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Angiogenesis & Cardiovascular Regeneration

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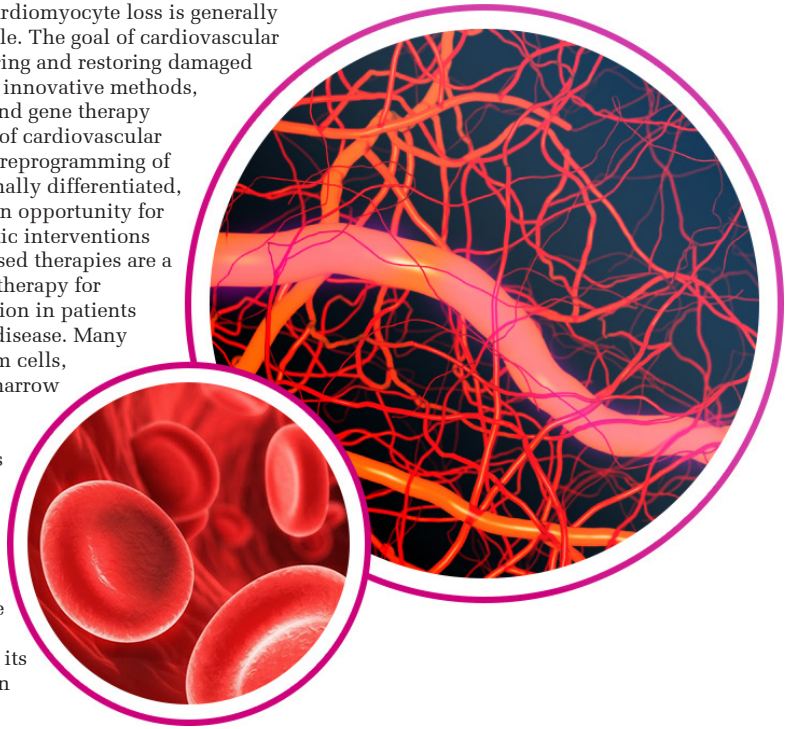
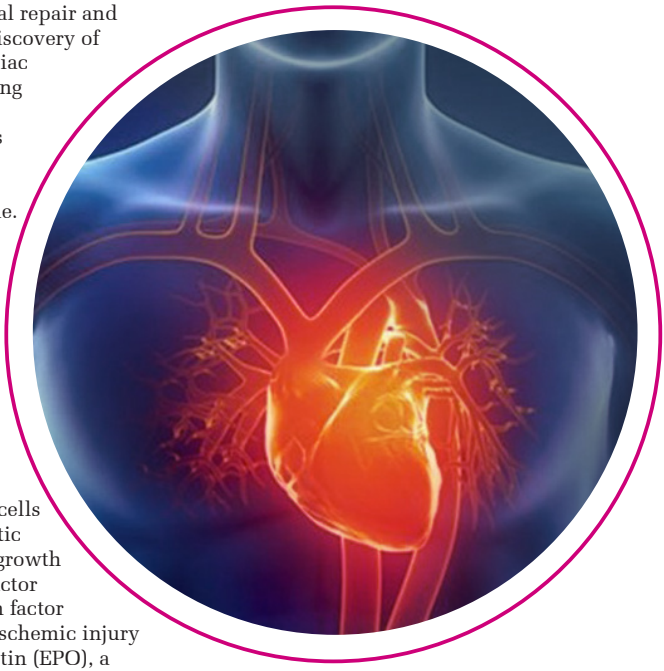
Angiogenesis & Cardiovascular Regeneration

Angiogenesis is the normal physiological process by which new blood vessels and capillary beds sprout from preexisting vessels, resulting in the creation or expansion of a vascular network within a region of tissue. The construction and maintenance of architecture of blood vessels functions primarily to provide the hosting tissue, and those cells involved in its structure, with a means for importing those nutrients required for survival and maintenance, and removing unnecessary waste. Consequently, the angiogenic process is a fundamental component of embryonic growth and development, tissue repair and wound healing, the resolution of inflammatory responses, and the onset of neoplasia. The expansion of a vascular network is a relatively fragile process governed by a delicate balance between stimulatory and inhibitory factors, and is, therefore, highly susceptible to instances of disruptive interference at several levels. Occurrences of angiogenic perversion can result in pathological angiogenesis, which is characterized by the abnormally rapid and uncontrolled proliferation of blood vessels. Pathological angiogenesis is critical to the transitioning of a tumor to malignancy, and a contributing factor to a multitude of other diseases, including ischemic chronic wounds, cardiovascular disease, diabetic retinopathy, rheumatoid arthritis, macular degeneration, and psoriasis. Due to its involvement in such an array of diseases, the ability to manipulate angiogenesis, through both natural and synthetic inhibitors and activators, represents a promising prospect for the prevention and treatment of diseases characterized by abnormal vascularization **(Ref. 1)**.

Regeneration, the process of regrowth of damaged tissues or organs in response to injury, is a property that varies among organisms. Organ and tissue regeneration promotes survival, longevity and optimal health **(Ref. 2 & 3)**. In humans, many tissues, such as skin, liver, blood, and intestinal mucosa, routinely and efficiently undergo regeneration. One of the least regenerative organs in the human body is the heart. The self-regenerative capacity of the heart is insufficient to make up for the cardiac muscle loss after an ischemic injury. This limitation has triggered interest in different stem cell-based therapies aimed at repairing failing human hearts. Heart disease is the leading cause of death in developed countries. Myocardial infarction (MI) and normal aging lead to loss of viable cardiomyocytes, which may lead to heart failure. This cardiomyocyte loss is generally considered irreversible. The goal of cardiovascular regeneration is repairing and restoring damaged heart tissues through innovative methods, including stem cell and gene therapy **(Ref. 4)**. The process of cardiovascular regeneration enables reprogramming of cells that were terminally differentiated, which may provide an opportunity for developing therapeutic interventions **(Ref. 5)**. Stem cell-based therapies are a potential alternative therapy for myocardial regeneration in patients with ischemic heart disease. Many different types of stem cells, such as crude bone marrow mononuclear cells, mesenchymal stem cells, adult stem cells from adipose or cardiac tissue, and embryonic stem cells, have been used in clinical trials. The selection of a suitable cell type is the most important criteria for its successful application **(Ref. 6 & 7)**.



Adult stem cells, especially mesenchymal stem cells, secrete a variety of growth factors, extracellular matrix (ECM) molecules, paracrine cytokines, and chemokines that are believed to play a major role in cardiac repair **(Ref. 8)**. Under hypoxic conditions, stem cells can release growth factors and cytokines such as transforming growth factor (TGF)-β, interleukin (IL)-6, vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF-2 or basic FGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), angiopoietin (Ang)-1, stromal cell-derived factor (SDF)-1, matrix metalloproteinase (MMP)-9, and tumor necrosis factor (TNF)-α, among others. These secreted cytokines and their relative signaling pathways, which represent key mechanisms for heart regeneration, may serve as a promising future therapeutic strategy for myocardial infarction patients. TGF-β, IL-6 family members, including IL-6, Oncostatin-M, cardiotrophin-1 (CT-1), and leukemia inhibitory factor (LIF), as well as several chemokines are key players in cardiomyocyte regeneration. TGF-β contributes to cardiac repair and renewing cardiac function after MI by reducing inflammation, promoting myofibroblasts and ECM placement, Ischemia-reperfusion injury and myocardial infarction induced IL-6 production by cardiac myocytes **(Ref. 8 & 9)**. On the other hand, IL-6 family members protect myocytes against oxidative stress by inducing an anti-apoptotic program. Another cytokine, Granulocyte Colony-Stimulating Factor (G-CSF), is believed to be involved in myocardium regeneration, myocardial fibrosis reduction, healing acceleration and cardiomyocyte protection. Cardiac repair following cytokine therapy depends on a number of variables, and further research is required to accurately determine the true therapeutic potential of such therapy. Chemokine superfamily members are rapidly upregulated in the infarcted myocardium and may modulate infarct angiogenesis and fibrous tissue deposition. Upregulated CXCL8 may induce neutrophil infiltration. Other chemokines, such as the CC chemokines Monocyte Chemoattractant Protein (MCP)-1, Macrophage Inflammatory Protein (MIP)-1α, and CCL4 may regulate monocyte and lymphocyte recruitment. Stromal-Cell Derived Factor-1 (SDF-1α) is the most extensively studied chemokine for cardiogenesis.



Growth factors promote myocardial repair and improved cardiac function. The discovery of growth factor involvement in cardiac regeneration mechanisms, including angiogenesis, anti-apoptosis, cardiomyocyte proliferation, CSCs chemotaxis, ECM remodeling and others, has generated increased interest in cardiovascular medicine. VEGF, due to its angiogenic property, is seen as a promising molecule for promoting neovascularization in the infarcted heart. VEGF also mediates eNOS phosphorylation and helps in the regulation of angioblast and embryonic endothelial cell (EC) proliferation. VEGF is required for effective cardiomyocyte differentiation of human induced pluripotent stem cells (iPSCs). Several other anti-apoptotic growth factors, such as fibroblast growth factor (FGF), hepatocyte growth factor (HGF) and platelet-derived growth factor (PDGF), induce mitigation of the ischemic injury in the cardiac tissues. Erythropoietin (EPO), a glycoprotein hormone, protects the myocardium from ischemic injury and promotes cardiac remodeling. Hypoxic ischemic cardiomyocytes contain EPO receptors that are potential targets for EPO treatment. Thus, the paracrine secretion of cytokines, chemokines, and growth factors increases cardiac recovery and tissue regeneration **(Ref. 9 & 10)**.

Besides cytokines and growth factors, small molecules may also play an important role in cardiac regenerative therapy. A variety of cells, such as cardiac fibroblasts, iPSCs, and cardiomyocytes, can serve as a cell source for cardiac repair and regenerative medicine. Small molecules can be used to improve or enable cell reprogramming towards pluripotency. Treatment of multipotent cells with small molecules may also activate repair mechanisms, opening new avenues to regenerative medicine. Small molecules may be used for stem cell differentiation to cardiomyocytes, which is an importance source for replacement therapy. Among small molecules, ascorbic acid has been identified to increase cardiogenic differentiation of embryonic stem cells (ESCs). Other cardiogenic small molecules include cardiogenols, isoxazolyl-serine-based agonists of peroxisome proliferator-activated receptors (PPARs), verapamil, SB203580, sulfonylhydrazones, and cinchona alkaloid derivatives. AG1478, BMS-189453, Diazoxide, 1-EBIO, Retinoic acid (RA), and Purmorphamine are some other small molecules that enhance graft integration, cardiac differentiation and heart regeneration. Retinoic acid enhances cardiomyogenesis and ventricular cardiomyocyte development in mouse ESCs. Noggin, dorsomorphin or other BMP antagonists also promote cardiomyogenesis in mouse ESCs during developmental stages. Cardiomyogenesis can also be promoted by modulating calcium signaling pathways by using small molecules. Cyclosporine, a calcineurin inhibitor, as well as verapamil, an L-type calcium channel blocker, have been identified as cardiomyogenesis promoters. Small molecules targeting BMPs, TGF-β, and Wnt enable the efficient cardiac differentiation of iPSCs in humans. Cardiogenic small molecules discovered in phenotypic screening assays are of immense use and investigating their cellular targets could potentially shed more light on the process of cardiac differentiation. Small molecules could replace cardiac reprogramming transcription factors and can serve as an initial step towards cardiac cell induction and enhancement of reprogramming for *in vitro* applications. Cardiogenic small molecules have proven to be important keys for determining novel drug targets and may serve as promising therapeutics for the treatment of ischemic cardiomyopathy **(Ref. 11, 12 & 13)**.

A summary of methods for the differentiation of human iPSCs into cardiomyocytes is presented in the following picture (Adapted from Ref. 14).

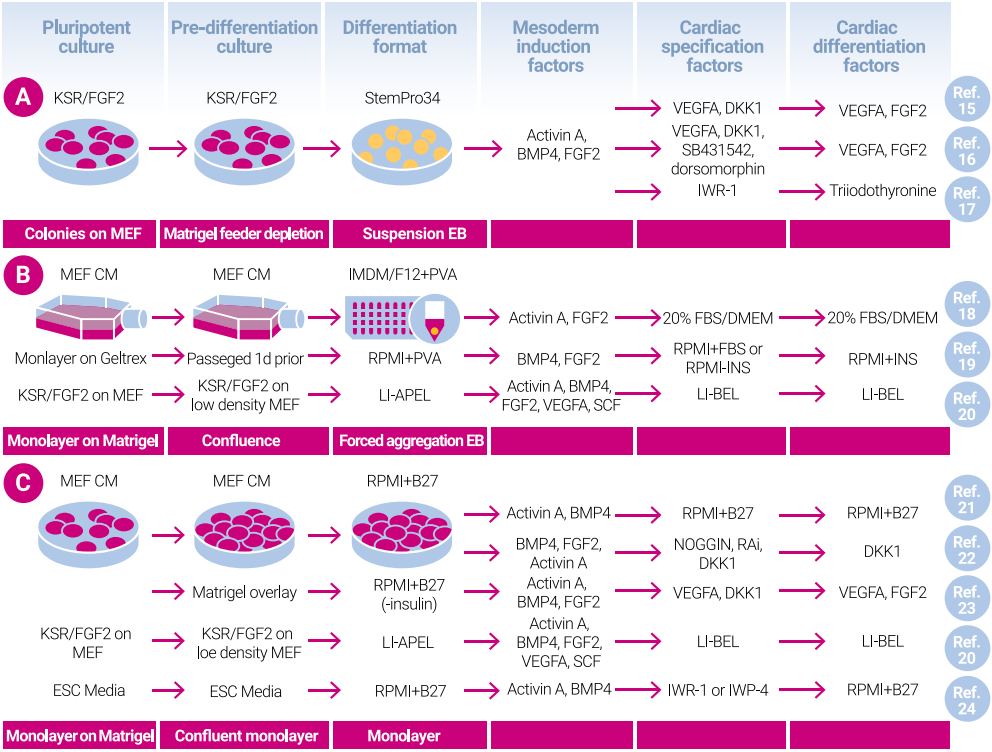


Figure: Three approaches for differentiating iPSCs into cardiomyocytes, divided into six steps: pluripotent culture, pre-differentiation culture, differentiation format, treatment with mesoderm induction factors, treatment with cardiac specification factors, and treatment with cardiac differentiation factors. (A) Methods using suspension of embryoid bodies (EBs) in StemPro34; (B) Methods using forced aggregation of EBs; (C), Methods using monolayer differentiation.

Abbreviations: KSR, Knockout Serum Replacement; FGF-2, fibroblast growth factor 2; StemPro34, proprietary medium from Invitrogen; BMP-4, bone morphogenic protein 4; VEGF-A, vascular endothelial growth factor A; DKK-1, dickkopf homolog 1; SB431542, TGF-β/Activin/NODAL signaling inhibitor (ALK4,5,7); dorsomorphin, BMP signaling inhibitor (ALK2,3,6); IWR-1, WNT signaling inhibitor; MEF CM, mouse embryonic fibroblast conditioned hESC medium; IMDM/F12+PVA, IMDM/F12-based media supplemented with polyvinyl alcohol; RPMI, Roswell Park Memorial Institute 1640 basal medium; FBS, fetal bovine serum; DMEM, basal media; RPMI+PVA, RPMI-based media supplemented with polyvinyl alcohol; RPMI-INS, RPMI-based media without insulin; B27, media supplement; NOGGIN, BMP signaling inhibitor; RAi, retinoic acid signaling inhibitor; LI-APEL, low insulin, Albucult, polyvinyl alcohol, essential lipids media; SCF, stem cell factor (KITLG); LI-BEL, low insulin, bovine serum albumin, essential lipids media; IWP-4, WNT signaling inhibitor **(Ref. 14)**.

