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(54) **Title:** COMPOSITIONS AND METHODS FOR IDENTIFYING AND TREATING METASTATIC SMALL BOWEL NEUROENDOCRINE TUMORS

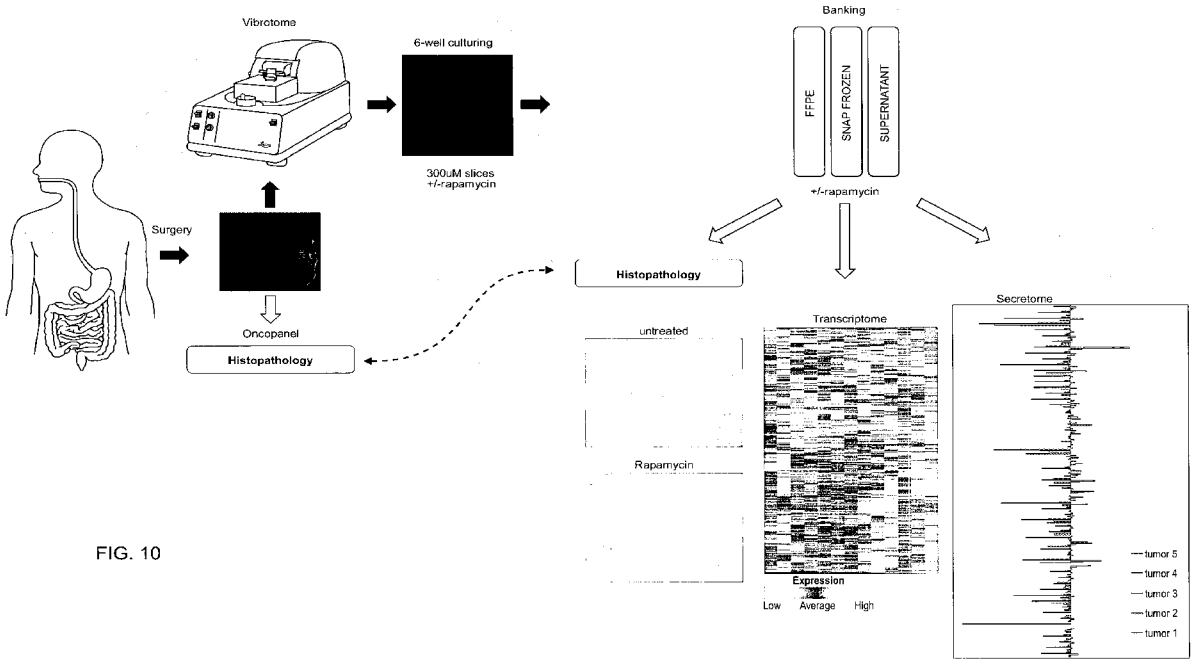



FIG. 10

(57) **Abstract:** The present invention relates to compositions and methods for identifying and treating metastatic small bowel neuroendocrine tumors.

*[Continued on next page]*

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# COMPOSITIONS AND METHODS FOR IDENTIFYING AND TREATING METASTATIC SMALL BOWEL NEUROENDOCRINE TUMORS

## RELATED APPLICATIONS

This application claims the benefit of priority under 35 U.S.C. § 119(e) to U.S. Provisional Application No: 62/534,764, filed July 20, 2017, which is incorporated herein by reference in its entirety.

## GOVERNMENT LICENSE RIGHTS

This invention was made with government support under grant number CA151532 awarded by the National Institutes of Health and under grant number P50CA127003 awarded by the National Cancer Institute. The government has certain rights in the invention.

## BACKGROUND OF THE INVENTION

Small bowel neuroendocrine tumors, although rare across the cancer landscape (1 per 100,000), are the most common carcinoid tumor and originate most frequently in the terminal ileum. Tumor growth in SINET is slow and many patients present with advanced disease for which few treatment options exist. Prior to the invention described herein, this slow growing characteristic has meant that the development of *in vitro* and *in vivo* models to study this tumor type have been extremely limited. The lack of cell lines and animal models has been a major obstacle in the development of therapeutic agents for advanced carcinoid tumors. As such, prior to the invention described herein, there was a pressing need to identify disease models and therapeutic modalities for small bowel neuroendocrine tumors.

## SUMMARY OF THE INVENTION

The invention is based, at least in part, upon the identification of secreted protein biomarkers of metastatic neuroendocrine tumors. Accordingly, provided herein is a method of determining whether a small bowel neuroendocrine tumor (SINET) in a subject, e.g., a human subject, will metastasize. First, a test sample is obtained from a subject having or at risk of developing SINET. The expression level of at least one SINET-associated gene in the test sample is determined. Next, the expression level of the SINET-associated gene in the test

sample is compared with the expression level of the SINET-associated gene in a reference sample. Finally, it is determined that the SINET in the subject will metastasize if the expression level of the SINET-associated gene in the test sample is differentially expressed as compared to the level of the SINET-associated gene in the reference sample.

Also provided is a method of determining whether a neuroendocrine tumor (NET) in a subject, e.g., a human subject, will metastasize. First, a test sample is obtained from a subject having or at risk of developing NET. The expression level of at least one NET-associated gene in the test sample is determined. Next, the expression level of the NET-associated gene in the test sample is compared with the expression level of the NET-associated gene in a reference sample. Finally, it is determined that the NET in the subject will metastasize if the expression level of the NET-associated gene in the test sample is differentially expressed as compared to the level of the NET-associated gene in the reference sample.

For example, the expression level of the SINET-associated gene in the test sample is upregulated (i.e., increased) by at least 2 fold, at least 3 fold, at least 4 fold, at least 5 fold, at least 6 fold, at least 7 fold, at least 8 fold, at least 9 fold, at least 10 fold, at least 15 fold, at least 20 fold, at least 25 fold, at least 30 fold, at least 35 fold, at least 40 fold, at least 45 fold, at least 50 fold, at least 60 fold, at least 70 fold, at least 80 fold, at least 90 fold, at least 100 fold, at least 125 fold, at least 150 fold, at least 175 fold, at least 200 fold, at least 250 fold, at least 300 fold, at least 350 fold, at least 400 fold or at least 500 fold as compared to the level of the SINET-associated gene in the reference sample.

Alternatively, the expression level of the SINET-associated gene in the test sample is downregulated (i.e., decreased) by at least 2 fold, at least 3 fold, at least 4 fold, at least 5 fold, at least 6 fold, at least 7 fold, at least 8 fold, at least 9 fold, at least 10 fold, at least 15 fold, at least 20 fold, at least 25 fold, at least 30 fold, at least 35 fold, at least 40 fold, at least 45 fold, at least 50 fold, at least 60 fold, at least 70 fold, at least 80 fold, at least 90 fold, at least 100 fold, at least 125 fold, at least 150 fold, at least 175 fold, at least 200 fold, at least 250 fold, at least 300 fold, at least 350 fold, at least 400 fold or at least 500 fold as compared to the level of the SINET-associated gene in the reference sample.

In some cases, the test sample is obtained from resected SINET tissue, which is comprised of tumor tissue, stromal tissue, and all tissue encompassing the tumor

microenvironment. In another aspect, the test sample is obtained from blood or plasma. For example, the sample comprises circulating tumor cells.

The reference sample is obtained from immortalized healthy normal control fibroblastic cell lines (e.g., normal human fibroblasts), benign SINET tissue, or cancerous SINET tissue. For example, the reference sample is obtained from healthy normal tissue from the same individual as the test sample. Alternatively, the reference sample is obtained from one or more healthy normal tissues from different individuals.

Optionally, the sample comprises deoxyribonucleic acid (DNA) or ribonucleic acid (RNA). Exemplary SINET-associated genes comprise interleukin-2 (IL-2), IL-6, IL-12, IL-13, vascular endothelial growth factor (VEGF), and monocyte chemoattractant protein-1 (MCP-1), urinary plasminogen activator (uPA), hepatocyte growth factor (HGF), RANTES (regulated on activation, normal T cell expressed and secreted, alternatively, chemokine (C-C motif) ligand 5; alternatively CCL5), and Eotaxin. It is determined that the SINET in the subject will metastasize if the expression level of the SINET-associated gene in the test sample is higher than the level of the SINET-associated gene in the reference sample.

In other cases, the SINET-associated gene comprises stem cell factor (SCF) and soluble epidermal growth factor receptor (sEGFR), granulocyte macrophage colony stimulating factor (GM-CSF), soluble vascular endothelial growth factor receptor 2 (sVEGFR2), and soluble interleukin 6 receptor, alpha (sIL-6RA). It is determined that the SINET in the subject will metastasize if the expression level of the SINET-associated gene in the test sample is lower than the level of the SINET-associated gene in the reference sample.

For example, the expression level of the SINET-associated gene is detected via an Affymetrix Gene Array hybridization, next generation sequencing, ribonucleic acid sequencing (RNA-seq), a real time reverse transcriptase polymerase chain reaction (real time RT-PCR) assay, immunohistochemistry (IHC), immunofluorescence, methylation-specific PCR, or a bead-based multiplex assay.

In some cases, the subject is treated with a chemotherapeutic agent, radiation therapy, cryotherapy, hormone therapy, or immunotherapy. For example, the chemotherapeutic agent comprises a somatostatin analog. For example, the somatostatin analogue comprises octreotide long-acting repeatable (LAR).

In one aspect, the method also includes administering an inhibitor of the SINET-associated gene with a higher level of expression compared to the level of the SINET-associated gene in the reference sample, thereby treating the small bowel neuroendocrine tumor. In some cases, the chemotherapeutic agent is administered in combination with an inhibitor of the SINET-associated gene. For example, tumor-specific inhibitors, e.g., Rapamycin, Cabozantinib, and/or Erlotinib, are combined with stroma inhibition via Withaferin A.

For example, the inhibitor comprises a polypeptide, a small molecule inhibitor, RNA interference (RNAi), an antibody, or any fragment or combination thereof. In one aspect, the antibody or antibody fragment is partially humanized, fully humanized, or chimeric. Optionally, the antibody or antibody fragment comprises a nanobody, an Fab, an Fab', an (Fab')2, an Fv, a single-chain variable fragment (ScFv), a diabody, a triabody,a tetrabody, a Bis-scFv, a minibody, an Fab2, an Fab3 fragment, or any combination thereof.

An exemplary small molecule inhibitor comprises an inhibitor of NFκB activity. In some cases, the inhibitor of NFκB activity comprises Withaferin A (WFA). Other suitable inhibitors include those that target the janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway, e.g., Ruxolitinib and Momelotinib. Preferably, expression levels of VEGF, IL-6, and MCP-1 are increased following administration of WFA.

For example, compositions described herein are administered at a concentration of 1-1000 nM, e.g., about 1 nM, about 5 nM, about 10 nM, abot 25 nM, about 50 nM, about 75 nM, about 100 nM, about 200 nM, about 300 nM, about 400 nM, about 500 nM, about 600 nM, about 700 nM, about 800 nM, about 900 nM, or about 1000 nM.

Also provided is a composition for predicting whether a SINET will metastasize comprising a SINET-associated gene, wherein the SINET-associated gene comprises IL-2, IL-6, IL-12, IL-13, VEGF, MCP-1, uPA, HGF, RANTES, Eotaxin, GM-CSF, sVEGFR2, and sIL-6RA synthesized complementary deoxyribonucleic acid (cDNA). In some cases, the composition comprises or further comprises SCF, sEGFR, GM-CSF, sVEGFR2, and/or sIL-6RA synthesized cDNA. Preferably, the SINET-associated gene is immobilized on a solid support. In some cases, the SINET-associated gene is linked to a detectable label. Exemplary detectable labels include a fluorescent label, a luminescent label, a chemiluminescent label, a radiolabel, a SYBR Green label, or a Cy3-label.

Additionally, provided is a composition for predicting whether a SINET will metastasize comprising a SINET-associated gene, wherein the SINET-associated gene comprises a neuroendocrine tumor (NET) specific gene, a cell surface eithelial gene, a stimulant of malignant cell proliferation gene, an epithelial-mesenchymal transition gene, a metastatic transition gene, a mesenchymal-like gene, a matrix-remodeling gene, a hypoxia and angiogenesis gene, a tumor-associated stromal cells and myofibroblasts gene, and a stromal-specific gene.

For example, the NET-specific gene comprises CGA. In another example, the cell surface eithelial gene is selected from the group consisting of CD34, PECAM1, MUC16, KRT5, KRT6A, KRT6B, and KRT17. Exemplary stimulants of malignant cell proliferation genes include EGFR, FGF-2, HGF, and CXCL12. For example, the epithelial-mesenchymal gene is selected from the group consisting of CDH1, CDH2, MMP1, MMP2, ITGA1, ITGA2, ITGA3 ITGA5, ITGA7, ITGA11, TGFB1, and TGFBI. Suitable metastatic transition genes are selected from the group consisting of YAP1, HAS2, LOX, S100A4, GSTP1, and CD81. For example, the mesenchymal-like gene is selected from the group consisting of THY1, NT5E, ENG, and CD44. An exemplary matrix-remodeling gene includes FAP. For example, the hypoxia and angiogenesis gene is selected from the group consisting of VEGFA, VEGFC, HIF1A, and CAV1. In one aspect, the tumor-associated stromal cells and myofibroblasts gene is selected from the group consisting of PDGFRA, PDGFRB, NRG1, TNC, POSTN, and ACTA2. Finally, in one example, the stromal-specific gene is selected from the group consisting of P4HA1, P4HB, and VIM.

Also provided is a kit comprising a package with a SINET-associated gene, wherein the SINET-associated gene comprises IL-2, IL-6, IL-12, IL-13, VEGF, MCP-1, uPA, HGF, RANTES, Eotaxin, GM-CSF, sVEGFR2, and sIL-6RA, and instructions for use thereof in the evaluation of SINET progression and metastasis.

Further provided is a kit comprising a package with a SINET-associated gene, wherein the SINET-associated gene comprises a neuroendocrine tumor (NET) specific gene, a cell surface eithelial gene, a stimulant of malignant cell proliferation gene, an epithelial-mesenchymal transition gene, a metastatic transition gene, a mesenchymal-like gene, a matrix-remodeling gene, a hypoxia and angiogenesis gene, a tumor-associated stromal cells and myofibroblasts gene, and a stromal-specific gene. For example, the NET-specific gene comprises CGA. In another example, the cell surface eithelial gene is selected from the group

consisting of CD34, PECAM1, MUC16, KRT5, KRT6A, KRT6B, and KRT17. In one aspect, the stimulants of malignant cell proliferation gene is selected from the group consisting of EGFR, FGF-2, HGF, and CXCL12. For example, the epithelial-mesenchymal gene is selected from the group consisting of CDH1, CDH2, MMP1, MMP2, ITGA1, ITGA2, ITGA3 ITGA5, ITGA7, ITGA11, TGFB1, and TGFBI. In one example, the metastatic transition gene is selected from the group consisting of YAP1, HAS2, LOX, S100A4, GSTP1, and CD81. In another example, the mesenchymal-like gene is selected from the group consisting of THY1, NT5E, ENG, and CD44. For example, the matrix-remodeling gene comprises FAP. In one example, the hypoxia and angiogenesis gene is selected from the group consisting of VEGFA, VEGFC, HIF1A, and CAV1. In another example, the tumor-associated stromal cells and myofibroblasts gene is selected from the group consisting of PDGFRA, PDGFRB, NRG1, TNC, POSTN, and ACTA2. In one aspect, the stromal-specific gene is selected from the group consisting of P4HA1, P4HB, and VIM.

Ex vivo methods of screening therapeutic agents for a neuroendocrine tumor are carried out by establishing an ex vivo organotypic neuroendocrine tumor tissue slice culture; administering a candidate compound to the culture; and determining that the candidate compound is a therapeutic agent for a neuroendocrine tumor if the candidate compound inhibits the neuroendocrine tumor. Preferably, the proliferation of the neuroendocrine tumor is inhibited. For example, proliferation is evaluated using a bromodeoxyuridine (BrDU) cell proliferation assay. In some cases, the method also includes detecting a level of a candidate compound-specific target. In other cases, the method also provides for detecting a level of a secretory protein in supernatant of the tissue slices prior to and following administration of the candidate compound. In another case, the method includes gene expression measurements via RNA-Seq transcriptional profiling of the tissue slices prior to and following administration of the candidate compound.

An exemplary candidate compound comprises a mechanistic target of rapamycin (mTOR) inhibitor comprising Rapamycin. Other suitable compounds include Erlotinib Cabozantinib, a histone deacetylase (HDAC) inhibitor, and a cyclin-dependendt kinase (CDK) 4/6 inhibitor.

In some cases, the compound is administered at a dose of 1-1000 nM, e.g., about 1 nM, about 5 nM, about 10 nM, about 25 nM, about 50 nM, about 75 nM, about 100 nM, about 200

nM, about 300 nM, about 400 nM, about 500 nM, about 600 nM, about 700 nM, about 800 nM, about 900 nM, or about 1000 nM. For example, the Rapamycin is administered at a dose of 100 nM. In one aspect, the composition is administered at least one time per month, e.g., twice per month, once per week, twice per week, once per day, twice per day, every 8 hours, every 4 hours, every 2 hours, or every hour.

In one aspect, administration of Rapamycin results in a reduction of secretion of osteoponin, IL-16, VEGF, MCP-1, IL-10, macrophage inflammatory protein-1a (MIP-1a), MIP-1b, interferon-γ-inducible protein-10 (IP-10), IL-8, and/or urinary plasminogen activator (uPA) from the culture.

Also provided is a method of generating a neuroendocrine-associated fibroblast culture comprising: obtaining a tissue sample from a patient; dissecting the tissue sample into pieces; enzymatically disaggregating the tissue sample; mechanically disaggregating the tissue sample; filtering and centrifuging the cells; plating the cells on polymer tissue culture plates; and culturing the cells, thereby generating a neuroendocrine-associated fibroblast culture. In one aspect, the tissue sample is enzymatically disaggregated with collagenase II at 2 mg/ml. In some cases, the tissue sample is mechanically disaggregated with an 18-guage needle and syringe.

Definitions

Unless specifically stated or obvious from context, as used herein, the term "about" is understood as within a range of normal tolerance in the art, for example within 2 standard deviations of the mean. "About" can be understood as within 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, 0.05%, or 0.01% of the stated value. Unless otherwise clear from context, all numerical values provided herein are modified by the term "about."

The term "antineoplastic agent" is used herein to refer to agents that have the functional property of inhibiting a development or progression of a neoplasm in a human, e.g., a small bowel neuroendocrine tumor. Inhibition of metastasis is frequently a property of antineoplastic agents.

By "agent" is meant any small compound, antibody, nucleic acid molecule, or polypeptide, or fragments thereof.

By "alteration" is meant a change (increase or decrease) in the expression levels or activity of a gene or polypeptide as detected by standard art-known methods such as those described herein. As used herein, an alteration includes at least a 1% change in expression

levels, e.g., at least a 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% change in expression levels. For example, an alteration includes at least a 5%-10% change in expression levels, preferably a 25% change, more preferably a 40% change, and most preferably a 50% or greater change in expression levels.

By "ameliorate" is meant decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease.

The term "antibody" (Ab) as used herein includes monoclonal antibodies, polyclonal antibodies, multispecific antibodies (*e.g.*, bispecific antibodies), and antibody fragments, so long as they exhibit the desired biological activity. The term "immunoglobulin" (Ig) is used interchangeably with "antibody" herein.

An "isolated antibody" is one that has been separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody is purified: (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight; (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator; or (3) to homogeneity by SDS-PAGE under reducing or non-reducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody *in situ* within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

The basic four-chain antibody unit is a heterotetrameric glycoprotein composed of two identical light (L) chains and two identical heavy (H) chains. An IgM antibody consists of 5 of the basic heterotetramer unit along with an additional polypeptide called J chain, and therefore contain 10 antigen binding sites, while secreted IgA antibodies can polymerize to form polyvalent assemblages comprising 2-5 of the basic 4-chain units along with J chain. In the case of IgGs, the 4-chain unit is generally about 150,000 daltons. Each L chain is linked to an H chain by one covalent disulfide bond, while the two H chains are linked to each other by one or more disulfide bonds depending on the H chain isotype. Each H and L chain also has regularly spaced intrachain disulfide bridges. Each H chain has at the N-terminus, a variable domain ($V_H$)

followed by three constant domains ($C_H$) for each of the α and γ chains and four $C_H$ domains for μ and ε isotypes. Each L chain has at the N-terminus, a variable domain ($V_L$) followed by a constant domain ($C_L$) at its other end. The $V_L$ is aligned with the $V_H$ and the $C_L$ is aligned with the first constant domain of the heavy chain ($C_H1$). Particular amino acid residues are believed to form an interface between the light chain and heavy chain variable domains. The pairing of a $V_H$ and $V_L$ together forms a single antigen-binding site. For the structure and properties of the different classes of antibodies, see, *e.g.*, Basic and Clinical Immunology, 8th edition, Daniel P. Stites, Abba I. Terr and Tristram G. Parslow (eds.), Appleton & Lange, Norwalk, Conn., 1994, page 71, and Chapter 6.

The L chain from any vertebrate species can be assigned to one of two clearly distinct types, called kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains ($C_L$). Depending on the amino acid sequence of the constant domain of their heavy chains ($C_H$), immunoglobulins can be assigned to different classes or isotypes. There are five classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, having heavy chains designated alpha (α), delta (δ), epsilon (ε), gamma (γ) and mu (μ), respectively. The γ and α classes are further divided into subclasses on the basis of relatively minor differences in $C_H$ sequence and function, *e.g.*, humans express the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2.
The term "variable" refers to the fact that certain segments of the V domains differ extensively in sequence among antibodies. The V domain mediates antigen binding and defines specificity of a particular antibody for its particular antigen. However, the variability is not evenly distributed across the 110-amino acid span of the variable domains. Instead, the V regions consist of relatively invariant stretches called framework regions (FRs) of 15-30 amino acids separated by shorter regions of extreme variability called "hypervariable regions" that are each 9-12 amino acids long. The variable domains of native heavy and light chains each comprise four FRs, largely adopting a β-sheet configuration, connected by three hypervariable regions, which form loops connecting, and in some cases forming part of, the β-sheet structure. The hypervariable regions in each chain are held together in close proximity by the FRs and, with the hypervariable regions from the other chain, contribute to the formation of the antigen-binding site of antibodies (see Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)). The constant domains are not

involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody dependent cellular cytotoxicity (ADCC).

The term "hypervariable region" when used herein refers to the amino acid residues of an antibody that are responsible for antigen binding. The hypervariable region generally comprises amino acid residues from a "complementarity determining region" or "CDR" (*e.g.*, around about residues 24-34 (L1), 50-56 (L2) and 89-97 (L3) in the $V_L$, and around about 31-35 (H1), 50-65 (H2) and 95-102 (H3) in the $V_H$ when numbered in accordance with the Kabat numbering system; Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)); and/or those residues from a "hypervariable loop" (*e.g.*, residues 24-34 (L1), 50-56 (L2) and 89-97 (L3) in the $V_L$, and 26-32 (H1), 52-56 (H2) and 95-101 (H3) in the $V_H$ when numbered in accordance with the Chothia numbering system; Chothia and Lesk, J. Mol. Biol. 196:901-917 (1987)); and/or those residues from a "hypervariable loop"/CDR (*e.g.*, residues 27-38 (L1), 56-65 (L2) and 105-120 (L3) in the $V_L$, and 27-38 (H1), 56-65 (H2) and 105-120 (H3) in the $V_H$ when numbered in accordance with the IMGT numbering system; Lefranc, M.P. et al. Nucl. Acids Res. 27:209-212 (1999), Ruiz, M. e al. Nucl. Acids Res. 28:219-221 (2000)). Optionally the antibody has symmetrical insertions at one or more of the following points 28, 36 (L1), 63, 74-75 (L2) and 123 (L3) in the $V_L$, and 28, 36 (H1), 63, 74-75 (H2) and 123 (H3) in the $V_H$ when numbered in accordance with AHo; Honneger, A. and Plunkthun, A. J. Mol. Biol. 309:657-670 (2001)).

By "germline nucleic acid residue" is meant the nucleic acid residue that naturally occurs in a germline gene encoding a constant or variable region. "Germline gene" is the DNA found in a germ cell (i.e., a cell destined to become an egg or in the sperm). A "germline mutation" refers to a heritable change in a particular DNA that has occurred in a germ cell or the zygote at the single-cell stage, and when transmitted to offspring, such a mutation is incorporated in every cell of the body. A germline mutation is in contrast to a somatic mutation which is acquired in a single body cell. In some cases, nucleotides in a germline DNA sequence encoding for a variable region are mutated (i.e., a somatic mutation) and replaced with a different nucleotide.

The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single

antigenic site. Furthermore, in contrast to polyclonal antibody preparations that include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they may be synthesized uncontaminated by other antibodies. The modifier "monoclonal" is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies useful in the present invention may be prepared by the hybridoma methodology first described by Kohler et al., Nature, 256:495 (1975), or may be made using recombinant DNA methods in bacterial, eukaryotic animal or plant cells (see, *e.g.*, U.S. Pat. No. 4,816,567). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson *et al.*, Nature, 352:624-628 (1991) and Marks *et al.*, J. Mol. Biol., 222:581-597 (1991), for example.

Monoclonal antibodies include "chimeric" antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (see U.S. Pat. No. 4,816,567; and Morrison *et al.*, Proc. Natl. Acad. Sci. USA, 81:6851-6855 (1984)). Also provided are variable domain antigen-binding sequences derived from human antibodies. Accordingly, chimeric antibodies of primary interest herein include antibodies having one or more human antigen binding sequences (*e.g.*, CDRs) and containing one or more sequences derived from a non-human antibody, *e.g.*, an FR or C region sequence. In addition, chimeric antibodies of primary interest herein include those comprising a human variable domain antigen binding sequence of one antibody class or subclass and another sequence, *e.g.*, FR or C region sequence, derived from another antibody class or subclass. Chimeric antibodies of interest herein also include those containing variable domain antigen-binding sequences related to those described herein or derived from a different species, such as a non-human primate (*e.g.*, Old World Monkey, Ape, etc). Chimeric antibodies also include primatized and humanized antibodies. Furthermore, chimeric antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine

antibody performance. For further details, see Jones *et al.*, Nature 321:522-525 (1986); Riechmann *et al.*, Nature 332:323-329 (1988); and Presta, Curr. Op. Struct. Biol. 2:593-596 (1992).

A "humanized antibody" is generally considered to be a human antibody that has one or more amino acid residues introduced into it from a source that is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization is traditionally performed following the method of Winter and co-workers (Jones *et al.*, Nature, 321:522-525 (1986); Reichmann *et al.*, Nature, 332:323-327 (1988); Verhoeyen *et al.*, Science, 239:1534-1536 (1988)), by substituting import hypervariable region sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Pat. No. 4,816,567) wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species.

A "human antibody" is an antibody containing only sequences present in an antibody naturally produced by a human. However, as used herein, human antibodies may comprise residues or modifications not found in a naturally occurring human antibody, including those modifications and variant sequences described herein. These are typically made to further refine or enhance antibody performance.

An "intact" antibody is one that comprises an antigen-binding site as well as a $C_L$ and at least heavy chain constant domains, $C_H$ 1, $C_H$ 2 and $C_H$ 3. The constant domains may be native sequence constant domains (*e.g.*, human native sequence constant domains) or amino acid sequence variant thereof. Preferably, the intact antibody has one or more effector functions. An "antibody fragment" comprises a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies (see U.S. Pat. No. 5,641,870; Zapata *et al.*, Protein Eng. 8(10): 1057-1062 [1995]); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

The phrase "functional fragment or analog" of an antibody is a compound having qualitative biological activity in common with a full-length antibody. For example, a functional fragment or analog of an anti-IgE antibody is one that can bind to an IgE immunoglobulin in

such a manner so as to prevent or substantially reduce the ability of such molecule from having the ability to bind to the high affinity receptor, $Fc_{\varepsilon}RI$.

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, and a residual "Fc" fragment, a designation reflecting the ability to crystallize readily. The Fab fragment consists of an entire L chain along with the variable region domain of the H chain ($V_H$), and the first constant domain of one heavy chain ($C_H$ 1). Each Fab fragment is monovalent with respect to antigen binding, *i.e.*, it has a single antigen-binding site. Pepsin treatment of an antibody yields a single large $F(ab')_2$ fragment that roughly corresponds to two disulfide linked Fab fragments having divalent antigen-binding activity and is still capable of cross-linking antigen. Fab' fragments differ from Fab fragments by having additional few residues at the carboxy terminus of the $C_H1$ domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. $F(ab')_2$ antibody fragments originally were produced as pairs of Fab' fragments that have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

The "Fc" fragment comprises the carboxy-terminal portions of both H chains held together by disulfides. The effector functions of antibodies are determined by sequences in the Fc region, which region is also the part recognized by Fc receptors (FcR) found on certain types of cells.

"Fv" is the minimum antibody fragment that contains a complete antigen-recognition and -binding site. This fragment consists of a dimer of one heavy- and one light-chain variable region domain in tight, non-covalent association. From the folding of these two domains emanate six hypervariable loops (three loops each from the H and L chain) that contribute the amino acid residues for antigen binding and confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

"Single-chain Fv" also abbreviated as "sFv" or "scFv" are antibody fragments that comprise the $V_H$ and $V_L$ antibody domains connected into a single polypeptide chain. Preferably, the sFv polypeptide further comprises a polypeptide linker between the $V_H$ and $V_L$ domains that enables the sFv to form the desired structure for antigen binding. For a review of

sFv, see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenburg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994); Borrebaeck 1995, *infra*.

The term "diabodies" refers to small antibody fragments prepared by constructing sFv fragments (see preceding paragraph) with short linkers (about 5-10 residues) between the $V_H$ and $V_L$ domains such that inter-chain but not intra-chain pairing of the V domains is achieved, resulting in a bivalent fragment, *i.e.*, fragment having two antigen-binding sites. Bispecific diabodies are heterodimers of two "crossover" sFv fragments in which the $V_H$ and $V_L$ domains of the two antibodies are present on different polypeptide chains. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger *et al.*, Proc. Natl. Acad. Sci. USA, 90:6444-6448 (1993).

As used herein, an antibody that "internalizes" is one that is taken up by (*i.e.*, enters) the cell upon binding to an antigen on a mammalian cell (*e.g.*, a cell surface polypeptide or receptor). The internalizing antibody will of course include antibody fragments, human or chimeric antibody, and antibody conjugates. For certain therapeutic applications, internalization *in vivo* is contemplated. The number of antibody molecules internalized will be sufficient or adequate to kill a cell or inhibit its growth, especially an infected cell. Depending on the potency of the antibody or antibody conjugate, in some instances, the uptake of a single antibody molecule into the cell is sufficient to kill the target cell to which the antibody binds. For example, certain toxins are highly potent in killing such that internalization of one molecule of the toxin conjugated to the antibody is sufficient to kill the infected cell.

As used herein, an antibody is said to be "immunospecific," "specific for" or to "specifically bind" an antigen if it reacts at a detectable level with the antigen, preferably with an affinity constant, $K_a$, of greater than or equal to about $10^4$ $M^{-1}$, or greater than or equal to about $10^5$ $M^{-1}$, greater than or equal to about $10^6$ $M^{-1}$, greater than or equal to about $10^7$ $M^{-1}$, or greater than or equal to $10^8$ $M^{-1}$. Affinity of an antibody for its cognate antigen is also commonly expressed as a dissociation constant $K_D$, and in certain embodiments, HuM2e antibody specifically binds to M2e if it binds with a $K_D$ of less than or equal to $10^{-4}$ M, less than or equal to about $10^{-5}$ M, less than or equal to about $10^{-6}$ M, less than or equal to $10^{-7}$ M, or less than or equal to $10^{-8}$ M. Affinities of antibodies can be readily determined using conventional

techniques, for example, those described by Scatchard *et al.* (*Ann. N.Y. Acad. Sci. USA* 51:660 (1949)).

Binding properties of an antibody to antigens, cells or tissues thereof may generally be determined and assessed using immunodetection methods including, for example, immunofluorescence-based assays, such as immuno-histochemistry (IHC) and/or fluorescence-activated cell sorting (FACS).

An antibody having a "biological characteristic" of a designated antibody is one that possesses one or more of the biological characteristics of that antibody which distinguish it from other antibodies. For example, in certain embodiments, an antibody with a biological characteristic of a designated antibody will bind the same epitope as that bound by the designated antibody and/or have a common effector function as the designated antibody.
The term "antagonist" antibody is used in the broadest sense, and includes an antibody that partially or fully blocks, inhibits, or neutralizes a biological activity of an epitope, polypeptide, or cell that it specifically binds. Methods for identifying antagonist antibodies may comprise contacting a polypeptide or cell specifically bound by a candidate antagonist antibody with the candidate antagonist antibody and measuring a detectable change in one or more biological activities normally associated with the polypeptide or cell.

Antibody "effector functions" refer to those biological activities attributable to the Fc region (a native sequence Fc region or amino acid sequence variant Fc region) of an antibody, and vary with the antibody isotype. Examples of antibody effector functions include: C1q binding and complement dependent cytotoxicity; Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (*e.g.*, B cell receptor); and B cell activation.

By "binding to" a molecule is meant having a physicochemical affinity for that molecule.

By "control" or "reference" is meant a standard of comparison. In one aspect, as used herein, "changed as compared to a control" sample or subject is understood as having a level that is statistically different than a sample from a normal, untreated, or control sample. Control samples include, for example, cells in culture, one or more laboratory test animals, or one or more human subjects. Methods to select and test control samples are within the ability of those in the art. An analyte can be a naturally occurring substance that is characteristically expressed or produced by the cell or organism (e.g., an antibody, a protein) or a substance produced by a

reporter construct (e.g, β-galactosidase or luciferase). Depending on the method used for detection, the amount and measurement of the change can vary. Determination of statistical significance is within the ability of those skilled in the art, e.g., the number of standard deviations from the mean that constitute a positive result.

"Detect" refers to identifying the presence, absence, or amount of the agent (e.g., a nucleic acid molecule, for example deoxyribonucleic acid (DNA) or ribonucleic acid (RNA)) to be detected.

By "detectable label" is meant a composition that when linked (e.g., joined - directly or indirectly) to a molecule of interest renders the latter detectable, via, for example, spectroscopic, photochemical, biochemical, immunochemical, or chemical means. Direct labeling can occur through bonds or interactions that link the label to the molecule, and indirect labeling can occur through the use of a linker or bridging moiety which is either directly or indirectly labeled. Bridging moieties may amplify a detectable signal. For example, useful labels may include radioactive isotopes, magnetic beads, metallic beads, colloidal particles, fluorescent labeling compounds, electron-dense reagents, enzymes (for example, as commonly used in an enzyme-linked immunosorbent assay (ELISA)), biotin, digoxigenin, or haptens. When the fluorescently labeled molecule is exposed to light of the proper wave length, its presence can then be detected due to fluorescence. Among the most commonly used fluorescent labeling compounds are fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, p-phthaldehyde and fluorescamine. The molecule can also be detectably labeled using fluorescence emitting metals such as 152 Eu, or others of the lanthanide series. These metals can be attached to the molecule using such metal chelating groups as diethylenetriaminepentacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA). The molecule also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the chemiluminescent-tagged molecule is then determined by detecting the presence of luminescence that arises during the course of chemical reaction. Examples of particularly useful chemiluminescent labeling compounds are luminol, isoluminol, theromatic acridinium ester, imidazole, acridinium salt and oxalate ester.

A "detection step" may use any of a variety of known methods to detect the presence of nucleic acid (e.g., methylated DNA) or polypeptide. The types of detection methods in which probes can be used include Western blots, Southern blots, dot or slot blots, and Northern blots.

As used herein, the term "diagnosing" refers to classifying pathology or a symptom, determining a severity of the pathology (e.g., grade or stage), monitoring pathology progression, forecasting an outcome of pathology, and/or determining prospects of recovery.

By the terms “effective amount” and “therapeutically effective amount” of a formulation or formulation component is meant a sufficient amount of the formulation or component, alone or in a combination, to provide the desired effect. For example, by “an effective amount”is meant an amount of a compound, alone or in a combination, required to ameliorate the symptoms of a disease, e.g., cancer, relative to an untreated patient. The effective amount of active compound(s) used to practice the present invention for therapeutic treatment of a disease varies depending upon the manner of administration, the age, body weight, and general health of the subject. Ultimately, the attending physician or veterinarian will decide the appropriate amount and dosage regimen. Such amount is referred to as an “effective” amount.

The term “expression profile” is used broadly to include a genomic expression profile. Profiles may be generated by any convenient means for determining a level of a nucleic acid sequence, e.g., quantitative hybridization of microRNA, labeled microRNA, amplified microRNA, complementary/synthetic DNA (cDNA), etc., quantitative polymerase chain reaction (PCR), and ELISA for quantitation, and allow the analysis of differential gene expression between two samples. A subject or patient tumor sample is assayed. Samples are collected by any convenient method, as known in the art. According to some embodiments, the term “expression profile” means measuring the relative abundance of the nucleic acid sequences in the measured samples.

By “FDR” is meant False Discovery Rate. When performing multiple statistical tests, for example, in comparing the signal of two groups in multiple data features, there is an increasingly high probability of obtaining false positive results, by random differences between the groups that can reach levels that would otherwise be considered statistically significant. In some cases, in order to limit the proportion of such false discoveries, statistical significance is defined only for data features in which the differences reached a p-value (by two-sided t-test) below a threshold, which is dependent on the number of tests performed and the distribution of p-values obtained in these tests.

By "fragment" is meant a portion, e.g., a portion of a polypeptide or nucleic acid molecule. This portion contains, preferably, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%,

80%, or 90% of the entire length of the reference nucleic acid molecule or polypeptide. For example, a fragment may contain 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100, 200, 300, 400, 500, 600, 700, 800, 900, or 1000 nucleotides or amino acids. However, the invention also comprises polypeptides and nucleic acid fragments, so long as they exhibit the desired biological activity of the full length polypeptides and nucleic acid, respectively. A nucleic acid fragment of almost any length is employed. For example, illustrative polynucleotide segments with total lengths of about 10,000, about 5000, about 3000, about 2,000, about 1,000, about 500, about 200, about 100, about 50 base pairs in length (including all intermediate lengths) are included in many implementations of this invention. Similarly, a polypeptide fragment of almost any length is employed. For example, illustrative polypeptide segments with total lengths of about 10,000, about 5,000, about 3,000, about 2,000, about 1,000, about 5,000, about 1,000, about 500, about 200, about 100, or about 50 amino acids in length (including all intermediate lengths) are included in many implementations of this invention.

"Hybridization" means hydrogen bonding, which may be Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding, between complementary nucleobases. For example, adenine and thymine are complementary nucleobases that pair through the formation of hydrogen bonds.

By "hybridize" is meant pair to form a double-stranded molecule between complementary polynucleotide sequences (e.g., a gene described herein), or portions thereof, under various conditions of stringency. (See, e.g., Wahl, G. M. and S. L. Berger (1987) Methods Enzymol. 152:399; Kimmel, A. R. (1987) Methods Enzymol. 152:507).

The terms "isolated," "purified, " or "biologically pure" refer to material that is free to varying degrees from components which normally accompany it as found in its native state. "Isolate" denotes a degree of separation from original source or surroundings. "Purify" denotes a degree of separation that is higher than isolation.

A "purified" or "biologically pure" protein is sufficiently free of other materials such that any impurities do not materially affect the biological properties of the protein or cause other adverse consequences. That is, a nucleic acid or peptide of this invention is purified if it is substantially free of cellular material, viral material, or culture medium when produced by recombinant DNA techniques, or chemical precursors or other chemicals when chemically synthesized. Purity and homogeneity are typically determined using analytical chemistry

techniques, for example, polyacrylamide gel electrophoresis or high performance liquid chromatography. The term "purified" can denote that a nucleic acid or protein gives rise to essentially one band in an electrophoretic gel. For a protein that can be subjected to modifications, for example, phosphorylation or glycosylation, different modifications may give rise to different isolated proteins, which can be separately purified.

Similarly, by "substantially pure" is meant a nucleotide or polypeptide that has been separated from the components that naturally accompany it. Typically, the nucleotides and polypeptides are substantially pure when they are at least 60%, 70%, 80%, 90%, 95%, or even 99%, by weight, free from the proteins and naturally-occurring organic molecules with they are naturally associated.

By "isolated nucleic acid" is meant a nucleic acid that is free of the genes which flank it in the naturally-occurring genome of the organism from which the nucleic acid is derived. The term covers, for example: (a) a DNA which is part of a naturally occurring genomic DNA molecule, but is not flanked by both of the nucleic acid sequences that flank that part of the molecule in the genome of the organism in which it naturally occurs; (b) a nucleic acid incorporated into a vector or into the genomic DNA of a prokaryote or eukaryote in a manner, such that the resulting molecule is not identical to any naturally occurring vector or genomic DNA; (c) a separate molecule such as a synthetic cDNA, a genomic fragment, a fragment produced by polymerase chain reaction (PCR), or a restriction fragment; and (d) a recombinant nucleotide sequence that is part of a hybrid gene, i.e., a gene encoding a fusion protein. Isolated nucleic acid molecules according to the present invention further include molecules produced synthetically, as well as any nucleic acids that have been altered chemically and/or that have modified backbones. For example, the isolated nucleic acid is a purified cDNA or RNA polynucleotide. Isolated nucleic acid molecules also include messenger ribonucleic acid (mRNA) molecules.

By an "isolated polypeptide" is meant a polypeptide of the invention that has been separated from components that naturally accompany it. Typically, the polypeptide is isolated when it is at least 60%, by weight, free from the proteins and naturally-occurring organic molecules with which it is naturally associated. Preferably, the preparation is at least 75%, more preferably at least 90%, and most preferably at least 99%, by weight, a polypeptide of the invention. An isolated polypeptide of the invention may be obtained, for example, by extraction

from a natural source, by expression of a recombinant nucleic acid encoding such a polypeptide; or by chemically synthesizing the protein. Purity can be measured by any appropriate method, for example, column chromatography, polyacrylamide gel electrophoresis, or by HPLC analysis.

The term "immobilized" or "attached" refers to a probe (e.g., nucleic acid or protein) and a solid support in which the binding between the probe and the solid support is sufficient to be stable under conditions of binding, washing, analysis, and removal. The binding may be covalent or non-covalent. Covalent bonds may be formed directly between the probe and the solid support or may be formed by a cross linker or by inclusion of a specific reactive group on either the solid support or the probe or both molecules. Non-covalent binding may be one or more of electrostatic, hydrophilic, and hydrophobic interactions. Included in non-covalent binding is the covalent attachment of a molecule to the support and the non-covalent binding of a biotinylated probe to the molecule. Immobilization may also involve a combination of covalent and non-covalent interactions.

By "marker" is meant any protein or polynucleotide having an alteration in expression level or activity that is associated with a disease or disorder, e.g., SINET.

By "small bowel neuroendocrine tumor-associated gene" is meant a nucleic acid associated with the pathogenesis of a small bowel neuroendocrine tumor.

By "modulate" is meant alter (increase or decrease). Such alterations are detected by standard art-known methods such as those described herein.

The term, "normal amount" refers to a normal amount of a complex in an individual known not to be diagnosed with SINET. The amount of the molecule can be measured in a test sample and compared to the "normal control level," utilizing techniques such as reference limits, discrimination limits, or risk defining thresholds to define cutoff points and abnormal values (e.g., for SINET). The "normal control level" means the level of one or more proteins (or nucleic acids) or combined protein indices (or combined nucleic acid indices) typically found in a subject known not to be suffering from SINET. Such normal control levels and cutoff points may vary based on whether a molecule is used alone or in a formula combining other proteins into an index. Alternatively, the normal control level can be a database of protein patterns from previously tested subjects who did not convert to SINET over a clinically relevant time horizon. In another aspect, the normal control level can be a level relative to a housekeeping gene.

The level that is determined may be the same as a control level or a cut off level or a threshold level, or may be increased or decreased relative to a control level or a cut off level or a threshold level. In some aspects, the control subject is a matched control of the same species, gender, ethnicity, age group, smoking status, body mass index (BMI), current therapeutic regimen status, medical history, or a combination thereof, but differs from the subject being diagnosed in that the control does not suffer from the disease in question or is not at risk for the disease.

Relative to a control level, the level that is determined may be an increased level. As used herein, the term "increased" with respect to level (e.g., expression level, biological activity level, etc.) refers to any % increase above a control level. The increased level may be at least or about a 1% increase, at least or about a 5% increase, at least or about a 10% increase, at least or about a 15% increase, at least or about a 20% increase, at least or about a 25% increase, at least or about a 30% increase, at least or about a 35% increase, at least or about a 40% increase, at least or about a 45% increase, at least or about a 50% increase, at least or about a 55% increase, at least or about a 60% increase, at least or about a 65% increase, at least or about a 70% increase, at least or about a 75% increase, at least or about a 80% increase, at least or about a 85% increase, at least or about a 90% increase, or at least or about a 95% increase, relative to a control level.

Relative to a control level, the level that is determined may be a decreased level. As used herein, the term "decreased" with respect to level (e.g., expression level, biological activity level, etc.) refers to any % decrease below a control level. The decreased level may be at least or about a 1% decrease, at least or about a 5% decrease, at least or about a 10% decrease, at least or about a 15% decrease, at least or about a 20% decrease, at least or about a 25% decrease, at least or about a 30% decrease, at least or about a 35% decrease, at least or about a 40% decrease, at least or about a 45% decrease, at least or about a 50% decrease, at least or about a 55% decrease, at least or about a 60% decrease, at least or about a 65% decrease, at least or about a 70% decrease, at least or about a 75% decrease, at least or about a 80% decrease, at least or about a 85% decrease, at least or about a 90% decrease, or at least or about a 95% decrease, relative to a control level.

Nucleic acid molecules useful in the methods of the invention include any nucleic acid molecule that encodes a polypeptide of the invention or a fragment thereof. Such nucleic acid

molecules need not be 100% identical with an endogenous nucleic acid sequence, but will typically exhibit substantial identity, e.g., at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identity. Polynucleotides having "substantial identity" to an endogenous sequence are typically capable of hybridizing with at least one strand of a double-stranded nucleic acid molecule.

For example, stringent salt concentration will ordinarily be less than about 750 mM NaCl and 75 mM trisodium citrate, preferably less than about 500 mM NaCl and 50 mM trisodium citrate, and more preferably less than about 250 mM NaCl and 25 mM trisodium citrate. Low stringency hybridization can be obtained in the absence of organic solvent, e.g., formamide, while high stringency hybridization can be obtained in the presence of at least about 35% formamide, and more preferably at least about 50% formamide. Stringent temperature conditions will ordinarily include temperatures of at least about 30° C, more preferably of at least about 37° C, and most preferably of at least about 42° C. Varying additional parameters, such as hybridization time, the concentration of detergent, e.g., sodium dodecyl sulfate (SDS), and the inclusion or exclusion of carrier DNA, are well known to those skilled in the art. Various levels of stringency are accomplished by combining these various conditions as needed. In a preferred embodiment, hybridization will occur at 30° C in 750 mM NaCl, 75 mM trisodium citrate, and 1% SDS. In a more preferred embodiment, hybridization will occur at 37° C in 500 mM NaCl, 50 mM trisodium citrate, 1% SDS, 35% formamide, and 100 μg/ml denatured salmon sperm DNA (ssDNA). In a most preferred embodiment, hybridization will occur at 42° C in 250 mM NaCl, 25 mM trisodium citrate, 1% SDS, 50% formamide, and 200 μg/ml ssDNA. Useful variations on these conditions will be readily apparent to those skilled in the art.

For most applications, washing steps that follow hybridization will also vary in stringency. Wash stringency conditions can be defined by salt concentration and by temperature. As above, wash stringency can be increased by decreasing salt concentration or by increasing temperature. For example, stringent salt concentration for the wash steps will preferably be less than about 30 mM NaCl and 3 mM trisodium citrate, and most preferably less than about 15 mM NaCl and 1.5 mM trisodium citrate. Stringent temperature conditions for the wash steps will ordinarily include a temperature of at least about 25° C, more preferably of at least about 42° C, and even more preferably of at least about 68° C. In a preferred embodiment, wash steps will occur at 25° C in 30 mM NaCl, 3 mM trisodium citrate, and 0.1% SDS. In a more preferred

embodiment, wash steps will occur at 42 C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. In a more preferred embodiment, wash steps will occur at 68° C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. Additional variations on these conditions will be readily apparent to those skilled in the art. Hybridization techniques are well known to those skilled in the art and are described, for example, in Benton and Davis (Science 196:180, 1977); Grunstein and Hogness (Proc. Natl. Acad. Sci., USA 72:3961, 1975); Ausubel et al. (Current Protocols in Molecular Biology, Wiley Interscience, New York, 2001); Berger and Kimmel (Guide to Molecular Cloning Techniques, 1987, Academic Press, New York); and Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, New York.

By "neoplasia" is meant a disease or disorder characterized by excess proliferation or reduced apoptosis. Illustrative neoplasms for which the invention can be used include, but are not limited to pancreatic cancer, leukemias (e.g., acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroleukemia, chronic leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia), polycythemia vera, lymphoma (Hodgkin's disease, non-Hodgkin's disease), Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors such as sarcomas and carcinomas (e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, nile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, uterine cancer, testicular cancer, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, glioblastoma multiforme, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodenroglioma, schwannoma, meningioma, melanoma, neuroblastoma, and retinoblastoma).

As used herein, in one aspect, "next-generation sequencing" (NGS), also known as high-throughput sequencing, is the catch-all term used to describe a number of different sequencing

methodologies including, but not limited to, illumina® sequencing, Roche 454 sequencing™, Ion torrent™: Proton / personal genome machine (PGM) sequencing, and SOLiD sequencing. These recent technologies allow for sequencing DNA and RNA much more quickly and cheaply than the previously used Sanger sequencing. *See*, LeBlanc et al., 2015 Cancers, 7: 1925-1958, incorporated herein by reference; and Goodwin et al., 2016 Nature Reviews Genetics, 17: 333-351, incorporated herein by reference.

As used herein, "obtaining" as in "obtaining an agent" includes synthesizing, purchasing, or otherwise acquiring the agent.

Unless specifically stated or obvious from context, as used herein, the term "or" is understood to be inclusive. Unless specifically stated or obvious from context, as used herein, the terms "a", "an", and "the" are understood to be singular or plural.

The phrase "pharmaceutically acceptable carrier" is art recognized and includes a pharmaceutically acceptable material, composition or vehicle, suitable for administering compounds of the present invention to mammals. The carriers include liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject agent from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations.

By "protein" or "polypeptide" or "peptide" is meant any chain of more than two natural or unnatural amino acids, regardless of post-translational modification (e.g., glycosylation or

phosphorylation), constituting all or part of a naturally-occurring or non-naturally occurring polypeptide or peptide, as is described herein.

"Primer set" means a set of oligonucleotides that may be used, for example, for PCR. A primer set would consist of at least 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 30, 40, 50, 60, 80, 100, 200, 250, 300, 400, 500, 600, or more primers.

The terms "preventing" and "prevention" refer to the administration of an agent or composition to a clinically asymptomatic individual who is at risk of developing, susceptible, or predisposed to a particular adverse condition, disorder, or disease, and thus relates to the prevention of the occurrence of symptoms and/or their underlying cause.

The term "prognosis," "staging," and "determination of aggressiveness" are defined herein as the prediction of the degree of severity of the neoplasia, e.g., small bowel neuroendocrine tumor, and of its evolution as well as the prospect of recovery as anticipated from usual course of the disease. Once the aggressivenes has been determined, appropriate methods of treatments are chosen.

Ranges can be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another aspect includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it is understood that the particular value forms another aspect. It is further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. It is also understood that there are a number of values disclosed herein, and that each value is also herein disclosed as "about" that particular value in addition to the value itself. It is also understood that throughout the application, data are provided in a number of different formats and that this data represent endpoints and starting points and ranges for any combination of the data points. For example, if a particular data point "10" and a particular data point "15" are disclosed, it is understood that greater than, greater than or equal to, less than, less than or equal to, and equal to10 and 15 are considered disclosed as well as between 10 and 15. It is also understood that each unit between two particular units are also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

Ranges provided herein are understood to be shorthand for all of the values within the range. For example, a range of 1 to 50 is understood to include any number, combination of

numbers, or sub-range from the group consisting 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 as well as all intervening decimal values between the aforementioned integers such as, for example, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, and 1.9. With respect to sub-ranges, "nested sub-ranges" that extend from either end point of the range are specifically contemplated. For example, a nested sub-range of an exemplary range of 1 to 50 may comprise 1 to 10, 1 to 20, 1 to 30, and 1 to 40 in one direction, or 50 to 40, 50 to 30, 50 to 20, and 50 to 10 in the other direction.

By "reduces" is meant a negative alteration of at least 10%, 25%, 50%, 75%, or 100%.

A "reference sequence" is a defined sequence used as a basis for sequence comparison or a gene expression comparison. A reference sequence may be a subset of or the entirety of a specified sequence; for example, a segment of a full-length cDNA or gene sequence, or the complete cDNA or gene sequence. For polypeptides, the length of the reference polypeptide sequence will generally be at least about 16 amino acids, preferably at least about 20 amino acids, more preferably at least about 25 amino acids, and even more preferably about 35 amino acids, about 50 amino acids, or about 100 amino acids. For nucleic acids, the length of the reference nucleic acid sequence will generally be at least about 40 nucleotides, preferably at least about 60 nucleotides, more preferably at least about 75 nucleotides, and even more preferably about 100 nucleotides or about 300 or about 500 nucleotides or any integer thereabout or there between.

The term "sample" as used herein refers to a biological sample obtained for the purpose of evaluation *in vitro*. Exemplary tissue samples for the methods described herein include tissue samples from tumors or the surrounding microenvironment (i.e., the stroma). With regard to the methods disclosed herein, the sample or patient sample preferably may comprise any body fluid or tissue. In some embodiments, the bodily fluid includes, but is not limited to, blood, plasma, serum, lymph, breast milk, saliva, mucous, semen, vaginal secretions, cellular extracts, inflammatory fluids, cerebrospinal fluid, feces, vitreous humor, or urine obtained from the subject. In some aspects, the sample is a composite panel of at least two of a blood sample, a plasma sample, a serum sample, and a urine sample. In exemplary aspects, the sample comprises blood or a fraction thereof (e.g., plasma, serum, fraction obtained via leukopheresis). Preferred

samples are whole blood, serum, plasma, or urine. A sample can also be a partially purified fraction of a tissue or bodily fluid.

A reference sample can be a "normal" sample, from a donor not having the disease or condition fluid, or from a normal tissue in a subject having the disease or condition. A reference sample can also be from an untreated donor or cell culture not treated with an active agent (e.g., no treatment or administration of vehicle only). A reference sample can also be taken at a "zero time point" prior to contacting the cell or subject with the agent or therapeutic intervention to be tested or at the start of a prospective study.

A "solid support" describes a strip, a polymer, a bead, or a nanoparticle. The strip may be a nucleic acid-probe (or protein) coated porous or non-porous solid support strip comprising linking a nucleic acid probe to a carrier to prepare a conjugate and immobilizing the conjugate on a porous solid support. Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite. The nature of the carrier can be either soluble to some extent or insoluble for the purposes of the present invention. The support material may have virtually any possible structural configuration so long as the coupled molecule is capable of binding to a binding agent (e.g., an antibody or nucleic acid molecule). Thus, the support configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, or test strip, etc. For example, the supports include polystyrene beads. Those skilled in the art will know many other suitable carriers for binding antibody or antigen, or will be able to ascertain the same by use of routine experimentation. In other aspects, the solid support comprises a polymer, to which an agent is chemically bound, immobilized, dispersed, or associated. A polymer support may be a network of polymers, and may be prepared in bead form (e.g., by suspension polymerization). The location of active sites introduced into a polymer support depends on the type of polymer support. For example, in a swollen-gel-bead polymer support the active sites are distributed uniformly throughout the beads, whereas in a macroporous-bead polymer support they are predominantly on the internal surfaces of the macropores. The solid support, e.g., a device contains a binding agent alone or together with a binding agent for at least one, two, three or more other molecules.

By "specifically binds" is meant a compound or antibody that recognizes and binds a polypeptide of the invention, but which does not substantially recognize and bind other molecules in a sample, for example, a biological sample, which naturally includes a polypeptide of the invention.

A "specific binding agent" describes agents having greater than 10-fold, preferably greater than 100-fold, and most preferably, greater than 1000-fold affinity for the target molecule as compared to another molecule. As the skilled artisan will appreciate the term specific is used to indicate that other biomolecules present in the sample do not significantly bind to the binding agent specific for the target molecule. Preferably, the level of binding to a biomolecule other than the target molecule results in a binding affinity which is at most only 10% or less, only 5% or less only 2% or less or only 1% or less of the affinity to the target molecule, respectively. A preferred specific binding agent will fulfill both the above minimum criteria for affinity as well as for specificity. For example, an antibody has a binding affinity in the low micromolar ($10^{-6}$), nanomolar ($10^{-7}$-$10^{-9}$), with high affinity antibodies in the low nanomolar ($10^{-9}$) or pico molar ($10^{-12}$) range for its specific target molecule.

By "substantially identical" is meant a polypeptide or nucleic acid molecule exhibiting at least 50% identity to a reference amino acid sequence (for example, any one of the amino acid sequences described herein) or nucleic acid sequence (for example, any one of the nucleic acid sequences described herein). Preferably, such a sequence is at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical at the amino acid level or nucleic acid to the sequence used for comparison.

Sequence identity is typically measured using sequence analysis software (for example, Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, Wis. 53705, BLAST, BESTFIT, GAP, or PILEUP/PRETTYBOX programs). Such software matches identical or similar sequences by assigning degrees of homology to various substitutions, deletions, and/or other modifications. Conservative substitutions typically include substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid, asparagine, glutamine; serine, threonine; lysine, arginine; and phenylalanine, tyrosine. In an exemplary approach to determining the degree of identity, a BLAST program may be used, with a probability score between $e^{-3}$ and $e^{-100}$ indicating a closely related sequence.

The term "subject" as used herein includes all members of the animal kingdom prone to suffering from the indicated disorder. In some aspects, the subject is a mammal, and in some aspects, the subject is a human. The methods are also applicable to companion animals such as dogs and cats as well as livestock such as cows, horses, sheep, goats, pigs, and other domesticated and wild animals.

A subject "suffering from or suspected of suffering from" a specific disease, condition, or syndrome has a sufficient number of risk factors or presents with a sufficient number or combination of signs or symptoms of the disease, condition, or syndrome such that a competent individual would diagnose or suspect that the subject was suffering from the disease, condition, or syndrome. Methods for identification of subjects suffering from or suspected of suffering from conditions associated with cancer (e.g., small bowel neuroendocrine tumor) is within the ability of those in the art. Subjects suffering from, and suspected of suffering from, a specific disease, condition, or syndrome are not necessarily two distinct groups.

As used herein, "susceptible to" or "prone to" or "predisposed to" or "at risk of developing" a specific disease or condition refers to an individual who based on genetic, environmental, health, and/or other risk factors is more likely to develop a disease or condition than the general population. An increase in likelihood of developing a disease may be an increase of about 10%, 20%, 50%, 100%, 150%, 200%, or more.

The terms "treating" and "treatment" as used herein refer to the administration of an agent or formulation to a clinically symptomatic individual afflicted with an adverse condition, disorder, or disease, so as to effect a reduction in severity and/or frequency of symptoms, eliminate the symptoms and/or their underlying cause, and/or facilitate improvement or remediation of damage. It will be appreciated that, although not precluded, treating a disorder or condition does not require that the disorder, condition or symptoms associated therewith be completely eliminated.

As used herein, in one aspect, the "tumor microenvironment" (TME) is the cellular environment in which a tumor exists, e.g., surrounding blood vessels, immune cells, fibroblasts, bone marrow-derived inflammatory cells, lymphocytes, signaling molecules and the extracellular matrix (ECM). The tumor and the surrounding microenvironment are closely related and interact constantly. Tumors can influence the microenvironment by releasing extracellular signals, promoting tumor angiogenesis and inducing peripheral immune tolerance, while the immune

cells in the microenvironment can affect the growth and evolution of cancerous cells, such as in immuno-editing.

In some cases, a composition of the invention is administered orally or systemically. Other modes of administration include rectal, topical, intraocular, buccal, intravaginal, intracisternal, intracerebroventricular, intratracheal, nasal, transdermal, within/on implants, or parenteral routes. The term "parenteral'' includes subcutaneous, intrathecal, intravenous, intramuscular, intraperitoneal, or infusion. Intravenous or intramuscular routes are not particularly suitable for long-term therapy and prophylaxis. They could, however, be preferred in emergency situations. Compositions comprising a composition of the invention can be added to a physiological fluid, such as blood. Oral administration can be preferred for prophylactic treatment because of the convenience to the patient as well as the dosing schedule. Parenteral modalities (subcutaneous or intravenous) may be preferable for more acute illness, or for therapy in patients that are unable to tolerate enteral administration due to gastrointestinal intolerance, ileus, or other concomitants of critical illness. Inhaled therapy may be most appropriate for pulmonary vascular diseases (e.g., pulmonary hypertension).

Pharmaceutical compositions may be assembled into kits or pharmaceutical systems for use in arresting cell cycle in rapidly dividing cells, e.g., cancer cells. Kits or pharmaceutical systems according to this aspect of the invention comprise a carrier means, such as a box, carton, tube, having in close confinement therein one or more container means, such as vials, tubes, ampoules, bottles, syringes, or bags. The kits or pharmaceutical systems of the invention may also comprise associated instructions for using the kit.

Any compositions or methods provided herein can be combined with one or more of any of the other compositions and methods provided herein.

Any compositions or methods provided herein can be combined with one or more of any of the other compositions and methods provided herein.

The transitional term "comprising," which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. By contrast, the transitional phrase "consisting of" excludes any element, step, or ingredient not specified in the claim. The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All published foreign patents and patent applications cited herein are incorporated herein by reference. Genbank and NCBI submissions indicated by accession number cited herein are incorporated herein by reference. All other published references, documents, manuscripts and scientific literature cited herein are incorporated herein by reference. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic showing the workflow from tissue aggregation to target protein quantification.

FIG. 2A-FIG. 2I is a series of photomicrographs with panel A through panel I showing SINET primary carcinoid (CAR) tumor hematoxylin and eosin (H&E) stain (FIG. 2A), staining of neuroendocrine tumor cells for CgA (FIG. 2B), and staining of adjacent fibroblasts for Vimentin (FIG. 2C). Also shown are patient-derived cancer-associated short-term tumor-CAF "mixed" cell line morphology (FIG. 2D), CAF cells stained for CgA (FIG. 2E), CAF cells stained for Vimentin (FIG. 2F), a xenograft model statined for H&E (FIG. 2G), and fibroblastic cells stained with Hoechst 33358 (FIG. 2H), and tumor cells (FIG. 2I) stained by Hoechst 33258.

FIG. 3A is a series of bar charts showing median secretion levels in normal human fibroblasts (blue) and CAFs (red). FIG. 3B is a $Log_2$[CAF/Normal] Scatterplot.

FIG. 4A-FIG. 4C shows the results of an experiment, wherein 3 individual multiplex assays comprising cytokines, chemokines, receptors, growth factors, and hormones were utilized to assess NAF supernatants resulting in a total 61 targets being tested (FIG. 4A), of which a number of detectable targets were duplicated across the assays and 7 were not detected above LLOQ, resulting in a total of 47 detectable targets, the majority of which were detected in greater than 75% of the NAF samples at 24, 48 and 72hr time points (FIG. 4B). FIG. 4C is a pie chart

showing low, moderate and high expression levels associated with each of the time points, 24, 48 and 72hr.

FIG. 5A-FIG. 5J is a heat map and a series of bar charts showing heatmap representation of hierarchical clustering of $log_2$(fold change) values for comparison of secretion levels in CAF's relative to the normal human fibroblasts, where red indicates over-expressed and green suppressed secretion levels associated with the CAFs (FIG. 5A). A subset of the secreted proteins are plotted as pg/mg (normalized to total protein) at the 48hr timepoint, including IL-6 (FIG. 5B), MCP-1 (FIG. 5C), VEGF (FIG. 5D), IL-12 (FIG. 5E), IFNg (FIG. 5H), IL-1ra (FIG. 5I) and IL-10 (FIG. 5J) which are all more highly secreted/over-expressed; and SCF (FIG. 5F) and sEGFR (FIG. 5G) that were suppressed in CAF supernatants collected from SINETs relative to normal human fibroblasts.

FIG. 6A-FIG. 6K is a series of graphs showing upregulated concentrations [pg/ml] of MCP-1 (FIG. 6A), IL-6 (FIG. 6B), VEGF (FIG. 6H), IL-12 (FIG. 6I), IFNg (FIG. 6E), IL-1ra (FIG. 6F), IL-10 (FIG. 6G) and downregulated concentrations of sEGFR (FIG. 6C) and SCF (FIG. 6D) that were statistically significant between the healthy control and metastatic SINET plasma samples. FIG. 6J shows that up- and down-regulation of secretion levels were compared and concordance between the supernatants and plasma was calculated. Linear correlation of plasma and NAF supernatants was plotted as $log_2$(fold change), where concordance was observed (FIG. 6K).

FIG. 7A is a heatmap representation of multiplex secretion profiling results plotted as $log_2$(Fold Change) comparing expression levels in the CAR24 and CAR26 CAFs treated with increasing doses of WFA over the concentration range 10-1000nM relative to DMSO control, where red and green indicates over- and under-expression and (#) in brackets on y-axis after protein label indicates bead encoding reference map. FIG. 7B is a line graph showing cell viability in CAR24 and CAR26 CAFs treated with increasing doses of WFA over the concentration range 10-1000nM. FIG. 7C is a bar chart showing VEGF-A, MCP-1 and IL-6 mRNA gene expression in CAR24 and CAR26 CAFs treated for 24hr with 100nM WFA.

FIG. 8 is a series of photomicrographs showing tumor, stroma, and tumor-stroma mix CAR cell lines.

FIG. 9 is a series of photomicrographs showing organotypic slice culture morphology. At 48 hr (right) and 72 hr (left), with hematoxylin and eosin (H&E) staining on top, alpha-

methylacyl-CoA racemase (AMACR) immunohistochemistry (AMACR IHC) in the middle row, and mitosis (arrow heads) on the bottom.

FIG. 10 is a schematic for using tissue slice cultures to evaluate response of neuroendocrine tumors to Rapamycin.

FIG. 11A-FIG. 11I shows the identification of genes differentially expressed between the WFA-treated and untreated CAF cell lines, CAR24 and CAR26. FIG. 11A shows a volcano plot illustrating fold change (logbase2) versus adjusted significant P value (-logbase10), where red and green data points represent a significance level of adj $p<0.05$ and $log2FC>\pm3.5$. FIG. 11B and FIG. 11C is a bar chart showing the top 10 MSigDB Hallmark data sets enriched in genes that were upregulated (FIG. 11B) and downregulated (FIG. 11C) in response to treatment with 100nM WFA. FIG. 11D is a heatmap representation of hierarchical clustering of NFkB signaling genes as defined by the MSigDB Hallmark data set, where red and green indicate up- and downregulated genes in response to treatment with 100nM WFA. FIG. 11E is a heatmap showing gene expression pattern in the CAR24 and CAR26 CAF cell lines that facilitate characterization of tumor-associated stromal fibroblasts. FIG. 11F is a volcano plot illustrating fold change (logbase2) versus adjusted significant P value (-logbase10), where red and green data points represent a significance level of adj $p<0.05$ and $log2FC>\pm3.5$. The top 10 MSigDB Hallmark data sets enriched in genes that were upregulated (FIG. 11G) and downregulated (FIG. 11H) in response to treatment with 100nM WFA. FIG. 11I is a heatmap representation of hierarchical clustering of EMT signaling genes as defined by the MSigDB Hallmark data set, where red and green indicate up- and downregulated genes in response to treatment with 100nM WFA.

FIG. 12 shows images of untreated CAR15 NAFs in vitro in 6-well plates at time 0hr, 72hr and Day 5 (top panel), of CAR15 NAF's treated with 100uM uPA inhibitor or 100nM Survivin at 72hrs and Day 5 (middle panel). Inset: uPA concentration [pg/ml] measured in cell culture supernatant from CAR15 treated with either uPA or survivin inhibitor. Gene expression knockdown and secretion levels relative to untreated control for CAR15 treated with either 100nM of uPA or survivin inhibitor (bottom panel).

## DETAILED DESCRIPTION OF THE INVENTION

The invention is based, at least in part, upon the identification of secreted protein biomarkers of metastatic neuroendocrine tumors.

Prior to the invention described herein, the biology of SINETS was poorly understood, as SINETS are a biologically diverse group of well-differentiated tumors, and tumor size is an unreliable predictor of metastatic potential (Vinik et al., Pancreas, 39:713–734 (2010)). While tumor growth is often slower than that of other malignancies, many patients present with advanced disease for which few treatment options currently exist (Gilbert et al., Endocr Relat Cancer, 17:623-36 (2010)). The slow growing characteristics of SINETs has meant that the development of in vitro models to study this tumor type have been limited (Evers et al., Gastroenterology, 101:303-311 (1991); Pfragner et al., Culture of guman neruoendocrine tumor cells. In: culture of human tumor cells. Pfragner R and Reshney RI (eds.). John Wiley & Sons. Hoboken NJ. pp. 373-403 (2004); Pfragner et al., AntiCancer Res, 29:1951-1962 (2009)), and stable human cell lines that recapitulate the NET biology are uncommon. Prior to the invention described herein, the genetic drivers of neuroendocrine tumors were also poorly understood. While pancreatic neuroendocrine tumors are characterized by recurrent mutations in the tumor suppressor gene MEN1, as well as ATRX and DAXX, genes implicated in chromatin remodeling (Jiao et al., Science, 331:1199-1203 (2011)), whole genome profiling of SINETs revealed recurrent mutations in the cyclin dependent kinase inhibitor CDKN1B, in only 8% of cases (Francis et al., Nat Genet., 45: 1483-1486 (2013)).

Prior to the invention described herein, the lack of targetable mutations, together with a lack of cell lines and animal models has been a major obstacle in the development of innovative therapeutic agents for SINETs (Öberg KE, The management of Neuroendocrine Tumors: Current and Future Medical Therapy Options, 24:382-93 (2012)). With this slow growth and relatively quiet mutational landscape, the tumor microenvironment (TME) may have increased importance. Tumor-promoting inflammation has been established as a hallmark of cancer (Hanahan D and Weinberg RA, Cell, 144:646-674 (2011)) and almost all cancers have an inflammatory TME, irrespective of etiology linked to inflammation (Erez et al., Biochem Biophys Res Comm, 437:397-402 (2013)). Cancer Associated Fibroblasts (CAFs) are a heterogeneous and an activated cell subtype in the TME that promote tumor growth by directly stimulating tumor cell proliferation (Bhomick et al., Nature 432:332-337 (2004)). CAF-tumor interactions in the TME

are partially defined by cancer cells inducing a reactive response in stroma and the activated stroma driving cancer cell malignancy in return (De WO and Mareel M. , J Pathol 200:429-447 (2003)). Cancer associated fibroblasts have been shown to have pro-tumorigenic effects (Östman et al., Curr. Opin. Genet. Devel 19:67-73 (2009); Trimboli et al., Nature, 461:1084-1091 (2009)); and a prominent functional role in cancer progression and metastasis (Kalluri R and Zaisberg M., Nat Rev Cancer, 6:392-401 (2006)).

Prior to the invention described herein, a lack of cell lines and animal models had been an obstacle in developing new therapeutic agents for advanced carcinoid tumors. Described herein is a collection of short term carcinoid cell lines, which are used as a model of disease. Carcinoid cells in culture grow slowly and are importantly attached to stromal fibroblasts, referred to as CAF's (Carcinoid Associated Fibroblasts), also known as neuroendocrine-associated fibroblasts (NAFs). NAFs include all cell types that eincompass the entire stromal microenvironment, i.e., all cells except for tumor cells. These "short-term" NAF cultures are derived directly from the tissue from neuroendocrine patients. Described herein is the generation of a large collection of these patient-derived CAF cell lines.

Tumors are complex tissues composed of multiple distinct cell types, including recruited normal cells, which form tumor-associated stroma. These stromal cells are active participants in tumorigenesis and contribute to the development and expression of certain hallmark capabilities (Hanahan D and Weinberg R, 2011 Cell, 144: 646-674, incorporated herein by reference). Accordingly, the "tumor microenvironment" (TME) is the cellular environment in which a tumor exists, e.g., surrounding blood vessels, immune cells, fibroblasts, bone marrow-derived inflammatory cells, lymphocytes, signaling molecules and the extracellular matrix (ECM). The tumor and the surrounding microenvironment are closely related and interact constantly. Tumors can influence the microenvironment by releasing extracellular signals, promoting tumor angiogenesis and inducing peripheral immune tolerance, while the immune cells in the microenvironment can affect the growth and evolution of cancerous cells, such as in immuno-editing.

The tumor's microenvironment is not only useful in elucidating how these tumors progress and become invasive, but is also useful in identifying new therapeutic pathways of disease. As described in detail below, CAF-secreted biomarker signatures are vital in understanding the neuroendocrine tumor microenvironment. Specifically, described herein are

prognostic, diagnostic, and pharmcodynamic biomarkers of metastatic small bowel neuroendocrine tumors. Also provided are rapid screening methods of secreted proteins in patient-derived cultures.

Accordingly, described herein are CAF cell culture supernatants from short-term primary cell lines derived from metastatic small bowel neuroendocrine tumors. As described in detail below, the secreted levels of proteins were measured utilizing a multiplexed bead-based approach, to develop a metastatic-associated secretion signature. Over-expression of secreted proteins (interleukin-6 (IL-6), IL-8, IL-12, IL-13, IL-2, monocyte chemoattractant protein-1 (MCP-1) and vascular endothelial growth factor (VEGF) associated with immune and inflammatory response and NFkB and janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathways was evident, indicating that small molecules that inhibit either or both may be therapeutically important in the context of the CAF cell microenvironment.

As described in detail below, by way of confirming the signature, IL-6, MCP-1, and VEGF were identified as over-expressed in the plasma from matched metastatic patients compared to healthy donors. Finally, CAF short-term cultures were highly sensitive to inhibition of the NFkB pathway by Withaferin A (WFA) at an IC50 of ~100nM concentration and suppression of the secreted signature was observed in a dose dependent manner.

Neuroendocrine Tumors

Neuroendocrine tumors (NETs), defined as epithelial tumors with predominant neuroendocrine differentiation, are among the most frequent types of small bowel neoplasm (Xavier et al., 2016 World Journal of Gastrointestinal Pathophysiology, 7(1): 117-124, incorporated herein by reference). They represent a rare, slow-growing neoplasm with some characteristics common to all forms and others attributable to the organ of origin.

Traditionally, neuroendocrine tumors have been classified by their anatomic site of origin. NETs can arise in many different areas of the body, and are most often located in the intestine, pancreas or the lungs. The various kinds of cells that can give rise to NETs are present in endocrine glands and are also diffusely distributed throughout the body, e.g., Kulchitsky cells or enterochromaffin-like cells, which are relatively more common in the gastrointestinal and pulmonary systems. NETs include certain tumors of the gastrointestinal tract and of the pancreatic islet cells, certain thymus and lung tumors, and medullary carcinoma of the parafollicular cells of the thyroid. Neuroendocrine tumors, despite differing embryological

origin, have common phenotypic characteristics. For example, NETs show tissue immunoreactivity for markers of neuroendocrine differentiation (pan-neuroendocrine tissue markers) and may secrete various peptides and hormones.

Several nomenclatures, grading, and classification systems have emerged for neuroendocrine tumors. Thus, while the European Neuroendocrine Tumor Society (ENETS) (Eriksson et al., 2008 Neuroendocrinology, 87: 8-19, incorporated herein by reference; Jensen et al., 2006 Neuroendocrinology, 84: 165-172, incorporated herein by reference) favor the use of World Health Organization classification system, the North American Neuroendocrine Tumor Society (NANETS) (Klimstra et al., 2010 Pancreas, 39: 707-712, incorporated herein by reference) propose that some basic data elements (proliferative rate, extent of local spread, immunohistochemical markers) should be specified and documented on pathological reports and that a specified system of nomenclature, grading and staging should be used. This can assure that the basic data are recorded, allowing retrospective comparison of NETs regardless of the specific classification system used.

The World Health Organization (WHO) classification scheme places neuroendocrine tumors into three main categories, which emphasize the tumor grade rather than the anatomical origin:

- well-differentiated neuroendocrine tumours, further subdivided into tumors with benign and those with uncertain behavior
- well-differentiated (low grade) neuroendocrine carcinomas with low-grade malignant behavior
- poorly differentiated (high grade) neuroendocrine carcinomas, which are the large cell neuroendocrine and small cell carcinomas.

