg
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**TAS-301**

3-Bis-(4-methoxyphenyl)methylene-2-indolinone

[193620-69-8] C<sub>23</sub>H<sub>19</sub>NO<sub>3</sub> FW 357.40

Inhibitor of migration and proliferation in vascular smooth muscle cells; inhibitor of restenosis.

## ▶ ≥95% (HPLC), solid

<a href="#">T9324-10MG</a>	10 mg
<a href="#">T9324-25MG</a>	25 mg

**Temozolomide**

NEW

4-Methyl-5-oxo-2,3,4,6,8-pentazabicyclo[4.3.0]nona-2,7,9-triene-9-carbox-

amide; 8-Carbamoyl-3-methylimidazo[5,1-d]-1,2,3,5-tetrazin-4(3H)-one;

3-Methyl-4-oxo-8-imidazo[5,1-d][1,2,3,5]tetrazinecarboxamide

[85622-93-1] C<sub>6</sub>H<sub>8</sub>N<sub>6</sub>O<sub>2</sub> FW 194.15

## ▶ ≥98% (HPLC), solid

Temozolomide is a DNA methylating agent and drug resistance-modifying agent; anti-tumor and anti-angiogenic. Temozolomide induces G2/M arrest and apoptosis through adduction of a methyl group to O6 position of guanine in genomic DNA and functional inactivation of DNA repair protein O(6)-alkylguanine DNA alkyltransferase (AGT) in base excision repair (BER) pathway.

store at: 2-8°C

<a href="#">T2577-25MG</a>	25 mg
<a href="#">T2577-100MG</a>	100 mg