All the above methods have utilized iPSCs that were differentiated into cardiomyocytes. Since obtaining enough iPSCs for practical applications in regenerative medicine could present a real challenge, iPSCs were viewed as a promising solution. However, currently, reprogramming efficiency is very low and there are safety issues that might limit the use of iPSCs. Transdifferentiation, which is the direct conversion of one mature somatic cell into another mature somatic cell, offers another option for obtaining cardiomyocyte-like cells by using forced expression of transcription factors and microRNAs, yet, these genetic manipulations can raise safety issues as well. The discovery that iPSCs can be obtained by

chemical induction led to the discovery that it is possible to transdifferentiate induced cardiomyocyte-like cells (iCMs) from fibroblasts by using a defined chemical cocktail comprised of CHIR 99021, E 616452, Forskolin, Valproic Acid, Tranylcypromine, TTNPB, L-Ascorbic Acid, Rolipram and PD 0325901, together with LIF, NRG-1 and G-CSF **(Ref. 25)**.

An important aspect of cardiovascular diseases and cardiovascular regeneration includes the identification of biomarkers. Cardiac biomarkers are released into the blood when the heart is damaged or stressed. They can potentially be used to detect a wide range of cardiac conditions like acute coronary syndrome (ACS) and cardiac ischemia. Traditional cardiac biomarkers include glucose level, lipid profile, and hormonal biomarkers. Physiological cardiac biomarkers are based on serum lipid, triglyceride to HDLp ratio, LDL cholesterol level, Sphingolipids, Omega-3 Index, Lipophorin-cholesterol ratio and ST2 level. Other cardiac biomarkers, such as imaging, anatomical, immunohistochemical, therapeutic and genetic biomarkers may be important in risk prediction and morbidity status. The most important markers in cardiovascular disease include molecular markers, both surface and internal markers. Cardiac troponins (cTn), including Troponin I (cTnI) and Cardiac Troponin-T (cTnT), and natriuretic peptides are the most prominent molecular biomarkers used in clinical cardiology, especially in cases of ACS. High levels of cTn1 are generally associated with increased risk of heart failure **(Ref. 26 & 27)**.

Transcription factors may also function as cardiac biomarkers. During cardiogenesis, cardiac progenitors expressing the transcription factors Nkx2.5 and Isl1 may give rise to myocytes. Nkx2.5, or cardiac homeobox protein, is a marker of cardiomyocyte differentiation and is necessary for proper development of the ventricular myocardial lineage. Isl1, a LIM homeodomain transcription factor, is a pan-cardiac progenitor marker, and is expressed in cardiac progenitor fields during early development. Nkx2.5 is present at high levels in embryonic differentiated cardiomyocytes and is expressed throughout cardiac development while Isl1, which is downregulated in myocardial differentiation, is mostly restricted to a progenitor cell state in the heart. Nkx2.5 acts in combination with both MEF2C and Hand2, also considered core cardiac transcription factors, to control ventricular identity. Tbx5, another transcription factor, is predominantly expressed in first heart field (FHF) precursors and was down regulated in the early stages of embryoid body (EB) differentiation of Nkx2.5OE ESCs. GATA-4, 5, and 6 are expressed in the heart and regulate developmental processes, including differentiation and migration of cardiomyoctes. GATA-4 is one of the first transcription factors expressed in cardiac cells and is important in transcriptional regulation during cardiac development **(Ref. 26 & 27)**.

Additional gene markers for cardiac mesoderm and cardiomyocytes include Brachyury, atrial natriuretic factor, mesoderm posterior factor 1, myosin light chain 2 atrial and ventricular transcripts, and α-myosin heavy chain (MHC-α). NT-proBNP and sST2 are two promising biomarkers for identifying patients with little potential to benefit from Implantable Cardioverter Defibrillator (ICD) therapy. Other cardiac-specific structural genes identified include ion channel proteins (MYH7, MYH6, MLC-2A) and ionic channels (CACNA1C, CACNA1D, hERG, HCN-2). Many cell membrane proteins, such as potassium voltage- gated channel subfamily A member 6 (KCNA6), and N-cadherin, a calcium-dependent transmembrane adhesion protein, are also important markers in cardiovascular diseases. Cell surface markers are generally used to verify heart muscle cells. Other common cardiac cell membrane markers include β1- and β2-adrenergic receptors, Connexin 43, and Popeye domain containing 2 (POPDC2), which has a high frequency of expression along with MHC-α. Recently, miRNAs have also been identified as regulators of cardiovascular diseases and may provide new insights into disease mechanisms. Many miRNAs have been implicated in cardiovascular disease as viable biomarkers and drug targets **(Ref. 28)**.

Ischemic cardiomyopathy, myocardial infarction and congestive heart failure have become major clinical issues due to their role in increasing morbidity and mortality. Cardiac regenerative therapy, including drugs, growth factors and numerous pharmacological and device therapies have improved adverse cardiac remodeling and mortality in heart failure. However, few of these strategies have found success in clinical trials. A number of issues will need to be addressed for the advancement of regenerative medicine as a field. Stem cell-based therapies using multipotent and pluripotent stem cells could potentially achieve the elusive goal of true cardiac regeneration. Until now, both clinical as well as preclinical studies have utilized simple delivery methods for regenerative therapeutics. Recently, the focus has shifted to advanced delivery concepts such as the use of biomaterial carriers, multimodal therapeutic strategies, nanoparticulate encapsulation, and minimally invasive delivery systems. These potential strategies may lead to a whole new world of cardiac regeneration in the future **(Ref. 29 & 30)**.

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Angiogenesis/Cardiovascular Related Proteins

Activin A

Activin A is a TGF-β family member that exhibits a wide range of biological activities, including regulation of cellular proliferation and differentiation, and promotion of neuronal survival. Elevated levels of Activin A in human colorectal tumors and in postmenopausal women have been implicated in colorectal and breast cancers, respectively. The biological activity of Activin A can be neutralized by inhibins and by the diffusible TGF-β antagonist, follistatin. Activin A binds to the two forms of activin receptor type I (Act RI-A and Act RI-B) and two forms of activin receptor type II (Act RII-A and Act RII-B). Activins are homodimers or heterodimers of different β subunits. They are produced as precursor proteins with an amino terminal propeptide that is cleaved to release the C-terminal bioactive ligand.

ANG-1

ANG-1 (Angiopoietin-1) is a secreted ligand for Tie-2, a tyrosine-kinase receptor expressed primarily on vascular endothelial cells and early hematopoietic cells. ANG-1/Tie-2 signaling promotes angiogenesis during the development, remodeling, and repair of the vascular system. Transgenic mice lacking expression of either ANG-1 or Tie-2 fail to develop a fully functional cardiovascular system and die before birth. Postnatally, the angiogenic activity of ANG-1/Tie-2 is required during normal tissue repair and remodeling of the female endometrium in the menstrual cycle. ANG-1/Tie-2 signaling appears to be regulated by Angiopoietin-2 (ANG-2), a natural antagonist for Tie-2 that exerts its effects through an internal autocrine loop mechanism. In addition to suppressing endothelial cell activation by inhibiting the expression of adhesion and inflammatory molecules, ANG-1 enhances endothelial cell survival and capillary morphogenesis, and lessens capillary permeability. As such, ANG-1 has potential to become an effective therapeutic agent for treating various endothelium disorders, including several severe human pulmonary diseases. The efficacy of cell-based ANG-1 gene therapy for acute lung injury (ALI) has recently been studied in a rat model of ALI. The results of this study show that such therapy can markedly improve lung condition and suggest that ANG-1 therapy may represent a potential new strategy for the treatment and/or prevention of acute respiratory distress injury (ARDI), a significant cause of morbidity and mortality in critically ill patients.

ANG-2

ANG-2 binds to the endothelial cell specific receptor Tie-2, but, in contrast to ANG-1, does not induce tyrosine phosphorylation. Consequently, ANG-2 modulates ANG-1 activation of Tie-2 and, depending on the physiological and biochemical environment, can act either as an agonist or antagonist of Tie-2 induced angiogenesis. The signaling interactions of ANG-1, ANG-2 and Tie-2, along with less characterized ANG-3 and ANG-4, are required for embryonic and adult angiogenesis. Physiologically, ANG-1 and ANG-2 are associated with sprouting, tube formation, and structural integrity of newly formed blood vessels. Mature human ANG-2 is a secreted protein containing 480 amino acid residues. ANG-2 is composed of an alpha-helix-rich “coiled coil” N-terminal domain and fibrinogen-like C-terminal domain. ANG-2 exists predominantly in the form of a disulfide-linked dimer.

ANGPTL-3

ANGPTL-3 (Angiopoietin like protein 3) is a member of the angiopoietin family of structurally related proteins, characterized by a coiled N-terminal domain and a C-terminal fibrinogen like domain. It is primarily expressed in the liver and can exert activities related to both angiogenesis and lipid metabolism. ANGPTL-3 inhibits lipoprotein lipase (LPL) and endothelial lipase (EL), which has the effect of increasing plasma levels of triglycerides and HDL associated cholesterol. The fibrinogen like portion of the ANGPTL-3 protein can bind alpha-5/beta-3 integrins leading to endothelial cell adhesion and migration.

ANGPTL-7

Angiopoietin-like 7 (ANGPTL-7), or Cornea-Derived Transcript 6 (CDT6), is a member of the angiopoietin family of structurally related proteins, characterized by a coiled N-terminal domain and a C-terminal fibrinogen-like domain. While ANGPTL-7 shares the structural features of the angiopoietin family, it plays a critical role in blocking the vascular endothelial Tie2 receptor to which other family members bind. Through the blocking of the Tie2 receptor, ANGPTL-7 does not act as a “true” angiopoietin, but rather as a morphogen that contributes to the avascularity and transparency of the cornea during both embryo and adult development. Human ANGPTL-7 is expressed at high levels in the avascular corneal stromal layer,

a site of pathological angiogenesis normally devoid of blood vessels, suggesting that the protein acts as a negative regulator of angiogenesis in a manner similar to that of angiopoietin-1 and angiopoietin-2. In mouse xenograft models, ANGPTL-7 overexpression has been shown to lead to increased extracellular matrix components typical of a mature corneal stromal layer, as well as the reduction of tumor growth and aberrant blood vessel formation. Overexpression in human melanoma models shows a contradictory, up-regulation of endostatin, an endogenous angiostatic factor, in comparison to the down-regulation observed in mouse models.

ApoA-I

ApoA-I is a 29.0 kDa protein produced in the liver and intestine, and secreted as the predominant constituent of nascent high density lipoprotein (HDL) particle. ApoA-I, which is found exclusively in HDL, has a unique ability to capture and solubilize free cholesterol. This ApoA-I ability enables HDL to remove excess peripheral cholesterol, and return it to the liver for recycling and excretion. This process, called reverse cholesterol transport, is thought to inhibit atherogenesis. For this reason, HDL is also known as the "good cholesterol." The therapeutic potential of ApoA-I has been recently assessed in patients with acute coronary syndromes, using a recombinant form of a naturally occurring variant of ApoA-I (called ApoA-I Milano). The availability of recombinant normal ApoA-I should facilitate further investigation into the potential usefulness of ApoA-I in preventing atherosclerotic vascular diseases.

ApoE2, E3, E4

ApoE belongs to a group of proteins that bind reversibly with lipoprotein and play an important role in lipid metabolism. In addition to facilitating solubilization of lipids, these proteins help to maintain the structural integrity of lipoproteins, serve as ligands for lipoprotein receptors, and regulate the activity of enzymes involved in lipid metabolism. Significant quantities of ApoE are produced in the liver and brain, and to some extent in almost every organ. ApoE is an important constituent of all plasma lipoproteins. Its interaction with specific ApoE receptor enables uptake of chylomicron remnants by liver cells, which is an essential step during normal lipid metabolism. It also binds with the LDL receptor (apo B/E). Defects in ApoE are a cause of hyperlipoproteinemia type III. ApoE exists in three major isoforms; E2, E3, and E4, which differ from one another by a single amino acid substitution. Compared with E3 and E4, E2 exhibits the lowest receptor binding affinity. E2 allele carriers had significantly lower levels of total cholesterol, low-density lipoprotein cholesterol, and non-high-density lipoprotein cholesterol, as well as increased ApoE levels.

Apo-SAA

Human Apo-SAA is a 104 amino acid polypeptide that circulates primarily in association with high-density lipoproteins (HDL). The level of Apo-SAA, normally 1-5 µg/ml in plasma, increases 500-1000 fold within 24 hours of an inflammatory stimulus and, under these conditions, is the most abundant HDL apolipoprotein. The human SAA gene codes for a 122 amino acid polypeptide, which contains an 18 amino acid N-terminal signal sequence. Recombinant Apo-SAA is a consensus SAA molecule corresponding to human Apo-SAA1α, except for the presence of an N-terminal methionine, the substitution of asparagine for aspartic acid at position 60, and arginine for histidine at position 71 (the latter two substituted residues are present in Apo-SAA2β).

Apo-SAA1

Apo-SAA1 Serum amyloid A proteins (SAA) represent a family of apolipoproteins that circulate in association with high-density lipoproteins (HDL). The level of Apo-SAA, normally 1-5 µg/ml in plasma, increases 500-1000 fold within 24 hours of an inflammatory stimulus and, under these conditions, is the most abundant HDL apolipoprotein. The human SAA gene codes for a 122 amino acid nonglycosylated polypeptide, which contains an 18 amino acid N-terminal sequence.

4-1BB Ligand

4-1BB Ligand (4-1BBL), a member of the TNF superfamily, is expressed in B cells, dendritic cells, activated T cells and macrophages. 4-1BBL binds to its receptor, 4-1BB, and provides a co-stimulatory signal for T cell activation and expansion. The human 4-1BBL gene codes for a 254 amino acid type II transmembrane containing a 28 amino acid cytoplasmic domain, a 21 amino acid transmembrane domain, and a 205 amino acid extracellular domain. The soluble form of 4-1BBL contains the TNF-like portion of the extracellular domain of 4-1BBL.

BMP-2
BMPs (Bone Morphogenetic Proteins) belong to the TGF-β superfamily of structurally related signaling proteins. BMP-2 is a potent osteoinductive cytokine, capable of inducing bone and cartilage formation in association with osteoconductive carriers such as collagen and synthetic hydroxyapatite. In addition to its osteogenic activity, BMP-2 plays an important role in cardiac morphogenesis, and is expressed in a variety of tissues, including lung, spleen, brain, liver, prostate, ovary, and small intestine. The functional form of BMP-2 is a 26 kDa protein composed of two identical 114 amino acid polypeptide chains linked by a single disulfide bond. Each BMP-2 monomer is expressed as the C-terminal part of a precursor polypeptide, which also contains a 23 amino acid signal sequence for secretion, and a 259 amino acid propeptide. After dimerization of this precursor, the covalent bonds between the propeptide (which is also a disulfide-linked homodimer) and the mature BMP-2 ligand are cleaved by a furin-type protease.