Additionally, the WHO scheme recognizes mixed tumors with both neuroendocrine and epithelial carcinoma features, such as goblet cell cancer, a rare gastrointestinal tract tumor. Placing a given tumor into one of categories depends on well-defined histological features: size, lymphovascular invasion, mitotic counts, Ki-67 labelling index, invasion of adjacent organs, presence of metastases and whether they produce hormones

Symptoms from secreted hormones might prompt measurement of the corresponding hormones in the blood or their associated urinary products, for initial diagnosis or to assess the interval change in the tumor. Secretory activity of the tumor cells is sometimes dissimilar to the

tissue immunoreactivity to particular hormones. Given the diverse secretory activity of NETs, there are many other potential markers, but a limited panel is usually sufficient for clinical purposes. Aside from the hormones of secretory tumors, the most important markers are: chromogranin A (CgA), urine 5-hydroxyindoleacetic acid (5-HIAA), neuron-specific enolase (NSE, gamma-gamma dimer), and synaptophysin (P38). *See*, e.g., Xavier et al., 2016 World Journal of Gastrointestinal Pathophysiology, 7(1): 117-124, incorporated herein by reference.

CT-scans, MRIs, sonography (ultrasound), and endoscopy (including endoscopic ultrasound) are common diagnostic tools for neuroendocrine tumors. CT-scans using contrast medium can detect 95 percent of tumors over 3 cm in size, but generally not tumors under 1 cm.

Even if the tumor has advanced and metastasized, making curative surgery infeasible, surgery often has a role in neuroendocrine cancers for palliation of symptoms and possibly increased lifespan. Somatostatin analogs such as octreotide are used for treatment of small bowel neuroendocrine tumors (Xavier et al., 2016 World Journal of Gastrointestinal Pathophysiology, 7(1): 117-124, incorporated herein by reference). Cholecystectomy is recommended if there is a consideration of long-term treatment with somatostatin analogs. Radionuclide therapy, chemotherapy, radiofrequency ablation, and cryoablation are other useful therapies for this condition.

Small intestinal neuroendocrine tumors were first distinguished from other tumors in 1907 (Modlin et al., 2004 Human Pathology, 35 (12): 1440–51; Arnold et al., 2003 "Chapter 15 Neuroendocrine Gastro-Entero-Pancreatic (GEP) Tumors". In Scheppach W, Bresalier RS, Tytgat GN. Gastrointestinal and Liver Tumors. Berlin: Springer. pp. 195–233). They were named carcinoid tumors because their slow growth was considered to be "cancer-like" rather than truly cancerous. However, in 1938 it was recognized that some of these small bowel tumors could be malignant.

Small bowel neuroendocrine tumors, although rare across the cancer landscape (1 per 100,000), are the most common carcinoid tumor and originate most frequently in the terminal ileum (Isac et al., 2003 Acta Oncol., 42: 672-92; Pasieka JL, 2009 Surg Clin N Am., 89: 1123-37). They are a biologically diverse group of well-differentiated tumors, where tumor size is an unreliable predictor of metastatic potential (Vinik et al., 2010 Pancreas, 39: 713–734; Yao et al., 2008 J Clin Oncol., 26: 3063-72). Tumor growth is slow and many patients present with

advanced disease for which few treatment options exist (Moertel CG, 1983 J Clin Oncol., 11: 727-740; Gilbert et al., 2010 Endocr Relat Cancer, 17: 623-36).

This slow growing characteristic has meant that the development of *in vitro* and *in vivo* models to study this tumor type have been extremely limited. Prior to the invention described herein, the lack of cell lines and animal models has been a major obstacle in the development of therapeutic agents for advanced carcinoid tumors (Öberg KE, 2012, Clin. Oncol., 24(4): 282-93). Neuroendocrine tumor cells grow slowly in culture and are importantly attached to fibroblasts, termed Neuroendocrine Associated Fibroblasts (NAFs). These cancer associated fibroblasts have pro-tumorigenic effects (Östman A and Augsten M, 2009 Curr. Opin. Genet. Devel., 19: 67-73), are attractive targets for cancer therapy, and are valuable clinical biomarkers of prognosis (Räsänen K and Vaheri A, 2010 Exp. Cell Res., 316: 2713-2722).

As described herein, NAF-associated short-term cultures were developed, thereby allowing for the investigation of the carcinoid tumor microenvironment with a view to better understanding the mechanisms that drive tumor progression facilitating improvements in therapeutic intervention. Secreted proteins drive cancer associated fibroblast development within the tumor microenvironment at the crossroads of pro-malignant tumor-stroma interactions (Mishra et al., 2011 J Leuk. Biol., 89: 31-39). Secreted cytokines and chemokines are involved in a diverse array of processes including leukocyte infiltration, angiogenesis, and regulation of malignancy-related functions (Ben-Baruch A, 2006 Cancer Met. Rev., 25: 357-371).

Described herein is the development of a collection of short term NAF cell cultures from patient tumors. As described in detail below, NAF supernatants were collected, and *in vitro* multiplexed analysis of secreted proteins was peformed to identify a signature profile that characterizes metastatic SINETs. As described herein, NAF secretion profiles can be replicated in plasma derived from the same patients. Finally, the results presented herein identify secreted biomarkers that are implicated in SINET growth and metastasis.

In a disease where in vitro and in vivo models are limited, generation and characterization of patient-derived cancer-associated fibroblast (CAF) cultures, described below, elucidated the role CAFs play in the pathogenesis of small intestine neuroendocrine tumors (SINET) biology and insight into the mechanisms by which CAFs drive SINET tumorigenesis. As described in detail below, the small bowel neuroendocrine tumor (SINET) microenvironment was investigated to shed light on tumor-stromal interactions and to identify stromal biomarkers

of clinical utility. Experiments established and histologically characterized patient-derived cancer-associated fibroblasts (CAFs) in vitro from disaggregated freshly resected small intestine neuroendocrine tumors. More specifically, short-term Neuroendocrine-Associated Fibroblast (NAF) cell cultures were generated from disaggregated resected tissue. A panel of secreted proteins was screened in the supernatants over the time course, 24-72hr. As described in the examples below, these NAFs have unique secretion profiles with respect to normal human fibroblasts. Accordingly, a panel of up- and downregulated secreted markers that characterize the SINET patient population was identified. CAFs, in comparison to normal human fibroblasts exhibited pro-oncogenic characteristics, including high secretion of IL-6, MCP-1 and VEGF and other related cytokines and chemokines associated with an NFkB activated state that is distinct from normal human fibroblasts. The secretion profiling was replicated in matched patient plasma, confirming the identification of MCP-1, IL-6, and VEFG as upregulated NAF-specific biomarkers that correlated with the differential expression found in the short-term culture supernatants. In other words, this pro-oncogenic signature was recapitulated in plasma from the originating metastatic SINET patients.

As described in detail below, the NAFs were treated with Withaferin A (WFA), a potent inhibitor of NFkB activation, resulting in significant dose-dependent cell death, suppression of the upregulated secreted proteins, and knockdown of transcriptional activity of their corresponding genes. Consistent with their NFkB activated state, experiments found that CAFs were highly sensitive to Withaferin A, which resulted in CAFs cell death, suppression of the pro-oncogenic secretion signature/profile, transcriptional downregulation of mRNA levels of the associated/corresponding genes and ultimately blockade of EMT in the treated CAFs. These results provide the first characterization of cancer-associated fibroblasts in small intestine neuroendocrine tumors, and suggest that these fibroblasts have pro-oncogenic properties consistent with an NFkB activated state. Thus, targeting CAFs in small intestine neuroendocrine tumors has therapeutic potential.

As described herein, the short-term NAF cultures were characterized and a panel of upregulated biomarkers including IL-6, MCP-1 and VEGF was identified. Targeting the NFkB pathway in the stromal environment in SINETs has important clinical implications. Finally, NAF short-term cultures are a valuable tool in elucidating the underlying poorly understood SINET biology.

Gene Expression Profiling

In general, methods of gene expression profiling can be divided into two large groups: methods based on hybridization analysis of polynucleotides, and methods based on sequencing of polynucleotides. Methods known in the art for the quantification of mRNA expression in a sample include northern blotting and in situ hybridization, RNAse protection assays, RNA-seq, and reverse transcription polymerase chain reaction (RT-PCR). Alternatively, antibodies are employed that recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes. Representative methods for sequencing-based gene expression analysis include Serial Analysis of Gene Expression (SAGE), and gene expression analysis by massively parallel signature sequencing (MPSS). For example, RT-PCR is used to compare mRNA levels in different sample populations, in normal and tumor tissues, with or without drug treatment, to characterize patterns of gene expression, to discriminate between closely related mRNAs, and/or to analyze RNA structure. As described herein, a bead-based multiplexing approach screens for biomarkers of metastatic SINET disease.

In some cases, a first step in gene expression profiling by RT-PCR is the reverse transcription of the RNA template into cDNA, followed by amplification in a PCR reaction. For example, extracted RNA is reverse-transcribed using a GeneAmp RNA PCR kit (Perkin Elmer, Calif., USA), following the manufacturer's instructions. The cDNA is then used as template in a subsequent PCR amplification and quantitative analysis using, for example, a TaqMan RTM (Life Technologies, Inc., Grand Island, N.Y.) assay.

Microarrays

Differential gene expression can also be identified, or confirmed using a microarray technique. In these methods, polynucleotide sequences of interest (including cDNAs and oligonucleotides) are plated, or arrayed, on a microchip substrate. The arrayed sequences are then hybridized with specific DNA probes from cells or tissues of interest. Just as in the RT-PCR method, the source of mRNA typically is total RNA isolated from human tumors or tumor cell lines and corresponding normal tissues or cell lines. Thus, RNA is isolated from a variety of primary tumors or tumor cell lines. If the source of mRNA is a primary tumor, mRNA is extracted from frozen or archived tissue samples.

In the microarray technique, PCR-amplified inserts of cDNA clones are applied to a substrate in a dense array. The microarrayed genes, immobilized on the microchip, are suitable for hybridization under stringent conditions.

In some cases, fluorescently labeled cDNA probes are generated through incorporation of fluorescent nucleotides by reverse transcription of RNA extracted from tissues of interest (e.g., SINET tissue). Labeled cDNA probes applied to the chip hybridize with specificity to loci of DNA on the array. After washing to remove non-specifically bound probes, the chip is scanned by confocal laser microscopy or by another detection method, such as a charge-coupled device (CCD) camera. Quantification of hybridization of each arrayed element allows for assessment of corresponding mRNA abundance.

In some configurations, dual color fluorescence is used. With dual color fluorescence, separately labeled cDNA probes generated from two sources of RNA are hybridized pairwise to the array. The relative abundance of the transcripts from the two sources corresponding to each specified gene is thus determined simultaneously. In various configurations, the miniaturized scale of the hybridization can afford a convenient and rapid evaluation of the expression pattern for large numbers of genes. In various configurations, such methods can have sensitivity required to detect rare transcripts, which are expressed at fewer than 1000, fewer than 100, or fewer than 10 copies per cell. In various configurations, such methods can detect at least approximately two-fold differences in expression levels (Schena et al., Proc. Natl. Acad. Sci. USA 93(2): 106-149 (1996)). In various configurations, microarray analysis is performed by commercially available equipment, following manufacturer's protocols, such as by using the Affymetrix GenChip technology, or Incyte's microarray technology.

RNA-seq

RNA sequencing (RNA-seq), also called whole transcriptome shotgun sequencing (WTSS), uses next-generation sequencing (NGS) to reveal the presence and quantity of RNA in a biological sample at a given moment in time.

RNA-Seq is used to analyze the continually changing cellular transcriptome. *See*, e.g., Wang et al., 2009 Nat Rev Genet, 10(1): 57-63, incorporated herein by reference. Specifically, RNA-Seq facilitates the ability to look at alternative gene spliced transcripts, post-transcriptional modifications, gene fusion, mutations/SNPs and changes in gene expression. In addition to mRNA transcripts, RNA-Seq can look at different populations of RNA to include total RNA,

small RNA, such as miRNA, tRNA, and ribosomal profiling. RNA-Seq can also be used to determine exon/intron boundaries and verify or amend previously annotated 5' and 3' gene boundaries.

Prior to RNA-Seq, gene expression studies were done with hybridization-based microarrays. Issues with microarrays include cross-hybridization artifacts, poor quantification of lowly and highly expressed genes, and needing to know the sequence of interest. Because of these technical issues, transcriptomics transitioned to sequencing-based methods. These progressed from Sanger sequencing of Expressed Sequence Tag libraries, to chemical tag-based methods (e.g., serial analysis of gene expression), and finally to the current technology, NGS of cDNA (notably RNA-Seq).

Gene Signature

Described herein is a gene signature which identifies biomarkers of metastatic small bowel neuroendocrine tumors. Exemplary distinguishing genes are provided below.

An exemplary human Angiopoietin amino acid sequence is set forth below (SEQ ID NO: 1; GenBank Accession No: AAM92271, Version 1, incorporated herein by reference):

```
  1 mtvflsfafl aailthigcs nqrrspensg rrynriqhgq caytfilpeh dgncresttd
 61 qyntnalqrd aphvepdfss qklqhlehvm enytqwlqkl enyivenmks emaqiqqnav
121 qnhtatmlei gtsllsqtae qtrkltdvet qvlnqtsrle iqllenslst yklekqllqq
181 tneilkihek nsllehkile megkhkeeld tlkeekenlq glvtrqtyii qelekqlnra
241 ttnnsvlqkq qlelmdtvhn lvnlctkevl lkggkreeek pfrdcadvyq agfnksgiyt
301 iyinnmpepk kvfcnmdvng ggwtviqhre dgsldfqrgw keykmgfgnp sgeywlgnef
361 ifaitsqrqy mlrielmdwe gnraysqydr fhignekqny rlylkghtgt agkqsslilh
421 gadfstkdad ndncmckcal mltggwwfda cgpsnlngmf ytagqnhgkl ngikwhyfkg
481 psyslrsttm mirpldf
```

An exemplary human *Angiopoietin* nucleic acid sequence is set forth below (SEQ ID NO: 2; GenBank Accession No: AY124380, Version 1, incorporated herein by reference):

```
   1 atgacagttt tcctttcctt tgctttcctc gctgccattc tgactcacat agggtgcagc
 61 aatcagcgcc gaagtccaga aaacagtggg agaagatata accggattca acatgggcaa
121 tgtgcctaca ctttcattct tccagaacac gatggcaact gtcgtgagag tacgacagac
181 cagtacaaca caaacgctct gcagagagat gctccacacg tggaaccgga tttctcttcc
241 cagaaacttc aacatctgga acatgtgatg gaaaattata ctcagtggct gcaaaaactt
301 gagaattaca ttgtggaaaa catgaagtcg gagatggccc agatacagca gaatgcagtt
361 cagaaccaca cggctaccat gctggagata ggaaccagcc tcctctctca gactgcagag
421 cagaccagaa agctgacaga tgttgagacc caggtactaa atcaaacttc tcgacttgag
481 atacagctgc tggagaattc attatccacc tacaagctag agaagcaact tcttcaacag
541 acaaatgaaa tcttgaagat ccatgaaaaa aacagtttat tagaacataa aatcttagaa
601 atggaaggaa aacacaagga agagttggac accttaaagg aagagaaaga gaaccttcaa
661 ggcttggtta ctcgtcaaac atatataatc caggagctgg aaaagcaatt aaacagagct
721 accaccaaca acagtgtcct tcagaagcag caactggagc tgatggacac agtccacaac
781 cttgtcaatc tttgcactaa agaagtttta ctaaagggag gaaaaagaga ggaagagaaa
841 ccatttagag actgtgcaga tgtatatcaa gctggtttta ataaaagtgg aatctacact
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 901 atttatatta ataatatgcc agaacccaaa aaggtgtttt gcaatatgga tgtcaatggg
 961 ggaggttgga ctgtaataca acatcgtgaa gatggaagtc tagatttcca aagaggctgg
1021 aaggaatata aaatgggttt tggaaatccc tccggtgaat attggctggg gaatgagttt
1081 atttttgcca ttaccagtca gaggcagtac atgctaagaa ttgagttaat ggactgggaa
1141 gggaaccgag cctattcaca gtatgacaga ttccacatag gaaatgaaaa gcaaaactat
1201 aggttgtatt taaaaggtca cactgggaca gcaggaaaac agagcagcct gatcttacac
1261 ggtgctgatt tcagcactaa agatgctgat aatgacaact gtatgtgcaa atgtgccctc
1321 atgttaacag gaggatggtg gtttgatgct tgtggcccct ccaatctaaa tggaatgttc
1381 tatactgcgg gacaaaacca tggaaaactg aatgggataa agtggcacta cttcaaaggg
1441 cccagttact ccttacgttc cacaactatg atgattcgac ctttagattt ttga
```

An exemplary human epidermal growth factor (EGF) amino acid sequence is set forth below (SEQ ID NO: 3; GenBank Accession No: NP_001954, Version 2, incorporated herein by reference):

```
   1 mlltliillp vvskfsfvsl sapqhwscpe gtlagngnst cvgpapflif shgnsifrid
  61 tegtnyeqlv vdagvsvimd fhynekriyw vdlerqllqr vflngsrqer vcnieknvsg
 121 mainwineev iwsnqqegii tvtdmkgnns hillsalkyp anvavdpver fifwssevag
 181 slyradldgv gvkalletse kitavsldvl dkrlfwiqyn regsnslics cdydggsvhi
 241 skhptqhnlf amslfgdrif ystwkmktiw iankhtgkdm vrinlhssfv plgelkvvhp
 301 laqpkaeddt wepeqklckl rkgncsstvc gqdlqshlcm caegyalsrd rkycedvnec
 361 afwnhgctlg ckntpgsyyc tcpvgfvllp dgkrchqlvs cprnvsecsh dcvltsegpl
 421 cfcpegsvle rdgktcsgcs spdnggcsql cvplspvswe cdcfpgydlq ldekscaasg
 481 pqpfllfans qdirhmhfdg tdygtllsqq mgmvyaldhd pvenkiyfah talkwieran
 541 mdgsqrerli eegvdvpegl avdwigrrfy wtdrgkslig rsdlngkrsk iitkenisqp
 601 rgiavhpmak rlfwtdtgin priessslqg lgrlviassd liwpsgitid fltdklywcd
 661 akqsvieman ldgskrrrlt qndvghpfav avfedyvwfs dwampsvmrv nkrtgkdrvr
 721 lqgsmlkpss lvvvhplakp gadpclyqng gcehickkrl gtawcscreg fmkasdgktc
 781 laldghqlla ggevdlknqv tpldilsktr vsednitesq hmlvaeimvs dqddcapvgc
 841 smyarciseg edatcqclkg fagdgklcsd idecemgvpv cppasskcin teggyvcrcs
 901 egyqgdgihc ldidecqlge hscgenasct nteggytcmc agrlsepgli cpdstppphl
 961 reddhhysvr nsdsecplsh dgyclhdgvc myiealdkya cncvvgyige rcqyrdlkww
1021 elrhaghgqq qkvivvavcv vvlvmlllls lwgahyyrtq kllsknpknp yeessrdvrs
1081 rrpadtedgm sscpqpwfvv ikehqdlkng gqpvagedgq aadgsmqpts wrqepqlcgm
1141 gteqgcwipv ssdkgscpqv mersfhmpsy gtqtleggve kphsllsanp lwqqraldpp
1201 hqmeltq
```

An exemplary human *EGF* nucleic acid sequence is set forth below (SEQ ID NO: 4; GenBank Accession No: NM_001963, Version 3, incorporated herein by reference):

```
   1 aaaaagagaa actgttggga gaggaatcgt atctccatat ttcttctttc agccccaatc
  61 caagggttgt agctggaact ttccatcagt tcttcctttc tttttcctct ctaagccttt
 121 gccttgctct gtcacagtga agtcagccag agcagggctg ttaaactctg tgaaatttgt
 181 cataagggtg tcaggtattt cttactggct tccaaagaaa catagataaa gaaatctttc
 241 ctgtggcttc ccttggcagg ctgcattcag aaggtctctc agttgaagaa agagcttgga
 301 ggacaacagc acaacaggag agtaaaagat gccccagggc tgaggcctcc gctcaggcag
 361 ccgcatctgg ggtcaatcat actcaccttg cccgggccat gctccagcaa aatcaagctg
 421 ttttcttttg aaagttcaaa ctcatcaaga ttatgctgct cactcttatc attctgttgc
 481 cagtagtttc aaaatttagt tttgttagtc tctcagcacc gcagcactgg agctgtcctg
 541 aaggtactct cgcaggaaat gggaattcta cttgtgtggg tcctgcaccc ttcttaattt
 601 tctcccatgg aaatagtatc tttaggattg acacagaagg aaccaattat gagcaattgg
 661 tggtggatgc tggtgtctca gtgatcatgg attttcatta taatgagaaa agaatctatt
 721 gggtggattt agaaagacaa cttttgcaaa gagtttttct gaatgggtca aggcaagaga
```

781 gagtatgtaa tatagagaaa aatgtttctg gaatggcaat aaattggata aatgaagaag
841 ttatttggtc aaatcaacag gaaggaatca ttacagtaac agatatgaaa ggaaataatt
901 cccacattct tttaagtgct ttaaaatatc ctgcaaatgt agcagttgat ccagtagaaa
961 ggtttatatt ttggtcttca gaggtggctg gaagccttta tagagcagat ctcgatggtg
1021 tgggagtgaa ggctctgttg gagacatcag agaaaataac agctgtgtca ttggatgtgc
1081 ttgataagcg gctgttttgg attcagtaca acagagaagg aagcaattct cttatttgct
1141 cctgtgatta tgatggaggt tctgtccaca ttagtaaaca tccaacacag cataatttgt
1201 ttgcaatgtc ccttttggt gaccgtatct tctattcaac atggaaaatg aagacaattt
1261 ggatagccaa caaacacact ggaaaggaca tggttagaat taacctccat tcatcatttg
1321 taccacttgg tgaactgaaa gtagtgcatc cacttgcaca acccaaggca gaagatgaca
1381 cttgggagcc tgagcagaaa ctttgcaaat tgaggaaagg aaactgcagc agcactgtgt
1441 gtgggcaaga cctccagtca cacttgtgca tgtgtgcaga gggatacgcc ctaagtcgag
1501 accggaagta ctgtgaagat gttaatgaat gtgctttttg gaatcatggc tgtactcttg
1561 ggtgtaaaaa caccctgga tcctattact gcacgtgccc tgtaggattt gttctgcttc
1621 ctgatgggaa acgatgtcat caacttgttt cctgtccacg caatgtgtct gaatgcagcc
1681 atgactgtgt tctgacatca gaaggtccct tatgtttctg tcctgaaggc tcagtgcttg
1741 agagagatgg gaaaacatgt agcggttgtt cctcacccga taatggtgga tgtagccagc
1801 tctgcgttcc tcttagccca gtatcctggg aatgtgattg ctttcctggg tatgacctac
1861 aactggatga aaaaagctgt gcagcttcag gaccacaacc atttttgctg tttgccaatt
1921 ctcaagatat tcgacacatg cattttgatg gaacagacta tggaactctg ctcagccagc
1981 agatgggaat ggtttatgcc ctagatcatg accctgtgga aaataagata tactttgccc
2041 atacagccct gaagtggata gagagagcta atatggatgg ttcccagcga gaaaggctta
2101 ttgaggaagg agtagatgtg ccagaaggtc ttgctgtgga ctggattggc cgtagattct
2161 attggacaga cagagggaaa tctctgattg gaaggagtga tttaaatggg aaacgttcca
2221 aaataatcac taaggagaac atctctcaac cacgaggaat tgctgttcat ccaatggcca
2281 agagattatt ctggactgat acagggatta atccacgaat tgaaagttct tccctccaag
2341 gccttggccg tctggttata gccagctctg atctaatctg gcccagtgga ataacgattg
2401 acttcttaac tgacaagttg tactggtgcg atgccaagca gtctgtgatt gaaatggcca
2461 atctggatgg ttcaaaacgc cgaagactta cccagaatga tgtaggtcac ccatttgctg
2521 tagcagtgtt tgaggattat gtgtggttct cagattgggc tatgccatca gtaatgagag
2581 taaacaagag gactggcaaa gatagagtac gtctccaagg cagcatgctg aagccctcat
2641 cactggttgt ggttcatcca ttggcaaaac caggagcaga tccctgctta tatcaaaacg
2701 gaggctgtga acatatttgc aaaaagaggc ttggaactgc ttggtgttcg tgtcgtgaag
2761 gttttatgaa agcctcagat gggaaaacgt gtctggctct ggatggtcat cagctgttgg
2821 caggtggtga agttgatcta aagaaccaag taacaccatt ggacatcttg tccaagacta
2881 gagtgtcaga agataacatt acagaatctc aacacatgct agtggctgaa atcatggtgt
2941 cagatcaaga tgactgtgct cctgtgggat gcagcatgta tgctcggtgt atttcagagg
3001 gagaggatgc cacatgtcag tgtttgaaag gatttgctgg ggatggaaaa ctatgttctg
3061 atatagatga atgtgagatg ggtgtcccag tgtgcccccc tgcctcctcc aagtgcatca
3121 acaccgaagg tggttatgtc tgccggtgct cagaaggcta ccaaggagat gggattcact
3181 gtcttgatat tgatgagtgc caactggggg agcacagctg tggagagaat gccagctgca
3241 caaatacaga gggaggctat acctgcatgt gtgctggacg cctgtctgaa ccaggactga
3301 tttgccctga ctctactcca ccccctcacc tcagggaaga tgaccaccac tattccgtaa
3361 gaaatagtga ctctgaatgt cccctgtccc acgatgggta ctgcctccat gatggtgtgt
3421 gcatgtatat tgaagcattg gacaagtatg catgcaactg tgttgttggc tacatcgggg
3481 agcgatgtca gtaccgagac ctgaagtggt gggaactgcg ccacgctggc cacgggcagc
3541 agcagaaggt catcgtggtg gctgtctgcg tggtggtgct tgtcatgctg ctcctcctga
3601 gcctgtgggg ggcccactac tacaggactc agaagctgct atcgaaaaac ccaaagaatc
3661 cttatgagga gtcgagcaga gatgtgagga gtcgcaggcc tgctgacact gaggatggga
3721 tgtcctcttg ccctcaacct tggtttgtgg ttataaaaga acaccaagac ctcaagaatg
3781 ggggtcaacc agtggctggt gaggatggcc aggcagcaga tgggtcaatg caaccaactt
3841 catggaggca ggagccccag ttatgtggaa tgggcacaga gcaaggctgc tggattccag
3901 tatccagtga taagggctcc tgtccccagg taatggagcg aagctttcat atgccctcct
3961 atgggacaca gacccttgaa gggggtgtcg agaagcccca ttctctccta tcagctaacc
4021 cattatggca acaaagggcc ctggacccac cacaccaaat ggagctgact cagtgaaaac
4081 tggaattaaa aggaaagtca agaagaatga actatgtcga tgcacagtat cttttctttc

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4141 aaaagtagag caaaactata ggttttggtt ccacaatctc tacgactaat cacctactca
4201 atgcctggag acagatacgt agttgtgctt ttgtttgctc ttttaagcag tctcactgca
4261 gtcttatttc caagtaagag tactgggaga atcactaggt aacttattag aaacccaaat
4321 tgggacaaca gtgctttgta aattgtgttg tcttcagcag tcaatacaaa tagatttttg
4381 tttttgttgt tcctgcagcc ccagaagaaa ttaggggtta aagcagacag tcacactggt
4441 ttggtcagtt acaaagtaat ttctttgatc tggacagaac atttatatca gtttcatgaa
4501 atgattggaa tattacaata ccgttaagat acagtgtagg catttaactc ctcattggcg
4561 tggtccatgc tgatgatttt gcaaaatgag ttgtgatgaa tcaatgaaaa atgtaattta
4621 gaaactgatt tcttcagaat tagatggctt atttttaaa atatttgaat gaaaacattt
4681 tatttttaaa atattacaca ggaggcttcg gagtttctta gtcattactg tccttttccc
4741 ctacagaatt ttccctcttg gtgtgattgc acagaatttg tatgtatttt cagttacaag
4801 attgtaagta aattgcctga tttgttttca ttatagacaa cgatgaattt cttctaatta
4861 tttaaataaa atcaccaaaa acataaacat tttattgtat gcctgattaa gtagttaatt
4921 atagtctaag gcagtactag agttgaacca aaatgatttg tcaagcttgc tgatgtttct
4981 gtttttcgtt ttttttttt ttccggagag aggataggat ctcactctgt tatccaggct
5041 ggagtgtgca atggcacaat catagctcag tgcagcctca aactcctggg ctcaagcaat
5101 cctcctgcct cagcctcccg agtaactagg accacaggca caggccacca tgcctggcta
5161 aggtttttat ttttatttt tgtagacatg gggatcacac aatgttgccc aggctggtct
5221 tgaactcctg gcctcaagca aggtcgtgct ggtaattttg caaaatgaat tgtgattgac
5281 tttcagcctc ccaacgtatt agattatagg cattagccat ggtgcccagc cttgtaactt
5341 ttaaaaaaat tttttaatct acaactctgt agattaaaat ttcacatggt gttctaatta
5401 aatatttttc ttgcagccaa gatattgtta ctacagataa cacaacctga tatggtaact
5461 ttaaattttg ggggctttga atcattcagt ttatgcatta actagtccct ttgtttatct
5521 ttcatttctc aacccccttgt actttggtga taccagacat cagaataaaa agaaattgaa
5581 gtacctgttt tcaaatggat actttatagg aattttggta aagatttggt gatgggagga
5641 tgacttgagg tttgtggata ttagttaatt attcagtatg atacctcacc cagctaattt
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An exemplary human Endoglin amino acid sequence is set forth below (SEQ ID NO: 5; GenBank Accession No: AAC63386, Version 1, incorporated herein by reference):

```
  1 mdrgtlplav alllascsls ptslaetvhc dlqpvgperg evtyttsqvs kgcvaqapna
 61 ilevhvlfle fptgpsqlel tlqaskqngt wprevllvls vnssvflhlq algiplhlay
121 nsslvtfqep pgvnttelps fpktqilewa aergpitsaa elndpqsill rlgqaqgsls
181 fcmleasqdm grtlewrprt palvrgchle gvaghkeahi lrvlpghsag prtvtvkvel
241 scapgdldav lilqgppyvs wlidanhnmq iwttgeysfk ifpeknirgf klpdtpqgll
301 gearmlnasi vasfvelpla sivslhassc ggrlqtspap iqttppkdtc spellmsliq
361 tkcaddamtl vlkkelvahl kctitgltfw dpsceaedrg dkfvlrsays scgmqvsasm
421 isneavvnil sssspqrkkv hclnmdslsf qlglylsphf lqasntiepg qqsfvqvrvs
481 psvsefllql dschldlgpe ggtveliqgr aakgncvsll spspegdprf sfllhfytvp
541 ipktgtlsct valrpktgsq dqevhrtvfm rlniispdls gctskglvlp avlgitfgaf
601 ligalltaal wyiyshtrsp skrepvvava apassessst nhsigstqst pcstssma
```

An exemplary human *Endoglin* nucleic acid sequence is set forth below (SEQ ID NO: 6; GenBank Accession No: NM_001114753, Version 2, incorporated herein by reference):

```
1 acttcctcta cccggttggc aggcggcctg gcccagcccc ttctctaagg aagcgcattt
 61 cctgcctccc tgggccggcc gggctggatg agccgggagc tccctgctgc cggtcatacc
121 acagccttca tctgcgccct ggggccagga ctgctgctgt cactgccatc cattggagcc
181 cagcaccccc tccccgccca tccttcggac agcaactcca gcccagcccc gcgtccctgt
241 gtccacttct cctgacccct cggccgccac cccagaaggc tggagcaggg acgccgtcgc
301 tccggccgcc tgctcccctc gggtccccgt gcgagcccac gccggccccg gtgcccgccc
361 gcagccctgc cactggacac aggataaggc ccagcgcaca ggccccccacg tggacagcat
421 ggaccgcggc acgctccctc tggctgttgc cctgctgctg gccagctgca gcctcagccc
481 cacaagtctt gcagaaacag tccattgtga ccttcagcct gtgggccccg agaggggcga
```

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 541 ggtgacatat accactagcc aggtctcgaa gggctgcgtg gctcaggccc ccaatgccat
 601 ccttgaagtc catgtcctct tcctggagtt cccaacgggc ccgtcacagc tggagctgac
 661 tctccaggca tccaagcaaa atggcacctg gccccgagag gtgcttctgg tcctcagtgt
 721 aaacagcagt gtcttcctgc atctccaggc cctgggaatc ccactgcact tggcctacaa
 781 ttccagcctg gtcaccttcc aagagccccc gggggtcaac accacagagc tgccatcctt
 841 ccccaagacc cagatccttg agtgggcagc tgagaggggc cccatcacct ctgctgctga
 901 gctgaatgac ccccagagca tcctcctccg actgggccaa gcccaggggt cactgtcctt
 961 ctgcatgctg gaagccagcc aggacatggg ccgcacgctc gagtggcggc cgcgtactcc
1021 agccttggtc cggggctgcc acttggaagg cgtggccggc cacaaggagg cgcacatcct
1081 gagggtcctg ccgggccact cggccgggcc ccggacggtg acggtgaagg tggaactgag
1141 ctgcgcaccc ggggatctcg atgccgtcct catcctgcag ggtcccccct acgtgtcctg
1201 gctcatcgac gccaaccaca acatgcagat ctggaccact ggagaatact ccttcaagat
1261 ctttccagag aaaaacattc gtggcttcaa gctcccagac acacctcaag gcctcctggg
1321 ggaggcccgg atgctcaatg ccagcattgt ggcatccttc gtggagctac cgctggccag
1381 cattgtctca cttcatgcct ccagctgcgg tggtaggctg cagacctcac ccgcaccgat
1441 ccagaccact cctcccaagg acacttgtag cccggagctg ctcatgtcct tgatccagac
1501 aaagtgtgcc gacgacgcca tgaccctggt actaaagaaa gagcttgttg cgcatttgaa
1561 gtgcaccatc acgggcctga ccttctggga ccccagctgt gaggcagagg acaggggtga
1621 caagtttgtc ttgcgcagtg cttactccag ctgtggcatg caggtgtcag caagtatgat
1681 cagcaatgag gcggtggtca atatcctgtc gagctcatca ccacagcgga aaaaggtgca
1741 ctgcctcaac atggacagcc tctctttcca gctgggcctc tacctcagcc cacacttcct
1801 ccaggcctcc aacaccatcg agccggggca gcagagcttt gtgcaggtca gagtgtcccc
1861 atccgtctcc gagttcctgc tccagttaga cagctgccac ctggacttgg ggcctgaggg
1921 aggcaccgtg gaactcatcc agggccgggc ggccaagggc aactgtgtga gcctgctgtc
1981 cccaagcccc gagggtgacc cgcgcttcag cttcctcctc cacttctaca cagtacccat
2041 acccaaaacc ggcaccctca gctgcacggt agccctgcgt cccaagaccg ggtctcaaga
2101 ccaggaagtc cataggactg tcttcatgcg cttgaacatc atcagccctg acctgtctgg
2161 ttgcacaagc aaaggcctcg tcctgcccgc cgtgctgggc atcacctttg gtgccttcct
2221 catcggggcc ctgctcactg ctgcactctg gtacatctac tcgcacacgc gttcccccag
2281 caagcgggag cccgtggtgg cggtggctgc cccggcctcc tcggagagca gcagcaccaa
2341 ccacagcatc gggagcaccc agagcacccc ctgctccacc agcagcatgg catagccccg
2401 gccccccgcg ctcgcccagc aggagagact gagcagccgc cagctgggag cactggtgtg
2461 aactcaccct gggagccagt cctccactcg acccagaatg gagcctgctc tccgcgccta
2521 cccttcccgc ctccctctca gaggcctgct gccagtgcag ccactggctt ggaacacctt
2581 ggggtccctc caccccacag aaccttcaac ccagtgggtc tgggatatgg ctgcccagga
2641 gacagaccac ttgccacgct gttgtaaaaa cccaagtccc tgtcatttga acctggatcc
2701 agcactggtg aactgagctg ggcaggaagg gagaacttga aacagattca ggccagccca
2761 gccaggccaa cagcacctcc ccgctgggaa gagaagaggg cccagcccag agccacctgg
2821 atctatccct gcggcctcca cacctgaact tgcctaacta actggcaggg gagacaggag
2881 cctagcggag cccagcctgg gagcccagag ggtggcaaga acagtgggcg ttgggagcct
2941 agctcctgcc acatggagcc ccctctgccg gtcgggcagc cagcagaggg ggagtagcca
3001 agctgcttgt cctgggcctg cccctgtgta ttcaccacca ataaatcaga ccatgaaacc
3061 agtgaaaaaa aaaaaaa
```

An exemplary human Eotaxin amino acid sequence is set forth below (SEQ ID NO: 7; GenBank Accession No: CAB07027, Version 1, incorporated herein by reference):

```
 1 mkvsaallwl lliaaafspq gltgpasvpt tccfnlanrk iplqrlesyr ritsgkcpqk
61 avifktklak dicadpkkrw vqdsmkyldq ksptpkp
```

An exemplary human *Eotaxin* nucleic acid sequence is set forth below (SEQ ID NO: 8; GenBank Accession No: Z92709, Version 1, incorporated herein by reference):

```
   1 ctctaatacg actcactata gggcgtcgac tcgatcaagg cccctcattc atcaggcacc
  61 aaatcacagg caagaaattg gtctactcta cttcattgct gaaaagaaag cctccaagaa
 121 agaaagagaa aaagcccttg aagctgcccc tgcttgctag ggatggccag tgagctggat
 181 gaaacagctg cagagcttgg atatctaaag attgatttta tttatttcca ctgagccact
 241 gaggtttttc aggcgtagag taaatccaaa gcccattaac tccaaagcca ttttccaagg
 301 aaaacacaaa aatgaataat cgcttgctga taattccttt aattcccgcc agagttatga
 361 aattattctt actacagaaa caatcattaa accacgtcag acaaacacct ctgaggacaa
 421 taatattccc aaatttattc tgccgagaat tttttaaaac ttcgtatctg ccacatgtgc
 481 aactcaggca ttcttggaaa ccatccctgc ggtagcatat ctttacttgg aagcagtggg
 541 aaaacttgga agaatatttg gagaaatatc cagactctga ggtctttcca acattcccaa
 601 tctgcccttc ttttttttct tttttgagac acagtctcac tctgttgccc aggttggagt
 661 gcagtggcat gatctctgcc cattgcaacc tttgtccccc gtgttcaagc aattctcatg
 721 cctcagcttc ctgagtagct gagactacaa acaccatcca ccatggctgg ctaatttttt
 781 gtatttttag taaagacagg ttttcaccat gttgcccagg ctggtcttga actcctgacc
 841 tcgagtgatc tgcctgcctc agtctcccaa agtgctggga ttacaagtgt gagccactgt
 901 acccggccct attccctaat aataaaaaac agtaacttct actcactgag tatctacagt
 961 gatttagtca ttcttctaag cagtttagat acatgaactc atttaattca cacgacaatt
1021 ccctaaagta cacatgatta gtatcctgct cttaccctag cagagagtgg ttaagtaagt
1081 tgtccatggt atcacagcta gtcagtcaca gagccatcat ccaaatgcag atatcctgaa
1141 ttcaggttct acattagact aacccaccgg gaatggagca ggaaagaaca gggaagactc
1201 cacatttttg gcctctattt ggtaattata gttaactttt taggtaatta tagaccaatt
1261 atcctagatg ggcacttaga gactttgcag gacagcaaga gctgtctcta atcctgtgcc
1321 catgacagac atcaccagtc aaccacaaca cagtatttaa ctaacgcaag tcaactcctc
1381 agaatcttta acataccttg tttgtgctac tgtaccaatc aatcaatttg atatgagagt
1441 gtgcaggaaa aaacaggaaa caggtttgca gtacctccac accagtattc aatgctgtaa
1501 tccgctgcag tgactccatt aaatactttg cctcccttat accctctcca actagggtgc
1561 ctagtgttat gaacaaaggg atatgtatag gttcttgtgt tgcctctctc tttgatattt
1621 ttagccatca gataccttgt ctgcaatgtg tgctcagaga gtgaggggag aactagatga
1681 ttgattttcc aaawtgtgtc cctaaacgtg ctccctgggg aataagggca cgagaggctg
1741 cctattctat ttcaaacaaa tccccttcac tacagtgtat ttgatgagtt ggggtttgtt
1801 ttaattccat ttggaaaagg gctttagcag ctaagcaaat ggttttaaag tgcctcagaa
1861 gtcaagatta atagaaacta tccagttctg atgtcctatc atgctaaaat ttcagggact
1921 aagattctgt gatcattaca ttgaaacaca gcagcaaagc tgtggtgtgt tgtccttcct
1981 ggttcagaga tgcaactatg tgcagggctg ctgagctctc tctgcatctg ggtgggagcc
2041 taatggaagt tttggggctc cttactggtc tccaaaatcc tcaagaccac catgtgaaca
2101 caggaatcaa ggaaggttct tagatcgact catcccccag gcctttggtt tccttgctcc
2161 tttccccgac tacaggtgtt tcatttcaac tcatccccta gggccttggt tttcttgctc
2221 tcttccccca ctacagatgt ttaacttcat ttcataacca catattcccc tccttttcca
2281 aggcaagatc cagatggatt aaaaattgta ccaagtccct cctactagtc ttgcctctct
2341 tctgttctgc ttgacttcct aggatctgga atctggtcag caatcaggaa tcccttcatc
2401 gtgaccccgc atgggcaaag gcttccctgg aatctcccac actgtctgct ccctataaaa
2461 ggcaggcaga tgggccagag gagcagagag gctgagacca acccagaaac caccaccttc
2521 tcacgccaaa gctcacacct tcagcctcca acatgaaggt ctccgcagca cttctgtggc
2581 tgctgctcat agcagctgcc ttcagccccc aggggctcac tgggccaggt aagccccccа
2641 actccttaca ggaaaggtaa ggtaaccacc tccagagcta ctaggtcagc aagaatcttt
2701 acagactcac tgcaaattct ccatttgaaa aatagggaaa caggttttgt gggtggacaa
2761 gaaatgcctc aaccgtcaca tccagtcact ggaagagcca gaactagaaa gctcccgagt
2821 cttttcccac attcaagagg gttgctgggt gcatccatac ccagctatcc ttacagtgtt
2881 tgggaatggg gaatggctct gtcttactgt gggcatggtg ggcatttttg gcagtgggag
2941 agaaggaaaa tctgttgatt agaagctcag tatgttaatt cgactccagg acagctttca
3001 gagacagtgg ctaagagaag aacgaggtcc caggggatc tcttgaggtg acttattttg
3061 acactctttg ggaaagttat ctaggagatt tgttccataa ctcattttcc catactctgg
3121 tgacaaattt actgagtgta tcggtcccac tgagccagtg catagcatgg taacaaacag
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3181 ttctaaatta tcaatgactt aacagaatta actaaattaa caaaagttac tttctcactt
3241 gtactaaata tctataatgt atgggctcag gcttctgcat tttatactca ggattctaga
3301 ctgatggaga agttgcccat gtgggggaac attgatggat actgtgataa agcagaagaa
3361 agctctcagg agtcttgcat aggcaatgca ctgtggctca aaaatgacac ccatcacttt
3421 gtctccttct ttattgatca aaactaatta atgcctccaa ccaaacaaaa gtggccaaga
3481 aatgcaagtc taccttgtgt ctcaaaacag aggatggaga atatttggtg aaaattacca
3541 tgaccatcac atggccacgt aggtctttat aatgacagag ctagcatttg tcacattgac
3601 caagctttgt ccatacactc tacagtaatg atgagtcctc agtgcacagg ggaggatgct
3661 gaagacacag gacagcatcc tccagacaca taagacttca gagcagaggg attctccctc
3721 cacctctcgc aattccttgc tttctcctaa cttcctttac aaagtcatgc ttggaaatgt
3781 ctatgtatca tcatgtggct catttttttc tctgttcact ttttttcccc aaaattcagc
3841 ttctgtccca accacctgct gctttaacct ggccaatagg aagatacccc ttcagcgact
3901 agagagctac aggagaatca ccagtggcaa atgtccccag aaagctgtga tgtaagtaaa
3961 taaagttcac cctcccctgg acaaaaaaat aatgtctagg gcacagagtc aagaactgtg
4021 tcacagttgc tgggagtcat agactctgat agtttgacct ctatggtcca attcattaat
4081 tttcacaagt gagtgttcac tcccagctcc ctgcctggga gattgctgta gtcatatcaa
4141 tttcttcaag tcaagagcaa agatggtttt actgggcctt taagagcagc aactaaccca
4201 agagtctcat ccttcctcct ctccgtagca acccttttgtc caggggcaga tggtccttaa
4261 atatttgggg tcaaatgggc agaattttca aaaacaatcc ttccaattgc atcctgtatc
4321 tccccacagc ttcaagacca aactggccaa ggatatctgt gccgacccca agaagaggtg
4381 ggtgcaggat tccatgaagt atctggacca aaaatctcca actccaaagc cataaataat
4441 caccatttttt gaaaccaaac cagagcctga gtgttgccta atttgttttc ccttcttaca
4501 atgcattctg aggtaacctc attatcagtc caaagggcat gggttttatt atatatatat
4561 atatatattt ttttttaaaa aaaaacgtat tgcatttaat ttattgaggc tttaaaactt
4621 atcctccatg aatatcagtt acttttaaac tgtaaagctt tgtgcagatt ctttaccccc
4681 tgggagcccc aattcgatcc cctgtcacgt gtgggcaatg ttccccctct cctctcttcc
4741 tccctggaat ctttaaaggt cctggcaaag atgatcagta tgaaaatgtc attgttcttg
4801 tgaacccaaa gtgtgactca ttaaatggaa gtaaatgttg ttttaggaat acataaagta
4861 tgtgcatatt t
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An exemplary human Fibroblast growth factor (FGF) Basic amino acid sequence is set forth below (SEQ ID NO: 9; GenBank Accession No: NP_001997, Version 5, incorporated herein by reference):

```
  1 mvgvgggdve dvtprpggcq isgrgargcn gipgaaawea alprrrprrh psvnprsraa
 61 gsprtrgrrt eerpsgsrlg drgrgralpg grlggrgrgr apervggrgr grgtaapraa
121 paargsrpgp agtmaagsit tlpalpedgg sgafppghfk dpkrlyckng gfflrihpdg
181 rvdgvreksd phiklqlqae ergvvsikgv canrylamke dgrllaskcv tdecffferl
241 esnnyntyrs rkytswyval krtgqyklgs ktgpgqkail flpmsaks
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An exemplary human *FGF Basic* nucleic acid sequence is set forth below (SEQ ID NO: 10; GenBank Accession No: NM_002006, Version 4, incorporated herein by reference):

```
  1 cggccccaga aaacccgagc gagtaggggg cggcgcgcag gagggaggag aactgggggc
 61 gcgggaggct ggtgggtgtg gggggtggag atgtagaaga tgtgacgccg cggcccggcg
121 ggtgccagat tagcggacgc ggtgcccgcg gttgcaacgg gatcccgggc gctgcagctt
181 gggaggcggc tctccccagg cggcgtccgc ggagacaccc atccgtgaac cccaggtccc
241 gggccgccgg ctcgccgcgc accaggggcc ggcggacaga agagcggccg agcggctcga
301 ggctgggggа ccgcgggcgc ggccgcgcgc tgccgggcgg gaggctgggg ggccggggcc
361 ggggccgtgc cccggagcgg gtcggaggcc ggggccgggg ccgggggacg gcggctcccc
421 gcgcggctcc agcggctcgg ggatcccggc cgggccccgc agggaccatg gcagccggga
481 gcatcaccac gctgcccgcc ttgcccgagg atggcggcag cggcgccttc ccgcccggcc
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 541 acttcaagga ccccaagcgg ctgtactgca aaaacggggg cttcttcctg cgcatccacc
 601 ccgacggccg agttgacggg gtccgggaga agagcgaccc tcacatcaag ctacaacttc
 661 aagcagaaga gagaggagtt gtgtctatca aaggagtgtg tgctaaccgt tacctggcta
 721 tgaaggaaga tggaagatta ctggcttcta aatgtgttac ggatgagtgt ttctttttg
 781 aacgattgga atctaataac tacaatactt accggtcaag gaaatacacc agttggtatg
 841 tggcactgaa acgaactggg cagtataaac ttggatccaa aacaggacct gggcagaaag
 901 ctatactttt tcttccaatg tctgctaaga gctgatttta atggccacat ctaatctcat
 961 ttcacatgaa agaagaagta tattttagaa atttgttaat gagagtaaaa gaaaataaat
1021 gtgtatagct cagtttggat aattggtcaa acaatttttt atccagtagt aaaatatgta
1081 accattgtcc cagtaaagaa aaataacaaa agttgtaaaa tgtatattct ccctttttata
1141 ttgcatctgc tgttacccag tgaagcttac ctagagcaat gatctttttc acgcatttgc
1201 tttattcgaa aagaggcttt taaaatgtgc atgtttagaa acaaaatttc ttcatggaaa
1261 tcatatacat tagaaaatca cagtcagatg tttaatcaat ccaaaatgtc cactatttct
1321 tatgtcattc gttagtctac atgtttctaa acatataaat gtgaatttaa tcaattcctt
1381 tcatagtttt ataattctct ggcagttcct tatgatagag tttataaaac agtcctgtgt
1441 aaactgctgg aagttcttcc acagtcaggt caattttgtc aaacccttct ctgtacccat
1501 acagcagcag cctagcaact ctgctggtga tgggagttgt attttcagtc ttcgccaggt
1561 cattgagatc catccactca catcttaagc attcttcctg gcaaaaattt atggtgaatg
1621 aatatggctt taggcggcag atgatataca tatctgactt cccaaaagct ccaggatttg
1681 tgtgctgttg ccgaatactc aggacggacc tgaattctga ttttatacca gtctcttcaa
1741 aaacttctcg aaccgctgtg tctcctacgt aaaaaaagag atgtacaaat caataataat
1801 tacactttta gaaactgtat catcaaagat tttcagttaa agtagcatta tgtaaaggct
1861 caaaacatta ccctaacaaa gtaaagtttt caatacaaat tctttgcctt gtggatatca
1921 agaaatccca aaatattttc ttaccactgt aaattcaaga agcttttgaa atgctgaata
1981 tttctttggc tgctacttgg aggcttatct acctgtacat ttttggggtc agctcttttt
2041 aacttcttgc tgctcttttt cccaaaaggt aaaaatatag attgaaaagt taaaacattt
2101 tgcatggctg cagttccttt gtttcttgag ataagattcc aaagaactta gattcatttc
2161 ttcaacaccg aaatgctgga ggtgtttgat cagttttcaa gaaacttgga atataaataa
2221 ttttataatt caacaaaggt tttcacattt tataaggttg atttttcaat taaatgcaaa
2281 tttgtgtggc aggattttta ttgccattaa catatttttg tggctgcttt ttctacacat
2341 ccagatggtc cctctaactg ggctttctct aattttgtga tgttctgtca ttgtctccca
2401 aagtatttag gagaagccct ttaaaaagct gccttcctct accactttgc tggaaagctt
2461 cacaattgtc acagacaaag atttttgttc caatactcgt tttgcctcta tttttcttgt
2521 ttgtcaaata gtaaatgata tttgcccttg cagtaattct actggtgaaa aacatgcaaa
2581 gaagaggaag tcacagaaac atgtctcaat tcccatgtgc tgtgactgta gactgtctta
2641 ccatagactg tcttacccat cccctggata tgctcttgtt ttttccctct aatagctatg
2701 gaaagatgca tagaaagagt ataatgtttt aaaacataag gcattcgtct gccatttttc
2761 aattacatgc tgacttccct tacaattgag atttgcccat aggttaaaca tggttagaaa
2821 caactgaaag cataaaagaa aaatctaggc cgggtgcagt ggctcatgcc tatattccct
2881 gcactttggg aggccaaagc aggaggatcg cttgagccca ggagttcaag accaacctgg
2941 tgaaaccccg tctctacaaa aaaacacaaa aaatagccag gcatggtggc gtgtacatgt
3001 ggtctcagat acttgggagg ctgaggtggg agggttgatc acttgaggct gagaggtcaa
3061 ggttgcagtg agccataatc gtgccactgc agtccagcct aggcaacaga gtgagacttt
3121 gtctcaaaaa aagagaaatt ttccttaata agaaaagtaa tttttactct gatgtgcaat
3181 acatttgtta ttaaatttat tatttaagat ggtagcacta gtcttaaatt gtataaaata
3241 tcccctaaca tgtttaaatg tccatttta ttcattatgc tttgaaaaat aattatgggg
3301 aaatacatgt ttgttattaa atttattatt aaagatagta gcactagtct taaatttgat
3361 ataacatctc ctaacttgtt taaatgtcca tttttattct ttatgtttga aaataaatta
3421 tggggatcct atttagctct tagtaccact aatcaaaagt tcggcatgta gctcatgatc
3481 tatgctgttt ctatgtcgtg gaagcaccgg atgggggtag tgagcaaatc tgccctgctc
3541 agcagtcacc atagcagctg actgaaaatc agcactgcct gagtagtttt gatcagttta
3601 acttgaatca ctaactgact gaaaattgaa tgggcaaata agtgcttttg tctccagagt
3661 atgcgggaga cccttccacc tcaagatgga tatttcttcc ccaaggattt caagatgaat
3721 tgaaattttt aatcaagata gtgtgcttta ttctgttgta ttttttatta ttttaatata
3781 ctgtaagcca aactgaaata acatttgctg ttttataggt ttgaagaaca taggaaaaac
3841 taagaggttt tgtttttatt tttgctgatg aagagatatg tttaaatatg ttgtattgtt
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3901 ttgtttagtt acaggacaat aatgaaatgg agtttatatt tgttatttct attttgttat
3961 atttaataat agaattagat tgaaataaaa tataatggga aataatctgc agaatgtggg
4021 ttttcctggt gtttccctct gactctagtg cactgatgat ctctgataag gctcagctgc
4081 tttatagttc tctggctaat gcagcagata ctcttcctgc cagtggtaat acgatttttt
4141 aagaaggcag tttgtcaatt ttaatcttgt ggataccttt atactcttag ggtattattt
4201 tatacaaaag ccttgaggat tgcattctat tttctatatg acccctcttga tatttaaaaa
4261 acactatgga taacaattct tcatttacct agtattatga aagaatgaag gagttcaaac
4321 aaatgtgttt cccagttaac tagggtttac tgtttgagcc aatataaatg tttaactgtt
4381 tgtgatggca gtattcctaa agtacattgc atgttttcct aaatacagag tttaaataat
4441 ttcagtaatt cttagatgat tcagcttcat cattaagaat atcttttgtt ttatgttgag
4501 ttagaaatgc cttcatatag acatagtctt tcagacctct actgtcagtt ttcatttcta
4561 gctgctttca gggttttatg aattttcagg caaagcttta atttatacta agcttaggaa
4621 gtatggctaa tgccaacggc agtttttttc ttcttaattc cacatgactg aggcatatat
4681 gatctctggg taggtgagtt gttgtgacaa ccacaagcac ttttttttt tttaaagaaa
4741 aaaaggtagt gaatttttaa tcatctggac tttaagaagg attctggagt atacttaggc
4801 ctgaaattat atatatttgg cttggaaatg tgtttttctt caattacatc tacaagtaag
4861 tacagctgaa attcagagga cccataagag ttcacatgaa aaaaatcaat ttatttgaaa
4921 aggcaagatg caggagagag gaagccttgc aaacctgcag actgcttttt gcccaatata
4981 gattgggtaa ggctgcaaaa cataagctta attagctcac atgctctgct ctcacgtggc
5041 accagtggat agtgtgagag aattaggctg tagaacaaat ggccttctct ttcagcattc
5101 acaccactac aaaatcatct tttatatcaa cagaagaata agcataaact aagcaaaagg
5161 tcaataagta cctgaaacca agattggcta gagatatatc ttaatgcaat ccattttctg
5221 atggattgtt acgagttggc tatataatgt atgtatggta ttttgatttg tgtaaaagtt
5281 ttaaaaatca agctttaagt acatggacat ttttaaataa aatatttaaa gacaatttag
5341 aaaattgcct taatatcatt gttggctaaa tagaataggg gacatgcata ttaaggaaaa
5401 ggtcatggag aaataatatt ggtatcaaac aaatacattg atttgtcatg atacacattg
5461 aatttgatcc aatagtttaa ggaataggta ggaaaatttg gtttctattt ttcgatttcc
5521 tgtaaatcag tgacataaat aattcttagc ttattttata tttccttgtc ttaaatactg
5581 agctcagtaa gttgtgttag gggattattt ctcagttgag actttcttat atgacatttt
5641 actatgtttt gacttcctga ctattaaaaa taaatagtag atacaatttt cataaagtga
5701 agaattatat aatcactgct ttataactga ctttattata tttatttcaa agttcattta
5761 aaggctacta ttcatcctct gtgatggaat ggtcaggaat ttgttttctc atagtttaat
5821 tccaacaaca atattagtcg tatccaaaat aacctttaat gctaaacttt actgatgtat
5881 atccaaagct tctcattttc agacagatta atccagaagc agtcataaac agaagaatag
5941 gtggtatgtt cctaatgata ttatttctac taatggaata aactgtaata ttagaaatta
6001 tgctgctaat tatatcagct ctgaggtaat ttctgaaatg ttcagactca gtcggaacaa
6061 attggaaaat ttaaattttt attcttagct ataaagcaag aaagtaaaca cattaatttc
6121 ctcaacattt ttaagccaat taaaaatata aaagatacac accaatatct tcttcaggct
6181 ctgacaggcc tcctggaaac ttccacatat ttttcaactg cagtataaag tcagaaaata
6241 aagttaacat aactttcact aacacacaca tatgtagatt tcacaaaatc cacctataat
6301 tggtcaaagt ggttgagaat atatttttta gtaattgcat gcaaaatttt tctagcttcc
6361 atcctttctc cctcgtttct tctttttttg ggggagctgg taactgatga aatcttttcc
6421 caccttttct cttcaggaaa tataagtggt tttgtttggt taacgtgata cattctgtat
6481 gaatgaaaca ttggagggaa acatctactg aatttctgta atttaaaata ttttgctgct
6541 agttaactat gaacagatag aagaatctta cagatgctgc tataaataag tagaaaatat
6601 aaatttcatc actaaaatat gctattttaa aatctatttc ctatattgta tttctaatca
6661 gatgtattac tcttattatt tctattgtat gtgttaatga ttttatgtaa aaatgtaatt
6721 gcttttcatg agtagtatga ataaaattga ttagtttgtg ttttcttgtc tccc
```

An exemplary human Follistatin amino acid sequence is set forth below (SEQ ID NO: 11; GenBank Accession No: AAH04107, Version 1, incorporated herein by reference):

```
  1 mvrarhqpgg lclllllcq fmedrsaqag ncwlrqakng rcqvlyktel skeeccstgr
 61 lstswteedv ndntlfkwmi fnggapncip cketcenvdc gpgkkcrmnk knkprcvcap
121 dcsnitwkgp vcgldgktyr necallkarc keqpelevqy qgrckktcrd vfcpgsstcv
```

```
181 vdqtnnaycv tcnricpepa sseqylcgnd gvtyssachl rkatcllgrs iglayegkci
241 kakscediqc tggkkclwdf kvgrgrcslc delcpdsksd epvcasdnat yasecamkea
301 acssgvllev khsgscnsis edteeeeede dqdysfpiss ilew
```

An exemplary human *Follistatin* nucleic acid sequence is set forth below (SEQ ID NO: 12; GenBank Accession No: BC004107, Version 2, incorporated herein by reference):

```
   1 cccccgtcta gatttaaagc gcggctgcgc ccggcttctg acgtccattg aatcgcgcgg
  61 gcggccggcg gcgagcgcgg ggctgcgccg ggatcgctgc gccctccgcc gctggcctct
 121 gcgacgcgcg ccgctcgccc gagccacccg ccgccgcgcc ggctccccgc gccgctgcgc
 181 tcctcgcccc gcgcctgccc ccaggatggt ccgcgcgagg caccagccgg gtgggctttg
 241 cctcctgctg ctgctgctct gccagttcat ggaggaccgc agtgcccagg ctgggaactg
 301 ctggctccgt caagcgaaga acggccgctg ccaggtcctg tacaagaccg aactgagcaa
 361 ggaggagtgc tgcagcaccg gccggctgag cacctcgtgg accgaggagg acgtgaatga
 421 caacacactc ttcaagtgga tgattttcaa cgggggcgcc cccaactgca tcccctgtaa
 481 agaaacgtgt gagaacgtgg actgtggacc tgggaaaaaa tgccgaatga acaagaagaa
 541 caaaccccgc tgcgtctgcg ccccggattg ttccaacatc acctggaagg gtccagtctg
 601 cgggctggat gggaaaacct accgcaatga atgtgcactc ctaaaggcaa gatgtaaaga
 661 gcagccagaa ctggaagtcc agtaccaagg cagatgtaaa aagacttgtc gggatgtttt
 721 ctgtccaggc agctccacat gtgtggtgga ccagaccaat aatgcctact gtgtgacctg
 781 taatcggatt tgcccagagc ctgcttcctc tgagcaatat ctctgtggga atgatggagt
 841 cacctactcc agtgcctgcc acctgagaaa ggctacctgc ctgctgggca gatctattgg
 901 attagcctat gagggaaagt gtatcaaagc aaagtcctgt gaagatatcc agtgcactgg
 961 tgggaaaaaa tgtttatggg atttcaaggt tgggagaggc cggtgttccc tctgtgatga
1021 gctgtgccct gacagtaagt cggatgagcc tgtctgtgcc agtgacaatg ccacttatgc
1081 cagcgagtgt gccatgaagg aagctgcctg ctcctcaggt gtgctactgg aagtaaagca
1141 ctccggatct tgcaactcca tttcggaaga caccgaggaa gaggaggaag atgaagacca
1201 ggactacagc tttcctatat cttctattct agagtggtaa actctctata agtgttcagt
1261 gttgacatag cctttgtgca aaaaaaaaaa aaaaaaaaaa aaaaaagaaa aaaaaaaaaa
1321 aaaaaa
```

An exemplary human granulocyte-colony stimulating factor (G-CSF) amino acid sequence is set forth below (SEQ ID NO: 13; GenBank Accession No: P09919, Version 1, incorporated herein by reference):

```
   1 magpatqspm klmalqlllw hsalwtvqea tplgpasslp qsfllkcleq vrkiqgdgaa
  61 lqeklvseca tyklchpeel vllghslgip waplsscpsq alqlagclsq lhsglflyqg
 121 llqalegisp elgptldtlq ldvadfatti wqqmeelgma palqptqgam pafasafqrr
 181 aggvlvashl qsflevsyrv lrhlaqp
```

An exemplary human *G-CSF* nucleic acid sequence is set forth below (SEQ ID NO: 14; GenBank Accession No: M17706, Version 1, incorporated herein by reference):

```
   1 aaaaaacagc ccggagcctg cagcccagcc ccacccagac ccatggctgg acctgccacc
  61 cagagcccca tgaagctgat ggccctgcag ctgctgctgt ggcacagtgc actctggaca
 121 gtgcaggaag ccacccccct gggccctgcc agctccctgc cccagagctt cctgctcaag
 181 tgcttagagc aagtgaggaa gatccagggc gatggcgcag cgctccagga gaagctgtgt
 241 gccacctaca agctgtgcca ccccgaggag ctggtgctgc tcggacactc tctgggcatc
 301 ccctgggctc ccctgagcag ctgccccagc caggccctgc agctggcagg ctgcttgagc
 361 caactccata gcggcctttt cctctaccag gggctcctgc aggccctgga agggatctcc
 421 cccgagttgg gtcccacctt ggacacactg cagctggacg tcgccgactt tgccaccacc
 481 atctggcagc agatggaaga actgggaatg gcccctgccc tgcagcccac ccagggtgcc
```

```
541 atgccggcct tcgcctctgc tttccagcgc cgggcaggag gggtcctagt tgcctcccat
601 ctgcagagct tcctggaggt gtcgtaccgc gttctacgcc accttgccca gccctgagcc
```

An exemplary human granulocyte macrophage colony stimulating factor (GM-CSF) amino acid sequence is set forth below (SEQ ID NO: 15; GenBank Accession No: P04141, Version 1, incorporated herein by reference):

```
  1 mwlqsllllg tvacsisapa rspspstqpw ehvnaiqear rllnlsrdta aemnetvevi
 61 semfdlqept clqtrlelyk qglrgsltkl kgpltmmash ykqhcpptpe tscatqiitf
121 esfkenlkdf llvipfdcwe pvqe
```

An exemplary human *GM-CSF* nucleic acid sequence is set forth below (SEQ ID NO: 16; GenBank Accession No: M13207, Version 1, incorporated herein by reference):

```
   1 aagcttgctg agagtggctg cagtctcgct gctggatgtg cacatggtgg tcattccctc
  61 tgctcacagg ggcaggggtc ccccttact ggactcaggt tgcccctgc tccaggtcct
 121 gggtgggagc ccatgtgaac tgtcagtggg gcaggtctgt gagagctccc ctcacactca
 181 agtctctcac agtggccaga gaagaggaag gctggagtca gaatgaggca ccagggcggg
 241 catagcctgc ccaaaggccc ctgggattac aggcaggatg gggagcccta tctaagtgtc
 301 tcccacgccc caccccagcc attccaggcc aggaagtcca aactgtgccc ctcagaggga
 361 gggggcagcc tcaggcccat tcagactgcc cagggagggc tggagagccc tcaggaaggc
 421 gggtgggtgg gctgtcggtt cttggaaagg ttcattaatg aaaaccccca agcctgacca
 481 cctagggaaa aggctcaccg ttcccatgtg tggctgataa gggccaggag attccacagt
 541 tcaggtagtt cccccgcctc cctggcattt tgtggtcacc attaatcatt tcctctgtgt
 601 atttaagagc tcttttgcca gtgagcccag tacacagaga gaaaggctaa agttctctgg
 661 aggatgtggc tgcagagcct gctgctcttg ggcactgtgg cctgcagcat ctctgcaccc
 721 gcccgctcgc ccagccccag cacgcagccc tgggagcatg tgaatgccat ccaggaggcc
 781 cggcgtctcc tgaacctgag tagagacact gctgctgaga tggtaagtga gagaatgtgg
 841 gcctgtgcct aggccaccca gctggcccct gactggccac gcctgtcagc ttgataacat
 901 gacattttcc ttttctacag aatgaaacag tagaagtcat ctcagaaatg tttgacctcc
 961 aggtaagatg cttctctctg acatagcttt ccagaagccc ctgccctggg gtggaggtgg
1021 ggactccatt ttagatggca ccacacaggg ttgtccactt tctctccagt cagctggctg
1081 caggaggagg gggtagcaac tgggtgctca agaggctgct ggccgtgccc ctatggcagt
1141 cacatgagct cctttatcag ctgagcggcc atgggcagac ctagcattca atggccagga
1201 gtcaccaggg gacaggtggt aaagtggggg tcacttcatg agacaggagc tgtgggtttg
1261 gggcgctcac tgtgccccga gaccaagtcc tgttgagaca gtgctgacta cagagaggca
1321 cagaggggtt tcaggaacaa cccttgccca cccagcaggt ccaggtgagg ccccaccccc
1381 ctctccctga atgatggggt gagagtcacc tccttcccta aggctgggct cctctccagg
1441 tgccgctgag ggtggcctgg gcggggcagt gagaagggca ggttcgtgcc tgccatggac
1501 agggcagggt ctatgactgg acccacgctg tgcccctccc aagccctact cctgggggct
1561 gggggcagca gcaaaaagga gtggtggaga gttcttgtac cactgtgggc acttggccac
1621 tgctcaccga cgaacgacat tttccacagg agccgacctg cctacagacc cgcctggagc
1681 tgtacaagca gggcctgcgg ggcagcctca ccaagctcaa gggccccttg accatgatgg
1741 ccagccacta caagcagcac tgccctccaa ccccggtgag tgcctacggc agggcctcca
1801 gcaggaatgt cttaatctag ggggtggggt cgacatgggg agagatctat ggctgtggct
1861 gttcaggacc ccaggggttt tctgtgccaa cagttatgta atgattagcc ctccagagag
1921 gaggcagaca gcccatttca tcccaaggag tcagagccac agagcgctga agcccacagt
1981 gctccccagc aggagctgct cctatcctgg tcattattgt cattacggtt aatgaggtca
2041 gaggtgaggg caaacccaag gaaacttggg gcctgcccaa ggcccagagg aagtgcccag
2101 gcccaagtgc caccttctgg caggactttc ctctggcccc acatggggtg cttgaattgc
2161 agaggatcaa ggaagggagg ctacttggaa tggacaagga cctcaggcac tccttctgcg
2221 ggaagggagc aaagtttgtg gccttgactc cactccttct gggtgcccag agacgacctc
```

```
2281 agcccagctg ccctgctctg ccctgggacc aaaaaggcag gcgtttgact gcccagaagg
2341 ccaacctcag gctggcactt aagtcaggcc cttgactctg gctgccactg gcagagctat
2401 gcactccttg gggaacacgt gggtggcagc agcgtcacct gacccaggtc agtgggtgtg
2461 tcctggagtg ggcctcctgg cctctgagtt ctaagaggca gtagagaaac atgctggtgc
2521 ttccttcccc cacgttaccc acttgcctgg actcaagtgt tttttatttt tctttttta
2581 aaggaaactt cctgtgcaac ccagattatc acctttgaaa gtttcaaaga gaacctgaag
2641 gactttctgc ttgtcatccc ctttgactgc tgggagccag tccaggagtg agaccggcca
2701 gatgaggctg gccaagccgg ggagctgctc tctcatgaaa caagagctag aaactcagga
2761 tggtcatctt ggagggacca aggggtgggc cacagccatg gtgggagtgg cctggacctg
2821 ccctgggcca cactgaccct gatacaggca tggcagaaga atgggaatat tttatactga
2881 cagaaatcag taatatttat atatttatat ttttaaaata tttatttatt tatttattta
2941 agttcatatt ccatatttat tcaagatgtt ttaccgtaat aattattatt aaaaatatgc
3001 ttctacttgt ccagtgttct agtttgtttt taaccatgag caaatgccag tgggtgcctg
3061 ccttcccatg aggcagggga gggaggaaac ggggaggtgg agaggggcg ggggcctccc
3121 aggcgttggg cactatccaa gggccaacac tgtcagagca gaggggaggt gagagccggg
3181 catagtcgga attc
```

An exemplary human heparin-binding EGF-like growth factor (HB-EGF) amino acid sequence is set forth below (SEQ ID NO: 17; GenBank Accession No: Q99075, Version 1, incorporated herein by reference):

```
  1 mkllpsvvlk lflaavlsal vtgeslerlr rglaagtsnp dpptvstdql lplgggrdrk
 61 vrdlqeadld llrvtlsskp qalatpnkee hgkrkkkgkg lgkkrdpclr kykdfcihge
121 ckyvkelrap scichpgyhg erchglslpv enrlytydht tilavvavvl ssvcllvivg
181 llmfryhrrg gydveneekv klgmtnsh
```

An exemplary human *HB-EGF* nucleic acid sequence is set forth below (SEQ ID NO: 18; GenBank Accession No: NM_001945, Version 2, incorporated herein by reference):

```
  1 attcggccga aggagctacg cgggccacgc tgctggctgg cctgacctag gcgcgcgggg
 61 tcgggcggcc gcgcgggcgg gctgagtgag caagacaaga cactcaagaa gagcgagctg
121 cgcctgggtc ccggccaggc ttgcacgcag aggcgggcgg cagacggtgc ccggcggaat
181 ctcctgagct ccgccgccca gctctggtgc cagcgcccag tggccgccgc ttcgaaagtg
241 actggtgcct cgccgcctcc tctcggtgcg ggaccatgaa gctgctgccg tcggtggtgc
301 tgaagctctt tctggctgca gttctctcgg cactggtgac tggcgagagc ctggagcggc
361 ttcggagagg gctagctgct ggaaccagca acccggaccc tcccactgta tccacggacc
421 agctgctacc cctaggaggc ggccgggacc ggaaagtccg tgacttgcaa gaggcagatc
481 tggacctttt gagagtcact ttatcctcca agccacaagc actggccaca ccaaacaagg
541 aggagcacgg gaaaagaaag aagaaaggca aggggctagg gaagaagagg gacccatgtc
601 ttcggaaata caaggacttc tgcatccatg gagaatgcaa atatgtgaag gagctccggg
661 ctccctcctg catctgccac ccgggttacc atggagagag gtgtcatggg ctgagcctcc
721 cagtggaaaa tcgcttatat acctatgacc acacaaccat cctggccgtg gtggctgtgg
781 tgctgtcatc tgtctgtctg ctggtcatcg tggggcttct catgtttagg taccatagga
841 gaggaggtta tgatgtggaa aatgaagaga aagtgaagtt gggcatgact aattcccact
901 gagagagact tgtgctcaag gaatcggctg gggactgcta cctctgagaa gacacaaggt
961 gatttcagac tgcagagggg aaagacttcc atctagtcac aaagactcct tcgtccccag
1021 ttgccgtcta ggattgggcc tcccataatt gctttgccaa aataccagag ccttcaagtg
1081 ccaaacagag tatgtccgat ggtatctggg taagaagaaa gcaaaagcaa gggaccttca
1141 tgcccttctg attcccctcc accaaacccc acttcccctc ataagtttgt ttaaacactt
1201 atcttctgga ttagaatgcc ggttaaattc catatgctcc aggatctttg actgaaaaaa
1261 aaaaagaaga agaagaagga gagcaagaag gaaagatttg tgaactggaa gaaagcaaca
1321 aagattgaga agccatgtac tcaagtacca ccaagggatc tgccattggg accctccagt
1381 gctggatttg atgagttaac tgtgaaatac cacaagcctg agaactgaat tttgggactt
```

```
1441 ctacccagat ggaaaaataa caactatttt tgttgttgtt gtttgtaaat gcctcttaaa
1501 ttatatattt attttattct atgtatgtta atttatttag tttttaacaa tctaacaata
1561 atatttcaag tgcctagact gttactttgg caatttcctg gccctccact cctcatcccc
1621 acaatctggc ttagtgccac ccacctttgc cacaaagcta ggatggttct gtgacccatc
1681 tgtagtaatt tattgtctgt ctacatttct gcagatcttc cgtggtcaga gtgccactgc
1741 gggagctctg tatggtcagg atgtaggggt taacttggtc agagccactc tatgagttgg
1801 acttcagtct tgcctaggcg attttgtcta ccatttgtgt tttgaaagcc caaggtgctg
1861 atgtcaaagt gtaacagata tcagtgtctc cccgtgtcct ctccctgcca agtctcagaa
1921 gaggttgggc ttccatgcct gtagctttcc tggtccctca cccccatggc cccaggccca
1981 cagcgtggga actcactttc ccttgtgtca agacatttct ctaactcctg ccattcttct
2041 ggtgctactc catgcagggg tcagtgcagc agaggacagt ctggagaagg tattagcaaa
2101 gcaaaaggct gagaaggaac agggaacatt ggagctgact gttcttggta actgattacc
2161 tgccaattgc taccgagaag gttggaggtg gggaaggctt tgtataatcc cacccacctc
2221 accaaaacga tgaagttatg ctgtcatggt cctttctgga agtttctggt gccatttctg
2281 aactgttaca acttgtattt ccaaacctgg ttcatattta tactttgcaa tccaaataaa
2341 gataacccct attccataaa aaaaaaaaaa aaaaaaaaaa a
```

An exemplary hepatocyte growth factor (HGF) amino acid sequence is set forth below (SEQ ID NO: 19; GenBank Accession No: P14210, Version 2, incorporated herein by reference):