BMP-3
TGF-β family members are key modulators of cell proliferation, differentiation, matrix synthesis, and apoptosis. As implied by their name, BMPs initiate, promote, and regulate the development, growth, and remodeling of bone and cartilage. In addition to this role, BMPs are also involved in prenatal development and postnatal growth, remodeling and maintenance of a variety of other tissues and organs. BMP-3 is abundantly found in adult bone and, to a lesser extent, fetal cartilage. BMP-3 inhibits osteogenesis and bone formation by activating a signaling cascade that antagonizes the signaling of pro-osteogenic BMPs.

BMP-4
Bone morphogenetic proteins (BMPs) constitute a subfamily within the TGF-β superfamily of structurally related signaling proteins. Members of this superfamily are widely distributed throughout the body, and are involved in diverse physiological processes during both pre- and postnatal life. Like BMP-7, BMP-4 is involved in the development and maintenance of bone and cartilage. Reduced expression of BMP-4 is associated with a number of bone diseases, including the heritable disorder Fibrodysplasia Ossificans Progressiva.

BMP-6
TGF-β family members are key modulators of cell proliferation, differentiation, matrix synthesis, and apoptosis. As implied by their name, BMPs initiate, promote, and regulate the development, growth, and remodeling of bone and cartilage. In addition to this role, BMPs are also involved in prenatal development and postnatal growth, remodeling, and maintenance of a variety of other tissues and organs. Increasing evidence indicates that BMP-Smad signaling has a tumor suppressing activity, and that BMPs can inhibit tumor growth. BMP-6 is abnormally expressed in breast cancer cell lines, however, its function in promoting breast cancer development is unknown. The mature and functional form of BMP-6 is a homodimer of two identical 139 amino acid polypeptide chains linked by a single disulfide bond. Each monomer is expressed as the C-terminal part of a precursor polypeptide, which contains a 20 amino acid signal peptide and a 354 amino acid propeptide. This precursor undergoes intracellular dimerization, and upon secretion it is processed by a furin-type protease.

BMP-7
TGF-β family members are key modulators of cell proliferation, differentiation, matrix synthesis, and apoptosis. As implied by their name, BMPs initiate, promote, and regulate the development, growth, and remodeling of bone and cartilage. In addition to this role, BMPs are also involved in prenatal development and postnatal growth, remodeling, and maintenance of a variety of other tissues and organs. BMP-7, also known as osteogenic protein-1 or OP-1, is a potent bone inducing agent, which in the presence of an appropriate osteoconductive carrier (e.g. collagen sponge or synthetic hydroxyapatite) can be used in the treatment of bone defects. A bone-graft substitute, called OP-1TM-implant, made of recombinant human BMP-7 associated with bovine bone-derived collagen, has recently been approved by the FDA as a device for treating critical-size bone fractures. The potential use of BMP-7 in dental reconstructive surgeries is currently under investigation.

BMP-10
Bone morphogenetic proteins (BMPs) constitute a subfamily within the TGF-β superfamily of structurally related signaling proteins. Members of this superfamily are widely distributed throughout the body and are involved in diverse physiological processes during both pre- and postnatal life. BMP-10 plays a crucial role in the development of the embryonic heart by acting to stimulate and maintain cardiomyocyte proliferation. It can signal through various receptor complexes usually containing BMPR-1A, BMPR-

1B, ALK1, ALK3, or ALK6. The interaction of BMP-10 with its specific receptors can induce signaling initiated by the phosphorylation of SMAD transcription factors, including SMAD1, SMAD5, or SMAD8, but can also induce SMAD independent processes. BMP-10 is structurally related to BMP-9, and both can inhibit endothelial cell proliferation and migration.

BMP-13/CDMP-2

BMP-13 (CDMP-2) is expressed in hypertrophic chondrocytes during embryonic development of long bones. Continued postnatal expression of BMP-13 in articular cartilage suggests that it plays a regulatory role in the growth and maintenance of articular cartilage. Adenovirus-mediated BMP-13 gene transfer to rabbit bone marrow stem cells have been reported to augment periosteal repair of osteochondral defects. The functional form of BMP-13/CDMP-2 is a disulfide-linked homodimer of two 120 amino-acid polypeptide chains. This 27.5 kDa protein is obtained by proteolytic processing of a biologically inactive precursor protein of 97.7kDa.

C5a

Complement 5a (C5a) is an enzymatically generated glycoprotein belonging to the anaphylatoxin family of structurally and functionally related proteins. Generated upon the activation of the complement system, C5a, together with C4a, C3a, and the membrane attack complex (C5b-9), functions as a central player in host defense by inducing smooth muscle cell contraction, increased vascular permeability, and histamine release from mast cells and basophilic leukocytes through cell degranulation. In addition to acting as a direct mediator of localized inflammatory response, C5a also initiates both the synthesis and release of IL-8 from monocytes and bronchial epithelial cells, stimulates the proliferation of neurons and hepatocytes, and functions as a potent chemoattractant. Where C5a deficiency, a rare defect of the complement pathway caused by the mutation of the C5a gene, is associated with susceptibility to severe infections, excessive C5a activation has been linked to liver fibrosis, sepsis, adult respiratory distress syndrome, rheumatoid arthritis, Alzheimer's disease, and ischemic heart disease. Human C5a shares 60% and 54% sequence identity to mouse and rat C5a, respectively. The human C5 gene encodes a 1,676 amino acid glycoprotein that is comprised of a disulfide-linked C5 alpha and a C5 beta chain, the former of which contains the active, 74 amino acid C5a anaphylatoxin chain.

Cardiotrophin-1

CT-1 is a member of the IL-6 family of cytokines which also includes LIF, CNTF, OSM (Oncostatin M), IL-11, IL-6 and possibly NNT-1/BSF-3. CT-1 is a pleiotropic cytokine which is expressed in various tissues including the adult heart, skeletal muscle, ovary, colon, prostate, and fetal lung, and signals through the LIF receptor and the gp130 receptor subunit. CT-1 has the ability to induce cardiac myocyte hypertrophy, and enhances the survival of cardiomyocyte and different neuronal populations. Biologically active human CT-1 is synthesized as a 201 amino acid polypeptide lacking a hydrophobic N-terminal secretion signal sequence.

CD40 Ligand

CD40, a member of the TNF receptor superfamily, is a cell surface protein expressed on B cells, dendritic cells, monocytes, thymic epithelial cells and, at low levels, on T cells. Signaling though CD40 plays an important role in the proliferation and differentiation of B cells, and is critical for immunoglobulin (Ig) class switching. The membrane-anchored CD40 Ligand is expressed almost exclusively on activated CD4+ T lymphocytes. Failure to express CD40L leads to "immunodeficiency with hyper-IgM", a disease characterized by failure to produce IgG, IgA and IgE. The human CD40L gene codes for a 261 amino acid type II transmembrane protein, which contains a 22 amino acid cytoplasmic domain, a 24 amino acid transmembrane domain, and a 215 amino acid extracellular domain. The soluble form of CD40L is an 18 kDa protein comprising the entire TNF homologous region of CD40L and is generated *in vivo* by an intracellular proteolytic processing of the full length CD40L.

CNTF

CNTF is a potent neural factor that was originally characterized as a vital factor for the survival of chick ciliary neurons *in vitro*. CNTF is also important for the survival of other neural cell types, including primary sensory neurons, motor neurons, basal forebrain neurons and type 2 astrocytes. CNTF is highly conserved across species and exhibits cross-species bioactivity.

CTGF

CTGF is a member of the CCN family of secreted cysteine-rich regulatory proteins, and is the major mitogenic and chemoattractant protein produced by umbilical vein and vascular endothelial cells. CTGF stimulates the proliferation and differentiation of chondrocytes, induces angiogenesis, promotes cell adhesion of fibroblasts, endothelial and epithelial cells, and binds to IGF, TGF-β1 and BMP-4. Cell migration and adhesion are signaled through binding to specific cell surface integrins and to heparin sulfate proteoglycans CTGF (98 a.a.), a lower molecular weight isoform containing the C-terminal portion of the full length CTGF protein, exerts full heparin binding, cell adhesion, and mitogenic CTGF activity. Mature Human CTGF is a 38.0 kDa secreted protein containing 323 amino acid residues. CTGF is comprised of four distinct structural domains (modules), which are identified as IGF binding protein (IGFBP), von Willebrand Factor C (VWFC), thrombospondin type-I (TSP type-I), and C-terminal cysteine knot-like (CTCK) domains. Full length CTGF can be proteolytically cleaved in certain tissues to yield N-terminal truncated isoforms, which, depending on the isoform, contain only the TSP type-I and CTCK domains or contain only the CTCK domain.

CTGFL/WISP-2

CTGFL/WISP-2 is a 28.6 kDa protein that belongs to the CCN family of cysteine-rich regulatory proteins. Members of this family stimulate mitosis, adhesion, apoptosis, extracellular matrix production, growth arrest, and migration of multiple cell types. The protein is expressed in primary osteoblasts, fibroblasts, the ovaries, testes, and heart. In addition to promoting adhesion of osteoblasts, CTGFL/WISP-2 inhibits osteocalcin production, as well as binding of fibrinogen to integrin receptors.

CYR61

CYR61 is a member of the CCN family of secreted cysteine-rich regulatory proteins. CYR61 induces angiogenesis by stimulating the proliferation, migration, and adhesion of endothelial cells. Cell migration and adhesion are mediated through binding to specific cell surface integrins and to heparin sulfate proteoglycans. Increased expression of CYR61 is associated with several types of cancer, and correlates with the progression and estrogen independence of human breast cancers.

DLL-1

Human soluble DLL-1 comprises the extracellular signaling domain of DLL-1, a member of the Delta/Serrate/Lag-2 (DSL) family of single-pass type I trans-membrane proteins that serve as ligands for Notch receptors. It is expressed primarily in the heart, pancreas and epidermis. DLL-1 functions to specifically activate the Notch-1 and Notch-2 receptors. Proteolytic cleavage of DLL-1 produces a secreted extracellular domain, sDLL-1, that interacts with Notch receptors expressed on adjacent cells. Notch signaling plays an essential role in controlling cell fate decisions during prenatal development and postnatal stem cell renewal, and differentiation in many tissues. Human sDLL-1 blocks monocyte differentiation into macrophages, but permits differentiation into dendritic cells. In hematopoietic progenitor cells, hsDLL-1, suppresses differentiation into B-cells, while promoting differentiation into T-cells and NK cell precursors. In cell culture, human sDLL-1 has been shown to promote expansion of hematopoietic progenitor cells and suppress apoptosis by inhibiting differentiation. Overexpression of Notch receptors appears to inhibit differentiation in several mammalian cell lines, and increasing evidence suggests that Notch signaling is frequently downregulated in human malignancies. The human DLL-1 gene consists of a 528 amino acid extracellular domain with one DSL domain, eight EGF-like repeats, a 23 amino acid transmembrane domain, and a 155 amino acid cytoplasmic domain.

DLL-4

Human sDLL-4 comprises the extracellular signaling domain of DLL, a member of a structurally-related family of single-pass type I trans-membrane proteins that serve as ligands for Notch receptors. DLL-4 functions to specifically activate the Notch-1 and Notch-4 receptors. The Notch signaling pathway regulates endothelial cell differentiation, proliferation and apoptosis, and is essential for the development, maintenance and remodeling of the vascular system. Targeted deletion of the DLL-4 gene in mice resulted in severe vascular defects and death before birth. Up-regulation of DLL-4 expression has been implicated in the vascular development of certain tumors. The human DLL-4 gene consists of a 503 amino acid extracellular domain with one DSL domain, eight EGF-like repeats, a 21 a.a. transmembrane domain, and a 135 a.a. cytoplasmic domain.

EGF
EGF is a potent growth factor that stimulates the proliferation of various epidermal and epithelial cells. Additionally, EGF has been shown to inhibit gastric secretion, and to be involved in wound healing. EGF signals through a receptor known as c-erbB, which is a class I tyrosine kinase receptor. This receptor also binds with TGF-α and VGF (vaccinia virus growth factor).

EGF Receptor (EGFR)
EGF Receptor (EGFR, ErbB1) is a transmembrane protein that exerts tyrosine kinase activity upon ligand-induced activation. EGFR can be activated by binding EGF, or at least six other structurally related protein ligands, including TGF-α, HB-EGF, Betacellulin (BTC), Amphiregulin, Epiregulin, and Epigen. Upon activation, EGFR initiates a signaling cascade, which includes dimerization and internalization, tyrosine phosphorylation, DNA synthesis of target genes and, ultimately, cell proliferation. EGFR signaling plays a role in the growth and differentiation of normal cells, but elevated EGFR activity is correlated with the development and pathogenesis of certain cancers.

EGF-L7
EGF-L7 (Epidermal growth factor-like protein 7, Multiple EGF-like domains protein 7, VE-statin) is a multi-domain protein containing two EGF-like domains and one EMI domain. It is expressed almost exclusively in endothelial cells and functions to promote normal development of the vascular system, particularly tubulogenesis. EGF-L7 is capable of antagonistic binding to Notch receptors, resulting in the inhibition of Notch signaling in HUVEC and neural stem cells. In research models inducing hypoxia and subsequent reoxygenation (H/R), EGF-L7 can inhibit ICAM-1 expression and enhance the inhibition of NF-κB activation. Additionally, EGF-L7 can chemoattract endothelial cells and bind to the extracellular matrix. The overexpression of EGF-L7 is observed in various cancers, and is generally correlated with increased metastasis and a poor prognosis.

EG-VEGF
EG-VEGF is a secreted angiogenetic mitogen growth factor expressed in the steroidogenic glands, ovary, testis, adrenal gland, and placenta. EG-VEGF induces proliferation, migration, and fenestration (formation of membrane discontinuities) in capillary endothelial cells derived from endocrine glands. The human EG-VEGF gene codes for a 105 amino acid polypeptide containing an N-terminal signal sequence of 19 amino acids.

ENA-78
ENA-78 is a CXC chemokine that signals through the CXCR2 receptor. It is expressed in monocytes, platelets, endothelial cells, and mast cells. ENA-78 is a chemoattractant for neutrophils. The three naturally occurring variants of human ENA-78; ENA 5-78, ENA 9-78 and ENA 10-78, contain 74, 70, and 69 amino acid residues, respectively, and possess the same biological activity. ENA-78 contains the four conserved cysteine residues present in CXC chemokines, and also contains the 'ELR' motif common to CXC chemokine that bind to the CXCR1 and CXCR2 receptors.

Endostatin
Endostatin is a naturally occurring 20 kDa polypeptide derived from the C-terminal portion of type XVIII collagen. It functions as an anti-angiogenic cytokine that is expressed in various organs, with the highest levels in liver, lung and kidney. Endostatin inhibits angiogenesis by blocking the pro-angiogenic activities of VEGF and FGF-basic.

EPO
Erythropoietin (EPO) is a glycoprotein hormone that is principally known for its role in erythropoiesis, where it is responsible for stimulating proliferation and differentiation of erythroid progenitor cells. The differentiation of CFU-E (Colony Forming Unit-Erythroid) cells into erythrocytes can only be accomplished in the presence of EPO. Physiological levels of EPO in adult mammals are maintained primarily by the kidneys, whereas levels in fetal or neonatal mammals are maintained by the liver. EPO also can exert various non-hematopoietic activities, including vascularization and proliferation of smooth muscle, neural protection during hypoxia, and stimulation of certain B cells.

E-Selectin
Selectins are a family of calcium-dependent type 1 transmembrane proteins. Endothelial (E)-selectin is a heavily glycosylated transmembrane protein expressed by activated endothelial cells in microvascular linings. E-selectin, along with P-selectin and L-selectin, initiate recruitment of circulating leukocytes from blood to sites of inflammation in the vascular lining through interaction with specific cell surface-associated carbohydrate determinants. E-selectin consists of an N-terminal type 1 lectin domain, an EGF-like domain, 6 sushi (CCP/SCR) domains, a transmembrane sequence, and a short cytoplasmic domain.

FGF-acidic
FGF-acidic is one of 23 known members of the FGF family. Proteins of this family play a central role during prenatal development, postnatal growth and regeneration of a variety of tissues, by promoting cellular proliferation and differentiation. FGF-acidic is a non-glycosylated, heparin-binding growth factor that is expressed in the brain, kidney, retina, smooth muscle cells, bone matrix, osteoblasts, astrocytes and endothelial cells. FGF-acidic has the ability to signal through all the FGF receptors.

FGF-basic
FGF-basic is one of 23 known members of the FGF family. Proteins of this family play a central role during prenatal development, postnatal growth and regeneration of a variety of tissues, by promoting cellular proliferation and differentiation. FGF-basic is a non-glycosylated, heparin-binding growth factor that is expressed in the brain, pituitary, kidney, retina, bone, testis, adrenal gland, liver, monocytes, epithelial cells and endothelial cells. FGF-basic signals through FGFR 1b, 1c, 2c, 3c and 4.

FGF-4
FGF-4 is a heparin-binding growth factor that is a member of the FGF family. Proteins of this family play a central role during prenatal development, postnatal growth and regeneration of a variety of tissues, by promoting cellular proliferation and differentiation. FGF-4 signals through the FGFR 1c, 2c, 3c, and 4.

FGF-5
FGF-5 is a secreted, heparin-binding growth factor that belongs to the FGF family. Proteins of this family play a central role during prenatal development, postnatal growth and regeneration of a variety of tissues, by promoting cellular proliferation and differentiation. FGF-5 binds to FGFR 1c and 2c, and plays a regulatory role in the hair growth cycle.

FGF-6
FGF-6 is a secreted, heparin-binding growth factor that is a member of the FGF family. Proteins of this family play a central role during prenatal development, postnatal growth and regeneration of a variety of tissues, by promoting cellular proliferation and differentiation. FGF-6 is expressed in leukemia cell lines with platelet megakaryocytic differentiation potential. It signals through FGFR 1c, 2c, and 4.

FGF-8a, FGF-8b
FGF-8a, -8b is a heparin-binding growth factor belonging to the FGF family. Proteins of this family play a central role during prenatal development, postnatal growth and regeneration of a variety of tissues, by promoting cellular proliferation and differentiation. There are 4 known alternate spliced forms of FGF8; FGF-8A, FGF-8B, FGF-8E and FGF-8F. The human and murine FGF-8A and B are identical, unlike human and mouse FGF-8E and F, which are 98% identical. FGF-8 targets mammary carcinoma cells and other cells expressing the FGF receptors.

FGF-9
FGF-9 is a heparin-binding growth factor that belongs to the FGF family. Proteins of this family play a central role during prenatal development, postnatal growth and regeneration of a variety of tissues, by promoting cellular proliferation and differentiation. FGF-9 targets glial cells, astrocytes cells and other cells that express the FGFR 1c, 2c, 3b, 3c, and 4.

FGF-10
FGF-10 is a heparin-binding growth factor that belongs to the FGF family. Proteins of this family play a central role during prenatal development, postnatal growth and regeneration of a variety of tissues, by promoting cellular proliferation and differentiation. FGF-10 is most related to KGF/FGF-7, and is expressed during the development and, preferentially, in adult lungs. It signals through the FGFR 2b.

FGF-16
FGF-16 is a heparin-binding growth factor that is a member of the FGF family. Proteins of this family play a central role during prenatal development, postnatal growth and regeneration of a variety of tissues, by promoting cellular proliferation and differentiation. FGF-16 signals through FGFR 2c and 3c. FGF-16 plays a role in the development of the central nervous system.

FGF-17
FGF-17 is a heparin-binding growth factor that is a member of the FGF family. Proteins of this family play a central role during prenatal development, postnatal growth and regeneration of a variety of tissues, by promoting cellular proliferation and differentiation. FGF-17 signals through the FGFR 1c, 2c, 3c, and 4. FGF-17 signals induction and patterning of brain development during embryogenesis.

FGF-18
FGF-18 is a heparin-binding growth factor that belongs to the FGF family. Proteins of this family play a central role during prenatal development, postnatal growth and regeneration of a variety of tissues, by promoting cellular proliferation and differentiation. FGF-18 is an essential regulator of long bone and calvarial development. FGF-18 signals through FGFR 1c, 2c, 3c, and 4.

FGF-19
The FGF family plays central roles during prenatal development and postnatal growth and regeneration of a variety of tissues, by promoting cellular proliferation and differentiation. FGF-19, a member of the FGF family, is a high-affinity heparin-dependent ligand for FGFR4. FGF-19 is expressed during brain development and embryogenesis.

FGF-20
FGF-20 is a secreted, heparin-binding growth factor that is a member of the FGF family. Proteins of this family play a central role during prenatal development, postnatal growth and regeneration of a variety of tissues, by promoting cellular proliferation and differentiation. FGF-20 signals through the FGFR 2c and 3c, and is expressed during limb and brain development.

FGF-21
FGF-21 is a secreted growth factor that is a member of the FGF family. Proteins of this family play a central role during prenatal development, postnatal growth and regeneration of a variety of tissues, by promoting cellular proliferation and differentiation. FGF-21, in the presence of β-Klotho as a protein cofactor, signals through the FGFR 1c and 4 receptors, and stimulates insulin-independent glucose uptake by adipocytes.

FGF-23
The FGF family plays a central role during prenatal development, postnatal growth and regeneration of a variety of tissues, by promoting cellular proliferation and differentiation. FGF-23, FGF-21 and FGF-19 constitute an atypical FGF subfamily whose ligands act as circulating hormones and require the participation of a *Klotho* protein as a co-receptor for their signaling. FGF-23 is a bone-derived hormone that acts in the kidney to regulate phosphate homeostasis and vitamin D metabolism. The signaling receptor for FGF-23, a Klotho-FGFR1 (IIIc) complex, is an essential regulator of the renal sodium phosphate co-transporter and key vitamin D-metabolizing enzymes CYP27B1 and CYP24A1.

FGF-BP-1
The Fibroblast Growth Factor (FGF) Superfamily is comprised of multifunctional proteins that serves to regulate several complex biological processes related to the development, restoration, and/or redistribution of prenatal and postnatal tissue, as well as angiogenesis, wound healing, nerve regeneration, chronic inflammation, and cancer growth. Members of the FGF Superfamily function through paracrine, autocrine and intracrine pathways to promote spatial and temporal integrations of several cell responses, such as proliferation, growth, differentiation, and migration. Fibroblast growth factor binding protein 1 (FGF-BP-1) is a secreted glycoprotein, which contains both a heparin-binding domain and a distinct FGF-binding region, that is shed into circulation where it acts as a chaperone molecule for FGFs, most notably FGF-acidic and FGF-basic. Once secreted, FGF-BP-1 can bind FGFs in a reversible manner to mobilize them from inactive storage on heparan sulfate proteoglycans in the extracellular matrix, and deliver them to high affinity receptors on the cell surface where they can exert biological function, all the while protecting against proteolytic degradation. Expressed within the squamous epithelium, FGF-BP-1

functions synergistically with FGFs as a mitogen for keratinocytes and an antagonist for angiogenesis under normal physiological conditions and instances of tissue repair, while also acting as an angiogenic switch for the malignant progression of epithelial cells. First discovered at elevated levels within A431 human epidermoid carcinoma cells, FGF-BP-1 is also expressed at elevated levels in many squamous cell carcinomas and tumors where it has been shown to be a rate-determining factor, interacting with the heparan sulfate proteoglycan perlecan to potentiate neovascularization of tumor masses.

FGFR1a, FGFR2a

The FGF family plays a central role during prenatal development and postnatal growth, and the regeneration of a variety of tissues, by promoting cellular proliferation and differentiation. The FGF ligands bind to a family of type I transmembrane tyrosine kinase receptors, which leads to dimerization and activation by sequential autophosphorylation of specific tyrosine residues. Four genes encoding structurally related FGF receptors (FGFR-1 to -4) are known. Alternative splicing of the mRNAs generates numerous forms of FGFR-1 to -3. Alternate forms of FGF receptors can exhibit different specificities with respect to ligand binding. For example, the form designated as FGFR1a (IIc) interacts predominantly with FGF-acidic (FGF1) and FGF-basic (FGF2). A frequent splicing event involving FGFR-1 and -2 results in receptors containing all three Ig domains, referred to as the alpha isoform, or only IgII and IgIII, referred to as the beta isoform. Only the alpha isoform has been identified for FGFR-3 and FGFR-4. Additional splicing events for FGFR-1 to -3, involving the C-terminal half of the IgIII domain encoded by two mutually exclusive alternative exons, generate FGF receptors with alternative IgIII domains (IIIb and IIIc).

FGFR3

The FGF family plays a central role during prenatal development and postnatal growth, and the regeneration of a variety of tissues, by promoting cellular proliferation and differentiation. The FGF ligands bind to a family of type I transmembrane tyrosine kinase receptors, which leads to dimerization and activation by sequential autophosphorylation of specific tyrosine residues. Four genes encoding structurally related FGF receptors (FGFR-1 to -4) are known. Alternative splicing of the mRNAs generates numerous forms of FGFR-1 to -3. Alternate forms of FGF receptors can exhibit different specificities with respect to ligand binding. For example, the form designated as FGFR1a (IIc) interacts predominantly with FGF-acidic (FGF1) and FGF-basic (FGF2). A frequent splicing event involving FGFR-1 and -2 results in receptors containing all three Ig domains, referred to as the alpha isoform, or only IgII and IgIII, referred to as the beta isoform. Only the alpha isoform has been identified for FGFR-3 and FGFR-4. Additional splicing events for FGFR-1 to -3, involving the C-terminal half of the IgIII domain encoded by two mutually exclusive alternative exons, generate FGF receptors with alternative IgIII domains (IIIb and IIIc).

Fractalkine (CX3CL1)

Fractalkine is a CX3CL chemokine that signals through the CX3CR1 receptor. Fractalkine has been shown to chemoattract monocytes, microglia cells and NK cells. Fractalkine is, at this time, the only CXC3C chemokine that contains three amino acid residues between the first and second cysteine residues of the chemokine domain. The Fractalkine gene encodes for a 397 amino acid precursor protein containing a 24 amino acid signal sequence, a chemokine domain, and a "mucin-like stalk" sequence, which is followed by the transmembrane domain containing approximately 20 amino acids, and a C-terminal cytoplasmic domain. The extracellular chemokine domain contains 76 amino acid residues, including the four conserved cysteine residues found in other chemokines.

FRP-1

Secreted Frizzled Related Proteins (sFRPs) modulate WNT signaling by binding directly to WNT proteins in a manner that affects their receptor binding and signaling capabilities. sFRP-1 is a widely distributed protein that can bind directly to WNT1, WNT2, and possibly other WNT proteins, and generally exerts anti-proliferative effects consistent with activity as a WNT antagonist. It also inhibits apoptosis, and has been found to be down-regulated in many solid tumors, but up-regulated in uterine leiomyomas.

FRP-4

Secreted Frizzled-Related Proteins (sFRPs) are a family of glycosylated Wnt antagonists characterized by a conserved cysteine-rich domain that shares homology with the cysteine-rich, extracellular domain Frizzled proteins use for the binding of Wnt proteins and receptors. Lacking the transmembrane and intracellular domains of the Frizzled proteins, sFRPs function as soluble modulators of the Wnt

signaling pathway through the direct binding of Wnt proteins to this cysteine-rich domain, and the resultant inhibition of Wnt receptor binding and signaling capabilities. sFRP-4 is widely distributed in a variety of embryonic and adult tissues where it can function as a circulating antiangiogenic factor, a potent proapoptotic factor, an inhibitor of insulin secretion, and a suppressor of both tumor growth and metastatic potential through disruption of the Wnt signaling pathway. Research has demonstrated the existence of a direct correlation between the downregulation and/or absence of circulating sFRP-4 and the progression of several cancer types, including ovarian, endometrial, prostate and lung. Upregulation of circulating sFRP-4 has been linked to the deterioration of glucose metabolism in the case of type 2 diabetes, as well as the suppression of the keratinocyte hyperproliferation and epidermal hyperlasia that are definitive of psoriasis.

GASP-1

Growth and differentiation factor-associated serum protein-1 (GASP-1) is a secreted inhibitory TGF-β binding protein that contains multiple protease inhibitor structural domains. It is expressed primarily in the ovary, testis, and brain, and can act as a potent soluble inhibitor of myostatin and GDF-11, but not Activin A. The GASP-1 gene encodes a 571 amino acid protein that contains a 29 amino acid secretion signal sequence, and multiple identifiable structural features, including a WAP domain, a follistatin/Kazal domain, an immunoglobulin domain, two tandem Kunitz domains, and a netrin domain.

GCP-2 (CXCL6)

CXCL6, also known as GCP-2 in humans, is a connective tissue-derived CXC chemokine that can signal through the CXCR1 and CXCR2 receptors. Human GCP-2, which is cross-reactive with murine cells, selectively attracts neutrophils, and has also been shown to exert anti-angiogenic activity.

G-CSF

G-CSF is a hematopoietic growth factor that stimulates the development of committed progenitor cells to neutrophils and enhances the functional activities of the mature end-cell. It is produced in response to specific stimulation by a variety of cells, including macrophages, fibroblasts, endothelial cells and bone marrow stroma. G-CSF is being used clinically to facilitate hematopoietic recovery after bone marrow transplantation. Human and murine G-CSF are cross-species reactive.

GDF-2

GDF-2 belongs to the TGF-β cytokine family, whose members play an important role during prenatal development and postnatal growth, and the remodeling and maintenance of a variety of tissues and organs. GDF-2 is expressed mainly in non-parenchymal cells of the liver, but is also found in other various cells and tissues. GDF-2 can signal through the ALK1 receptor, and has been implicated in a number of physiologic events including the regulation of the hepatic reticuloendothelial system, glucose homeostasis, iron homeostasis, and the inhibition of angiogenesis.

GDF-5

GDF-5 is expressed in long bones during embryonic development and postnatally in articular cartilage. Mutations in the GDF-5 gene have been implicated in Hunter-Thompson type dwarfism and in Grebe Syndrome, which is characterized by short stature, extra digits, and short and deformed extremities. The mature and functional form of GDF-5 is a homodimer of two 120 amino-acid polypeptide chain (monomers) linked by a single disulfide bond. Each GDF-5 monomer is expressed as the C-terminal part of a precursor polypeptide, which also contains a 27 amino acid signal peptide and a 354 amino acid propeptide. This precursor undergoes intracellular dimerization, and upon secretion it is processed by a furin-type protease.

GDF-11

GDF-11 is a myostatin-homologous protein that acts as an inhibitor of nerve tissue growth. GDF-11 has been shown to suppress neurogenesis through a myostatin-like pathway, which involves the arrest of the progenitor cell cycle in the G1 phase. Similarities between myostatin and GDF-11, which are 90% identical in their amino acid sequence, suggest that the regulatory mechanisms responsible for maintaining proper tissue size during neural and muscular development might be the same.