```
  1 mwvtkllpal llqhvllhll llpiaipyae gqrkrrntih efkksakttl ikidpalkik
 61 tkkvntadqc anrctrnkgl pftckafvfd karkqclwfp fnsmssgvkk efghefdlye
121 nkdyirncii gkgrsykgtv sitksgikcq pwssmipheh sflpssyrgk dlqenycrnp
181 rgeeggpwcf tsnpevryev cdipqcseve cmtcngesyr glmdhtesgk icqrwdhqtp
241 hrhkflpery pdkgfddnyc rnpdgqprpw cytldphtrw eycaiktcad ntmndtdvpl
301 etteciqgqg egyrgtvnti wngipcqrwd sqyphehdmt penfkckdlr enycrnpdgs
361 espwcfttdp nirvgycsqi pncdmshgqd cyrgngknym gnlsqtrsgl tcsmwdknme
421 dlhrhifwep dasklnenyc rnpdddahgp wcytgnplip wdycpisrce gdttptivnl
481 dhpviscakt kqlrvvngip trtnigwmvs lryrnkhicg gslikeswvl tarqcfpsrd
541 lkdyeawlgi hdvhgrgdek ckqvlnvsql vygpegsdlv lmklarpavl ddfvstidlp
601 nygctipekt scsvygwgyt glinydgllr vahlyimgne kcsqhhrgkv tlneseicag
661 aekigsgpce gdyggplvce qhkmrmvlgv ivpgrgcaip nrpgifvrva yyakwihkii
721 ltykvpqs
```

An exemplary human *HGF* nucleic acid sequence is set forth below (SEQ ID NO: 20; GenBank Accession No: NM_000601, Version 1, incorporated herein by reference):

```
  1 gaggaaagga gggggctgga agagagtaaa gggctgttgt taaacagttt cttaccgtaa
 61 gagggagttc agacctagat ctttccagtt aatcacacaa caaacttagc tcatcgcaat
121 aaaaagcagc tcagagccga ctggctcttt taggcactga ctccgaacag gattctttca
181 cccaggcatc tcctccagag ggatccgcca gcccgtccag cagcaccatg tgggtgacca
241 aactcctgcc agccctgctg ctgcagcatg tcctcctgca tctcctcctg ctccccatcg
301 ccatccccta tgcagaggga caaaggaaaa gaagaaatac aattcatgaa ttcaaaaaat
361 cagcaaagac taccctaatc aaaatagatc cagcactgaa gataaaaacc aaaaaagtga
421 atactgcaga ccaatgtgct aatagatgta ctaggaataa aggacttcca ttcacttgca
481 aggcttttgt ttttgataaa gcaagaaaac aatgcctctg gttccccttc aatagcatgt
541 caagtggagt gaaaaaagaa tttggccatg aatttgacct ctatgaaaac aaagactaca
601 ttagaaactg catcattggt aaaggacgca gctacaaggg aacagtatct atcactaaga
661 gtggcatcaa atgtcagccc tggagttcca tgataccaca cgaacacagc tttttgcctt
721 cgagctatcg gggtaaagac ctacaggaaa actactgtcg aaatcctcga ggggaagaag
781 ggggaccctg gtgtttcaca agcaatccag aggtacgcta cgaagtctgt gacattcctc
841 agtgttcaga agttgaatgc atgacctgca atggggagag ttatcgaggt ctcatggatc
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```
 901 atacagaatc aggcaagatt tgtcagcgct gggatcatca gacaccacac cggcacaaat
 961 tcttgcctga aagatatccc gacaagggct ttgatgataa ttattgccgc aatcccgatg
1021 gccagccgag gccatggtgc tatactcttg accctcacac ccgctgggag tactgtgcaa
1081 ttaaaacatg cgctgacaat actatgaatg acactgatgt tcctttggaa acaactgaat
1141 gcatccaagg tcaaggagaa ggctacaggg gcactgtcaa taccatttgg aatggaattc
1201 catgtcagcg ttgggattct cagtatcctc acgagcatga catgactcct gaaaatttca
1261 agtgcaagga cctacgagaa aattactgcc gaaatccaga tgggtctgaa tcaccctggt
1321 gttttaccac tgatccaaac atccgagttg gctactgctc ccaaattcca aactgtgata
1381 tgtcacatgg acaagattgt tatcgtggga atggcaaaaa ttatatgggc aacttatccc
1441 aaacaagatc tggactaaca tgttcaatgt gggacaagaa catggaagac ttacatcgtc
1501 atatcttctg ggaaccagat gcaagtaagc tgaatgagaa ttactgccga aatccagatg
1561 atgatgctca tggaccctgg tgctacacgg gaaatccact cattccttgg gattattgcc
1621 ctatttctcg ttgtgaaggt gataccacac ctacaatagt caatttagac catcccgtaa
1681 tatcttgtgc caaaacgaaa caattgcgag ttgtaaatgg gattccaaca cgaacaaaca
1741 taggatggat ggttagtttg agatacagaa ataaacatat ctgcggagga tcattgataa
1801 aggagagttg ggttcttact gcacgacagt gtttcccttc tcgagacttg aaagattatg
1861 aagcttggct tggaattcat gatgtccacg gaagaggaga tgagaaatgc aaacaggttc
1921 tcaatgtttc ccagctggta tatggccctg aaggatcaga tctggtttta atgaagcttg
1981 ccaggcctgc tgtcctggat gattttgtta gtacgattga tttacctaat tatggatgca
2041 caattcctga aaagaccagt tgcagtgttt atggctgggg ctacactgga ttgatcaact
2101 atgatggcct attacgagtg gcacatctct atataatggg aaatgagaaa tgcagccagc
2161 atcatcgagg gaaggtgact ctgaatgagt ctgaaatatg tgctggggct gaaaagattg
2221 gatcaggacc atgtgagggg gattatggtg gcccacttgt ttgtgagcaa cataaaatga
2281 gaatggttct tggtgtcatt gttcctggtc gtggatgtgc cattccaaat cgtcctggta
2341 tttttgtccg agtagcatat tatgcaaaat ggatacacaa aattatttta acatataagg
2401 taccacagtc atagctgaag taagtgtgtc tgaagcaccc accaatacaa ctgtctttta
2461 catgaagatt tcagagaatg tggaatttaa aatgtcactt acaacaatcc taagacaact
2521 actggagagt catgtttgtt gaaattctca ttaatgttta tgggtgtttt ctgttgtttt
2581 gtttgtcagt gttattttgt caatgttgaa gtgaattaag gtacatgcaa gtgtaataac
2641 atatctcctg aagatacttg aatggattaa aaaaacacac aggtatattt gctggatgat
2701 aaagatttca tgggaaaaaa aatcaattaa tctgtctaag ctgctttctg atgttggttt
2761 cttaataatg agtaaaccac aaattaaatg ttattttaac ctcaccaaaa caatttatac
2821 cttgtgtccc taaattgtag ccctatatta aattatatta catttcatat gctatatgtt
2881 atagttcatt catttctctt caccatgtat cctgcaatac tggtacacga acacactttt
2941 tacaaaacca catacccatg tacacatgcc taggtacaca tgtgcatgca ctacagttta
3001 aattatggtg tacctaatgt aacccctaaa tattttagaa gtatgtacct atagttttac
3061 ctcaaaaaaa ccagaaatct ctaaagacca gtagaaatat taaaaaatga tgcaagatca
3121 aaatgattag ctaattctcc atacataatc tgcagatgat cttctttggt tggcatttca
3181 ggtgtggcca tcacccagag ttaaataaca cctaatctag gtgtttacat gtattcatta
3241 tcctagttat ttcatgtagt ttctaattct taaaggaaag agggtaatag ttctatttgt
3301 gtaatttgtt tcctccaaac ttaaggccac ttatttacac aagatatttg tagatctatt
3361 ttcctaaagc atttcttaag tgctcagatc agtatctaat tgaagaagtt taaaagtgtt
3421 ttggtcatta aaaatgtact taaataggtt aaatctaagc cttgctgctg tgattggctt
3481 ctagctcact gcctttaaat tttaaaaaat ttaagaggaa aatttccaag tctccaaagt
3541 tttataaata cccttcatca agtcatgcat taaagtatat attggagaaa aaaataaaaa
3601 tacttttctc aacctggaag attttagcct aataaagctt ttttgaagta aaagacaact
3661 tgtaaaagga aagaaactag tttgtctcaa ctctgtattc atttatttct tttttgaagt
3721 agagtggaat ctgttgaatc agatatttta tcaagatatg tttatttttt cttatttcat
3781 tttacaaagt tcactcctaa tgccatatgt aacagacatt taaattttgt gttctgtata
3841 acagccaaat tatcatattt atcattgtat ttgtcatgct tagctaaaga tcatgtattt
3901 gttgagaaat agaataacaa aaagtaatag gataggcttt gaatttttgc agaaatcttc
3961 ctgtacaaaa caccttttaaa aataatttttt tgaatggtgt gaatccagta gtcccatttc
4021 tctgacttag ttttcttgag tgatttttat caaggccaag tccccaaaca attccctacc
4081 agctctttag agtactgttc aatctggact aaaatggttt taagtttatg gagagcttag
4141 tccacagaat atagggcggc gagtccagaa atgcttatac aatttttttt tcataataag
4201 atatgtgctg gcatcaagaa acttaaagtg gaagcaaaaa gacatccaac tagttgctgg
```

```
4261 tctctatcat cttatctgat ggtatttcta ttttccttat ataatacacc attttagtaa
4321 gaactcctag aaatttcaag agcatattgc caaaatataa agtatatttc atagtttctt
4381 ctggctgaac cagtgaaatt ttattattgc atattaatga tatttgtaaa acttttataa
4441 aaattgtcat aattttaaat actcacattt taaaaatact tctttaatga ctcttcctct
4501 aaatttcctg gaaatacaga taaagattag ctagatacaa gatacagcta agtatttaga
4561 cattttgagg ctagtatttt tcattttatt aaaggctaaa aacaatacca ccaataaatc
4621 atcaaacaaa ccgtacaaag taattctctc tttgggaggc tcctttcgtg atagagggac
4681 atgggtggaa ttgacaatga aacttagatg aacaaggtcc atgttatttt aggtggtaga
4741 acagggtaga gtcatgtcat tatttgctgg tggaagacac tatttaccag gtgttctttg
4801 ctgaataaat cattaaacat ttttaaaaat ccaacaatcc actttatttt gtgtcattga
4861 caaaaggatc ttttaaatca gaaggtttca atgcaatttt tggtttggct gtttgaataa
4921 tggttatgta ctgttataat tgtagacatt ttctcacgtc taccaggaat tgaagtgtaa
4981 aactaaaata tttttcataa tgcctctgcc gtgcagaagg aatgataatc cttttgtata
5041 cttctttaat tttattgtaa aatgtgtaat gacttttacc tatatgctgt gggcaggtcc
5101 tcagtaaaat ctattgagtc aatttctagt attaacaggc ttttgcttgc tatctaagtg
5161 tttcaaatta tgggaagtgt gagacactgg aaggcaagaa aattaacaat aatggcatgt
5221 gatagcaaaa ttgtatttca cttattcctg tgaatatttc ttgttggtac caatggtact
5281 gtacaaagtg aatgttatag ccacaacatt ctcttgaaaa gaacactgtc aagaagtggg
5341 aaattgctgt caggcatttc attgttgttt ttaaactttt ttaaaagaaa tactggtttt
5401 gcaatataga gatcatgtgg taaagaattt taataagatc ttatactaaa aagccttaaa
5461 tcaatttatt gagattcaaa aaatactatt ataattaatt acatcccata catataggca
5521 aactcattta aaaaataaaa ctaattttgg taaaagtaca tggcctttgt ttttaaaata
5581 cataatttta aaataaatca cttgtcatga taaagtccaa aaagaagtta tcattcaaca
5641 ttcaactaag gttggagcta agaatttact aatacaaaaa aagttaaaat tttttggacc
5701 atatatatct tgacagtgta acttttaagt aggttcattt ccatttgcac agaaagtttc
5761 tgtctttagg aaactgaaaa tgaaatactg tggatgctat gactgtttgt cttgtatgta
5821 aataggaaat taataagctg cctattgagt ggtatagctg tatgcttacc caaaaaaggg
5881 aacactgtgg ttatgacttg tattataaac tttctgtagt taataaagtt gttatttta
5941 taaccatgat tatattatta ttattaataa aatattttat caaaatgaaa aaaaaaaaaa
6001 aa
```

An exemplary human interferon gamma (IFNg) amino acid sequence is set forth below (SEQ ID NO: 21; GenBank Accession No: AAA53230, Version 1, incorporated herein by reference):

```
  1 mamlrvqpea qakvdvfred lctktenllg syfpkkisel daflkepaln eanlsnlkap
 61 ldipvpdpvk ekekeerkkq qekedkdekk kgededkgpp cgpvncneki vvllqrlkpe
121 ikdvieqlnl vttwlqlqip riedgnnfgv avqekvfelm tslhtklegf htqiskyfse
181 rgdavtkaak qphvgdyrql vheldeaeyr dirlmvmeir nayavlydii lknfeklkkp
241 rgetkgmiy
```

An exemplary human *IFNg* nucleic acid sequence is set forth below (SEQ ID NO: 22; GenBank Accession No: U10360, Version 1, incorporated herein by reference):

```
  1 atggccatgc tcagggtcca gcccgaggcc caagccaagg tggatgtgtt tcgtgaagac
 61 ctctgtacca agacagagaa cctgctcggg agctatttcc ccaagaagat ttctgagctg
121 gatgcatttt taaaggagcc agctctcaat gaagccaact tgagcaatct gaaggcccca
181 ttggacatcc cagtgcctga tccagtcaag gagaaagaga aagaggagcg gaagaaacag
241 caggagaagg aagacaagga tgaaaagaag aaggggagg atgaagacaa aggtcctccc
301 tgtggcccag tgaactgcaa tgaaaagatc gtggtccttc tgcagcgctt gaagcctgag
361 atcaaggatg tcattgagca gctcaacctg gtcaccacct ggttgcagct gcagatacct
421 cggattgagg atggtaacaa ttttggagtg gctgtccagg agaaggtgtt tgagctgatg
481 accagcctcc acaccaagct agaaggcttc cacactcaaa tctctaagta tttctctgag
```

```
 541 cgtggtgatg cagtgactaa agcagccaag cagccccatg tgggtgatta tcggcagctg
 601 gtgcacgagc tggatgaggc agagtaccgg gacatccggc tgatggtcat ggagatccgc
 661 aatgcttatg ctgtgttata tgacatcatc ctgaagaact tcgagaagct caagaagccc
 721 aggggagaaa caaagggaat gatctattga
```

An exemplary human insulin-like growth factor binding protein 1 (IGFBP-1) amino acid sequence is set forth below (SEQ ID NO: 23; GenBank Accession No: NP_000587, Version 1, incorporated herein by reference):

```
   1 msevpvarvw lvlllltvqv gvtagapwqc apcsaeklal cppvsascse vtrsagcgcc
  61 pmcalplgaa cgvatarcar glscralpge qqplhaltrg qgacvqesda saphaaeags
 121 pespesteit eeelldnfhl mapseedhsi lwdaistydg skalhvtnik kwkepcriel
 181 yrvveslaka qetsgeeisk fylpncnkng fyhsrqcets mdgeaglcwc vypwngkrip
 241 gspeirgdpn cqiyfnvqn
```

An exemplary human *IGFBP-1* nucleic acid sequence is set forth below (SEQ ID NO: 24; GenBank Accession No: NM_000596, Version 2, incorporated herein by reference):

```
   1 ggtgcactag caaaacaaac ttattttgaa cactcagctc ctagcgtgcg gcgctgccaa
  61 tcattaacct cctggtgcaa gtggcgcggc ctgtgccctt tataaggtgc gcgctgtgtc
 121 cagcgagcat cggccaccgc catcccatcc agcgagcatc tgccgccgcg ccgccgccac
 181 cctcccagag agcactggcc accgctccac catcacttgc ccagagtttg ggccaccgcc
 241 cgccgccacc agcccagaga gcatcggccc ctgtctgctg ctcgcgcctg gagatgtcag
 301 aggtccccgt tgctcgcgtc tggctggtac tgctcctgct gactgtccag gtcggcgtga
 361 cagccggcgc tccgtggcag tgcgcgccct gctccgccga gaagctcgcg ctctgcccgc
 421 cggtgtccgc ctcgtgctcg gaggtcaccc ggtccgccgg ctgcggctgt tgcccgatgt
 481 gcgccctgcc tctgggcgcc gcgtgcggcg tggcgactgc acgctgcgcc cggggactca
 541 gttgccgcgc gctgccgggg gagcagcaac ctctgcacgc cctcacccgc ggccaaggcg
 601 cctgcgtgca ggagtctgac gcctccgctc cccatgctgc agaggcaggg agccctgaaa
 661 gcccagagag cacggagata actgaggagg agctcctgga taatttccat ctgatggccc
 721 cttctgaaga ggatcattcc atcctttggg acgccatcag tacctatgat ggctcgaagg
 781 ctctccatgt caccaacatc aaaaaatgga aggagccctg ccgaatagaa ctctacagag
 841 tcgtagagag tttagccaag gcacaggaga catcaggaga agaaatttcc aaattttacc
 901 tgccaaactg caacaagaat ggattttatc acagcagaca gtgtgagaca tccatggatg
 961 gagaggcggg actctgctgg tgcgtctacc cttggaatgg gaagaggatc cctgggtctc
1021 cagagatcag gggagacccc aactgccaga tatattttaa tgtacaaaac tgaaaccaga
1081 tgaaataatg ttctgtcacg tgaaatattt aagtatatag tatatttata ctctagaaca
1141 tgcacattta tatatatatg tatatgtata tatatatagt aactactttt tatactccat
1201 acataacttg atatagaaag ctgtttattt attcactgta agtttatttt ttctacacag
1261 taaaaacttg tactatgtta ataacttgtc ctatgtcaat ttgtatatca tgaaacactt
1321 ctcatcatat tgtatgtaag taattgcatt tctgctcttc caaagctcct gcgtctgttt
1381 ttaaagagca tggaaaaata ctgcctagaa aatgcaaaat gaaataagag agagtagttt
1441 ttcagctagt ttgaaggagg acggttaact tgtatattcc accattcaca tttgatgtac
1501 atgtgtaggg aaagttaaaa gtgttgatta cataatcaaa gctacctgtg gtgatgttgc
1561 cacctgttaa aatgtacact ggatatgttg ttaaacacgt gtctataatg gaaacattta
1621 caataaatat tctgcatgga aatactgtta aaaaaaaaaa
```

An exemplary human interleukin-10 (IL-10) amino acid sequence is set forth below (SEQ ID NO: 25; GenBank Accession No: AAK38162, Version 1, incorporated herein by reference):

```
   1 mhssallccl vlltgvrasp gqgtqsensc thfpgnlpnm lrdlrdafsr vktffqmkdq
  61 ldnlllkesl ledfkgylgc qalsemiqfy leevmpqaen qdpdikahvn slgenlktlr
```

```
121 lrlrrchrfl pcenkskave qvknafnklq ekgiykamse fdifinyiea ymtmkirn
```

An exemplary human *IL-10* nucleic acid sequence is set forth below (SEQ ID NO: 26; GenBank Accession No: AY029171, Version 1, incorporated herein by reference):

```
  1 atgcacagct cagcactgct ctgttgcctg gtcctcctga ctggggtgag ggccagccca
 61 ggccagggca cccagtctga gaacagctgc acccacttcc caggcaacct gcctaacatg
121 cttcgagatc tccgagatgc cttcagcaga gtgaagactt tctttcaaat gaaggatcag
181 ctggacaact tgttgttaaa ggagtccttg ctggaggact ttaagggtta cctgggttgc
241 caagccttgt ctgagatgat ccagttttac ctggaggagg tgatgcccca agctgagaac
301 caagacccag acatcaaggc gcatgtgaac tccctggggg agaacctgaa gaccctcagg
361 ctgaggctac ggcgctgtca tcgatttctt ccctgtgaaa acaagagcaa ggccgtggag
421 caggtgaaga atgcctttaa taagctccaa gagaaaggca tctacaaagc catgagtgag
481 tttgacatct tcatcaacta catagaagcc tacatgacaa tgaagatacg aaactga
```

An exemplary human interleukin- 12 (IL-12) amino acid sequence is set forth below (SEQ ID NO: 27; GenBank Accession No: AAD16432, Version 1, incorporated herein by reference):

```
  1 mwppgsasqp ppspaaatgl hpaarpvslq crlsmcpars lllvatlvll dhlslarnlp
 61 vatpdpgmfp clhhsqnllr avsnmlqkar qtlefypcts eeidheditk dktstveacl
121 pleltknesc lnsretsfit ngsclasrkt sfmmalclss iyedlkmyqv efktmnakll
181 mdpkrqifld qnmlavidel mqalnfnset vpqkssleep dfyktkiklc illhafrira
241 vtidrvmsyl nas
```

An exemplary human *IL-12* nucleic acid sequence is set forth below (SEQ ID NO: 28; GenBank Accession No: AF101062, Version 1, incorporated herein by reference):

```
  1 atgtggcccc ctgggtcagc ctcccagcca ccgccctcac ctgccgcggc cacaggtctg
 61 catccagcgg ctcgccctgt gtccctgcag tgccggctca gcatgtgtcc agcgcgcagc
121 ctcctccttg tggctaccct ggtcctcctg gaccacctca gtttggccag aaacctcccc
181 gtggccactc cagacccagg aatgttccca tgccttcacc actcccaaaa cctgctgagg
241 gccgtcagca acatgctcca gaaggccaga caaactctag aattttaccc ttgcacttct
301 gaagagattg atcatgaaga tatcacaaaa gataaaacca gcacagtgga ggcctgttta
361 ccattggaat taaccaagaa tgagagttgc ctaaattcca gagagacctc tttcataact
421 aatgggagtt gcctggcctc cagaaagacc tcttttatga tggccctgtg ccttagtagt
481 atttatgaag acttgaagat gtaccaggtg gagttcaaga ccatgaatgc aaagcttctg
541 atggatccta agaggcagat ctttctagat caaaacatgc tggcagttat tgatgagctg
601 atgcaggccc tgaatttcaa cagtgagact gtgccacaaa aatcctccct tgaagaaccg
661 gatttttata aaactaaaat caagctctgc atacttcttc atgctttcag aattcgggca
721 gtgactattg atagagtgat gagctatctg aatgcttcct aa
```

An exemplary human interleukin-13 (IL-13) amino acid sequence is set forth below (SEQ ID NO: 29; GenBank Accession No: AAH96141, Version 2, incorporated herein by reference):

```
  1 mallttvia ltclggfasp gpvppstalr elieelvnit qnqkaplcng smvwsinlta
 61 gmycaalesl invsgcsaie ktqrmlsgfc phkvsagqfs slhvrdtkie vaqfvkdlll
121 hlkklfregq fnrnfesiii crdrt
```

An exemplary human *IL-13* nucleic acid sequence is set forth below (SEQ ID NO: 30; GenBank Accession No: BC096141, Version 1, incorporated herein by reference):

```
   1 aagccaccca gcctatgcat ccgctcctca atcctctcct gttggcactg ggcctcatgg
  61 cgcttttgtt gaccacggtc attgctctca cttgccttgg cggctttgcc tccccaggcc
 121 ctgtgcctcc ctctacagcc ctcagggagc tcattgagga gctggtcaac atcacccaga
 181 accagaaggc tccgctctgc aatggcagca tggtatggag catcaacctg acagctggca
 241 tgtactgtgc agccctggaa tccctgatca acgtgtcagg ctgcagtgcc atcgagaaga
 301 cccagaggat gctgagcgga ttctgcccgc acaaggtctc agctgggcag ttttccagct
 361 tgcatgtccg agacaccaaa atcgaggtgg cccagtttgt aaaggacctg ctcttacatt
 421 taaagaaact ttttcgcgag ggacagttca accgaaactt cgaaagcatc attatttgca
 481 gagacaggac ctgactattg a
```

An exemplary human interleukin-15 (IL-15) amino acid sequence is set forth below (SEQ ID NO: 31; GenBank Accession No: CAA62616, Version 1, incorporated herein by reference):

```
   1 mriskphlrs isiqcylcll lnshflteag ihvfilgcfs aglpkteanw vnvisdlkki
  61 edliqsmhid atlytesdvh psckvtamkc fllelqvisl esgdasihdt venliilann
 121 slssngnvte sgckeceele eknikeflqs fvhivqmfin ts
```

An exemplary human *IL-15* nucleic acid sequence is set forth below (SEQ ID NO: 32; GenBank Accession No: X91233, Version 1, incorporated herein by reference):

```
   1 ggcattgtaa tcagacagaa ctggcctcaa atcctggctg tcatgtactt gctatgggcc
  61 tagagtagct tacctaaatg ctactaacct tcctccatac cattattgta aagattaaag
 121 gtgatgcatc tgttaagtaa ctaatagagt gcttattaaa aggtaggtgt tcaataagta
 181 ttaattccct ttctttcttt ttcttactag tgcacttgtg tttttaatgg atcatacttt
 241 accctagatt gtattgtagg aggcatcgtg gatggatggc tgctggaaac cccttgccat
 301 agccagctct tcttcaatac ttaaggattt accgtggctt tgagtaatga gaatttccgg
 361 taagaagaaa aatagatgaa aatatcctat ggaatttccc ttaaaggtcg tctgaatctc
 421 agagtctttg caataagtta catggttatt ctccaaagat cttgagatat cacagatgtc
 481 tgttcacatt tggattgttc ttattttgaa aataaatagg tttttaaaaa ctctattgac
 541 catcttgata ggctcttctt gtcattataa atgtgttatt tcacttatcc cactcttttg
 601 tgttctctaa atgtctttgt actcactaaa ttgtgtagtc ttagagggca gggtgtgggt
 661 atcattcatc tttttgaaag gaagcatgaa caattagtgg ttaaggtggc agttaacact
 721 gctttctgaa actttaaaag cttcgacaac acaaaagagg caggtgaaag taccaaaact
 781 ctggtaagtt gtaggataaa tgattttcct aaatcaccaa gaaagattat tagtcactct
 841 caagatggaa tacagtatct gtaattggtt ccattttatc caatttttca ccaaataata
 901 ttaatataat tcattttcat aatttacatg aagttaatat aactattgca tctctgttag
 961 taatgcatgt tattaacctg tgctgtataa aatattttga cctattaaaa aagaaagaag
1021 gatgaggagg aggtcaaaga taatataaaa actttaagtg gtgacattgg tatgtatgta
1081 aattaacaaa tatgtcaact ttgttaaatt atctttgaca tgcatctgca gaaatatctg
1141 ttaaggaact ttgtgcataa gagacagagt tggaggtggg agagaaagtg aaaaaagata
1201 aattatagtt ttattatttt tgataagggg cagtaattat gaaattatga caaacttaca
1261 tctttagacc tagaaatatg ttgacatgtt attttaaacc tcacttttta actaaaaaat
1321 ttaaccattt gtctatgatt atatttttca gaaaccacat ttgagaagta tttccatcca
1381 gtgctacttg tgtttacttc taaacagtca ttttctaact gaagctggca ttcatgtctt
1441 cattttgggg gtaattttat ctttaggcat aaataacatt atgttcatgg tcatgatgat
1501 tgtccttgga tatattttcc attaaattag tttacgttca gtttgcttat atctctaggt
1561 actcagtatc tgggggatag aaggcagact acagagattt agagaggttt ggtaaacacc
1621 taactgagca tttttctaca ttgtggtaat agtccaaaca agcattatag ccctcaaata
1681 aattgggcct tttgatattt aactgaactt ggaagtatac cacttattga tagactacat
```

1741 atttttcatg gcaattaaaa gtagatattt agaatttgct tatgttactt ttttatctgt
1801 ccctgacact gactcctcct atcccttgat ctttatccta gttcagttta aaacatttct
1861 ttctttattt aagccttttg ttgtttcctt ctaataaaat tcatatgttt ccatgactat
1921 taacttttt cttctctctt agatgcagct aatataccca gttggcccaa agcacctaac
1981 ctatagttat ataatctgac tctcagttca gttttactct actaatgcct tcatggtatt
2041 gggaaccata gatttgtgca ggtaattctt catcataaga cagattagtg ttgactatca
2101 tgcttctgtg taagatccat caggaagtga gtgattattt ttcctcaagc tctaagcatc
2161 attccaatgt tacttggtca gtataagtgt attttgtctg gatattaaat tttaattttt
2221 atgaaatttg tgaaagtgag taagtatatg atcattcagc ctacactgga atgaagtctg
2281 tactgtttat ggagaaagct gctgcaagca tagtaagagt gtgagcaaca tgaaaggggc
2341 atgtttaatg tagtgtaaaa aaaatttact atcaaaatca ttacatgaaa atgattatta
2401 ctcattttaa gaattttacc tatttattag acttcaaagt ctctgtaaat ctctacttaa
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14881 gttcttattg ctctagtcaa acggtgctta taaatatctt tcagaaagct taggagaaat
14941 ctgtatccta tttgacttcc aataatca

An exemplary human interleukein 17 (IL-17) amino acid sequence is set forth below (SEQ ID NO: 33; GenBank Accession No: NP_002181, Version 1, incorporated herein by reference):

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  1 mtpgktslvs lllllsleai vkagitiprn pgcpnsedkn fprtvmvnln ihnrntntnp
 61 krssdyynrs tspwnlhrne dperypsviw eakcrhlgci nadgnvdyhm nsvpiqqeil
121 vlrrepphcp nsfrlekilv svgctcvtpi vhhva
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An exemplary human *IL-17* nucleic acid sequence is set forth below (SEQ ID NO: 34; GenBank Accession No: NM_002190, Version 2, incorporated herein by reference):

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 901 aaaggtaaaa cctgtattta tttgagctat ttaaggatct atttatgttt aagtatttag
 961 aaaaaggtga aaaagcacta ttatcagttc tgcctaggta aatgtaagat agaattaaat
1021 ggcagtgcaa aatttctgag tctttacaac atacggatat agtatttcct cctctttgtt
1081 tttaaaagtt ataacatggc tgaaaagaaa gattaaacct actttcatat gtattaattt
1141 aaattttgca atttgttgag gttttacaag agatacagca agtctaactc tctgttccat
1201 taaaccctta taataaaatc cttctgtaat aataaagttt caaaagaaaa tgtttatttg
1261 ttctcattaa atgtatttta gcaaactcag ctcttcccta ttgggaagag ttatgcaaat
1321 tctcctataa gcaaaacaaa gcatgtcttt gagtaacaat gacctggaaa tacccaaaat
1381 tccaagttct cgatttcaca tgccttcaag actgaacacc gactaaggtt ttcatactat
1441 tagccaatgc tgtagacaga agcattttga taggaataga gcaaataaga taatggccct
1501 gaggaatggc atgtcattat taaagatcat atggggaaaa tgaaaccctc cccaaaatac
1561 aagaagttct gggaggagac attgtcttca gactacaatg tccagtttct cccctagact
1621 caggcttcct ttggagatta aggcccctca gagatcaaca gaccaacatt tttctcttcc
1681 tcaagcaaca ctcctagggc ctggcttctg tctgatcaag gcaccacaca acccagaaag
1741 gagctgatgg ggcagaacga actttaagta tgagaaaagt tcagcccaag taaaataaaa
1801 actcaatcac attcaattcc agagtagttt caagtttcac atcgtaacca ttttcgccc
```

An exemplary human interleukin 18 (IL-18) amino acid sequence is set forth below (SEQ ID NO: 35; GenBank Accession No: NP_001553, Version 1, incorporated herein by reference):

```
  1 maaepvednc infvamkfid ntlyfiaedd enlesdyfgk lesklsvirn lndqvlfidq
 61 gnrplfedmt dsdcrdnapr tifiismykd sqprgmavti svkcekistl scenkiisfk
121 emnppdnikd tksdiiffqr svpghdnkmq fesssyegyf lacekerdlf klilkkedel
181 gdrsimftvq ned
```

An exemplary human *IL-18* nucleic acid sequence is set forth below (SEQ ID NO: 36; GenBank Accession No: NM_001562, Version 3, incorporated herein by reference):

```
   1 attctctccc cagcttgctg agccctttgc tcccctggcg actgcctgga cagtcagcaa
  61 ggaattgtct cccagtgcat tttgccctcc tggctgccaa ctctggctgc taaagcggct
 121 gccacctgct gcagtctaca cagcttcggg aagaggaaag gaacctcaga ccttccagat
 181 cgcttcctct cgcaacaaac tatttgtcgc aggaataaag atggctgctg aaccagtaga
 241 agacaattgc atcaactttg tggcaatgaa atttattgac aatacgcttt actttatagc
 301 tgaagatgat gaaaacctgg aatcagatta ctttggcaag cttgaatcta aattatcagt
 361 cataagaaat ttgaatgacc aagttctctt cattgaccaa ggaaatcggc ctctatttga
 421 agatatgact gattctgact gtagagataa tgcaccccgg accatattta ttataagtat
 481 gtataaagat agccagccta gaggtatggc tgtaactatc tctgtgaagt gtgagaaaat
 541 ttcaactctc tcctgtgaga acaaaattat ttcctttaag gaaatgaatc ctcctgataa
 601 catcaaggat acaaaaagtg acatcatatt ctttcagaga agtgtcccag gacatgataa
 661 taagatgcaa tttgaatctt catcatacga aggatacttt ctagcttgtg aaaaagagag
 721 agacctttt aaactcattt tgaaaaaaga ggatgaattg ggggatagat ctataatgtt
 781 cactgttcaa aacgaagact agctattaaa atttcatgcc gggcgcagtg gctcacgcct
 841 gtaatcccag ccctttggga ggctgaggcg ggcagatcac cagaggtcag gtgttcaaga
 901 ccagcctgac caacatggtg aaacctcatc tctactaaaa atacaaaaaa ttagctgagt
 961 gtagtgacgc atgccctcaa tcccagctac tcaagaggct gaggcaggag aatcacttgc
1021 actccggagg tagaggttgt ggtgagccga gattgcacca ttgcgctcta gcctgggcaa
1081 caacagcaaa actccatctc aaaaaataaa ataaataaat aaacaaataa aaaattcata
1141 atgtgaaaaa aaaaaaaaaa aaa
```

An exemplary human interleukin 1 beta (IL-1b) amino acid sequence is set forth below (SEQ ID NO: 37; GenBank Accession No: P01584, Version 2, incorporated herein by reference):

```
   1 maevpelase mmayysgned dlffeadgpk qmkcsfqdld lcpldggiql risdhhyskg
  61 frqaasvvva mdklrkmlvp cpqtfqendl stffpfifee epiffdtwdn eayvhdapvr
 121 slnctlrdsq qkslvmsgpy elkalhlqgq dmeqqvvfsm sfvqgeesnd kipvalglke
 181 knlylscvlk ddkptlqles vdpknypkkk mekrfvfnki einnklefes aqfpnwyist
 241 sqaenmpvfl ggtkggqdit dftmqfvss
```

An exemplary human *IL-1b* nucleic acid sequence is set forth below (SEQ ID NO: 38; GenBank Accession No: NM_000576, Version 2, incorporated herein by reference):

```
   1 accaaacctc ttcgaggcac aaggcacaac aggctgctct gggattctct tcagccaatc
  61 ttcattgctc aagtgtctga agcagccatg gcagaagtac ctgagctcgc cagtgaaatg
 121 atggcttatt acagtggcaa tgaggatgac ttgttctttg aagctgatgg ccctaaacag
 181 atgaagtgct ccttccagga cctggacctc tgccctctgg atggcggcat ccagctacga
 241 atctccgacc accactacag caagggcttc aggcaggccg cgtcagttgt tgtggccatg
 301 gacaagctga ggaagatgct ggttccctgc ccacagacct tccaggagaa tgacctgagc
 361 accttctttc ccttcatctt tgaagaagaa cctatcttct tcgacacatg ggataacgag
 421 gcttatgtgc acgatgcacc tgtacgatca ctgaactgca cgctccggga ctcacagcaa
 481 aaaagcttgg tgatgtctgg tccatatgaa ctgaaagctc tccacctcca gggacaggat
 541 atggagcaac aagtggtgtt ctccatgtcc tttgtacaag gagaagaaag taatgacaaa
 601 atacctgtgg ccttgggcct caaggaaaag aatctgtacc tgtcctgcgt gttgaaagat
 661 gataagccca ctctacagct ggagagtgta gatcccaaaa attacccaaa gaagaagatg
 721 gaaaagcgat ttgtcttcaa caagatagaa atcaataaca agctggaatt tgagtctgcc
 781 cagttcccca actggtacat cagcacctct caagcagaaa acatgcccgt cttcctggga
 841 gggaccaaag gcggccagga tataactgac ttcaccatgc aatttgtgtc ttcctaaaga
 901 gagctgtacc cagagagtcc tgtgctgaat gtggactcaa tccctagggc tggcagaaag
```

```
 961 ggaacagaaa ggtttttgag tacggctata gcctggactt tcctgttgtc tacaccaatg
1021 cccaactgcc tgccttaggg tagtgctaag aggatctcct gtccatcagc caggacagtc
1081 agctctctcc tttcagggcc aatccccagc ccttttgttg agccaggcct ctctcacctc
1141 tcctactcac ttaaagcccg cctgacagaa accacggcca catttggttc taagaaaccc
1201 tctgtcattc gctcccacat tctgatgagc aaccgcttcc ctatttattt atttatttgt
1261 ttgtttgttt tattcattgg tctaatttat tcaaaggggg caagaagtag cagtgtctgt
1321 aaaagagcct agtttttaat agctatggaa tcaattcaat ttggactggt gtgctctctt
1381 taaatcaagt cctttaatta agactgaaaa tatataagct cagattattt aaatgggaat
1441 atttataaat gagcaaatat catactgttc aatggttctg aaataaactt cactgaag
```

An exemplary human interleukin 1 receptor agonist (IL-1ra) amino acid sequence is set forth below (SEQ ID NO: 39; GenBank Accession No: P18510, Version 1, incorporated herein by reference):

```
  1 meicrglrsh litlllflfh seticrpsgr ksskmqafri wdvnqktfyl rnnqlvagyl
 61 qgpnvnleek idvvpiepha lflgihggkm clscvksgde trlqleavni tdlsenrkqd
121 krfafirsds gpttsfesaa cpgwflctam eadqpvsltn mpdegvmvtk fyfqede
```

An exemplary human *IL-1ra* nucleic acid sequence is set forth below (SEQ ID NO: 40; GenBank Accession No: X77090, Version 1, incorporated herein by reference):

```
   1 gatcccacag ctatagttca tggtgctggg atttgaacct ctggccacca gagcccacct
  61 taatgtgtcc tcctcctgtt gtcataacag aaaagtacaa caccatgatg acacatcagg
 121 ctatcctggc aggttcccag gctgccccaa tgcccaactt tctaggttta caaagttgac
 181 atttacgaag tttccaggtt tacaaatcta gtttctgatt ctttagtcag caggaatttc
 241 tctacaaaag ctgcttcgaa aatttccagc caaaccttac acaccttggc accacatctt
 301 ggtgagccaa ggcgaagaga acaggaagtg aaggccccat gggaagtccc tgcggtcggg
 361 agcacccagg cggggcgggg ggtgggggggc tttcctgtgg ccggctccct gcccctccca
 421 cccccattca ggccctgtga gttgaatgaa gagaccctgg gaatgagtcc aggtctgcag
 481 ggttagagga aattgaaggc ccttaccaga tccctgttga gaagtttatg aattatgagc
 541 ccttctgcaa atgagagggt tcttccctgt caggagggac agattgtagg tggcaagatt
 601 ggtggcagcc agtaggctgg tctgctcctt cctctctatt tcatatgtgt atgaaggcat
 661 tacctgcagc aagggcctgt gtaaatgcat gtgatttaca gagcatttta tgtactgcgt
 721 gtcattcatg cttccggtga gccctaagtc taagataggg cagatagcat caggtccatt
 781 ttgcagctgt caaaatgagg tctgaagggc agaagtggtg tgcccacaca cacacaactg
 841 gttggctgca gacctgggga ctagacccgg gacttcgtcc tgcccagggg tctcttgcca
 901 ctgctcccca tcaacttgga tggctttaag catttgtgag ttgtctgctc cctgatggca
 961 gaatgcagag acatgaagct acaagcaggt tcgctcccaa cggcaaaaag gaggaggggt
1021 gttcagaaca tcaggtgctt ctagagaaag cagggagaga gtatctggcc ttgtggacaa
1081 tgtcacggca gaggccaggt atagggcatg ggggtaactg gaagcgggat ggaccctctt
1141 attccctaag acatggcttc cacgtagtgc tcaaacaagg cctttgccct tgctgttccc
1201 tccacctgga atattcttcc ccttccttga cattgctcag gtctccactc ttatgtcacc
1261 ctctcagaga gggcttccct ggccactttc cctaaaatag ccacccactc ctaggtccct
1321 caaaagcata tcctgctttg gattttccct atagcaatat gccctatgaa gttatttttat
1381 ttgctaactt gtttcttgtc tgttttcctt tgttagagcg ttggggacct tgtctggctt
1441 gttcccaatg cctggaagag tgcctggcac acaggattaa gccaacacat atgttttgaa
1501 tgaatgtgtg cacacatgca tgagctggcg gcagtcgggg ttggggtaag cacgaaggcc
1561 cagctcagtt ctctgcatgt gacctcccat cttacgcaga taagaaccag tttggtttct
1621 gctagcctga gtcaccctcc tggaaactgg gcctgcttgg catcaagtca gccatcagcc
1681 ggcccatctc ctcatgctgg ccaaccctct gtgagtgtgt gggaggggag gctgggctcc
1741 tccttgtact ctctgaggtg ctctggaagg aggggcagct ccaccctggg agggactgtg
1801 gcccaggtac tgcccgggtg ctactttatg ggcagcagct cagttgagtt agagtctgga
1861 agacctcaga agacctcctg tcctatgagg ccctccccat ggctttaggt aagctccttc
```

```
1921 cactctcatt ttttcacctg agaaatgaga gaggaaaatg tctacaattg gtgtttatca
1981 aatgctttca ggctctggtg agcaagcgtc caggaaaatg tcaagcgcat ggagctccag
2041 gcctgtctgg gggatctggg cacggggagg catccatggg agaccatgca ggcactctga
2101 ggcaggggct gcaagctagt gcctgctggg gcagcaggtg aacagagagg tgtaactgct
2161 gtgacagaag tc
```

An exemplary human interleukin 2 (IL-2) amino acid sequence is set forth below (SEQ ID NO: 41; GenBank Accession No: AAB46883, Version 1, incorporated herein by reference):

```
  1 myrmqllsci alslalvtns aptssstkkt qlqlehllld lqmilnginn yknpkltrml
 61 tfkfympkka telkhlqcle eelkpleevl nlaqsknfhl rprdlisnin vivlelkgse
121 ttfmceyade tativeflnr witfcqsiis tlt
```

An exemplary human *IL-2* nucleic acid sequence is set forth below (SEQ ID NO: 42; GenBank Accession No: M13879, Version 1, incorporated herein by reference):

```
   1 agtggttttt ggagtcagta cattctcttt tcaaatcctt ctctgcccct tactggcaat
  61 aagggctgag tgacctagag gcaaattact taacttctct gagcctcagt tttctaatct
 121 gcaaaatagg agccatcact tcacaagtct gtaagactta tattagacta agtgcctgcc
 181 tgtacactgt tctcttttc tctctttcta tatacctgaa ggcattatag tgctagatgt
 241 ctgtttaaag accagacaat attgtcttaa aaaaacaaac aaaaacacag acaataccat
 301 ctttaaaaaa aaaaaaaaag tccaggtaag aaataaataa ggccatagaa tggaagcttt
 361 acaaggactc tctttgagac aggatctcct caagtgtccc caggttaaat tagaagtata
 421 tatccgtaca attgttcagc cagtttgtgc actgtactga ggatgaatga acacctatcc
 481 taaatatcct agtcttctga ctaaaaacaa gatcatattt cataacgatt attgttacat
 541 tcatagtgtc ccaggtgatt tagaggataa ataaaaatcc attaaagagg taaagacata
 601 aaaacgagaa acatggactg gtttacacat aacacataca aagtctatta taaaactagc
 661 atcagtatcc ttgaatcgaa acctttttct gagtatttaa caatcgcacc ctttaaaaaa
 721 tgtacataga cattaagaga cttaaacaga tatataatca ttttaaatta aaatagcgtt
 781 aaacagtacc tcaagctcaa taagcatttt aagtattcta atcttagtat ttctctagct
 841 gacatgtaag aagcaatcta tcttattgta tgcaattagc tcattgtgtg gataaaaagg
 901 taaaaccatt ctgaaacagg aaaccaatac acttcctgtt taatcaacaa atctaaacat
 961 ttattctttt catctgttta ctcttgctct tgtccaccac aatatgctat tcacatgttc
1021 agtgtagttt tatgacaaag aaaattttct gagttacttt tgtatcccca ccccttaaa
1081 gaaaggagga aaaactgttt catacagaag gcgttaattg catgaattag agctatcacc
1141 taagtgtggg ctaatgtaac aaagagggat ttcacctaca tccattcagt cagtctttgg
1201 gggtttaaag aaattccaaa gagtcatcag aagaggaaaa atgaaggtaa tgtttttca
1261 gactggtaaa gtctttgaaa atatgtgtaa tatgtaaaac attttgacac ccccataata
1321 tttttccaga attaacagta taaattgcat ctcttgttca agagttccct atcactcttt
1381 aatcactact cacagtaacc tcaactcctg ccacaatgta caggatgcaa ctcctgtctt
1441 gcattgcact aagtcttgca cttgtcacaa acagtgcacc tacttcaagt tctacaaaga
1501 aaacacagct acaactggag catttactgc tggatttaca gatgattttg aatggaatta
1561 atgtaagtat atttcctttc ttactaaaat tattacattt agtaatctag ctggagatca
1621 tttcttaata acaatgcatt atactttctt agaattacaa gaatcccaaa ctcaccagga
1681 tgctcacatt taagttttac atgcccaaga aggtaagtac aatattttat gttcaatttc
1741 tgttttaata aaattcaaag taatatgaaa atttgcacag atgggactaa tagcagctca
1801 tctgaggtaa agagtaactt taatttgttt ttttgaaaac ccaagtttga taatgaagcc
1861 tctattaaaa cagttttacc tatattttta atatatattt gtgtgttggt gggggtggga
1921 gaaaacataa aaataatatt ctctcacttt at
```

An exemplary human interleukin 4 (IL-4) amino acid sequence is set forth below (SEQ ID NO: 43; GenBank Accession No: NP_000580, Version 1, incorporated herein by reference):

```
  1 mgltsqllpp lffllacagn fvhghkcdit lqeiiktlns lteqktlcte ltvtdifaas
 61 knteketfc raatvlrqfy shhekdtrcl gataqqfhrh kqlirflkrl drnlwglagl
121 nscpvkeanq stlenflerl ktimrekysk css
```

An exemplary human *IL-4* nucleic acid sequence is set forth below (SEQ ID NO: 44; GenBank Accession No: NM_000589, Version 3, incorporated herein by reference):

```
  1 tgcatcgtta gcttctcctg ataaactaat tgcctcacat tgtcactgca aatcgacacc
 61 tattaatggg tctcacctcc caactgcttc cccctctgtt cttcctgcta gcatgtgccg
121 gcaactttgt ccacggacac aagtgcgata tcaccttaca ggagatcatc aaaactttga
181 acagcctcac agagcagaag actctgtgca ccgagttgac cgtaacagac atctttgctg
241 cctccaagaa cacaactgag aaggaaacct tctgcagggc tgcgactgtg ctccggcagt
301 tctacagcca ccatgagaag gacactcgct gcctgggtgc gactgcacag cagttccaca
361 ggcacaagca gctgatccga ttcctgaaac ggctcgacag gaacctctgg ggcctggcgg
421 gcttgaattc ctgtcctgtg aaggaagcca accagagtac gttggaaaac ttcttggaaa
481 ggctaaagac gatcatgaga gagaaatatt caaagtgttc gagctgaata ttttaattta
541 tgagtttttg atagctttat tttttaagta tttatatatt tataactcat cataaaataa
601 agtatatata gaatctaaaa aaaaaaaaaa aaaaaaaaaa aa
```

An exemplary human interleukin 5 (IL-5) amino acid sequence is set forth below (SEQ ID NO: 45; GenBank Accession No: NP_000870, Version 1, incorporated herein by reference):

```
  1 mrmllhlsll algaayvyai pteiptsalv ketlallsth rtllianetl ripvpvhknh
 61 qlcteeifqg igtlesqtvq ggtverlfkn lslikkyidg qkkkcgeerr rvnqfldylq
121 eflgvmntew iies
```

An exemplary human *IL-5* nucleic acid sequence is set forth below (SEQ ID NO: 46; GenBank Accession No: NM_000879, Version 2, incorporated herein by reference):

```
  1 atgcactttc tttgccaaag gcaaacgcag aacgtttcag agccatgagg atgcttctgc
 61 atttgagttt gctagctctt ggagctgcct acgtgtatgc catccccaca gaaattccca
121 caagtgcatt ggtgaaagag accttggcac tgctttctac tcatcgaact ctgctgatag
181 ccaatgagac tctgaggatt cctgttcctg tacataaaaa tcaccaactg tgcactgaag
241 aaatctttca gggaataggc acactggaga gtcaaactgt gcaaggggt actgtggaaa
301 gactattcaa aaacttgtcc ttaataaaga aatacattga cggccaaaaa aaaaagtgtg
361 gagaagaaag acggagagta aaccaattcc tagactacct gcaagagttt cttggtgtaa
421 tgaacaccga gtggataata gaaagttgag actaaactgg tttgttgcag ccaaagattt
481 tggaggagaa ggacatttta ctgcagtgag aatgagggcc aagaaagagt caggccttaa
541 ttttcagtat aatttaactt cagagggaaa gtaaatattt caggcatact gacactttgc
601 cagaaagcat aaaattctta aaatatattt cagatatcag aatcattgaa gtattttcct
661 ccaggcaaaa ttgatatact tttttcttat ttaacttaac attctgtaaa atgtctgtta
721 acttaatagt atttatgaaa tggttaagaa tttggtaaat tagtatttat ttaatgttat
781 gttgtgttct aataaaacaa aaatagacaa ctgttc
```

An exemplary human interleukin 6 (IL-6) amino acid sequence is set forth below (SEQ ID NO: 47; GenBank Accession No: NP_000591, Version 1, incorporated herein by reference):

```
  1 mnsfstsafg pvafslglll vlpaafpapv ppgedskdva aphrqpltss eridkqiryi
```

```
  61 ldgisalrke tcnksnmces skealaennl nlpkmaekdg cfqsgfneet clvkiitgll
 121 efevyleylq nrfesseeqa ravqmstkvl iqflqkkakn ldaittpdpt tnaslltklq
 181 aqnqwlqdmt thlilrsfke flqsslralr qm
```

An exemplary human *IL-6* nucleic acid sequence is set forth below (SEQ ID NO: 48; GenBank Accession No: NM_000600, Version 4, incorporated herein by reference):

```
   1 gtctcaatat tagagtctca acccccaata aatataggac tggagatgtc tgaggctcat
  61 tctgccctcg agcccaccgg gaacgaaaga gaagctctat ctcccctcca ggagcccagc
 121 tatgaactcc ttctccacaa gcgccttcgg tccagttgcc ttctccctgg ggctgctcct
 181 ggtgttgcct gctgccttcc ctgccccagt acccccagga gaagattcca aagatgtagc
 241 cgccccacac agacagccac tcacctcttc agaacgaatt gacaaacaaa ttcggtacat
 301 cctcgacggc atctcagccc tgagaaagga gacatgtaac aagagtaaca tgtgtgaaag
 361 cagcaaagag gcactggcag aaaacaacct gaaccttcca aagatggctg aaaaagatgg
 421 atgcttccaa tctggattca atgaggagac ttgcctggtg aaaatcatca ctggtctttt
 481 ggagtttgag gtatacctag agtacctcca gaacagattt gagagtagtg aggaacaagc
 541 cagagctgtg cagatgagta caaaagtcct gatccagttc ctgcagaaaa aggcaaagaa
 601 tctagatgca ataaccaccc ctgacccaac cacaaatgcc agcctgctga cgaagctgca
 661 ggcacagaac cagtggctgc aggacatgac aactcatctc attctgcgca gctttaagga
 721 gttcctgcag tccagcctga gggctcttcg gcaaatgtag catgggcacc tcagattgtt
 781 gttgttaatg ggcattcctt cttctggtca gaaacctgtc cactgggcac agaacttatg
 841 ttgttctcta tggagaacta aaagtatgag cgttaggaca ctattttaat tatttttaat
 901 ttattaatat ttaaatatgt gaagctgagt taatttatgt aagtcatatt tatattttta
 961 agaagtacca cttgaaacat tttatgtatt agttttgaaa taataatgga aagtggctat
1021 gcagtttgaa tatcctttgt ttcagagcca gatcatttct tggaaagtgt aggcttacct
1081 caaataaatg gctaacttat acatattttt aaagaaatat ttatattgta tttatataat
1141 gtataaatgg ttttttatacc aataaatggc attttaaaaa attcagcaaa aaaaaaa
```

An exemplary human interleukin 7 (IL-7) amino acid sequence is set forth below (SEQ ID NO: 49; GenBank Accession No: AAA59156, Version 1, incorporated herein by reference):

```
   1 mfhvsfryif glpplilvll pvassdcdie gkdgkqyesv lmvsidqlld smkeigsncl
  61 nnefnffkrh icdankegmf lfraarklrq flkmnstgdf dlhllkvseg ttillnctgq
 121 vkgrkpaalg eaqptkslee nkslkeqkkl ndlcflkrll qeiktcwnki lmgtkeh
```

An exemplary human *IL-7* nucleic acid sequence is set forth below (SEQ ID NO: 50; GenBank Accession No: J04156, Version 1, incorporated herein by reference):

```
   1 gaattcctct ggtcctcatc caggtgcgcg ggaagcaggt gcccaggaga gaggggataa
  61 tgaagattcc atgctgatga tcccaaagat tgaacctgca gaccaagcgc aaagtagaaa
 121 ctgaaagtac actgctggcg gatcctacgg aagttatgga aaaggcaaag cgcagagcca
 181 cgccgtagtg tgtgccgccc cccttgggat ggatgaaact gcagtcgcgg cgtgggtaag
 241 aggaaccagc tgcagagatc accctgccca acacagactc ggcaactccg cggaagacca
 301 gggtcctggg agtgactatg ggcggtgaga gcttgctcct gctccagttg cggtcatcat
 361 gactacgccc gcctcccgca gaccatgttc catgtttctt ttaggtatat ctttggactt
 421 cctcccctga tccttgttct gttgccagta gcatcatctg attgtgatat tgaaggtaaa
 481 gatggcaaac aatatgagag tgttctaatg gtcagcatcg atcaattatt ggacagcatg
 541 aaagaaattg gtagcaattg cctgaataat gaatttaact tttttaaaag acatatctgt
 601 gatgctaata aggaaggtat gtttttattc cgtgctgctc gcaagttgag gcaatttctt
 661 aaaatgaata gcactggtga ttttgatctc cacttattaa aagtttcaga aggcacaaca
 721 atactgttga actgcactgg ccaggttaaa ggaagaaaac cagctgccct gggtgaagcc
 781 caaccaacaa agagtttgga agaaaataaa tctttaaagg aacagaaaaa actgaatgac
```

```
 841 ttgtgtttcc taaagagact attacaagag ataaaaactt gttggaataa aattttgatg
 901 ggcactaaag aacactgaaa aatatggagt ggcaatatag aaacacgaac tttagctgca
 961 tcctccaaga atctatctgc ttatgcagtt tttcagagtg gaatgcttcc tagaagttac
1021 tgaatgcacc atggtcaaaa cggattaggg catttgagaa atgcatattg tattactaga
1081 agatgaatac aaacaatgga aactgaatgc tccagtcaac aaactatttc ttatatatgt
1141 gaacatttat caatcagtat aattctgtac tgatttttgt aagacaatcc atgtaaggta
1201 tcagttgcaa taatacttct caaacctgtt taaatatttc aagacattaa atctatgaag
1261 tatataatgg tttcaaagat tcaaaattga cattgcttta ctgtcaaaat aattttatgg
1321 ctcactatga atctattata ctgtattaag agtgaaaatt gtcttcttct gtgctggaga
1381 tgttttagag ttaacaatga tatatggata atgccggtga gaataagaga gtcataaacc
1441 ttaagtaagc aacagcataa caaggtccaa gatacctaaa agagatttca agagatttaa
1501 ttaatcatga atgtgtaaca cagtgccttc aataaatggt atagcaaatg ttttgacatg
1561 aaaaaaggac aatttcaaaa aaataaaat
```

An exemplary human interleukin 8 (IL-8) amino acid sequence is set forth below (SEQ ID NO: 51; GenBank Accession No: NP_000575, Version 1, incorporated herein by reference):

```
  1 mtsklavall aaflisaalc egavlprsak elrcqcikty skpfhpkfik elrviesgph
 61 canteiivkl sdgrelcldp kenwvqrvve kflkraens
```

An exemplary human *IL-8* nucleic acid sequence is set forth below (SEQ ID NO: 52; GenBank Accession No: NM_000584, Version 3, incorporated herein by reference):

```
   1 gagggtgcat aagttctcta gtagggtgat gatataaaaa gccaccggag cactccataa
  61 ggcacaaact ttcagagaca gcagagcaca caagcttcta ggacaagagc caggaagaaa
 121 ccaccggaag gaaccatctc actgtgtgta aacatgactt ccaagctggc cgtggctctc
 181 ttggcagcct tcctgatttc tgcagctctg tgtgaaggtg cagttttgcc aaggagtgct
 241 aaagaactta gatgtcagtg cataaagaca tactccaaac ctttccaccc caaatttatc
 301 aaagaactga gagtgattga gagtggacca cactgcgcca acacagaaat tattgtaaag
 361 ctttctgatg gaagagagct ctgtctggac cccaaggaaa actgggtgca gagggttgtg
 421 gagaagtttt tgaagagggc tgagaattca taaaaaaatt cattctctgt ggtatccaag
 481 aatcagtgaa gatgccagtg aaacttcaag caaatctact tcaacacttc atgtattgtg
 541 tgggtctgtt gtagggttgc cagatgcaat acaagattcc tggttaaatt tgaatttcag
 601 taaacaatga atagtttttc attgtaccat gaaatatcca gaacatactt atatgtaaag
 661 tattatttat ttgaatctac aaaaaacaac aaataatttt taaatataag gattttccta
 721 gatattgcac gggagaatat acaaatagca aaattgaggc caagggccaa gagaatatcc
 781 gaactttaat ttcaggaatt gaatgggttt gctagaatgt gatatttgaa gcatcacata
 841 aaaatgatgg gacaataaat tttgccataa agtcaaattt agctggaaat cctggatttt
 901 tttctgttaa atctggcaac cctagtctgc tagccaggat ccacaagtcc ttgttccact
 961 gtgccttggt ttctccttta tttctaagtg gaaaaagtat tagccaccat cttacctcac
1021 agtgatgttg tgaggacatg tggaagcact ttaagttttt tcatcataac ataaattatt
1081 ttcaagtgta acttattaac ctatttatta tttatgtatt tatttaagca tcaaatattt
1141 gtgcaagaat ttggaaaaat agaagatgaa tcattgattg aatagttata aagatgttat
1201 agtaaattta ttttatttta gatattaaat gatgttttat tagataaatt tcaatcaggg
1261 tttttagatt aaacaaacaa acaattgggt acccagttaa attttcattt cagataaaca
1321 acaaataatt ttttagtata agtacattat tgtttatctg aaatttttaat tgaactaaca
1381 atcctagttt gatactccca gtcttgtcat tgccagctgt gttggtagtg ctgtgttgaa
1441 ttacggaata atgagttaga actattaaaa cagccaaaac tccacagtca atattagtaa
1501 tttcttgctg gttgaaactt gtttattatg tacaaataga ttcttataat attatttaaa
1561 tgactgcatt tttaaataca aggctttata tttttaactt taagatgttt ttatgtgctc
1621 tccaaatttt ttttactgtt tctgattgta tggaaatata aaagtaaata tgaaacattt
1681 aaaatataat ttgttgtcaa agtaaaaaaa aaaaaaaa
```

An exemplary human interleukin 9 (IL-9) amino acid sequence is set forth below (SEQ ID NO: 53; GenBank Accession No: NP_000581, Version 1, incorporated herein by reference):

```
  1 mllamvltsa lllcsvaggg cptlagildi nflinkmqed paskchcsan vtsclclgip
 61 sdnctrpcfs erlsqmtntt mqtryplifs rvkksvevlk nnkcpyfsce qpcnqttagn
121 altflkslle ifqkekmrgm rgki
```

An exemplary human *IL-9* nucleic acid sequence is set forth below (SEQ ID NO: 54; GenBank Accession No: NM_000590, Version 1, incorporated herein by reference):

```
   1 ccgctgtcaa gatgcttctg gccatggtcc ttacctctgc cctgctcctg tgctccgtgg
  61 caggccaggg gtgtccaacc ttggcgggga tcctggacat caacttcctc atcaacaaga
 121 tgcaggaaga tccagcttcc aagtgccact gcagtgctaa tgtgaccagt tgtctctgtt
 181 tgggcattcc ctctgacaac tgcaccagac catgcttcag tgagagactg tctcagatga
 241 ccaataccac catgcaaaca agatacccac tgattttcag tcgggtgaaa aaatcagttg
 301 aagtactaaa gaacaacaag tgtccatatt tttcctgtga acagccatgc aaccaaacca
 361 cggcaggcaa cgcgctgaca tttctgaaga gtcttctgga aattttccag aaagaaaaga
 421 tgagagggat gagaggcaag atatgaagat gaaatattat ttatcctatt tattaaattt
 481 aaaaagcttt ctctttaagt tgctacaatt taaaaatcaa gtaagctact ctaaatcagt
 541 atcagttgtg attatttgtt taacattgta tgtctttatt ttgaaataaa t
```

An exemplary human interleukin 10 (IP-10) amino acid sequence is set forth below (SEQ ID NO: 55; GenBank Accession No: NP_000563, Version 1, incorporated herein by reference):

```
  1 mhssallccl vlltgvrasp gqgtqsensc thfpgnlpnm lrdlrdafsr vktffqmkdq
 61 ldnlllkesl ledfkgylgc qalsemiqfy leevmpqaen qdpdikahvn slgenlktlr
121 lrlrrchrfl pcenkskave qvknafnklq ekgiykamse fdifinyiea ymtmkirn
```

An exemplary human *IP-10* nucleic acid sequence is set forth below (SEQ ID NO: 56; GenBank Accession No: NM_000572, Version 2, incorporated herein by reference):

```
   1 acacatcagg ggcttgctct tgcaaaacca aaccacaaga cagacttgca aaagaaggca
  61 tgcacagctc agcactgctc tgttgcctgg tcctcctgac tggggtgagg gccagcccag
 121 gccagggcac ccagtctgag aacagctgca cccacttccc aggcaacctg cctaacatgc
 181 ttcgagatct ccgagatgcc ttcagcagag tgaagacttt ctttcaaatg aaggatcagc
 241 tggacaactt gttgttaaag gagtccttgc tggaggactt taagggttac ctgggttgcc
 301 aagccttgtc tgagatgatc cagttttacc tggaggaggt gatgccccaa gctgagaacc
 361 aagacccaga catcaaggcg catgtgaact ccctgggggа gaacctgaag accctcaggc
 421 tgaggctacg gcgctgtcat cgatttcttc cctgtgaaaa caagagcaag gccgtggagc
 481 aggtgaagaa tgcctttaat aagctccaag agaaaggcat ctacaaagcc atgagtgagt
 541 ttgacatctt catcaactac atagaagcct acatgacaat gaagatacga aactgagaca
 601 tcagggtggc gactctatag actctaggac ataaattaga ggtctccaaa atcggatctg
 661 gggctctggg atagctgacc cagccccttg agaaacctta ttgtacctct cttatagaat
 721 atttattacc tctgatacct caacccccat ttctatttat ttactgagct tctctgtgaa
 781 cgatttagaa agaagcccaa tattataatt tttttcaata tttattattt tcacctgttt
 841 ttaagctgtt tccatagggt gacacactat ggtatttgag tgttttaaga taaattataa
 901 gttacataag ggaggaaaaa aaatgttctt tggggagcca acagaagctt ccattccaag
 961 cctgaccacg ctttctagct gttgagctgt tttccctgac ctccctctaa tttatcttgt
1021 ctctgggctt ggggcttcct aactgctaca aatactctta ggaagagaaa ccagggagcc
1081 cctttgatga ttaattcacc ttccagtgtc tcggagggat tcccctaacc tcattcccca
```

```
1141 accacttcat tcttgaaagc tgtggccagc ttgttattta taacaaccta aatttggttc
1201 taggccgggc gcggtggctc acgcctgtaa tcccagcact ttgggaggct gaggcgggtg
1261 gatcacttga ggtcaggagt tcctaaccag cctggtcaac atggtgaaac cccgtctcta
1321 ctaaaaatac aaaaattagc cgggcatggt ggcgcgcacc tgtaatccca gctacttggg
1381 aggctgaggc aagagaattg cttgaaccca ggagatggaa gttgcagtga gctgatatca
1441 tgcccctgta ctccagcctg ggtgacagag caagactctg tctcaaaaaa taaaaataaa
1501 aataaatttg gttctaatag aactcagttt taactagaat ttattcaatt cctctgggaa
1561 tgttacattg tttgtctgtc ttcatagcag attttaattt tgaataaata aatgtatctt
1621 attcacatc
```

An exemplary human leptin amino acid sequence is set forth below (SEQ ID NO: 57; GenBank Accession No: NP_000221, Version 1, incorporated herein by reference):

```
  1 mhwgtlcgfl wlwpylfyvq avpiqkvqdd tktliktivt rindishtqs vsskqkvtgl
 61 dfipglhpil tlskmdqtla vyqqiltsmp srnviqisnd lenlrdllhv lafskschlp
121 wasgletlds lggvleasgy stevvalsrl qgslqdmlwq ldlspgc
```

An exemplary human *Leptin* nucleic acid sequence is set forth below (SEQ ID NO: 58; GenBank Accession No: NM_000230, Version 2, incorporated herein by reference):

```
   1 gtaggaatcg cagcgccagc ggttgcaagg cccaagaagc ccatcctggg aaggaaaatg
  61 cattggggaa ccctgtgcgg attcttgtgg ctttggccct atcttttcta tgtccaagct
 121 gtgcccatcc aaaaagtcca agatgacacc aaaaccctca tcaagacaat tgtcaccagg
 181 atcaatgaca tttcacacac gcagtcagtc tcctccaaac agaaagtcac cggtttggac
 241 ttcattcctg ggctccaccc catcctgacc ttatccaaga tggaccagac actggcagtc
 301 taccaacaga tcctcaccag tatgccttcc agaaacgtga tccaaatatc caacgacctg
 361 gagaacctcc gggatcttct tcacgtgctg gccttctcta agagctgcca cttgccctgg
 421 gccagtggcc tggagacctt ggacagcctg gggggtgtcc tggaagcttc aggctactcc
 481 acagaggtgg tggccctgag caggctgcag gggtctctgc aggacatgct gtggcagctg
 541 gacctcagcc ctgggtgctg aggccttgaa ggtcactctt cctgcaagga ctacgttaag
 601 ggaaggaact ctggcttcca ggtatctcca ggattgaaga gcattgcatg gacacccctt
 661 atccaggact ctgtcaattt ccctgactcc tctaagccac tcttccaaag gcataagacc
 721 ctaagcctcc ttttgcttga aaccaaagat atatacacag gatcctattc tcaccaggaa
 781 gggggtccac ccagcaaaga gtgggctgca tctgggattc ccaccaaggt cttcagccat
 841 caacaagagt tgtcttgtcc cctcttgacc catctccccc tcactgaatg cctcaatgtg
 901 accaggggtg atttcagaga gggcagaggg gtaggcagag cctttggatg accagaacaa
 961 ggttccctct gagaattcca aggagttcca tgaagaccac atccacacac gcaggaactc
1021 ccagcaacac aagctggaag cacatgttta tttattctgc attttattct ggatggattt
1081 gaagcaaagc accagcttct ccaggctctt tggggtcagc cagggccagg ggtctccctg
1141 gagtgcagtt tccaatccca tagatgggtc tggctgagct gaacccattt tgagtgactc
1201 gagggttggg ttcatctgag caagagctgg caaaggtggc tctccagtta gttctctcgt
1261 aactggtttc atttctactg tgactgatgt tacatcacag tgtttgcaat ggtgttgccc
1321 tgagtggatc tccaaggacc aggttatttt aaaaagattt gttttgtcaa gtgtcatatg
1381 taggtgtctg cacccagggg tggggaatgt ttgggcagaa gggagaagga tctagaatgt
1441 gttttctgaa taacatttgt gtggtgggtt ctttggaagg agtgagatca ttttcttatc
1501 ttctgcaatt gcttaggatg tttttcatga aaatagctct ttcaggggggg ttgtgaggcc
1561 tggccaggca ccccctggag agaagtttct ggccctggct gaccccaaag agcctggaga
1621 agctgatgct ttgcttcaaa tccatccaga ataaaacgca aagggctgaa agccatttgt
1681 tggggcagtg gtaagctctg gctttctccg actgctaggg agtggtcttt cctatcatgg
1741 agtgacggtc ccacactggt gactgcgatc ttcagagcag gggtccttgg tgtgaccctc
1801 tgaatggtcc agggttgatc acactctggg tttattacat ggcagtgttc ctatttgggg
1861 cttgcatgcc aaattgtagt tcttgtctga ttggctcacc caagcaaggc caaaattacc
1921 aaaaatcttg gggggttttt actccagtgg tgaagaaaac tcctttagca ggtggtcctg
1981 agacctgaca agcactgcta ggcgagtgcc aggactcccc aggccaggcc accaggatgg
```

```
2041 cccttcccac tggaggtcac attcaggaag atgaaagagg aggtttgggg tctgccacca
2101 tcctgctgct gtgtttttgc tatcacacag tgggtggtgg atctgtccaa ggaaacttga
2161 atcaaagcag ttaactttaa gactgagcac ctgcttcatg ctcagccctg actggtgcta
2221 taggctggag aagctcaccc aataaacatt aagattgagg cctgccctca gggatcttgc
2281 attcccagtg gtcaaaccgc actcacccat gtgccaaggt ggggtattta ccacagcagc
2341 tgaacagcca aatgcatggt gcagttgaca gcaggtggga aatggtatga gctgaggggg
2401 gccgtgccca ggggcccaca gggaaccctg cttgcacttt gtaacatgtt tacttttcag
2461 ggcatcttag cttctattat agccacatcc ctttgaaaca agataactga gaatttaaaa
2521 ataagaaaat acataagacc ataacagcca acaggtggca ggaccaggac tatagcccag
2581 gtcctctgat acccagagca ttacgtgagc caggtaatga gggactggaa ccagggagac
2641 cgagcgcttt ctggaaaaga ggagtttcga ggtagagttt gaaggaggtg agggatgtga
2701 attgcctgca gagagaagcc tgttttgttg gaaggtttgg tgtgtggaga tgcagaggta
2761 aaagtgtgag cagtgagtta cagcgagagg cagagaaaga agagacagga gggcaagggc
2821 catgctgaag ggaccttgaa gggtaaagaa gtttgatatt aaaggagtta agagtagcaa
2881 gttctagaga agaggctggt gctgtggcca gggtgagagc tgctctggaa aatgtgaccc
2941 agatcctcac aaccacctaa tcaggctgag gtgtcttaag ccttttgctc acaaaacctg
3001 gcacaatggc taattcccag agtgtgaaac ttcctaagta taaatggttg tctgtttttg
3061 taacttaaaa aaaaaaaaaa aagtttggcc gggtgcggtg gctcacgcct gtaatcccag
3121 cactttggga ggccaaggtg gggggatcac aaggtcacta gatggcgagc atcctggcca
3181 acatggtgaa accccgtctc tactaaaaac acaaaagtta gctgagcgtg gtggcgggcg
3241 cctgtagtcc cagccactcg ggaggctgag acaggagaat cgcttaaacc tgggaggcgg
3301 agagtacagt gagccaagat cgcgccactg cactccggcc tgatgacaga gcgagattcc
3361 gtcttaaaaa aaaaaaaaaa aaagtttgtt tttaaaaaaa tctaaataaa ataactttgc
3421 cccctgcaaa aaaaaaaaaa aaaa
```

An exemplary human monocyte chemotactic protein 1 (MCP-1 or MCAF) amino acid sequence is set forth below (SEQ ID NO: 59; GenBank Accession No: AAB29926, Version 1, incorporated herein by reference):

```
 1 mkvsaallcl lliaatfipq glaqpdaina pvtccynftn rkisvqrlas yrritsskcp
61 keavifktiv akeicadpkq kwvqdsmdhl dkqtqtpkt
```

An exemplary human *MCP-1* nucleic acid sequence is set forth below (SEQ ID NO: 60; GenBank Accession No: S69738, Version 1, incorporated herein by reference):

```
  1 tcaaactgaa gctcgcactc tcgcctccag catgaaagtc tctgccgccc ttctgtgcct
 61 gctgctcata gcagccacct tcattcccca agggctcgct cagccagatg caatcaatgc
121 cccagtcacc tgctgctata acttcaccaa taggaagatc tcagtgcaga ggctcgcgag
181 ctatagaaga atcaccagca gcaagtgtcc caaagaagct gtgatcttca agaccattgt
241 ggccaaggag atctgtgctg accccaagca gaagtgggtt caggattcca tggaccacct
301 ggacaagcaa acccaaactc cgaagacttg aacactcact ccacaaccca agaatctgca
361 gctaacttat tttcccctag ctttccccag acatcctgtt ttattttatt ataatgaatt
421 ttgtttgttg atgtgaaaca ttatgcctta agtaatgtta attcttattt aagttattga
481 tgttttaagt ttatctttca tggtactagt gtttttaga tacagagact tggggaaatt
541 gcttttcctc ttgaaccaca gttctacccc tgggatgttt tgagggtctt tgcaagaatc
601 atttttttaa cattccaatg catttaatac aaagaattgc taaaatatta ttgtggaaat
661 g
```

An exemplary human macrophage inflammatory protein (MIP-1a; also known as chemokine (C-C motif) ligand 3 CCL3) amino acid sequence is set forth below (SEQ ID NO: 61; GenBank Accession No: NP_002974, Version 1, incorporated herein by reference):

```
  1 mqvstaalav llctmalcnq fsaslaadtp taccfsytsr qipqnfiady fetssqcskp
 61 gvifltkrsr qvcadpseew vqkyvsdlel sa
```

An exemplary human *MIP-1a* nucleic acid sequence is set forth below (SEQ ID NO: 62; GenBank Accession No: NM_002983, Version 2, incorporated herein by reference):

```
   1 agctggtttc agacttcaga aggacacggg cagcagacag tggtcagtcc tttcttggct
  61 ctgctgacac tcgagcccac attccgtcac ctgctcagaa tcatgcaggt ctccactgct
 121 gcccttgctg tcctcctctg caccatggct ctctgcaacc agttctctgc atcacttgct
 181 gctgacacgc cgaccgcctg ctgcttcagc tacacctccc ggcagattcc acagaatttc
 241 atagctgact actttgagac gagcagccag tgctccaagc ccggtgtcat cttcctaacc
 301 aagcgaagcc ggcaggtctg tgctgacccc agtgaggagt gggtccagaa atatgtcagc
 361 gacctggagc tgagtgcctg aggggtccag aagcttcgag gcccagcgac ctcggtgggc
 421 ccagtgggga ggagcaggag cctgagcctt gggaacatgc gtgtgacctc cacagctacc
 481 tcttctatgg actggttgtt gccaaacagc cacactgtgg gactcttctt aacttaaatt
 541 ttaatttatt tatactattt agtttttgta atttattttc gatttcacag tgtgtttgtg
 601 attgtttgct ctgagagttc ccctgtcccc tccccttcc ctcacaccgc gtctggtgac
 661 aaccgagtgg ctgtcatcag cctgtgtagg cagtcatggc accaaagcca ccagactgac
 721 aaatgtgtat cggatgcttt tgttcagggc tgtgatcggc ctggggaaat aataaagatg
 781 ctcttttaaa aggtaaaaaa aaaaaaaaaa aaa
```

An exemplary human macrophage inflammatory protein (MIP-1b; also known as chemokine (C-C motif) ligand 4 CCL4) amino acid sequence is set forth below (SEQ ID NO: 63; GenBank Accession No: P13236, Version 1, incorporated herein by reference):

```
  1 mklcvtvlsl lmlvaafcsp alsapmgsdp ptaccfsyta rklprnfvvd yyetsslcsq
 61 pavvfqtkrs kqvcadpses wvqeyvydle ln
```