GDNF

GDNF is a disulfide-linked, homodimeric neurotrophic factor structurally related to Artemin, Neurturin

and Persephin. These proteins belong to the cysteine-knot superfamily of growth factors that assume stable dimeric protein structures. GDNF signals through a multicomponent receptor system, composed of a RET and one of the four GFRα (α1-α4) receptors. GDNF specifically promotes dopamine uptake and survival, and morphological differentiation of midbrain neurons. Using a Parkinson's disease mouse model, GDNF has been shown to improve conditions such as bradykinesia, rigidity, and postural instability. The functional human GDNF ligand is a disulfide-linked homodimer consisting of two 15 kDa polypeptide chains called monomers. Each monomer contains seven conserved cysteine residues, including Cys-101, which is used for inter-chain disulfide bridging, and others that are involved in the intramolecular ring formation known as the cysteine knot configuration.

GRO-α/MGSA, GRO-β, GRO-γ

All three isoforms of GRO are CXC chemokines that can signal through the CXCR1 or CXCR2 receptors. The GRO proteins chemoattract and activate neutrophils and basophils. GRO/MGSA also stimulates mitogenesis in certain human melanoma cells.

HB-EGF

HB-EGF is an EGF-related growth factor that signals through the EGF receptor, and stimulates the proliferation of smooth muscle cells (SMC), fibroblasts, epithelial cells, and keratinocytes. HB-EGF is expressed in numerous cell types and tissues, including vascular endothelial cells, and vascular SMC, macrophages, skeletal muscle, keratinocytes, and certain tumor cells. The ability of HB-EGF to specifically bind heparin and heparin sulfate proteoglycans is distinct from other EGF-like molecules, and may be related to the enhanced mitogenic activity, relative to EGF, that HB-EGF exerts on smooth muscle cells. The human HB-EGF gene encodes a 208 amino acid transmembrane protein, which can be proteolytically cleaved to produce soluble HB-EGF.

Heregulin-β1

Neuregulin/Heregulin is a family of structurally related polypeptide growth factors derived from alternatively spliced genes (NRG1, NRG2, NRG3 and NRG4). To date, there are over 14 soluble and transmembrane proteins derived from the NRG1 gene. Proteolytic processing of the extracellular domain of the transmembrane NRG1 isoforms releases soluble growth factors. HRG1-β1 contains an Ig domain and an EGF-like domain; the latter is necessary for direct binding to receptor tyrosine kinases erb3 and erb4. This binding induces erb3 and erb4 heterodimerization with erb2, stimulating intrinsic kinase activity that leads to tyrosine phosphorylation. Although HRG1-β1's biological effects are still unclear, it has been found to promote motility and invasiveness of breast cancer cells, which may also involve up-regulation of expression and function of the autocrine motility-promoting factor (AMF).

HGF

HGF is a potent, mesenchymally-derived mitogen for mature parenchymal hepatocytes, and acts as a growth factor for a broad spectrum of tissues and cell types. HGF signals through a transmembrane tyrosine kinase receptor known as MET. Activities of HGF include the induction of cell proliferation, motility, morphogenesis, inhibition of cell growth, and enhancement of neuron survival. HGF is a crucial mitogen for liver regeneration processes, especially after partial hepatectomy and other liver injuries. Human and murine HGF are cross-reactive. Human HGF is expressed as a linear, polypeptide-precursor glycoprotein containing 697 amino acid residues. Proteolytic processing of this precursor generates the biologically active heterodimeric form of HGF, which consists of two polypeptide chains (α-chain and β-chain) held together by a single disulfide bond resulting in formation of a biologically active heterodimer. The α-chain consists of 463 amino acid residues and four kringle domains. The β-chain consists of 234 amino acid residues.

HPRG

Histidine-proline-rich glycoprotein (HPRG), a member of the Cystatin structural superfamily, is an abundantly secreted multi-domain glycoprotein. Although the physiological function is largely unknown, HPRG potentially regulates physiological processes such as cell adhesion and migration, fibrinolysis, coagulation, complement activation, immune complex clearance and phagocytosis of apoptotic cells. HPRG can exert anti-angiogneic activity by stimulating apoptosis of endothelial cells.

ICAM-1

ICAMs are members of the Ig superfamily of calcium-independent transmembrane glycoproteins. ICAM-1 is a ligand for the lymphocyte function-associated antigen (LFA) and Mac-1 integrins, as well as the

major human rhinovirus receptor. The primary function of ICAM-1 is to provide adhesion between endothelial cells and leukocytes after stress or injury. The human ICAM-1 gene codes for a 505 amino acid transmembrane glycoprotein containing a 29 amino acid cytoplasmic domain, a 23 amino acid transmembrane domain, and a 453 amino acid extracellular domain.

IFN-γ

IFN-γ is an acid-labile interferon produced by CD4 and CD8 T lymphocytes as well as activated NK cells. IFN-γ receptors are present in most immune cells, which respond to IFN-γ signaling by increasing the surface expression of class I MHC proteins. This promotes the presentation of antigen to T-helper (CD4+) cells. IFN-γ signaling in antigen-presenting cells, and antigen-recognizing B and T lymphocytes, regulates the antigen-specific phases of the immune response. Additionally, IFN-γ stimulates a number of lymphoid cell functions, including the anti-microbial and anti-tumor responses of macrophages, NK cells, and neutrophils. Human IFN-γ is species-specific and is biologically active only in human and primate cells.

IGF-BP1

IGF-BPs controls the distribution, function and activity of IGFs in various cell tissues and body fluids. Currently, there are seven named IGF-BPs that form high-affinity complexes with both IGF-I and IGF-II. IGF-BP1 is a 25.4 kDa, cysteine-rich, secreted protein expressed in the liver, deciduas, kidneys, and in amniotic fluid, where it is the most abundant IGF-BP. Levels of IGF-BP1 in serum are lowest after food consumption. IGF-BP1 binds to both IGF-I and IGF-II with equal affinity. Phosphorylated IGF-BP1 hinders IGF actions, whereas nonphosphorylated IGF-BP1 is stimulatory.

IGF-BP2

IGF-BPs control the distribution, function and activity of IGFs in various cell tissues and body fluids. Currently, there are seven named IGF-BPs that form high affinity complexes with both IGF-I and IGF-II. IGF-BP2 is a cysteine-rich, secreted protein produced by bone cells, and is most abundant in the brain. IGF-BP2 has been shown to inhibit IGF-II action in human breast and ovarian carcinoma cells.

IGF-BP3

IGF-BP3 is a 30 kDa, cysteine-rich secreted protein. It is the major IGF binding protein present in the plasma of human and animals, and it is also found in α-granules of platelets. In addition to its ability to modulate the activity of IGF-I and IGF-II, IGF-BP3 exerts inhibitory effects on follicle stimulating hormone (FSH) activity. Decreased plasma levels of IGF-BP3 often results in dwarfism, whereas elevated levels of IGF-BP3 may lead to acromegaly. The expression of IGF-BP3 in fibroblasts is stimulated by mitogenic growth factors, such as Bombesin, Vasopressin, PDGF, and EGF.

IGF-I, -I LR3, -II

The IGFs are mitogenic, polypeptide growth factors that stimulate the proliferation and survival of various cell types, including muscle, bone, and cartilage tissue *in vitro*. IGFs are predominantly produced by the liver, although a variety of tissues produce the IGFs at distinctive times. The IGFs belong to the Insulin gene family, which also contains insulin and relaxin. The IGFs are similar to insulin by structure and function, but have a much higher growth-promoting activity than insulin. IGF-II expression is influenced by placenta lactogen, while IGF-I expression is regulated by growth hormone. Both IGF-I and IGF-II signal through the tyrosine kinase type I receptor (IGF-IR), but IGF-II can also signal through the IGF-II/Mannose-6-phosphate receptor. Mature IGFs are generated by proteolytic processing of inactive precursor proteins, which contain N-terminal and C-terminal propeptide regions. Recombinant human IGF-I and IGF-II are globular proteins containing 70 and 67 amino acids, respectively, and 3 intra-molecular disulfide bonds. IGF-I LR3 is a recombinant analog of human IGF-I comprised of the complete IGF-I sequence, with an Arginine substitution for the third position Glutamic acid, and a 13 amino acid length N terminus peptide extension. Specifically engineered for higher biological potency *in vitro*, IGF-I LR3 has an increased half-life and a binding aversion to native proteins within the body that make it ideal for both research and large-scale culturing.

IL-1α

IL-1α is a non-secreted, proinflammatory cytokine produced in a variety of cells, including monocytes, tissue macrophages, keratinocytes, and other epithelial cells. Both IL-1α and IL-1β bind to the same receptor and have similar, if not identical, biological properties. These cytokines have a broad range of

activities including the stimulation of thymocyte proliferation by inducing IL-2 release, B-cell maturation and proliferation, mitogenic FGF-like activity and the release of prostaglandin and collagenase from synovial cells. However, whereas IL-1β is a secreted cytokine, IL-1α is predominantly a cell-associated cytokine.

IL-1β

IL-1β is a proinflammatory cytokine produced in a variety of cells, including monocytes, tissue macrophages, keratinocytes, and other epithelial cells. Both IL-1α and IL-1β bind to the same receptor and have similar, if not identical, biological properties. These cytokines have a broad range of activities including the stimulation of thymocyte proliferation by inducing IL-2 release, B-cell maturation and proliferation, mitogenic FGF-like activity, and the release of prostaglandin and collagenase from synovial cells. However, whereas IL-1β is a secreted cytokine, IL-1α is predominantly a cell-associated cytokine.

IL-6

IL-6 is a pleiotropic cytokine that plays an important role in host defense by regulating immune and inflammatory responses. Produced by T cells, monocytes, fibroblasts, endothelial cells and keratinocytes, IL-6 has diverse biological functions. It stimulates B cell differentiation and antibody production, synergizes with IL-3 in megakaryocyte development and platelet production, induces expression of hepatic acute-phase proteins, and regulates bone metabolism. IL-6 signals through the IL-6 receptor system that consists of two chains, IL-6R α and gp130. Murine IL-6 is inactive on human cells, while both human and murine are equally active on murine cells.

IL-8 (CXCL8)

IL-8 is a proinflammatory CXC chemokine that can signal through the CXCR1 and CXCR2 receptors. It is secreted by monocytes and endothelial cells. IL-8 chemoattracts and activates neutrophils.

IL-11

IL-11 is a multifunctional cytokine produced by stromal cells, such as fibroblasts, epithelial cells and osteoclasts. It is expressed in a wide variety of tissues, including thymus, lung, bone, connective tissue and central nervous system. IL-11 plays an important regulatory role in hematopoiesis by stimulating growth of myeloid, erythroid and megakaryocyte progenitor cells. It also regulates bone metabolism, inhibits production of proinflammatory cytokines, and protects against gastromucosal injury.

IL-12

IL-12 is a disulfide-linked heterodimeric protein (p70), composed of two subunits, p35 and p40, which are encoded by two different genes. Accumulating data indicates that p40 secretion precedes that of IL-12 expression. In addition, to its ability to covalently bind to p35 to form IL-12, p40 can bind to p19 to form IL-23, or it can form the homodimer designated IL-12 p80. Elevated levels of IL-12 p80 correlate to macrophage recruitment and increased inflammation in asthma and respiratory viral infection models.

IL-17A

The originally described IL-17 protein, now known as IL-17A, is a homodimer of two 136 amino acid chains that are secreted by activated T-cells, which act on stromal cells to induce production of proinflammatory and hematopoietic bioactive molecules. Today, IL-17 represents a family of structurally-related cytokines that share a highly conserved C-terminal region, but differ from one another in their N-terminal regions and in their distinct biological roles. The six known members of this family, IL-17A through IL-17F, are secreted as homodimers. IL-17A exhibits cross-species bioactivity between human and murine cells.

IL-17B

IL-17B is a disulfide-linked homodimer of two 161 amino acid polypeptide chains. It belongs to the IL-17 family of structurally-related cytokines that share a highly conserved C-terminal region, but differ from one another in their N-terminal regions and in their distinct biological roles. The six known members of this family, IL-17A through IL-17F, are secreted as homodimers. IL-17B is expressed by T-cells, and has been shown to stimulate release of TNF-α and IL-1β from cells of the monocyte lineage.

IL-17F

IL-17F, a member of the IL-17 family of structurally related cytokines, has been shown to stimulate the proliferation and activation of T-cells and PBMCs. IL-17F also regulates cartilage matrix turnover and inhibits angiogenesis. The mature human IL-17F is a homodimeric protein with a total weight of 30.1

kDa, consisting of two 133 amino acid residue chains.

IL-24
IL-24 is a secreted glycoprotein belonging to the IL-10 structural family of cytokines. It is produced by a variety of cell types, including B cells, CD4+ cells, NK cells, lymph node DCs, monocytes, and melanoma cells. IL-24 can signal through the IL20R1/IL20R2 and IL22R1/IL20R2 receptors to initiate a signaling cascade, which includes the induction of JAK1/STAT3 phosphorylation. IL-24 is, functionally, a pleiotropic protein, but is generally characterized as an anti-cancer cytokine that can selectively inhibit growth of a wide variety of human cancer cells through activities that include: the induction of differentiation and apoptosis; and the suppression of angiogenesis and cell proliferation.

IL-35
IL-35 (Interleukin-35) is a glycosylated, heterodimeric protein consisting of the p35 subunit from IL-12 (IL-12α) and the β subunit from IL-27 (EBI3). IL-35 can be expressed by regulatory T-cells (Tregs), macrophages, and certain trophoblast and dendritic cells. It is induced in response to inflammation, and generally acts as an inflammation suppressor. IL-35 suppresses inflammation by exerting multiple activities, including the induction of regulatory T-cells and the suppression of Th17 cells. Recombinant Human IL-35 produced from *HEK293 cells* is a glycosylated, heterodimeric protein that migrates as a diffuse band centered at an apparent molecular weight of about 60 kDa by SDS-PAGE analysis under non-reducing conditions.

IP-10
IP-10 is a CXC chemokine that signals through the CXCR3 receptor. IP-10 selectively chemoattracts Th1 lymphocytes and monocytes, and inhibits cytokine-stimulated hematopoietic progenitor cell proliferation. Additionally, it is angiostatic and mitogenic for vascular smooth muscle cells.

KGF
KGF (Keratinocyte Growth Factor) is one of 23 known members of the FGF family. Proteins of this family play a central role during prenatal development, postnatal growth, and the regeneration of a variety of tissues, by promoting cellular proliferation and differentiation. KGF/FGF-7 is a mitogen factor specific for epithelial cells and keratinocytes. KGF/FGF-7 signals through FGFR 2b. KGF/FGF-7 plays a role in kidney and lung development, as well as in angiogenesis and wound healing.

Klotho
Klotho is a glycosylated protein that plays an important role in the regulation of phosphate and calcium homeostasis. Human Klotho exists in both membrane bound and secreted forms, and is predominantly expressed in the kidney convoluted tubules, and, to a lesser extent, in the brain, reproductive organs, endocrine glands, urinary bladder, skeletal muscle, placenta, and colon. The full length transmembrane form has a large extracellular domain composed of two homologous subunits termed KL1 and KL2, which contain 516 and 439 amino acid residues, respectively. The predominant circulating form, which is derived from alternative RNA splicing, contains the KL1 subunit and constitutes the N-terminal sequence of transmembrane Klotho. A third Klotho protein of about 128 kDa has been identified in the blood and cerebrospinal fluid. This circulating protein arises from the action of an as yet unidentified protease, which cleaves transmembrane Klotho just above and/or within the plasma membrane. Klotho has been shown to play a key role in the signaling cascade of fibroblast growth factor-23 (FGF-23), a bone-derived hormone that acts in the kidney to inhibit phosphate reabsorption and vitamin D biosynthesis. Klotho promotes FGF-23 signaling through binding to FGFRI (IIIc) which converts this canonical FGF receptor into a specific receptor for FGF-23. In the absence of Klotho the function of FGF-23 is literally abolished.

Leptin
Encoded by the ob (obese) gene, Leptin is an adipose-derived cytokine that suppresses appetite and increases thermogenesis. Leptin exerts its anorectic effect via signaling through a hypothalamic receptor termed OB-R. Leptin has been shown to reduce body weight, food consumption, and plasma glucose levels in various *in vivo* models.

LIF
LIF is a pleiotrophic factor produced by multiple cell types, including T cells, myelomonocytic lineages,

fibroblasts, liver, heart and melanoma. LIF promotes long-term maintenance of embryonic stem cells by suppressing spontaneous differentiation. Other activities include the stimulation of acute phase protein synthesis by hepatocytes, stimulation of differentiation of cholinergic nerves, and suppression of adipogenesis by inhibiting the lipoprotein lipase in adipocytes. While human LIF is active on mouse cells and is widely used in the maintenance of murine ESC to prevent spontaneous differentiation, mouse LIF is not active on human cells due to its inability to bind to the human LIF receptor.

MANF

MANF is a secreted neurotrophic factor that is expressed in brain, neuronal and certain non-neuronal tissues. It has been shown to promote the survival, growth and function of dopamine-specific neurons. MANF and its structural homolog CDNF each contain a N-terminal, saposin-like, lipid-binding domain, and a carboxyl-terminal domain that is not homologous to previously characterized protein structures. MANF and CDNF can prevent 6-OHDA-induced degeneration of dopaminergic neurons by triggering survival pathways in a rat experimental model of Parkinson's disease.

Maspin

Maspin (mammary serine protease inhibitor) is a non-inhibitory serpin that is expressed predominantly in normal mammary epithelial cells, but at significantly reduced levels or absent in most breast carcinomas. It has the ability to block the growth, invasiveness, and metastatic potential of breast and lung tumors. This anti-tumor activity is achieved, in part, by the contribution of maspin to the inhibition of angiogenesis, and its ability to preferentially promote apoptosis of tumor cells.

MCPs

The MCP proteins are members of the CC chemokine family that signal through CCR2 and, with the exception of MCP-1, other CCR receptors. The MCP proteins chemoattract and activate monocytes, activated T cells, basophils, NK cells, and immature dendritic cells. The MCP family cross-reacts across species. MCP chemokines contain the four highly conserved cysteine residues present in CC chemokines. The human MCP genes each encode for a 99 amino acid polypeptide (98 a.a. for MCP-4) containing a putative N-terminal signal sequence of 23 amino acids. The mature human protein contains 76 amino acid residues (75 a.a. for MCP-4). The murine and rat homologs of MCP-1 contain an extended C-terminal sequence that results in a mature protein containing 125 amino acid residues. Mature murine MCP-5 contains 82 amino acid residues, including a fifth cysteine residue.

MD-2/LY96

Myeloid differentiation protein-2 (MD-2), also referred to as LY69, is an accessory glycoprotein secreted in hematopoietic, nervous, and reproductive tissues at various stages of development where it regulates innate immune responses to microbial pathogens through interaction with the extracellular domains of TLR-2 and TLR-4. The association of MD-2 with the extracellular domain of TLR-4, which is constitutively expressed in cells of the immune system, localizes TLR-4 to the cell surface and forms the TLR-4/MD-2 receptor complex necessary for signal transduction in response to inflammatory signals. The activation of TLR-4/MD-2 begins with the detection of LPS by circulating LPS-Binding Protein (LBP), which in turn facilitates an association between LPS and CD14 for the formation of a CD14/LPS complex that transports and presents LPS to the TLR-4/MD-2 signaling complex, and culminates in the activation of downstream signaling events. MD-2's possession of two dedicated functional domains allows for its simultaneous interaction with both TLR-4 and LPS, the major cell wall component of gram-negative bacteria that acts as the key ligand for TLR-4. Response to LPS is an intricate process that involves several co-stimulatory molecules, including myeloid differentiation factor 88 (MyD88), NF-κB, LBP, and CD14, in addition to TLR-4 and MD-2, and results in the secretion of proinflammatory cytokines and chemokines from the NF-κB, Wnt/β-catenin, and mitogen-activated protein kinase (MAPK) pathways. MD-2 interacts with TLR-2 in a similar, albeit far weaker, manner to initiate immune response to cell wall components of both gram-negative and gram-positive bacteria. Once secreted, MD-2 can polymerize into a heterogenous collection of large, disulfide-linked oligomers that are each able to bind several TLR-4 molecules, resulting in large clusters localized to the cell surface prior to activation.

Midkine

Midkine (MK) and the functionally-related protein pleiotrophin are heparin-binding neurotrophic factors that signal through the same receptor, known as anaplastic lymphoma kinase (ALK). MK plays an important regulatory role in epithelial-mesenchymal interactions during fetal development and in

postnatal lung development. MK chemoattracts embryonic neurons, neutrophils and macrophages, and exerts angiogenic, growth and survival activities during tumorigenesis.

MIG
MIG, a CXC chemokine, is produced by IFN-γ stimulated monocytes, macrophages and endothelial cells. It signals through the CXCR3 receptor. MIG selectively chemoattracts Th1 lymphocytes, and also exerts other activities, including inhibition of tumor growth, angiogenesis, and inhibition of colony formation of hematopoietic progenitors. Human MIG is active on murine cells.

MIP-1α
Both MIP-1α and MIP-1β are structurally and functionally related CC chemokines. They participate in host response to invading bacterial, viral, parasite and fungal pathogens, by regulating the trafficking, and activation state, of selected subgroups of inflammatory cells (e.g. macrophages, lymphocytes and NK cells). While both MIP-1α and MIP-1β exert similar effects on monocytes, their effect on lymphocytes differ; with MIP-1α selectively attracting CD8+ lymphocytes, and MIP-1β selectively attracting CD4+ lymphocytes. Additionally, MIP-1α and MIP-1β have also been shown to be potent chemoattractants for B cells, eosinophils and dendritic cells. Both human and murine MIP-1α and MIP-1β are active on human and murine hematopoietic cells.

MIP-5 (CCL15)
MIP-5 (CCL15) is a CC chemokine that is expressed in the heart, skeletal muscle and adrenal gland. MIP-5 primarily signals through the CCR1 receptor, but has also been found to bind to CCR3. MIP-5 is chemotactic towards T cells and monocytes.

MMPs (Matrix Metalloproteinases)
MMPs are a family of endoproteases that require zinc and calcium for expressing catalytic activity. These enzymes play a central role in the maintenance and remodeling of the extracellular matrix. Elevated expression of their activity, caused either by up-regulation of their expression or down-regulation of their cognate inhibitors, has been implicated in various degenerative disorders, including arthritis, cardiovascular disease, skeletal growth-plate disorders, and cancer metastasis.

MMP-1 is a secreted collagenase with specificity toward Type I, II, III, VII, and X collagens.
MMP-2 is a secreted collagenase with specificity toward Type IV, V, VII, and X collagens.
MMP-3 degrades fibronectin, laminin, collagens III, IV, and X, and cartilage proteoglycans.

Myostatin
Myostatin is a TGF-β family member that acts as an inhibitor of skeletal muscle growth. This muscle-specific cytokine interacts with Activin type I and type II receptors, and suppresses myoblast proliferation by arresting cell-cycle in the G1 phase. Suppression of myostatin activity facilitates muscle formation, and may be useful in reducing and/or preventing adiposity and type-2 diabetes. Myostatin activity can be blocked by the activin-binding protein follistatin, and by the propeptide of myostatin. The amino acid sequence of mature myostatin is extremely conserved across species, and is the same in murine, rat, chicken, turkey, porcine, and human. Myostatin is expressed as the C-terminal part of a precursor polypeptide, which also contains a short N-terminal signal sequence for secretion, and a propeptide of 243 amino acids. After dimerization of this precursor, the covalent bonds between the propeptide and the mature ligand are cleaved by furin-type proteases. However, the resulting two proteins remain associated through non-covalent interactions, and are secreted as a latent complex.

Myostatin-Propeptide
Mature Myostatin is obtained by proteolytic processing of a biologically-inactive precursor protein, which contains an N-terminal propeptide of 243 amino acid residues. Myostatin-Propeptide exhibits high binding affinity for myostatin, and has been shown to be a potent inhibitor of myostatin. Over-expression of myostatin-propeptide in mice resulted in large increases (up to 200%) in skeletal muscle mass, similar to those observed in myostatin knockout mice.

β-NGF
β-NGF is a neurotrophic factor structurally related to BDNF, NT-3 and NT-4. These proteins belong to the cysteine-knot family of growth factors that assume stable dimeric structures. β-NGF is a potent neurotrophic factor that signals through its receptor β-NGFR, and plays a crucial role in the development

and preservation of the sensory and sympathetic nervous systems. β-NGF also acts as a growth and differentiation factor for B lymphocytes, and enhances B-cell survival.

NOV

NOV is a member of the CCN family of secreted, cysteine-rich regulatory proteins. The full length NOV protein contains four structural domains that confer distinct, and sometimes opposing, biological activities. Elevated expression of NOV is associated with certain tumors, including Wilm's tumor and most nephroblastomas. However, in other tumor types and certain cancer cell lines, increased tumorgenicity and proliferation is correlated with decreased NOV expression. Additionally, NOV induces cell adhesion and cell migration by signaling through specific cell surface integrins, and by binding to heparin sulfate proteoglycans and to fibulin 1C. NOV has also been reported to exert proangiogenic activities.

Oncostatin M

Oncostatin M (OSM) is a growth and differentiation factor that participates in the regulation of neurogenesis, osteogenesis and hematopoiesis. Produced by activated T cells, monocytes and Kaposi's sarcoma cells, OSM can exert both stimulatory and inhibitory effects on cell proliferation. It stimulates the proliferation of fibroblasts, smooth muscle cells and Kaposi's sarcoma cells, but inhibits the growth of some normal and tumor cell lines. It also promotes cytokine release (e.g. IL-6, GM-CSF and G-CSF) from endothelial cells, and enhances the expression of low-density lipoprotein receptors in hepatoma cells. OSM shares several structural and functional characteristics with LIF, IL-6, and CNTF. Human OSM is active on murine cells. The human OSM gene encodes for a 252 amino acid polypeptide, containing 25 amino acid signal sequence for secretion and a 227 precursor protein. Proteolytic processing of this precursor removes an 18 amino acid C-terminal peptide, and generates the mature OSM form.

OPG (Osteoprotegerin)

OPG (Osteoprotegerin) is a member of the TNFR superfamily that can act as a decoy receptor for RANKL. Binding of soluble OPG to sRANKL inhibits osteoclastogenesis by interrupting the signaling between stromal cells and osteoclastic progenitor cells, thereby leading to excess accumulation of bone and cartilage. OPG is expressed in a wide variety of tissues, including the adult heart, lung, kidney, liver, spleen, prostate, lymph node, and bone marrow. OPG is secreted both as a monomeric and a dimeric protein. Its primary structure consists of seven distinct domains, four of which correspond to the extracellular cysteine-rich domains of TNFR proteins and constitute the soluble OPG.

OTOR

OTOR, also called Otoraplin and MIAL, is a secreted cytokine of the MIA/OTOR family. Members of this family, which include MIA, MIA2, and TANGO, share a Src homology-3 (SH3)-like domain. OTOR is predominantly expressed in the cochlea of the inner ear, and, to a lesser extent, in fetal brain tissue and some cartilage tissues. OTOR appears to be involved in early chondrogenesis of the otic capsule, which is required for normal inner ear development and auditory function.

PAI-1

Plasminogen Activator Inhibitor-1 (PAI-1, Serpin E1) is a member of the serpin family of serine protease inhibitors, and is the primary inhibitor of urokinase and tissue plasminogen activator (tPA). PAI-1 is expressed predominantly in adipose, liver and vascular tissues, but is also produced by certain tumor cells. Elevated levels of PAI-1 are associated with obesity, diabetes and cardiovascular disease, and increased production of PAI-1 is induced by various obesity-related factors, such as TNF-α, glucose, insulin, and very-low-density lipoprotein. The obesity-related elevation of PAI-1 levels, along with the consequential deficiency in plasminogen activators, can lead directly to increased risk of thrombosis and other coronary diseases. Accordingly, PAI-1 has been implicated as an important molecular link between obesity and coronary disease. PAI-1 can also specifically bind vitronectin (VTN) to form a stable active complex with an increased circulatory half-life relative to free PAI-1.

PDGF-AA, -AB, -BB

PDGFs are disulfide-linked dimers consisting of two 12.0-13.5 kDa polypeptide chains, designated PDGF-A and PDGF-B chains. The three naturally occurring PDGFs, PDGF-AA, PDGF-BB and PDGF-AB, are potent mitogens for a variety of cell types, including smooth muscle cells, connective tissue cells, bone and cartilage cells, and some blood cells. The PDGFs are stored in platelet α-granules, and are released upon platelet activation. The PDGFs are involved in a number of biological processes, including hyperplasia, chemotaxis, embryonic neuron development, and respiratory tubule epithelial

cell development. Two distinct signaling receptors used by PDGFs have been identified and named PDGFR-α and PDGFR-β. PDGFR-α is a high-affinity receptor for each of the three PDGF forms. On the other hand, PDGFR-β interacts with only PDGF-BB and PDGF-AB.

PDGF-CC

PDGF-CC The platelet-derived growth factor (PDGF) family of heparin- binding growth factors consists of five known members, denoted PDGF-AA, PDGF-BB, PDGF-AB, PDGF-CC and PDGF-DD. The mature and active form of these proteins, an anti-parallel, disulfide-linked dimer of two 12-14 kDa, polypeptide chains, is obtained through proteolytic processing of biologically inactive precursor proteins, which contain an N-terminal CUB domain and a PDGF/VEGF homologous domain. The PDGFs interact with two related protein tyrosine kinase receptors, PDGFR-α and PDGFR-β, and are potent mitogens for a variety of cell types, including smooth muscle cells, connective tissue cells, bone and cartilage cells, and certain tumor cells. They play an important role in a number of biological processes, including hyperplasia, chemotaxis, embryonic neuron development, and respiratory tubules' epithelial cell development. Mature PDGFs are stored in platelet α-granules, and are released upon platelet activation. PDGF-AA, -AB, -BB and –CC signal primarily through the PDGF-Rα receptor, whereas PDGF-DD interacts almost exclusively with the PDGF-Rβ receptor.

PECAM-1

PECAM is a transmembrane glycoprotein that belongs to the Ig-related superfamily of adhesion molecules. It is highly expressed at endothelial cell junctions, and is also expressed in platelets and most leukocyte sub-types. The primary function of PECAM-1 is the mediation of leukocyte- endothelial cell adhesion and signal transduction. PECAM-1 has been implicated in the pathogenesis of various inflammation-related disorders, including thrombosis, multiple sclerosis (MS), and rheumatoid arthritis. The human PECAM-1 gene codes for a 738 amino acid transmembrane glycoprotein that contains a 118 amino acid cytoplasmic domain, a 19 amino acid transmembrane domain, and a 574 amino acid extracellular domain.