An exemplary human *MIP-1b* nucleic acid sequence is set forth below (SEQ ID NO: 64; GenBank Accession No: NM_002984, Version 3, incorporated herein by reference):

```
   1 agcacaggac acagctgggt tctgaagctt ctgagttctg cagcctcacc tctgagaaaa
  61 cctcttttcc accaatacca tgaagctctg cgtgactgtc ctgtctctcc tcatgctagt
 121 agctgccttc tgctctccag cgctctcagc accaatgggc tcagaccctc ccaccgcctg
 181 ctgcttttct tacaccgcga ggaagcttcc tcgcaacttt gtggtagatt actatgagac
 241 cagcagcctc tgctcccagc cagctgtggt attccaaacc aaaagaagca agcaagtctg
 301 tgctgatccc agtgaatcct gggtccagga gtacgtgtat gacctggaac tgaactgagc
 361 tgctcagaga caggaagtct tcagggaagg tcacctgagc ccggatgctt ctccatgaga
 421 cacatctcct ccatactcag gactcctctc cgcagttcct gtcccttctc ttaatttaat
 481 ctttttttatg tgccgtgtta ttgtattagg tgtcatttcc attatttata ttagtttagc
 541 caaaggataa gtgtccccta tggggatggt ccactgtcac tgtttctctg ctgttgcaaa
 601 tacatggata acacatttga ttctgtgtgt tttcataata aaactttaaa ataaaatgca
 661 gacagtt
```

An exemplary human osteopontin amino acid sequence is set forth below (SEQ ID NO: 65; GenBank Accession No: AAA86886, Version 1, incorporated herein by reference):

```
  1 mriavicfcl lgitcaipvk qadsgsseek qlynkypdav atwlnpdpsq kqnllapqna
 61 vsseetndfk qetlpsksne shdhmddmdd eddddhvdsq dsidsndsdd vddtddshqs
121 deshhsdesd elvtdfptdl patevftpvv ptvdtydgrg dsvvyglrsk skkfrrpdiq
181 ypdatdedit shmeseelng aykaipvaqd lnapsdwdsr gkdsyetsql ddqsaethsh
241 kqsrlykrka ndesnehsdv idsqelskvs refhshefhs hedmlvvdpk skeedkhlkf
301 risheldsas sevn
```

An exemplary human *osteopontin* nucleic acid sequence is set forth below (SEQ ID NO: 66; GenBank Accession No: J04765, Version 1, incorporated herein by reference):

```
   1 gaggcagcag cagcaggagg aggcagacac agcatcgtcg ggaccagact cgtctcaggc
  61 cagttgcagc cttctcagcc aaacgccgac caaggaaaac tcactaccat gagaattgca
 121 gtgatttgct tttgcctcct aggcatcacc tgtgccatac cagttaaaca ggctgattct
 181 ggaagttctg aggaaaagca gctttacaac aaatacccag atgctgtggc cacatggcta
 241 aaccctgacc catctcagaa gcagaatctc ctagccccac agacccttcc aagtaagtcc
 301 aacgaaagcc atgaccacat ggatgatatg gatgatgaag atgatgatga ccatgtggac
 361 agccaggact ccattgactc gaacgactct gatgatgtag atgacactga tgattctcac
 421 cagtctgatg agtctcacca ttctgatgaa tctgatgaac tggtcactga ttttcccacg
 481 gacctgccag caaccgaagt tttcactcca gttgtcccca cagtagacac atatgatggc
 541 cgaggtgata gtgtggttta tggactgagg tcaaaatcta agaagtttcg cagacctgac
 601 atccagtacc ctgatgctac agacgaggac atcacctcac acatggaaag cgaggagttg
 661 aatggtgcat acaaggccat ccccgttgcc caggacctga acgcgccttc tgattgggac
 721 agccgtggga aggacagtta tgaaacgagt cagctggatg accagagtgc tgaaacccac
 781 agccacaagc agtccagatt atataagcgg aaagccaatg atgagagcaa tgagcattcc
 841 gatgtgattg atagtcagga actttccaaa gtcagccgtg aattccacag ccatgaattt
 901 cacagccatg aagatatgct ggttgtagac cccaaaagta aggaagaaga taaacacctg
 961 aaatttcgta tttctcatga attagatagt gcatcttctg aggtcaatta aaaggagaaa
1021 aaatacaatt tctcactttg catttagtca aaagaaaaaa tgctttatag caaaatgaaa
1081 gagaacatga aatgcttctt tctcagttta ttggttgaat gtgtatctat ttgagtctgg
1141 aaataactaa tgtgtttgat aattagttta gtttgtggct tcatggaaac tccctgtaaa
1201 ctaaaagctt cagggttatg tctatgttca ttctatagaa gaaatgcaaa ctatcactgt
1261 attttaatat ttgttattct ctcatgaata gaaatttatg tagaagcaaa caaaatactt
1321 ttacccactt aaaaagagaa tataacattt tatgtcacta taatcttttg ttttttaagt
1381 tagtgtatat tttgttgtga ttatcttttt gtggtgtgaa taaatctttt atcttgaatg
1441 taataag
```

An exemplary human plasminogen activator inhibitor-1 (PAI-1) amino acid sequence is set forth below (SEQ ID NO: 67; GenBank Accession No: NP_000593, Version 1, incorporated herein by reference):

```
  1 mqmspaltcl vlglalvfge gsavhhppsy vahlasdfgv rvfqqvaqas kdrnvvfspy
 61 gvasvlamlq lttggetqqq iqaamgfkid dkgmapalrh lykelmgpwn kdeisttdai
121 fvqrdlklvq gfmphffrlf rstvkqvdfs everarfiin dwvkthtkgm isnllgkgav
181 dqltrlvlvn alyfngqwkt pfpdssthrr lfhksdgstv svpmmaqtnk fnytefttpd
241 ghyydilelp yhgdtlsmfi aapyekevpl saltnilsaq lishwkgnmt rlprllvlpk
301 fsletevdlr kplenlgmtd mfrqfqadft slsdqeplhv aqalqkvkie vnesgtvass
361 stavivsarm apeeiimdrp flfvvrhnpt gtvlfmgqvm ep
```

An exemplary human *PAI-1* nucleic acid sequence is set forth below (SEQ ID NO: 68; GenBank Accession No: NM_000602, Version 4, incorporated herein by reference):

```
   1 ggcccacaga ggagcacagc tgtgtttggc tgcagggcca agagcgctgt caagaagacc
  61 cacacgcccc cctccagcag ctgaattcct gcagctcagc agccgccgcc agagcaggac
 121 gaaccgccaa tcgcaaggca cctctgagaa cttcaggatg cagatgtctc cagccctcac
 181 ctgcctagtc ctgggcctgg cccttgtctt tggtgaaggg tctgctgtgc accatccccc
 241 atcctacgtg gcccacctgg cctcagactt cggggtgagg gtgtttcagc aggtggcgca
 301 ggcctccaag gaccgcaacg tggttttctc accctatggg gtggcctcgg tgttggccat
 361 gctccagctg acaacaggag gagaaaccca gcagcagatt caagcagcta tgggattcaa
 421 gattgatgac aagggcatgg cccccgccct ccggcatctg tacaaggagc tcatggggcc
 481 atggaacaag gatgagatca gcaccacaga cgcgatcttc gtccagcggg atctgaagct
 541 ggtccagggc ttcatgcccc acttcttcag gctgttccgg agcacggtca agcaagtgga
 601 cttttcagag gtggagagag ccagattcat catcaatgac tgggtgaaga cacacacaaa
 661 aggtatgatc agcaacttgc ttgggaaagg agccgtggac cagctgacac ggctggtgct
 721 ggtgaatgcc ctctacttca acggccagtg gaagactccc ttccccgact ccagcaccca
 781 ccgccgcctc ttccacaaat cagacggcag cactgtctct gtgcccatga tggctcagac
 841 caacaagttc aactatactg agttcaccac gcccgatggc cattactacg acatcctgga
 901 actgccctac cacggggaca ccctcagcat gttcattgct gccccttatg aaaaagaggt
 961 gcctctctct gccctcacca acattctgag tgcccagctc atcagccact ggaaaggcaa
1021 catgaccagg ctgccccgcc tcctggttct gcccaagttc tccctggaga ctgaagtcga
1081 cctcaggaag cccctagaga acctgggaat gaccgacatg ttcagacagt ttcaggctga
1141 cttcacgagt ctttcagacc aagagcctct ccacgtcgcg caggcgctgc agaaagtgaa
1201 gatcgaggtg aacgagagtg gcacggtggc ctcctcatcc acagctgtca tagtctcagc
1261 ccgcatggcc cccgaggaga tcatcatgga cagacccttc ctctttgtgg tccggcacaa
1321 ccccacagga acagtccttt tcatgggcca agtgatggaa ccctgaccct ggggaaagac
1381 gccttcatct gggacaaaac tggagatgca tcgggaaaga agaaactccg aagaaaagaa
1441 ttttagtgtt aatgactctt tctgaaggaa gagaagacat ttgccttttg ttaaaagatg
1501 gtaaaccaga tctgtctcca agaccttggc ctctccttgg aggaccttta ggtcaaactc
1561 cctagtctcc acctgagacc ctgggagaga agtttgaagc acaactccct taaggtctcc
1621 aaaccagacg gtgacgcctg cgggaccatc tggggcacct gcttccaccc gtctctctgc
1681 ccactcgggt ctgcagacct ggttcccact gaggcccttt gcaggatgga actacggggc
1741 ttacaggagc ttttgtgtgc ctggtagaaa ctatttctgt tccagtcaca ttgccatcac
1801 tcttgtactg cctgccaccg cggaggaggc tggtgacagg ccaaaggcca gtggaagaaa
1861 caccctttca tctcagagtc cactgtggca ctggccaccc ctccccagta caggggtgct
1921 gcaggtggca gagtgaatgt cccccatcat gtggcccaac tctcctggcc tggccatctc
1981 cctccccaga aacagtgtgc atgggttatt ttggagtgta ggtgacttgt ttactcattg
2041 aagcagattt ctgcttcctt ttatttttat aggaatagag gaagaaatgt cagatgcgtg
2101 cccagctctt caccccccaa tctcttggtg gggaggggtg tacctaaata tttatcatat
2161 ccttgccctt gagtgcttgt tagagagaaa gagaactact aaggaaaata atattattta
2221 aactcgctcc tagtgtttct ttgtggtctg tgtcaccgta tctcaggaag tccagccact
2281 tgactggcac acacccctcc ggacatccag cgtgacggag cccacactgc caccttgtgg
2341 ccgcctgaga ccctcgcgcc ccccgcgccc ctctttttcc ccttgatgga aattgaccat
2401 acaatttcat cctccttcag gggatcaaaa ggacggagtg gggggacaga gactcagatg
2461 aggacagagt ggtttccaat gtgttcaata gatttaggag cagaaatgca aggggctgca
2521 tgacctacca ggacagaact ttccccaatt acagggtgac tcacagccgc attggtgact
2581 cacttcaatg tgtcatttcc ggctgctgtg tgtgagcagt ggacacgtga gggggggtgg
2641 ggtgagagag acaggcagct cggattcaac taccttagat aatatttctg aaaacctacc
2701 agccagaggg tagggcacaa agatggatgt aatgcacttt gggaggccaa ggcgggagga
2761 ttgcttgagc ccaggagttc aagaccagcc tgggcaacat accaagaccc ccgtctcttt
2821 aaaaatatat atattttaaa tatacttaaa tatatatttc taatatcttt aaatatatat
2881 atatatttta aagaccaatt tatgggagaa ttgcacacag atgtgaaatg aatgtaatct
2941 aatagaagcc taatcagccc accatgttct ccactgaaaa atcctctttc tttggggttt
3001 ttctttcttt ctttttgat tttgcactgg acggtgacgt cagccatgta caggatccac
3061 aggggtggtg tcaaatgcta ttgaaattgt gttgaattgt atgctttttc acttttgata
3121 aataaacatg taaaaatgtt tcaaaaaaat aataaaataa ataaatacga agaatatgtc
```

```
3181 aggacagtca aaaaaaaaaa aaaaaaa
```

An exemplary human platelet-derived growth factor-AA (PDGF-AA) amino acid sequence is set forth below (SEQ ID NO: 69; GenBank Accession No: NP_148983, Version 1, incorporated herein by reference):

```
   1 mrtlaclll gcgylahvla eeaeiprevi erlarsqihs irdlqrllei dsvgsedsld
  61 tslrahgvha tkhvpekrpl pirrkrsiee avpavcktrt viyeiprsqv dptsanfliw
 121 ppcvevkrct gccntssvkc qpsrvhhrsv kvakveyvrk kpklkevqvr leehlecaca
 181 ttslnpdyre edtdvr
```

An exemplary human *PDGF-AA* nucleic acid sequence is set forth below (SEQ ID NO: 70; GenBank Accession No: NM_033023, Version 4, incorporated herein by reference):

```
   1 acgcgcgccc tgcggagccc gcccaactcc ggcgagccgg gcctgcgcct actcctcctc
  61 ctcctctccc ggcggcggct gcggcggagg cgccgactcg gccttgcgcc cgccctcagg
 121 cccgcgcggg cggcgcagcg aggccccggg cggcgggtgg tggctgccag gcggctcggc
 181 cgcgggcgct gcccggcccc ggcgagcgga gggcggagcg cggcgccgga gccgagggcg
 241 cgccgcggag ggggtgctgg gccgcgctgt gcccggccgg gcggcggctg caagaggagg
 301 ccggaggcga gcgcggggcc ggcggtgggc gcgcagggcg gctcgcagct cgcagccggg
 361 gccgggccag gcgtccaggc aggtgatcgg tgtggcggcg gcggcggcgg cggccccaga
 421 ctccctccgg agttcttctt ggggctgatg tccgcaaata tgcagaatta ccggccgggt
 481 cgctcctgaa gccagcgcgg ggagcgagcg cggcggcggc cagcaccggg aacgcaccga
 541 ggaagaagcc cagcccccgc cctccgcccc ttccgtcccc acccccctacc cggcggccca
 601 ggaggctccc cgcgctgcgg gcgcgcactc cctgtttctc ctcctcctgg ctggcgctgc
 661 ctgcctctcc gcactcactg ctcgcgccgg gcgcgctccg ccagctccgt gctccccgcg
 721 ccaccctcct ccgggccgcg ctccctaagg gatggtactg aatttcgccg ccacaggaga
 781 ccggctggag cgcccgcccc gcggcctcgc ctctcctccg agcagccagc gcctcgggac
 841 gcgatgagga ccttggcttg cctgctgctc ctcggctgcg gatacctcgc ccatgttctg
 901 gccgaggaag ccgagatccc ccgcgaggtg atcgagaggc tggcccgcag tcagatccac
 961 agcatccggg acctccagcg actcctggag atagactccg tagggagtga ggattctttg
1021 gacaccagcc tgagagctca cggggtccat gccactaagc atgtgcccga gaagcggccc
1081 ctgcccattc ggaggaagag aagcatcgag gaagctgtcc ccgctgtctg caagaccagg
1141 acggtcattt acgagattcc tcggagtcag gtcgacccca cgtccgccaa cttcctgatc
1201 tggccccccgt gcgtggaggt gaaacgctgc accggctgct gcaacacgag cagtgtcaag
1261 tgccagccct cccgcgtcca ccaccgcagc gtcaaggtgg ccaaggtgga atacgtcagg
1321 aagaagccaa aattaaaaga agtccaggtg aggttagagg agcatttgga gtgcgcctgc
1381 gcgaccacaa gcctgaatcc ggattatcgg gaagaggaca cggatgtgag gtgaggatga
1441 gccgcagccc tttcctggga catggatgta catggcgtgt tacattcctg aacctactat
1501 gtacggtgct ttattgccag tgtgcggtct ttgttctcct ccgtgaaaaa ctgtgtccga
1561 gaacactcgg gagaacaaag agacagtgca catttgttta atgtgacatc aaagcaagta
1621 ttgtagcact cggtgaagca gtaagaagct tccttgtcaa aaagagagag agagaaagag
1681 agagagaaaa caaaaccaca aatgacaaaa acaaaacgga ctcacaaaaa tatctaaact
1741 cgatgagatg gagggtcgcc ccgtgggatg gaagtgcaga ggtctcagca gactggattt
1801 ctgtccgggt ggtcacaggt gctttttttgc cgaggatgca gagcctgctt tgggaacgac
1861 tccagagggg tgctggtggg ctctgcaggg gcccgcagga agcaggaatg tcttggaaac
1921 cgccacgcga actttagaaa ccacacctcc tcgctgtagt atttaagccc atacagaaac
1981 cttcctgaga gccttaagtg gtttttttttt ttgtttttgt tttgtttttt ttttttttgt
2041 ttttttttttt ttttttttac accataaagt gattattaag ctttcctttt tactctttgg
2101 ctagcttttt ttttttttttt ttttttttaa ttatctcttg gatgacattt acaccgataa
2161 cacacaggct gctgtaactg tcaggacagt gcgacggtat ttttcctagc aagatgcaaa
```

```
2221 ctaatgagat gtattaaaat aaacatggta tacctaccta tgcatcattt cctaaatgtt
2281 tctggctttg tgtttctccc ttaccctgct ttatttgtta atttaagcca ttttgaaaga
2341 actatgcgtc aaccaatcgt acgccgtccc tgcggcacct gccccagagc ccgtttgtgg
2401 ctgagtgaca acttgttccc cgcagtgcac acctagaatg ctgtgttccc acgcggcacg
2461 tgagatgcat tgccgcttct gtctgtgttg ttggtgtgcc ctggtgccgt ggtggcggtc
2521 actccctctg ctgccagtgt ttggacagaa cccaaattct ttatttttgg taagatattg
2581 tgctttacct gtattaacag aaatgtgtgt gtgtggtttg ttttttttgta aaggtgaagt
2641 ttgtatgttt acctaatatt acctgttttg tatacctgag agcctgctat gttctttttt
2701 tgttgatcca aaattaaaaa aaaaaatacc accaacaaaa
```

An exemplary human platelet-derived growth factor-bb (PDGF-bb) amino acid sequence is set forth below (SEQ ID NO: 71; GenBank Accession No: CAA45383, Version 1, incorporated herein by reference):

```
  1 mslgsltiae pamiaecktr tevfeisrrl idrtnanflv wppcvevqrc sgccnnrnvq
 61 crptqvqlrp vqvrkieivr kkpifkkatv tledhlackc etvaaarpvt rspggsqeqr
121 aktpqtrvti rtvrvrrppk gkhrkfkhth dktalketlg a
```

An exemplary human *PDGF-AA BB* nucleic acid sequence is set forth below (SEQ ID NO: 72; GenBank Accession No: X63966, Version 1, incorporated herein by reference):

```
  1 aagcttacct gctatgtcct tgggttcgtt aaccatcgct gaaccggcta tgatcgccga
 61 atgtaagacg cgtaccgaag ttttcgaaat ctcgagacgt ttgattgacc gcaccaacgc
121 caacttcctg gtttggccgc catgtgttga agtccaacgc tgcagtggtt gctgtaacaa
181 cagaaacgtt cagtgtcgac ctactcaggt tcaactgcgt cctgtccaag ttcgtaagat
241 cgaaattgta cgtaagaaac caatcttcaa gaaagccact gtaactctag aagaccacct
301 ggcatgcaag tgtgaaactg ttgcagctgc tcgccctgtt actagatctc cgggtggttc
361 ccaggaacaa cgcgctaaaa ccccacaaac ccgggttacc atcagaactg ttcgcgtccg
421 tagacctccc aagggtaaac accgcaaatt caagcacacc cacgacaaaa ccgctttaaa
481 ggaaacctta ggtgcttagt aaggatccga attc
```

An exemplary human platelet and endothelial cell adhesion molecule 1 (PECAM1) amino acid sequence is set forth below (SEQ ID NO: 73; GenBank Accession No: NP_000433, Version 4, incorporated herein by reference):

```
  1 mqprwaqgat mwlgvlltll lcsslegqen sftinsvdmk slpdwtvqng knltlqcfad
 61 vsttshvkpq hqmlfykddv lfynissmks tesyfipevr iydsgtykct vivnnkektt
121 aeyqvlvegv psprvtldkk eaiqggivrv ncsvpeekap ihftieklel nekmvklkre
181 knsrdqnfvi lefpveeqdr vlsfrcqari isgihmqtse stkselvtvt esfstpkfhi
241 sptgmimega qlhikctiqv thlaqefpei iiqkdkaiva hnrhgnkavy svmamvehsg
301 nytckvessr iskvssivvn itelfskpel essfthldqg erlnlscsip gappanftiq
361 kedtivsqtq dftkiasksd sgtyictagi dkvvkksntv qivvcemlsq prisydaqfe
421 vikgqtievr cesisgtlpi syqllktskv lenstknsnd pavfkdnpte dveyqcvadn
481 chshakmlse vlrvkviapv devqisilss kvvesgediv lqcavnegsg pitykfyrek
541 egkpfyqmts natqafwtkq kaskeqegey yctafnranh assvprskil tvrvilapwk
601 kgliavviig viialliiaa kcyflrkaka kqmpvemsrp avpllnsnne kmsdpnmean
661 shyghnddvr nhamkpindn keplnsdvqy tevqvssaes hkdlgkkdte tvysevrkav
721 pdavesrysr tegsldgt
```

An exemplary human *PECAM1* nucleic acid sequence is set forth below (SEQ ID NO: 74; GenBank Accession No: NM_000442, Version 4, incorporated herein by reference):

```
   1 ccaggcccca ttgttcccgg tttccagcca tggctgccat tacctgacca gcgccacagc
  61 cggtctctct gcaggcgccg ggagaagtga ccagagcaat ttctgctttt cacagggcgg
 121 gtttctcaac ggtgacttgt gggcagtgcc ttctgctgag cgagtcatgg cccgaaggca
 181 gaactaactg tgcctgcagt cttcactctc aggatgcagc cgaggtgggc ccaaggggcc
 241 acgatgtggc ttggagtcct gctgaccctt ctgctctgtt caagccttga gggtcaagaa
 301 aactctttca caatcaacag tgttgacatg aagagcctgc cggactggac ggtgcaaaat
 361 gggaagaacc tgaccctgca gtgcttcgcg gatgtcagca ccacctctca cgtcaagcct
 421 cagcaccaga tgctgttcta taaggatgac gtgctgtttt acaacatctc ctccatgaag
 481 agcacagaga gttattttat tcctgaagtc cggatctatg actcagggac atataaatgt
 541 actgtgattg tgaacaacaa agagaaaacc actgcagagt accaggtgtt ggtggaagga
 601 gtgcccagtc ccagggtgac actggacaag aaagaggcca tccaaggtgg gatcgtgagg
 661 gtcaactgtt ctgtcccaga ggaaaaggcc ccaatacact tcacaattga aaaacttgaa
 721 ctaaatgaaa aaatggtcaa gctgaaaaga gagaagaatt ctcgagacca gaattttgtg
 781 atactggaat tccccgttga ggaacaggac cgcgttttat ccttccgatg tcaagctagg
 841 atcatttctg ggatccatat gcagacctca gaatctacca agagtgaact ggtcaccgtg
 901 acggaatcct tctctacacc caagttccac atcagcccca ccggaatgat catggaagga
 961 gctcagctcc acattaagtg caccattcaa gtgactcacc tggcccagga gtttccagaa
1021 atcataattc agaaggacaa ggcgattgtg gcccacaaca gacatggcaa caaggctgtg
1081 tactcagtca tggccatggt ggagcacagt ggcaactaca cgtgcaaagt ggagtccagc
1141 cgcatatcca aggtcagcag catcgtggtc aacataacag aactattttc caagcccgaa
1201 ctggaatctt ccttcacaca tctggaccaa ggtgaaagac tgaacctgtc ctgctccatc
1261 ccaggagcac ctccagccaa cttcaccatc cagaaggaag atacgattgt gtcacagact
1321 caagatttca ccaagatagc ctcaaagtcg gacagtggga cgtatatctg cactgcaggt
1381 attgacaaag tggtcaagaa aagcaacaca gtccagatag tcgtatgtga aatgctctcc
1441 cagcccagga tttcttatga tgcccagttt gaggtcataa aaggacagac catcgaagtc
1501 cgttgcgaat cgatcagtgg aactttgcct atttcttacc aacttttaaa aacaagtaaa
1561 gttttggaga atagtaccaa gaactcaaat gatcctgcgg tattcaaaga caaccccact
1621 gaagacgtcg aataccagtg tgttgcagat aattgccatt cccatgccaa aatgttaagt
1681 gaggttctga gggtgaaggt gatagccccg gtggatgagg tccagatttc tatcctgtca
1741 agtaaggtgg tggagtctgg agaggacatt gtgctgcaat gtgctgtgaa tgaaggatct
1801 ggtcccatca cctataagtt ttacagagaa aaagagggca aacccttcta tcaaatgacc
1861 tcaaatgcca cccaggcatt ttggaccaag cagaaggcta gcaaggaaca ggagggagag
1921 tattactgca cagccttcaa cagagccaac cacgcctcca gtgtccccag aagcaaaata
1981 ctgacagtca gagtcattct tgccccatgg aagaaaggac ttattgcagt ggttatcatc
2041 ggagtgatca ttgctctctt gatcattgcg gccaaatgtt attttctgag gaaagccaag
2101 gccaagcaga tgccagtgga aatgtccagg ccagcagtac cacttctgaa ctccaacaac
2161 gagaaaatgt cagatcccaa tatggaagct aacagtcatt acggtcacaa tgacgatgtc
2221 agaaaccatg caatgaaacc aataaatgat aataaagagc ctctgaactc agacgtgcag
2281 tacacggaag ttcaagtgtc ctcagctgag tctcacaaag atctaggaaa gaaggacaca
2341 gagacagtgt acagtgaagt ccggaaagct gtccctgatg ccgtggaaag cagatactct
2401 agaacggaag gctcccttga tggaacttag acagcaaggc cagatgcaca tccctggaag
2461 gacatccatg ttccgagaag aacagataat ccctgtattt caagacctct gtgcacttat
2521 ttatgaacct gccctgctcc cacagaacac agcaattcct caggctaagc tgccggttct
2581 taaatccatc ctgctaagtt aatgttgggt agaaagagat acagaggggc tgttgaattt
2641 cccacatacc ctccttccac caagttggaa catccttgga aattggaaga gcacaagagg
2701 agatccaggg caaggccatt gggatattct gaaacttgaa tattttgttt tgtgcagaga
2761 taaagacctt ttccatgcac cctcatacac agaaaccaat tttctttttt atactcaatc
2821 atttctagcg catggcctgg ttagaggctg gttttttctc ttttcctttg gtccttcaaa
2881 ggcttgtagt tttggctagt ccttgttctt tggaaataca cagtgctgac cagacagcct
2941 ccccctgtcc cctctatgac ctcgccctcc acaaatggga aaaccagact acttgggagc
3001 accgcctgtg aaataccaac ctgaagacac cgttcattca ggcaacgcac aaaacagaaa
3061 atgaaggtgg aacaagcaca gatgttcttc aactgttttt gtctacactc tttctctttt
3121 cctctaccat gctgaaggct gaaagacagg aagatggtgc catcagcaaa tattattctt
```

3181 aattgaaaac ttgaaatgtg tatgtttctt actaattttt aaaaatgtat tccttgccag
3241 ggcaggcaag gtggctcacg cctgtaatcc cagcacttca ggaggctgag gtgggcggat
3301 cacctgaggt caggagtttg agaccagcct gatgaaaccc tgtctctact aaaaatacaa
3361 gaattagccg ggcgtggtgg cgcatgcctg tagtatcagc tactcaagag gctgaggtga
3421 gattatcgct tgaacccagg aaacggaggt tgtagtgagc ggagatcgcg ccactgcact
3481 ccagcctgag tgacagagtg agaatccatc tcaaaaaaaa caaaaaacaa aattgcttgc
3541 taaagaagtg gtctcctgag gtcttaagac attcctgaca gtgtcttgag tgggtgggag
3601 agaggctgct gtcattgcgc tgtggaattt cacagatgag aaccacgcct agccaaaatc
3661 acttttcctg tttgcctcag tgacacagct gcagggaccc tcgtggatgt tgtattaaat
3721 aaatttgacc tttgctcttt gcagatctgt gaaatgttgt cttctgaggg gccacatgca
3781 tctatagtgc tgaggactcc ttgggcctct gaagtcacag agagaaccga gcaggtctat
3841 gtttttgttt tgttgttttg agacggagat tcgctcttgt tgcccgggct ggactgcagc
3901 ggcgcaacct ctgctcactg caacctccgc ctcctgggtt caagcagttc tcctgtctca
3961 gcctcccgag tagctgggat tacaggcaca tgtcaccacg cctggctaat ttttgtattt
4021 ttagtagaga tggggtttca ccacgttggc caggctgatc tcgaatgcct gacctttggt
4081 gatctgcccg ccttgtcctc atgtgtgctc cacaggcctt tgggttggga ttgcaggcgt
4141 gagccaccat gcccagccta gactcttttg acaatatgat gaaagctgtt ggttcctttc
4201 cccaacacac acacaccgag ttgtatcacg aaaatgtcat acaatttcca ggttttctga
4261 gtggtgggct cagattgagg tcaaaggatc agacgacctc taacgacctt catgtctctg
4321 ttgatgatct ggggacagcc agatcccctg tgtccaggga gttccttagt cccttgccac
4381 caccagagaa gggcaattgc cacgggagct gcaaagaccc tattcctact cctggtgcct
4441 tacttatgca gcacgactga atttttttgtt ttgttttgtt ttgttgagac aggggcttgc
4501 tctgttgccc aggctggagt gcagtggcac aacaatggct caccgcagcc tcgaacccct
4561 gggctcaagc gatcctccca tctcagcttc ctgggtagct gggaccagag gcgtgagccg
4621 ccatagctgg ctaatttta attttttttt tgcagagatg aggtttcacc atggtgccca
4681 ggctggtctc gaacttctgg gctcaagtga tcctccctcc ttggcctcgc aaagtgctgg
4741 gattgcaggc atgagccacc gcccccggcc tgtggagcac acatgagttt aaaattactt
4801 tcccttctgc ctatatttcc gaggaggaaa cttcatgcgc agggatcttt cttagtggat
4861 ttaatggcta aaaggtctgt ctgaatccag gacgctggct ttagccttcc tcggcagctg
4921 ccgtaacccc ggtgtctaaa cctgaagcat cccaggagca cccactccag gagttttctc
4981 ggccgcggaa ctcattagtt agagcgccct cttgtgttct catgtggtaa tcggtcactg
5041 aaggacttaa aatggtcctt agccaacaca cagtaaaact tttccctctt ctgaccccaa
5101 gaggtcagcc acccatttca tgagcatata ctggtcgccc catcagcgtt ctctgattgg
5161 ctaactgaac ccactccccg acctagactc aagacaggcg aagtgacgct taggtcaaca
5221 ttcactcact aaagcaacga ctgtcgggcg attttgtctc ccgctggttt tggaatggtg
5281 tctggagaca tttttggttg tcacagctgg gtgggtgtgc tcccggcatc tggtgggtag
5341 aaaccaagca tgctcctaaa catcctacag gcacagaacc gtctcccacg accaagcatg
5401 atcaagtccc aaatgccaat aatggccagg ttgagaaact ctgcacagaa gcatccagtt
5461 atttgtctgt ttgctcaaca agcttgtgct catcatgctc tgtgttcctg acgctgtgct
5521 gggtgttggc ggtgggaaga ttacaagagt cacatggcag ctgtcctcct ggaaggtaca
5581 acccagtaga gatgcagact aacagagagc caattacaaa gcagtgtgac aagcgtcatg
5641 gtggaaaatt aaaagctcaa acaagggcac atgggagggg cttccaacac agactttggg
5701 ggatccagga aggtctaaga ggaaagtggg tctcaccaaa gccttgacca taggcagagg
5761 gtaccagtgg aaaaggtggg gtgaagaaca ttgaggacaa aaggaagaag tgcaggaagg
5821 ccctgaggca agggagtggg gggtgccctg gagggatggc agcagggcag tctgtcagac
5881 ccaagtggcc tccagcccta gaagccaatt agtcctcctc aaaaagctgt cactgtcccc
5941 taagaattgc tgccaggctc ccactggcct gactcagtct ttgagagtct taaggaggag
6001 gtctctgaaa ggtacacacc aagaactctc cccagcacag ctgtttttaa gactctccac
6061 cagcgtcatt ggcgtgttgg gaagaaaccc tctgccacag aggccagctt cagcctttgc
6121 ctaacaccgc aagggcaaat ggaaaggtaa acgggaagga gatgtctccc cagcaggcta
6181 tttgaggaca gtcttccctg cagaagatct caacctgggg tccacagagt ggaaatgtta
6241 gagtagggag ctaggcaaac atgagcagga caggtgaggg cccccacagg aatgtcaggc
6301 taccatcagg tgatggtcag gtggttgtta aactgtctct gtaaaataat aattggttgc
6361 agccagctcc aagcaaggac agtctctcaa tagatacaaa acaccctgat ctggtgatca
6421 gccgcttccc gataagatct caggagctgg gcaagcagcc tggagcatgc gcaccaagag
6481 gcaaaatggc ggaatttaac cagtatatga cctaccttcc tctgggaacg cacgactggt

```
6541 aaggggaaaa atgcctcaag tgagcatgcg cgcaacttca gtaatcacac tgtgcatgcg
6601 acccccttcca agtgctggca ggtcaccaca tacgcggaca gcctgctgca agggaagaat
6661 caggggagat gagacgtaaa tcccagaact atgccaaata cataaaaccc caagttaagg
6721 gtcaggcagg gcacttagat ctctcaagtt gcctgcctga cccaagtgta gtgtacttcc
6781 ttttgttcct gctctaaaac tttttaataa actctcactc ctgctctaaa a
```

An exemplary human placental growth factor (PLGF) amino acid sequence is set forth below (SEQ ID NO: 75; GenBank Accession No: NP_002623, Version 2, incorporated herein by reference):

```
  1 mpvmrlfpcf lqllaglalp avppqqwals agngssevev vpfqevwgrs ycralerlvd
 61 vvseypseve hmfspscvsl lrctgccgde nlhcvpveta nvtmqllkir sgdrpsyvel
121 tfsqhvrcec rplrekmkpe rrrpkgrgkr rrekqrptdc hlcgdavprr
```

An exemplary human *PLGF* nucleic acid sequence is set forth below (SEQ ID NO: 76; GenBank Accession No: NM_002632, Version 5, incorporated herein by reference):

```
   1 cctcgcacgc actgcgggct ccggcgctgc gggctggccg ggcgctgcgg gctgaccggg
  61 cgctccggga actcggctcg ggaacctcgt ctgcggtggg cggggccggc ccggagcccc
 121 gccccggctc agtccctgaa acccaggcgc ggaccggctg cagtctcaga agggagctgc
 181 tgtctgcgga ggaaactgca tcgacggacg gccgcccagc tacgggagga cctggagtgg
 241 cactgggcgc ccgacggacc atccccggga cccgcctgcc cctcggcgcc ccgccccgcc
 301 gggccgctcc ccgtcgggtt ccccagccac agccttacct acgggctcct gactccgcaa
 361 ggcttccaga agatgctcga accaccggcc ggggcctcgg ggcagcagtg agggaggcgt
 421 ccagcccccc actcagctct tctcctcctg tgccaggggc tccccggggg atgagcatgg
 481 tggttttccc tcggagcccc ctggctcggg acgtctgaga agatgccggt catgaggctg
 541 ttcccttgct tcctgcagct cctggccggg ctggcgctgc ctgctgtgcc cccccagcag
 601 tgggccttgt ctgctgggaa cggctcgtca gaggtggaag tggtaccctt ccaggaagtg
 661 tggggccgca gctactgccg ggcgctggag aggctggtgg acgtcgtgtc cgagtacccc
 721 agcgaggtgg agcacatgtt cagcccatcc tgtgtctccc tgctgcgctg caccggctgc
 781 tgcggcgatg agaatctgca ctgtgtgccg gtggagacgg ccaatgtcac catgcagctc
 841 ctaaagatcc gttctgggga ccggccctcc tacgtggagc tgacgttctc tcagcacgtt
 901 cgctgcgaat gccggcctct gcgggagaag atgaagccgg aaaggaggag acccaagggc
 961 agggggaaga ggaggagaga gaagcagaga cccacagact gccacctgtg cggcgatgct
1021 gttccccgga ggtaacccac cccttggagg agagagaccc cgcacccggc tcgtgtattt
1081 attaccgtca cactcttcag tgactcctgc tggtacctgc cctctattta ttagccaact
1141 gtttccctgc tgaatgcctc gctcccttca agacgagggg cagggaagga caggaccctc
1201 aggaattcag tgccttcaac aacgtgagag aaagagagaa gccagccaca gacccctggg
1261 agcttccgct ttgaaagaag caagacacgt ggcctcgtga ggggcaagct aggccccaga
1321 ggccctggag gtctccaggg gcctgcagaa ggaaagaagg gggccctgct acctgttctt
1381 gggcctcagg ctctgcacag acaagcagcc cttgctttcg gagctcctgt ccaaagtagg
1441 gatgcggatc ctgctggggc cgccacggcc tggctggtgg gaaggccggc agcgggcgga
1501 ggggatccag ccacttcccc ctcttcttct gaagatcaga acattcagct ctggagaaca
1561 gtggttgcct gggggctttt gccactcctt gtcccccgtg atctcccctc acactttgcc
1621 atttgcttgt actgggacat tgttctttcc ggccaaggtg ccaccaccct gccccccccta
1681 agagacacat acagagtggg ccccgggctg gagaaagagc tgcctggatg agaaacagct
1741 cagccagtgg ggatgaggtc accaggggag gagcctgtgc gtcccagctg aaggcagtgg
1801 caggggagca ggttccccaa gggccctggc acccccacaa gctgtccctg cagggccatc
1861 tgactgccaa gccagattct cttgaataaa gtattctagt gtggaaacgc t
```

An exemplary human prolactin amino acid sequence is set forth below (SEQ ID NO: 77; GenBank Accession No: NP_001157030, Version 1, incorporated herein by reference):

```
  1 mnikgspwkg sllllvsnl llcqsvaplp icpggaarcq vtlrdlfdra vvlshyihnl
 61 ssemfsefdk rythgrgfit kainschtss latpedkeqa qqmnqkdfls livsilrswn
121 eplyhlvtev rgmqeapeai lskaveieeq tkrllegmel ivsqvhpetk eneiypvwsg
181 lpslqmadee srlsayynll hclrrdshki dnylkllkcr iihnnnc
```

An exemplary human *prolactin* nucleic acid sequence is set forth below (SEQ ID NO: 78; GenBank Accession No: NM_001163558, Version 2, incorporated herein by reference):

```
   1 ctgacgtttc tataaagtag gtcataagaa ccttcattcc agaagtaccc tcaaagacag
  61 agacaccaag aagaatcgga acatacaggc tttgatatca aaggtttata aagccaatat
 121 ctgggaaaga gaaaaccgtg agacttccag atcttctctg gtgaagtgtg tttcctgcaa
 181 cgatcacgaa catgaacatc aaaggatcgc catggaaagg gtccctcctg ctgctgctgg
 241 tgtcaaacct gctcctgtgc cagagcgtgg ccccttgcc catctgtccc ggcggggctg
 301 cccgatgcca ggtgaccctt cgagacctgt ttgaccgcgc cgtcgtcctg tcccactaca
 361 tccataacct ctcctcagaa atgttcagcg aattcgataa acggtatacc catggccggg
 421 ggttcattac caaggccatc aacagctgcc acacttcttc ccttgccacc cccgaagaca
 481 aggagcaagc ccaacagatg aatcaaaaag actttctgag cctgatagtc agcatattgc
 541 gatcctggaa tgagcctctg tatcatctgg tcacggaagt acgtggtatg caagaagccc
 601 cggaggctat cctatccaaa gctgtagaga ttgaggagca aaccaaacgg cttctagagg
 661 gcatggagct gatagtcagc caggttcatc ctgaaaccaa agaaaatgag atctaccctg
 721 tctggtcggg acttccatcc ctgcagatgg ctgatgaaga gtctcgcctt tctgcttatt
 781 ataacctgct ccactgccta cgcagggatt cacataaaat cgacaattat ctcaagctcc
 841 tgaagtgccg aatcatccac aacaacaact gctaagccca catccatttc atctatttct
 901 gagaaggtcc ttaatgatcc gttccattgc aagcttcttt tagttgtatc tcttttgaat
 961 ccatgcttgg gtgtaacagg tctcctctta aaaaataaaa actgactcct tagagacatc
1021 aaaatctaaa atgaaaaaaa aaa
```

An exemplary human RANTES (regulated on activation, normal T cell expressed and secreted, alternatively, chemokine (C-C motif) ligand 5; alternatively CCL5) amino acid sequence is set forth below (SEQ ID NO: 79; GenBank Accession No: NP_001265665, Version 1, incorporated herein by reference):

```
  1 mkvsaaalav iliatalcap asaspyssdt tpccfayiar plprahikey fytsgkcsnp
 61 avvhrsrmpk regqqvwqdf lydsrlnkgk lchpkeppsv cqpreemgsg vhqlfgdelg
121 wrvlepeltq iclflalvl aweasphypt ppap
```

An exemplary human *RANTES* (alternatively *CCL5*) nucleic acid sequence is set forth below (SEQ ID NO: 80; GenBank Accession No: NM_001278736, Version 1, incorporated herein by reference):

```
   1 gctgcagagg attcctgcag aggatcaaga cagcacgtgg acctcgcaca gcctctccca
  61 caggtaccat gaaggtctcc gcggcagccc tcgctgtcat cctcattgct actgccctct
 121 gcgctcctgc atctgcctcc ccatattcct cggacaccac accctgctgc tttgcctaca
 181 ttgcccgccc actgccccgt gcccacatca aggagtattt ctacaccagt ggcaagtgct
 241 ccaacccagc agtcgtccac aggtcaagga tgccaaagag agagggacag caagtctggc
```

```
 301 aggatttcct gtatgactcc cggctgaaca agggcaagct ttgtcacccg aaagaaccgc
 361 caagtgtgtg ccaacccaga gaagaaatgg gttcgggagt acatcaactc tttggagatg
 421 agctaggatg gagagtcctt gaacctgaac ttacacaaat ttgcctgttt ctgcttgctc
 481 ttgtcctagc ttgggaggct tcccctcact atcctacccc acccgctcct tgaagggccc
 541 agattctacc acacagcagc agttacaaaa accttcccca ggctggacgt ggtggctcac
 601 gcctgtaatc ccagcacttt gggaggccaa ggtgggtgga tcacttgagg tcaggagttc
 661 gagaccagcc tggccaacat gatgaaaccc catctctact aaaaatacaa aaaattagcc
 721 gggcgtggta gcgggcgcct gtagtcccag ctactcggga ggctgaggca ggagaatggc
 781 gtgaacccgg gaggcggagc ttgcagtgag ccgagatcgc gccactgcac tccagcctgg
 841 gcgacagagc gagactccgt ctcaaaaaaa aaaaaaaaaa aaaaaataca aaaattagcc
 901 gggcgtggtg gcccacgcct gtaatcccag ctactcggga ggctaaggca ggaaaattgt
 961 ttgaacccag gaggtggagg ctgcagtgag ctgagattgt gccacttcac tccagcctgg
1021 gtgacaaagt gagactccgt cacaacaaca acaacaaaaa gcttccccaa ctaaagccta
1081 gaagagcttc tgaggcgctg ctttgtcaaa aggaagtctc taggttctga gctctggctt
1141 tgccttggct ttgccagggc tctgtgacca ggaaggaagt cagcatgcct ctagaggcaa
1201 ggaggggagg aacactgcac tcttaagctt ccgccgtctc aacccctcac aggagcttac
1261 tggcaaacat gaaaaatcgg cttaccatta aagttctcaa tgcaaccata aaaaaaaaa
```

An exemplary human soluble CD40 ligand (sCD40L) amino acid sequence is set forth below (SEQ ID NO: 81; GenBank Accession No: NP_000065, Version 1, incorporated herein by reference):

```
   1 mietynqtsp rsaatglpis mkifmylltv flitqmigsa lfavylhrrl dkiedernlh
  61 edfvfmktiq rcntgersls llnceeiksq fegfvkdiml nkeetkkens femqkgdqnp
 121 qiaahvisea sskttsvlqw aekgyytmsn nlvtlengkq ltvkrqglyy iyaqvtfcsn
 181 reassqapfi aslclkspgr ferillraan thssakpcgq qsihlggvfe lqpgasvfvn
 241 vtdpsqvshg tgftsfgllk l
```

An exemplary human *sCD40L* nucleic acid sequence is set forth below (SEQ ID NO: 82; GenBank Accession No: NM_000074, Version 2, incorporated herein by reference):

```
   1 actttgacag tcttctcatg ctgcctctgc caccttctct gccagaagat accatttcaa
  61 ctttaacaca gcatgatcga aacatacaac caaacttctc cccgatctgc ggccactgga
 121 ctgcccatca gcatgaaaat ttttatgtat ttacttactg tttttcttat cacccagatg
 181 attgggtcag cacttttgc tgtgtatctt catagaaggt tggacaagat agaagatgaa
 241 aggaatcttc atgaagattt tgtattcatg aaaacgatac agagatgcaa cacaggagaa
 301 agatccttat ccttactgaa ctgtgaggag attaaaagcc agtttgaagg ctttgtgaag
 361 gatataatgt taaacaaaga ggagacgaag aaagaaaaca gctttgaaat gcaaaaaggt
 421 gatcagaatc ctcaaattgc ggcacatgtc ataagtgagg ccagcagtaa aacaacatct
 481 gtgttacagt gggctgaaaa aggatactac accatgagca acaacttggt aaccctggaa
 541 aatgggaaac agctgaccgt taaaagacaa ggactctatt atatctatgc ccaagtcacc
 601 ttctgttcca atcgggaagc ttcgagtcaa gctccattta tagccagcct ctgcctaaag
 661 tcccccggta gattcgagag aatcttactc agagctgcaa atacccacag ttccgccaaa
 721 ccttgcgggc aacaatccat tcacttggga ggagtatttg aattgcaacc aggtgcttcg
 781 gtgtttgtca atgtgactga tccaagccaa gtgagccatg gcactggctt cacgtccttt
 841 ggcttactca aactctgaac agtgtcacct tgcaggctgt ggtggagctg acgctgggag
 901 tcttcataat acagcacagc ggttaagccc acccccctgtt aactgcctat ttataaccct
 961 aggatcctcc ttatggagaa ctatttatta tacactccaa ggcatgtaga actgtaataa
1021 gtgaattaca ggtcacatga aaccaaaacg ggccctgctc cataagagct tatatatctg
1081 aagcagcaac cccactgatg cagacatcca gagagtccta tgaaaagaca aggccattat
1141 gcacaggttg aattctgagt aaacagcaga taacttgcca agttcagttt tgtttctttg
1201 cgtgcagtgt ctttccatgg ataatgcatt tgatttatca gtgaagatgc agaagggaaa
1261 tggggagcct cagctcacat tcagttatgg ttgactctgg gttcctatgg ccttgttgga
```

```
1321 gggggccagg ctctagaacg tctaacacag tggagaaccg aaacccccc ccccccccg
1381 ccacctctc ggacagttat tcattctctt tcaatctctc tctctccatc tctctctttc
1441 agtctctctc tctcaacctc tttcttccaa tctctctttc tcaatctctc tgtttccctt
1501 tgtcagtctc ttccctcccc cagtctctct tctcaatccc cctttctaac acacacacac
1561 acacacacac acacacacac acacacacac acacacacac agagtcaggc cgttgctagt
1621 cagttctctt ctttccaccc tgtccctatc tctaccacta tagatgaggg tgaggagtag
1681 ggagtgcagc cctgagcctg cccactcctc attacgaaat gactgtattt aaaggaaatc
1741 tattgtatct acctgcagtc tccattgttt ccagagtgaa cttgtaatta tcttgttatt
1801 tatttttga ataataaaga cctcttaaca ttaa
```

An exemplary human stem cell factor (SCF) amino acid sequence is set forth below (SEQ ID NO: 83; GenBank Accession No: P21583, Version 1, incorporated herein by reference):

```
  1 mkktqtwilt ciylqlllfn plvktegicr nrvtnnvkdv tklvanlpkd ymitlkyvpg
 61 mdvlpshcwi semvvqlsds ltdlldkfsn iseglsnysi idklvnivdd lvecvkenss
121 kdlkksfksp eprlftpeef frifnrsida fkdfvvaset sdcvvsstls pekdsrvsvt
181 kpfmlppvaa sslrndssss nrkaknppgd sslhwaamal palfsliigf afgalywkkr
241 qpsltraven iqineednei smlqekeref qev
```

An exemplary human *SCF* nucleic acid sequence is set forth below (SEQ ID NO: 84; GenBank Accession No: M59964, Version 1, incorporated herein by reference):

```
  1 ccgcctcgcg ccgagactag aagcgctgcg ggaagcaggg acagtggaga gggcgctgcg
 61 ctcgggctac ccaatgcgtg gactatctgc cgccgctgtt cgtgcaatat gctggagctc
121 cagaacagct aaacggagtc gccacaccac tgtttgtgct ggatcgcagc gctgcctttc
181 cttatgaaga agacacaaac ttggattctc acttgcattt atcttcagct gctcctattt
241 aatcctctcg tcaaaactga agggatctgc aggaatcgtg tgactaataa tgtaaaagac
301 gtcactaaat tggtggcaaa tcttccaaaa gactacatga taaccctcaa atatgtcccc
361 gggatggatg ttttgccaag tcattgttgg ataagcgaga tggtagtaca attgtcagac
421 agcttgactg atcttctgga caagttttca aatatttctg aaggcttgag taattattcc
481 atcatagaca aacttgtgaa tatagtcgat gaccttgtgg agtgcgtcaa agaaaactca
541 tctaaggatc taaaaaaatc attcaagagc ccagaaccca ggctctttac tcctgaagaa
601 ttctttagaa tttttaatag atccattgat gccttcaagg actttgtagt ggcatctgaa
661 actagtgatt gtgtggtttc ttcaacatta agtcctgaga aagattccag agtcagtgtc
721 acaaaaccat ttatgttacc ccctgttgca gccagctccc ttaggaatga cagcagtagc
781 agtaatagga aggccaaaaa tccccctgga gactccagcc tacactgggc agccatggca
841 ttgccagcat tgttttctct tataattggc tttgcttttg gagccttata ctggaagaag
901 agacagccaa gtcttacaag ggcagttgaa aatatacaaa ttaatgaaga ggataatgag
961 ataagtatgt tgcaagagaa agagagagag tttcaagaag tgtaaattgt ggcttgtatc
1021 aacactgtta ctttcgtaca ttggctggta acagttcatg tttgcttcat aaatgaagca
1081 gctttaaaca aattcatatt ctgtctggag tgacagacca catctttatc tgttcttgct
1141 acccatgact ttatatggat gattcagaaa ttggaacaga atgttttact gtgaaactgg
1201 cactgaatta atcatctata aagaagaact tgcatggagc aggactctat tttaaggact
1261 gcgggacttg ggtctcattt agaacttgca gctgatgttg gaagagaaag cacgtgtctc
1321 agactgcatg taccatttgc atggctccag aaatgtctaa atgctgaaaa aacacctagc
1381 tttattcttc agatacaaac tgcag
```

An exemplary human epidermal growth factor receptor serum (sEGFR) amino acid sequence is set forth below (SEQ ID NO: 85; GenBank Accession No: NP_001171602, Version 1, incorporated herein by reference):

```
   1 mlltliillp vvskfsfvsl sapqhwscpe gtlagngnst cvgpapflif shgnsifrid
  61 tegtnyeqlv vdagvsvimd fhynekriyw vdlerqllqr vflngsrqer vcnieknvsg
 121 mainwineev iwsnqqegii tvtdmkgnns hillsalkyp anvavdpver fifwssevag
 181 slyradldgv gvkalletse kitavsldvl dkrlfwiqyn regsnslics cdydggsvhi
 241 skhptqhnlf amslfgdrif ystwkmktiw iankhtgkdm vrinlhssfv plgelkvvhp
 301 laqpkaeddt wepdvnecaf wnhgctlgck ntpgsyyctc pvgfvllpdg krchqlvscp
 361 rnvsecshdc vltsegplcf cpegsvlerd gktcsgcssp dnggcsqlcv plspvswecd
 421 cfpgydlqld ekscaasgpq pfllfansqd irhmhfdgtd ygtllsqqmg mvyaldhdpv
 481 enkiyfahta lkwieranmd gsqrerliee gvdvpeglav dwigrrfywt drgksligrs
 541 dlngkrskii tkenisqprg iavhpmakrl fwtdtginpr iessslqglg rlviassdli
 601 wpsgitidfl tdklywcdak qsviemanld gskrrrltqn dvghpfavav fedyvwfsdw
 661 ampsvmrvnk rtgkdrvrlq gsmlkpsslv vvhplakpga dpclyqnggc ehickkrlgt
 721 awcscregfm kasdgktcla ldghqllagg evdlknqvtp ldilsktrvs ednitesqhm
 781 lvaeimvsdq ddcapvgcsm yarciseged atcqclkgfa gdgklcsdid ecemgvpvcp
 841 passkcinte ggyvcrcseg yqgdgihcld idecqlgehs cgenasctnt eggytcmcag
 901 rlsepglicp dstppphlre ddhhysvrns dsecplshdg yclhdgvcmy iealdkyacn
 961 cvvgyigerc qyrdlkwwel rhaghgqqqk vivvavcvvv lvmllllslw gahyyrtqkl
1021 lsknpknpye essrdvrsrr padtedgmss cpqpwfvvik ehqdlknggq pvagedgqaa
1081 dgsmqptswr qepqlcgmgt eqgcwipvss dkgscpqvme rsfhmpsygt qtleggvekp
1141 hsllsanplw qqraldpphq meltq
```

An exemplary human *sEGFR* nucleic acid sequence is set forth below (SEQ ID NO: 86; GenBank Accession No: NM_001178131, Version 2, incorporated herein by reference):

```
   1 aaaaagagaa actgttggga gaggaatcgt atctccatat ttcttctttc agccccaatc
  61 caagggttgt agctggaact ttccatcagt tcttcctttc tttttcctct ctaagccttt
 121 gccttgctct gtcacagtga agtcagccag agcagggctg ttaaactctg tgaaatttgt
 181 cataagggtg tcaggtattt cttactggct tccaaagaaa catagataaa gaaatctttc
 241 ctgtggcttc ccttggcagg ctgcattcag aaggtctctc agttgaagaa agagcttgga
 301 ggacaacagc acaacaggag agtaaaagat gccccagggc tgaggcctcc gctcaggcag
 361 ccgcatctgg ggtcaatcat actcaccttg cccgggccat gctccagcaa aatcaagctg
 421 ttttcttttg aaagttcaaa ctcatcaaga ttatgctgct cactcttatc attctgttgc
 481 cagtagtttc aaaatttagt tttgttagtc tctcagcacc gcagcactgg agctgtcctg
 541 aaggtactct cgcaggaaat gggaattcta cttgtgtggg tcctgcaccc ttcttaattt
 601 tctcccatgg aaatagtatc tttaggattg acacagaagg aaccaattat gagcaattgg
 661 tggtggatgc tggtgtctca gtgatcatgg attttcatta taatgagaaa agaatctatt
 721 gggtggattt agaaagacaa cttttgcaaa gagtttttct gaatgggtca aggcaagaga
 781 gagtatgtaa tatagagaaa aatgtttctg gaatggcaat aaattggata aatgaagaag
 841 ttatttggtc aaatcaacag gaaggaatca ttacagtaac agatatgaaa ggaaataatt
 901 cccacattct tttaagtgct ttaaaatatc ctgcaaatgt agcagttgat ccagtagaaa
 961 ggtttatatt ttggtcttca gaggtggctg gaagccttta tagagcagat ctcgatggtg
1021 tgggagtgaa ggctctgttg gagacatcag agaaaataac agctgtgtca ttggatgtgc
1081 ttgataagcg gctgttttgg attcagtaca acagagaagg aagcaattct cttatttgct
1141 cctgtgatta tgatggaggt tctgtccaca ttagtaaaca tccaacacag cataatttgt
1201 ttgcaatgtc ccttttggt gaccgtatct tctattcaac atggaaaatg aagacaattt
1261 ggatagccaa caaacacact ggaaaggaca tggttagaat taacctccat tcatcatttg
1321 taccacttgg tgaactgaaa gtagtgcatc cacttgcaca acccaaggca gaagatgaca
1381 cttgggagcc tgatgttaat gaatgtgctt tttggaatca tggctgtact cttgggtgta
1441 aaaacacccc tggatcctat tactgcacgt gccctgtagg atttgttctg cttcctgatg
```

1501 ggaaacgatg tcatcaactt gtttcctgtc cacgcaatgt gtctgaatgc agccatgact
1561 gtgttctgac atcagaaggt cccttatgtt tctgtcctga aggctcagtg cttgagagag
1621 atgggaaaac atgtagcggt tgttcctcac ccgataatgg tggatgtagc cagctctgcg
1681 ttcctcttag cccagtatcc tgggaatgtg attgctttcc tgggtatgac ctacaactgg
1741 atgaaaaaag ctgtgcagct tcaggaccac aaccattttt gctgtttgcc aattctcaag
1801 atattcgaca catgcatttt gatggaacag actatggaac tctgctcagc cagcagatgg
1861 gaatggttta tgccctagat catgaccctg tggaaaataa gatatacttt gcccatacag
1921 ccctgaagtg gatagagaga gctaatatgg atggttccca gcgagaaagg cttattgagg
1981 aaggagtaga tgtgccagaa ggtcttgctg tggactggat tggccgtaga ttctattgga
2041 cagacagagg gaaatctctg attggaagga gtgatttaaa tgggaaacgt tccaaaataa
2101 tcactaagga gaacatctct caaccacgag gaattgctgt tcatccaatg gccaagagat
2161 tattctggac tgatacaggg attaatccac gaattgaaag ttcttccctc caaggccttg
2221 gccgtctggt tatagccagc tctgatctaa tctggcccag tggaataacg attgacttct
2281 taactgacaa gttgtactgg tgcgatgcca agcagtctgt gattgaaatg gccaatctgg
2341 atggttcaaa acgccgaaga cttacccaga atgatgtagg tcacccattt gctgtagcag
2401 tgtttgagga ttatgtgtgg ttctcagatt gggctatgcc atcagtaatg agagtaaaca
2461 agaggactgg caaagataga gtacgtctcc aaggcagcat gctgaagccc tcatcactgg
2521 ttgtggttca tccattggca aaaccaggag cagatccctg cttatatcaa aacggaggct
2581 gtgaacatat ttgcaaaaag aggcttggaa ctgcttggtg ttcgtgtcgt gaaggtttta
2641 tgaaagcctc agatgggaaa acgtgtctgg ctctggatgg tcatcagctg ttggcaggtg
2701 gtgaagttga tctaaagaac caagtaacac cattggacat cttgtccaag actagagtgt
2761 cagaagataa cattacagaa tctcaacaca tgctagtggc tgaaatcatg gtgtcagatc
2821 aagatgactg tgctcctgtg ggatgcagca tgtatgctcg gtgtatttca gagggagagg
2881 atgccacatg tcagtgtttg aaaggatttg ctggggatgg aaaactatgt tctgatatag
2941 atgaatgtga gatgggtgtc ccagtgtgcc cccctgcctc ctccaagtgc atcaacaccg
3001 aaggtggtta tgtctgccgg tgctcagaag gctaccaagg agatgggatt cactgtcttg
3061 atattgatga gtgccaactg ggggagcaca gctgtggaga gaatgccagc tgcacaaata
3121 cagagggagg ctatacctgc atgtgtgctg gacgcctgtc tgaaccagga ctgatttgcc
3181 ctgactctac tccacccccc cacctcaggg aagatgacca ccactattcc gtaagaaata
3241 gtgactctga atgtcccctg tcccacgatg ggtactgcct ccatgatggt gtgtgcatgt
3301 atattgaagc attggacaag tatgcatgca actgtgttgt tggctacatc ggggagcgat
3361 gtcagtaccg agacctgaag tggtgggaac tgcgccacgc tggccacggg cagcagcaga
3421 aggtcatcgt ggtggctgtc tgcgtggtgg tgcttgtcat gctgctcctc ctgagcctgt
3481 ggggggccca ctactacagg actcagaagc tgctatcgaa aaacccaaag aatccttatg
3541 aggagtcgag cagagatgtg aggagtcgca ggcctgctga cactgaggat gggatgtcct
3601 cttgccctca accttggttt gtggttataa aagaacacca agacctcaag aatgggggtc
3661 aaccagtggc tggtgaggat ggccaggcag cagatgggtc aatgcaacca acttcatgga
3721 ggcaggagcc ccagttatgt ggaatgggca cagagcaagg ctgctggatt ccagtatcca
3781 gtgataaggg ctcctgtccc caggtaatgg agcgaagctt tcatatgccc tcctatggga
3841 cacagaccct tgaaggggt gtcgagaagc cccattctct cctatcagct aacccattat
3901 ggcaacaaag ggccctggac ccaccacacc aaatggagct gactcagtga aaactggaat
3961 taaaaggaaa gtcaagaaga atgaactatg tcgatgcaca gtatcttttc tttcaaaagt
4021 agagcaaaac tataggtttt ggttccacaa tctctacgac taatcaccta ctcaatgcct
4081 ggagacagat acgtagttgt gcttttgttt gctcttttaa gcagtctcac tgcagtctta
4141 tttccaagta agagtactgg gagaatcact aggtaactta ttagaaaccc aaattgggac
4201 aacagtgctt tgtaaattgt gttgtcttca gcagtcaata caaatagatt tttgtttttg
4261 ttgttcctgc agccccagaa gaaattaggg gttaaagcag acagtcacac tggtttggtc
4321 agttacaaag taatttcttt gatctggaca gaacatttat atcagtttca tgaaatgatt
4381 ggaatattac aataccgtta agatacagtg taggcattta actcctcatt ggcgtggtcc
4441 atgctgatga ttttgcaaaa tgagttgtga tgaatcaatg aaaaatgtaa tttagaaact
4501 gatttcttca gaattagatg gcttattttt taaaatattt gaatgaaaac attttatttt
4561 taaaatatta cacaggaggc ttcggagttt cttagtcatt actgtccttt tcccctacag
4621 aattttccct cttggtgtga ttgcacagaa tttgtatgta ttttcagtta caagattgta
4681 agtaaattgc ctgatttgtt ttcattatag acaacgatga atttcttcta attatttaaa
4741 taaaatcacc aaaaacataa acattttatt gtatgcctga ttaagtagtt aattatagtc
4801 taaggcagta ctagagttga accaaaatga tttgtcaagc ttgctgatgt ttctgttttt

```
4861 cgtttttttt ttttttccgg agagaggata ggatctcact ctgttatcca ggctggagtg
4921 tgcaatggca caatcatagc tcagtgcagc ctcaaactcc tgggctcaag caatcctcct
4981 gcctcagcct cccgagtaac taggaccaca ggcacaggcc accatgcctg gctaaggttt
5041 ttatttttat tttttgtaga catggggatc acacaatgtt gcccaggctg gtcttgaact
5101 cctggcctca agcaaggtcg tgctggtaat tttgcaaaat gaattgtgat tgactttcag
5161 cctcccaacg tattagatta taggcattag ccatggtgcc cagccttgta acttttaaaa
5221 aaatttttta atctacaact ctgtagatta aaatttcaca tggtgttcta attaaatatt
5281 tttcttgcag ccaagatatt gttactacag ataacacaac ctgatatggt aactttaaat
5341 tttgggggct ttgaatcatt cagtttatgc attaactagt ccctttgttt atctttcatt
5401 tctcaacccc ttgtactttg gtgataccag acatcagaat aaaaagaaat tgaagtacct
5461 gttttcaaat ggatacttta taggaatttt ggtaaagatt tggtgatggg aggatgactt
5521 gaggtttgtg gatattagtt aattattcag tatgatacct cacccagcta attt
```

An exemplary human Fas soluble ligand (alternatively CD95L or s FASL) amino acid sequence is set forth below (SEQ ID NO: 87; GenBank Accession No: P48023, Version 1, incorporated herein by reference):

```
  1 mqqpfnypyp qiywvdssas spwappgtvl pcptsvprrp gqrrpppppp ppplpppppp
 61 pplpplplpp lkkrgnhstg lcllvmffmv lvalvglglg mfqlfhlqke laelrestsq
121 mhtasslekq ighpspppek kelrkvahlt gksnsrsmpl ewedtygivl lsgvkykkgg
181 lvinetglyf vyskvyfrgq scnnlplshk vymrnskypq dlvmmegkmm sycttgqmwa
241 rssylgavfn ltsadhlyvn vselslvnfe esqtffglyk l
```

An exemplary human *sFASL* nucleic acid sequence is set forth below (SEQ ID NO: 88; GenBank Accession No: BC017502, Version 1, incorporated herein by reference):

```
  1 cagggtcccg tccttgacac ctcagcctct acaggactga gaagaagtaa aaccgtttgc
 61 tggggctggc ctgactcacc agctgccatg cagcagccct tcaattaccc atatccccag
121 atctactggg tggacagcag tgccagctct ccctgggccc ctccaggcac agttcttccc
181 tgtccaacct ctgtgcccag aaggcctggt caaaggaggc caccaccacc accgccaccg
241 ccaccactac cacctccgcc gccgccgcca ccactgcctc cactaccgct gccacccctg
301 aagaagagag ggaaccacag cacaggcctg tgtctccttg tgatgttttt catggttctg
361 gttgccttgg taggattggg cctggggatg tttcagctct tccacctaca gaaggagctg
421 gcagaactcc gagagtctac cagccagatg cacacagcat catctttgga gaagcaaata
481 ggccacccca gtccaccccc tgaaaaaaag gagctgagga aagtggccca tttaacaggc
541 aagtccaact caaggtccat gcctctggaa tgggaagaca cctatggaat tgtcctgctt
601 tctggagtga agtataagaa gggtggcctt gtgatcaatg aaactgggct gtactttgta
661 tattccaaag tatacttccg gggtcaatct tgcaacaacc tgcccctgag ccacaaggtc
721 tacatgagga actctaagta tccccaggat ctggtgatga tggaggggaa gatgatgagc
781 tactgcacta ctgggcagat gtgggcccgc agcagctacc tgggggcagt gttcaatctt
841 accagtgctg atcatttata tgtcaacgta tctgagctct ctctggtcaa ttttgaggaa
901 tctcagacgt ttttcggctt atataagctc taagagaagc actttgggat tctttccatt
961 atgattcttt gttacaggca ccgagaatgt tgtattcagt gagggtcttc ttacatgcat
1021 ttgaggtcaa gtaagaagac atgaaccaag tggaccttga gaccacaggg ttcaaaatgt
1081 ctgtagctcc tcaactcacc taatgtttat gagccagaca aatggaggaa tatgacggaa
1141 gaacatagaa ctctgggctg ccatgtgaag agggagaagc atgaaaaagc agctaccagg
1201 tgttctacac tcatcttagt gcctgagagt atttaggcag attgaaaagg acacctttta
1261 actcacctct caaggtgggc cttgctacct caagggggac tgtctttcag atacatggtt
1321 gtgacctgag gatttaaggg atggaaaagg aagactagag gcttgcataa taagctaaag
1381 aggctgaaag aggccaatgc cccactggca gcatcttcac ttctaaatgc atatcctgag
1441 ccatcggtga aactaacaga taagcaagag agatgttttg gggactcatt tcattcctaa
1501 cacagcatgt gtatttccag tgcaattgta ggggtgtgtg tgtgtgtgtg tgtgtgtgtg
1561 tgtgtatgac taaagagaga atgtagatat tgtgaagtac atattaggaa aatatgggtt
```

```
1621 gcatttggtc aagattttga atgcttcctg acaatcaact ctaatagtgc ttaaaaatca
1681 ttgattgtca gctactaatg atgttttcct ataatataat aaatatttat gtagatgtgc
1741 atttttgtga aatgaaaaca tgtaataaaa agtatatgtt aggatacaaa aaaaaaaaaa
1801 aaaaa
```

An exemplary human Receptor tyrosine-protein kinase erbB-2, (also known as CD340 (cluster of differentiation 340), proto-oncogene Neu, Erbb2 (rodent), or ERBB2 (human), or HER2/neu) amino acid sequence is set forth below (SEQ ID NO: 89; GenBank Accession No: NP_001276867, Version 1, incorporated herein by reference):

```
   1 mklrlpaspe thldmlrhly qgcqvvqgnl eltylptnas lsflqdiqev qgyvliahnq
  61 vrqvplqrlr ivrgtqlfed nyalavldng dplnnttpvt gaspgglrel qlrslteilk
 121 ggvliqrnpq lcyqdtilwk difhknnqla ltlidtnrsr achpcspmck gsrcwgesse
 181 dcqsltrtvc aggcarckgp lptdccheqc aagctgpkhs dclaclhfnh sgicelhcpa
 241 lvtyntdtfe smpnpegryt fgascvtacp ynylstdvgs ctlvcplhnq evtaedgtqr
 301 cekcskpcar vcyglgmehl revravtsan iqefagckki fgslaflpes fdgdpasnta
 361 plqpeqlqvf etleeitgyl yisawpdslp dlsvfqnlqv irgrilhnga ysltlqglgi
 421 swlglrslre lgsglalihh nthlcfvhtv pwdqlfrnph qallhtanrp edecvgegla
 481 chqlcarghc wgpgptqcvn csqflrgqec veecrvlqgl preyvnarhc lpchpecqpq
 541 ngsvtcfgpe adqcvacahy kdppfcvarc psgvkpdlsy mpiwkfpdee gacqpcpinc
 601 ths
```

An exemplary human *sHER2 neu* nucleic acid sequence is set forth below (SEQ ID NO: 90; GenBank Accession No: NM_001289938, Version 1, incorporated herein by reference):

```
   1 aagttcctgt gttctttatt ctactctccg ctgaagtcca cacagtttaa attaaagttc
  61 ccggattttt gtgggcgcct gccccgcccc tcgtcccccc gctgtgtcca tatatcgagg
 121 cgatagggtt aagggaaggc ggacgcctga tgggttaatg agcaaactga agtgttttcc
 181 atgatctttt ttgagtcgca attgaagtac cacctcccga gggtgattgc ttccccatgc
 241 ggggtagaac ctttgctgtc ctgttcacca ctctacctcc agcacagaat ttggcttatg
 301 cctactcaat gtgaagatga tgaggatgaa aacctttgtg atgatccact tccacttaat
 361 gaatggtggc aaagcaaagc tatattcaag accacatgca aagctactcc ctgagcaaag
 421 agtcacagat aaaacggggg caccagtaga atggccagga caaacgcagt gcagcacaga
 481 gactcagacc ctggcagcca tgcctgcgca ggcagtgatg agagtgacat gtactgttgt
 541 ggacatgcac aaaagtgagt gtgcaccggc acagacatga agctgcggct ccctgccagt
 601 cccgagaccc acctggacat gctccgccac ctctaccagg gctgccaggt ggtgcaggga
 661 aacctggaac tcacctacct gcccaccaat gccagcctgt ccttcctgca ggatatccag
 721 gaggtgcagg gctacgtgct catcgctcac aaccaagtga ggcaggtccc actgcagagg
 781 ctgcggattg tgcgaggcac ccagctcttt gaggacaact atgccctggc cgtgctagac
 841 aatggagacc cgctgaacaa taccacccct gtcacagggg cctccccagg aggcctgcgg
 901 gagctgcagc ttcgaagcct cacagagatc ttgaaaggag gggtcttgat ccagcggaac
 961 ccccagctct gctaccagga cacgattttg tggaaggaca tcttccacaa gaacaaccag
1021 ctggctctca cactgataga caccaaccgc tctcgggcct gccacccctg ttctccgatg
1081 tgtaagggct cccgctgctg gggagagagt tctgaggatt gtcagagcct gacgcgcact
1141 gtctgtgccg gtggctgtgc ccgctgcaag gggccactgc ccactgactg ctgccatgag
1201 cagtgtgctg ccggctgcac gggccccaag cactctgact gcctggcctg cctccacttc
1261 aaccacagtg gcatctgtga gctgcactgc ccagccctgg tcacctacaa cacagacacg
1321 tttgagtcca tgcccaatcc cgagggccgg tatacattcg gcgccagctg tgtgactgcc
1381 tgtccctaca actacctttc tacggacgtg ggatcctgca ccctcgtctg ccccctgcac
1441 aaccaagagg tgacagcaga ggatggaaca cagcggtgtg agaagtgcag caagccctgt
1501 gcccgagtgt gctatggtct gggcatggag cacttgcgag aggtgagggc agttaccagt
```

```
1561 gccaatatcc aggagtttgc tggctgcaag aagatctttg ggagcctggc atttctgccg
1621 gagagctttg atggggaccc agcctccaac actgccccgc tccagccaga gcagctccaa
1681 gtgtttgaga ctctggaaga gatcacaggt tacctataca tctcagcatg gccggacagc
1741 ctgcctgacc tcagcgtctt ccagaacctg caagtaatcc ggggacgaat tctgcacaat
1801 ggcgcctact cgctgaccct gcaagggctg ggcatcagct ggctggggct gcgctcactg
1861 agggaactgg gcagtggact ggccctcatc caccataaca cccacctctg cttcgtgcac
1921 acggtgccct gggaccagct ctttcggaac ccgcaccaag ctctgctcca cactgccaac
1981 cggccagagg acgagtgtgt gggcgagggc ctggcctgcc accagctgtg cgcccgaggg
2041 cactgctggg gtccagggcc cacccagtgt gtcaactgca gccagttcct tcggggccag
2101 gagtgcgtgg aggaatgccg agtactgcag gggctcccca gggagtatgt gaatgccagg
2161 cactgtttgc cgtgccaccc tgagtgtcag ccccagaatg gctcagtgac ctgttttgga
2221 ccggaggctg accagtgtgt ggcctgtgcc cactataagg accctccctt ctgcgtggcc
2281 cgctgcccca gcggtgtgaa acctgacctc tcctacatgc ccatctggaa gtttccagat
2341 gaggagggcg catgccagcc ttgccccatc aactgcaccc actcgtgagt ccaacggtct
2401 tttctgcaga aaggaggact ttcctttcag gggtctttct ggggctctta ctataaaagg
2461 ggaccaactc tccctttgtc atatcttgtt tctgatgaca aaaataacac attgttaaaa
2521 ttgtaaaatt aaaacatgaa atataaatta atgccctagc aaaaaaaaaa aaaaaaaaaa
2581 aaaaaaaaaa
```

An exemplary human interleukin 6 receptor, alpha (IL-6Ra) amino acid sequence is set forth below (SEQ ID NO: 91; GenBank Accession No: NP_000556, Version 1, incorporated herein by reference):

```
  1 mlavgcalla allaapgaal aprrcpaqev argvltslpg dsvtltcpgv epednatvhw
 61 vlrkpaagsh psrwagmgrr lllrsvqlhd sgnyscyrag rpagtvhllv dvppeepqls
121 cfrksplsnv vcewgprstp slttkavllv rkfqnspaed fqepcqysqe sqkfscqlav
181 pegdssfyiv smcvassvgs kfsktqtfqg cgilqpdppa nitvtavarn prwlsvtwqd
241 phswnssfyr lrfelryrae rsktfttwmv kdlqhhcvih dawsglrhvv qlraqeefgq
301 gewsewspea mgtpwtesrs ppaenevstp mqalttnkdd dnilfrdsan atslpvqdss
361 svplptflva ggslafgtll ciaivlrfkk twklralkeg ktsmhppysl gqlvperprp
421 tpvlvplisp pvspsslgsd ntsshnrpda rdprspydis ntdyffpr
```