PEDF

PEDF is a noninhibitory serpin with neurotrophic, anti-angiogenic, and anti-tumorigenic properties. It is a 50 kDa glycoprotein produced and secreted in many tissues throughout the body. A major component of the anti-angiogenic action of PEDF is the induction of apoptosis in proliferating endothelial cells. In addition, PEDF is able to inhibit the activity of angiogenic factors, such as VEGF and FGF-2. The neuroprotective effects of PEDF are achieved through suppression of neuronal apoptosis induced by peroxide, glutamate, or other neurotoxins. The recent identification of a lipase-linked cell membrane receptor for PEDF (PEDF-R) that binds to PEDF with high affinity (1) should facilitate further elucidation of the underlying mechanisms of this pluripotent serpin. To date, PEDF-R is the only signaling receptor known to be used by a serpin family member. The unique range of PEDF activities implicate it as a potential therapeutic agent for the treatment of vasculature-related neurodegenerative diseases, such as age-related macular degeneration (AMD) and proliferative diabetic retinopathy (PDR). PEDF also has the potential to be useful in the treatment of various angiogenesis-related diseases including a number of cancers.

PF-4 (CXCL4)

PF-4 (Platelet Factor-4, CXCL4) is a CXC chemokine that is expressed in megakaryocytes and stored in the α-granules of platelets. PF-4 is chemotactic towards neutrophils and monocytes, and has been shown to inhibit angiogenesis.

PlGF-1

PlGF-1 is an angiogenic factor that belongs to the cysteine-knot superfamily of growth factors. PlGF-1 is expressed in placental tissues, the colon, and mammary carcinomas. It signals through the VEGFR-1/FLT1 receptor, and stimulates endothelial cell proliferation and migration.

PlGF-2

PlGF-2 is an angiogenic factor that belongs to the cysteine-knot superfamily of growth factors. PlGF-2 is expressed in umbilical vein endothelial cells and placenta. It signals through the VEGFR-1/FLT1 receptor, and stimulates endothelial cell proliferation and migration. PlGF-2 also signals through Neuropilin (NP-1), and can bind with high affinity to heparin.

PlGF-3
PlGF-3 is an angiogenic factor that belongs to the cysteine-knot superfamily of growth factors. PlGF-3 is expressed exclusively in the placenta. It signals through the VEGFR-1/FLT1 receptor, and stimulates endothelial cell proliferation and migration. PlGF-3 lacks heparin binding affinity.

Prokineticin-2
Prokineticin-2 (PK2) is a cysteine-rich secreted protein that is expressed in the testis and, in lower levels, in the small intestine. PK2 regulates various biological functions, including gastrointestinal motility, angiogenesis and circadian rhythms. It is closely related to EG-VEGF (Prokineticin-1), and binds to two orphan B-protein-coupled receptors termed PK-R1 and PK-R2.

PTHrP
PTHrP is a polypeptide hormone produced by almost every tissue of the body. PTHrP is closely related to parathyroid hormone (PTH), which is secreted from the parathyroid gland, and plays a central role in regulating the extracellular concentrations of calcium and phosphorous.

RANTES (CCL5)
RANTES is a CC chemokine that can signal through the CCR1, CCR3, CCR5 and US28 (cytomegalovirus receptor) receptors. It is a chemoattractant towards monocytes, memory T cells (CD4+/CD45RO), basophils, and eosinophils. RANTES also has the capability to inhibit certain strains of HIV-1, HIV-2 and simian immunodeficiency virus (SIV).

Relaxin-2
Relaxin-2 is a peptide hormone structurally related to insulin, which is expressed in the placenta, decidua, prostate, and ovaries during pregnancy. Of the three known relaxin genes, relaxin-2 is the only relaxin known to circulate in the blood. Relaxin-2 binds specifically to the LGR7 and LGR8 receptors, previously identified as "orphan" G protein-coupled receptors. Signaling by relaxin-2 through its target receptors enhances the growth of pubic ligaments, and the ripening of the cervix during birth.

Relaxin-3
Relaxin-3 is a secreted protein structurally related to insulin that is expressed primarily in the brain and central nervous system. Relaxin-3 has been identified as the ligand for the GPCR135 receptor, previously known as "somatostatin-like" or "angiotensin-like" peptide receptor, and has also been identified for binding specifically to the LGR7 receptor, previously identified as an "orphan" G protein-coupled receptor. Signaling by relaxin-3 through its target receptors is, most likely, part of a CNS processing system, activated in response to signaling by neuropeptides and other factors. Intracerebroventricular injections of relaxin-3 have been shown to cause a significant increase of food intake and body weight in Wistar rats.

Resistin
Resistin belongs to a family of tissue-specific cytokines termed FIZZ (found in inflammatory zones) and RELM. The four known members of this family, resistin, RELMα, RELMβ, and RELMγ, share a highly conserved C-terminal domain, characterized by 10 cysteine residues with a unique spacing motif of C-X11-C-X8-C-X-C-X3-C-X10-C-X-C-X-C-X9-C-C. Resistin is an adipose-derived cytokine (adipokine) whose physiological function and molecular targets are largely unknown. Studies have shown that resistin suppresses insulin's ability to stimulate glucose uptake, and postulated that resistin might be an important link between obesity and Type 2 diabetes. Other studies have indicated that resistin expression is severely suppressed in obesity, and that it may act as a feedback regulator of Adipogenesis.

R-Spondin-3
The R-Spondin (Rspo) proteins belong to the Rspo family of Wnt modulators. Currently, the family consists of four structurally-related, secreted ligands (Rspo 1-4), all containing furin-like and thrombospondin structural domains. The Rspo proteins can interact with the Frizzled/LRP6 receptor complex in a manner that causes the stabilization, and resulting accumulation, of the intracellular signaling protein, β-catenin. This activity effectively activates and increases the subsequent nuclear signaling of β-catenin. R-Spondin can also bind to the previously discovered G-protein coupled receptors, LGR-4 and LGR-5. Rspo/β-catenin signaling can act as an inducer of the transformed phenotype, and can also regulate the proliferation and differentiation of certain stem cell populations.

Slit2-N
Slit2 is a member of the Slit family that signals through the Roundabout (Robo) receptor as a repellent for axon guidance and neuronal migration, and also acts as a chemoattractant to vascular endothelial cells and a chemotaxis inhibitor for leukocytes. Slit2 is expressed primarily in the fetal lung, kidney, and adult spinal cord, and to a lesser extent in the adult adrenal gland, thyroid and trachea. Slit2 is initially synthesized as a 1499 amino acid precursor, which is subsequently cleaved into N-terminal and C-terminal fragments, designated as Slit2-N and Slit2-C respectively. The neurodevelopment-related activities, as measured by the ability to repel olfactory bulb axons and to induce branching in dorsal root ganglia axons, are contained only in the N-terminal fragment.

SPARC/Osteonectin
SPARC/Osteonectin is a secreted, evolutionarily-conserved, collagen-binding glycoprotein that is involved in a variety of cellular activities. It is highly expressed in tissues undergoing morphogenesis, remodeling and wound repair. SPARC/Osteonectin and its related peptides bind to numerous proteins of the extracellular matrix (ECM), affect ECM protein expression, influence cellular adhesion and migration, and modulate growth factor- induced cell proliferation and angiogenesis. SPARC/Osteonectin consists of three domains: an N-terminal acidic region that binds calcium ions with low affinity, a module containing two EF-hand motifs that bind calcium with high affinity, and a cysteine-rich follistatin-like domain.

TGF-α
TGF-α is an EGF-related polypeptide growth factor that signals through the EGF receptor, and stimulates the proliferation of a wide range of epidermal and epithelial cells. It is produced by monocytes, keratinocytes, and various tumor cells. TGF-α induces transformation anchorage independence in cultured cells. Human, murine and rat TGF-α are cross-species reactive.

TGF-β
TGF-β The three mammalian isoforms of TGF-β, TGF-β1, -β2, and -β3, signal through the same receptor and elicit similar biological responses. They are multifunctional cytokines that regulate cell proliferation, growth, differentiation and motility, as well as synthesis and deposition of the extracellular matrix. They are involved in various physiological processes, including embryogenesis, tissue remodeling and wound healing. They are secreted predominantly as latent complexes, which are stored at the cell surface and in the extracellular matrix. The release of biologically active TGF-β isoform from a latent complex involves proteolytic processing of the complex and/or induction of conformational changes by proteins such as thrombospondin-1.

TGF-β1 is the most abundant isoform secreted by almost every cell type. It was originally identified for its ability to induce phenotypic transformation of fibroblasts, and recently it has been implicated in the formation of skin tumors.

TGF-β2 has been shown to exert suppressive effects on IL-2-dependent T-cell growth, and may also have an autocrine function in enhancing tumor growth by suppressing immuno-surveillance of tumor development.

TGF-β3's physiological role is still unknown, but its expression pattern suggests a role in the regulation of certain development processes.

Thrombomodulin
Thrombomodulin (TM, CD141, THBD) is an endothelial cell-expressed, transmembrane glycoprotein that can form a complex with the coagulation factor, thrombin. The thrombomodulin/thrombin complex converts protein C to its activated form, protein Ca, which in turn proteolytically cleaves and deactivates factor Va and factor VIIIa, two essential components of the coagulation mechanism. This inactivation reduces the generation of additional thrombin, and thereby effectively prevents continued coagulation. Reduced levels of thrombomodulin can correlate with the pathogenesis of certain cardiovascular diseases, such as atherosclerosis and thrombosis. However, the serum levels of the truncated circulating form of thrombomodulin are typically elevated during inflammation and in the presence of various inflammatory-related diseases. The thrombomodulin protein contains 575 amino acids, including an 18 a.a. signal sequence, a 497 a.a. extracellular domain, a 24 a.a. transmembrane sequence, and a 36 a.a. cytoplasmic region.

TIMP-1
TIMP-1 is an extracellular inhibitor of MMPs, including MMP-1, -2, -3, -7, -8, -9, -10, -11, -12, -13, and -16. It belongs to the I35 (TIMP) family of irreversible protease inhibitors that function as key modulators

of extracellular matrix degradation during tissue development and remodeling. TIMP-1 can also act through an MMP-independent mechanism to promote erythropoiesis by stimulating proliferation and differentiation of erythroid progenitors.

TIMP-2

TIMP-2 is an extracellular inhibitor of MMPs, including MMP-1, -2, -3, -7, -8, -9, -10, -12, -13, -14, -15, -16 and -19. It belongs to the I35 (TIMP) family of irreversible protease inhibitors that function as key modulators of extracellular matrix degradation during tissue development and remodeling. TIMP-2 can also act through a MMP-independent mechanism inhibiting endothelial cell proliferation *in vitro* and demonstrates anti-angiogenic activities *in vivo*.

Tissue Factor

Tissue Factor is a transmembrane glycoprotein of the cytokine receptor superfamily that acts as a receptor for coagulation factor VII (fVII) to trigger initiation of the coagulation cascade in response to vascular injury. Expression of tissue factor occurs constitutively within most extravascular and perivascular cells and at high levels within critical organs and tissue. Tissue factor is not normally expressed freely on the surface of circulating blood cells due to its pro-coagulant effect, but is instead stored on the surface of mononuclear and endothelial cells in microparticles that can shed into circulation in response to vascular injury, pro-inflammatory cytokines, or microbial ligands. Tissue factor can also be shed into circulation by cancer cells where its expression in a number of cancer types has been linked to tumor progression, metastatic potential, thrombosis, and angiogenesis. Expression of tissue factor has been shown to be inducible by select cytokines in a number of cell types, including IL-1β and TNF-α in vascular endothelial cells and macrophages, and TNF-α, IL-6, and FGF-Basic in monocytes, among others.

TL-1A

TL-1A belongs to the TNF superfamily of ligands. It is expressed predominantly in endothelial cells, and to a lesser extent in the placenta, lung, kidney, skeletal muscle, pancreas, small intestine and colon. TL-1A inhibits endothelial cell proliferation and angiogenesis, and has been shown to induce NF-κB activation, caspase activity, and apoptosis in responding cell lines. TL-1A interacts with TNFRSF25/DR3 receptor, but can also bind to a decoy receptor TNFRSF21/DR6.

TLR-4

Characterized by N-terminal domains rich in leucine repeats and C-terminal intracellular Toll/interleukin (IL)-1 (TIL) domains, the structurally-related members of the Toll-like Receptor (TLR) family are abundantly expressed, transmembrane signaling receptors that play integral roles in the induction of innate and adaptive immunity. As members of the larger family of pattern recognition receptors, TLRs recognize and respond to pathogen-associated molecular patterns (PAMPs) and endogenous damage-associated molecular patterns (DAMPs) by initiating activation of NF-κB and the release of inflammatory mediators. Constitutively expressed in cells of the immune system, TLR-4 is secreted at significantly amplified levels in response to high concentrations of LPS, the major cell wall component of gram-negative bacteria that acts as the key ligand for TLR-4 inflammatory response. TLR-4 mounts a defense against infection through an intricate process involving interaction with co-stimulatory molecules, such as myeloid differentiation factor 88 (MyD88), NF-κB, LPS-Binding Protein (LBP), CD14, and MD-2, and the instigation of intracellular signaling cascade that prompts the NF-κB, Wnt/β-catenin, and mitogen-activated protein kinase (MAPK) pathways to secrete proinflammatory cytokines and chemokines. Myeloid differentiation protein-2 (MD-2), also referred to as LY96, is essential to TLR-4-mediated response to LPS due to its binding of both the extracellular domain of TLR-4, which serves to localize TLR-4 on the cell surface, and LPS to form the TLR-4/MD-2/LPS complex, which can be used for the in vitro removal of endotoxin from biological samples. The activation of TLR-4/MD-2 begins with the detection of LPS by circulating LBP, which in turn facilitates an association between LPS and CD14 for the formation of a CD14-LPS complex that transports and presents LPS to the TLR-4/MD-2 signaling complex, and culminates in the activation of downstream signaling events. Inflammatory response can also be triggered by the formation of a heterodimeric complex between TLR-6 and TLR-4, the internalization of which results in NF-κB-dependent secretion of CXCL1, as well as the production of proinflammatory cytokines, such as IL-1β, and the production of inflammatory regulating chemokines, such as CXCL2, CCL5 and CCL9. Considering TLR-4's connections to immunity, inflammatory response, proliferation, apoptosis and angiogenesis, it is no surprise that irregular expression of TLR-4 has been linked to various malignant cell types, a number of autoimmune conditions genetically linked to psoriasis, and a number of other diseases.

TNF-α
TNF-α is a pleiotropic pro-inflammatory cytokine secreted by various cells, including adipocytes, activated monocytes, macrophages, B cells, T cells and fibroblasts. It belongs to the TNF family of ligands, and signals through two receptors, TNFR1 and TNFR2. TNF-α is cytotoxic to a wide variety of tumor cells, and is an essential factor in mediating the immune response against bacterial infections. TNF-α also plays a role in the induction of septic shock, autoimmune diseases, rheumatoid arthritis, inflammation, and diabetes. Human and murine TNF-α demonstrate significant cross- species reactivity. TNF-α exists in two forms; a type II transmembrane protein, and a mature soluble protein. The TNF-α transmembrane protein is proteolitically cleaved to yield a soluble, biologically active, 17 kDa TNF-α, which forms a non-covalently linked homotrimer in solution.