An exemplary human *IL6Ra* nucleic acid sequence is set forth below (SEQ ID NO: 92; GenBank Accession No: NM_000565, Version 3, incorporated herein by reference):

```
  1 ggcggtcccc tgttctcccc gctcaggtgc ggcgctgtgg caggaagcca ccccctcggt
 61 cggccggtgc gcggggctgt tgcgccatcc gctccggctt tcgtaaccgc accctgggac
121 ggcccagaga cgctccagcg cgagttcctc aaatgttttc ctgcgttgcc aggaccgtcc
181 gccgctctga gtcatgtgcg agtgggaagt cgcactgaca ctgagccggg ccagagggag
241 aggagccgag cgcggcgcgg ggccgaggga ctcgcagtgt gtgtagagag ccgggctcct
301 gcggatgggg gctgcccccg gggcctgagc ccgcctgccc gcccaccgcc ccgccccgcc
361 cctgccaccc ctgccgcccg gttcccatta gcctgtccgc ctctgcggga ccatggagtg
421 gtagccgagg aggaagcatg ctggccgtcg gctgcgcgct gctggctgcc ctgctggccg
481 cgccgggagc ggcgctggcc ccaaggcgct gccctgcgca ggaggtggcg agaggcgtgc
541 tgaccagtct gccaggagac agcgtgactc tgacctgccc gggggtagag ccggaagaca
601 atgccactgt tcactgggtg ctcaggaagc cggctgcagg ctcccacccc agcagatggg
661 ctggcatggg aaggaggctg ctgctgaggt cggtgcagct ccacgactct ggaaactatt
721 catgctaccg ggccggccgc ccagctggga ctgtgcactt gctggtggat gttcccccg
781 aggagcccca gctctcctgc ttccggaaga gccccctcag caatgttgtt tgtgagtggg
841 gtcctcggag caccccatcc ctgacgacaa aggctgtgct cttggtgagg aagtttcaga
901 acagtccggc cgaagacttc caggagccgt gccagtattc ccaggagtcc cagaagttct
961 cctgccagtt agcagtcccg gagggagaca gctctttcta catagtgtcc atgtgcgtcg
1021 ccagtagtgt cgggagcaag ttcagcaaaa ctcaaacctt tcagggttgt ggaatcttgc
1081 agcctgatcc gcctgccaac atcacagtca ctgccgtggc cagaaacccc cgctggctca
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1141 gtgtcacctg gcaagacccc cactcctgga actcatcttt ctacagacta cggtttgagc
1201 tcagatatcg ggctgaacgg tcaaagacat tcacaacatg gatggtcaag gacctccagc
1261 atcactgtgt catccacgac gcctggagcg gcctgaggca cgtggtgcag cttcgtgccc
1321 aggaggagtt cgggcaaggc gagtggagcg agtggagccc ggaggccatg ggcacgcctt
1381 ggacagaatc caggagtcct ccagctgaga acgaggtgtc cacccccatg caggcactta
1441 ctactaataa agacgatgat aatattctct tcagagattc tgcaaatgcg acaagcctcc
1501 cagtgcaaga ttcttcttca gtaccactgc ccacattcct ggttgctgga gggagcctgg
1561 ccttcggaac gctcctctgc attgccattg ttctgaggtt caagaagacg tggaagctgc
1621 gggctctgaa ggaaggcaag acaagcatgc atccgccgta ctctttgggg cagctggtcc
1681 cggagaggcc tcgacccacc ccagtgcttg ttcctctcat ctccccaccg gtgtccccca
1741 gcagcctggg gtctgacaat acctcgagcc acaaccgacc agatgccagg gacccacgga
1801 gcccttatga catcagcaat acagactact tcttccccag atagctggct gggtggcacc
1861 agcagcctgg accctgtgga tgataaaaca caaacgggct cagcaaaaga tgcttctcac
1921 tgccatgcca gcttatctca ggggtgtgcg gcctttggct tcacggaaga gccttgcgga
1981 aggttctacg ccaggggaaa atcagcctgc tccagctgtt cagctggttg aggtttcaaa
2041 cctccctttc caaatgccca gcttaaaggg gctagagtga acttgggcca ctgtgaagag
2101 aaccatatca agactctttg gacactcaca cggacactca aaagctgggc aggttggtgg
2161 gggcctcggt gtggagaagc ggctggcagc ccacccctca acacctctgc acaagctgca
2221 ccctcaggca ggtgggatgg atttccagcc aaagcctcct ccagccgcca tgctcctggc
2281 ccactgcatc gtttcatctt ccaactcaaa ctcttaaaac ccaagtgcct tagcaaattc
2341 tgtttttcta ggcctgggga cggcttttac ttaaaccgcc aaggctgggg gaagaagctc
2401 tctcctccct ttcttcccta cagttgaaaa acagctgagg gtgagtgggt gaataataca
2461 gtatctcagg gcctggtcgt tttcaacaga attataatta gttcctcatt agcattttgc
2521 taaatgtgaa tgatgatcct aggcatttgc tgaatacaga ggcaactgca ttggctttgg
2581 gttgcaggac ctcaggtgag aagcagagga aggagaggag aggggcacag ggtctctacc
2641 atcccctgta gagtgggagc tgagtggggg atcacagcct ctgaaaacca atgttctctc
2701 ttctccacct cccacaaagg agagctagca gcagggaggg cttctgccat ttctgagatc
2761 aaaacggttt tactgcagct ttgtttgttg tcagctgaac ctgggtaact agggaagata
2821 atattaagga agacaatgtg aaaagaaaaa tgagcctggc aagaatgtgt ttaaacttgg
2881 tttttaaaaa actgctgact gttttctctt gagagggtgg aatatccaat attcgctgtg
2941 tcagcataga agtaacttac ttaggtgtgg gggaagcacc ataactttgt ttagcccaaa
3001 accaagtcaa gtgaaaaagg aggaagagaa aaaatatttt cctgccaggc atggtggccc
3061 acgcacttcg ggaggtcgag gcaggaggat cacttgagtc cagaagtttg agatcagcct
3121 gggcaatgtg ataaaacccc atctctacaa aaagcataaa aattagccaa gtgtggtaga
3181 gtgtgcctga agtcccagat acttgggggg ctgaggtggg aggatctctt gagcctggga
3241 ggtcaaggct gcagtgagcc gagattgcac cactgcactc cagcctgggt gacagagcaa
3301 gtgagaccct gtctcaaaaa aagaaaaaga aaaagaaaaa atattttccc tattagagaa
3361 gagattgtgg tttcattctg tattttgttt ttgtcttaaa aagtggaaaa atagcctgcc
3421 tcttctctac tctagggaaa aaccagcgtg tgactactcc cccaggtggt tatggagagg
3481 gtgtccggtc cctgtcccag tgccgagaag gaagcctccc acgactgccc ggcagggtcc
3541 tagaaattcc ccaccctgaa agccctgagc tttctgctat caaagaggtt ttaaaaaaat
3601 cccatttaaa aaaaatccct tacctcggtg ccttcctctt tttatttagt tccttgagtt
3661 gattcagctc tgcaagaatt gaagcaggac taaatgtcta gttgtaacac catgattaac
3721 cacttcagct gacttttctg tccgagcttt gaaaattcag tggtgttagt ggttacccag
3781 ttagctctca agttatcagg gtattccaga gtggggatat gatttaaatc agccgtgtaa
3841 ccatggaccc aatatttacc agaccacaaa acttttctaa tactctaccc tcttagaaaa
3901 accaccacca tcaccagaca ggtgcgaaag gatgaaagtg accatgtttt gtttacggtt
3961 ttccaggttt aagctgttac tgtcttcagt aagccgtgat tttcattgct gggcttgtct
4021 gtagatttta gaccctattg ctgcttgagg caactcatct taggttggca aaaaggcagg
4081 atggccgggc gcggtggctc acgcctgtaa tcctagcact ttgggaggcc aaggtgggag
4141 gattgcttga gctcaggagt ttgagaccaa cctgggtaac atagtgagac accatctcta
4201 ttatgaacaa taacagttaa gaaaaaaaaa ggcaggcagg cggttatggt ggttccctcc
4261 catcccacca cataaagttt ctgagacttg agaacagcaa aatgctgtta aagggaaata
4321 ttaagaatga gaatctgcag taagggtgat tctgtgccca cagttcttca attctttata
4381 ccgttttacc cacatgtggt gttaccaaag ccgggcagaa ccatgctagc ggaagatgtg
4441 aaatccagat agctcattat tgccaagagc taggcagctt tgatctccaa attgttattg

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4501 ctttcatttt tattgtaatg gaattgcttt gttttgtttt tttgtttttg tattgaagag
4561 ggttgttttc cctttatttt tcataagcta atgtaaatga agaaaaaatg tcttctctgg
4621 gctgtaggcc tggctcagcg tacacaggta tacatcctaa gctctctatg ttctctaatc
4681 tgtggtgact gaacatgtgt ctcaatgcac ggggcatttc tacctgtgtt tctgcagcac
4741 ccccactgcc ttgagtcccc agcagtgctg ttatttgcct aacacctgta gccatctgcc
4801 acgcagccag acgtgaaacg ctgagacaga gaccatttag gttaaatacg acagcttatc
4861 ctgctgggtg gggaaagtaa aaaatatgct ggttcaaggc ctaaagtaaa atgatcaata
4921 atgtttgtag cattaatgaa atattttcaa gaaatgtgtc caggggtagc actggctatg
4981 ttgacgaggc ctttggtaac tcagagagct cttggccctg atggggactt gcccttacgc
5041 tttctttatc aggctctgag ttcacacgga gcctctggca cttccctgct gtcttgggag
5101 aaaggaaact ggttgccgcg gcaggttgtg gaatctgttg ctggaaccag gctggaagcc
5161 cacctggtag tgaacagggc ccagtggggc aggctgggca tgttgtggtc tatgggtttg
5221 tttcctggag aatgttcagg aatgtcttcc cagctgcttt ggtgctgagc tctattatct
5281 cacagcacgt ccagaaggct aacccaggtg gggaggatgc tgacaccagc tccaggtgga
5341 gttggtggtc ttaatttgga gatgcagggg caacctgtga ccctttgagg caagagccct
5401 gcacccagct gtcccgtgca gccgtgggca ggggctgcac acggaggggc aggcgggcca
5461 gttcagggtc cgtgccaggc cctcctcagt gccctgtgaa ggcctcctgt cctccgtgcg
5521 gctgggcacc agcaccaggg agtttctatg gcaaccttag tgattattaa ggaacactgt
5581 cagttttatg aacatatgct caaatgaaat tctactttag gaggaaagga ttggaacagc
5641 atgtcacaag gctgttaatt aacagagaga ccttattgga tggagatcac atctgttaaa
5701 tagaatacct caactctacg ttgttttctt ggagataaat aatagtttca agtttttgtt
5761 tgtttgtttt acctaattac ctgaaagcaa ataccaaagg ctgatgtctg tatatggggc
5821 aaagggtcag tatatttttc agtgtttttt tttctaccag ctattttgca tttaaagtga
5881 acattgtgtt tggaataaat actcttaaaa aataaaaaaa aaaaaaaa
```

An exemplary human angiopoietin-1 receptor (alternatively, CD202B, or TIE-2) amino acid sequence is set forth below (SEQ ID NO: 93; GenBank Accession No: NP_000450, Version 2, incorporated herein by reference):

```
   1 mdslaslvlc gvslllsgtv egamdlilin slplvsdaet sltciasgwr phepitigrd
  61 fealmnqhqd plevtqdvtr ewakkvvwkr ekaskingay fcegrvrgea irirtmkmrq
 121 qasflpatlt mtvdkgdnvn isfkkvlike edaviyknqs fihsvprhev pdilevhlph
 181 aqpqdagvys aryiggnlft saftrlivrr ceaqkwgpec nhlctacmnn gvchedtgec
 241 icppgfmgrt cekacelhtf grtckercsg qegcksyvfc lpdpygcsca tgwkglqcne
 301 achpgfygpd cklrcscnng emcdrfqgcl cspgwqglqc eregiprmtp kivdlpdhie
 361 vnsgkfnpic kasgwplptn eemtlvkpdg tvlhpkdfnh tdhfsvaift ihrilppdsg
 421 vwvcsvntva gmvekpfnis vkvlpkplna pnvidtghnf avinissepy fgdgpikskk
 481 llykpvnhye awqhiqvtne ivtlnylepr teyelcvqlv rrgeggeghp gpvrrfttas
 541 iglppprgln llpksqttln ltwqpifpss eddfyvever rsvqksdqqn ikvpgnltsv
 601 llnnlhpreq yvvrarvntk aqgewsedlt awtlsdilpp qpenikisni thssaviswt
 661 ildgysissi tirykvqgkn edqhvdvkik natitqyqlk glepetayqv difaennigs
 721 snpafshelv tlpesqapad lgggkmllia ilgsagmtcl tvllafliil qlkranvqrr
 781 maqafqnvre epavqfnsgt lalnrkvknn pdptiypvld wndikfqdvi gegnfgqvlk
 841 arikkdglrm daaikrmkey askddhrdfa gelevlcklg hhpniinllg acehrgylyl
 901 aieyaphgnl ldflrksrvl etdpafaian stastlssqq llhfaadvar gmdylsqkqf
 961 ihrdlaarni lvgenyvaki adfglsrgqe vyvkktmgrl pvrwmaiesl nysvyttnsd
1021 vwsygvllwe ivslggtpyc gmtcaelyek lpqgyrlekp lncddevydl mrqcwrekpy
1081 erpsfaqilv slnrmleerk tyvnttlyek ftyagidcsa eeaa
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An exemplary human *TIE-2* nucleic acid sequence is set forth below (SEQ ID NO: 94; GenBank Accession No: NM_000459, Version 4, incorporated herein by reference):

```
   1 ttattctcag tttcccgcct atgagaggat acccctattg tttctgaaaa tgctgaccgg
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  61 gacccacact tccaacaaaa attcctctgc ccctacagca gcagcaaaag cagcagcaga
 121 agcaacagca acagataagt gttttgatga attgcgagat ggatagggct tgagtgcccc
 181 cagccctgct gataccaaat gcctttaaga tacagccttt cccatcctaa tctacaaagg
 241 aaacaggaaa aaggaactta aaactccctg tgctcagaca gaaatgagac tgttacagcc
 301 tgcttctgtg ctgttccttc ttgcctctaa cttgtaaaca agacgtagta ggacgatgct
 361 aatggaaagt cacaaaccgc tgggtttttg aaaggatcct tgggacctca tgcacatttg
 421 tggaaactgg atggagagat ttggggaagc atggactctt tagccagctt agttctctgt
 481 ggagtcagct tgctcctttc tggaactgtg gaaggtgcca tggacttgat cttgatcaat
 541 tccctacctc ttgtatctga tgctgaaaca tctctcacct gcattgcctc tgggtggcgc
 601 ccccatgagc ccatcaccat aggaagggac tttgaagcct taatgaacca gcaccaggat
 661 ccgctggaag ttactcaaga tgtgaccaga gaatgggcta aaaaagttgt ttggaagaga
 721 gaaaaggcta gtaagatcaa tggtgcttat ttctgtgaag ggcgagttcg aggagaggca
 781 atcaggatac gaaccatgaa gatgcgtcaa caagcttcct tcctaccagc tactttaact
 841 atgactgtgg acaagggaga taacgtgaac atatctttca aaaaggtatt gattaaagaa
 901 gaagatgcag tgatttacaa aaatggttcc ttcatccatt cagtgccccg gcatgaagta
 961 cctgatattc tagaagtaca cctgcctcat gctcagcccc aggatgctgg agtgtactcg
1021 gccaggtata taggaggaaa cctcttcacc tcggccttca ccaggctgat agtccggaga
1081 tgtgaagccc agaagtgggg acctgaatgc aaccatctct gtactgcttg tatgaacaat
1141 ggtgtctgcc atgaagatac tggagaatgc atttgccctc ctgggtttat gggaaggacg
1201 tgtgagaagg cttgtgaact gcacacgttt ggcagaactt gtaaagaaag gtgcagtgga
1261 caagagggat gcaagtctta tgtgttctgt ctccctgacc cctatgggtg ttcctgtgcc
1321 acaggctgga agggtctgca gtgcaatgaa gcatgccacc ctggttttta cgggccagat
1381 tgtaagctta ggtgcagctg caacaatggg gagatgtgtg atcgcttcca aggatgtctc
1441 tgctctccag gatggcaggg gctccagtgt gagagagaag gcataccgag gatgacccca
1501 aagatagtgg atttgccaga tcatatagaa gtaaacagtg gtaaatttaa tcccatttgc
1561 aaagcttctg gctggccgct acctactaat gaagaaatga ccctggtgaa gccggatggg
1621 acagtgctcc atccaaaaga ctttaaccat acggatcatt tctcagtagc catattcacc
1681 atccaccgga tcctcccccc tgactcagga gtttgggtct gcagtgtgaa cacagtggct
1741 gggatggtgg aaaagccctt caacatttct gttaaagttc ttccaaagcc cctgaatgcc
1801 ccaaacgtga ttgacactgg acataacttt gctgtcatca acatcagctc tgagccttac
1861 tttggggatg gaccaatcaa atccaagaag cttctataca aacccgttaa tcactatgag
1921 gcttggcaac atattcaagt gacaaatgag attgttacac tcaactattt ggaacctcgg
1981 acagaatatg aactctgtgt gcaactggtc cgtcgtggag agggtgggga agggcatcct
2041 ggacctgtga gacgcttcac aacagcttct atcggactcc ctcctccaag aggtctaaat
2101 ctcctgccta aaagtcagac cactctaaat ttgacctggc aaccaatatt tccaagctcg
2161 gaagatgact tttatgttga agtggagaga aggtctgtgc aaaaaagtga tcagcagaat
2221 attaaagttc caggcaactt gacttcggtg ctacttaaca acttacatcc cagggagcag
2281 tacgtggtcc gagctagagt caacaccaag gcccaggggg aatggagtga agatctcact
2341 gcttggaccc ttagtgacat tcttcctcct caaccagaaa acatcaagat ttccaacatt
2401 acacactcct cagctgtgat ttcttggaca atattggatg gctattctat ttcttctatt
2461 actatccgtt acaaggttca aggcaagaat gaagaccagc acgttgatgt gaagataaag
2521 aatgccacca tcactcagta tcagctcaag ggcctagagc ctgaaacagc ataccaggtg
2581 gacatttttg cagagaacaa catagggtca agcaacccag ccttttctca tgaactggtg
2641 accctcccag aatctcaagc accagcggac ctcggagggg ggaagatgct gcttatagcc
2701 atccttggct ctgctggaat gacctgcctg actgtgctgt tggcctttct gatcatattg
2761 caattgaaga gggcaaatgt gcaaaggaga atggcccaag ccttccaaaa cgtgagggaa
2821 gaaccagctg tgcagttcaa ctcagggact ctggccctaa acaggaaggt caaaaacaac
2881 ccagatccta caatttatcc agtgcttgac tggaatgaca tcaaatttca agatgtgatt
2941 ggggagggca attttggcca agttcttaag gcgcgcatca agaaggatgg gttacggatg
3001 gatgctgcca tcaaaagaat gaaagaatat gcctccaaag atgatcacag ggactttgca
3061 ggagaactgg aagttctttg taaacttgga caccatccaa acatcatcaa tctcttagga
3121 gcatgtgaac atcgaggcta cttgtacctg gccattgagt acgcgcccca tggaaacctt
3181 ctggacttcc ttcgcaagag ccgtgtgctg gagacggacc cagcatttgc cattgccaat
3241 agcaccgcgt ccacactgtc ctcccagcag ctccttcact tcgctgccga cgtggcccgg
3301 ggcatggact acttgagcca aaaacagttt atccacaggg atctggctgc cagaaacatt
3361 ttagttggtg aaaactatgt ggcaaaaata gcagattttg gattgtcccg aggtcaagag
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3421 gtgtatgtga aaaagacaat gggaaggctc ccagtgcgct ggatggccat cgagtcactg
3481 aattacagtg tgtacacaac caacagtgat gtatggtcct atggtgtgtt actatgggag
3541 attgttagct taggaggcac accctactgc gggatgactt gtgcagaact ctacgagaag
3601 ctgccccagg gctacagact ggagaagccc ctgaactgtg atgatgaggt gtatgatcta
3661 atgagacaat gctggcggga gaagccttat gagaggccat catttgccca gatattggtg
3721 tccttaaaca gaatgttaga ggagcgaaag acctacgtga ataccacgct ttatgagaag
3781 tttacttatg caggaattga ctgttctgct gaagaagcgg cctaggacag aacatctgta
3841 taccctctgt ttccctttca ctggcatggg agacccttga cacctgctga gaaaacatgc
3901 ctctgccaaa ggatgtgata tataagtgta catatgtgct gtacacctgg gaccttcacc
3961 actgtagatc ccatgcatgg atctatgtag tatgctctga ctctaatagg actgtatata
4021 ctgttttaag aatgggctga aatcagaatg cctgtttgtg gtttcatatg caataatata
4081 ttttttaaa aatgtggact tcataggaag gcgtgagtac aattagtata atgcataact
4141 cattgttgtc ctagatattt tgatatttac ctttatgttg aatgctatta aatgttttcc
4201 tgtgtcaaag taaaatattg ttaataaacc taacaatgac cctgatagta caggttaagt
4261 gagagaacta tatgaattct aacaagtcat aggttaatat ttaagacact gaaaaatcta
4321 agtgatataa atcagattct tctctctcaa ttttatccct cacctgtagc agccagtccc
4381 gtttcattta gtcatgtgac cactctgtct tgtgtttcca cagcctgcaa gtcagtccag
4441 gatgctaaca tctaaaaata gacttaaatc tcattgctta caagcctaag aatctttaga
4501 gaagtataca taagtttagg ataaaataat gggattttct tttcttttct ctggtaatat
4561 tgacttgtat attttaagaa ataacagaaa gcctgggtga catttgggag acatgtgaca
4621 tttatatatt gaattaatat ccctacatgt attgcacatt gtaaaaagtt ttagttttga
4681 tgagttgtga gtttaccttg tatactgtag gcacactttg cactgatata tcatgagtga
4741 ataaatgtct tgcctactca cgtctcatcc aaaaaaaaaa aaaaaaa
```

An exemplary human vascular endothelial growth factor receptor 1 (VEGF1) amino acid sequence is set forth below (SEQ ID NO: 95; GenBank Accession No: NP_002010, Version 2, incorporated herein by reference):

```
   1 mvsywdtgvl lcallsclll tgssgsklk dpelslkgtq himqagqtlh lqcrgeaahk
  61 wslpemvske serlsitksa cgrngkqfcs tltlntaqan htgfysckyl avptskkket
 121 esaiyifisd tgrpfvemys eipeiihmte grelvipcrv tspnitvtlk kfpldtlipd
 181 gkriiwdsrk gfiisnatyk eiglltceat vnghlyktny lthrqtntii dvqistprpv
 241 kllrghtlvl nctattplnt rvqmtwsypd eknkrasvrr ridqsnshan ifysvltidk
 301 mqnkdkglyt crvrsgpsfk svntsvhiyd kafitvkhrk qqvletvagk rsyrlsmkvk
 361 afpspevvwl kdglpateks aryltrgysl iikdvteeda gnytillsik qsnvfknlta
 421 tlivnvkpqi yekavssfpd palyplgsrq iltctaygip qptikwfwhp cnhnhsearc
 481 dfcsnneesf ildadsnmgn riesitqrma iiegknkmas tlvvadsris giyiciasnk
 541 vgtvgrnisf yitdvpngfh vnlekmpteg edlklsctvn kflyrdvtwi llrtvnnrtm
 601 hysiskqkma itkehsitln ltimnvslqd sgtyacrarn vytgeeilqk keitirdqea
 661 pyllrnlsdh tvaisssttl dchangvpep qitwfknnhk iqqepgiilg pgsstlfier
 721 vteedegvyh ckatnqkgsv essayltvqg tsdksnleli tltctcvaat lfwllltlfi
 781 rkmkrsssei ktdylsiimd pdevpldeqc erlpydaskw efarerlklg kslgrgafgk
 841 vvqasafgik ksptcrtvav kmlkegatas eykalmtelk ilthighhln vvnllgactk
 901 qggplmvive yckygnlsny lkskrdlffl nkdaalhmep kkekmepgle qgkkprldsv
 961 tssesfassg fqedkslsdv eeeedsdgfy kepitmedli sysfqvargm eflssrkcih
1021 rdlaarnill sennvvkicd fglardiykn pdyvrkgdtr lplkwmapes ifdkiystks
1081 dvwsygvllw eifslggspy pgvqmdedfc srlregmrmr apeystpeiy qimldcwhrd
1141 pkerprfael veklgdllqa nvqqdgkdyi pinailtgns gftystpafs edffkesisa
1201 pkfnsgssdd vryvnafkfm sleriktfee llpnatsmfd dyqgdsstll aspmlkrftw
1261 tdskpkaslk idlrvtsksk esglsdvsrp sfchsscghv segkrrftyd haelerkiac
1321 cspppdynsv vlystppi
```

An exemplary human *VEGF1* nucleic acid sequence is set forth below (SEQ ID NO: 96 GenBank Accession No: NM_002019, Version 4, incorporated herein by reference):

```
   1 atcgaggtcc gcgggaggct cggagcgcgc caggcggaca ctcctctcgg ctcctccccg
  61 gcagcggcgg cggctcggag cgggctccgg ggctcgggtg cagcggccag cgggcgcctg
 121 gcggcgagga ttacccgggg aagtggttgt ctcctggctg gagccgcgag acgggcgctc
 181 agggcgcggg gccggcggcg gcgaacgaga ggacggactc tggcggccgg gtcgttggcc
 241 gcggggagcg cgggcaccgg gcgagcaggc cgcgtcgcgc tcaccatggt cagctactgg
 301 gacaccgggg tcctgctgtg cgcgctgctc agctgtctgc ttctcacagg atctagttca
 361 ggttcaaaat taaaagatcc tgaactgagt ttaaaaggca cccagcacat catgcaagca
 421 ggccagacac tgcatctcca atgcaggggg gaagcagccc ataaatggtc tttgcctgaa
 481 atggtgagta aggaaagcga aaggctgagc ataactaaat ctgcctgtgg aagaaatggc
 541 aaacaattct gcagtacttt aaccttgaac acagctcaag caaaccacac tggcttctac
 601 agctgcaaat atctagctgt acctacttca aagaagaagg aaacagaatc tgcaatctat
 661 atatttatta gtgatacagg tagacctttc gtagagatgt acagtgaaat ccccgaaatt
 721 atacacatga ctgaaggaag ggagctcgtc attccctgcc gggttacgtc acctaacatc
 781 actgttactt taaaaaagtt tccacttgac actttgatcc ctgatggaaa acgcataatc
 841 tgggacagta gaaagggctt catcatatca aatgcaacgt acaaagaaat agggcttctg
 901 acctgtgaag caacagtcaa tgggcatttg tataagacaa actatctcac acatcgacaa
 961 accaatacaa tcatagatgt ccaaataagc acaccacgcc cagtcaaatt acttagaggc
1021 catactcttg tcctcaattg tactgctacc actcccttga acacgagagt tcaaatgacc
1081 tggagttacc ctgatgaaaa aaataagaga gcttccgtaa ggcgacgaat tgaccaaagc
1141 aattcccatg ccaacatatt ctacagtgtt cttactattg acaaaatgca gaacaaagac
1201 aaaggacttt atacttgtcg tgtaaggagt ggaccatcat tcaaatctgt taacacctca
1261 gtgcatatat atgataaagc attcatcact gtgaaacatc gaaaacagca ggtgcttgaa
1321 accgtagctg gcaagcggtc ttaccggctc tctatgaaag tgaaggcatt tccctcgccg
1381 gaagttgtat ggttaaaaga tgggttacct gcgactgaga aatctgctcg ctatttgact
1441 cgtggctact cgttaattat caaggacgta actgaagagg atgcagggaa ttatacaatc
1501 ttgctgagca taaaacagtc aaatgtgttt aaaaacctca ctgccactct aattgtcaat
1561 gtgaaacccc agatttacga aaaggccgtg tcatcgtttc cagacccggc tctctaccca
1621 ctgggcagca gacaaatcct gacttgtacc gcatatggta tccctcaacc tacaatcaag
1681 tggttctggc acccctgtaa ccataatcat tccgaagcaa ggtgtgactt ttgttccaat
1741 aatgaagagt cctttatcct ggatgctgac agcaacatgg gaaacagaat tgagagcatc
1801 actcagcgca tggcaataat agaaggaaag aataagatgg ctagcacctt ggttgtggct
1861 gactctagaa tttctggaat ctacatttgc atagcttcca ataaagttgg gactgtggga
1921 agaaacataa gcttttatat cacagatgtg ccaaatgggt ttcatgttaa cttggaaaaa
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2041 gacgttactt ggattttact gcggacagtt aataacagaa caatgcacta cagtattagc
2101 aagcaaaaaa tggccatcac taaggagcac tccatcactc ttaatcttac catcatgaat
2161 gtttccctgc aagattcagg cacctatgcc tgcagagcca ggaatgtata cacaggggaa
2221 gaaatcctcc agaagaaaga aattacaatc agagatcagg aagcaccata cctcctgcga
2281 aacctcagtg atcacacagt ggccatcagc agttccacca ctttagactg tcatgctaat
2341 ggtgtccccg agcctcagat cacttggttt aaaaacaacc acaaaataca acaagagcct
2401 ggaattattt taggaccagg aagcagcacg ctgtttattg aaagagtcac agaagaggat
2461 gaaggtgtct atcactgcaa agccaccaac cagaagggct ctgtggaaag ttcagcatac
2521 ctcactgttc aaggaacctc ggacaagtct aatctggagc tgatcactct aacatgcacc
2581 tgtgtggctg cgactctctt ctggctccta ttaaccctct ttatccgaaa aatgaaaagg
2641 tcttcttctg aaataaagac tgactaccta tcaattataa tggacccaga tgaagttcct
2701 ttggatgagc agtgtgagcg gctcccttat gatgccagca agtgggagtt tgcccgggag
2761 agacttaaac tgggcaaatc acttggaaga ggggcttttg gaaaagtggt tcaagcatca
2821 gcatttggca ttaagaaatc acctacgtgc cggactgtgg ctgtgaaaat gctgaaagag
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2941 ggccaccatc tgaacgtggt taacctgctg ggagcctgca ccaagcaagg agggcctctg
3001 atggtgattg ttgaatactg caaatatgga aatctctcca actacctcaa gagcaaacgt
3061 gacttatttt ttctcaacaa ggatgcagca ctacacatgg agcctaagaa agaaaaaatg
3121 gagccaggcc tggaacaagg caagaaacca agactagata gcgtcaccag cagcgaaagc
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3181 tttgcgagct ccggctttca ggaagataaa agtctgagtg atgttgagga agaggaggat
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3421 gatatttata agaaccccga ttatgtgaga aaaggagata ctcgacttcc tctgaaatgg
3481 atggctcctg aatctatctt tgacaaaatc tacagcacca agagcgacgt gtggtcttac
3541 ggagtattgc tgtgggaaat cttctcctta ggtgggtctc catacccagg agtacaaatg
3601 gatgaggact tttgcagtcg cctgagggaa ggcatgagga tgagagctcc tgagtactct
3661 actcctgaaa tctatcagat catgctggac tgctggcaca gagacccaaa agaaaggcca
3721 agatttgcag aacttgtgga aaaactaggt gatttgcttc aagcaaatgt acaacaggat
3781 ggtaaagact acatcccaat caatgccata ctgacaggaa atagtgggtt tacatactca
3841 actcctgcct tctctgagga cttcttcaag gaaagtattt cagctccgaa gtttaattca
3901 ggaagctctg atgatgtcag atacgtaaat gctttcaagt tcatgagcct ggaaagaatc
3961 aaaacctttg aagaactttt accgaatgcc acctccatgt ttgatgacta ccagggcgac
4021 agcagcactc tgttggcctc tcccatgctg aagcgcttca cctggactga cagcaaaccc
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4201 aggttcacct acgaccacgc tgagctggaa aggaaaatcg cgtgctgctc cccgccccca
4261 gactacaact cggtggtcct gtactccacc ccacccatct agagtttgac acgaagcctt
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4381 atatataagt ttacaccttt atctttccat gggagccagc tgctttttgt gatttttta
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4501 gtgaagaaca ctactgctaa atcctcatgt tactcagtgt tagagaaatc cttcctaaac
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4681 acccagggca acaagcccgt tagccccagg gatcactggc tggcctgagc aacatctcgg
4741 gagtcctcta gcaggcctaa gacatgtgag gaggaaaagg aaaaaaagca aaaagcaagg
4801 gagaaaagag aaaccgggag aaggcatgag aaagaatttg agacgcacca tgtgggcacg
4861 gaggggacg gggctcagca atgccatttc agtggcttcc cagctctgac ccttctacat
4921 ttgagggccc agccaggagc agatggacag cgatgagggg acatttttctg gattctggga
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5161 gagttaggtt gtctccaggc catgatggcc ttacactgaa aatgtcacat tctattttgg
5221 gtattaatat atagtccaga cacttaactc aatttcttgg tattattctg ttttgcacag
5281 ttagttgtga aagaaagctg agaagaatga aaatgcagtc ctgaggagag gagttttctc
5341 catatcaaaa cgagggctga tggaggaaaa aggtcaataa ggtcaaggga aaaccccgtc
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5461 acgtttcctt ttcatttaat ggggattcca ctatctcaca ctaatctgaa aggatgtgga
5521 agagcattag ctggcgcata ttaagcactt taagctcctt gagtaaaaag gtggtatgta
5581 atttatgcaa ggtatttctc cagttgggac tcaggatatt agttaatgag ccatcactag
5641 aagaaaagcc cattttcaac tgctttgaaa cttgcctggg gtctgagcat gatgggaata
5701 gggagacagg gtaggaaagg gcgcctactc ttcagggtct aaagatcaag tgggccttgg
5761 atcgctaagc tggctctgtt tgatgctatt tatgcaagtt agggtctatg tatttatgat
5821 gtctgcacct tctgcagcca gtcagaagct ggagaggcaa cagtggattg ctgcttcttg
5881 gggagaagag tatgcttcct tttatccatg taatttaact gtagaacctg agctctaagt
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6001 tgaagagatg ggaccgtcat cagcacattc cctagtgagc ctactggctc ctggcagcgg
6061 cttttgtgga agactcacta gccagaagag aggagtggga cagtcctctc caccaagatc
6121 taaatccaaa caaaagcagg ctagagccag aagagaggac aaatctttgt tcttcctctt
6181 ctttacatac gcaaaccacc tgtgacagct ggcaatttta taaatcaggt aactggaagg
6241 aggttaaaca cagaaaaaag aagacctcag tcaattctct actttttttt ttttttccaa
6301 atcagataat agcccagcaa atagtgataa caaataaaac cttagctatt catgtcttga
6361 tttcaataat taattcttaa tcattaagag accataataa atactccttt tcaagagaaa
6421 agcaaaacca ttagaattgt tactcagctc cttcaaactc aggtttgtag catacatgag
6481 tccatccatc agtcaaagaa tggttccatc tggagtctta atgtagaaag aaaaatggag

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6541 acttgtaata atgagctagt tacaaagtgc ttgttcatta aaatagcact gaaaattgaa
6601 acatgaatta actgataata ttccaatcat ttgccattta tgacaaaaat ggttggcact
6661 aacaaagaac gagcacttcc tttcagagtt tctgagataa tgtacgtgga acagtctggg
6721 tggaatgggg ctgaaaccat gtgcaagtct gtgtcttgtc agtccaagaa gtgacaccga
6781 gatgttaatt ttagggaccc gtgccttgtt tcctagccca caagaatgca aacatcaaac
6841 agatactcgc tagcctcatt taaattgatt aaaggaggag tgcatctttg gccgacagtg
6901 gtgtaactgt atgtgtgtgt gtgtgtgtgt gtgtgtgtgt gtgtgtgggt gtatgtgtgt
6961 tttgtgcata actatttaag gaaactggaa ttttaaagtt acttttatac aaaccaagaa
7021 tatatgctac agatataaga cagacatggt ttggtcctat atttctagtc atgatgaatg
7081 tattttgtat accatcttca tataataaac ttccaaaaac aca
```

An exemplary human vascular endothelial growth factor receptor 2 (VEGFR2) amino acid sequence is set forth below (SEQ ID NO: 97; GenBank Accession No: NP_002244, Version 1, incorporated herein by reference):

```
   1 mqskvllava lwlcvetraa svglpsvsld lprlsiqkdi ltikanttlq itcrgqrdld
  61 wlwpnnqsgs eqrvevtecs dglfcktlti pkvigndtga ykcfyretdl asviyvyvqd
 121 yrspfiasvs dqhgvvyite nknktvvipc lgsisnlnvs lcarypekrf vpdgnriswd
 181 skkgftipsy misyagmvfc eakindesyq simyivvvvg yriydvvlsp shgielsvge
 241 klvlnctart elnvgidfnw eypsskhqhk klvnrdlktq sgsemkkfls tltidgvtrs
 301 dqglytcaas sglmtkknst fvrvhekpfv afgsgmeslv eatvgervri pakylgyppp
 361 eikwykngip lesnhtikag hvltimevse rdtgnytvil tnpiskekqs hvvslvvyvp
 421 pqigekslis pvdsyqygtt qtltctvyai ppphhihwyw qleeecanep sqavsvtnpy
 481 pceewrsved fqggnkievn knqfaliegk nktvstlviq aanvsalykc eavnkvgrge
 541 rvisfhvtrg peitlqpdmq pteqesvslw ctadrstfen ltwyklgpqp lpihvgelpt
 601 pvcknldtlw klnatmfsns tndilimelk naslqdqgdy vclaqdrktk krhcvvrqlt
 661 vlervaptit gnlenqttsi gesievscta sgnpppqimw fkdnetlved sgivlkdgnr
 721 nltirrvrke deglytcqac svlgcakvea ffiiegaqek tnleiiilvg taviamffwl
 781 llviilrtvk ranggelktg ylsivmdpde lpldehcerl pydaskwefp rdrlklgkpl
 841 grgafgqvie adafgidkta tcrtvavkml kegathsehr almselkili highhlnvvn
 901 llgactkpgg plmvivefck fgnlstylrs krnefvpykt kgarfrqgkd yvgaipvdlk
 961 rrldsitssq ssassgfvee kslsdveeee apedlykdfl tlehlicysf qvakgmefla
1021 srkcihrdla arnillsekn vvkicdfgla rdiykdpdyv rkgdarlplk wmapetifdr
1081 vytiqsdvws fgvllweifs lgaspypgvk ideefcrrlk egtrmrapdy ttpemyqtml
1141 dcwhgepsqr ptfselvehl gnllqanaqq dgkdyivlpi setlsmeeds glslptspvs
1201 cmeeeevcdp kfhydntagi sqylqnskrk srpvsvktfe dipleepevk vipddnqtds
1261 gmvlaseelk tledrtklsp sfggmvpsks resvasegsn qtsgyqsgyh sddtdttvys
1321 seeaellkli eigvqtgsta qilqpdsgtt lssppv
```

An exemplary human *VEGFR2* nucleic acid sequence is set forth below (SEQ ID NO: 98; GenBank Accession No: NM_002253, Version 2, incorporated herein by reference):

```
   1 actgagtccc gggaccccgg gagagcggtc aatgtgtggt cgctgcgttt cctctgcctg
  61 cgccgggcat cacttgcgcg ccgcagaaag tccgtctggc agcctggata tcctctccta
 121 ccggcacccg cagacgcccc tgcagccgcg gtcggcgccc gggctcccta gccctgtgcg
 181 ctcaactgtc ctgcgctgcg gggtgccgcg agttccacct ccgcgcctcc ttctctagac
 241 aggcgctggg agaaagaacc ggctcccgag ttctgggcat ttcgcccggc tcgaggtgca
 301 ggatgcagag caaggtgctg ctggccgtcg ccctgtggct ctgcgtggag acccgggccg
 361 cctctgtggg tttgcctagt gtttctcttg atctgcccag gctcagcata caaaaagaca
 421 tacttacaat taaggctaat acaactcttc aaattacttg caggggacag agggacttgg
 481 actggctttg gcccaataat cagagtggca gtgagcaaag ggtggaggtg actgagtgca
 541 gcgatggcct cttctgtaag acactcacaa ttccaaaagt gatcggaaat gacactggag
 601 cctacaagtg cttctaccgg gaaactgact tggcctcggt catttatgtc tatgttcaag
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 661 attacagatc tccatttatt gcttctgtta gtgaccaaca tggagtcgtg tacattactg
 721 agaacaaaaa caaaactgtg gtgattccat gtctcgggtc catttcaaat ctcaacgtgt
 781 cactttgtgc aagataccca gaaaagagat ttgttcctga tggtaacaga atttcctggg
 841 acagcaagaa gggctttact attcccagct acatgatcag ctatgctggc atggtcttct
 901 gtgaagcaaa aattaatgat gaaagttacc agtctattat gtacatagtt gtcgttgtag
 961 ggtataggat ttatgatgtg gttctgagtc cgtctcatgg aattgaacta tctgttggag
1021 aaaagcttgt cttaaattgt acagcaagaa ctgaactaaa tgtggggatt gacttcaact
1081 gggaataccc ttcttcgaag catcagcata agaaacttgt aaaccgagac ctaaaaaccc
1141 agtctgggag tgagatgaag aaatttttga gcaccttaac tatagatggt gtaacccgga
1201 gtgaccaagg attgtacacc tgtgcagcat ccagtgggct gatgaccaag aagaacagca
1261 catttgtcag ggtccatgaa aaacctttg ttgcttttgg aagtggcatg gaatctctgg
1321 tggaagccac ggtgggggag cgtgtcagaa tccctgcgaa gtaccttggt tacccacccc
1381 cagaaataaa atggtataaa aatggaatac cccttgagtc caatcacaca attaaagcgg
1441 ggcatgtact gacgattatg gaagtgagtg aaagagacac aggaaattac actgtcatcc
1501 ttaccaatcc catttcaaag gagaagcaga gccatgtggt ctctctggtt gtgtatgtcc
1561 caccccagat tggtgagaaa tctctaatct ctcctgtgga ttcctaccag tacggcacca
1621 ctcaaacgct gacatgtacg gtctatgcca ttcctccccc gcatcacatc cactggtatt
1681 ggcagttgga ggaagagtgc gccaacgagc ccagccaagc tgtctcagtg acaaaccccat
1741 acccttgtga agaatggaga agtgtggagg acttccaggg aggaaataaa attgaagtta
1801 ataaaaatca atttgctcta attgaaggaa aaaacaaaac tgtaagtacc cttgttatcc
1861 aagcggcaaa tgtgtcagct ttgtacaaat gtgaagcggt caacaaagtc gggagaggag
1921 agagggtgat ctccttccac gtgaccaggg gtcctgaaat tactttgcaa cctgacatgc
1981 agcccactga gcaggagagc gtgtctttgt ggtgcactgc agacagatct acgtttgaga
2041 acctcacatg gtacaagctt ggcccacagc ctctgccaat ccatgtggga gagttgccca
2101 cacctgtttg caagaacttg gatactcttt ggaaattgaa tgccaccatg ttctctaata
2161 gcacaaatga cattttgatc atggagctta agaatgcatc cttgcaggac caaggagact
2221 atgtctgcct tgctcaagac aggaagacca agaaaagaca ttgcgtggtc aggcagctca
2281 cagtcctaga gcgtgtggca cccacgatca caggaaacct ggagaatcag acgacaagta
2341 ttggggaaag catcgaagtc tcatgcacgg catctgggaa tccccctcca cagatcatgt
2401 ggtttaaaga taatgagacc cttgtagaag actcaggcat tgtattgaag gatgggaacc
2461 ggaacctcac tatccgcaga gtgaggaagg aggacgaagg cctctacacc tgccaggcat
2521 gcagtgttct tggctgtgca aaagtggagg catttttcat aatagaaggt gcccaggaaa
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2641 tacttcttgt catcatccta cggaccgtta agcgggccaa tggaggggaa ctgaagacag
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3301 tgaccttgga gcatctcatc tgttacagct tccaagtggc taagggcatg gagttcttgg
3361 catcgcgaaa gtgtatccac agggacctgg cggcacgaaa tatcctctta tcggagaaga
3421 acgtggttaa aatctgtgac tttggcttgg cccgggatat ttataaagat ccagattatg
3481 tcagaaaagg agatgctcgc ctccctttga aatggatggc cccagaaaca atttttgaca
3541 gagtgtacac aatccagagt gacgtctggt cttttggtgt tttgctgtgg gaaatatttt
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3841 tatcagagac tttgagcatg gaagaggatt ctggactctc tctgcctacc tcacctgttt
3901 cctgtatgga ggaggaggaa gtatgtgacc ccaaattcca ttatgacaac acagcaggaa
3961 tcagtcagta tctgcagaac agtaagcgaa agagccggcc tgtgagtgta aaaacatttg
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4021 aagatatccc gttagaagaa ccagaagtaa aagtaatccc agatgacaac cagacggaca
4081 gtggtatggt tcttgcctca gaagagctga aaactttgga agacagaacc aaattatctc
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6001 tccatctcaa agaaaaaagg taaaaataaa ataaaatgga gaagaaggaa tcaga
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An exemplary human transforming growth factor alpha (TGFa) amino acid sequence is set forth below (SEQ ID NO: 99; GenBank Accession No: NP_003227, Version 1, incorporated herein by reference):

```
  1 mvpsagqlal falgivlaac qalenstspl sadppvaaav vshfndcpds htqfcfhgtc
 61 rflvqedkpa cvchsgyvga rcehadllav vaasqkkqai talvvvsiva lavliitcvl
121 ihccqvrkhc ewcralicrh ekpsallkgr tacchsetvv
```

An exemplary human *TGFa* nucleic acid sequence is set forth below (SEQ ID NO: 100; GenBank Accession No: NM_003236, Version 3, incorporated herein by reference):

```
  1 gtcagctgtg ccccggtcgc cgagtggcga ggaggtgacg gtagccgcct tcctatttcc
 61 gcccggcggg cagcgctgcg gggcgagtgc cagcagagag gcgctcggtc ctccctccgc
121 cctcccgcgc cgggggcagg ccctgcctag tctgcgtctt tttcccccgc accgcggcgc
181 cgctccgcca ctcgggcacc gcaggtaggg caggaggctg gagagcctgc tgcccgcccg
241 cccgtaaaat ggtcccctcg gctggacagc tcgccctgtt cgctctgggt attgtgttgg
301 ctgcgtgcca ggccttggag aacagcacgt ccccgctgag tgcagacccg cccgtggctg
361 cagcagtggt gtcccatttt aatgactgcc cagattccca cactcagttc tgcttccatg
```

```
 421 gaacctgcag gtttttggtg caggaggaca agccagcatg tgtctgccat tctgggtacg
 481 ttggtgcacg ctgtgagcat gcggacctcc tggccgtggt ggctgccagc cagaagaagc
 541 aggccatcac cgccttggtg gtggtctcca tcgtggccct ggctgtcctt atcatcacat
 601 gtgtgctgat acactgctgc caggtccgaa aacactgtga gtggtgccgg gccctcatct
 661 gccggcacga gaagcccagc gccctcctga agggaagaac cgcttgctgc cactcagaaa
 721 cagtggtctg aagagcccag aggaggagtt tggccaggtg gactgtggca gatcaataaa
 781 gaaaggcttc ttcaggacag cactgccaga gatgcctggg tgtgccacag accttcctac
 841 ttggcctgta atcacctgtg cagcctttg tgggccttca aaactctgtc aagaactccg
 901 tctgcttggg gttattcagt gtgacctaga gaagaaatca gcggaccacg atttcaagac
 961 ttgttaaaaa agaactgcaa agagacggac tcctgttcac ctaggtgagg tgtgtgcagc
1021 agttggtgtc tgagtccaca tgtgtgcagt tgtcttctgc cagccatgga ttccaggcta
1081 tatatttctt tttaatgggc cacctcccca caacagaatt ctgcccaaca caggagattt
1141 ctatagttat tgttttctgt catttgccta ctggggaaga aagtgaagga ggggaaactg
1201 tttaatatca catgaagacc ctagctttaa gagaagctgt atcctctaac cacgagaccc
1261 tcaaccagcc caacatcttc catggacaca tgacattgaa gaccatccca agctatcgcc
1321 acccttggag atgatgtctt atttattaga tggataatgg ttttatttt aatctcttaa
1381 gtcaatgtaa aaagtataaa acccccttcag acttctacat taatgatgta tgtgttgctg
1441 actgaaaagc tatactgatt agaaatgtct ggcctcttca agacagctaa ggcttgggaa
1501 aagtcttcca gggtgcggag atggaaccag aggctgggtt actggtagga ataaaggtag
1561 gggttcagaa atggtgccat tgaagccaca aagccggtaa atgcctcaat acgttctggg
1621 agaaaactta gcaaatccat cagcagggat ctgtcccctc tgttggggag agaggaagag
1681 tgtgtgtgtc tacacaggat aaacccaata catattgtac tgctcagtga ttaaatgggt
1741 tcacttcctc gtgagccctc ggtaagtatg tttagaaata gaacattagc cacgagccat
1801 aggcatttca ggccaaatcc atgaaagggg gaccagtcat ttattttcca ttttgttgct
1861 tggttggttt gttgctttat ttttaaaagg agaagtttaa ctttgctatt tattttcgag
1921 cactaggaaa actattccag taatttttt ttcctcattt ccattcagga tgccggcttt
1981 attaacaaaa actctaacaa gtcacctcca ctatgtgggt cttcctttcc cctcaagaga
2041 aggagcaatt gttcccctga gcatctgggt ccatctgacc catggggcct gcctgtgaga
2101 aacagtgggt cccttcaaat acatagtgga tagctcatcc ctaggaattt tcattaaaat
2161 ttggaaacag agtaatgaag aaataatata taaactcctt atgtgaggaa atgctactaa
2221 tatctgaaaa gtgaaagatt tctatgtatt aactcttaag tgcacctagc ttattacatc
2281 gtgaaaggta catttaaaat atgttaaatt ggcttgaaat tttcagagaa ttttgtcttc
2341 ccctaattct tcttccttgg tctggaagaa caatttctat gaattttctc tttatttttt
2401 tttataattc agacaattct atgacccgtg tcttcatttt tggcactctt atttaacaat
2461 gccacacctg aagcacttgg atctgttcag agctgacccc ctagcaacgt agttgacaca
2521 gctccaggtt tttaaattac taaaataagt tcaagtttac atcccttggg ccagatatgt
2581 gggttgaggc ttgactgtag catcctgctt agagaccaat caacggacac tggtttttag
2641 acctctatca atcagtagtt agcatccaag agactttgca gaggcgtagg aatgaggctg
2701 gacagatggc ggaagcagag gttccctgcg aagacttgag atttagtgtc tgtgaatgtt
2761 ctagttccta ggtccagcaa gtcacacctg ccagtgccct catccttatg cctgtaacac
2821 acatgcagtg agaggcctca catatacgcc tccctagaag tgccttccaa gtcagtcctt
2881 tggaaaccag caggtctgaa aaagaggctg catcaatgca agcctggttg gaccattgtc
2941 catgcctcag gatagaacag cctggcttat ttggggattt ttcttctaga aatcaaatga
3001 ctgataagca ttggatccct ctgccattta atggcaatgg tagtctttgg ttagctgcaa
3061 aaatactcca tttcaagtta aaaatgcatc ttctaatcca tctctgcaag ctccctgtgt
3121 ttccttgccc tttagaaaat gaattgttca ctacaattag agaatcattt aacatcctga
3181 cctggtaagc tgccacacac ctggcagtgg ggagcatcgc tgtttccaat ggctcaggag
3241 acaatgaaaa gcccccattt aaaaaaataa caaacatttt ttaaaaggcc tccaatactc
3301 ttatggagcc tggatttttc ccactgctct acaggctgtg actttttttа agcatcctga
3361 caggaaatgt tttcttctac atggaaagat agacagcagc caaccctgat ctggaagaca
3421 gggccccggc tggacacacg tggaaccaag ccagggatgg gctggccatt gtgtccccgc
3481 aggagagatg ggcagaatgg ccctagagtt cttttccctg agaaaggaga aaaagatggg
3541 attgccactc acccacccac actggtaagg gaggagaatt tgtgcttctg gagcttctca
3601 agggattgtg ttttgcaggt acagaaaact gcctgttatc ttcaagccag gttttcgagg
3661 gcacatgggt caccagttgc tttttcagtc aatttggccg ggatggacta atgaggctct
3721 aacactgctc aggagacccc tgccctctag ttggttctgg gctttgatct cttccaacct
```

```
3781 gcccagtcac agaaggagga atgactcaaa tgcccaaaac caagaacaca ttgcagaagt
3841 aagacaaaca tgtatatttt taaatgttct aacataagac ctgttctctc tagccattga
3901 tttaccaggc tttctgaaag atctagtggt tcacacagag agagagagag tactgaaaaa
3961 gcaactcctc ttcttagtct taataattta ctaaaatggt caacttttca ttatctttat
4021 tataataaac ctgatgcttt tttttagaac tccttactct gatgtctgta tatgttgcac
4081 tgaaaaggtt aatatttaat gttttaattt attttgtgtg gtaagttaat tttgatttct
4141 gtaatgtgtt aatgtgatta gcagttattt tccttaatat ctgaattata cttaaagagt
4201 agtgagcaat ataagacgca attgtgtttt tcagtaatgt gcattgttat tgagttgtac
4261 tgtaccttat ttggaaggat gaaggaatga atcttttttt cctaaatcaa aaaaaaaaaa
4321 aaaaaa
```

An exemplary human tumor necrosis factor alpha (TNFa) amino acid sequence is set forth below (SEQ ID NO: 101; GenBank Accession No: NP_000585, Version 2, incorporated herein by reference):

```
   1 mstesmirdv elaeealpkk tggpqgsrrc lflslfsfli vagattlfcl lhfgvigpqr
  61 eefprdlsli splaqavrss srtpsdkpva hvvanpqaeg qlqwlnrran allangvelr
 121 dnqlvvpseg lyliysqvlf kgqgcpsthv llthtisria vsyqtkvnll saikspcqre
 181 tpegaeakpw yepiylggvf qlekgdrlsa einrpdyldf aesgqvyfgi ial
```

An exemplary human *TNFa* nucleic acid sequence is set forth below (SEQ ID NO: 102; GenBank Accession No: NM_000594, Version 3, incorporated herein by reference):

```
   1 cagacgctcc ctcagcaagg acagcagagg accagctaag agggagagaa gcaactacag
  61 acccccccctg aaaacaaccc tcagacgcca catcccctga caagctgcca ggcaggttct
 121 cttcctctca catactgacc cacggctcca ccctctctcc cctggaaagg acaccatgag
 181 cactgaaagc atgatccggg acgtggagct ggccgaggag gcgctcccca agaagacagg
 241 ggggccccag ggctccaggc ggtgcttgtt cctcagcctc ttctccttcc tgatcgtggc
 301 aggcgccacc acgctcttct gcctgctgca ctttggagtg atcggccccc agagggaaga
 361 gttccccagg gacctctctc taatcagccc tctggcccag gcagtcagat catcttctcg
 421 aaccccgagt gacaagcctg tagcccatgt tgtagcaaac cctcaagctg aggggcagct
 481 ccagtggctg aaccgccggg ccaatgccct cctggccaat ggcgtggagc tgagagataa
 541 ccagctggtg gtgccatcag agggcctgta cctcatctac tcccaggtcc tcttcaaggg
 601 ccaaggctgc ccctccaccc atgtgctcct cacccacacc atcagccgca tcgccgtctc
 661 ctaccagacc aaggtcaacc tcctctctgc catcaagagc ccctgccaga gggagacccc
 721 agaggggggct gaggccaagc cctggtatga gcccatctat ctgggagggg tcttccagct
 781 ggagaagggt gaccgactca gcgctgagat caatcggccc gactatctcg actttgccga
 841 gtctgggcag gtctactttg ggatcattgc cctgtgagga ggacgaacat ccaaccttcc
 901 caaacgcctc ccctgcccca atccctttat taccccctcc ttcagacacc ctcaacctct
 961 tctggctcaa aaagagaatt gggggcttag ggtcggaacc caagcttaga actttaagca
1021 acaagaccac cacttcgaaa cctgggattc aggaatgtgt ggcctgcaca gtgaagtgct
1081 ggcaaccact aagaattcaa actggggcct ccagaactca ctggggccta cagctttgat
1141 ccctgacatc tggaatctgg agaccaggga gcctttggtt ctggccagaa tgctgcagga
1201 cttgagaaga cctcacctag aaattgacac aagtggacct taggccttcc tctctccaga
1261 tgtttccaga cttccttgag acacggagcc cagccctccc catggagcca gctccctcta
1321 tttatgtttg cacttgtgat tatttattat ttatttatta tttatttatt tacagatgaa
1381 tgtatttatt tgggagaccg gggtatcctg ggggacccaa tgtaggagct gccttggctc
1441 agacatgttt tccgtgaaaa cggagctgaa caataggctg ttcccatgta gccccctggc
1501 ctctgtgcct tcttttgatt atgtttttta aaatatttat ctgattaagt tgtctaaaca
1561 atgctgattt ggtgaccaac tgtcactcat tgctgagcct ctgctcccca ggggagttgt
1621 gtctgtaatc gccctactat tcagtggcga gaaataaagt ttgcttagaa aagaaaaaaa
1681 aaaaaa
```

An exemplary human urokinase (urinary plasminogen activator or uPa) amino acid sequence is set forth below (SEQ ID NO: 103; GenBank Accession No: P00749, Version 2, incorporated herein by reference):

```
  1 mrallarlll cvlvvsdskg snelhqvpsn cdclnggtcv snkyfsnihw cncpkkfggq
 61 hceidksktc yegnghfyrg kastdtmgrp clpwnsatvl qqtyhahrsd alqlglgkhn
121 ycrnpdnrrr pwcyvqvglk plvqecmvhd cadgkkpssp peelkfqcgq ktlrprfkii
181 ggefttienq pwfaaiyrrh rggsvtyvcg gslispcwvi sathcfidyp kkedyivylg
241 rsrlnsntqg emkfevenli lhkdysadtl ahhndiallk irskegrcaq psrtiqticl
301 psmyndpqfg tsceitgfgk enstdylype qlkmtvvkli shrecqqphy ygsevttkml
361 caadpqwktd scqgdsggpl vcslqgrmtl tgivswgrgc alkdkpgvyt rvshflpwir
421 shtkeengla l
```

An exemplary human *uPa* nucleic acid sequence is set forth below (SEQ ID NO: 104; GenBank Accession No: NM_002658, Version 4, incorporated herein by reference):

```
   1 ctgatataga gcaggcgccg cgggtcgcag cacagtgcgg agaccgcagc cccggagccc
  61 gggccagggt ccacctgtcc ccgcagcgcc ggctcgcgcc ctcctgccgc agccaccgag
 121 ccgccgtcta gcgccccgac ctcgccacca tgagagccct gctggcgcgc ctgcttctct
 181 gcgtcctggt cgtgagcgac tccaaaggca gcaatgaact tcatcaagtt ccatcgaact
 241 gtgactgtct aaatggagga acatgtgtgt ccaacaagta cttctccaac attcactggt
 301 gcaactgccc aaagaaattc ggagggcagc actgtgaaat agataagtca aaaacctgct
 361 atgaggggaa tggtcacttt taccgaggaa aggccagcac tgacaccatg ggccggccct
 421 gcctgccctg gaactctgcc actgtccttc agcaaacgta ccatgcccac agatctgatg
 481 ctcttcagct gggcctgggg aaacataatt actgcaggaa cccagacaac cggaggcgac
 541 cctggtgcta tgtgcaggtg ggcctaaagc cgcttgtcca agagtgcatg gtgcatgact
 601 gcgcagatgg aaaaaagccc tcctctcctc cagaagaatt aaaatttcag tgtggccaaa
 661 agactctgag gccccgcttt aagattattg ggggagaatt caccaccatc gagaaccagc
 721 cctggtttgc ggccatctac aggaggcacc ggggggctc tgtcacctac gtgtgtggag
 781 gcagcctcat cagcccttgc tgggtgatca gcgccacaca ctgcttcatt gattacccaa
 841 agaaggagga ctacatcgtc tacctgggtc gctcaaggct taactccaac acgcaagggg
 901 agatgaagtt tgaggtggaa aacctcatcc tacacaagga ctacagcgct gacacgcttg
 961 ctcaccacaa cgacattgcc ttgctgaaga tccgttccaa ggagggcagg tgtgcgcagc
1021 catcccggac tatacagacc atctgcctgc cctcgatgta taacgatccc cagtttggca
1081 caagctgtga gatcactggc tttggaaaag agaattctac cgactatctc tatccggagc
1141 agctgaaaat gactgttgtg aagctgattt cccaccggga gtgtcagcag ccccactact
1201 acggctctga agtcaccacc aaaatgctgt gtgctgctga cccacagtgg aaaacagatt
1261 cctgccaggg agactcaggg ggacccctcg tctgttccct ccaaggccgc atgactttga
1321 ctggaattgt gagctggggc cgtggatgtg ccctgaagga caagccaggc gtctacacga
1381 gagtctcaca cttcttaccc tggatccgca gtcacaccaa ggaagagaat ggcctggccc
1441 tctgagggtc cccagggagg aaacgggcac cacccgcttt cttgctggtt gtcatttttg
1501 cagtagagtc atctccatca gctgtaagaa gagactggga agataggctc tgcacagatg
1561 gatttgcctg tgccacccac cagggcgaac gacaatagct ttaccctcag gcataggcct
1621 gggtgctggc tgcccagacc cctctggcca ggatggaggg gtggtcctga ctcaacatgt
1681 tactgaccag caacttgtct ttttctggac tgaagcctgc aggagttaaa aagggcaggg
1741 catctcctgt gcatgggtga agggagagcc agctcccccg acggtgggca tttgtgaggc
1801 ccatggttga gaaatgaata atttcccaat taggaagtgt aacagctgag gtctcttgag
1861 ggagcttagc caatgtggga gcagcggttt ggggagcaga gacactaacg acttcagggc
1921 agggctctga tattccatga atgtatcagg aaatatatat gtgtgtgtat gtttgcacac
1981 ttgtgtgtgg gctgtgagtg taagtgtgag taagagctgg tgtctgattg ttaagtctaa
2041 atatttcctt aaactgtgtg gactgtgatg ccacacagag tggtctttct ggagaggtta
2101 taggtcactc ctggggcctc ttgggtcccc cacgtgacag tgcctgggaa tgtattattc
```

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2161 tgcagcatga cctgtgacca gcactgtctc agtttcactt tcacatagat gtccctttct
2221 tggccagtta tcccttcctt ttagcctagt tcatccaatc ctcactgggt ggggtgagga
2281 ccactcctgt acactgaata tttatatttc actattttta tttatatttt tgtaatttta
2341 aataaaagtg atcaataaaa tgtgattttt ctgatgacaa aaaaaaaaaa aaaaaaaa
```

An exemplary human vascular endothelial growth factor (VEGF) amino acid sequence is set forth below (SEQ ID NO: 105; GenBank Accession No: AAA35789, Version 1, incorporated herein by reference):

```
  1 mnfllswvhw slalllylhh akwsqaapma egggqnhhev vkfmdvyqrs ychpietlvd
 61 ifqeypdeie yifkpscvpl mrcggccnde glecvptees nitmqimrik phqgqhigem
121 sflqhnkcec rpkkdrarqe npcgpcserr khlfvqdpqt ckcsckntds rckarqleln
181 ertcrcdkpr r
```

An exemplary human *VEGF* nucleic acid sequence is set forth below (SEQ ID NO: 106; GenBank Accession No: AY047581, Version 1, incorporated herein by reference):

```
  1 tcgggcctcc gaaaccatga actttctgct gtcttgggtg cattggagcc ttgccttgct
 61 gctctacctc caccatgcca agtggtccca ggctgcaccc atggcagaag gaggggggca
121 gaatcatcac gaagtggtga agttcatgga tgtctatcag cgcagctact gccatccaat
181 cgagaccctg gtggacatct tccaggagta ccctgatgag atcgagtaca tcttcaagcc
241 atcctgtgtg cccctgatgc gatgcggggg ctgctgcaat gacgagggcc tggagtgtgt
301 gcccactgag gagtccaaca tcaccatgca gattatgcgg atcaaacctc accaaggcca
361 gcacatagga gagatgagct tcctacagca caacaaatgt gaatgcagac caaagaaaga
421 tagagcaaga caagaaaatc cctgtgggcc ttgctcagag cggagaaagc atttgtttgt
481 acaagatccg cagacgtgta aatgttcctg caaaaacaca gactcgcgtt gcaaggcgag
541 gcagcttgag ttaaacgaac gtacttgcag atgtgacaag ccgaggcggt gagccgggca
601 ggaggaagga gcctccctca gggtttcggg aaccagatct
```

An exemplary human vascular endothelial growth factor A (VEGFA) amino acid sequence is set forth below (SEQ ID NO: 107; GenBank Accession No: P15692, Version 2, incorporated herein by reference):

```
  1 mnfllswvhw slalllylhh akwsqaapma egggqnhhev vkfmdvyqrs ychpietlvd
 61 ifqeypdeie yifkpscvpl mrcggccnde glecvptees nitmqimrik phqgqhigem
121 sflqhnkcec rpkkdrarqe kksvrgkgkg qkrkrkksry kswsvyvgar cclmpwslpg
181 phpcgpcser rkhlfvqdpq tckcsckntd srckarqlel nertcrcdkp rr
```

An exemplary human *VEGFA* nucleic acid sequence is set forth below (SEQ ID NO: 108; GenBank Accession No: NM_001317010, Version 1, incorporated herein by reference):

```
  1 tcgcggaggc ttggggcagc cgggtagctc ggaggtcgtg gcgctggggg ctagcaccag
 61 cgctctgtcg ggaggcgcag cggttaggtg gaccggtcag cggactcacc ggccagggcg
121 ctcggtgctg gaatttgata ttcattgatc cgggttttat ccctcttctt ttttcttaaa
181 catttttttt taaaactgta ttgtttctcg ttttaattta tttttgcttg ccattcccca
241 cttgaatcgg gccgacggct tggggagatt gctctacttc cccaaatcac tgtggatttt
301 ggaaaccagc agaaagagga aagaggtagc aagagctcca gagagaagtc gaggaagaga
361 gagacggggt cagagagagc gcgcgggcgt gcgagcagcg aaagcgacag gggcaaagtg
```

```
 421 agtgacctgc ttttgggggt gaccgccgga gcgcggcgtg agccctcccc cttgggatcc
 481 cgcagctgac cagtcgcgct gacggacaga cagacagaca ccgcccccag ccccagctac
 541 cacctcctcc ccggccggcg gcggacagtg gacgcggcgg cgagccgcgg gcaggggccg
 601 gagcccgcgc ccggaggcgg ggtggagggg gtcggggctc gcggcgtcgc actgaaactt
 661 ttcgtccaac ttctgggctg ttctcgcttc ggaggagccg tggtccgcgc gggggaagcc
 721 gagccgagcg gagccgcgag aagtgctagc tcgggccggg aggagccgca gccggaggag
 781 ggggaggagg aagaagagaa ggaagaggag agggggccgc agtggcgact cggcgctcgg
 841 aagccgggct catggacggg tgaggcggcg gtgtgcgcag acagtgctcc agccgcgcgc
 901 gctccccagg ccctggcccg ggcctcgggc cggggaggaa gagtagctcg ccgaggcgcc
 961 gaggagagcg ggccgcccca cagcccgagc cggagaggga gcgcgagccg cgccggcccc
1021 ggtcgggcct ccgaaaccat gaactttctg ctgtcttggg tgcattggag ccttgccttg
1081 ctgctctacc tccaccatgc caagtggtcc caggctgcac ccatggcaga aggaggaggg
1141 cagaatcatc acgaagtggt gaagttcatg gatgtctatc agcgcagcta ctgccatcca
1201 atcgagaccc tggtggacat cttccaggag taccctgatg agatcgagta catcttcaag
1261 ccatcctgtg tgcccctgat gcgatgcggg ggctgctgca atgacgaggg cctggagtgt
1321 gtgcccactg aggagtccaa catcaccatg cagattatgc ggatcaaacc tcaccaaggc
1381 cagcacatag gagagatgag cttcctacag cacaacaaat gtgaatgcag accaaagaaa
1441 gatagagcaa gacaagaaaa tccctgtggg ccttgctcag agcggagaaa gcatttgttt
1501 gtacaagatc cgcagacgtg taaatgttcc tgcaaaaaca cagactcgcg ttgcaaggcg
1561 aggcagcttg agttaaacga acgtacttgc agatgtgaca agccgaggcg gtgagccggg
1621 caggaggaag gagcctccct cagggtttcg ggaaccagat ctctcaccag gaaagactga
1681 tacagaacga tcgatacaga aaccacgctg ccgccaccac accatcacca tcgacagaac
1741 agtccttaat ccagaaacct gaaatgaagg aagaggagac tctgcgcaga gcactttggg
1801 tccggagggc gagactccgg cggaagcatt cccgggcggg tgacccagca cggtccctct
1861 tggaattgga ttcgccattt tatttttctt gctgctaaat caccgagccc ggaagattag
1921 agagttttat ttctgggatt cctgtagaca cacccaccca catacataca tttatatata
1981 tatatattat atatatataa aaataaatat ctctatttta tatatataaa atatatatat
2041 tctttttta aattaacagt gctaatgtta ttggtgtctt cactggatgt atttgactgc
2101 tgtggacttg agttgggagg ggaatgttcc cactcagatc ctgacaggga agaggaggag
2161 atgagagact ctggcatgat ctttttttg tcccacttgg tggggccagg gtcctctccc
2221 ctgcccagga atgtgcaagg ccagggcatg ggggcaaata tgacccagtt ttgggaacac
2281 cgacaaaccc agccctggcg ctgagcctct ctaccccagg tcagacggac agaaagacag
2341 atcacaggta cagggatgag gacaccggct ctgaccagga gtttggggag cttcaggaca
2401 ttgctgtgct ttggggattc cctccacatg ctgcacgcgc atctcgcccc caggggcact
2461 gcctggaaga ttcaggagcc tgggcggcct tcgcttactc tcacctgctt ctgagttgcc
2521 caggagacca ctggcagatg tcccggcgaa gagaagagac acattgttgg aagaagcagc
2581 ccatgacagc tccccttcct gggactcgcc ctcatcctct tcctgctccc cttcctgggg
2641 tgcagcctaa aaggacctat gtcctcacac cattgaaacc actagttctg tccccccagg
2701 agacctggtt gtgtgtgtgt gagtggttga ccttcctcca tcccctggtc cttcccttcc
2761 cttcccgagg cacagagaga cagggcagga tccacgtgcc cattgtggag gcagagaaaa
2821 gagaaagtgt tttatatacg gtacttattt aatatccctt tttaattaga aattaaaaca
2881 gttaatttaa ttaaagagta gggttttttt tcagtattct tggttaatat ttaatttcaa
2941 ctatttatga gatgtatctt ttgctctctc ttgctctctt atttgtaccg gtttttgtat
3001 ataaaattca tgtttccaat ctctctctcc ctgatcggtg acagtcacta gcttatcttg
3061 aacagatatt taattttgct aacactcagc tctgccctcc ccgatcccct ggctccccag
3121 cacacattcc tttgaaataa ggtttcaata tacatctaca tactatatat atatttggca
3181 acttgtattt gtgtgtatat atatatatat atgtttatgt atatatgtga ttctgataaa
3241 atagacattg ctattctgtt ttttatatgt aaaaacaaaa caagaaaaaa tagagaattc
3301 tacatactaa atctctctcc ttttttaatt ttaatatttg ttatcattta tttattggtg
3361 ctactgttta tccgtaataa ttgtggggaa aagatattaa catcacgtct ttgtctctag
3421 tgcagttttt cgagatattc cgtagtacat atttatttt aaacaacgac aaagaaatac
3481 agatatatct taaaaaaaaa aaagcatttt gtattaaaga atttaattct gatctcaaaa
3541 aaaaaaaaaa aaaa
```

An exemplary human vascular endothelial growth factor C (VEGFC) amino acid sequence is set forth below (SEQ ID NO: 109; GenBank Accession No: P49767, Version 1, incorporated herein by reference):

```
  1 mhllgffsva csllaaallp gpreapaaaa afesgldlsd aepdageata yaskdleeql
 61 rsvssvdelm tvlypeywkm ykcqlrkggw qhnreqanln srteetikfa aahynteilk
121 sidnewrktq cmprevcidv gkefgvatnt ffkppcvsvy rcggccnseg lqcmntstsy
181 lsktlfeitv plsqgpkpvt isfanhtscr cmskldvyrq vhsiirrslp atlpqcqaan
241 ktcptnymwn nhicrclaqe dfmfssdagd dstdgfhdic gpnkeldeet cqcvcraglr
301 pascgphkel drnscqcvck nklfpsqcga nrefdentcq cvckrtcprn qplnpgkcac
361 ectespqkcl lkgkkfhhqt cscyrrpctn rqkacepgfs yseevcrcvp sywkrpqms
```

An exemplary human *VEGFC* nucleic acid sequence is set forth below (SEQ ID NO: 110; GenBank Accession No: NM_005429, Version 4, incorporated herein by reference):

```
   1 acttcgggga aggggaggga ggagggggac gagggctctg gcgggtttgg aggggctgaa
  61 catcgcgggg tgttctggtg tcccccgccc cgcctctcca aaaagctaca ccgacgcgga
 121 ccgcggcggc gtcctccctc gccctcgctt cacctcgcgg gctccgaatg cggggagctc
 181 ggatgtccgg tttcctgtga ggcttttacc tgacacccgc cgcctttccc cggcactggc
 241 tgggagggcg ccctgcaaag ttgggaacgc ggagccccgg acccgctccc gccgcctccg
 301 gctcgcccag ggggggtcgc cgggaggagc ccgggggaga gggaccagga ggggcccgcg
 361 gcctcgcagg ggcgcccgcg cccccacccc tgcccccgcc agcggaccgg tcccccaccc
 421 ccggtccttc caccatgcac ttgctgggct tcttctctgt ggcgtgttct ctgctcgccg
 481 ctgcgctgct cccgggtcct cgcgaggcgc ccgccgccgc cgccgccttc gagtccggac
 541 tcgacctctc ggacgcggag cccgacgcgg gcgaggccac ggcttatgca agcaaagatc
 601 tggaggagca gttacggtct gtgtccagtg tagatgaact catgactgta ctctacccag
 661 aatattggaa aatgtacaag tgtcagctaa ggaaaggagg ctggcaacat aacagagaac
 721 aggccaacct caactcaagg acagaagaga ctataaaatt tgctgcagca cattataata
 781 cagagatctt gaaaagtatt gataatgagt ggagaaagac tcaatgcatg ccacgggagg
 841 tgtgtataga tgtggggaag gagtttggag tcgcgacaaa caccttcttt aaacctccat
 901 gtgtgtccgt ctacagatgt gggggttgct gcaatagtga ggggctgcag tgcatgaaca
 961 ccagcacgag ctacctcagc aagacgttat ttgaaattac agtgcctctc tctcaaggcc
1021 ccaaaccagt aacaatcagt tttgccaatc acacttcctg ccgatgcatg tctaaactgg
1081 atgtttacag acaagttcat tccattatta gacgttccct gccagcaaca ctaccacagt
1141 gtcaggcagc gaacaagacc tgccccacca attacatgtg gaataatcac atctgcagat
1201 gcctggctca ggaagatttt atgttttcct cggatgctgg agatgactca acagatggat
1261 tccatgacat ctgtggacca aacaaggagc tggatgaaga gacctgtcag tgtgtctgca
1321 gagcggggct tcggcctgcc agctgtggac cccacaaaga actagacaga aactcatgcc
1381 agtgtgtctg taaaaacaaa ctcttcccca gccaatgtgg ggccaaccga gaatttgatg
1441 aaaacacatg ccagtgtgta tgtaaaagaa cctgccccag aaatcaaccc ctaaatcctg
1501 gaaaatgtgc ctgtgaatgt acagaaagtc cacagaaatg cttgttaaaa ggaaagaagt
1561 tccaccacca aacatgcagc tgttacagac ggccatgtac gaaccgccag aaggcttgtg
1621 agccaggatt ttcatatagt gaagaagtgt gtcgttgtgt cccttcatat tggaaaagac
1681 cacaaatgag ctaagattgt actgttttcc agttcatcga ttttctatta tggaaaactg
1741 tgttgccaca gtagaactgt ctgtgaacag agagaccctt gtgggtccat gctaacaaag
1801 acaaaagtct gtctttcctg aaccatgtgg ataactttac agaaatggac tggagctcat
1861 ctgcaaaagg cctcttgtaa agactggttt tctgccaatg accaaacagc caagattttc
1921 ctcttgtgat ttctttaaaa gaatgactat ataatttatt tccactaaaa atattgtttc
1981 tgcattcatt tttatagcaa caacaattgg taaaactcac tgtgatcaat atttttatat
2041 catgcaaaat atgtttaaaa taaaatgaaa attgtattat aagctgaaaa aaaaaaaaaa
2101 aaa
```

An exemplary human vascular endothelial growth factor D (VEGFD) amino acid sequence is set forth below (SEQ ID NO: 111; GenBank Accession No: NP_004460, Version 1, incorporated herein by reference):

```
  1 myrewvvvnv fmmlyvqlvq gssnehgpvk rssqstlers eqqiraassl eellrithse
 61 dwklwrcrlr lksftsmdsr sashrstrfa atfydietlk videewqrtq cspretcvev
121 aselgkstnt ffkppcvnvf rcggccnees licmntstsy iskqlfeisv pltsvpelvp
181 vkvanhtgck clptaprhpy siirrsiqip eedrcshskk lcpidmlwds nkckcvlqee
241 nplagtedhs hlqepalcgp hmmfdedrce cvcktpcpkd liqhpkncsc feckesletc
301 cqkhklfhpd tcscedrcpf htrpcasgkt acakhcrfpk ekraaqgphs rknp
```

An exemplary human *VEGFD* nucleic acid sequence is set forth below (SEQ ID NO: 112; GenBank Accession No: NM_004469, Version 4, incorporated herein by reference):

```
   1 aagacacatg cttctgcaag cttccatgaa ggttgtgcaa aaaagtttca atccagagtt
  61 gggttccagc tttctgtagc tgtaagcatt ggtggccaca ccacctcctt acaaagcaac
 121 tagaacctgc ggcatacatt ggagagattt ttttaatttt ctggacatga agtaaattta
 181 gagtgctttc taatttcagg tagaagacat gtccaccttc tgattatttt tggagaacat
 241 tttgattttt ttcatctctc tctccccacc cctaagattg tgcaaaaaaa gcgtaccttg
 301 cctaattgaa ataatttcat tggattttga tcagaactga ttatttggtt ttctgtgtga
 361 agttttgagg tttcaaactt tccttctgga gaatgccttt tgaaacaatt ttctctagct
 421 gcctgatgtc aactgcttag taatcagtgg atattgaaat attcaaaatg tacagagagt
 481 gggtagtggt gaatgttttc atgatgttgt acgtccagct ggtgcagggc tccagtaatg
 541 aacatggacc agtgaagcga tcatctcagt ccacattgga acgatctgaa cagcagatca
 601 gggctgcttc tagtttggag gaactacttc gaattactca ctctgaggac tggaagctgt
 661 ggagatgcag gctgaggctc aaaagtttta ccagtatgga ctctcgctca gcatcccatc
 721 ggtccactag gtttgcggca actttctatg acattgaaac actaaaagtt atagatgaag
 781 aatggcaaag aactcagtgc agccctagag aaacgtgcgt ggaggtggcc agtgagctgg
 841 ggaagagtac caacacattc ttcaagcccc cttgtgtgaa cgtgttccga tgtggtggct
 901 gttgcaatga agagagcctt atctgtatga acaccagcac ctcgtacatt tccaaacagc
 961 tctttgagat atcagtgcct ttgacatcag tacctgaatt agtgcctgtt aaagttgcca
1021 atcatacagg ttgtaagtgc ttgccaacag ccccccgcca tccatactca attatcagaa
1081 gatccatcca gatccctgaa gaagatcgct gttcccattc caagaaactc tgtcctattg
1141 acatgctatg ggatagcaac aaatgtaaat gtgttttgca ggaggaaaat ccacttgctg
1201 gaacagaaga ccactctcat ctccaggaac cagctctctg tgggccacac atgatgtttg
1261 acgaagatcg ttgcgagtgt gtctgtaaaa caccatgtcc caaagatcta atccagcacc
1321 ccaaaaactg cagttgcttt gagtgcaaag aaagtctgga gacctgctgc cagaagcaca
1381 agctatttca cccagacacc tgcagctgtg aggacagatg ccccttttcat accagaccat
1441 gtgcaagtgg caaaacagca tgtgcaaagc attgccgctt tccaaaggag aaaagggctg
1501 cccaggggcc ccacagccga aagaatcctt gattcagcgt tccaagttcc ccatccctgt
1561 catttttaac agcatgctgc tttgccaagt tgctgtcact gtttttttcc caggtgttaa
1621 aaaaaaaatc cattttacac agcaccacag tgaatccaga ccaaccttcc attcacacca
1681 gctaaggagt ccctggttca ttgatggatg tcttctagct gcagatgcct ctgcgcacca
1741 aggaatggag aggaggggac ccatgtaatc cttttgttta gttttgtttt tgttttttgg
1801 tgaatgagaa aggtgtgctg gtcatggaat ggcaggtgtc atatgactga ttactcagag
1861 cagatgagga aaactgtagt ctctgagtcc tttgctaatc gcaactcttg tgaattattc
1921 tgattctttt ttatgcagaa tttgattcgt atgatcagta ctgactttct gattactgtc
1981 cagcttatag tcttccagtt taatgaacta ccatctgatg tttcatattt aagtgtattt
2041 aaagaaaata aacaccatta ttcaagccat ataaaaaaaa aaaa
```

An exemplary human chromogranin A (CGA) amino acid sequence is set forth below (SEQ ID NO: 113; GenBank Accession No: P10645, Version 7, incorporated herein by reference):

```
   1 mrsaavlall lcagqvtalp vnspmnkgdt evmkcivevi sdtlskpspm pvsqecfetl
  61 rgderilsil rhqnllkelq dlalqgaker ahqqkkhsgf edelsevlen qssqaelkea
 121 veepsskdvm ekredskeae ksgeatdgar pqalpepmqe skaegnnqap geeeeeeeea
 181 tnthppaslp sqkypgpqae gdseglsqgl vdrekglsae pgwqakreee eeeeeeaeag
 241 eeavpeeegp tvvlnphpsl gykeirkges rsealavdga gkpgaeeaqd pegkgeqehs
 301 qqkeeeeema vvpqglfrgg ksgeleqeee rlskewedsk rwskmdqlak eltaekrleg
 361 qeeeednrds smklsfrara ygfrgpgpql rrgwrpssre dsleaglplq vrgypeekke
 421 eegsanrrpe dqeleslsai eaelekvahq lqalrrg
```

An exemplary human *CGA* nucleic acid sequence is set forth below (SEQ ID NO: 114; GenBank Accession No: NM_001275, Version 3, incorporated herein by reference):

```
   1 gtcatttccg gggtcggggt atataagcgg ggcgcgaggg cgctgctgct gccaccgctc
  61 ctgccactgc agtgctcgag ccccgtgcag gggagcttgc gggaggatcg accgacagac
 121 ggacgcacgc cgaggcactg cgcccccagc cccgcgccgg tgccaccgca gcccgacccc
 181 ggccgccagt ccagccgccc ctcgcccggt gcctaggtgc ccggccccac accgccagct
 241 gctcggcgcc cgggtccgcc atgcgctccg ccgctgtcct ggctcttctg ctctgcgccg
 301 ggcaagtcac tgcgctccct gtgaacagcc ctatgaataa aggggatacc gaggtgatga
 361 aatgcatcgt tgaggtcatc tccgacacac tttccaagcc cagccccatg cctgtcagcc
 421 aggaatgttt tgagacactc cgaggagatg aacggatcct ttccattctg agacatcaga
 481 atttactgaa ggagctccaa gacctcgctc tccaaggcgc caaggagagg gcacatcagc
 541 agaagaaaca cagcggtttt gaagatgaac tctcagaggt tcttgagaac cagagcagcc
 601 aggccgagct gaaagaggcg gtggaagagc catcatccaa ggatgttatg gagaaaagag
 661 aggattccaa ggaggcagag aaaagtggtg aagccacaga cggagccagg ccccaggccc
 721 tcccggagcc catgcaggag tccaaggctg aggggaacaa tcaggcccct ggggaggaag
 781 aggaggagga ggaggaggcc accaacaccc accctccagc cagcctcccc agccagaaat
 841 acccaggccc acaggccgag ggggacagtg agggcctctc tcagggtctg gtggacagag
 901 agaagggcct gagtgcagag ccagggtggc aggcaaagag agaagaggag gaggaggagg
 961 aggaggaggc tgaggctgga gaggaggctg tccccgagga agaaggcccc actgtagtgc
1021 tgaaccccca cccgagcctt ggctacaagg agatccggaa aggcgagagt cggtcggagg
1081 ctctggctgt ggatggagct gggaagcctg gggctgagga ggctcaggac cccgaaggga
1141 agggagaaca ggagcactcc cagcagaaag aggaggagga ggagatggca gtggtcccgc
1201 aaggcctctt ccggggtggg aagagcggag agctggagca ggaggaggag cggctctcca
1261 aggagtggga ggactccaaa cgctggagca agatggacca gctggccaag gagctgacgg
1321 ctgagaagcg gctggagggg caggaggagg aggaggacaa ccgggacagt tccatgaagc
1381 tctccttccg ggcccgggcc tacggcttca ggggccctgg gccgcagctg cgacgaggct
1441 ggaggccatc ctcccgggag gacagccttg aggcgggcct gcccctccag gtccgaggct
1501 accccgagga gaagaaagag gaggagggca gcgcaaaccg cagaccagag gaccaggagc
1561 tggagagcct gtcggccatt gaagcagagc tggagaaagt ggcccaccag ctgcaggcac
1621 tacggcgggg ctgagacacc ggctggcagg gctggcccca gggcaccctg tggccctggc
1681 tctgctgtcc ccttggcagg tcctggccag atggcccgga tgctgcttcc ggtagggagg
1741 cagcctccag cctgcccaag cccaggccac cctatcgccc cctacgcgcc ttgtctccta
1801 ctcctgactc ctacctgccc tggaacatcc tttgcagggc agccccacaa ctttaaacat
1861 tgacgattcc ttctctgaac acaggcagct ttctagaagt ttcccttcct ccatcctatc
1921 cactgggcac aactgcaata acttctgacc ttttggtgaa agctgagaac tcctgactgt
1981 aacatattct gtatgaactt tatctaaaga aaaataaatc tgttctgggc tctttcctct
2041 gaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaa
```

An exemplary human hematopoietic progenitor cell antigen (CD34) amino acid sequence is set forth below (SEQ ID NO: 115; GenBank Accession No: NP_001020280, Version 1, incorporated herein by reference):

```
   1 mlvrrgarag prmprgwtal cllsllpsgf msldnngtat pelptqgtfs nvstnvsyqe
  61 tttpstlgst slhpvsqhgn eattnitett vkftstsvit svygntnssv qsqtsvistv
 121 fttpanvstp ettlkpslsp gnvsdlstts tslatsptkp ytssspilsd ikaeikcsgi
 181 revkltqgic leqnktssca efkkdrgegl arvlcgeeqa dadagaqvcs lllaqsevrp
 241 qclllvlanr teissklqlm kkhqsdlkkl gildfteqdv ashqsysqkt lialvtsgal
 301 lavlgitgyf lmnrrswspt gerlgedpyy tengggqgys sgpgtspeaq gkasvnrgaq
 361 engtgqatsr nghsarqhvv adtel
```

An exemplary human *CD34* nucleic acid sequence is set forth below (SEQ ID NO: 116; GenBank Accession No: M81104, Version 1, incorporated herein by reference):

```
   1 ccttttttgg cctcgacggc ggcaacccag cctccctcct aacgccctcc gcctttggga
  61 ccaaccaggg gagctcaagt tagtagcagc caaggagagg cgctgccttg ccaagactaa
 121 aaagggaggg gagaagagag gaaaaaagca agaatccccc acccctctcc cgggcggagg
 181 gggcgggaag agcgcgtcct ggccaagccg agtagtgtct tccactcggt gcgtctctct
 241 aggagccgcg cgggaaggat gctggtccgc aggggcgcgc gcgagggccc aggatgccgc
 301 ggggctggac cgcgctttgc ttgctgagtt tgctgccttc tgggttcatg agtcttgaca
 361 acaacggtac tgctacccca gagttaccta cccagggaac attttcaaat gtttctacaa
 421 atgtatccta ccaagaaact acaacaccta gtacccttgg aagtaccagc ctgcaccctg
 481 tgtctcaaca tggcaatgag gccacaacaa acatcacaga aacgacagtc aaattcacat
 541 ctacctctgt gataacctca gtttatggaa acacaaactc ttctgtccag tcacagacct
 601 ctgtaatcag cacagtgttc accaccccag ccaacgtttc aactccagag acaaccttga
 661 agcctagcct gtcacctgga aatgtttcag acctttcaac cactagcact agccttgcaa
 721 catctcccac taaaccctat acatcatctt ctcctatcct aagtgacatc aaggcagaaa
 781 tcaaatgttc aggcatcaga gaagtgaaat tgactcaggg catctgcctg gagcaaaata
 841 agacctccag ctgtgcggag tttaagaagg acaggggaga gggcctggcc cgagtgctgt
 901 gtggggagga gcaggctgat gctgatgctg gggcccaggt atgctccctg ctccttgccc
 961 agtctgaggt gaggcctcag tgtctactgc tggtcttggc caacagaaca gaaatttcca
1021 gcaaactcca acttatgaaa aagcaccaat ctgacctgaa aaagctgggg atcctagatt
1081 tcactgagca agatgttgca agccaccaga gctattccca aaagaccctg attgcactgg
1141 tcacctcggg agccctgctg gctgtcttgg gcatcactgg ctatttcctg atgaatcgcc
1201 gcagctggag ccccacagga gaaaggctgg gcgaagaccc ttattacacg gaaaacggtg
1261 gaggccaggg ctatagctca ggacctggga cctcccctga ggctcaggga aaggccagtg
1321 tgaaccgagg ggctcagaaa aacgggaccg gccaggccac ctccagaaac ggccattcag
1381 caagacaaca cgtggtggct gataccgaat tgtgactcgg ctaggtgggg caaggctggg
1441 cagtgtccga gagagcaccc ctctctgcat ctgaccacgt gctaccccca tgctggaggt
1501 gacatctctt acgcccaacc cttccccact gcacacacct cagaggctgt tcttggggcc
1561 ctacaccttg aggagggggc aggtaaactc ctgtccttta cacattcggc tccctggagc
1621 cagactctgg tcttctttgg gtaaacgtgt gacgggggaa agccaaggtc tggagaagct
1681 cccaggaaca atcgatggcc ttgcagcact cacacaggac ccccttcccc tacccccctcc
1741 tctctgccgc aatacaggaa cccccagggg aaagatgagc ttttctaggc tacaattttc
1801 tcccaggaag ctttgatttt taccgtttct tccctgtatt ttctttctct actttgagga
1861 aaccaaagta acctttttgca cctgctctct tgtaatgata tagccagaaa aacgtgttgc
1921 cttgaaccac ttccctcatc tctcctccaa gacactgtgg acttggtcac cagctcctcc
1981 cttgttctct aagttccact gagctccatg tgccccctct accatttgca gagtcctgca
2041 cagttttctg gctggagcct agaacaggcc tcccaagttt taggacaaac agctcagttc
2101 tagtctctct ggggccacac agaaactctt tttgggctcc tttttctccc tctggatcaa
2161 agtaggcagg accatgggac caggtcttgg agctgagcct ctcacctgta ctcttccgaa
2221 aaatcctctt cctctgaggc tggatcctag ccttatcctc tgatctccat ggcttcctcc
```

```
2281 tccctcctgc cgactcctgg gttgagctgt tgcctcagtc ccccaacaga tgcttttctg
2341 tctctgcctc cctcaccctg agccccttcc ttgctctgca cccccatatg gtcatagccc
2401 agatcagctc ctaaccctta tcaccagctg cctcttctgt gggtgaccca ggtccttgtt
2461 tgctgttgat ttctttccag aggggttgag cagggatcct ggtttcaatg acggttggaa
2521 atagaaattt ccagagaaga gagtattggg tagatatttt ttctgaatac aaagtgatgt
2581 gtttaaatac tgcaattaaa gtgatactga aacac
```

An exemplary human mucin 16 (MUC16) amino acid sequence is set forth below (SEQ ID NO: 117; GenBank Accession No: Q8WXI7, Version 3, incorporated herein by reference):

```
   1 mlkpsglpgs ssptrslmtg srstkatpem dsgltgatls pktstgaivv tehtlpftsp
  61 dktlasptss vvgrttqslg vmssalpest srgmthseqr tspslspqvn gtpsrnypat
 121 smvsglsspr trtsstegnf tkeastytlt vettsgpvte kytvptetst tegdstetpw
 181 dtryipvkit spmktfadst askenapvsm tpaettvtds htpgrtnpsf gtlyssfldl
 241 spkgtpnsrg etslelilst tgypfsspep gsaghsrist saplsssasv ldnkisetsi
 301 fsgqsltspl spgvpearas tmpnsaipfs mtlsnaetsa ervrstissl gtpsistkqt
 361 aetiltfhaf aetmdipsth iaktlasewl gspgtlggts tsaltttsps ttlvseetnt
 421 hhstsgkete gtlntsmtpl etsapgeese mtatlvptlg fttldskirs psqvssshpt
 481 relrttgsts grqssstaah gssdilratt sstskasswt sestaqqfse pqhtqwvets
 541 psmkterppa stsvaapitt svpsvvsgft tlktsstkgi wleetsadtl igestagptt
 601 hqfavptgis mtggsstrgs qgtthlltra tassetsadl tlatngvpvs vspavsktaa
 661 gssppggtkp sytmvssvip etsslqssaf regtslgltp lntrhpfssp epdsaghtki
 721 stsipllssa svledkvsat stfshhkats sittgtpeis tktkpssavl ssmtlsnaat
 781 spervrnats plthpspsge etagsvltls tsaettdspn ihptgtltse ssespstlsl
 841 psvsgvkttf ssstpsthlf tsgeeteets npsvsqpets vsrvrttlas tsvptpvfpt
 901 mdtwptrsaq fssshlvsel ratsstsvtn stgsalpkis hltgtatmsq tnrdtfndsa
 961 apqsttwpet sprfktglps atttvstsat slsatvmvsk ftspatssme atsirepstt
1021 ilttettngp gsmavastni pigkgyiteg rldtshlpig ttassetsmd ftmakesvsm
1081 svspsqsmda agsstpgrts qfvdtfsddv yhltsreiti prdgtssalt pqmtathpps
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An exemplary human *MUC16* nucleic acid sequence is set forth below (SEQ ID NO: 118; GenBank Accession No: NM_024690, Version 2, incorporated herein by reference):

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40981 gtcaatggtt tcacacagcg gagctctgtg cccaccacta gcattcctgg gacccccaca
41041 gtggacctgg gaacatctgg gactccagtt tctaaacctg gtccctcggc tgccagccct
41101 ctcctggtgc tattcactct caacttcacc atcaccaacc tgcggtatga ggagaacatg
41161 cagcaccctg gctccaggaa gttcaacacc acggagaggg tccttcaggg cctgctcagg
41221 tccctgttca agagcaccag tgttggccct ctgtactctg gctgcagact gactttgctc
41281 aggcctgaaa aggatgggac agccactgga gtggatgcca tctgcaccca ccaccctgac
41341 cccaaaagcc ctaggctgga cagagagcag ctgtattggg agctgagcca gctgacccac
41401 aatatcactg agctgggccc ctatgccctg gacaacgaca gcctctttgt caatggtttc
41461 actcatcgga gctctgtgtc caccaccagc actcctggga cccccacagt gtatctggga
41521 gcatctaaga ctccagcctc gatatttggc ccttcagctg ccagccatct cctgatacta
41581 ttcaccctca acttcaccat cactaacctg cggtatgagg agaacatgtg gcctggctcc

```
41641 aggaagttca acactacaga gagggtcctt cagggcctgc taaggccctt gttcaagaac
41701 accagtgttg gccctctgta ctctggctgc aggctgacct tgctcaggcc agagaaagat
41761 ggggaagcca ccggagtgga tgccatctgc acccaccgcc ctgaccccac aggccctggg
41821 ctggacagag agcagctgta tttggagctg agccagctga cccacagcat cactgagctg
41881 ggcccctaca cactggacag ggacagtctc tatgtcaatg gtttcaccca tcggagctct
41941 gtacccacca ccagcaccgg ggtggtcagc gaggagccat tcacactgaa cttcaccatc
42001 aacaacctgc gctacatggc ggacatgggc caacccggct ccctcaagtt caacatcaca
42061 gacaacgtca tgcagcacct gctcagtcct ttgttccaga ggagcagcct gggtgcacgg
42121 tacacaggct gcagggtcat cgcactaagg tctgtgaaga acggtgctga gacacgggtg
42181 gacctcctct gcacctacct gcagcccctc agcggcccag gtctgcctat caagcaggtg
42241 ttccatgagc tgagccagca gacccatggc atcacccggc tgggccccta ctctctggac
42301 aaagacagcc tctaccttaa cggttacaat gaacctggtc cagatgagcc tcctacaact
42361 cccaagccag ccaccacatt cctgcctcct ctgtcagaag ccacaacagc catggggtac
42421 cacctgaaga ccctcacact caacttcacc atctccaatc tccagtattc accagatatg
42481 ggcaagggct cagctacatt caactccacc gaggggqtcc ttcagcacct gctcagaccc
42541 ttgttccaga agagcagcat gggccccttc tacttgggtt gccaactgat ctccctcagg
42601 cctgagaagg atggggcagc cactggtgtg gacaccacct gcacctacca ccctgaccct
42661 gtgggccccg ggctggacat acagcagctt tactgggagc tgagtcagct gacccatggt
42721 gtcacccaac tgggcttcta tgtcctggac agggatagcc tcttcatcaa tggctatgca
42781 ccccagaatt tatcaatccg gggcgagtac cagataaatt tccacattgt caactggaac
42841 ctcagtaatc cagaccccac atcctcagag tacatcaccc tgctgaggga catccaggac
42901 aaggtcacca cactctacaa aggcagtcaa ctacatgaca cattccgctt ctgcctggtc
42961 accaacttga cgatggactc cgtgttggtc actgtcaagg cattgttctc ctccaatttg
43021 gaccccagcc tggtggagca agtctttcta gataagaccc tgaatgcctc attccattgg
43081 ctgggctcca cctaccagtt ggtggacatc catgtgacag aaatggagtc atcagtttat
43141 caaccaacaa gcagctccag cacccagcac ttctacctga atttcaccat caccaaccta
43201 ccatattccc aggacaaagc ccagccaggc accaccaatt accagaggaa caaaaggaat
43261 attgaggatg cgctcaacca actcttccga aacagcagca tcaagagtta tttttctgac
43321 tgtcaagttt caacattcag gtctgtcccc aacaggcacc acaccggggt ggactccctg
43381 tgtaacttct cgccactggc tcggagagta gacagagttg ccatctatga ggaatttctg
43441 cggatgaccc ggaatggtac ccagctgcag aacttcaccc tggacaggag cagtgtcctt
43501 gtggatgggt attctcccaa cagaaatgag cccttaactg ggaattctga ccttcccttc
43561 tgggctgtca tcctcatcgg cttggcagga ctcctgggag tcatcacatg cctgatctgc
43621 ggtgtcctgg tgaccacccg ccggcggaag aaggaaggag aatacaacgt ccagcaacag
43681 tgcccaggct actaccagtc acacctagac ctggaggatc tgcaatgact ggaacttgcc
43741 ggtgcctggg gtgcctttcc cccagccagg gtccaaagaa gcttggctgg ggcagaaata
43801 aaccatattg gtcgga
```

An exemplary human keratin 5 (KRT5) amino acid sequence is set forth below (SEQ ID NO: 119; GenBank Accession No: P13647, Version 3, incorporated herein by reference):

```
  1 msrqssvsfr sggsrsfsta saitpsvsrt sftsvsrsgg gggggfgrvs lagacgvggy
 61 gsrslynlgg skrisistsg gsfrnrfgag agggygfggg agsgfgfggg agggfglggg
121 agfgggfggp gfpvcppggi qevtvnqsll tplnlqidps iqrvrteere qiktlnnkfa
181 sfidkvrfle qqnkvldtkw tllqeqgtkt vrqnleplfe qyinnlrrql dsivgergrl
241 dselrnmqdl vedfknkyed einkrttaen efvmlkkdvd aaymnkvele akvdalmdei
301 nfmkmffdae lsqmqthvsd tsvvlsmdnn rnldldsiia evkaqyeeia nrsrteaesw
361 yqtkyeelqq tagrhgddlr ntkheisemn rmiqrlraei dnvkkqcanl qnaiadaeqr
421 gelalkdarn klaeleealq kakqdmarll reyqelmntk laldveiaty rkllegeecr
481 lsgegvgpvn isvvtssvss gygsgsgygg glggglgggl ggglaggssg syyssssggv
541 glggglsvgg sgfsassgrg lgvgfgsggg ssssvkfvst tsssrksfks
```

An exemplary human *KRT5* nucleic acid sequence is set forth below (SEQ ID NO: 120; GenBank Accession No: NM_000424, Version 3, incorporated herein by reference):

```
   1 tcgacagctc tctcgcccag cccagttctg gaagggataa aaaggggca tcaccgttcc
  61 tgggtaacag agccaccttc tgcgtcctgc tgagctctgt tctctccagc acctcccaac
 121 ccactagtgc ctggttctct tgctccacca ggaacaagcc accatgtctc gccagtcaag
 181 tgtgtccttc cggagcgggg gcagtcgtag cttcagcacc gcctctgcca tcaccccgtc
 241 tgtctcccgc accagcttca cctccgtgtc ccggtccggg ggtggcggtg gtggtggctt
 301 cggcagggtc agccttgcgg gtgcttgtgg agtgggtggc tatggcagcc ggagcctcta
 361 caacctgggg ggctccaaga ggatatccat cagcactagt ggtggcagct tcaggaaccg
 421 gtttggtgct ggtgctggag gcggctatgg ctttggaggt ggtgccggta gtggatttgg
 481 tttcggcggt ggagctggtg gtggctttgg gctcggtggc ggagctggct ttggaggtgg
 541 cttcggtggc cctggctttc ctgtctgccc tcctggaggt atccaagagg tcactgtcaa
 601 ccagagtctc ctgactcccc tcaacctgca aatcgacccc agcatccaga gggtgaggac
 661 cgaggagcgc gagcagatca agaccctcaa caataagttt gcctccttca tcgacaaggt
 721 gcggttcctg gagcagcaga acaaggttct ggacaccaag tggaccctgc tgcaggagca
 781 gggcaccaag actgtgaggc agaacctgga gccgttgttc gagcagtaca tcaacaacct
 841 caggaggcag ctggacagca tcgtggggga acggggccgc ctggactcag agctgagaaa
 901 catgcaggac ctggtggaag acttcaagaa caagtatgag gatgaaatca acaagcgtac
 961 cactgctgag aatgagtttg tgatgctgaa gaaggatgta gatgctgcct acatgaacaa
1021 ggtggagctg gaggccaagg ttgatgcact gatggatgag attaacttca tgaagatgtt
1081 ctttgatgcg gagctgtccc agatgcagac gcatgtctct gacacctcag tggtcctctc
1141 catggacaac aaccgcaacc tggacctgga tagcatcatc gctgaggtca aggcccagta
1201 tgaggagatt gccaaccgca gccggacaga agccgagtcc tggtatcaga ccaagtatga
1261 ggagctgcag cagacagctg gccggcatgg cgatgacctc cgcaacacca agcatgagat
1321 ctctgagatg aaccggatga tccagaggct gagagccgag attgacaatg tcaagaaaca
1381 gtgcgccaat ctgcagaacg ccattgcgga tgccgagcag cgtggggagc tggccctcaa
1441 ggatgccagg aacaagctgg ccgagctgga ggaggccctg cagaaggcca agcaggacat
1501 ggcccggctg ctgcgtgagt accaggagct catgaacacc aagctggccc tggacgtgga
1561 gatcgccact taccgcaagc tgctggaggg cgaggaatgc agactcagtg gagaaggagt
1621 tggaccagtc aacatctctg ttgtcacaag cagtgtttcc tctggatatg gcagtggcag
1681 tggctatggc ggtggcctcg gtggaggtct tggcggcggc ctcggtggag gtcttgccgg
1741 aggtagcagt ggaagctact actccagcag cagtgggggt gtcggcctag gtggtgggct
1801 cagtgtgggg ggctctggct tcagtgcaag cagtggccga gggctggggg tgggctttgg
1861 cagtggcggg ggtagcagct ccagcgtcaa atttgtctcc accacctcct cctcccggaa
1921 gagcttcaag agctaagaac ctgctgcaag tcactgcctt ccaagtgcag caacccagcc
1981 catggagatt gcctcttcta ggcagttgct caagccatgt tttatccttt tctggagagt
2041 agtctagacc aagccaattg cagaaccaca ttctttggtt cccaggagag ccccattccc
2101 agcccctggt ctcccgtgcc gcagttctat attctgcttc aaatcagcct tcaggtttcc
2161 cacagcatgg cccctgctga cacgagaacc caaagttttc ccaaatctaa atcatcaaaa
2221 cagaatcccc accccaatcc caaattttgt tttggttcta actacctcca gaatgtgttc
2281 aataaaatgc ttttataata taaaaaaaaa aaaaaaaaaa
```

An exemplary human keratin 6A (KRT6A) amino acid sequence is set forth below (SEQ ID NO: 121; GenBank Accession No: P02538, Version 3, incorporated herein by reference):

```
   1 maststtirs hsssrrgfsa nsarlpgvsr sgfssvsvsr srgsgglgga cggagfgsrs
  61 lyglggskri sigggscais ggygsraggs ygfggagsgf gfgggagigf glgggaglag
 121 gfggpgfpvc ppggiqevtv nqslltplnl qidptiqrvr aeereqiktl nnkfasfidk
 181 vrfleqqnkv letkwtllqe qgtktvrqnl eplfeqyinn lrrqldsivg ergrldselr
 241 gmqdlvedfk nkyedeinkr taaenefvtl kkdvdaaymn kvelqakadt ltdeinflra
 301 lydaelsqmq thisdtsvvl smdnnrnldl dsiiaevkaq yeeiaqrsra eaeswyqtky
 361 eelqvtagrh gddlrntkqe iaeinrmiqr lrseidhvkk qcanlqaaia daeqrgemal
 421 kdaknklegl edalqkakqd larllkeyqe lmnvklaldv eiatyrklle geecrlngeg
```

```
481 vgqvnisvvq stvssgygga sgvgsglglg ggssysygsg lgvgggfsss sgraigggls
541 svgggsstik ytttssssrk sykh
```

An exemplary human *KRT6A* nucleic acid sequence is set forth below (SEQ ID NO: 122; GenBank Accession No: NM_005554, Version 3, incorporated herein by reference):

```
   1 atatttcata cctttctaga aactgggtgt gatctcactg ttggtaaagc ccagcccttc
  61 ccaacctgca agctcacctt ccaggactgg gcccagccca tgctctccat atataagctg
 121 ctgccccgag cctgattcct agtcctgctt ctcttccctc tctcctccag cctctcacac
 181 tctcctcagc tctctcatct cctggaacca tggccagcac atccaccacc atcaggagcc
 241 acagcagcag ccgccggggt ttcagtgcca actcagccag gctccctggg gtcagccgct
 301 ctggcttcag cagcgtctcc gtgtcccgct ccaggggcag tggtggcctg ggtggtgcat
 361 gtggaggagc tggctttggc agccgcagtc tgtatggcct ggggggctcc aagaggatct
 421 ccattggagg gggcagctgt gccatcagtg gcggctatgg cagcagagcc ggaggcagct
 481 atggctttgg tggcgccggg agtggatttg gtttcggtgg tggagccggc attggctttg
 541 gtctgggtgg tggagccggc cttgctggtg gctttggggg ccctggcttc cctgtgtgcc
 601 cccctggagg catccaagag gtcaccgtca accagagtct cctgactccc ctcaacctgc
 661 aaatcgatcc caccatccag cgggtgcggg ctgaggagcg tgaacagatc aagaccctca
 721 acaacaagtt tgcctccttc atcgacaagg tgcggttcct ggagcagcag aacaaggttc
 781 tggaaacaaa gtggaccctg ctgcaggagc agggcaccaa gactgtgagg cagaacctgg
 841 agccgttgtt cgagcagtac atcaacaacc tcaggaggca gctggacagc attgtcgggg
 901 aacggggccg cctggactca gagctcagag gcatgcagga cctggtggag gacttcaaga
 961 acaaatatga ggatgaaatc aacaagcgca cagcagcaga gaatgaattt gtgactctga
1021 agaaggatgt ggatgctgcc tacatgaaca aggttgaact gcaagccaag gcagacactc
1081 tcacagacga gatcaacttc ctgagagcct tgtatgatgc agagctgtcc cagatgcaga
1141 cccacatctc agacacatct gtggtgctgt ccatggacaa caaccgcaac ctggacctgg
1201 acagcatcat cgctgaggtc aaggcccaat atgaggagat tgctcagaga agccgggctg
1261 aggctgagtc ctggtaccag accaagtacg aggagctgca ggtcacagca ggcagacatg
1321 gggacgacct gcgcaacacc aagcaggaga ttgctgagat caaccgcatg atccagaggc
1381 tgagatctga gatcgaccac gtcaagaagc agtgcgccaa cctgcaggcc gccattgctg
1441 atgctgagca gcgtggggag atggccctca aggatgccaa gaacaagctg gaagggctgg
1501 aggatgccct gcagaaggcc aagcaggacc tggcccggct gctgaaggag taccaggagc
1561 tgatgaatgt caagctggcc ctggacgtgg agatcgccac ctaccgcaag ctgctggagg
1621 gtgaggagtg caggctgaat ggcgaaggcg ttggacaagt caacatctct gtggtgcagt
1681 ccaccgtctc cagtggctat ggcggtgcca gtggtgtcgg cagtggctta ggcctgggtg
1741 gaggaagcag ctactcctat ggcagtggtc ttggcgttgg aggtggcttc agttccagca
1801 gtggcagagc cattgggggt ggcctcagct ctgttggagg cggcagttcc accatcaagt
1861 acaccaccac ctcctcctcc agcaggaaga gctataagca ctaaagtgcg tctgctagct
1921 ctcggtccca cagtcctcag gcccctctct ggctgcagag ccctctcctc aggttgcctt
1981 tcctctcctg gcctccagtc tcccctgctg tcccaggtag agctgggtat ggatgcttag
2041 tgccctcact tcttctctct ctctctatac catctgagca cccattgctc accatcagat
2101 caacctctga ttttacatca tgatgtaatc accactggag cttcactgtt actaaattat
2161 taatttcttg cctccagtgt tctatctctg aggctgagca ttataagaaa atgacctctg
2221 ctccttttca ttgcagaaaa ttgccagggg cttatttcag aacaacttcc acttactttc
2281 cactggctct caaactctct aacttataag tgttgtgaac ccccacccag gcagtatcca
2341 tgaaagcaca agtgactagt cctatgatgt acaaagcctg tatctctgtg atgatttctg
2401 tgctcttcgc tgtttgcaat tgctaaataa agcagattta taatacaata
```

An exemplary human keratin 6B (KRT6B) amino acid sequence is set forth below (SEQ ID NO: 123; GenBank Accession No: NP_005546, Version 2, incorporated herein by reference):

```
   1 maststtirs hsssrrgfsa nsarlpgvsr sgfssisvsr srgsgglgga cggagfgsrs
  61 lyglggskri sigggscais ggygsraggs ygfggagsgf gfgggagigf glgggaglag
```

```
121 gfggpgfpvc ppggiqevtv nqslltplnl qidpaiqrvr aeereqiktl nnkfasfidk
181 vrfleqqnkv ldtkwtllqe qgtktvrqnl eplfeqyinn lrrqldnivg ergrldselr
241 nmqdlvedlk nkyedeinkr taaenefvtl kkdvdaaymn kvelqakadt ltdeinflra
301 lydaelsqmq thisdtsvvl smdnnrnldl dsiiaevkaq yeeiaqrsra eaeswyqtky
361 eelqitagrh gddlrntkqe iaeinrmiqr lrseidhvkk qcanlqaaia daeqrgemal
421 kdaknklegl edalqkakqd larllkeyqe lmnvklaldv eiatyrklle geecrlngeg
481 vgqvnisvvq stvssgygga sgvgsglglg ggssysygsg lgvgggfsss sgratgggls
541 svgggsstik ytttssssrk sykh
```

An exemplary human *KRT6B* nucleic acid sequence is set forth below (SEQ ID NO: 124; GenBank Accession No: NM_005555, Version 3, incorporated herein by reference):

```
   1 cgcctccagc ctctcacact ctcctaagcc ctctcatctc ctggaaccat ggccagcaca
  61 tccaccacca tcaggagcca cagcagcagc cgccggggtt tcagtgccaa ctcagccagg
 121 ctccctgggg tcagccgctc tggcttcagc agcatctccg tgtcccgctc caggggcagt
 181 ggtggcctgg gtggcgcatg tggaggagct ggctttggca gccgcagtct gtatggcctg
 241 gggggctcca agaggatctc cattggaggg ggcagctgtg ccatcagtgg cggctatggc
 301 agcagagccg gaggcagcta tggctttggt ggcgccggga gtggatttgg tttcggtggt
 361 ggagccggca ttggctttgg tctgggtggt ggagccggcc ttgctggtgg ctttgggggc
 421 cctggcttcc ctgtgtgccc ccctggaggc atccaagagg tcactgtcaa ccagagtctc
 481 ctgactcccc tcaacctgca aattgacccc gccatccagc gggtgcgggc cgaggagcgt
 541 gagcagatca agaccctcaa caacaagttt gcctccttca tcgacaaggt gcggttccta
 601 gagcagcaga acaaggttct ggacaccaag tggaccctgc tgcaggagca gggcaccaag
 661 actgtgaggc agaacctgga gccgttgttc gagcagtaca tcaacaacct caggaggcag
 721 ctggacaaca tcgtggggga acggggtcgt ctggactcgg agctgagaaa catgcaggac
 781 ctggtggagg acctcaagaa caaatatgag gatgaaatca acaagcgcac agcagcagag
 841 aatgaatttg tgactctgaa gaaggatgtg gatgctgcct acatgaacaa ggttgaactg
 901 caagccaagg cagacactct tacagatgag atcaacttcc tgagagcctt gtatgatgca
 961 gagctgtccc agatgcagac ccacatctca gacacatccg tggtgctatc catggacaac
1021 aaccgcaacc tggacctgga cagcatcatc gctgaggtca aggcccaata tgaggagatt
1081 gctcagagga gcagggctga ggctgagtcc tggtaccaga caaagtacga ggagctgcag
1141 atcacagcag gcagacatgg ggacgacctg cgcaacacca agcaggagat tgctgagatc
1201 aaccgcatga tccagaggct gagatctgag atcgaccacg tcaagaagca gtgtgccaac
1261 ctacaggccg ccattgctga tgctgagcag cgtggggaga tggccctcaa ggatgctaag
1321 aacaagctgg aagggctgga ggatgccctg cagaaggcca agcaggacct ggcccggctg
1381 ctgaaggagt accaggagct gatgaacgtc aagctggccc tggatgtgga gatcgccacc
1441 taccgcaagc tgctggaggg cgaggagtgc aggctgaatg gcgaaggcgt tggacaagtc
1501 aacatctctg tagtgcagtc caccgtctcc agtggctatg gcggtgccag cggtgtcggc
1561 agtggcttag gcctgggtgg aggaagcagc tactcctatg gcagtggtct tggcgttgga
1621 ggcggcttta gttccagcag cggcagagcc actgggggtg gcctcagctc tgttggaggc
1681 ggcagttcca ccatcaagta caccaccacc tcctcctcca gcaggaagag ctacaagcac
1741 tgaagtgctg ccgccagctc tcagtcccac agctctcagg ccccctctctg gcagcagagc
1801 cctctcctca ggttgcttgt cctcccctgg cctccagtct cccctgccct cccgggtaga
1861 gctgggatgc cctcactttt cttctcatca atacctgttc cactgagctc ctgttgctta
1921 ccatcaagtc aacagttatc agcactcaga catgcgaatg tccttttag ttcccgtatt
1981 attacaggta tctgagtctg ccataattct gagaagaaaa tgacctatat ccccataaga
2041 actgaaactc agtctaggtc cagctgcaga tgaggagtcc tctctttaat tgctaaccat
2101 cctgcccatt atagctacac tcaggagttc tcatctgaca agtcagttgt cctgatcttc
2161 tcttgcagtg tccctgaatg gcaagtgatg taccttctga tgcagtctgc attcctgcac
2221 tgctttctct gctctctttg ccttcttttg ttctgttgaa taaagcatat tgagaatgtg
2281 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa a
```

An exemplary human keratin 17 (KRT17) amino acid sequence is set forth below (SEQ ID NO: 125; GenBank Accession No: Q04695, Version 2, incorporated herein by reference):

```
   1 mttsirqfts sssikgssgl gggssrtscr lsgglgagsc rlgsagglgs tlggssyssc
  61 ysfgsgggyg ssfggvdgll aggekatmqn lndrlasyld kvraleeant elevkirdwy
 121 qrqapgpard ysqyyrtiee lqnkiltatv dnanillqid narlaaddfr tkfeteqalr
 181 lsveadingl rrvldeltla radlemqien lkeelaylkk nheeemnalr gqvggeinve
 241 mdaapgvdls rilnemrdqy ekmaeknrkd aedwffskte elnrevatns elvqsgksei
 301 selrrtmqal eielqsqlsm kaslegnlae tenrycvqls qiqgligsve eqlaqlrcem
 361 eqqnqeykil ldvktrleqe iatyrrlleg edahltqykk epvttrqvrt iveevqdgkv
 421 issreqvhqt tr
```

An exemplary human *KRT17* nucleic acid sequence is set forth below (SEQ ID NO: 126; GenBank Accession No: NM_000422, Version 2, incorporated herein by reference):

```
   1 atcgctacgc ccacttggtg gcctataaag gaagcgggcg aaccccggca gccctacaca
  61 acttggggcc cctctcctct ccagcccttc tcctgtgtgc ctgcctcctg ccgccgccac
 121 catgaccacc tccatccgcc agttcacctc ctccagctcc atcaagggct cctccggcct
 181 gggggggcggc tcgtcccgca cctcctgccg gctgtctggc ggcctgggtg ccggctcctg
 241 caggctggga tctgctggcg gcctgggcag caccctcggg ggtagcagct actccagctg
 301 ctacagcttt ggctctggtg gtggctatgg cagcagcttt gggggtgttg atgggctgct
 361 ggctggaggt gagaaggcca ccatgcagaa cctcaatgac cgcctggcct cctacctgga
 421 caaggtgcgt gccctggagg aggccaacac tgagctggag gtgaagatcc gtgactggta
 481 ccagaggcag gccccggggc ccgcccgtga ctacagccag tactacagga caattgagga
 541 gctgcagaac aagatcctca cagccaccgt ggacaatgcc aacatcctgc tacagattga
 601 caatgcccgt ctggctgctg atgacttccg caccaagttt gagacagagc aggccctgcg
 661 cctgagtgtg gaggccgaca tcaatggcct gcgcagggtg ctggatgagc tgaccctggc
 721 cagagccgac ctggagatgc agattgagaa cctcaaggag gagctggcct acctgaagaa
 781 gaaccacgag gaggagatga acgccctgcg aggccaggtg ggtggtgaga tcaatgtgga
 841 gatggacgct gccccaggcg tggacctgag ccgcatcctc aacgagatgc gtgaccagta
 901 tgagaagatg gcagagaaga accgcaagga tgccgaggat tggttcttca gcaagacaga
 961 ggaactgaac cgcgaggtgg ccaccaacag tgagctggtg cagagtggca agagtgagat
1021 ctcggagctc cggcgcacca tgcaggcctt ggagatagag ctgcagtccc agctcagcat
1081 gaaagcatcc ctggagggca acctggcgga gacagagaac cgctactgcg tgcagctgtc
1141 ccagatccag gggctgattg gcagcgtgga ggagcagctg gcccagcttc gctgcgagat
1201 ggagcagcag aaccaggaat acaaaatcct gctggatgtg aagacgcggc tggagcagga
1261 gattgccacc taccgccgcc tgctggaggg agaggatgcc cacctgactc agtacaagaa
1321 agaaccggtg accacccgtc aggtgcgtac cattgtggaa gaggtccagg atggcaaggt
1381 catctcctcc cgcgagcagg tccaccagac cacccgctga ggactcagct accccggccg
1441 gccacccagg aggcagggag gcagccgccc catctgcccc acagtctccg gcctctccag
1501 cctcagcccc ctgcttcagt cccttcccca tgcttccttg cctgatgaca ataaagcttg
1561 ttgactcagc tatg
```

An exemplary human fibroblast growth factor 2 (FGF2) amino acid sequence is set forth below (SEQ ID NO: 127; GenBank Accession No: P09038, Version 3, incorporated herein by reference):

```
   1 mvgvgggdve dvtprpggcq isgrgargcn gipgaaawea alprrrprrh psvnprsraa
  61 gsprtrgrrt eerpsgsrlg drgrgralpg grlggrgrgr apervggrgr grgtaapraa
 121 paargsrpgp agtmaagsit tlpalpedgg sgafppghfk dpkrlyckng gfflrihpdg
 181 rvdgvreksd phiklqlqae ergvvsikgv canrylamke dgrllaskcv tdecffferl
 241 esnnyntyrs rkytswyval krtgqyklgs ktgpgqkail flpmsaks
```

An exemplary human *FGF2* nucleic acid sequence is set forth below (SEQ ID NO: 128; GenBank Accession No: NM_002006, Version 4, incorporated herein by reference):

```
   1 cggccccaga aaacccgagc gagtaggggg cggcgcgcag gagggaggag aactgggggc
  61 gcgggaggct ggtgggtgtg gggggtggag atgtagaaga tgtgacgccg cggcccggcg
 121 ggtgccagat tagcggacgc ggtgcccgcg gttgcaacgg gatcccgggc gctgcagctt
 181 gggaggcggc tctccccagg cggcgtccgc ggagacaccc atccgtgaac cccaggtccc
 241 gggccgccgg ctcgccgcgc accaggggcc ggcggacaga agagcggccg agcggctcga
 301 ggctgggggа ccgcgggcgc ggccgcgcgc tgccgggcgg gaggctgggg ggccggggcc
 361 ggggccgtgc cccggagcgg gtcggaggcc ggggccgggg ccgggggacg gcggctcccc
 421 gcgcggctcc agcggctcgg ggatcccggc cgggccccgc agggaccatg gcagccggga
 481 gcatcaccac gctgcccgcc ttgcccgagg atggcggcag cggcgccttc ccgcccggcc
 541 acttcaagga ccccaagcgg ctgtactgca aaaacggggg cttcttcctg cgcatccacc
 601 ccgacggccg agttgacggg gtccgggaga agagcgaccc tcacatcaag ctacaacttc
 661 aagcagaaga gagaggagtt gtgtctatca aaggagtgtg tgctaaccgt tacctggcta
 721 tgaaggaaga tggaagatta ctggcttcta aatgtgttac ggatgagtgt ttctttttg
 781 aacgattgga atctaataac tacaatactt accggtcaag gaaatacacc agttggtatg
 841 tggcactgaa acgaactggg cagtataaac ttggatccaa aacaggacct gggcagaaag
 901 ctatactttt tcttccaatg tctgctaaga gctgatttta atggccacat ctaatctcat
 961 ttcacatgaa agaagaagta tattttagaa atttgttaat gagagtaaaa gaaaataaat
1021 gtgtatagct cagtttggat aattggtcaa acaatttttt atccagtagt aaaatatgta
1081 accattgtcc cagtaaagaa aaataacaaa agttgtaaaa tgtatattct ccctttttata
1141 ttgcatctgc tgttacccag tgaagcttac ctagagcaat gatctttttc acgcatttgc
1201 tttattcgaa aagaggcttt taaaatgtgc atgtttagaa acaaaatttc ttcatggaaa
1261 tcatatacat tagaaaatca cagtcagatg tttaatcaat ccaaaatgtc cactatttct
1321 tatgtcattc gttagtctac atgtttctaa acatataaat gtgaatttaa tcaattcctt
1381 tcatagtttt ataattctct ggcagttcct tatgatagag tttataaaac agtcctgtgt
1441 aaactgctgg aagttcttcc acagtcaggt caatttttgtc aaacccttct ctgtacccat
1501 acagcagcag cctagcaact ctgctggtga tgggagttgt attttcagtc ttcgccaggt
1561 cattgagatc catccactca catcttaagc attcttcctg gcaaaaattt atggtgaatg
1621 aatatggctt taggcggcag atgatataca tatctgactt cccaaaagct ccaggatttg
1681 tgtgctgttg ccgaatactc aggacggacc tgaattctga ttttatacca gtctcttcaa
1741 aaacttctcg aaccgctgtg tctcctacgt aaaaaaagag atgtacaaat caataataat
1801 tacactttta gaaactgtat catcaaagat tttcagttaa agtagcatta tgtaaaggct
1861 caaaacatta ccctaacaaa gtaaagtttt caatacaaat tctttgcctt gtggatatca
1921 agaaatccca aaatattttc ttaccactgt aaattcaaga agcttttgaa atgctgaata
1981 tttctttggc tgctacttgg aggcttatct acctgtacat ttttggggtc agctcttttt
2041 aacttcttgc tgctcttttt cccaaaaggt aaaaatatag attgaaaagt taaaacattt
2101 tgcatggctg cagttccttt gtttcttgag ataagattcc aaagaactta gattcatttc
2161 ttcaacaccg aaatgctgga ggtgtttgat cagttttcaa gaaacttgga atataaataa
2221 ttttataatt caacaaaggt tttcacattt tataaggttg atttttcaat taaatgcaaa
2281 tttgtgtggc aggattttta ttgccattaa catatttttg tggctgcttt ttctacacat
2341 ccagatggtc cctctaactg ggctttctct aattttgtga tgttctgtca ttgtctccca
2401 aagtatttag gagaagccct ttaaaaagct gccttcctct accactttgc tggaaagctt
2461 cacaattgtc acagacaaag atttttgttc caatactcgt tttgcctcta tttttcttgt
2521 ttgtcaaata gtaaatgata tttgcccttg cagtaattct actggtgaaa aacatgcaaa
2581 gaagaggaag tcacagaaac atgtctcaat tcccatgtgc tgtgactgta gactgtctta
2641 ccatagactg tcttacccat cccctggata tgctcttgtt ttttccctct aatagctatg
2701 gaaagatgca tagaaagagt ataatgtttt aaaacataag gcattcgtct gccatttttc
2761 aattacatgc tgacttccct tacaattgag atttgcccat aggttaaaca tggttagaaa
2821 caactgaaag cataaaagaa aaatctaggc cgggtgcagt ggctcatgcc tatattccct
2881 gcactttggg aggccaaagc aggaggatcg cttgagccca ggagttcaag accaacctgg
2941 tgaaaccccg tctctacaaa aaaacacaaa aaatagccag gcatggtggc gtgtacatgt
3001 ggtctcagat acttgggagg ctgaggtggg agggttgatc acttgaggct gagaggtcaa
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3061 ggttgcagtg agccataatc gtgccactgc agtccagcct aggcaacaga gtgagacttt
3121 gtctcaaaaa aagagaaatt ttccttaata agaaaagtaa tttttactct gatgtgcaat
3181 acatttgtta ttaaatttat tatttaagat ggtagcacta gtcttaaatt gtataaaata
3241 tcccctaaca tgtttaaatg tccatttttа ttcattatgc tttgaaaaat aattatgggg
3301 aaatacatgt ttgttattaa atttattatt aaagatagta gcactagtct taaatttgat
3361 ataacatctc ctaacttgtt taaatgtcca tttttattct ttatgtttga aaataaatta
3421 tggggatcct atttagctct tagtaccact aatcaaaagt tcggcatgta gctcatgatc
3481 tatgctgttt ctatgtcgtg gaagcaccgg atgggggtag tgagcaaatc tgccctgctc
3541 agcagtcacc atagcagctg actgaaaatc agcactgcct gagtagtttt gatcagttta
3601 acttgaatca ctaactgact gaaaattgaa tgggcaaata agtgcttttg tctccagagt
3661 atgcgggaga cccttccacc tcaagatgga tatttcttcc ccaaggattt caagatgaat
3721 tgaaattttt aatcaagata gtgtgcttta ttctgttgta ttttttatta ttttaatata
3781 ctgtaagcca aactgaaata acatttgctg ttttataggt ttgaagaaca taggaaaaac
3841 taagaggttt tgtttttatt tttgctgatg aagagatatg tttaaatatg ttgtattgtt
3901 ttgtttagtt acaggacaat aatgaaatgg agtttatatt tgttatttct attttgttat
3961 atttaataat agaattagat tgaaataaaa tataatggga aataatctgc agaatgtggg
4021 ttttcctggt gtttccctct gactctagtg cactgatgat ctctgataag gctcagctgc
4081 tttatagttc tctggctaat gcagcagata ctcttcctgc cagtggtaat acgatttttt
4141 aagaaggcag tttgtcaatt ttaatcttgt ggataccttt atactcttag ggtattattt
4201 tatacaaaag ccttgaggat tgcattctat tttctatatg accctcttga tatttaaaaa
4261 acactatgga taacaattct tcatttacct agtattatga aagaatgaag gagttcaaac
4321 aaatgtgttt cccagttaac tagggtttac tgtttgagcc aatataaatg tttaactgtt
4381 tgtgatggca gtattcctaa agtacattgc atgttttcct aaatacagag tttaaataat
4441 ttcagtaatt cttagatgat tcagcttcat cattaagaat atcttttgtt ttatgttgag
4501 ttagaaatgc cttcatatag acatagtctt tcagacctct actgtcagtt ttcatttcta
4561 gctgctttca gggttttatg aattttcagg caaagcttta atttatacta agcttaggaa
4621 gtatggctaa tgccaacggc agtttttttc ttcttaattc cacatgactg aggcatatat
4681 gatctctggg taggtgagtt gttgtgacaa ccacaagcac ttttttttтt tttaaagaaa
4741 aaaaggtagt gaatttttaa tcatctggac tttaagaagg attctggagt atacttaggc
4801 ctgaaattat atatatttgg cttggaaatg tgtttttctt caattacatc tacaagtaag
4861 tacagctgaa attcagagga cccataagag ttcacatgaa aaaaatcaat ttatttgaaa
4921 aggcaagatg caggagagag gaagccttgc aaacctgcag actgcttttt gcccaatata
4981 gattgggtaa ggctgcaaaa cataagctta attagctcac atgctctgct ctcacgtggc
5041 accagtggat agtgtgagag aattaggctg tagaacaaat ggccttctct ttcagcattc
5101 acaccactac aaaatcatct tttatatcaa cagaagaata agcataaact aagcaaaagg
5161 tcaataagta cctgaaacca agattggcta gagatatatc ttaatgcaat ccatttttctg
5221 atggattgtt acgagttggc tatataatgt atgtatggta ttttgatttg tgtaaaagtt
5281 ttaaaaatca agctttaagt acatggacat ttttaaataa aatatttaaa gacaatttag
5341 aaaattgcct taatatcatt gttggctaaa tagaataggg gacatgcata ttaaggaaaa
5401 ggtcatggag aaataatatt ggtatcaaac aaatacattg atttgtcatg atacacattg
5461 aatttgatcc aatagtttaa ggaataggta ggaaaatttg gtttctattt ttcgatttcc
5521 tgtaaatcag tgacataaat aattcttagc ttattttata tttccttgtc ttaaatactg
5581 agctcagtaa gttgtgttag gggattattt ctcagttgag actttcttat atgacatttt
5641 actatgtttt gacttcctga ctattaaaaa taaatagtag atacaatttt cataaagtga
5701 agaattatat aatcactgct ttataactga ctttattata tttatttcaa agttcattta
5761 aaggctacta ttcatcctct gtgatggaat ggtcaggaat ttgttttctc atagtttaat
5821 tccaacaaca atattagtcg tatccaaaat aacctttaat gctaaacttt actgatgtat
5881 atccaaagct tctcattttc agacagatta atccagaagc agtcataaac agaagaatag
5941 gtggtatgtt cctaatgata ttatttctac taatggaata aactgtaata ttagaaatta
6001 tgctgctaat tatatcagct ctgaggtaat ttctgaaatg ttcagactca gtcggaacaa
6061 attggaaaat ttaaattttt attcttagct ataaagcaag aaagtaaaca cattaatttc
6121 ctcaacattt ttaagccaat taaaaatata aaagatacac accaatatct tcttcaggct
6181 ctgacaggcc tcctggaaac ttccacatat ttttcaactg cagtataaag tcagaaaata
6241 aagttaacat aactttcact aacacacaca tatgtagatt tcacaaaatc cacctataat
6301 tggtcaaagt ggttgagaat atatttttta gtaattgcat gcaaaatttt tctagcttcc
6361 atcctttctc cctcgtttct tctttttttg ggggagctgg taactgatga aatcttttcc

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6421 cacctttttct cttcaggaaa tataagtggt tttgtttggt taacgtgata cattctgtat
6481 gaatgaaaca ttggagggaa acatctactg aatttctgta atttaaaata ttttgctgct
6541 agttaactat gaacagatag aagaatctta cagatgctgc tataaataag tagaaaatat
6601 aaatttcatc actaaaatat gctattttaa aatctatttc ctatattgta tttctaatca
6661 gatgtattac tcttattatt tctattgtat gtgttaatga ttttatgtaa aaatgtaatt
6721 gcttttcatg agtagtatga ataaaattga ttagtttgtg ttttcttgtc tccc
```

An exemplary human stromal cell-derived factor 1 (CXCL12 or SDF-1) amino acid sequence is set forth below (SEQ ID NO: 129; GenBank Accession No: P48061, Version 1, incorporated herein by reference):

```
  1 mnakvvvvlv lvltalclsd gkpvslsyrc pcrffeshva ranvkhlkil ntpncalqiv
 61 arlknnnrqv cidpklkwiq eylekalnkr fkm
```

An exemplary human *CXCL12* nucleic acid sequence is set forth below (SEQ ID NO: 130; GenBank Accession No: CR450283, Version 1, incorporated herein by reference):

```
  1 atgaacgcca aggtcgtggt cgtgctggtc ctcgtgctga ccgcgctctg cctcagcgac
 61 gggaagcccg tcagcctgag ctacagatgc ccatgccgat tcttcgaaag ccatgttgcc
121 agagccaacg tcaagcatct caaaattctc aacactccaa actgtgccct tcagattgta
181 gcccggctga agaacaacaa cagacaagtg tgcattgacc cgaagctaaa gtggattcag
241 gagtacctgg agaaagcttt aaacaag
```

An exemplary human cadherin 1 (CDH1) amino acid sequence is set forth below (SEQ ID NO: 131; GenBank Accession No: AAI46663, Version 1, incorporated herein by reference):

```
  1 mgpwsrslsa lllllqvssw lcqepepchp gfdaesytft vprrhlergr vlgrvnfedc
 61 tgrqrtayfs ldtrfkvgtd gvitvkrplr fhnpqihflv yawdstyrkf stkvtlntvg
121 hhhrppphqa svsgiqaell tfpnsspglr rqkrdwvipp iscpenekgp fpknlvqiks
181 nkdkegkvfy sitgqgadtp pvgvfiiere tgwlkvtepl dreriatytl fshavssngn
241 avedpmeili tvtdqndnkp eftqevfkgs vmegalpgts vmevtatdad ddvntynaai
301 aytilsqdpe lpdknmftin rntgvisvvt tgldresfpa ytlvvqaadl qgeglsttat
361 avitvtdtnd nppifnptty kgqvpenean vvittlkvtd adapntpawe avytilnddg
421 gqfvvttnpv nndgilktak gldfeakqqy ilhvavtnvv pfevslttst atvtvdvldv
481 neapifvppe krvevsedfg vgqeitsyta qepdtfmeqk ityriwrdta nwleinpdtg
541 aistraeldr edfehvknst ytaliiatdn gspvatgtgt lllilsdvnd napipeprti
601 ffcernpkpq viniidadlp pilasqsigi tdmshctcpa pqlpaif
```

An exemplary human *CDH1* nucleic acid sequence is set forth below (SEQ ID NO: 132; GenBank Accession No: NM_004360, Version 4, incorporated herein by reference):

```
  1 tcagtggcgt cggaactgca aagcacctgt gagcttgcgg aagtcagttc agactccagc
 61 ccgctccagc ccggcccgac ccgaccgcac ccggcgcctg ccctcgctcg gcgtccccgg
121 ccagccatgg gcccttggag ccgcagcctc tcggcgctgc tgctgctgct gcaggtctcc
181 tcttggctct gccaggagcc ggagccctgc caccctggct ttgacgccga gagctacacg
241 ttcacggtgc cccggcgcca cctggagaga ggccgcgtcc tgggcagagt gaattttgaa
301 gattgcaccg gtcgacaaag gacagcctat ttttccctcg acacccgatt caaagtgggc
361 acagatggtg tgattacagt caaaaggcct ctacggtttc ataacccaca gatccatttc
421 ttggtctacg cctgggactc cacctacaga aagttttcca ccaaagtcac gctgaataca
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```
 481 gtggggcacc accaccgccc cccgccccat caggcctccg tttctggaat ccaagcagaa
 541 ttgctcacat ttcccaactc ctctcctggc ctcagaagac agaagagaga ctgggttatt
 601 cctcccatca gctgcccaga aaatgaaaaa ggcccatttc ctaaaaacct ggttcagatc
 661 aaatccaaca aagacaaaga aggcaaggtt ttctacagca tcactggcca aggagctgac
 721 acacccccctg ttggtgtctt tattattgaa agagaaacag gatggctgaa ggtgacagag
 781 cctctggata gagaacgcat tgccacatac actctcttct ctcacgctgt gtcatccaac
 841 gggaatgcag ttgaggatcc aatggagatt ttgatcacgg taaccgatca gaatgacaac
 901 aagcccgaat tcacccagga ggtctttaag gggtctgtca tggaaggtgc tcttccagga
 961 acctctgtga tggaggtcac agccacagac gcggacgatg atgtgaacac ctacaatgcc
1021 gccatcgctt acaccatcct cagccaagat cctgagctcc ctgacaaaaa tatgttcacc
1081 attaacagga acacaggagt catcagtgtg gtcaccactg ggctggaccg agagagtttc
1141 cctacgtata ccctggtggt tcaagctgct gaccttcaag gtgaggggtt aagcacaaca
1201 gcaacagctg tgatcacagt cactgacacc aacgataatc ctccgatctt caatcccacc
1261 acgtacaagg gtcaggtgcc tgagaacgag gctaacgtcg taatcaccac actgaaagtg
1321 actgatgctg atgcccccaa taccccagcg tgggaggctg tatacaccat attgaatgat
1381 gatggtggac aatttgtcgt caccacaaat ccagtgaaca acgatggcat tttgaaaaca
1441 gcaaagggct tggattttga ggccaagcag cagtacattc tacacgtagc agtgacgaat
1501 gtggtacctt ttgaggtctc tctcaccacc tccacagcca ccgtcaccgt ggatgtgctg
1561 gatgtgaatg aagcccccat ctttgtgcct cctgaaaaga gagtggaagt gtccgaggac
1621 tttggcgtgg gccaggaaat cacatcctac actgcccagg agccagacac atttatggaa
1681 cagaaaataa catatcggat ttggagagac actgccaact ggctggagat taatccggac
1741 actggtgcca tttccactcg ggctgagctg gacagggagg attttgagca cgtgaagaac
1801 agcacgtaca cagccctaat catagctaca gacaatggtt ctccagttgc tactggaaca
1861 gggacacttc tgctgatcct gtctgatgtg aatgacaacg cccccatacc agaacctcga
1921 actatattct tctgtgagag gaatccaaag cctcaggtca taaacatcat tgatgcagac
1981 cttcctccca atacatctcc cttcacagca gaactaacac acggggcgag tgccaactgg
2041 accattcagt acaacgaccc aacccaagaa tctatcattt tgaagccaaa gatggcctta
2101 gaggtgggtg actacaaaat caatctcaag ctcatggata accagaataa agaccaagtg
2161 accaccttag aggtcagcgt gtgtgactgt gaaggggccg ctggcgtctg taggaaggca
2221 cagcctgtcg aagcaggatt gcaaattcct gccattctgg ggattcttgg aggaattctt
2281 gctttgctaa ttctgattct gctgctcttg ctgtttcttc ggaggagagc ggtggtcaaa
2341 gagcccttac tgcccccaga ggatgacacc cgggacaacg tttattacta tgatgaagaa
2401 ggaggcggag aagaggacca ggactttgac ttgagccagc tgcacagggg cctggacgct
2461 cggcctgaag tgactcgtaa cgacgttgca ccaaccctca tgagtgtccc ccggtatctt
2521 ccccgccctg ccaatcccga tgaaattgga aattttattg atgaaaatct gaaagcggct
2581 gatactgacc ccacagcccc gccttatgat tctctgctcg tgtttgacta tgaaggaagc
2641 ggttccgaag ctgctagtct gagctccctg aactcctcag agtcagacaa agaccaggac
2701 tatgactact tgaacgaatg gggcaatcgc ttcaagaagc tggctgacat gtacggaggc
2761 ggcgaggacg actaggggac tcgagagagg cgggccccag acccatgtgc tgggaaatgc
2821 agaaatcacg ttgctggtgg tttttcagct cccttccctt gagatgagtt tctggggaaa
2881 aaaaagagac tggttagtga tgcagttagt atagctttat actctctcca ctttatagct
2941 ctaataagtt tgtgttagaa aagtttcgac ttatttctta aagctttttt ttttttccca
3001 tcactcttta catggtggtg atgtccaaaa gatacccaaa ttttaatatt ccagaagaac
3061 aactttagca tcagaaggtt cacccagcac cttgcagatt ttcttaagga attttgtctc
3121 acttttaaaa agaaggggag aagtcagcta ctctagttct gttgttttgt gtatataatt
3181 ttttaaaaaa aatttgtgtg cttctgctca ttactacact ggtgtgtccc tctgcctttt
3241 ttttttttt aagacagggt ctcattctat cggccaggct ggagtgcagt ggtgcaatca
3301 cagctcactg cagccttgtc ctcccaggct caagctatcc ttgcacctca gcctcccaag
3361 tagctgggac cacaggcatg caccactacg catgactaat tttttaaata tttgagacgg
3421 ggtctccctg tgttacccag gctggtctca aactcctggg ctcaagtgat cctcccatct
3481 tggcctccca gagtattggg attacagaca tgagccactg cacctgccca gctccccaac
3541 tccctgccat tttttaagag acagtttcgc tccatcgccc aggcctggga tgcagtgatg
3601 tgatcatagc tcactgtaac ctcaaactct ggggctcaag cagttctccc accagcctcc
3661 tttttatttt tttgtacaga tggggtcttg ctatgttgcc caagctggtc ttaaactcct
3721 ggcctcaagc aatccttctg ccttggcccc ccaaagtgct gggattgtgg gcatgagctg
3781 ctgtgcccag cctccatgtt ttaatatcaa ctctcactcc tgaattcagt tgctttgccc
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3841 aagataggag ttctctgatg cagaaattat tgggctcttt tagggtaaga agtttgtgtc
3901 tttgtctggc cacatcttga ctaggtattg tctactctga agacctttaa tggcttccct
3961 ctttcatctc ctgagtatgt aacttgcaat gggcagctat ccagtgactt gttctgagta
4021 agtgtgttca ttaatgttta tttagctctg aagcaagagt gatatactcc aggacttaga
4081 atagtgccta aagtgctgca gccaaagaca gagcggaact atgaaaagtg ggcttggaga
4141 tggcaggaga gcttgtcatt gagcctggca atttagcaaa ctgatgctga ggatgattga
4201 ggtgggtcta cctcatctct gaaaattctg gaaggaatgg aggagtctca acatgtgttt
4261 ctgacacaag atccgtggtt tgtactcaaa gcccagaatc cccaagtgcc tgcttttgat
4321 gatgtctaca gaaaatgctg gctgagctga acacatttgc ccaattccag gtgtgcacag
4381 aaaaccgaga atattcaaaa ttccaaattt ttttcttagg agcaagaaga aaatgtggcc
4441 ctaaaggggg ttagttgagg ggtagggggt agtgaggatc ttgatttgga tctcttttta
4501 tttaaatgtg aatttcaact tttgacaatc aaagaaaaga cttttgttga aatagcttta
4561 ctgtttctca agtgttttgg agaaaaaaat caaccctgca atcacttttt ggaattgtct
4621 tgatttttcg gcagttcaag ctatatcgaa tatagttctg tgtagagaat gtcactgtag
4681 ttttgagtgt atacatgtgt gggtgctgat aattgtgtat tttctttggg ggtggaaaag
4741 gaaaacaatt caagctgaga aaagtattct caaagatgca tttttataaa ttttattaaa
4801 caattttgtt aaaccattaa aaaaaaaaaa aaaaaaaaaa aaaaa
```

An exemplary human cadherin 2 (CDH2) amino acid sequence is set forth below (SEQ ID NO: 133; GenBank Accession No: P19022, Version 4, incorporated herein by reference):

```
   1 mcriagalrt llpllaallq asveasgeia lcktgfpedv ysavlskdvh egqpllnvkf
  61 sncngkrkvq yessepadfk vdedgmvyav rsfplsseha kfliyaqdke tqekwqvavk
 121 lslkptltee svkesaevee ivfprqfskh sghlqrqkrd wvippinlpe nsrgpfpqel
 181 vrirsdrdkn lslrysvtgp gadqpptgif iinpisgqls vtkpldreqi arfhlrahav
 241 dingnqvenp idivinvidm ndnrpeflhq vwngtvpegs kpgtyvmtvt aidaddpnal
 301 ngmlryrivs qapstpspnm ftinnetgdi itvaagldre kvqqytliiq atdmegnpty
 361 glsntatavi tvtdvndnpp eftamtfyge vpenrvdiiv anltvtdkdq phtpawnavy
 421 risggdptgr faiqtdpnsn dglvtvvkpi dfetnrmfvl tvaaenqvpl akgiqhppqs
 481 tatvsvtvid vnenpyfapn pkiirqeegl hagtmlttft aqdpdrymqq nirytklsdp
 541 anwlkidpvn gqittiavld respnvknni ynatflasdn gippmsgtgt lqiylldind
 601 napqvlpqea etcetpdpns initaldydi dpnagpfafd lplspvtikr nwtitrlngd
 661 faqlnlkikf leagiyevpi iitdsgnppk snisilrvkv cqcdsngdct dvdrivgagl
 721 gtgaiiaill ciiillilvl mfvvwmkrrd kerqakqlli dpeddvrdni lkydeeggge
 781 edqdydlsql qqpdtvepda ikpvgirrmd erpihaepqy pvrsaaphpg digdfinegl
 841 kaadndptap pydsllvfdy egsgstagsl sslnssssgg eqdydylndw gprfkkladm
 901 ygggdd
```

An exemplary human *CDH2* nucleic acid sequence is set forth below (SEQ ID NO: 134; GenBank Accession No: NM_001792, Version 4, incorporated herein by reference):

```
   1 cctccaccgg ccaaggtccc cgccgctgca tccctcgcgg cttccgctgc gctccgggcc
  61 ggagccgagc cgcctgcgct gccacagcag ccgcctccac acactcgcag acgctcacac
 121 gctctccctc cctgttcccc cgccccctcc ccagctcctt gatctctggg tctgttttat
 181 tactcctggt gcgagtcccg cggactccgc ggcccgctat ttgtcatcag ctcgctctcc
 241 attggcgggg agcggagagc agcgaagaag ggggtgggga ggggagggga agggaagggg
 301 gtggaaactg cctggagccg tttctccgcg ccgctgttgg tgctgccgct gcctcctcct
 361 cctccgccgc cgccgccgcc gccgccgcct cctccggctc ttcgctcggc ccctctccgc
 421 ctccatgtgc cggatagcgg gagcgctgcg gaccctgctg ccgctgctgg cggccctgct
 481 tcaggcgtct gtagaggctt ctggtgaaat cgcattatgc aagactggat ttcctgaaga
 541 tgtttacagt gcagtcttat cgaaggatgt gcatgaagga cagcctcttc tcaatgtgaa
 601 gtttagcaac tgcaatggaa aaagaaaagt acaatatgag agcagtgagc ctgcagattt
 661 taaggtggat gaagatggca tggtgtatgc cgtgagaagc tttccactct cttctgagca
```

```
 721 tgccaagttc ctgatatatg cccaagacaa agagacccag gaaaagtggc aagtggcagt
 781 aaaattgagc ctgaagccaa ccttaactga ggagtcagtg aaggagtcag cagaagttga
 841 agaaatagtg ttcccaagac aattcagtaa gcacagtggc cacctacaaa ggcagaagag
 901 agactgggtc atccctccaa tcaacttgcc agaaaactcc aggggacctt ttcctcaaga
 961 gcttgtcagg atcaggtctg atagagataa aaacctttca ctgcggtaca gtgtaactgg
1021 gccaggagct gaccagcctc caactggtat cttcattatc aaccccatct cgggtcagct
1081 gtcggtgaca aagcccctgg atcgcgagca gatagcccgg tttcatttga gggcacatgc
1141 agtagatatt aatggaaatc aagtggagaa ccccattgac attgtcatca atgttattga
1201 catgaatgac aacagacctg agttcttaca ccaggtttgg aatgggacag ttcctgaggg
1261 atcaaagcct ggaacatatg tgatgaccgt aacagcaatt gatgctgacg atcccaatgc
1321 cctcaatggg atgttgaggt acagaatcgt gtctcaggct ccaagcaccc cttcacccaa
1381 catgtttaca atcaacaatg agactggtga catcatcaca gtggcagctg gacttgatcg
1441 agaaaaagtg caacagtata cgttaataat tcaagctaca gacatggaag gcaatcccac
1501 atatggcctt tcaaacacag ccacggccgt catcacagtg acagatgtca atgacaatcc
1561 tccagagttt actgccatga cgttttatgg tgaagttcct gagaacaggg tagacatcat
1621 agtagctaat ctaactgtga ccgataagga tcaaccccat acaccagcct ggaacgcagt
1681 gtacagaatc agtggcggag atcctactgg acggttcgcc atccagaccg acccaaacag
1741 caacgacggg ttagtcaccg tggtcaaacc aatcgacttt gaaacaaata ggatgtttgt
1801 ccttactgtt gctgcagaaa atcaagtgcc attagccaag ggaattcagc acccgcctca
1861 gtcaactgca accgtgtctg ttacagttat tgacgtaaat gaaaaccctt attttgcccc
1921 caatcctaag atcattcgcc aagaagaagg gcttcatgcc ggtaccatgt tgacaacatt
1981 cactgctcag gacccagatc gatatatgca gcaaaatatt agatacacta aattatctga
2041 tcctgccaat tggctaaaaa tagatcctgt gaatggacaa ataactacaa ttgctgtttt
2101 ggaccgagaa tcaccaaatg tgaaaaacaa tatatataat gctactttcc ttgcttctga
2161 caatggaatt cctcctatga gtggaacagg aacgctgcag atctatttac ttgatattaa
2221 tgacaatgcc cctcaagtgt tacctcaaga ggcagagact tgcgaaactc cagaccccaa
2281 ttcaattaat attacagcac ttgattatga cattgatcca aatgctggac catttgcttt
2341 tgatcttcct ttatctccag tgactattaa gagaaattgg accatcactc ggcttaatgg
2401 tgattttgct cagcttaatt taaagataaa atttcttgaa gctggtatct atgaagttcc
2461 catcataatc acagattcgg gtaatcctcc caaatcaaat atttccatcc tgcgcgtgaa
2521 ggtttgccag tgtgactcca acggggactg cacagatgtg gacaggattg tgggtgcggg
2581 gcttggcacc ggtgccatca ttgccatcct gctctgcatc atcatcctgc ttatccttgt
2641 gctgatgttt gtggtatgga tgaaacgccg ggataaagaa cgccaggcca aacaactttt
2701 aattgatcca gaagatgatg taagagataa tattttaaaa tatgatgaag aaggtggagg
2761 agaagaagac caggactatg acttgagcca gctgcagcag cctgacactg tggagcctga
2821 tgccatcaag cctgtgggaa tccgacgaat ggatgaaaga cccatccacg ccgagcccca
2881 gtatccggtc cgatctgcag ccccacaccc tggagacatt ggggacttca ttaatgaggg
2941 ccttaaagcg gctgacaatg accccacagc tccaccatat gactccctgt tagtgtttga
3001 ctatgaaggc agtggctcca ctgctgggtc cttgagctcc cttaattcct caagtagtgg
3061 tggtgagcag gactatgatt acctgaacga ctgggggcca cggttcaaga aacttgctga
3121 catgtatggt ggaggtgatg actgaacttc agggtgaact tggtttttgg acaagtacaa
3181 acaatttcaa ctgatattcc caaaaagcat tcagaagcta ggctttaact ttgtagtcta
3241 ctagcacagt gcttgctgga ggctttggca taggctgcaa accaatttgg gctcagaggg
3301 aatatcagtg atccatactg tttggaaaaa cactgagctc agttacactt gaattttaca
3361 gtacagaagc actgggattt tatgtgcctt tttgtacctt tttcagattg gaattagttt
3421 tctgtttaag gctttaatgg tactgatttc tgaaacgata agtaaaagac aaaatatttt
3481 gtggtgggag cagtaagtta aaccatgata tgcttcaaca cgcttttgtt acattgcatt
3541 tgcttttatt aaaatacaaa attaaacaaa caaaaaaact catggagcga ttttattatc
3601 ttgggggatg agaccatgag attggaaaat gtacattact tctagtttta gactttagtt
3661 tgttttttt tttttcacta aaatcttaaa acttactcag ctggttgcaa ataaagggag
3721 ttttcatatc accaatttgt agcaaaattg aatttttca taaactagaa tgttagacac
3781 attttggtct taatccatgt acacttttt atttctgtat ttttccactt cactgtaaaa
3841 atagtatgtg tacataatgt tttattggca tagtctatgg agaagtgcag aaacttcaga
3901 acatgtgtat gtattatttg gactatggat tcaggttttt tgcatgttta tatctttcgt
3961 tatggataaa gtatttacaa aacagtgaca tttgattcaa ttgttgagct gtagttagaa
4021 tactcaattt ttaatttttt taatttttt attttttatt ttctttttgg tttggggagg
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```
4081 gagaaaagtt cttagcacaa atgttttaca taatttgtac caaaaaaaaa aaaaaaggaa
4141 aggaaagaaa ggggtggcct gacactggtg gcactactaa gtgtgtgttt ttttaaaaaa
4201 aaaatggaaa aaaaaaagct tttaaactgg agagacttct gacaacagct ttgcctctgt
4261 attgtgtacc agaatataaa tgatacacct ctgaccccag cgttctgaat aaaatgctaa
4321 ttttggatct ggtgaaaaa
```