TNF-β
TNF-β is a potent mediator of inflammatory and immune responses. It belongs to the TNF family of ligands, and signals through TNFR1 and TNFR2. TNF-β is produced by activated T and B lymphocytes, and has similar activities to TNF-α. Like TNF-α, TNF-β is involved in the regulation of various biological processes, including cell proliferation, differentiation, apoptosis, lipid metabolism, coagulation, and neurotransmission. TNF-β is secreted as a soluble polypeptide, but can form heterotrimers with lymphotoxin-β, which effectively anchors the TNF-β to the cell surface. TNF-β is cytotoxic to a wide range of tumor cells.

TWEAK
TWEAK belongs to the TNF family of ligands, and signals through TWEAKR, also known as TNFRSF12A. TWEAK is expressed in a variety of tissues, including the adult heart, pancreas, skeletal muscle, small intestine, spleen and peripheral blood lymphocytes. TWEAK has the ability to induce NF-κB activation and chemokine secretion, and to exert an apoptotic activity in certain cells, such as HT-29 human adenocarcinoma cells when cultured in the presence of IFN-γ. TWEAK also promotes proliferation and migration of endothelial cells. The human TWEAK gene encodes for a 249 amino acid type II transmembrane protein, which contains a 21 amino acid cytoplasmic domain, a 21 amino acid transmembrane domain, and a 207 amino acid extracellular domain.

VAP-1
VAP-1 is a type II membrane cell adhesion protein belonging to the copper/topaquinone oxidase family. It is primarily expressed on the high endothelial venules of peripheral lymph nodes and on hepatic endothelia. VAP-1 can catalyze the oxidative deamination of low molecular weight amines, and plays an important role in the migration of lymphocytes to inflamed tissue. Inhibition of VAP-1 can protect against inflammation-related damage to certain injured tissues. Additionally, VAP-1 can function as a significant prognostic marker for certain cancers and cardiovascular diseases.

Vaspin
Vaspin is a newly described adipocytokine expressed predominantly in visceral white adipose tissues. Structure analysis of vaspin predicts the presence of three β-sheets, nine α-helices, and one central loop, which are distinctive structural features of Serpin family members. The serpins are irreversible ("suicidal") serine-protease inhibitors, characterized by having more than 30% sequence homology with α1-antitrypsin and a conserved tertiary structure, which contains an exposed reactive center loop that acts as a pseudo-substrate for the target proteinase. Members of this family play an important role in a number of fundamental biological processes, including blood coagulation, fibrinolysis, complement activation, angiogenesis, inflammation, and tumor suppression. In humans, the serpins represent approximately 2% of total serum proteins, of which 70% is α1-antitrypsin. Vaspin exhibits 40.2% sequence identity with α1-antitrypsin. Yet, its protease inhibitory activity is still unknown. Vaspin mRNA expression in visceral fat is positively correlated with BMI and percent of body fat. Administration of vaspin to obese mice improved glucose tolerance and insulin sensitivity, reflected by normalized blood glucose levels. It also led to the reversal of altered expression of diabetes- relevant adipocytokines, including leptin, adiponectin, resistin, and TNF-α. These findings suggest a potential clinical use for Vaspin in ameliorating certain aberrations seen in the diabetic/obesity metabolic syndrome.

VCAM-1
VCAM is a 110 kDa, cell surface integral membrane glycoprotein that belongs to the Ig-related superfamily of adhesion molecules. The primary function of VCAM-1 is the mediation of leukocyte-endothelial cell adhesion and signal transduction. VCAM-1 may play a vital role in the development of several diseases,

including atherosclerosis and rheumatoid arthritis. The human VCAM-1 gene codes for a 715 amino acid transmembrane glycoprotein containing a 19 amino acid cytoplasmic domain, a 22 amino acid transmembrane domain, and a 674 amino acid extracellular domain.

VEGF-A

VEGF-A (Vascular Endothelial Growth Factor-A) is a potent growth and angiogenic cytokine. It stimulates proliferation and survival of endothelial cells, and promotes angiogenesis and vascular permeability. Expressed in vascularized tissues, VEGF plays a prominent role in normal and pathological angiogenesis. Substantial evidence implicates VEGF in the induction of tumor metastasis and intra-ocular neovascular syndromes. VEGF signals through the three receptors; *fms*-like tyrosine kinase (flt-1), KDR gene product (the murine homolog of KDR is the flk-1 gene product) and the flt4 gene product.

VEGF-B

VEGF-B, a member of the VEGF family, is a potent growth and angiogenic cytokine. It promotes DNA synthesis in endothelial cells, helps regulate angiogenesis and vascular permeability, and inhibits apoptosis in certain smooth muscle cells and neurons. VEGF-B is expressed in all tissues except the liver. It forms cell surface-associated, disulfide-linked homodimers, and can form heterodimers with VEGF-A. There are two known isoforms, formed by alternative splicing, which have been designated $VEGF\text{-}B_{167}$ and $VEGF\text{-}B_{186}$. Both forms have identical amino-terminal sequences encoding a cysteine knot-like structural motif, but differ in their carboxyl-terminal domains. Both VEGF-B isoforms signal only through the VEGFR1 receptor.

VEGF-C

VEGF-C, a member of the VEGF/PDGF family of structurally related proteins, is a potent angiogenic cytokine. It promotes endothelial cell growth, promotes lymphangiogesis, and can also affect vascular permeability. VEGF-C is expressed in various tissues, but is not produced in peripheral blood lymphocytes. It forms cell surfaced-associated, non- covalent, disulfide-linked homodimers, and can bind and activate both VEGFR-2 (flk1) and VEGFR-3 (flt4) receptors. During embryogenesis, VEGF-C may play a role in the formation of the venous and lymphatic vascular systems. Both VEGF-C and VEGF-D are over-expressed in certain cancers, and the resulting elevated levels of VEGF-C or VEGF-D tend to correlate with increased lymphatic metastasis.

VEGF-D

VEGF-D, a member of the VEGF/PDGF family of structurally related proteins, is a potent angiogenic cytokine. It promotes endothelial cell growth, promotes lymphangiogesis, and can also affect vascular permeability. VEGF-D is highly expressed in the lung, heart, small intestine and fetal lung, and at lower levels in the skeletal muscle, colon, and pancreas. It forms cell surface-associated, non-covalent, disulfide-linked homodimers, and can bind and activate both VEGFR-2 (flk1) and VEGFR-3 (flt4) receptors. During embryogenesis, VEGF-D may play a role in the formation of the venous and lymphatic vascular systems. It also participates in the growth and maintenance of differentiated lymphatic endothelium in adults. Both VEGF-C and VEGF-D are over-expressed in certain cancers, and the resulting elevated levels of VEGF-C or VEGF-D tend to correlate with increased lymphatic metastasis.

WISP-3

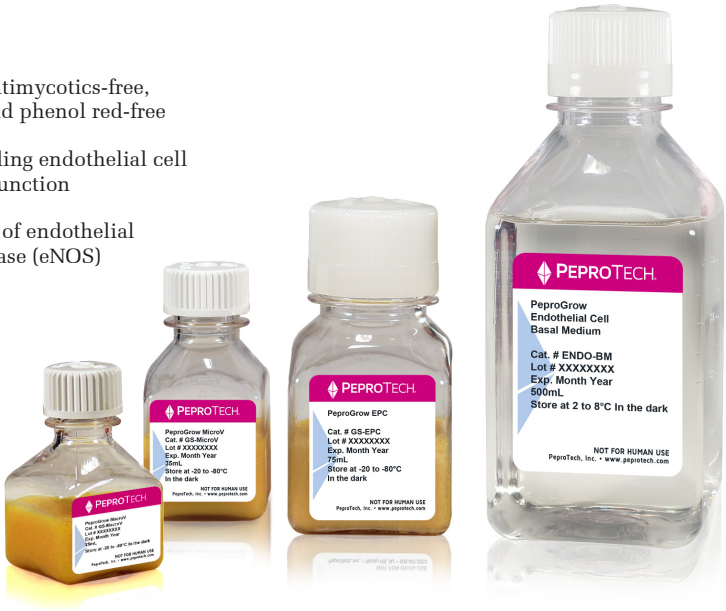
WISP-3 is a member of the CCN family of secreted cysteine rich regulatory proteins. It is predominantly expressed but it is also found with weaker expression in the placenta, ovary, prostate, small intestine, and skeletally-derived cells. WISP-3 is required for normal postnatal skeletal growth and cartilage homeostasis.

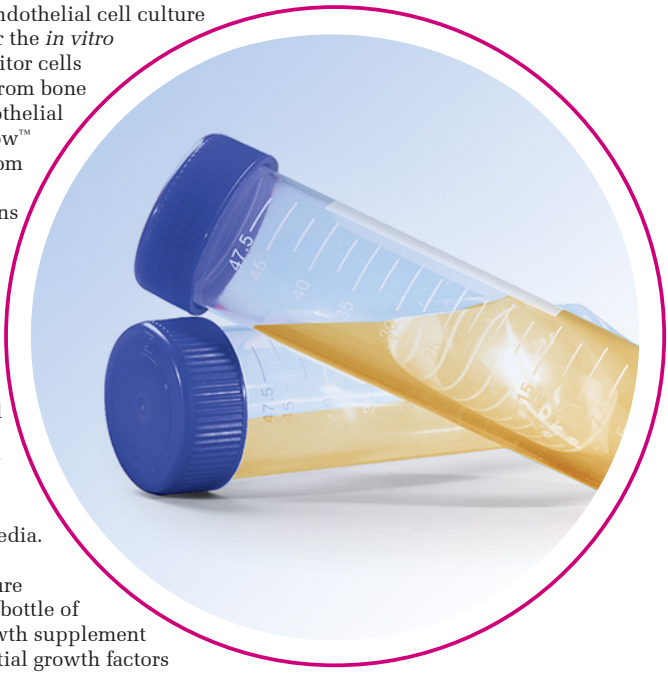
PeproGrow™ Endothelial Media

Maintenance Media for Endothelial Cells

PeproGrow™ EPC, PeproGrow™ MacroV, and PeproGrow™ MicroV

- Complete media
- Antibiotic-free, antimycotics-free, antifungal-free, and phenol red-free
- Maintain outstanding endothelial cell morphology and function
- Increased activity of endothelial nitric oxide synthase (eNOS)





PeproTech offers three separate endothelial cell culture media formulations developed for the *in vitro* cultivation of: endothelial progenitor cells (EPCs; PeproGrow EPC) derived from bone marrow or peripheral blood; endothelial cells from large vessels (PeproGrow™ MacroV); and endothelial cells from small vessels (PeproGrow™ MicroV). These media formulations maintain outstanding endothelial cell morphology and function, and increase the activity of endothelial nitric oxide synthase (eNOS), which account for a specific, crucial marker for endothelial cells. By doing this, the media provide an optimal cell culture environment for macrovascular and microvascular endothelial cells, as well as for EPCs; growing cells at rates that exceed commercially available media.

PeproTech's endothelial cell culture media kit is supplied as a 500mL bottle of basal medium and a separate growth supplement bottle that contains various essential growth factors and components for endothelial cell growth. Adding the growth supplement to the basal medium results in the complete culture medium. PeproTech's endothelial media do not contain antibiotics, antimycotics, antifungals, or phenol red, as these components can cause cell stress and masking effects that may reduce complete medium shelf life and influence experimental results.

Media Products

PeproGrow™ EPC Kit (ENDO-BM & GS-EPC)		**Catalog #700-EPC**
Basal Medium	ENDO-BM	500mL
Growth Supplement EPC	GS-EPC*	75mL

PeproGrow™ MacroV Kit (ENDO-BM & GS-MacroV)		**Catalog #700-MacroV**
Basal Medium	ENDO-BM	500mL
Growth Supplement MacroV	GS-MacroV*	25mL

PeproGrow™ MicroV Kit (ENDO-BM & GS-MicroV)		**Catalog #700-MicroV**
Basal Medium	ENDO-BM	500mL
Growth Supplement MicroV	GS-MicroV*	35mL

* Contains FBS

PeproGrow™ hESC Medium

Maintenance Medium for hESCs and hiPSCs

- Phenol red-free and insulin-free
- Complete and chemically-defined
- High plating efficiency
- Increased activity of endothelial nitric oxide synthase (eNOS)
- Developed in collaboration with and used in the Rutgers Stem Cell Training Course

PeproGrow™ hESC is a serum- and phenol red-free medium of a complete, chemically-defined formulation designed for feeder-free maintenance and expansion of both human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs) using Corning Matrigel® as a surface-coating matrix. This medium is intended for the culturing of hESCs and iPSCs in the undifferentiated, pluripotent state (SSEA4+/Oct4+), and demonstrates less than 15% spontaneous differentiation as indicated by flow cytometry. The proprietary formulation of the medium includes relevant growth factors, such as FGF2 (FGF-basic), but does not contain the insulin found in the majority of other hESC/ iPSC media currently available on the market. PeproGrow hESC, which was designed and developed by PeproTech in collaboration with the Stem Cell Training Course at Rutgers University, is supplied as a 100mL, or 500mL, bottle of basal medium and a separate, lyophilized growth factor component.

PeproGrow™ hESC Medium Kit

PeproGrow™ hESC Medium 500mL Kit		HESC-500
Basal Medium	BM-HESC-500	500mL
Growth Factor Component	GF-HESC-500	Vial for 500mL Basal Medium

PeproGrow™ hESC Medium 100mL Kit		HESC-100
Basal Medium	BM-HESC-100	100mL
Growth Factor Component	GF-HESC-100	Vial for 100mL Basal Medium

PeproTech Premium Products

As the leading manufacturer of a complete range of cytokine products, PeproTech proudly provides our customers with an extensive selection of products that guarantee the highest standards of quality, consistency, reliability and value.

Understanding the special needs of stem cell researchers, PeproTech has expanded our production capabilities in order to provide our customers with the following premium lines of products:

Animal-Free Product Line:

PeproTech's Animal-Free product line is designed to minimize potential risks that can arise from trace amounts of animal-derived adventitious agents, such as viruses, TSE/BSE and unknowns.

Expressed in *E.coli* bacterial culture, Animal-Free recombinant proteins are manufactured in a dedicated Animal-Free facility under strict Animal-Free conditions where the production protocols have been modified to include only Animal-Free reagents and chemicals. All product contact material is also qualified as animal component-free.

PeproTech's Animal-Free proteins maintain identical high biological activity and purity to the corresponding proteins that are produced using standard techniques that equal or enhance the performance of animal-derived media formulations. Products are lyophilized, with a minimum amount of salt, and without additives or preservatives added.

PEPROGMP®

Helping unlock the promise of Cellular Therapies and Regenerative Medicines

In response to our clients' needs, and the requirements of the cell and gene therapy markets, we are pleased to introduce our new state-of-the-art manufacturing facility in Cranbury, NJ.

The rapidly evolving field of regenerative medicine offers exciting opportunities to develop new solutions for an array of diseases, injuries, and genetic disorders. With the recent expansion of our new facility, PeproTech is able to meet the demand of the advancing markets in cell, gene, and tissue therapies. Our 65,000 square foot facility has significantly more square footage for GMP cleanrooms and supports the manufacturing of our bacterial expressed GMP products and expansion into cell culture derived GMP products.

Consistent with U.S. federal requirements and best practices for cell therapy, gene therapy, and tissue-engi- neered products for clinical applications, PeproGMP® Cytokines are manufactured and tested in compliance with relevant US FDA GMP (Good Manufacturing Practices) regulations and the ISO 9001 quality management systems standard, without the use of animal-derived materials.

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- Environmental Monitoring
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- Controlled Processes
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- Master Quality & Supply Agreement
- Aseptic Techniques & Sterile Filtration
- Management Review
- Compliant and Recall Procedures

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