An exemplary human matrix metalloproteinase 1 (MMP-1) amino acid sequence is set forth below (SEQ ID NO: 135; GenBank Accession No: P03956, Version 3, incorporated herein by reference):

```
   1 mhsfppllll lfwgvvshsf patletqeqd vdlvqkylek yynlkndgrq vekrrnsgpv
  61 veklkqmqef fglkvtgkpd aetlkvmkqp rcgvpdvaqf vltegnprwe qthltyrien
 121 ytpdlpradv dhaiekafql wsnvtpltft kvsegqadim isfvrgdhrd nspfdgpggn
 181 lahafqpgpg iggdahfded erwtnnfrey nlhrvaahel ghslglshst digalmypsy
 241 tfsgdvqlaq ddidgiqaiy grsqnpvqpi gpqtpkacds kltfdaitti rgevmffkdr
 301 fymrtnpfyp evelnfisvf wpqlpnglea ayefadrdev rffkgnkywa vqgqnvlhgy
 361 pkdiyssfgf prtvkhidaa lseentgkty ffvankywry deykrsmdpg ypkmiahdfp
 421 gighkvdavf mkdgffyffh gtrqykfdpk tkriltlqka nswfncrkn
```

An exemplary human *MMP-1* nucleic acid sequence is set forth below (SEQ ID NO: 136; GenBank Accession No: NM_002421, Version 3, incorporated herein by reference):

```
   1 agcatgagtc agacagcctc tggctttctg gaagggcaag gactctatat atacagaggg
  61 agcttcctag ctgggatatt ggagcagcaa gaggctggga agccatcact taccttgcac
 121 tgagaaagaa gacaaaggcc agtatgcaca gctttcctcc actgctgctg ctgctgttct
 181 ggggtgtggt gtctcacagc ttcccagcga ctctagaaac acaagagcaa gatgtggact
 241 tagtccagaa atacctggaa aaatactaca acctgaagaa tgatgggagg caagttgaaa
 301 agcggagaaa tagtggccca gtggttgaaa aattgaagca aatgcaggaa ttctttgggc
 361 tgaaagtgac tgggaaacca gatgctgaaa ccctgaaggt gatgaagcag cccagatgtg
 421 gagtgcctga tgtggctcag tttgtcctca ctgaggggaa ccctcgctgg gagcaaacac
 481 atctgaccta caggattgaa aattacacgc cagatttgcc aagagcagat gtggaccatg
 541 ccattgagaa agccttccaa ctctggagta atgtcacacc tctgacattc accaaggtct
 601 ctgagggtca agcagacatc atgatatctt ttgtcagggg agatcatcgg gacaactctc
 661 cttttgatgg acctggagga aatcttgctc atgcttttca accaggccca ggtattggag
 721 gggatgctca ttttgatgaa gatgaaaggt ggaccaacaa tttcagagag tacaacttac
 781 atcgtgttgc agctcatgaa ctcggccatt ctcttggact ctcccattct actgatatcg
 841 gggctttgat gtaccctagc tacaccttca gtggtgatgt tcagctagct caggatgaca
 901 ttgatggcat ccaagccata tatggacgtt cccaaaatcc tgtccagccc atcggcccac
 961 aaaccccaaa agcgtgtgac agtaagctaa cctttgatgc tataactacg attcggggag
1021 aagtgatgtt ctttaaagac agattctaca tgcgcacaaa tcccttctac ccggaagttg
1081 agctcaattt catttctgtt ttctggccac aactgccaaa tgggcttgaa gctgcttacg
1141 aatttgccga cagagatgaa gtccggtttt tcaaagggaa taagtactgg gctgttcagg
1201 gacagaatgt gctacacgga taccccaagg acatctacag ctcctttggc ttccctagaa
1261 ctgtgaagca tatcgatgct gctctttctg aggaaaacac tggaaaaacc tacttctttg
1321 ttgctaacaa atactggagg tatgatgaat ataaacgatc tatggatcca ggttatccca
1381 aaatgatagc acatgacttt cctggaattg gccacaaagt tgatgcagtt ttcatgaaag
1441 atggattttt ctatttcttt catggaacaa gacaatacaa atttgatcct aaaacgaaga
1501 gaattttgac tctccagaaa gctaatagct ggttcaactg caggaaaaat tgaacattac
1561 taatttgaat ggaaaacaca tggtgtgagt ccaaagaagg tgttttcctg aagaactgtc
1621 tattttctca gtcattttta acctctagag tcactgatac acagaatata atcttattta
1681 tacctcagtt tgcatatttt tttactattt agaatgtagc ccttttttgta ctgatataat
1741 ttagttccac aaatggtggg tacaaaaagt caagtttgtg gcttatggat tcatataggc
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1801 cagagttgca aagatctttt ccagagtatg caactctgac gttgatccca gagagcagct
1861 tcagtgacaa acatatcctt tcaagacaga aagagacagg agacatgagt ctttgccgga
1921 ggaaaagcag ctcaagaaca catgtgcagt cactggtgtc accctggata ggcaagggat
1981 aactcttcta acacaaaata agtgttttat gtttggaata aagtcaacct tgtttctact
2041 gttttataca ctttcaaaaa aaaaaaaaaa aaaaaaaaaa a
```

An exemplary human matrix metalloproteinase (MMP-2) amino acid sequence is set forth below (SEQ ID NO: 137; GenBank Accession No: P08253, Version 2, incorporated herein by reference):

```
   1 mealmargal tgplralcll gcllshaaaa pspiikfpgd vapktdkela vqylntfygc
  61 pkescnlfvl kdtlkkmqkf fglpqtgdld qntietmrkp rcgnpdvany nffprkpkwd
 121 knqityriig ytpdldpetv ddafarafqv wsdvtplrfs rihdgeadim infgrwehgd
 181 gypfdgkdgl lahafapgtg vggdshfddd elwtlgegqv vrvkygnadg eyckfpflfn
 241 gkeynsctdt grsdgflwcs ttynfekdgk ygfcphealf tmggnaegqp ckfpfrfqgt
 301 sydscttegr tdgyrwcgtt edydrdkkyg fcpetamstv ggnsegapcv fpftflgnky
 361 esctsagrsd gkmwcattan ydddrkwgfc pdqgyslflv aahefghamg lehsqdpgal
 421 mapiytytkn frlsqddikg iqelygaspd idlgtgptpt lgpvtpeick qdivfdgiaq
 481 irgeifffkd rfiwrtvtpr dkpmgpllva tfwpelpeki davyeapqee kavffagney
 541 wiysastler gypkpltslg lppdvqrvda afnwsknkkt yifagdkfwr ynevkkkmdp
 601 gfpkliadaw naipdnldav vdlqggghsy ffkgayylkl enqslksvkf gsiksdwlgc
```

An exemplary human *MMP-2* nucleic acid sequence is set forth below (SEQ ID NO: 138; GenBank Accession No: NM_004530, Version 5, incorporated herein by reference):

```
   1 acatctggcg gctgccctcc cttgtttccg ctgcatccag acttcctcag gcggtggctg
  61 gaggctgcgc atctggggct ttaaacatac aaagggattg ccaggacctg cggcggcggc
 121 ggcggcggcg ggggctgggg cgcgggggcc ggaccatgag ccgctgagcc gggcaaaccc
 181 caggccaccg agccagcgga ccctcggagc gcagccctgc gccgcggagc aggctccaac
 241 caggcggcga ggcggccaca cgcaccgagc cagcgacccc cgggcgacgc gcggggccag
 301 ggagcgctac gatggaggcg ctaatggccc ggggcgcgct cacgggtccc ctgagggcgc
 361 tctgtctcct gggctgcctg ctgagccacg ccgccgccgc gccgtcgccc atcatcaagt
 421 tccccggcga tgtcgccccc aaaacggaca aagagttggc agtgcaatac ctgaacacct
 481 tctatggctg ccccaaggag agctgcaacc tgtttgtgct gaaggacaca ctaaagaaga
 541 tgcagaagtt ctttggactg ccccagacag gtgatcttga ccagaatacc atcgagacca
 601 tgcggaagcc acgctgcggc aacccagatg tggccaacta caacttcttc cctcgcaagc
 661 ccaagtggga caagaaccag atcacataca ggatcattgg ctacacacct gatctggacc
 721 cagagacagt ggatgatgcc tttgctcgtg ccttccaagt ctggagcgat gtgaccccac
 781 tgcggttttc tcgaatccat gatggagagg cagacatcat gatcaacttt ggccgctggg
 841 agcatggcga tggatacccc tttgacggta aggacggact cctggctcat gccttcgccc
 901 caggcactgg tgttggggga gactcccatt ttgatgacga tgagctatgg accttgggag
 961 aaggccaagt ggtccgtgtg aagtatggga acgccgatgg ggagtactgc aagttccccc
1021 tcttgttcaa tggcaaggag tacaacagct gcactgatac cggccgcagc gatggcttcc
1081 tctggtgctc caccacctac aactttgaga aggatggcaa gtacggcttc tgtccccatg
1141 aagccctgtt caccatgggc ggcaacgctg aaggacagcc ctgcaagttt ccattccgct
1201 tccagggcac atcctatgac agctgcacca ctgagggccg cacggatggc taccgctggt
1261 gcggcaccac tgaggactac gaccgcgaca agaagtatgg cttctgccct gagaccgcca
1321 tgtccactgt tggtgggaac tcagaaggtg ccccctgtgt cttccccttc actttcctgg
1381 gcaacaaata tgagagctgc accagcgccg gccgcagtga cggaaagatg tggtgtgcga
1441 ccacagccaa ctacgatgat gaccgcaagt ggggcttctg ccctgaccaa gggtacagcc
1501 tgttcctcgt ggcagcccac gagtttggcc acgccatggg gctggagcac tcccaagacc
1561 ctggggccct gatggcaccc atttacacct acaccaagaa cttccgtctg tcccaggatg
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1621 acatcaaggg cattcaggag ctctatgggg cctctcctga cattgacctt ggcaccggcc
1681 ccacccccac gctgggccct gtcactcctg agatctgcaa acaggacatt gtatttgatg
1741 gcatcgctca gatccgtggt gagatcttct tcttcaagga ccggttcatt tggcggactg
1801 tgacgccacg tgacaagccc atggggcccc tgctggtggc cacattctgg cctgagctcc
1861 cggaaaagat tgatgcggta tacgaggccc cacaggagga gaaggctgtg ttctttgcag
1921 ggaatgaata ctggatctac tcagccagca ccctggagcg agggtacccc aagccactga
1981 ccagcctggg actgcccccc gatgtccagc gagtggatgc cgcctttaac tggagcaaaa
2041 acaagaagac atacatcttt gctggagaca aattctggag atacaatgag gtgaagaaga
2101 aaatggatcc tggcttcccc aagctcatcg cagatgcctg gaatgccatc cccgataacc
2161 tggatgccgt cgtggacctg cagggcggcg gtcacagcta cttcttcaag ggtgcctatt
2221 acctgaagct ggagaaccaa agtctgaaga gcgtgaagtt tggaagcatc aaatccgact
2281 ggctaggctg ctgagctggc cctggctccc acaggccctt cctctccact gccttcgata
2341 caccgggcct ggagaactag agaaggaccc ggaggggcct ggcagccgtg ccttcagctc
2401 tacagctaat cagcattctc actcctacct ggtaatttaa gattccagag agtggctcct
2461 cccggtgccc aagaatagat gctgactgta ctcctcccag gcgccccttc cccctccaat
2521 cccaccaacc ctcagagcca cccctaaaga gatactttga tattttcaac gcagccctgc
2581 tttgggctgc cctggtgctg ccacacttca ggctcttctc ctttcacaac cttctgtggc
2641 tcacagaacc cttggagcca atggagactg tctcaagagg gcactggtgg cccgacagcc
2701 tggcacaggg cagtgggaca gggcatggcc aggtggccac tccagacccc tggcttttca
2761 ctgctggctg ccttagaacc tttcttacat tagcagtttg ctttgtatgc actttgtttt
2821 tttctttggg tcttgttttt tttttccact tagaaattgc atttcctgac agaaggactc
2881 aggttgtctg aagtcactgc acagtgcatc tcagcccaca tagtgatggt tcccctgttc
2941 actctactta gcatgtccct accgagtctc ttctccactg gatggaggaa aaccaagccg
3001 tggcttcccg ctcagccctc cctgcccctc ccttcaacca ttccccatgg gaaatgtcaa
3061 caagtatgaa taaagacacc tactgagtgg ccgtgtttgc catctgtttt agcagagcct
3121 agacaagggc cacagaccca gccagaagcg gaaacttaaa aagtccgaat ctctgctccc
3181 tgcagggcac aggtgatggt gtctgctgga aaggtcagag cttccaaagt aaacagcaag
3241 agaacctcag ggagagtaag ctctagtccc tctgtcctgt agaaagagcc ctgaagaatc
3301 agcaatttg ttgctttatt gtggcatctg ttcgaggttt gcttcctctt taagtctgtt
3361 tcttcattag caatcatatc agttttaatg ctactactaa caatgaacag taacaataat
3421 atccccctca attaatagag tgctttctat gtgcaaggca cttttcacgt gtcacctatt
3481 ttaacctttc caaccacata aataaaaaag gccattatta gttgaatctt attgatgaag
3541 agaaaaaaaa aaaaaaaa
```

An exemplary human integrin subunit alpha 1 (INTGA1 or VLA1) amino acid sequence is set forth below (SEQ ID NO: 139; GenBank Accession No: NP_852478, Version 1, incorporated herein by reference):

```
   1 maprprarpg vavaccwllt vvlrccvsfn vdvknsmtfs gpvedmfgyt vqqyeneegk
  61 wvligsplvg qpknrtgdvy kcpvgrgesl pcvkldlpvn tsipnvtevk enmtfgstlv
 121 tnpnggflac gplyayrcgh lhyttgicsd vsptfqvvns iapvqecstq ldivivldgs
 181 nsiypwdsvt aflndllerm digpkqtqvg ivqygenvth efnlnkysst eevlvaakki
 241 vqrggrqtmt algidtarke afteargarr gvkkvmvivt dgeshdnhrl kkviqdcede
 301 niqrfsiail gsynrgnlst ekfveeiksi aseptekhff nvsdelalvt ivktlgerif
 361 aleatadqsa asfememsqt gfsahysqdw vmlgavgayd wngtvvmqka sqiiiprntt
 421 fnvestkkne plasylgytv nsatassgdv lyiagqpryn htgqviiyrm edgnikilqt
 481 lsgeqigsyf gsiltttdid kdsntdillv gapmymgtek eeqgkvyvya lnqtrfeyqm
 541 slepikqtcc ssrqhnsctt enknepcgar fgtaiaavkd lnldgfndiv igapleddhg
 601 gavyiyhgsg ktirkeyaqr ipsggdgktl kffgqsihge mdlngdgltd vtigglggaa
 661 lfwsrdvavv kvtmnfepnk vniqkknchm egketvcina tvcfdvklks kedtiyeadl
 721 qyrvtldslr qisrsffsgt qerkvqrnit vrksectkhs fymldkhdfq dsvritldfn
 781 ltdpengpvl ddslpnsvhe yipfakdcgn kekcisdlsl hvattekdll ivrsqndkfn
 841 vsltvkntkd sayntrtivh yspnlvfsgi eaiqkdsces nhnitckvgy pflrrgemvt
 901 fkilfqfnts ylmenvtiyl satsdseepp etlsdnvvni sipvkyevgl qfyssaseyh
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 961 isiaanetvp evinstedig neinifylir ksgsfpmpel klsisfpnmt sngypvlypt
1021 glsssenanc rphifedpfs insgkkmtts tdhlkrgtil dcntckfati tcnltssdis
1081 qvnvslilwk ptfiksyfss lnltirgelr senaslvlss snqkrelaiq iskdglpgrv
1141 plwvillsaf agllllmlli lalwkigffk rplkkkmek
```

An exemplary human *INTGA1* nucleic acid sequence is set forth below (SEQ ID NO: 140; GenBank Accession No: NM_181501, Version 1, incorporated herein by reference):

```
   1 ggtcctgccc tgcgaaccag cgcggccccc tggcgctgag gctgctccgg ccatggcccc
  61 tcggccccgc gcccgcccag gggtcgctgt cgcctgctgc tggctcctca ctgttgttct
 121 acgctgctgc gtatcattca atgttgatgt gaaaaattca atgactttca gcggcccggt
 181 ggaagacatg tttggatata ctgttcaaca atatgaaaat gaagaaggaa aatgggtgct
 241 tattggttct ccgttagttg gccaacccaa aaacagaact ggagatgtct ataagtgtcc
 301 agttgggaga ggtgaatcat taccttgtgt aaagttggat ctaccagtta atacatcaat
 361 tcccaatgtc acagaagtaa aggagaacat gacatttgga tcaactttag tcaccaaccc
 421 aaatggagga tttctggctt gtgggccctt atatgcctat agatgtggac atttgcatta
 481 cacaactgga atctgttctg acgtcagccc cacatttcaa gtcgtgaatt ccattgcccc
 541 tgtacaagaa tgcagcactc aactggacat agtcatagtg ctggatggtt ccaacagtat
 601 ttacccatgg gacagtgtta cagctttttt aaatgacctt cttgaaagaa tggatattgg
 661 tcctaaacag acacaggttg gaattgtaca gtatggagaa aacgtgaccc atgagttcaa
 721 cctcaataag tattcttcca ccgaagaggt acttgttgca gcaaagaaaa tagtccagag
 781 aggtggccgc cagactatga cagctcttgg aatagacaca gcaagaaagg aggcattcac
 841 ggaagcccgg ggtgcccgaa gaggagttaa aaaagtcatg gttattgtga cagatggaga
 901 gtctcatgac aatcatcgac tgaagaaggt catccaagac tgtgaagatg aaaacattca
 961 acggttttcc atagctattc ttggcagcta taaccgagga aatttaagca ctgaaaaatt
1021 tgtggaggaa ataaaatcaa ttgcaagtga acccactgaa aagcatttct tcaatgtctc
1081 tgatgaattg gctctagtca ccattgttaa aactctggga gaaagaatat ttgccctgga
1141 agccacagct gaccagtcag cagcttcatt tgaaatggaa atgtctcaga ctggcttcag
1201 tgctcattat tcacaggact gggtcatgct tggagcagta ggagcctatg attggaatgg
1261 aacagttgtc atgcagaagg ctagtcaaat cataatccct cgaaacacaa cctttaatgt
1321 tgagtctacc aaaaagaatg aaccgcttgc ttcttattta ggttacactg taaactctgc
1381 tactgcttct tctggagatg tgctctatat tgctggacag cctcggtaca atcatacagg
1441 ccaggtcatt atctacagga tggaagatgg aaacatcaaa attctccaga cgctcagtgg
1501 agaacagatt ggttcctact ttggcagtat tttaacaaca actgacattg acaaggattc
1561 taatactgac attcttctag tcggagcccc tatgtacatg ggaacagaga aggaggagca
1621 aggaaaagtg tatgtgtatg ctctcaatca gacaaggttt gaatatcaaa tgagcctgga
1681 acctattaag cagacgtgct gttcatctcg gcagcacaat tcatgcacaa cagaaaacaa
1741 aaatgagcca tgcggggctc gttttggaac tgcaattgct gctgtaaaag acctcaatct
1801 tgatggattt aatgacatcg tgataggagc tccgctggaa gatgatcacg ggggagctgt
1861 gtacatttat catggaagtg gcaagactat aaggaaagag tatgcacaac gtattccatc
1921 aggtggggat ggtaagacac tgaaattttt tggccagtct atccacggag aaatggattt
1981 aaatggtgac ggtctgacag atgtgactat tgggggcctt ggtggtgctg ccctcttctg
2041 gtcccgagat gtggccgtag ttaaagtgac catgaatttt gagccaaata aagtgaatat
2101 tcaaaagaaa aactgccata tggagggaaa ggaaacagta tgcataaatg ctacagtgtg
2161 ttttgatgtg aaattaaagt ctaaagaaga cacgatttat gaagctgatt tgcagtaccg
2221 tgtcacccta gattcactaa gacaaatatc acgaagtttt ttctctggaa ctcaagagag
2281 aaaggttcaa aggaacatca cagttcgaaa atcagaatgc actaagcact ccttctacat
2341 gttggacaag catgactttc aggactctgt gagaataacg ttggacttta atcttaccga
2401 tccagaaaat gggcctgttc ttgatgattc tctaccaaac tcagtacatg aatatattcc
2461 ctttgccaaa gattgtggaa ataaggaaaa atgtatctca gacctcagcc tgcatgtcgc
2521 caccactgaa aaggacctgc tgattgtccg atcccagaat gataagttca acgttagcct
2581 cacagtcaaa aatacaaagg acagtgccta taacaccagg acaatagtgc attattctcc
2641 aaatctagtt ttttcaggaa ttgaggctat ccaaaaagac agttgtgaat ctaatcataa
2701 tatcacatgt aaagttggat atcccttcct gagaagagga gagatggtaa ctttcaaaat
2761 attgtttcag tttaacacat cctatctcat ggaaaatgtg accatttatt taagtgcaac
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2821 aagtgacagc gaagaacctc ctgaaaccct ttctgataat gtagtaaaca tttctatccc
2881 ggtaaaatat gaagttggac tacagtttta cagctctgca agtgaatacc acatttcaat
2941 tgctgccaat gagacagtcc ctgaagttat taattctact gaggacattg gaaatgaaat
3001 taatatcttc tacttgatta gaaaaagtgg atcttttcca atgccagagc ttaagctgtc
3061 aatttcattc cccaatatga catcaaatgg ttaccctgtg ctgtacccaa ctggattgtc
3121 atcttctgag aatgcaaact gcagacccca tatctttgag gatcctttca gtatcaactc
3181 tggaaagaaa atgactacat caactgacca tctcaaacga ggcacaattc tggactgcaa
3241 tacatgtaaa tttgctacca tcacatgtaa tctcacttct tctgacatca gccaagtcaa
3301 tgtttcgctt atcttgtgga aaccaacttt tataaaatca tatttttcca gcttaaatct
3361 tactataagg ggagaacttc ggagtgaaaa tgcatctctg gttttaagta gcagcaatca
3421 aaaaagagag cttgctattc aaatatccaa agatgggcta ccgggcagag tgccattatg
3481 ggtcatcctg ctgagtgctt ttgccggatt gttgctgtta atgctgctca ttttagcact
3541 gtggaagatt ggattcttca aaagaccact gaaaaagaaa atggagaaat gaaatatttt
3601 atgaaagaaa ataataacaa ttattcaata atctatcctc aggtttgcct caaatatgtg
3661 acaagaaatg tataattcat gacatagtca tgtaactatg taatccatca gggattcatt
3721 acttggaaaa tgacaggtca tgcattatcc aaaaacaata ccaaaaagac atattttata
3781 aaatgacaaa aaatatttta cataattact cattttgtt gagtaagcaa aattacaaag
3841 tgtttttaaa aaaacctgta caaatatgtt tatgtattaa atcaccatcc aaaatattta
3901 aggaatatat aaaaagattt ttatgatcat agaaacatct attttcaaaa caatataaat
3961 taagcttttc cccttgattc ctgttggata tccatgttca gcatgacagt cagcactcgt
4021 aaatgccaag aaaagaatta cctgaaaaag atcatttctc cctattcaaa tgagaatatt
4081 ttcccttggt agaatccata tacaatatgg attgaaaatt aagtcaccaa gaatacattt
4141 agcatctttg tgttgggttc tatacctaaa aattttccct ccctgcccaa ggtgattgga
4201 aagtactgca attgagctaa aattttatct aggatggaaa atcaggatag actcgtttaa
4261 aaacaagtat attaaatggg ttaaattaag cttttacaga acatgcttaa ttttgatatt
4321 gagctctaaa tgcaaaactc ttttatactg aaaaaacact taaagtagtt ttgtgtggca
4381 tcacagtgat ttgtcatgaa aagccatata tgggggacat gctaaaatgg cttctgaatg
4441 aaatacgaca gcagagaaag atgccactga aatgctgaaa ttatctttgc tgagcagctt
4501 ttgaatgcta agggttccag tatgtgaccc aaagaaagag ttgtctcaac tccttggtac
4561 agggttcatt caaaccccca agctgtgaga gtgtgtttat ttttaatttt ttaaaaggta
4621 tttaatttcc aaccacactt cttatttttt tgaaaagaca attttccatt tcagtattac
4681 attttaccaa gaagtcactg ctttttaggt gtgttgcatc aatatttaaa taaaatccca
4741 gaaatgtatt ttaaagaatt tcaggtttga aaactcaaac caacaggaag atatcaaaaa
4801 aaaaaaaaaa a
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An exemplary human integrin subunit alpha 2 (INTGA2) amino acid sequence is set forth below (SEQ ID NO: 141; GenBank Accession No: P17301, Version 1, incorporated herein by reference):

```
   1 mgpertgaap lplllvlals qgilncclay nvglpeakif sgpsseqfgy avqqfinpkg
  61 nwllvgspws gfpenrmgdv ykcpvdlsta tceklnlqts tsipnvtemk tnmslglilt
 121 rnmgtggflt cgplwaqqcg nqyyttgvcs dispdfqlsa sfspatqpcp slidvvvvcd
 181 esnsiypwda vknflekfvq gldigptktq vgliqyannp rvvfnlntyk tkeemivats
 241 qtsqyggdlt ntfgaiqyar kyaysaasgg rrsatkvmvv vtdgeshdgs mlkavidqcn
 301 hdnilrfgia vlgylnrnal dtknlikeik aiasiptery ffnvsdeaal lekagtlgeq
 361 ifsiegtvqg gdnfqmemsq vgfsadyssq ndilmlgavg afgwsgtivq ktshghlifp
 421 kqafdqilqd rnhssylgys vaaistgest hfvagapran ytgqivlysv nengnitviq
 481 ahrgdqigsy fgsvlcsvdv dkdtitdvll vgapmymsdl kkeegrvylf tikkgilgqh
 541 qflegpegie ntrfgsaiaa lsdinmdgfn dvivgsplen qnsgavyiyn ghqgtirtky
 601 sqkilgsdga frshlqyfgr sldgygdlng dsitdvsiga fgqvvqlwsq siadvaieas
 661 ftpekitlvn knaqiilklc fsakfrptkq nnqvaivyni tldadgfssr vtsrglfken
 721 nerclqknmv vnqaqscpeh iiyiqepsdv vnsldlrvdi slenpgtspa leaysetakv
 781 fsipfhkdcg edglcisdlv ldvrqipaaq eqpfivsnqn krltfsvtlk nkresayntg
 841 ivvdfsenlf fasfslpvdg tevtcqvaas qksvacdvgy palkreqqvt ftinfdfnlq
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 901 nlqnqaslsf qalsesqeen kadnlvnlki pllydaeihl trstninfye issdgnvpsi
 961 vhsfedvgpk fifslkvttg svpvsmatvi ihipqytkek nplmyltgvq tdkagdiscn
1021 adinplkigq tsssvsfkse nfrhtkelnc rtascsnvtc wlkdvhmkge yfvnvttriw
1081 ngtfasstfq tvqltaaaei ntynpeiyvi edntvtiplm imkpdekaev ptgviigsii
1141 agillllalv ailwklgffk rkyekmtknp deidettels s
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An exemplary human *INTGA2* nucleic acid sequence is set forth below (SEQ ID NO: 142; GenBank Accession No: NM_002203, Version 3, incorporated herein by reference):

```
   1 ttttccctgc tctcaccggg cgggggagag aagccctctg gacagcttct agagtgtgca
  61 ggttctcgta tccctcggcc aagggtatcc tctgcaaacc tctgcaaacc cagcgcaact
 121 acggtccccc ggtcagaccc aggatggggc cagaacggac aggggccgcg ccgctgccgc
 181 tgctgctggt gttagcgctc agtcaaggca ttttaaattg ttgtttggcc tacaatgttg
 241 gtctcccaga agcaaaaata ttttccggtc cttcaagtga acagtttggc tatgcagtgc
 301 agcagtttat aaatccaaaa ggcaactggt tactggttgg ttcaccctgg agtggctttc
 361 ctgagaaccg aatgggagat gtgtataaat gtcctgttga cctatccact gccacatgtg
 421 aaaaactaaa tttgcaaact tcaacaagca ttccaaatgt tactgagatg aaaaccaaca
 481 tgagcctcgg cttgatcctc accaggaaca tgggaactgg aggttttctc acatgtggtc
 541 ctctgtgggc acagcaatgt gggaatcagt attacacaac gggtgtgtgt tctgacatca
 601 gtcctgattt tcagctctca gccagcttct cacctgcaac tcagccctgc ccttccctca
 661 tagatgttgt ggttgtgtgt gatgaatcaa atagtattta tccttgggat gcagtaaaga
 721 atttttgga aaaatttgta caaggcctgg atataggccc cacaaagaca caggtggggt
 781 taattcagta tgccaataat ccaagagttg tgtttaactt gaacacatat aaaaccaaag
 841 aagaaatgat tgtagcaaca tcccagacat cccaatatgg tggggacctc acaaacacat
 901 tcggagcaat tcaatatgca agaaaatatg cttattcagc agcttctggt gggcgacgaa
 961 gtgctacgaa agtaatggta gttgtaactg acggtgaatc acatgatggt tcaatgttga
1021 aagctgtgat tgatcaatgc aaccatgaca atatactgag gtttggcata gcagttcttg
1081 ggtacttaaa cagaaacgcc cttgatacta aaaatttaat aaaagaaata aaagcaatcg
1141 ctagtattcc aacagaaaga tacttttca atgtgtctga tgaagcagct ctactagaaa
1201 aggctgggac attaggagaa caaattttca gcattgaagg tactgttcaa ggaggagaca
1261 actttcagat ggaaatgtca caagtgggat tcagtgcaga ttactcttct caaaatgata
1321 ttctgatgct gggtgcagtg ggagcttttg gctggagtgg gaccattgtc cagaagacat
1381 ctcatggcca tttgatcttt cctaaacaag cctttgacca aattctgcag gacagaaatc
1441 acagttcata tttaggttac tctgtggctg caatttctac tggagaaagc actcactttg
1501 ttgctggtgc tcctcgggca aattataccg gccagatagt gctatatagt gtgaatgaga
1561 atggcaatat cacggttatt caggctcacc gaggtgacca gattggctcc tattttggta
1621 gtgtgctgtg ttcagttgat gtggataaag acaccattac agacgtgctc ttggtaggtg
1681 caccaatgta catgagtgac ctaaagaaag aggaaggaag agtctacctg tttactatca
1741 aagagggcat tttgggtcag caccaatttc ttgaaggccc cgagggcatt gaaaacactc
1801 gatttggttc agcaattgca gctctttcag acatcaacat ggatggcttt aatgatgtga
1861 ttgttggttc accactagaa aatcagaatt ctggagctgt atacatttac aatggtcatc
1921 agggcactat ccgcacaaag tattcccaga aaatcttggg atccgatgga gcctttagga
1981 gccatctcca gtactttggg aggtccttgg atggctatgg agatttaaat ggggattcca
2041 tcaccgatgt gtctattggt gcctttggac aagtggttca actctggtca caaagtattg
2101 ctgatgtagc tatagaagct tcattcacac cagaaaaaat cactttggtc aacaagaatg
2161 ctcagataat tctcaaactc tgcttcagtg caaagttcag acctactaag caaaacaatc
2221 aagtggccat tgtatataac atcacacttg atgcagatgg attttcatcc agagtaacct
2281 ccaggggggtt atttaaagaa aacaatgaaa ggtgcctgca gaagaatatg gtagtaaatc
2341 aagcacagag ttgccccgag cacatcattt atatacagga gccctctgat gttgtcaact
2401 ctttggattt gcgtgtggac atcagtctgg aaaaccctgg cactagccct gcccttgaag
2461 cctattctga gactgccaag gtcttcagta ttcctttcca caaagactgt ggtgaggacg
2521 gactttgcat ttctgatcta gtcctagatg tccgacaaat accagctgct caagaacaac
2581 cctttattgt cagcaaccaa aacaaaaggt taacattttc agtaacgctg aaaaataaaa
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2641 gggaaagtgc atacaacact ggaattgttg ttgatttttc agaaaacttg ttttttgcat
2701 cattctccct gccggttgat gggacagaag taacatgcca ggtggctgca tctcagaagt
2761 ctgttgcctg cgatgtaggc taccctgctt taaagagaga acaacaggtg acttttacta
2821 ttaactttga cttcaatctt caaaaccttc agaatcaggc gtctctcagt ttccaagcct
2881 taagtgaaag ccaagaagaa aacaaggctg ataatttggt caacctcaaa attcctctcc
2941 tgtatgatgc tgaaattcac ttaacaagat ctaccaacat aaatttttat gaaatctctt
3001 cggatgggaa tgttccttca atcgtgcaca gttttgaaga tgttggtcca aaattcatct
3061 tctccctgaa ggtaacaaca ggaagtgttc cagtaagcat ggcaactgta atcatccaca
3121 tccctcagta taccaaagaa aagaacccac tgatgtacct aactggggtg caaacagaca
3181 aggctggtga catcagttgt aatgcagata tcaatccact gaaaatagga caaacatctt
3241 cttctgtatc tttcaaaagt gaaaatttca ggcacaccaa agaattgaac tgcagaactg
3301 cttcctgtag taatgttacc tgctggttga aagacgttca catgaaagga gaatactttg
3361 ttaatgtgac taccagaatt tggaacggga ctttcgcatc atcaacgttc cagacagtac
3421 agctaacggc agctgcagaa atcaacacct ataaccctga gatatatgtg attgaagata
3481 acactgttac gattcccctg atgataatga aacctgatga gaaagccgaa gtaccaacag
3541 gagttataat aggaagtata attgctggaa tccttttgct gttagctctg gttgcaattt
3601 tatggaagct cggcttcttc aaaagaaaat atgaaaagat gaccaaaaat ccagatgaga
3661 ttgatgagac cacagagctc agtagctgaa ccagcagacc tacctgcagt gggaaccggc
3721 agcatcccag ccagggtttg ctgtttgcgt gaatggattt ctttttaaat cccatatttt
3781 ttttatcatg tcgtaggtaa actaacctgg tattttaaga gaaaactgca ggtcagtttg
3841 gaatgaagaa attgtggggg gtgggggagg tgcggggggc aggtagggaa ataataggga
3901 aaatacctat tttatatgat gggggaaaaa aagtaatctt taaactggct ggcccagagt
3961 ttacattcta atttgcattg tgtcagaaac atgaaatgct tccaagcatg acaacttta
4021 aagaaaaata tgatactctc agattttaag ggggaaaact gttctcttta aaatatttgt
4081 ctttaaacag caactacaga agtggaagtg cttgatatgt aagtacttcc acttgtgtat
4141 attttaatga atattgatgt taacaagagg ggaaaacaaa acacaggttt tttcaattta
4201 tgctgctcat ccaaagttgc cacagatgat acttccaagt gataatttta tttataaact
4261 aggtaaaatt tgttgttggt tccttttaga ccacggctgc cccttccaca ccccatcttg
4321 ctctaatgat caaaacatgc ttgaataact gagcttagag tatacctcct atatgtccat
4381 ttaagttagg agaggggcg atatagagaa taaggcacaa aattttgttt aaaactcaga
4441 atataacatg taaaatccca tctgctagaa gcccatcctg tgccagagga aggaaaagga
4501 ggaaatttcc tttctctttt aggaggcaca acagttctct tctaggattt gtttggctga
4561 ctggcagtaa cctagtgaat ttctgaaaga tgagtaattt ctttggcaac cttcctcctc
4621 ccttactgaa ccactctccc acctcctggt ggtaccatta ttatagaagc cctctacagc
4681 ctgactttct ctccagcggt ccaaagttat cccctccttt acccctcatc caaagttccc
4741 actccttcag gacagctgct gtgcattaga tattaggggg gaaagtcatc tgtttaattt
4801 acacacttgc atgaattact gtatataaac tccttaactt cagggagcta ttttcattta
4861 gtgctaaaca agtaagaaaa ataagctcga gtgaatttct aaatgttgga atgttatggg
4921 atgtaaacaa tgtaaagtaa gacatctcag gatttcacca gaagttacag atgaggcact
4981 ggaagccacc aaattagcag gtgcaccttc tgtggctgtc ttgtttctga agtacttaaa
5041 cttccacaag agtgaatttg acctaggcaa gtttgttcaa aaggtagatc ctgagatgat
5101 ttggtcagat tgggataagg cccagcaatc tgcattttaa caagcacccc agtcactagg
5161 atgcagatgg accacacttt gagaaacacc acccatttct acttttgca ccttattttc
5221 tctgttcctg agcccccaca ttctctagga gaaacttaga ggaaaagggc acagacacta
5281 catatctaaa gctttggaca agtccttgac ctctataaac ttcagagtcc tcattataaa
5341 atgggaagac tgagctggag ttcagcagtg atgcttttag ttttaaaagt ctatgatctg
5401 gacttcctat aatacaaata cacaatcctc caagaatttg acttggaaaa aaatgtcaaa
5461 ggaaaacagg ttatctgccc atgtgcatat ggacaacctt gactaccctg gcctggcccg
5521 tggtggcagt ccagggctat ctgtactgtt tacagaatta ctttgtagtt gacaacacaa
5581 aacaaacaaa aaaggcataa aatgccagcg gtttatagaa aaaacagcat ggtattctcc
5641 agttaggtat gccagagtcc aattctttta acagctgtga gaatttgctg cttcattcca
5701 acaaaatttt atttaaaaaa aaaaaaaaaa gactggagaa actagtcatt agcttgataa
5761 agaatattta acagctagtg gtgctggtgt gtacctgaag ctccagctac ttgagagact
5821 gagacaggaa gatcgcttga gcccaggagt tcaagtccag cctaagcaac atagcaagac
5881 cctgtctcaa aaaaatgact atttaaaaag acaatgtggc caggcacggt ggctcacacc
5941 tgtaatccca acactttggg aggctgaggc cggtggatca cgaggtcagg agtttgagac

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6001 tagcctggcc aacatggtga aaccccatct ctaataatat aaaaattagc tgggcgtagt
6061 agcaggtgcc tgtaatccca gttactcggg aagctgaggc aggagaatca cttgaacccg
6121 ggaggcagag gtttcagtga gccgagatcg cgccactgca ctccagcctg ggtgacaggg
6181 caagactctg tctcaaacaa acaaacaaaa aaaaagttag tactgtatat gtaaatacta
6241 gcttttcaat gtgctataca aacaattata gcacatcctt ccttttactc tgtctcacct
6301 cctttaggtg agtacttcct taaataagtg ctaaacatac atatacggaa cttgaaagct
6361 ttggttagcc ttgccttagg taatcagcct agtttacact gtttccaggg agtagttgaa
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6541 accttgtagg acagcagccc tgtcctagaa ggtatgttta gcagcattcc tggcctctag
6601 ctacccgatg ccagagcatg ctccccccgc agtcatgaca atcaaaaaat gtctccagac
6661 attgtcaaat gcctcctggg gggcagtatt tctcaagcac ttttaagcaa aggtaagtat
6721 tcatacaaga aatttagggg gaaaaaacat tgtttaaata aaagctatgt gttcctattc
6781 aacaatattt ttgctttaaa agtaagtaga gggcataaaa gatgtcatat tcaaatttcc
6841 atttcataaa tggtgtacag acaaggtcta tagaatgtgg taaaaacttg actgcaacac
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7081 gccaatttat tatagtcaca caagtgatta tactaaaaat tattataaag gttataattt
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7381 tatgaaatag gtgaaaatct taactatttc tttgaactct aaagactgaa actgtagcca
7441 ttatgtaaat aaagtttcat atgtacctgt ttatttggc agattaagtc aaaatatgaa
7501 tgtatatatt gcataactat gttagaattg tatatatttt aaagaaattg tcttggatat
7561 tttcctttat acataataga taagtctttt ttcaaatgtg gtgtttgatg tttttgatta
7621 aatgtgtttt gcctctttcc acaaaaactg taaaaataaa tgcatgtttg tacaaaaagt
7681 tgcagaattc atttgattta tgagaaacaa aaattaaatt gtagtcaaca gttagtagtt
7741 tttctcatat ccaagtataa caaacagaaa agtttcatta ttgtaaccca ctttttcat
7801 accacattat tgaatattgt tacaattgtt ttgaaaataa agccattttc tttgggcttt
7861 tataagttaa aaaaaaaa
```

An exemplary human integrin subunit alpha 3 (INTGA3) amino acid sequence is set forth below (SEQ ID NO: 143; GenBank Accession No: AAI36637, Version AAI36637.1, incorporated herein by reference):

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  1 mgpgpsrapr aprlmlcala lmvaaggcvv safnldtrfl vvkeagnpgs lfgysvalhr
 61 qterqqryll lagaprelav pdgytnrtga vylcpltahk ddcermnitv kndpghhiie
121 dmwlgvtvas qgpagrvlvc ahrytqvlws gsedqrrmvg kcyvrgndle ldssddwqty
181 hnemcnsntd yletgmcqlg tsggftqntv yfgapgaynw kgnsymiqrk ewdlseysyk
241 dpedqgnlyi gytmqvgsfi lhpknitivt gaprhrhmga vfllsqeagg dlrrrqvleg
301 sqvgayfgsa ialadlnndg wqdllvgapy yferkeevgg aiyvfmnqag tsfpahpsll
361 lhgpsgsafg lsvasigdin qdgfqdiavg apfeglgkvy iyhssskgll rqpqqvihge
421 klglpglatf gyslsgqmdv denfypdllv gslsdhivll rarpvinivh ktlvprpavl
481 dpalctatsc vqvelcfayn qsagnpnyrr nitlaytlea drdrrpprlr fagsesavfh
541 gffsmpemrc qklelllmdn lrdklrpiii smnyslplrm pdrprlglrs ldaypilnqa
601 qalenhtevq fqkecgpdnk cesnlqmraa fvseqqqkls rlqysrdvrk lllsinvtnt
661 rtsersgeda healltlvvp palllssvrp pgacqaneti fcelgnpfkr nqrmelliaf
721 evigvtlhtr dlqvqlqlst sshqdnlwpm iltllvdytl qtslsmvnhr lqsffggtvm
781 gesgmktved vgsplkyefq vgpmgeglvg lgtlvlglew pyevsngkwl lypteitvhg
841 ngswpcrppg dlinplnltl sdpgdrpssp qrrrrqldpg ggqgpppvtl aaakkakset
901 vltcatgrah cvwlecpipd apvvtnvtvk arvwnstfie dyrdfdrvrv ngwatlflrt
961 siptinmenk ttwfsvdids elveelpaei elwlvlvavg agllllglii lllwkcgffk
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```
1021 rartralyea krqkaemksq pseterltdd y
```

An exemplary human INTGA3 nucleic acid sequence is set forth below (SEQ ID NO: 144; GenBank Accession No: NG_029107, Version NG_029107.2, incorporated herein by reference):

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   1 atgcataagg gcccatgtgc acagacacat gttttgatca tcatacgtgt aggaaccctc
  61 tacccccagt ggagtgtcta gggagttagt gggtaaaagt agatgaagcc ctgcccccga
 121 cctctccaga tttcccacct gagcacagaa ccctgccagt aaagaggctt ctccacagga
 181 aatggcaagg cccttggggg gtggtgactc agccctgact cagccatgtg gcctcctggg
 241 ctccaaaggg ccaccttgac ttgaggttga gaatgctgta ggcacagcag agtcttaatc
 301 tcccagccag gaaagaaggg gactctgggg gccagggcag ggcatgtgca gcagggccag
 361 gccctgggca gtaggaaagg aagagagaga cagagggatg gcaggcaggg aagtccccgg
 421 atgtttgggg cctactcacc acgccctcat agagatcatt gcctattaat ccccagaaag
 481 cctctgcact ttccctcctt cacttccagc atccctctcg ccccacacct gtccctgaag
 541 tcccagtcaa atcagtaccc tgggcctttc ttactcattc cctctctccc tccctcagcc
 601 ctgctcctgc tcagcccact tcttggccaa attattacag tagctgcctt cccccacaac
 661 ccagtctgtc ctggcaaagt caacttcatg tggcagccag aatgttctga cagccccctt
 721 tgtcccacaa gcaccacccc taacatacaa tgcaaagtgg gtttagcctg tttaaatgtg
 781 agagcaacca gaacatgagg ccacatcctg gcctcctcta agtcatcccc gggttgggac
 841 tcagcccagg attggtacat agtaggctgt caatgaatgc ttgagcctgg cagattctga
 901 gccaggggaa tcgcctggac taggcctgca tctgggccat aggagaagga aatctgataa
 961 atccattcaa tcttcagcac tcctccctcc ctccctcttc agtaatttgc attttcaatt
1021 caagtcagat agacccctga gtctcagtcc aatagctgag atttggtaca cttcgttgaa
1081 cagatattag aaggtttggg atacaatgaa tgtagattgg ggaatagtga gagatttctc
1141 tccagccctt tcatttcaca catggagaaa ccgaggcctg gaacggaagg taacttgccc
1201 aaggtgagaa ggcagaagag agcttgcatt caacggaggg gcacaccatt gcaattcctt
1261 gttatttttc cagcagctgc ctgtgtgctt cacgtctctg tgctgatctg cccgagaggt
1321 gatggtgtcc attggtgtgc tctggggctc tgggagagtg agatgagggc tggggagagg
1381 gcaggtagag gaagacttgt gggaacacag caagcgctaa ataaacagaa gccgcctttg
1441 tgggatattg acattgtcat tgttccagct gggaaaactt cacctgaacc aggacccaat
1501 ttttctgcct ctcttctcca gctccttttct ttccctgttg tccagataca cctcctccag
1561 ggagcttcca tgacccccca gcagaactca ccatttgcat gttgttacgg tcacctgcag
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1981 ctcattacac atattattcc tgtgtccttg tttctctgtc tgtctgtgtg tttctaggtg
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2101 gggatgagat gatcctacag acgacggtgc cactgaaacc aaagaaccct gagatttctc
2161 tttctccatc tctccagctg agatccttct agtctccatg tctccctcca ctcccactcc
2221 atctccccag actggtctga cactccccca cattctttag ctcaggccct ccccctacca
2281 gtcgcccctg ctctgctcca cattccctct ggacactccc ctggagtgga aaaaccatcc
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2401 gtccaaagag ataaggcctg gcatggggcc aatctgtcat cgcaggactc tcaaagctgt
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37681 ccccatctct gtaaaccaca gccatgtcca gaataattct acactcccat ttccacccct
37741 agggaaggag gggagcagta gagaccctcc tcctgggaac tagcctgttt cctcctgagc
37801 aacccttcca ggataacaaa tggacccatt cccaacattg tggtcagggt agactgccca
37861 gtcttcctgg ccattccatc cactgtctct gcagctgccc tcggtctcca tctgcctctt
37921 cctctgctct ctgccttcct caactccttc ttcctctggg gcctggggtg gagaaactca
37981 tcctccgtat ctcagtgcag agagatggga tgcgtttcgg tcaagagttc tggctttgag
38041 gagttctggg tgggagaggg agaggcctgg cactccttcc tggtggctca aactctggat
38101 gctaatgttc tttctcttct ccctccaact ccagtgtgac ttctttaagc ggacccgcta
38161 ttatcagatc atgcccaagt accacgcagt gcggatccgg gaggaggagc gctacccacc
38221 tccagggagc accctgccca ccaagaagca ctgggtgacc agctggcaga ctcgggacca
38281 atactactga cgtcctccct gatcccaccc cctcctcccc cagtgtcccc tttcttccta
38341 tttatcataa gttatgcctc tgacagtcca caggggccac caccttggc tggtagcagc
38401 aggctcaggc acatacacct cgtcaagagc atgcacatgc tgtctggccc tggggatctt
38461 cccacaggag ggccagcgct gtggacctta caacgccgag tgcactgcat tcctgtgccc
38521 tagatgcacg tggggcccac tgctcgtgga ctgtgctggt gcatcacgga tggtgcatgg
38581 gctcgccgtg tctcagcctc tgccagcgcc aaaacaagcc aaagagcctc ccaccagagc
38641 cgggaggaaa aggcccctgc aatgtggtga cacctccccc tttcacactg gatccatctt
38701 gagccacagt cactggattg actttgctgt caaaactact gacagggagc agcccccggg
38761 ccgctggctg gtgggccccc aatgacaccc atgccagaga ggtggggatc ctgcctaagg
38821 ttgtctacgg gggcacttgg aggacctggc gtgctcagac ccaacagcaa aggaactaga
38881 aagaaggacc cagaacggct tgctttcctg catctctgtg aagcctctct ccttggccac
38941 agactgaact cgcagggaat gcagcaggaa ggaacaaaga caggcaaacg gcaacgtagc
39001 ctgggctcac tgtgctgggg cacggcggga tcctccacag agaggagggg accaattctg
39061 gacagacaga tgttgggagg atacagagga gatgccactt ctcactcacc actaccagcc
39121 agcctcagaa ggccccagag agaccctgca agaccacgga gggagcgaca cttgaatgta
39181 gaataggcag ggggccctgc cccaccccat ccagccagac cccacgctga ccatgcgtca
39241 ggggcctaga ggtggagttc ttagctatcc ttggctttca gagccagcct ggctctgccc
39301 cctcccccat gggctgtgtc ctaaggccca tttgagaagc tgaggctagt tccagaaaac
39361 ctctcctgac ccctgcctgt tggcaggccc actccccagc cccagcccct tccatggtac
39421 tgtagcaggg gaattccctc cccctccttg tgccttcttt gtatataggc ttctcacggc
39481 gaccaataaa cagctcccag tttgtatgca gctgcatctg cttccaccca ctccccagcc
39541 tttaccaacc ccaggtcaat ggatgatgat atcatccagc caacacctag gtaggatgaa
39601 gccaggtctg gggacttgcg ggtttgaggg taaagattga tggaggtggc caggtgcagt
39661 ggctcacacc tgtaatccca gcactttggg aggccaaggc atgcagatca cctgaggtca
39721 ggagttcaag accagcctgg ccaacatggt gaaaccctgt gtctactaaa aatacaaaag
39781 ttagctgggc gcagtggcgc atgcctataa tcccagctac ttgggaggct gaagtaggag

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39841 aatcacttga acccaggagg cagaggttgc agtgagccga gatcgtgcca ttgcactcca
39901 gcctgaacga cagagcaaga ctctgtctca aagaaaaata aaaagattga tggaggtgac
39961 actggccccc gctctcagga atcctctcat ctaagggtca gtcatagaga tccagaacag
40021 aagatgaggg gtaagccttg ggagacctgg atgaaaccca gaacgccttc ttggaggaca
40081 gcgtgctgac cctggggagg gacgagcagg cagaggtggc agtgtgcagg gtcgggaaga
40141 ggtaaaagct actcagctgt aggaacaggc agtcctggca ggctgtggag ggaggctggg
40201 tgcaagggtg gagagaggag agcccttagt cgggctgaat tcaggtaaga gcctgctttc
40261 ctgccttggt ttccccacaa ccaccaccag acgccaataa gagatcagaa ggtaaaccac
40321 tgatccaagg ctgcagagac tgaactgtca caaggtccag cctccaggag ctgagagctc
40381 tggtctttca gaagctcctt gggagtgttt gagcgcctgg cttacatggc aacagcacgt
40441 ggatcaagcc ttcgctttgc ttcctgccat gtcctgggtt cccaaagcag cttcctcctt
40501 tgccctcggt ttgtcccctc cacacaggcc tggggaatgg agtaaggctg ttccccctgt
40561 gacctggaat gtggcctagg tccttctgtt aattttcctt aaggctgtga actttggcaa
40621 gacttcactg gaggctggaa attgctaccc agagaagcgc agaggtagaa gccaggtcag
40681 atatgctcag agctcacaga cccaggctgt tctgggagac ccacctgatg cctgggtgcc
40741 tcccagcctc cttgtggtgg cagctgcctg ccccacctcc ctccaccagc gctcagctca
40801 caacagggtt ctgggcccaa tgtccgcccc tttccctctc ctcactttct gtgccgggat
40861 ttgccccttc ccagggtgac tgacaatgga atgtccactt tcccaaggaa aaccctagcc
40921 cctacccgga gctgccaagc tctcagaacc cagtgaatgg agaccacact ttattttcta
40981 gaatctggga tccagttctt tgggcataac atgtgtgggt tgtcaaagct cggcccagtc
41041 ttgtccttac agccacttcc tgcttaagac aggggtgttg acacatccct ctggccagtt
41101 tcacagaccc cctagtctcc tgtgagccac tgcttgagga agacccccccc cacacacaca
41161 cacactcttg aggataggtc attttcagaa ctagcgtgag ctacatatta tgaaagaaac
41221 ataactggca gagatatagc aatgcccact gtaaaagaac cctctgcaat gccaagtttc
41281 ttgagctcct tggagagtcc ccccccacca acccacactg tacatatagt gggagatttg
41341 ggaatcggtg ggggtgcagt ttacctcggc atcacctaac caaacttgac tatgatgtac
41401 cacatcacac cactgctgtt agcaccctgc agcaggctct gcagaaagag ttcttatcca
41461 agcacagagc ccacattatg gaagtccagc ctaaggtgag ggtcatggga
```

An exemplary human integrin subunit alpha 5 (INTGA5) amino acid sequence is set forth below (SEQ ID NO: 145; GenBank Accession No: NP_002196, Version NP_002196.4, incorporated herein by reference):

```
   1 mgsrtpespl havqlrwgpr rrppllplll lllpppprvg gfnldaeapa vlsgppgsff
  61 gfsvefyrpg tdgvsvlvga pkantsqpgv lqggavylcp wgasptqctp iefdskgsrl
 121 lesslssseg eepveykslq wfgatvrahg ssilacaply swrtekepls dpvgtcylst
 181 dnftrileya pcrsdfswaa gqgycqggfs aeftktgrvv lggpgsyfwq gqilsatqeq
 241 iaesyypeyl inlvqgqlqt rqassiydds ylgysvavge fsgddtedfv agvpkgnlty
 301 gyvtilngsd irslynfsge qmasyfgyav aatdvngdgl ddllvgapll mdrtpdgrpq
 361 evgrvyvylq hpagieptpt ltltghdefg rfgssltplg dldqdgyndv aigapfgget
 421 qqgvvfvfpg gpgglgskps qvlqplwaas htpdffgsal rggrdldgng ypdlivgsfg
 481 vdkavvyrgr pivsasaslt ifpamfnpee rscslegnpv acinlsfcln asgkhvadsi
 541 gftvelqldw qkqkggvrra lflasrqatl tqtlliqnga redcremkiy lrnesefrdk
 601 lspihialnf sldpqapvds hglrpalhyq sksriedkaq illdcgedni cvpdlqlevf
 661 geqnhvylgd knalnltfha qnvgeggaye aelrvtappe aeysglvrhp gnfsslscdy
 721 favnqsrllv cdlgnpmkag aslwgglrft vphlrdtkkt iqfdfqilsk nlnnsqsdvv
 781 sfrlsveaqa qvtlngvskp eavlfpvsdw hprdqpqkee dlgpavhhvy elinqgpssi
 841 sqgvlelscp qalegqqlly vtrvtglnct tnhpinpkgl eldpegslhh qqkreapsrs
 901 sassgpqilk cpeaecfrlr celgplhqqe sqslqlhfrv waktflqreh qpfslqceav
 961 ykalkmpyri lprqlpqker qvatavqwtk aegsygvplw iiilailfgl lllglliyil
1021 yklgffkrsl pygtamekaq lkppatsda
```

An exemplary human *INTGA5* nucleic acid sequence is set forth below (SEQ ID NO: 146; GenBank Accession No: NM_002205, Version NM_002205.4, incorporated herein by reference):

```
   1 attcgcctct gggaggttta ggaagcggct ccgggtcggt ggccccagga cagggaagag
  61 cgggcgctat ggggagccgg acgccagagt cccctctcca cgccgtgcag ctgcgctggg
 121 gccccggcg ccgacccccg ctgctgccgc tgctgttgct gctgctgccg ccgccaccca
 181 gggtcggggg cttcaactta gacgcggagg ccccagcagt actctcgggg cccccgggct
 241 ccttcttcgg attctcagtg gagttttacc ggccgggaac agacggggtc agtgtgctgg
 301 tgggagcacc caaggctaat accagccagc caggagtgct gcagggtggt gctgtctacc
 361 tctgtccttg gggtgccagc cccacacagt gcacccccat tgaatttgac agcaaaggct
 421 ctcggctcct ggagtcctca ctgtccagct cagagggaga ggagcctgtg gagtacaagt
 481 ccttgcagtg gttcggggca acagttcgag cccatggctc ctccatcttg gcatgcgctc
 541 cactgtacag ctggcgcaca gagaaggagc cactgagcga ccccgtgggc acctgctacc
 601 tctccacaga taacttcacc cgaattctgg agtatgcacc ctgccgctca gatttcagct
 661 gggcagcagg acagggttac tgccaaggag gcttcagtgc cgagttcacc aagactggcc
 721 gtgtggtttt aggtggacca ggaagctatt tctggcaagg ccagatcctg tctgccactc
 781 aggagcagat tgcagaatct tattaccccg agtacctgat caacctggtt caggggcagc
 841 tgcagactcg ccaggccagt tccatctatg atgacagcta cctaggatac tctgtggctg
 901 ttggtgaatt cagtggtgat gacacagaag actttgttgc tggtgtgccc aaagggaacc
 961 tcacttacgg ctatgtcacc atccttaatg gctcagacat tcgatccctc tacaacttct
1021 caggggaaca gatggcctcc tactttggct atgcagtggc cgccacagac gtcaatgggg
1081 acgggctgga tgacttgctg gtgggggcac ccctgctcat ggatcggacc cctgacgggc
1141 ggcctcagga ggtgggcagg gtctacgtct acctgcagca cccagccggc atagagccca
1201 cgcccaccct taccctcact ggccatgatg agtttggccg atttggcagc tccttgaccc
1261 ccctgggggа cctggaccag gatggctaca atgatgtggc catcggggct ccctttggtg
1321 gggagaccca gcagggagta gtgtttgtat ttcctggggg cccaggaggg ctgggctcta
1381 agccttccca ggttctgcag cccctgtggg cagccagcca caccccagac ttctttggct
1441 ctgcccttcg aggaggccga gacctggatg gcaatggata tcctgatctg attgtggggt
1501 cctttggtgt ggacaaggct gtggtataca ggggccgccc catcgtgtcc gctagtgcct
1561 ccctcaccat cttccccgcc atgttcaacc cagaggagcg gagctgcagc ttagagggga
1621 accctgtggc ctgcatcaac cttagcttct gcctcaatgc ttctggaaaa cacgttgctg
1681 actccattgg tttcacagtg gaacttcagc tggactggca gaagcagaag ggaggggtac
1741 ggcgggcact gttcctggcc tccaggcagg caaccctgac ccagaccctg ctcatccaga
1801 atggggctcg agaggattgc agagagatga agatctacct caggaacgag tcagaatttc
1861 gagacaaact ctcgccgatt cacatcgctc tcaacttctc cttggacccc caagccccag
1921 tggacagcca cggcctcagg ccagccctac attatcagag caagagccgg atagaggaca
1981 aggctcagat cttgctggac tgtggagaag acaacatctg tgtgcctgac ctgcagctgg
2041 aagtgtttgg ggagcagaac catgtgtacc tgggtgacaa gaatgccctg aacctcactt
2101 tccatgccca gaatgtgggt gagggtggcg cctatgaggc tgagcttcgg gtcaccgccc
2161 ctccagaggc tgagtactca ggactcgtca gacacccagg gaacttctcc agcctgagct
2221 gtgactactt tgccgtgaac cagagccgcc tgctggtgtg tgacctgggc aaccccatga
2281 aggcaggagc cagtctgtgg ggtggccttc ggtttacagt ccctcatctc cgggacacta
2341 agaaaaccat ccagtttgac ttccagatcc tcagcaagaa tctcaacaac tcgcaaagcg
2401 acgtggtttc ctttcggctc tccgtggagg ctcaggccca ggtcaccctg aacggtgtct
2461 ccaagcctga ggcagtgcta ttcccagtaa gcgactggca tccccgagac cagcctcaga
2521 aggaggagga cctgggacct gctgtccacc atgtctatga gctcatcaac caaggcccca
2581 gctccattag ccagggtgtg ctggaactca gctgtcccca ggctctggaa ggtcagcagc
2641 tcctatatgt gaccagagtt acgggactca actgcaccac caatcacccc attaacccaa
2701 agggcctgga gttggatccc gagggttccc tgcaccacca gcaaaaacgg gaagctccaa
2761 gccgcagctc tgcttcctcg ggacctcaga tcctgaaatg cccggaggct gagtgtttca
2821 ggctgcgctg tgagctcggg cccctgcacc aacaagagag ccaaagtctg cagttgcatt
2881 tccgagtctg ggccaagact ttcttgcagc gggagcacca gccatttagc ctgcagtgtg
2941 aggctgtgta caaagccctg aagatgccct accgaatcct gcctcggcag ctgccccaaa
3001 aagagcgtca ggtggccaca gctgtgcaat ggaccaaggc agaaggcagc tatggcgtcc
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3061 cactgtggat catcatccta gccatcctgt ttggcctcct gctcctaggt ctactcatct
3121 acatcctcta caagcttgga ttcttcaaac gctccctccc atatggcacc gccatggaaa
3181 aagctcagct caagcctcca gccacctctg atgcctgagt cctcccaatt tcagactccc
3241 attcctgaag aaccagtccc cccaccctca ttctactgaa aaggaggggt ctgggtactt
3301 cttgaaggtg ctgacggcca gggagaagct cctctcccca gcccagagac atacttgaag
3361 ggccagagcc agggggggtga ggagctgggg atccctcccc cccatgcact gtgaaggacc
3421 cttgtttaca catacctct tcatggatgg gggaactcag atccagggac agaggcccca
3481 gcctccctga agcctttgca ttttggagag tttcctgaaa caacttggaa agataactag
3541 gaaatccatt cacagttctt tgggccagac atgccacaag gacttcctgt ccagctccaa
3601 cctgcaaaga tctgtcctca gccttgccag agatccaaaa gaagccccca gctaagaacc
3661 tggaacttgg ggagttaaga cctggcagct ctggacagcc ccaccctggt gggccaacaa
3721 agaacactaa ctatgcatgg tgccccagga ccagctcagg acagatgcca cacaaggata
3781 gatgctggcc cagggcccag agcccagctc caaggggaat cagaactcaa atggggccag
3841 atccagcctg gggtctggag ttgatctgga acccagactc agacattggc acctaatcca
3901 ggcagatcca ggactatatt tgggcctgct ccagacctga tcctggaggc ccagttcacc
3961 ctgatttagg agaagccagg aatttcccag gaccctgaag gggccatgat ggcaacagat
4021 ctggaacctc agcctggcca gacacaggcc ctccctgttc cccagagaaa ggggagccca
4081 ctgtcctggg cctgcagaat ttgggttctg cctgccagct gcactgatgc tgcccctcat
4141 ctctctgccc aacccttccc tcaccttggc accagacacc caggacttat ttaaactctg
4201 ttgcaagtgc aataaatctg acccagtgcc cccactgacc agaactagaa aaaaaaaaaa
4261 aaaaaaa
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An exemplary human integrin subunit alpha 7 (INTGA7) amino acid sequence is set forth below (SEQ ID NO: 147; GenBank Accession No: AAC18968, Version AAC18968.1, incorporated herein by reference):

```
   1 magarsrdpw gasgicylfg sllvellfsr avafnldvmg alrkegepgs lfgfsvalhr
  61 qlqprpqswl lvgapqalal pgqqanrtgg lfacplslee tdcyrvdidq gadmqkeske
 121 nqwlgvsvrs qgpggkivtc ahryearqrv dqiletrdmi grcfvlsqdl airdeldgge
 181 wkfcegrpqg heqfgfcqqg taaafspdsh yllfgapgty nwkgllfvtn idssdpdqlv
 241 yktldpadrl pgpagdlaln sylgfsidsg kglvraeels fvagapranh kgavvilrkd
 301 sasrlvpevm lsgerltsgf gyslavadln sdgwpdlivg apyfferqee lggavyvyln
 361 qgghwagisp lrlcgspdsm fgislavlgd lnqdgfpdia vgapfdgdgk vfiyhgsslg
 421 vvakpsqvle geavgiksfg yslsgsldmd gnqypdllvg sladtavlfr arpilhvshe
 481 vsiaprsidl eqpncagghs vcvdlrvcfs yiavpssysp tvaldyvlda dtdrrlrgqv
 541 prvtflsrnl eepkhqasgt vwlkhqhdrv cgdamfqlqe nvkdklraiv vtlsyslqtp
 601 rlrrqapgqg lppvapilna hqpstqraei hflkqgcged kicqsnlqlv harfctrvsd
 661 tefqplpmdv dgttalfals gqpviglelm vtnlpsdpaq pqadgddahe aqllvmlpds
 721 lhysgvrald paekplclsn enashvecel gnpmkrgaqv tfylilstsg isiettelev
 781 elllatiseq elhpvsarar vfielplsia gmaipqqlff sgvvrgertm qserdvgskv
 841 kyevtvsnqg qslrtlgsaf lnimwpheia ngkwllypmq veleggqgpg qkglcsprpn
 901 ilhldvdsrd rrrreleppe qqepgerqep smswwpvssa ekkknitldc argtancvvf
 961 icplysfdra avlhvwgrlw nstfleeysa vkslevivra nitvkssikn lmlrdastvi
1021 pvmvyldpma vvaegvpwwv illavlagll vlallvlllw kmgffkrakh peatvpqyha
1081 vkipredrqq fkeektgtil rnnwgsprre gpdahpilaa dghpelgpdg hpgpgta
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An exemplary human INTGA7 nucleic acid sequence is set forth below (SEQ ID NO: 148; GenBank Accession No: NG_012343, Version NG_012343.1, incorporated herein by reference):

```
   1 acttggaagg gtgaagggag gtgggcagat ggcatcaagt tgtaaatgcc agggaagtta
  61 acgtggggaa ggggaaatct ggctgcttct ctaaccacgg cagctgttcc tcccttgccc
```

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 121 agtgctagga ctcagagttg actcaagttg ctctacaaag agctgggagg ggcggggtag
 181 gataggggaa ttagtggaac atcccacccc ttcaacagct atttgagggc cagactggcc
 241 agtgcctaaa cttgggcggg gtggggaagg aggaaactga tgttgataag aggtccatac
 301 cccacattga ggtgatccac caaagcttct gtcaggcagg tcgctgcagt gatagcctct
 361 cgcctcctct tttctgggga gaggggggaaa aggaattgga ggggagactt ggtttttga
 421 ggggtagtgt taaaggttcc ctacccatcc attactattc tgctagttgc cgaaatttct
 481 taactaatct ctgaatgccg gagctgaaaa ggaccttgca aaacatagcg caacctcttt
 541 cattttagag atgaggaaac tggtaccctg ggagggaaat ggactcactc agggacgcca
 601 ggaagtcagc ggcagcgccc aggactcctg actcccaggc actctttctc cactactcgg
 661 ccgcagaatc ggtaactccg agatttccag cccggactca ggaaacaagt gccccacctc
 721 cgttccggtg gtttcaggcc tccaagaagc ccatctctgg ggggttcccc acaccctcct
 781 ccctccagag tcgctccttc ccgccgccag gacgagaggc tcccagggcc aataggcagg
 841 gcgctccggg gcaggggcgg ggctaaggtg cggcaggtcg gggattgggg gcgttgccga
 901 ggggaccgga gtattgccca agggaccgga gccagttggc aagggaaagg agtttcaaaa
 961 aaagcctctc tgaaattccc tctcccccat gcccgttgcc cgctagctgg cgtctttccc
1021 tggatatggt tagttactcg agatccaggc tccgggctga agctaggccg cggccgaaga
1081 gaaaacggcc gacaggatat ttggctcacc ctgcagctcc ttgcgttcat tctgcttggc
1141 ctggtgttct tttaggaggc gggacagcat ggtcacgtcg ggctgggggc tgggtacgcc
1201 gggccccctc cggctccgga agctggaacg ctcacctcgg ctccccgggg ccatgtcacg
1261 tgaccgctgt gtcacgtgag gttgggaacc gccctcttga gaccttgggt gaagatcttg
1321 gcggggaaga gaggtagagg gttgcggagg gcaggtgaag tgttctttat tgggagctta
1381 gtttttggtg agtgttggaa gaagtatttt ctaatactta tattgccaag ccagttttta
1441 acatttcctg tggatctcag gcttcgaggg ctggtggtgt caggccgtct atcaccgttt
1501 aattgaggga gcagaagctc cctggcctca tttaaattat tctccttccc tctcctcacc
1561 tcctggcagt gctagctggt tctcagttga ttcccagttc cttccctcaa ggagaggatg
1621 ctttcctgtc tctcccaacc ctctttcttc tcactacccc actgaagtct ctcagctctg
1681 ggtgatcatt gtagagaagc attttaggca cttcagacag cctcctaggg agcttggcta
1741 acttggcggg ctgtgtgaat gtagaatttc atctctgtcc ttttgtggtc aggaatgcga
1801 acccatttca gtgttagcag aagcgtaagt gctgtgccaa agtaaaaagt aatttatata
1861 aggcctctgt gaactaaaaa gaaatgcttc cgggattaac tccagcgaga acaattataa
1921 acatcatgag catattcttg ctactggtac aatctctctc ggtgcacctt gcactaacat
1981 gttgggtgac tttgggcaag ttgctcacca ttctaggtta tagttttctc tttagtaaaa
2041 ctaggagaag ggattggatt aaatcggtgg ttctcaaccc tggctaagca ttagaatcta
2101 aacattagaa tcacagaaat cacaaggctt ataaaaatgc cgtgattagc cgggtgcggt
2161 ggctcacgcc cgtaatccca gcactttggg aggccgaggc gggcggatca cgaggtcagg
2221 agttcgagac caggctgacc aacatggtga aaccttgtat ctactaaaaa tacaaaattt
2281 agccaggcgt agtggcacaa gcctgtaatc ccagctactc aggagcctga ggcaggagaa
2341 tcgcttgaac ctgggaggca gaggttgcag tgagccgaga tcacgccact gaactccagc
2401 ctgggcgaca gagtgggact ctgtctcaaa aaaaaaaaaa aaaaagcctt gattccagac
2461 taattaaata gaatctaagg agtgaagacc aaacatcact atatatatgt atgtatatat
2521 gtatgtatac gtatatatgt gtatatatgt atgtatacgt atatatgtgt atatatgtat
2581 gtatatgtat atatgtatat ataaaattat tattattttt gagacagagt ctcgctctgt
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29641 atacaaaatt agctgggcgt ggtggcacgc acctgtagat ccagctactt gggaggctga
29701 ggcaggagaa tcgattgaac tcgaaaggtg gggttgcagt gagccgagat ggcgccattg
29761 cactccagcc tgggtgacag agcgagactc catctcaaaa aaaaaaaaaa aaaaaaaagc
29821 cgggcatggt ggctcatgcc tgtaatccca gcactttggg aggctgaggt gagtggatca
29881 cctgaggtca ggagttcaag accaagctgg ccaacatggt gaaatcctgt ctctgttaaa
29941 aatacaaaca aataaaaaaa attagctggg catggtgggg ggtgcctgta atcccagcta
30001 cttgggaggc tgagacagga gaatcgcttg aacccgggag gtggaggttg cagtgagcca
30061 agattgcgcc actgcactgc aacctggggg actgagcagg actctgtctc aaaaaaaaaa
30121 aaaaaaaaaa aaaaaagaaa tcagatgcag atctcgttct cagggatttt atagtccagt
30181 gggatgggag tggtgagcct gtagtcaagg acaaggcagg aagtgttgag ttgagaaaat
30241 ggagtgggag tttagaggga aaaaagcttg agaggaggta gcactggaac cagtcctcag
30301 aggaaggtgg ggtagtaggg tgaggatgta aggggatgag gtaggtgggg tccagcagga

30361 ccatggtagg caaagtcgtg gaggcagaga agtgtgatct gacttaacta gaatgtggca
30421 gtgaaaactg gaaaggtaaa tgtggccaag aaggccaaca agcacggaga acggcctcca
30481 ggggactgcc ctcatggcgg aactcagagc ttccacatac caggctctgc atggaagcat
30541 tcttgtacac ccagagctgt ataccgaatc atactggtat ccagggctca atgtaaaagt
30601 atgcacatgc acacgtcagt acacggaatc acatacatca ccggggtcat atgctgagcc
30661 atctgccaca tcgggggcta tgttcagaac cacacatgtc cttggggctc tggagaactg
30721 cccctgcctg tgcctgctct ttgggaccaa tcagagactg agccaccctt tggcaagtgt
30781 gaatcatcag tagaccaggc tctggagtgg catccaagct gttgggaacc ttcccagtct
30841 taggggagat tgatgcctct gtgaaactgg tcccaggatg cttgctccct gctcccatgg
30901 aaggaagaca gagcagagat aggggatcct gtccttcctc aatctttcca tcctctgctt
30961 cctctgccct gcttctccct cgacatccta gtgtggcttc ttccatcgga gcagccagag
31021 ctcatctttt cccaccaact atcaccgggc ctgtctggct gtgcagcctt cagccatgga
31081 agttgggggt ccagggactg tggggtaact gttgtgtgtg tgcatgtgtc tagtgtgtgt
31141 gggtatgtat gtgtgtgaat ataaggagaa ttcccagcat tcaggggatc aggaatgttc
31201 agggtgaaaa atgagattgc atgagagtga tgtgaggtga gaggtaatta gaagggtgca
31261 gatataaggg taagtctaca cagcctgagg cgtgcacaaa gggttggtgg gctcatgggg
31321 tgtgagcatg tgggagtgtg gggaggtcgc atgcatgctt ttttctatgg gcatgagtgt
31381 gcaaggagat gaatgtgtaa ggagatgcca tgcagtctga gcatgtagga gtcctgggcc
31441 tctgagtgtg agtgtgcagg ggcacattcc caccctggtg tgtaagggcc agcatggtcc
31501 tcatttaggg tggggctaga ctactgtatt gatggacaag agggtattgc tgtaaggggc
31561 gtgccgccca aggtacaagt acacggggtg catgtttatg aggcttgaga ggtatcattc
31621 cagagatgca ggggactagg aagccatttt cttcctcagg tcttgtttgt gttctggggg
31681 acactattgg gtctcttaag aagctagagg gggtacaaat cttgagtccg gtcctgatgc
31741 tccaccctca aggccctctt tcaggggcca agggagatac ccttggtcct gcctcttgga
31801 cgcccttctg gtctctctct tgctgtgaat gagaacctgg ggacacagca ctgatgggag
31861 caccgtgggt gctgcccacc acaccagatg ctattcagcc tatttccttt ctgccgcagc
31921 agggatggtg agggtgagga gctgtgccgc gctaggcatc tgctccaggg accgcagctc
31981 ttcaggctcc tcatggtctg gcctggtgtc cttatagatg ggattcttca aacgggcgaa
32041 gcaccccgag gccaccgtgc cccagtacca tgcggtgaag attcctcggg aagaccgaca
32101 gcagttcaag gaggagaaga cgggcaccat cctgaggaac aactggggca gcccccggcg
32161 ggagggcccg gatgcacacc ccatcctggc tgctgacggg catcccgagc tgggccccga
32221 tgggcatcca gggccaggca ccgcctaggt tcccatgtcc cagcctggcc tgtggctgcc
32281 ctccatccct tccccagaga tggctccttg ggatgaagag ggtagagtgg gctgctggtg
32341 tcgcatcaag atttggcagg atcggcttcc tcaggggcac agacctctcc cacccacaag
32401 aactcctccc acccaacttc cccttagagt gctgtgagat gagagtgggt aaatcaggga
32461 cagggccatg gggtagggtg agaagggcag gggtgtcctg atgcaaaggt ggggagaagg
32521 gatcctaatc ccttcctctc ccattcaccc tgtgtaacag gaccccaagg acctgcctcc
32581 ccggaagtgc cttaacctag agggtcgggg aggaggttgt gtcactgact caggctgctc
32641 cttctctagt ttcccctctc atctgacctt agtttgctgc catcagtcta gtggtttcgt
32701 ggtttcgtct atttattaaa aaatatttga gaacaaaacc tctgcctctt tgagtcttgc
32761 tctggcatcc ccagcatctc tgattctccc tggtgccccc agctcaggaa gaaggtggta
32821 gtggggagag agggtcaggg gggcttggca gggatgcagg caccatgact tttgtgacca
32881 gttcctagag acgcatgggt gtagcctcag gaggaaagcg agaggagctt taccatggga
32941 acgaaggaaa gggacaacat tgggaggcaa acgttgggag actagtccag aaacttgcag
33001 ttgaggatac aacagggtcc tagtgtttcc tccctgggtc agcgtagaag tagagctttt
33061 tcactgtcga aggcgggatt gaagttagag attgccctgg cagaggttgg ggagagaggg
33121 actagtaggt ggtacatgaa tgtcttctct cattctgcta ggtccctctc agtggaagat
33181 agataggctg gtgggtggct tgttctaatt ggaggctggg gaaggagcaa atgagtgcct
33241 tggagcttgg gaaagattat ttgacagcct ttcccatgat gtggggccca acaggtagcc
33301 acttcaaggg agggggctgt cgttccattt ggatttcgga gaactgggcg ttctcaagat
33361 ccttccaggt ctctctggtg aggcagcagc catccccaat gtgtttccag gtgggctcga
33421 aaacttgctg ccacatgaag gcccagcttc catatggttc tgccacatgc tcccagaaaa
33481 agagcacacc tccctgggag ggatgagaga gttagtgtca cttggctcca ttctgaccct
33541 gctccctatc gcgctgatca agacagtcaa acttcttggt gaaatgggag ctgctggtct
33601 gagagttcat ggagcaaact gtcgtgcccc tgacctttc tgcatcccct gctaccgcct
33661 tcaaagtgca tgtgaagaac ctcataactg aaaggagtgg ctggtgggag atctttaaag

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33721 cctgaccaga ataaccgagg gcatgcagaa ggggaaactg agaaacagga gtggagggct
33781 cattgtatta ttattattat tattattttt tgagacagag tctcagtctg ttgctcaggc
33841 tggagtgcaa tggcgtgatc tcggcgcact gcaacctcca cctctcaggt tcaagcgatt
33901 ctcctgcctc agcctcccaa gtagctggga ttacaggcat gagccaccac gcccggctac
33961 tttttgtatt tttcagtaga gacagggttt caccatgttg gccagtctgg tttcaaactc
34021 ctggcctcaa gagatccacc tgccttgcct cccaaagtgc tggattacag gcgtgagcca
34081 cctcgcccag ctgggcttat tgtattctga gatacacgca caacctctct cacaaaaccc
34141 agatgcatgc acaagctgct tcctggacat cgctgtgaac atcccaggga aacctcaggc
34201 ccaactcttg actgaagctg gggttcctca agctcctcgc ctcactatac tctccctagg
34261 tgatctcaaa cctagtaagt ccaaaacagc tttcttccat ctcagcaaat ggcacttttc
34321 atcagctctc ccctcagttg ctcatgctag aaacctggaa actattctga acgttctctc
34381 cacagtctga tggattctac tctacttccc ctactatctt tacctagaac actcttttat
34441 tttccccacc ccgtccacac tctgcttaat ccctcagatc tctctctctc tctctctttt
34501 tatttattta tttatttttt ttgatacagg gtctcactct gtggcccagg ctggagtgca
34561 gtggtgcgat catagttcac tgtaactttg aactcgggct caagtgatcc tcccacctca
34621 gcttcctgag tagctaggac tataggcatg tgccaccacg cctggctagc ttttgtattt
34681 ttttttttt ttttttttgt agagacggca tctcactatg ttgccttggc tggtcttg
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An exemplary human integrin subunit alpha 11 (INTGA11) amino acid sequence is set forth below (SEQ ID NO: 149; GenBank Accession No: NP_001004439, Version NP_001004439.1, incorporated herein by reference):

```
   1 mdlprglvva walslwpgft dtfnmdtrkp rvipgsrtaf fgytvqqhdi sgnkwlvvga
  61 pletngyqkt gdvykcpvih gnctklnlgr vtlsnvserk dnmrlglsla tnpkdnsfla
 121 csplwshecg ssyyttgmcs rvnsnfrfsk tvapalqrcq tymdivivld gsnsiypwve
 181 vqhflinilk kfyigpgqiq vgvvqygedv vhefhlndyr svkdvveaas hieqrggtet
 241 rtafgiefar seafqkggrk gakkvmivit dgeshdspdl ekviqqserd nvtryavavl
 301 gyynrrginp etflneikyi asdpddkhff nvtdeaalkd ivdalgdrif slegtnknet
 361 sfglemsqtg fsshvvedgv llgavgaydw ngavlketsa gkviplresy lkefpeelkn
 421 hgaylgytvt svvssrqgrv yvagaprfnh tgkvilftmh nnrsltihqa mrgqqigsyf
 481 gseitsvdid gdgvtdvllv gapmyfnegr ergkvyvyel rqnlfvyngt lkdshsyqna
 541 rfgssiasvr dlnqdsyndv vvgapledh agaiyifhgf rgsilktpkq ritaselatg
 601 lqyfgcsihg qldlnedgli dlavgalgna vilwsrpvvq inaslhfeps kinifhrdck
 661 rsgrdatcla aflcftpifl aphfqtttvg irynatmder rytprahlde ggdrftnrav
 721 llssgqelce rinfhvldta dyvkpvtfsv eysledpdhg pmlddgwptt lrvsvpfwng
 781 cnedehcvpd lvldarsdlp tameycqrvl rkpaqdcsay tlsfdttvfi iestrqrvav
 841 eatlenrgen aystvlnisq sanlqfasli qkedsdgsie cvneerrlqk qvcnvsypff
 901 rakakvafrl dfefsksifl hhleielaag sdsnerdstk ednvaplrfh lkyeadvlft
 961 rssslshyev kpnssleryd gigppfscif riqnlglfpi hgmmmkitip iatrsgnrll
1021 klrdfltdea ntscniwgns teyrptpvee dlrrapqlnh snsdvvsinc nirlvpnqei
1081 nfhllgnlwl rslkalkyks mkimvnaalq rqfhspfifr eedpsrqivf eiskqedwqv
1141 piwiivgstl ggllllallv lalwklgffr sarrrrepgl dptpkvle
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An exemplary human *INTGA11* nucleic acid sequence is set forth below (SEQ ID NO: 150; GenBank Accession No: NM_001004439, Version NM_001004439.1, incorporated herein by reference):

```
   1 gcaggcgccg cgccgaggag gctgccgctc tggcttgccg ccccccgccg ccgctgcaca
  61 ccggacccag ccgccgtgcc gcgggccatg gacctgccca ggggcctggt ggtggcctgg
 121 gcgctcagcc tgtggccagg gttcacggac accttcaaca tggacaccag gaagccccgg
 181 gtcatccctg gctccaggac cgccttcttt ggctacacag tgcagcagca cgacatcagt
 241 ggcaataagt ggctggtcgt gggcgcccca ctggaaacca atggctacca gaagacggga
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 301 gacgtgtaca agtgtccagt gatccacggg aactgcacca aactcaacct gggaagggtc
 361 accctgtcca acgtgtccga gcggaaagac aacatgcgcc tcggccttag tctcgccacc
 421 aaccccaagg acaacagctt cctggcctgc agccccctct ggtctcatga gtgtgggagc
 481 tcctactaca ccacagggat gtgttcaaga gtcaactcca acttcaggtt ctccaagacc
 541 gtggccccag ctctccaaag gtgccagacc tacatggaca tcgtcattgt cctggatggc
 601 tccaacagca tctacccctg ggtggaggtt cagcacttcc tcatcaacat cctgaaaaag
 661 ttttacattg gcccagggca gatccaggtt ggagttgtgc agtatggcga agatgtggtg
 721 catgagtttc acctcaacga ctacaggtct gtaaaagatg tggtggaagc tgccagccac
 781 attgagcaga gaggaggaac agagacccgg acggcatttg gcattgaatt tgcacgctca
 841 gaggctttcc agaagggtgg aaggaaagga gccaagaagg tgatgattgt catcacagat
 901 ggggagtccc acgacagccc agacctggag aaggtgatcc agcaaagcga aagagacaac
 961 gtaacaagat atgcggtggc cgtcctgggc tactacaacc gcaggggat caatccagaa
1021 acttttctaa atgaaatcaa atacatcgcc agtgaccctg atgacaagca cttcttcaat
1081 gtcactgatg aggctgcctt gaaggacatt gtcgatgccc tgggggacag aatcttcagc
1141 ctggaaggca ccaacaagaa cgagacctcc tttgggctgg agatgtcaca gacgggcttt
1201 tcctcgcacg tggtggagga tggggttctg ctgggagccg tcggtgccta tgactggaat
1261 ggagctgtgc taaaggagac gagtgccggg aaggtcattc ctctccgcga gtcctacctg
1321 aaagagttcc ccgaggagct caagaaccat ggtgcatacc tggggtacac agtcacatcg
1381 gtcgtgtcct ccaggcaggg gcgggtgtac gtggccggag ccccccggtt caaccacacg
1441 ggcaaggtca tcctgttcac catgcacaac aaccggagcc tcaccatcca ccaggctatg
1501 cggggccagc agataggctc ttactttggg agtgaaatca cctcggtgga catcgacggc
1561 gacggcgtga ctgatgtcct gctggtgggc gcacccatgt acttcaacga gggccgtgag
1621 cgaggcaagg tgtacgtcta tgagctgaga cagaacctgt ttgtttataa cggaacgcta
1681 aaggattcac acagttacca gaatgcccga tttgggtcct ccattgcctc agttcgagac
1741 ctcaaccagg attcctacaa tgacgtggtg gtgggagccc ccctggagga caaccacgca
1801 ggagccatct acatcttcca cggcttccga ggcagcatcc tgaagacacc taagcagaga
1861 atcacagcct cagagctggc taccggcctc cagtattttg gctgcagcat ccacgggcaa
1921 ttggacctca atgaggatgg gctcatcgac ctggcagtgg gagcccttgg caacgctgtg
1981 attctgtggt cccgcccagt ggttcagatc aatgccagcc tccactttga gccatccaag
2041 atcaacatct tccacagaga ctgcaagcgc agtggcaggg atgccacctg cctggccgcc
2101 ttcctctgct tcacgcccat cttcctggca ccccatttcc aaacaacaac tgttggcatc
2161 agatacaacg ccaccatgga tgagaggcgg tatacaccga gggcccacct ggacgagggc
2221 ggggaccgat tcaccaacag agccgtactg ctctcctccg gccaggagct ctgtgagcgg
2281 atcaacttcc atgtcctgga cactgctgac tacgtgaagc cagtgacctt ctcagtcgag
2341 tattccctgg aggaccctga ccatggcccc atgctggacg acggctggcc caccactctc
2401 agagtctcgg tgcccttctg gaacggctgc aatgaggatg agcactgtgt ccctgacctt
2461 gtgttggatg cccggagtga cctgcccacg gccatggagt actgccagag ggtgctgagg
2521 aagcctgcgc aggactgctc cgcatacacg ctgtccttcg acaccacagt cttcatcata
2581 gagagcacac gccagcgagt ggcggtggag gccacactgg agaacagggg cgagaacgcc
2641 tacagcacgg tcctaaatat ctcgcagtca gcaaacctgc agtttgccag cttgatccag
2701 aaggaggact cagacggtag cattgagtgt gtgaacgagg agaggaggct ccagaagcaa
2761 gtctgcaacg tcagctatcc cttcttccgg gccaaggcca aggtggcttt ccgtcttgat
2821 tttgagttca gcaaatccat cttcctacac cacctggaga tcgagctcgc tgcaggcagt
2881 gacagtaatg agcgggacag caccaaggaa gacaacgtgg ccccccttacg cttccacctc
2941 aaatacgagg ctgacgtcct cttcaccagg agcagcagcc tgagccacta cgaggtcaag
3001 cccaacagct cgctggagag atacgatggt atcgggcctc ccttcagctg catcttcagg
3061 atccagaact tgggcttgtt ccccatccac gggatgatga tgaagatcac cattcccatc
3121 gccaccagga gcggcaaccg cctactgaag ctgagggact tcctcacgga cgaggcgaac
3181 acgtcctgta acatctgggg caatagcact gagtaccggc ccaccccagt ggaggaagac
3241 ttgcgtcgtg ctccacagct gaatcacagc aactctgatg tcgtctccat caactgcaat
3301 atacggctgg tccccaacca ggaaatcaat ttccatctac tggggaacct gtggttgagg
3361 tccctaaaag cactcaagta caaatccatg aaaatcatgg tcaacgcagc cttgcagagg
3421 cagttccaca gccccttcat cttccgtgag gaggatccca gccgccagat cgtgtttgag
3481 atctccaagc aagaggactg gcaggtcccc atctggatca ttgtaggcag caccctgggg
3541 ggcctcctac tgctggccct gctggtcctg gcactgtgga agctcggctt ctttagaagt
3601 gccaggcgca ggagggagcc tggtctggac cccaccccca aagtgctgga gtgaggctcc
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3661 agaggagact ttgagttgat gggggccagg acaccagtcc aggtagtgtt gagacccagg
3721 cctgtggccc caccgagctg gagcggagag gaagccagct ggctttgcac ttgacctcat
3781 ctcccgagca atggcgcctg ctccctccag aatggaactc aagctggttt taagtggaac
3841 tgccctactg ggagactggg acacctttaa cacagacccc tagggattta aagggacacc
3901 cctacacaca cccaggccca tgccaaggcc tccctcaggc tctgtggagg gcatttgctg
3961 ccccagctac taaggtgcta ggaattcgta atcatcccca tcctccagag aaacccaggg
4021 aggaagactg taaatacgaa cccaatctgc acactccagg cctctagttc cagaaggatc
4081 caagacaaaa cagatctgaa ttctgccctt ttctctcacc catcccaccc ctccattggc
4141 tcccaagtca cacccactcc cttccccata gataggcccc tggggctccc gaagaatgaa
4201 cccaagagca agggcttgat ggtgacagct gcaagccagg gatgaagaaa gactctgaga
4261 tgtggagact gatggccagg caagtgggac caggatactg gacgctgtcc tgagatgaga
4321 ggtagccggg ctctgcaccc acgtgcattc acattgaccg caactcacac attcccccac
4381 cagctgcagc cccttgctct cagctgccaa ccctcccggg tcacttttgt tcccaggtac
4441 ctcatgggaa gcatgtggat gacacaatcc ctggggctgt gcattcccac gtcttcttgc
4501 tgcagcctgc ccctagacat ggacgcaccg gcctggctgc agctgggcag caggggtagg
4561 ggtagggagc ctcccctccc tgtatcaccc cctccctaca cacacacaca cacacacaca
4621 cacacacaca cacacacaca cacacacaca cacacactgc ctcccatcct tccctcatgc
4681 ccgccagtgc acagggaagg gcttggccag cgctgttgag gggtcccctc tggaatgcac
4741 tgaataaagc acgtgcaagg actcccggag cctgtgcagc cttggtggca aatatctcat
4801 ctgccggccc ccaggacaag tggtatgacc agtgataatg ccccaaggac aaggggcgtg
4861 cctggcgccc agtggagtaa tttatgcctt agtcttgttt tgaggtagaa atgcaagggg
4921 gacacatgaa aggcatcagt ccccctgtgc atagtacgac ctttactgtc gtatttttga
4981 aaaattaaaa atacagtgtt taaaaacaaa aaaaaaaaaa aaaaaaaaaa aaaaa
```

An exemplary human transforming growth factor beta 1 (TGFB1) amino acid sequence is set forth below (SEQ ID NO: 151; GenBank Accession No: P01137, Version 2, incorporated herein by reference):

```
  1 mppsglrlll lllpllwllv ltpgrpaagl stcktidmel vkrkrieair gqilsklrla
 61 sppsqgevpp gplpeavlal ynstrdrvag esaepepepe adyyakevtr vlmvethnei
121 ydkfkqsths iymffntsel reavpepvll sraelrllrl klkveqhvel yqkysnnswr
181 ylsnrllaps dspewlsfdv tgvvrqwlsr ggeiegfrls ahcscdsrdn tlqvdingft
241 tgrrgdlati hgmnrpflll matpleraqh lqssrhrral dtnycfsste knccvrqlyi
301 dfrkdlgwkw ihepkgyhan fclgpcpyiw sldtqyskvl alynqhnpga saapccvpqa
361 leplpivyyv grkpkveqls nmivrsckcs
```

An exemplary human *TGFB1* nucleic acid sequence is set forth below (SEQ ID NO: 152; GenBank Accession No: NM_000660, Version 6, incorporated herein by reference):

```
  1 acctccctcc gcggagcagc cagacagcga gggccccggc cgggggcagg ggggacgccc
 61 cgtccggggc acccccccgg ctctgagccg cccgcggggc cggcctcggc ccggagcgga
121 ggaaggagtc gccgaggagc agcctgaggc cccagagtct gagacgagcc gccgccgccc
181 ccgccactgc ggggaggagg gggaggagga gcgggaggag ggacgagctg gtcgggagaa
241 gaggaaaaaa acttttgaga cttttccgtt gccgctggga gccggaggcg cggggacctc
301 ttggcgcgac gctgccccgc gaggaggcag gacttgggga ccccagaccg cctccctttg
361 ccgccgggga cgcttgctcc ctccctgccc cctacacggc gtccctcagg cgccccccatt
421 ccggaccagc cctcgggagt cgccgacccg gcctcccgca aagacttttc cccagacctc
481 gggcgcaccc cctgcacgcc gccttcatcc ccggcctgtc tcctgagccc ccgcgcatcc
541 tagacccttt ctcctccagg agacggatct ctctccgacc tgccacagat cccctattca
601 agaccaccca ccttctggta ccagatcgcg cccatctagg ttatttccgt gggatactga
661 gacacccccg gtccaagcct cccctccacc actgcgccct tctccctgag gacctcagct
721 ttccctcgag gccctcctac cttttgccgg gagacccccа gcccctgcag gggcggggcc
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 781 tccccaccac accagccctg ttcgcgctct cggcagtgcc gggggggcgcc gcctccccca
 841 tgccgccctc cgggctgcgg ctgctgccgc tgctgctacc gctgctgtgg ctactggtgc
 901 tgacgcctgg ccggccggcc gcgggactat ccacctgcaa gactatcgac atggagctgg
 961 tgaagcggaa gcgcatcgag gccatccgcg gccagatcct gtccaagctg cggctcgcca
1021 gccccccgag ccaggggggag gtgccgcccg gcccgctgcc cgaggccgtg ctcgccctgt
1081 acaacagcac ccgcgaccgg gtggccgggg agagtgcaga accggagccc gagcctgagg
1141 ccgactacta cgccaaggag gtcacccgcg tgctaatggt ggaaacccac aacgaaatct
1201 atgacaagtt caagcagagt acacacagca tatatatgtt cttcaacaca tcagagctcc
1261 gagaagcggt acctgaaccc gtgttgctct cccgggcaga gctgcgtctg ctgaggctca
1321 agttaaaagt ggagcagcac gtggagctgt accagaaata cagcaacaat tcctggcgat
1381 acctcagcaa ccggctgctg gcacccagcg actcgccaga gtggttatct tttgatgtca
1441 ccggagttgt gcggcagtgg ttgagccgtg gaggggaaat tgagggcttt cgccttagcg
1501 cccactgctc ctgtgacagc agggataaca cactgcaagt ggacatcaac gggttcacta
1561 ccggccgccg aggtgacctg gccaccattc atggcatgaa ccggcctttc ctgcttctca
1621 tggccacccc gctggagagg gcccagcatc tgcaaagctc ccggcaccgc cgagccctgg
1681 acaccaacta ttgcttcagc tccacggaga agaactgctg cgtgcggcag ctgtacattg
1741 acttccgcaa ggacctcggc tggaagtgga tccacgagcc caagggctac catgccaact
1801 tctgcctcgg gccctgcccc tacatttgga gcctggacac gcagtacagc aaggtcctgg
1861 ccctgtacaa ccagcataac ccgggcgcct cggcggcgcc gtgctgcgtg ccgcaggcgc
1921 tggagccgct gcccatcgtg tactacgtgg gccgcaagcc caaggtggag cagctgtcca
1981 acatgatcgt gcgctcctgc aagtgcagct gaggtcccgc cccgccccgc cccgccccgg
2041 caggcccggc cccaccccgc cccgcccccg ctgccttgcc catgggggct gtatttaagg
2101 acacccgtgc cccaagccca cctggggccc cattaaagat ggagagagga ctgcggatct
2161 ctgtgtcatt gggcgcctgc ctggggtctc catccctgac gttcccccac tcccactccc
2221 tctctctccc tctctgcctc ctcctgcctg tctgcactat tcctttgccc ggcatcaagg
2281 cacaggggac cagtggggaa cactactgta gttagatcta tttattgagc accttgggca
2341 ctgttgaagt gccttacatt aatgaactca ttcagtcacc atagcaacac tctgagatgc
2401 agggactctg ataacaccca ttttaaaggt gaggaaacaa gcccagagag gttaagggag
2461 gagttcctgc ccaccaggaa cctgctttag tgggggatag tgaagaagac aataaaagat
2521 agtagttcag gccaggcggg gtggctcacg cctgtaatcc tagcactttt gggaggcaga
2581 gatgggagga ttacttgaat ccaggcattt gagaccagcc tgggtaacat agtgagaccc
2641 tatctctaca aaacactttt aaaaaatgta cacctgtggt cccagctact ctggaggcta
2701 aggtgggagg atcacttgat cctgggaggt caaggctgca g
```

An exemplary human transforming growth factor beta induced (TGFBI) amino acid sequence is set forth below (SEQ ID NO: 153; GenBank Accession No: Q15582, Version 1, incorporated herein by reference):

```
  1 malfvrllal alalalgpaa tlagpakspy qlvlqhsrlr grqhgpnvca vqkvigtnrk
 61 yftnckqwyq rkicgkstvi syeccpgyek vpgekgcpaa lplsnlyetl gvvgstttql
121 ytdrteklrp emegpgsfti fapsneawas lpaevldslv snvniellna lryhmvgrrv
181 ltdelkhgmt ltsmyqnsni qihhypngiv tvncarllka dhhatngvvh lidkvistit
241 nniqqiieie dtfetlraav aasglntmle gngqytllap tneafekips etlnrilgdp
301 ealrdllnnh ilksamcaea ivaglsvetl egttlevgcs gdmltingka iisnkdilat
361 ngvihyidel lipdsaktlf elaaesdvst aidlfrqagl gnhlsgserl tllaplnsvf
421 kdgtppidah trnllrnhii kdqlaskyly hgqtletlgg kklrvfvyrn slcienscia
481 ahdkrgrygt lftmdrvltp pmgtvmdvlk gdnrfsmlva aiqsagltet lnregvytvf
541 aptneafral pprersrllg dakelanilk yhigdeilvs ggigalvrlk slqgdklevs
601 lknnvvsvnk epvaepdima tngvvhvitn vlqppanrpq ergdeladsa leifkqasaf
661 srasqrsvrl apvyqkller mkh
```

An exemplary human *TGFBI* nucleic acid sequence is set forth below (SEQ ID NO: 154; GenBank Accession No: NM_000358, Version 2, incorporated herein by reference):

```
   1 ctccttgcac gggccggccc agcttccccg cccctggcgt ccgctccctc ccgctcgcag
  61 cttacttaac ctggcccggg cggcggaggc gctctcactt ccctggagcc gcccgcttgc
 121 ccgtcggtcg ctagctcgct cggtgcgcgt cgtcccgctc catggcgctc ttcgtgcggc
 181 tgctggctct cgccctggct ctggccctgg gccccgccgc gaccctggcg ggtcccgcca
 241 agtcgcccta ccagctggtg ctgcagcaca gcaggctccg gggccgccag cacggcccca
 301 acgtgtgtgc tgtgcagaag gttattggca ctaataggaa gtacttcacc aactgcaagc
 361 agtggtacca aaggaaaatc tgtggcaaat caacagtcat cagctacgag tgctgtcctg
 421 gatatgaaaa ggtccctggg gagaagggct gtccagcagc cctaccactc tcaaaccttt
 481 acgagaccct gggagtcgtt ggatccacca ccactcagct gtacacggac cgcacggaga
 541 agctgaggcc tgagatggag gggcccggca gcttcaccat cttcgccct agcaacgagg
 601 cctgggcctc cttgccagct gaagtgctgg actccctggt cagcaatgtc aacattgagc
 661 tgctcaatgc cctccgctac catatggtgg gcaggcgagt cctgactgat gagctgaaac
 721 acggcatgac cctcacctct atgtaccaga attccaacat ccagatccac cactatccta
 781 atgggattgt aactgtgaac tgtgcccggc tgctgaaagc cgaccaccat gcaaccaacg
 841 gggtggtgca cctcatcgat aaggtcatct ccaccatcac caacaacatc cagcagatca
 901 ttgagatcga ggacaccttt gagacccttc gggctgctgt ggctgcatca gggctcaaca
 961 cgatgcttga aggtaacggc cagtacacgc ttttggcccc gaccaatgag gccttcgaga
1021 agatccctag tgagactttg aaccgtatcc tgggcgaccc agaagccctg agagacctgc
1081 tgaacaacca catcttgaag tcagctatgt gtgctgaagc catcgttgcg gggctgtctg
1141 tagagaccct ggagggcacg acactggagg tgggctgcag cggggacatg ctcactatca
1201 acgggaaggc gatcatctcc aataaagaca tcctagccac caacggggtg atccactaca
1261 ttgatgagct actcatccca gactcagcca agacactatt tgaattggct gcagagtctg
1321 atgtgtccac agccattgac cttttcagac aagccggcct cggcaatcat ctctctggaa
1381 gtgagcggtt gaccctcctg gctcccctga attctgtatt caaagatgga acccctccaa
1441 ttgatgccca tacaaggaat ttgcttcgga accacataat taaagaccag ctggcctcta
1501 agtatctgta ccatggacag accctggaaa ctctgggcgg caaaaaactg agagtttttg
1561 tttatcgtaa tagcctctgc attgagaaca gctgcatcgc ggcccacgac aagaggggga
1621 ggtacgggac cctgttcacg atggaccggg tgctgacccc cccaatgggg actgtcatgg
1681 atgtcctgaa gggagacaat cgctttagca tgctggtagc tgccatccag tctgcaggac
1741 tgacggagac cctcaaccgg gaaggagtct acacagtctt tgctcccaca aatgaagcct
1801 tccgagccct gccaccaaga gaacggagca gactcttggg agatgccaag gaacttgcca
1861 acatcctgaa ataccacatt ggtgatgaaa tcctggttag cggaggcatc ggggccctgg
1921 tgcggctaaa gtctctccaa ggtgacaagc tggaagtcag cttgaaaaac aatgtggtga
1981 gtgtcaacaa ggagcctgtt gccgagcctg acatcatggc cacaaatggc gtggtccatg
2041 tcatcaccaa tgttctgcag cctccagcca acagacctca ggaaagaggg gatgaacttg
2101 cagactctgc gcttgagatc ttcaaacaag catcagcgtt ttccagggct tcccagaggt
2161 ctgtgcgact agcccctgtc tatcaaaagt tattagagag gatgaagcat tagcttgaag
2221 cactacagga ggaatgcacc acggcagctc tccgccaatt tctctcagat ttccacagag
2281 actgtttgaa tgttttcaaa accaagtatc acactttaat gtacatgggc cgcaccataa
2341 tgagatgtga gccttgtgca tgtgggggag gagggagaga gatgtacttt ttaaatcatg
2401 ttccccctaa acatggctgt taacccactg catgcagaaa cttggatgtc actgcctgac
2461 attcacttcc agagaggacc tatcccaaat gtggaattga ctgcctatgc caagtccctg
2521 gaaaaggagc ttcagtattg tggggctcat aaaacatgaa tcaagcaatc cagcctcatg
2581 ggaagtcctg gcacagtttt tgtaaagccc ttgcacagct ggagaaatgg catcattata
2641 agctatgagt tgaaatgttc tgtcaaatgt gtctcacatc tacacgtggc ttggaggctt
2701 ttatggggcc ctgtccaggt agaaaagaaa tggtatgtag agcttagatt tccctattgt
2761 gacagagcca tggtgtgttt gtaataataa aaccaaagaa acata
```

An exemplary human yes-associated protein 1 (YAP1) amino acid sequence is set forth below (SEQ ID NO: 155; GenBank Accession No: P46937, Version 2, incorporated herein by reference):

```
   1 mdpgqqpppq papqgqgqpp sqppqgqgpp sgpgqpapaa tqaapqappa ghqivhvrgd
  61 setdlealfn avmnpktanv pqtvpmrlrk lpdsffkppe pkshsrqast dagtagaltp
 121 qhvrahsspa slqlgavspg tltptgvvsg paatptaqhl rqssfeipdd vplpagwema
 181 ktssgqryfl nhidqtttwq dprkamlsqm nvtaptsppv qqnmmnsasg plpdgweqam
 241 tqdgeiyyin hknkttswld prldprfamn qrisqsapvk qppplapqsp qggvmggsns
 301 nqqqqmrlqq lqmekerlrl kqqellrqam rninpstans pkcqelalrs qlptleqdgg
 361 tqnpvsspgm sqelrtmttn ssdpflnsgt yhsrdestds glsmssysvp rtpddflnsv
 421 demdtgdtin qstlpsqqnr fpdyleaipg tnvdlgtleg dgmniegeel mpslqealss
 481 dilndmesvl aatkldkesf ltwl
```

An exemplary human *YAP1* nucleic acid sequence is set forth below (SEQ ID NO: 156; GenBank Accession No: NM_001130145, Version 2, incorporated herein by reference):

```
   1 gccgccgcca gggaaaagaa agggaggaag gaaggaacaa gaaaaggaaa taaagagaaa
  61 ggggaggcgg ggaaaggcaa cgagctgtcc ggcctccgtc aagggagttg gagggaaaaa
 121 gttctcaggc gccgcaggtc cgagtgcctc gcagcccctc ccgaggcgca gccgccagac
 181 cagtggagcc ggggcgcagg gcgggggcgg aggcgccggg gcgggggatg cggggccgcg
 241 gcgcagcccc ccggccctga gagcgaggac agcgccgccc ggcccgcagc cgtcgccgct
 301 tctccacctc ggcccgtgga gccggggcgt ccgggcgtag ccctcgctcg cctgggtcag
 361 ggggtgcgcg tcgggggagg cagaagccat ggatcccggg cagcagccgc cgcctcaacc
 421 ggcccccccag ggccaagggc agccgccttc gcagcccccg caggggcagg gcccgccgtc
 481 cggacccggg caaccggcac ccgcggcgac ccaggcggcg ccgcaggcac cccccgccgg
 541 gcatcagatc gtgcacgtcc gcgggggactc ggagaccgac ctggaggcgc tcttcaacgc
 601 cgtcatgaac cccaagacgg ccaacgtgcc ccagaccgtg cccatgaggc tccggaagct
 661 gcccgactcc ttcttcaagc cgccggagcc caaatcccac tcccgacagg ccagtactga
 721 tgcaggcact gcaggagccc tgactccaca gcatgttcga gctcattcct ctccagcttc
 781 tctgcagttg ggagctgttt ctcctgggac actgaccccc actggagtag tctctggccc
 841 agcagctaca cccacagctc agcatcttcg acagtcttct tttgagatac ctgatgatgt
 901 acctctgcca gcaggttggg agatggcaaa gacatcttct ggtcagagat acttcttaaa
 961 tcacatcgat cagacaacaa catggcagga ccccaggaag gccatgctgt cccagatgaa
1021 cgtcacagcc cccaccagtc caccagtgca gcagaatatg atgaactcgg cttcaggtcc
1081 tcttcctgat ggatgggaac aagccatgac tcaggatgga gaaatttact atataaacca
1141 taagaacaag accacctctt ggctagaccc aaggcttgac cctcgttttg ccatgaacca
1201 gagaatcagt cagagtgctc cagtgaaaca gccaccaccc ctggctcccc agagcccaca
1261 gggaggcgtc atgggtggca gcaactccaa ccagcagcaa cagatgcgac tgcagcaact
1321 gcagatggag aaggagaggc tgcggctgaa acagcaagaa ctgcttcggc aggcaatgcg
1381 gaatatcaat cccagcacag caaattctcc aaaatgtcag gagttagccc tgcgtagcca
1441 gttaccaaca ctggagcagg atggtgggac tcaaaatcca gtgtcttctc ccgggatgtc
1501 tcaggaattg agaacaatga cgaccaatag ctcagatcct ttccttaaca gtggcaccta
1561 tcactctcga gatgagagta cagacagtgg actaagcatg agcagctaca gtgtccctcg
1621 aaccccagat gacttcctga acagtgtgga tgagatggat acaggtgata ctatcaacca
1681 aagcaccctg ccctcacagc agaaccgttt cccagactac cttgaagcca ttcctgggac
1741 aaatgtggac cttggaacac tggaaggaga tggaatgaac atagaaggag aggagctgat
1801 gccaagtctg caggaagctt tgagttctga catccttaat gacatggagt ctgttttggc
1861 tgccaccaag ctagataaag aaagctttct tacatggtta tagagccctc aggcagactg
1921 aattctaaat ctgtgaagga tctaaggaga cacatgcacc ggaaatttcc ataagccagt
1981 tgcagttttc aggctaatac agaaaaagat gaacaaacgt ccagcaagat actttaatcc
2041 tctattttgc tcttccttgt ccattgctgc tgttaatgta ttgctgacct ctttcacagt
2101 tggctctaaa gaatcaaaag aaaaaaactt tttatttctt ttgctattaa aactactgtt
```

2161 cattttgggg gctgggggaa gtgagcctgt ttggatgatg gatgccattc cttttgccca
2221 gttaaatgtt caccaatcat tttaactaaa tactcagact tagaagtcag atgcttcatg
2281 tcacagcatt tagtttgttc aacagttgtt tcttcagctt cctttgtcca gtggaaaaac
2341 atgatttact ggtctgacaa gccaaaaatg ttatatctga tattaaatac ttaatgctga
2401 tttgaagaga tagctgaaac caaggctgaa gactgtttta ctttcagtat tttcttttcc
2461 tcctagtgct atcattagtc acataatgac cttgatttta ttttaggagc ttataaggca
2521 tgagacaatt tccatataaa tatattaatt attgccacat actctaatat agattttggt
2581 ggataatttt gtgggtgtgc attttgttct gttttgttgg gttttttgtt ttttttgttt
2641 ttggcagggt cggtgggggg gttggttggt tggttggttt tgtcggaacc taggcaaatg
2701 accatattag tgaatctgtt aatagttgta gcttgggatg gttattgtag ttgttttggt
2761 aaaatcttca tttcctggtt ttttttacca ccttatttaa atctcgatta tctgctctct
2821 cttttatata catacacaca cccaaacata acatttataa tagtgtggta gtggaatgta
2881 tccttttttа ggtttccctg ctttccagtt aatttttaaa atggtagcgc tttgtatgca
2941 tttagaatac atgactagta gtttatattt cactggtagt ttaaatctgg ttggggcagt
3001 ctgcagatgt ttgaagtagt ttagtgttct agaaagagct attactgtgg atagtgccta
3061 ggggagtgct ccacgccctc tgggcatacg gtagatatta tctgatgaat tggaaaggag
3121 caaaccagaa atggctttat tttctccctt ggactaattt ttaagtctcg attggaattc
3181 agtgagtagg ttcataatgt gcatgacaga aataagcttt atagtggttt accttcattt
3241 agctttggaa gttttctttg ccttagtttt ggaagtaaat tctagtttgt agttctcatt
3301 tgtaatgaac acattaacga ctagattaaa atattgcctt caagattgtt cttacttaca
3361 agacttgctc ctacttctat gctgaaaatt gaccctggat agaatactat aaggttttga
3421 gttagctgga aaagtgatca gattaataaa tgtatattgg tagttgaatt tagcaaagaa
3481 atagagataa tcatgattat acctttattt ttacaggaag agatgatgta actagagtat
3541 gtgtctacag gagtaataat ggtttccaaa gagtattttt taaaggaaca aaacgagcat
3601 gaattaactc ttcaatataa gctatgaagt aatagttggt tgtgaattaa agtggcacca
3661 gctagcacct ctgtgtttta agggtctttc aatgtttcta gaataagccc ttattttcaa
3721 gggttcataa caggcataaa atctcttctc ctggcaaaag ctgctatgaa aagcctcagc
3781 ttgggaagat agatttttt ccccccaatt acaaaatcta agtattttgg cccttcaatt
3841 tggaggaggg caaaagttgg aagtaagaag ttttatttta agtactttca gtgctcaaaa
3901 aaatgcaatc actgtgttgt atataatagt tcataggttg atcactcata ataattgact
3961 ctaaggcttt tattaagaaa acagcagaaa gattaaatct tgaattaagt ctgggggggaa
4021 atggccactg cagatggagt tttagagtag taatgaaatt ctacctagaa tgcaaaattg
4081 ggtatatgaa ttacatagca tgttgttggg attttttta atgtgcagaa gatcaaagct
4141 acttggaagg agtgcctata atttgccagt agccacagat taagattata tcttatatat
4201 cagcagatta gctttagctt agggggaggg tgggaaagtt tgggggggg gttgtgaaga
4261 tttaggggga ccttgataga gaactttata aacttctttc tctttaataa agacttgtct
4321 tacaccgtgc tgccattaaa ggcagctgtt ctagagtttc agtcacctaa gtacacccac
4381 aaaacaatat gaatatggag atcttccttt acccctcaac tttaatttgc ccagttatac
4441 ctcagtgttg tagcagtact gtgatacctg gcacagtgct ttgatcttac gatgccctct
4501 gtactgacct gaaggagacc taagagtcct ttccctttt gagtttgaat catagccttg
4561 atgtggtctc ttgttttatg tccttgttcc taatgtaaaa gtgcttaact gcttcttggt
4621 tgtattgggt agcattggga taagatttta actgggtatt cttgaattgc ttttacaata
4681 aaccaatttt ataatcttta aatttatcaa ctttttacat ttgtgttatt ttcagtcagg
4741 gcttcttaga tctacttatg gttgatggag cacattgatt tggagtttca gatcttccaa
4801 agcactattt gttgtaataa cttttctaaa tgtagtgcct ttaaaggaaa aatgaacaca
4861 gggaagtgac tttgctacaa ataatgttgc tgtgttaagt attcatatta aatacatgcc
4921 ttctatatgg aacatggcag aaagactgaa aaataacagt aattaattgt gtaattcaga
4981 attcatacca atcagtgttg aaactcaaac attgcaaaag tgggtggcaa tattcagtgc
5041 ttaacacttt tctagcgttg gtacatctga gaaatgagtg ctcaggtgga ttttatcctc
5101 gcaagcatgt tgttataaga attgtgggtg tgcctatcat aacaattgtt ttctgtatct
5161 tgaaaaagta ttctccacat tttaaatgtt ttatattaga gaattcttta atgcacactt
5221 gtcaaatata tatatatagt accaatgtta ccttttttatt ttttgtttta gatgtaagag
5281 catgctcata tgttaggtac ttacataaat tgttacatta ttttttctta tgtaatacct
5341 ttttgtttgt ttatgtggtt caaatatatt ctttccttaa actcttaaaa aaaaaa

An exemplary human hyaluronan synthase 2 (HAS2) amino acid sequence is set forth below (SEQ ID NO: 157; GenBank Accession No: Q92819, Version 1, incorporated herein by reference):

```
   1 mhcerflcil riigttlfgv slllgitaay ivgyqfiqtd nyyfsfglyg aflashliiq
  61 slfaflehrk mkksletpik lnktvalcia ayqedpdylr kclqsvkrlt ypgikvvmvi
 121 dgnseddlym mdifsevmgr dksatyiwkn nfhekgpget deshkessqh vtqlvlsnks
 181 icimqkwggk revmytafra lgrsvdyvqv cdsdtmldpa ssvemvkvle edpmvggvgg
 241 dvqilnkyds wisflssvry wmafnierac qsyfgcvqci sgplgmyrns llhefvedwy
 301 nqefmgnqcs fgddrhltnr vlslgyatky tarskcltet pieylrwlnq qtrwsksyfr
 361 ewlynamwfh khhlwmtyea iitgffpffl iatviqlfyr gkiwnillfl ltvqlvglik
 421 ssfasclrgn ivmvfmslys vlymssllpa kmfaiatink agwgtsgrkt ivvnfiglip
 481 vsvwftillg gviftiykes krpfseskqt vlivgtllya cywvmlltly vvlinkcgrr
 541 kkgqqydmvl dv
```

An exemplary human *HAS2* nucleic acid sequence is set forth below (SEQ ID NO: 158; GenBank Accession No: NM_005328, Version 2, incorporated herein by reference):

```
   1 gaagtcaaga cgtctggaaa gaattaccca gtcctggctt cgagcagccc attgaaccag
  61 agacttgaaa cagccccagc caaagacttt tctcccaatt ctgcgcttcc tgggttctgc
 121 tgagtcttcc acaggctttt ttttttttt ttttttttt taagacgaaa aagagatttt
 181 ctgttatcgg gggcagaaag actgaagccc aaaaaaaaaa aaaaaaaaaa aagaaaagaa
 241 aagaaaaaag aaaagttaat ttatttttaa agcataattt ttttaagaat tagactgaag
 301 tgcaacggaa acataaagag aatattagtg aaattatttt ttaaagtggg gaagaatcaa
 361 acatttaaga ctcccctatc ctttttaaat gttgttttta aatttcttat ttttttggc
 421 cggtcgtctc aaattcatct gatctcttat tacctcaatt ttggaaactg cccgccaccg
 481 accctccggg accacacaga caggctgagg acgactttat gaccaagagc tgaacaagat
 541 gcattgtgag aggtttctat gtatcctgag aataattgga accacactct ttggagtctc
 601 tctcctcctt ggaatcacag ctgcttatat tgttggctac cagtttatcc aaacggataa
 661 ttactatttc tcttttggac tgtatggtgc ctttttggca tcacacctca tcatccaaag
 721 cctgtttgcc tttttggagc accgaaaaat gaaaaaatcc ctagaaaccc ccataaagtt
 781 gaacaaaaca gttgcccttt gcatcgctgc ctatcaagaa gatccagact acttaaggaa
 841 atgtttgcaa tctgtgaaaa ggctaaccta ccctgggatt aaagttgtca tggtcataga
 901 tgggaactca gaagatgacc tttacatgat ggacatcttc agtgaagtca tgggcagaga
 961 caaatcagcc acttatatct ggaagaacaa cttccacgaa aagggtcccg gtgagacaga
1021 tgagtcacat aaagaaagct cgcaacacgt aacgcaattg gtcttgtcca acaaaagtat
1081 ctgcatcatg caaaaatggg gtggaaaaag agaagtcatg tacacagcct tcagagcact
1141 gggacgaagt gtggattatg tacaggtttg tgattcagac actatgcttg acccagcctc
1201 atctgtggag atggtaaaag ttttagaaga agatcccatg gttggaggtg ttgggggaga
1261 tgtccagatt ttaaacaagt acgattcctg gatctcattc ctcagcagtg taagatattg
1321 gatggctttt aatatagaaa gggcctgtca gtcttatttt gggtgtgttc agtgcattag
1381 tggacctctg ggaatgtaca gaaactcctt gttgcatgag tttgtggaag attggtacaa
1441 tcaagaattt atgggcaacc aatgtagctt tggtgatgac aggcatctca cgaaccgggt
1501 gctgagcctg ggctatgcaa caaaatacac agctcgatct aagtgcctta ctgaaacacc
1561 tatagaatat ctcagatggc taaaccagca gacccgttgg agcaagtcct acttccgaga
1621 atggctgtac aatgcaatgt ggtttcacaa acatcacttg tggatgacct acgaagcgat
1681 tatcactgga ttctttcctt tctttctcat tgccacagta atccagctct tctaccgggg
1741 taaaatttgg aacattctcc tcttcttgtt aactgtccag ctagtaggtc tcataaaatc
1801 atcttttgcc agctgcctta gaggaaatat cgtcatggtc ttcatgtctc tctactcagt
1861 gttatacatg tcgagtttac ttcccgccaa gatgtttgca attgcaacaa taaacaaagc
1921 tgggtggggc acatcaggaa ggaaaaccat tgttgttaat ttcataggac tcattccagt
1981 atcagtttgg tttacaatcc tcctgggtgg tgtgattttc accatttata aggagtctaa
2041 aaggccattt tcagaatcca aacagacagt tctaattgtt ggaacgttgc tctatgcatg
```

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2101 ctattgggtc atgcttttga cgctgtatgt agttctcatc aataagtgtg gcaggcggaa
2161 gaagggacaa caatatgaca tggtgcttga tgtatgatct tccatgtttt gacgtttgca
2221 gtcacacaca acaccttagt tcctctaggg gctgtacagt attgtggcat cagataatgc
2281 caccaaagga gacatatcac tgctgctggg acttgaacaa agacatttat atgggtttat
2341 tttcattctg ccaaagtaaa acaatacatc aacaagaaga aactcagatt taacctgtta
2401 tttctatgaa aatgggatga attctttgtt tatgcacttt ttccttactg tgcatccgcc
2461 tgaaagtgtt ttgccctata tacctcacta gccatgcttt atgtgggtta tcatggaaga
2521 aaaggatttt ggaaactcaa ggaaaagttc tttcaaccta tacaacctaa cttatggact
2581 gttttgatag atgataattt tttttttta ggaaggattt tctttttaac tttaccaaat
2641 gaaatgccaa aggaagtttt aaaggccgtt ggctgtgctg tattttgata taattgtact
2701 gtgtttttaa attttgtatg ccaatcttaa agacaaattt tgcatattct ctattttact
2761 tttctgccaa aataaacctg ttcttccttt tttaaaataa aataagttct taaaaaattt
2821 atacttaaaa aatcctgccc aaaatgtgaa gcttggttga ctgatgttca tgatagaaag
2881 aataaaatgt ttctctctct ctacctttta aaattgaata gtttatttct gtgaaagaag
2941 tatttaaact ttcaatattt taacttttg tttttatttc ttttagaaaa ggccaatata
3001 cctatcacac tttggaagta aaaatacaca ctttcgtgtg tacctaaaaa aaaaatcgtt
3061 gaaaatcaag gccaaaggta gtgcaatttt ttcattaaga tttaaaaaaa agggaatgat
3121 agtctttgaa agaaaacagt aggcatccag cactggacaa aacatgggta tcaaagatga
3181 ataatctttg gagattctgg cagtgttttc ccagaacaag tcaagtggaa agtggagaaa
3241 ttatctgtat aattttggac acatacaatg cagtt
```

An exemplary human lysyl oxidase (LOX) amino acid sequence is set forth below (SEQ ID NO: 159; GenBank Accession No: AAB23549, Version 1, incorporated herein by reference):

```
   1 mrfawtvlll gplqlcalvh cappaagqqq ppreppaapg awrqqiqwen ngqvfsllsl
  61 gsqyqpqrrr dpgaavpgaa nasaqqprtp illirdnrta aartrtagss gvtagrprpt
 121 arhwfqagys tsrarergas raenqtapge vpalsnlrpp srvdgmvgdd pynpykysdd
 181 npyynyydty erprpggryr pgygtgyfqy glpdlvadpy yiqastyvqk msmynlrcaa
 241 eenclastay radvrdydhr vllrfpqrvk nqgtsdflps rpryswewhs chqhyhsmde
 301 fshydlldan tqrrvaeghk asfcledtsc dygyhrrfac tahtqglspg cydtygadid
 361 cqwiditdvk pgnyilkvsv npsylvpesd ytnnvvrcdi rytghhayas gctispy
```

An exemplary human *LOX* nucleic acid sequence is set forth below (SEQ ID NO: 160; GenBank Accession No: AF039291, Version 1, incorporated herein by reference):

```
   1 ccgcgccgct ccccgttgcc ttccaggact gagaaagggg aaagggaagg gtgccacgtc
  61 cgagcagccg ccttgactgg ggaagggtct gaatcccacc cttggcattg cctggtggag
 121 actgagatac ccgtgctccg ctcgcctcct tggttgaaga tttctccttc cctcacgtga
 181 tttgagcccc gtttttattt tctgtgagcc acgtcctcct cgagcggggt caatctggca
 241 aaaggagtga tgcgcttcgc ctggaccgtg ctcctgctcg ggcctttgca gctctgcgcg
 301 ctagtgcact gcgcccctcc cgccgccggc caacagcagc ccccgcgcga gccgccggcg
 361 gctccgggcg cctggcgcca gcagatccaa tgggagaaca acgggcaggt gttcagcttg
 421 ctgagcctgg gctcacagta ccagcctcag cgccgccggg acccgggcgc cgccgtccct
 481 ggtgcagcca acgcctccgc ccagcagccc cgcactccga tcctgctgat ccgcgacaac
 541 cgcaccgccg cggcgcgaac gcggacggcc ggctcatctg gagtcaccgc tggccgcccc
 601 aggcccaccg cccgtcactg gttccaagct ggctactcga catctagagc ccgcgaagct
 661 ggcgcctcgc gcgcggagaa ccagacagcg ccgggagaag ttcctgcgct cagtaacctg
 721 cggccgccca gccgcgtgga cggcatggtg ggcgacgacc cttacaaccc ctacaagtac
 781 tctgacgaca acccttatta caactactac gatacttatg aaaggcccag acctgggggc
 841 aggtaccggc ccggatacgg cactggctac ttccagtacg gtctcccaga cctggtggcc
 901 gacccctact acatccaggc gtccacgtac gtgcagaaga tgtccatgta caacctgaga
 961 tgcgcggcgg aggaaaactg tctggccagt acagcataca gggcagatgt cagagattat
1021 gatcacaggg tgctgctcag atttccccaa agagtgaaaa accaagggac atcagatttc
```

```
1081 ttacccagcc gaccaagata ttcctgggaa tggcacagtt gtcatcaaca ttaccacagt
1141 atggatgagt ttagccacta tgacctgctt gatgccaaca cccagaggag agtggctgaa
1201 ggccacaaag caagtttctg tcttgaagac acatcctgtg actatggcta ccacaggcga
1261 tttgcatgta ctgcacacac acagggattg agtcctggct gttatgatac ctatggtgca
1321 gacatagact gccagtggat tgatattaca gatgtaaaac ctggaaacta tatcctaaag
1381 gtcagtgtaa accccagcta cctggttcct gaatctgact ataccaacaa tgttgtgcgc
1441 tgtgacattc gctacacagg acatcatgcg tatgcctcag gctgcacaat ttcaccgtat
1501 tagaaggcaa agcaaaactc ccaatggata aatcagtgcc tggtgttctg aagtgggaaa
1561 aaatagacta acttcagtag gatttatgta ttttgaaaaa gagaacagaa aacaacaaaa
1621 gaatttttgt ttggactgtt ttcaataaca aagcacataa ctggattttg aacgcttaag
1681 tcatcattac ttgggaaatt tttaatgttt attatttaca tcactttgtg aattaacaca
1741 gtgtttcaat tctgtaatta catatttgac tctttcaaag aaatccaaat ttctcatgtt
1801 ccttttgaaa ttgtagtgca aaatggtcag tattatctaa atgaatgagc caaaatgact
1861 ttgaactgaa acttttctaa agtgctggaa ctttagtgaa acataataat aatgggttta
1921 tacgacagca acgga
```

An exemplary human S100 calcium binding protein A4 (S100A4) amino acid sequence is set forth below (SEQ ID NO: 161; GenBank Accession No: AAH00838, Version 1, incorporated herein by reference):

```
  1 macplekald vmvstfhkys gkegdkfkln kselkelltr elpsflgkrt deaafqklms
 61 nldsnrdnev dfqeycvfls ciammcneff egfpdkqprk k
```

An exemplary human *S100A4* nucleic acid sequence is set forth below (SEQ ID NO: 162; GenBank Accession No: BC016300, Version 1, incorporated herein by reference):

```
  1 ggggattctt cccctctcta caaccctctc tcctcagcgc ttcttctttc ttggtttgat
 61 cctgactgct gtcatggcgt gccctctgga gaaggccctg gatgtgatgg tgtccacctt
121 ccacaagtac tcgggcaaag agggtgacaa gttcaagctc aacaagtcag aactaaagga
181 gctgctgacc cgggagctgc ccagcttctt ggggaaaagg acagatgaag ctgctttcca
241 gaagctgatg agcaacttgg acagcaacag ggacaacgag gtggacttcc aagagtactg
301 tgtcttcctg tcctgcatcg ccatgatgtg taacgaattc tttgaaggct tcccagataa
361 gcagcccagg aagaaatgaa aactcctctg atgtggttgg ggggtctgcc agctggggcc
421 ctccctgtcg ccagtgggca ctttttttt tccaccctgg ctccttcaga cacgtgcttg
481 atgctgagca agttcaataa agattcttgg aagttttaaa aaaaaaaaaa aaaaaaaaaa
541 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaccaaaaa aaaaaaaaaa aaaaaaaaaa
601 aaaaa
```

An exemplary human Glutathione S-transferase P1 (GSTP1) amino acid sequence is set forth below (SEQ ID NO: 163; GenBank Accession No: P09211, Version 2, incorporated herein by reference):

```
  1 mppytvvyfp vrgrcaalrm lladqgqswk eevvtvetwq egslkascly gqlpkfqdgd
 61 ltlyqsntil rhlgrtlgly gkdqqeaalv dmvndgvedl rckyisliyt nyeagkddyv
121 kalpgqlkpf etllsqnqgg ktfivgdqis fadynlldll lihevlapgc ldafpllsay
181 vgrlsarpkl kaflaspeyv nlpingngkq
```

An exemplary human *GSTP1* nucleic acid sequence is set forth below (SEQ ID NO: 164; GenBank Accession No: NM_000852, Version 3, incorporated herein by reference):

```
   1 tgggaaagag ggaaaggctt ccccggccag ctgcgcggcg actccgggga ctccagggcg
  61 cccctctgcg gccgacgccc ggggtgcagc ggccgccggg gctggggccg gcgggagtcc
 121 gcgggaccct ccagaagagc ggccggcgcc gtgactcagc actggggcgg agcggggcgg
 181 gaccaccctt ataaggctcg gaggccgcga ggccttcgct ggagtttcgc cgccgcagtc
 241 ttcgccacca tgccgcccta caccgtggtc tatttcccag ttcgaggccg ctgcgcggcc
 301 ctgcgcatgc tgctggcaga tcagggccag agctggaagg aggaggtggt gaccgtggag
 361 acgtggcagg agggctcact caaagcctcc tgcctatacg ggcagctccc caagttccag
 421 gacggagacc tcaccctgta ccagtccaat accatcctgc gtcacctggg ccgcaccctt
 481 gggctctatg ggaaggacca gcaggaggca gccctggtgg acatggtgaa tgacggcgtg
 541 gaggacctcc gctgcaaata catctccctc atctacacca actatgaggc gggcaaggat
 601 gactatgtga aggcactgcc cgggcaactg aagccttttg agaccctgct gtcccagaac
 661 cagggaggca agaccttcat tgtgggagac cagatctcct tcgctgacta caacctgctg
 721 gacttgctgc tgatccatga ggtcctagcc cctggctgcc tggatgcgtt ccccctgctc
 781 tcagcatatg tggggcgcct cagtgcccgg cccaagctca aggccttcct ggcctccct
 841 gagtacgtga acctccccat caatggcaac gggaaacagt gagggttggg gggactctga
 901 gcgggaggca gagtttgcct tcctttctcc aggaccaata aaatttctaa gagagctaaa
 961 aaaaaaaaaa aaaaaaaaaa aaaaa
```

An exemplary human Cluster of Differentiation 81 (CD81), also known as Target of the Antiproliferative Antibody 1 (TAPA-1), amino acid sequence is set forth below (SEQ ID NO: 165; GenBank Accession No: P60033, Version 1, incorporated herein by reference):

```
   1 mgvegctkci kyllfvfnfv fwlaggvilg valwlrhdpq ttnllylelg dkpapntfyv
  61 giyiliavga vmmfvgflgc ygaiqesqcl lgtfftclvi lfacevaagi wgfvnkdqia
 121 kdvkqfydqa lqqavvddda nnakavvktf hetldccgss tltalttsvl knnlcpsgsn
 181 iisnlfkedc hqkiddlfsg klyligiaai vvavimifem ilsmvlccgi rnssvy
```

An exemplary human *CD81* nucleic acid sequence is set forth below (SEQ ID NO: 166; GenBank Accession No: BC093047, Version 1, incorporated herein by reference):

```
   1 gcgagcgcgc aacggcggcg acggcggcga ccccaccgcg catcctgcca ggcctccggc
  61 gcccagcgcc ccacgcgccc ccgcgccccc gcgccccccgc gccccttttct tcgcgccccc
 121 gcccctcggc ccgccaggcc cccttgccgg ccacccgcca ggccccgcgc cggcccgccc
 181 gccgcccagg accggcccgc gccccgcagg ccgcccgccg cccgcgccgc catgggagtg
 241 gagggctgca ccaagtgcat caagtacctg ctcttcgtct tcaatttcgt cttctggctg
 301 gctggaggcg tgatcctggg tgtggccctg tggctccgcc atgacccgca gaccaccaac
 361 ctcctgtatc tggagctggg agacaagccc gcgcccaaca ccttctatgt aggcatctac
 421 atcctcatcg ctgtgggcgc tgtcatgatg ttcgttggct tcctgggctg ctacggggcc
 481 atccaggaat cccagtgcct gctggggacg ttcttcacct gcctggtcat cctgtttgcc
 541 tgtgaggtgg ccgccggcat ctggggcttt gtcaacaagg accagatcgc caaggatgtg
 601 aagcagttct atgaccaggc cctacagcag gccgtggtgg atgatgacgc caacaacgcc
 661 aaggctgtgg tgaagacctt ccacgagacg cttgactgct gtggctccag cacactgact
 721 gctttgacca cctcagtgct caagaacaat ttgtgtccct cgggcagcaa catcatcagc
 781 aacctcttca aggaggactg ccaccagaag atcgatgacc tcttctccgg gaagctgtac
 841 ctcatcggca ttgctgccat cgtggtcgct gtgatcatga tcttcgagat gatcctgagc
 901 atggtgctgt gctgtggcat ccggaacagc tccgtgtact gaggccccgc agctctggcc
 961 acagggacct ctgcagtgcc ccctaagtga cccggacact tccgaggggg ccatcaccgc
1021 ctgtgtatat aacgtttccg gtattactct gctacacgta gccttttttac ttttggggtt
1081 ttgtttttgt tctgaacttt cctgttacct tttcagggct gacgtcacat gtaggtggcg
```

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1141 tgtatgagtg gagacgggcc tgggtcttgg ggactggagg gcaggggtcc ttctgccctg
1201 gggtcccagg gtgctctgcc tgctcagcca ggcctctcct gggagccact cgcccagaga
1261 ctcagcttgg ccaacttggg gggctgtgtc cacccagccc gcccgtcctg tgggctgcac
1321 agctcacctt gttccctcct gccccggttc gagagccgag tctgtgggca ctctctgcct
1381 tcatgcacct gtcctttcta acacgtcgcc ttcaactgta atcacaacat cctgactccg
1441 tcatttaata aagaaggaac atcaaaaaaa aaaaaaaaaa aaaaaaaaaa a
```

An exemplary human Thymocyte antigen 1 (THY1), also known as Cluster of differentiation 90 (CD90), amino acid sequence is set forth below (SEQ ID NO: 167; GenBank Accession No: P04216, Version 2, incorporated herein by reference):

```
  1 mnlaisiall ltvlqvsrgq kvtsltaclv dqslrldcrh entssspiqy efsltretkk
 61 hvlfgtvgvp ehtyrsrtnf tskynmkvly lsaftskdeg tytcalhhsg hsppissqnv
121 tvlrdklvkc egisllaqnt swllllllsl sllqatdfms l
```

An exemplary human *THY1* nucleic acid sequence is set forth below (SEQ ID NO: 168; GenBank Accession No: BC065559, Version 1, incorporated herein by reference):

```
   1 ggaggctgca gcagcggaag accccagtcc agatccagga ctgagatccc agaaccatga
  61 acctggccat cagcatcgct ctcctgctaa cagtcttgca ggtctcccga gggcagaagg
 121 tgaccagcct aacggcctgc ctagtggacc agagccttcg tctggactgc cgccatgaga
 181 ataccagcag ttcacccatc cagtacgagt tcagcctgac ccgtgagaca aagaagcacg
 241 tgctctttgg cactgtgggg gtgcctgagc acacataccg ctcccgaacc aacttcacca
 301 gcaaatacaa catgaaggtc ctctacttat ccgccttcac tagcaaggac gagggcacct
 361 acacgtgtgc actccaccac tctggccatt ccccacccat ctcctcccag aacgtcacag
 421 tgctcagaga caaactggtc aagtgtgagg gcatcagcct gctggctcag aacacctcgt
 481 ggctgctgct gctcctgctc tccctctccc tcctccaggc cacggatttc atgtccctgt
 541 gactggtggg gcccatggag gagacaggaa gcctcaagtt ccagtgcaga gatcctactt
 601 ctctgagtca gctgaccccc tccccccaat ccctcaaacc ttgaggagaa gtggggaccc
 661 cacccctcat caggagttcc agtgctgcat gcgattatct acccacgtcc acgcggccac
 721 ctcaccctct ccgcacacct ctggctgtct ttttgtactt tttgttccag agctgcttct
 781 gtctggttta tttaggtttt atccttcctt ttctttgaga gttcgtgaag agggaagcca
 841 ggattgggga cctgatggag agtgagagca tgtgaggggt agtgggatgg tggggtacca
 901 gccactggag gggtcatcct tgcccatcgg gaccagaaac ctgggagaga cttggatgag
 961 gagtggttgg gctgtgcctg ggcctagcac ggacatggtc tgtcctgaca gcactcctcg
1021 gcaggcatgg ctggtgcctg aagaccccag atgtgagggc accaccaaga atttgtggcc
1081 taccttgtga gggagagaac tgagcatctc cagcattctc agccacaacc aaaaaaaaaa
1141 aaaaa
```

An exemplary human ecto-5'-nucleotidase (NT5E), also known as Cluster of differentiation 73 (CD73), amino acid sequence is set forth below (SEQ ID NO: 169; GenBank Accession No: AAH65937, Version 1, incorporated herein by reference):

```
  1 mcpraarapa tlllalgavl wpaagawelt ilhtndvhsr leqtsedssk cvnasrcmgg
 61 varlftkvqq irraepnvll ldagdqyqgt iwftvykgae vahfmnalry damalgnhef
121 dngvegliep llkeakfpil sanikakgpl asqisglylp ykvlpvgdev vgivgytske
181 tpflsnpgtn lvfedeital qpevdklktl nvnkiialgh sgfemdklia qkvrgvdvvv
241 gghsntflyt gnppskevpa gkypfivtsd dgrkvpvvqa yafgkylgyl kiefdergnv
301 isshgnpill nssipedpsi kadinkwrik ldnystqelg ktivyldgss qscrfrecnm
361 gnlicdamin nnlrhadetf wnhvsmciln gggirspide rnngtitwen laavlpfggt
```

```
421 fdlvqlkgst lkkafehsvh rygqstgefl qvggihvvyd lsrkpgdrvv kldvlctkcr
481 vpsydplkmd evykvilpnf langgdgfqm ikdellrhds gdqdinvvst yiskmkviyp
541 avegrikfst gshchgsfsl iflslwavif vlyq
```

An exemplary human *NT5E* nucleic acid sequence is set forth below (SEQ ID NO: 170; GenBank Accession No: NM_002526, Version 3, incorporated herein by reference):

```
   1 actcctcctc tctgcccctc agctcgctca tctttcttcc cgccccctct cttttccttc
  61 tttggttctt tgaagtgatg agctagcgca accacaaacc atacattcct tttgtagaaa
 121 aacccgtgcc tcgaatgagg cgagactcag agaggaccca ggcgcggggc ggacccctcc
 181 aattccttcc tcgcgccccc gaaagagcgg cgcaccagca gccgaactgc cggcgcccag
 241 gctccctggt ccggccggga tgcggccggt acccgctccc cgccgggaac aacctctcca
 301 ctcttcctgc agggagctgg tgccagccga cagccgcgcc agggccgctc cgggtaccag
 361 ggtcggatcg ggtgacgtcg cgaacttgcg cctggccgcc aagccggcct ccaggctgaa
 421 gaaggacccg ccccggcctt gacccgggcc ccgcccctcc agccggggca ccgagccccg
 481 gccctagctg ctcgccccta ctcgccggca ctcgcccggc tcgcccgctt tcgcacccag
 541 ttcacgcgcc acagctatgt gtccccgagc cgcgcgggcg cccgcgacgc tactcctcgc
 601 cctgggcgcg gtgctgtggc ctgcggctgg cgcctgggag cttacgattt tgcacaccaa
 661 cgacgtgcac agccggctgg agcagaccag cgaggactcc agcaagtgcg tcaacgccag
 721 ccgctgcatg ggtggcgtgg ctcggctctt caccaaggtt cagcagatcc gccgcgccga
 781 acccaacgtg ctgctgctgg acgccggcga ccagtaccag ggcactatct ggttcaccgt
 841 gtacaagggc gccgaggtgg cgcacttcat gaacgccctg cgctacgatg ccatggcact
 901 gggaaatcat gaatttgata atggtgtgga aggactgatc gagccactcc tcaaagaggc
 961 caaatttcca attctgagtg caaacattaa agcaaagggg ccactagcat ctcaaatatc
1021 aggactttat ttgccatata aagttcttcc tgttggtgat gaagttgtgg gaatcgttgg
1081 atacacttcc aaagaaaccc cttttctctc aaatccaggg acaaatttag tgtttgaaga
1141 tgaaatcact gcattacaac ctgaagtaga taagttaaaa actctaaatg tgaacaaaat
1201 tattgcactg ggacattcgg gttttgaaat ggataaactc atcgctcaga aagtgagggg
1261 tgtggacgtc gtggtgggag gacactccaa cacatttctt tacacaggca atccaccttc
1321 caaagaggtg cctgctggga agtacccatt catagtcact tctgatgatg ggcggaaggt
1381 tcctgtagtc caggcctatg cttttggcaa atacctaggc tatctgaaga tcgagtttga
1441 tgaaagagga aacgtcatct cttcccatgg aaatcccatt cttctaaaca gcagcattcc
1501 tgaagatcca agcataaaag cagacattaa caaatggagg ataaaattgg ataattattc
1561 tacccaggaa ttagggaaaa caattgtcta tctggatggc tcctctcaat catgccgctt
1621 tagagaatgc aacatgggca acctgatttg tgatgcaatg attaacaaca acctgagaca
1681 cacggatgaa atgttctgga accacgtatc catgtgcatt ttaaatggag gtggtatccg
1741 gtcgcccatt gatgaacgca acaatggcac aattacctgg gagaacctgg ctgctgtatt
1801 gccctttgga ggcacatttg acctagtcca gttaaaaggt tccaccctga agaaggcctt
1861 tgagcatagc gtgcaccgct acggccagtc cactggagag ttcctgcagg tgggcggaat
1921 ccatgtggtg tatgatcttt cccgaaaacc tggagacaga gtagtcaaat tagatgttct
1981 ttgcaccaag tgtcgagtgc ccagttatga ccctctcaaa atggacgagg tatataaggt
2041 gatcctccca aacttcctgg ccaatggtgg agatgggttc cagatgataa aagatgaatt
2101 attaagacat gactctggtg accaagatat caacgtggtt tctacatata tctccaaaat
2161 gaaagtaatt tatccagcag ttgaaggtcg gatcaagttt tccacaggaa gtcactgcca
2221 tggaagcttt tctttaatat ttctttcact ttgggcagtg atctttgttt tataccaata
2281 gccaaaaatt ctccttgcct ttaatgtgtg aaactgcatt ttttcaagtg agattcaaat
2341 ctgccttta ggacctggct ttgtgacagc aaaaaccatc tttacaggct cctagaagct
2401 gaaggttaga gcattataaa atgaagagac agacatgatt actcagggtc agcaacctag
2461 tgagttagaa aaaaaattaa catagggccc tataaggaga aagccaacta tgttaagttt
2521 acgtgtccaa attttaatga aattttacta acaattttaa accatatttt tcttcttcat
2581 atccatttct aatccatcaa acagcttatg tttacataaa attttatcat tcacaaggaa
2641 gttttaagca cactgtctca tttgatatcc acaacttatt tttggtagga aagagagatg
2701 tttttcccac ctgtcagatg aaaaaactga agctcaaaaa gggttgactt gaccatacag
2761 ctaatgctga cagatccaag acctagacct aggtcttttg aactcaagtc cagcattctc
2821 aactatatca agttactgtt cagaatactt aatatctcct ctcttcataa ttatcaatag
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```
2881 ccccaagctc atggatgaca aatctctgct ttatttcttg tctctatttt ttcactttat
2941 agctcctgtt ataatagcaa gtttaatggt ataaacacag gataccatcc tctcttgcaa
3001 cacccatgtg cctttgatga gtcaggtagc aagctgtagt agataatgag aaaggccaga
3061 ggctgcaaaa gacagtcaaa ggacacgaga gaaaggaagg ggaagaacag gactccagga
3121 ctgttttata ttatagaaaa gcaagagcta aagagcattt acacatgtta aacagatact
3181 tgttaagcat agtgcctgac acacggcatt agctgttatt ttatgagatt ccatcagctc
3241 tgcctctgtc ctctttcttc taacatgaag gtatcatgag aagagaacct tctaacataa
3301 gctgtaattc taaacctgca cttgtccctc tccagcaaga ggctagcact gaattcattc
3361 tactcatact acacacccag ttatggaatg tccagagttc tcgaagaaaa taaatgactt
3421 taggaagagg tatacatttt ttaagtcgct ctgcctccaa atctgaacag tcactgtaaa
3481 tcattcttaa gcccagatat gagaacttct gctggaaagt gggaccctct gagtgggtgg
3541 tcagaaaata cccatgctga tgaaatgacc tatgcccaaa gaacaaatac ttaacgtggg
3601 agtggaacca catgagcctg ctcagctctg cataagtaat tcaagaaatg ggaggcttca
3661 ccttaaaaac agtgtgcaaa tggcagctag aggttttgat aggaagtatg tttgtttctt
3721 agtgtttaca aatattaagt actcttgata caaaatatac ttttaaactt cataaccttt
3781 ttataaaagt tgttgcagca aaataatagc ctcggttcta tgcatatatg gattagctat
3841 aaaaaatgtc aataagattg tacaaggaaa attagagaaa gtcacattta gggtttattt
3901 tttacacttg gccagtaaaa tagggtaaat cctattagaa ttttttaaag aacttttttt
3961 aagtttccta aatctgtgtg tgtattgtga agtggtataa gaaatgactt tgaaccactt
4021 tgcaattgta gattcccaac aataaaattg aagataagct ctttggtcaa aaaaaaaaaa
4081 aaaaaa
```

An exemplary human endoglin (ENG) amino acid sequence is set forth below (SEQ ID NO: 171; GenBank Accession No: P17813, Version 2, incorporated herein by reference):

```
   1 mdrgtlplav alllascsls ptslaetvhc dlqpvgperg evtyttsqvs kgcvaqapna
  61 ilevhvlfle fptgpsqlel tlqaskqngt wprevllvls vnssvflhlq algiplhlay
 121 nsslvtfqep pgvnttelps fpktqilewa aergpitsaa elndpqsill rlgqaqgsls
 181 fcmleasqdm grtlewrprt palvrgchle gvaghkeahi lrvlpghsag prtvtvkvel
 241 scapgdldav lilqgppyvs wlidanhnmq iwttgeysfk ifpeknirgf klpdtpqgll
 301 gearmlnasi vasfvelpla sivslhassc ggrlqtspap iqttppkdtc spellmsliq
 361 tkcaddamtl vlkkelvahl kctitgltfw dpsceaedrg dkfvlrsays scgmqvsasm
 421 isneavvnil sssspqrkkv hclnmdslsf qlglylsphf lqasntiepg qqsfvqvrvs
 481 psvsefllql dschldlgpe ggtveliqgr aakgncvsll spspegdprf sfllhfytvp
 541 ipktgtlsct valrpktgsq dqevhrtvfm rlniispdls gctskglvlp avlgitfgaf
 601 ligalltaal wyiyshtrsp skrepvvava apassessst nhsigstqst pcstssma
```

An exemplary human *ENG* nucleic acid sequence is set forth below (SEQ ID NO: 172; GenBank Accession No: BC014271, Version 2, incorporated herein by reference):

```
   1 ccaccccaga aggctggagc agggacgccg tcgctccggc cgcctgctcc cctcgggtcc
  61 ccgtgcgagc ccacgccggc cccggtgccc gcccgcagcc ctgccactgg acacaggata
 121 aggcccagcg cacaggcccc cacgtggaca gcatggaccg cggcacgctc cctctggctg
 181 ttgccctgct gctggccagc tgcagcctca gccccacaag tcttgcagaa acagtccatt
 241 gtgaccttca gcctgtgggc cccgagaggg acgaggtgac atataccact agccaggtct
 301 cgaagggctg cgtggctcag gcccccaatg ccatccttga agtccatgtc ctcttcctgg
 361 agttcccaac gggcccgtca cagctggagc tgactctcca ggcatccaag caaaatggca
 421 cctggccccg agaggtgctt ctggtcctca gtgtaaacag cagtgtcttc ctgcatctcc
 481 aggccctggg aatcccactg cacttggcct acaattccag cctggtcacc ttccaagagc
 541 ccccgggggt caacaccaca gagctgccat ccttccccaa gacccagatc cttgagtggg
 601 cagctgagag gggccccatc acctctgctg ctgagctgaa tgacccccag agcatcctcc
 661 tccgactggg ccaagcccag gggtcactgt ccttctgcat gctggaagcc agccaggaca
 721 tgggccgcac gctcgagtgg cggccgcgta ctccagcctt ggtccggggc tgccacttgg
```

```
 781 aaggcgtggc cggccacaag gaggcgcaca tcctgagggt cctgccgggc cactcggccg
 841 ggccccggac ggtgacggtg aaggtggaac tgagctgcgc acccggggat ctcgatgccg
 901 tcctcatcct gcagggtccc ccctacgtgt cctggctcat cgacgccaac cacaacatgc
 961 agatctggac cactggagaa tactccttca agatctttcc agagaaaaac attcgtggct
1021 tcaagctccc agacacacct caaggcctcc tgggggaggc ccggatgctc aatgccagca
1081 ttgtggcatc cttcgtggag ctaccgctgg ccagcattgt ctcacttcat gcctccagct
1141 gcggtggtag gctgcagacc tcacccgcac cgatccagac cactcctccc aaggacactt
1201 gtagcccgga gctgctcatg tccttgatcc agacaaagtg tgccgacgac gccatgaccc
1261 tggtactaaa gaaagagctt gttgcgcatt tgaagtgcac catcacgggc ctgaccttct
1321 gggaccccag ctgtgaggca gaggacaggg gtgacaagtt tgtcttgcgc agtgcttact
1381 ccagctgtgg catgcaggtg tcagcaagta tgatcagcaa tgaggcggtg gtcaatatcc
1441 tgtcgagctc atcaccacag cggaaaaagg tgcactgcct caacatggac agcctctctt
1501 tccagctggg cctctacctc agcccacact tcctccaggc ctccaacacc atcgagccgg
1561 ggcagcagag ctttgtgcag gtcagagtgt ccccatccgt ctccgagttc ctgctccagt
1621 tagacagctg ccacctggac ttggggcctg agggaggcac cgtggaactc atccagggcc
1681 gggcggccaa gggcaactgt gtgagcctgc tgtccccaag ccccgagggt gacccgcgct
1741 tcagcttcct cctccacttc tacacagtac ccatacccaa aaccggcacc ctcagctgca
1801 cggtagccct gcgtcccaag accgggtctc aagaccagga agtccatagg actgtcttca
1861 tgcgcttgaa catcatcagc cctgacctgt ctggttgcac aagcaaaggc ctcgtcctgc
1921 ccgccgtgct gggcatcacc tttggtgcct tcctcatcgg ggccctgctc actgctgcac
1981 tctggtacat ctactcgcac acgcgttccc ccagcaagcg ggagcccgtg gtggcggtgg
2041 ctgccccggc ctcctcggag agcagcagca ccaaccacag catcgggagc acccagagca
2101 ccccctgctc caccagcagc atggcatagc cccggccccc cgcgctcgcc cagcaggaga
2161 gactgagcag ccgccagctg ggagcactgg tgtgaactca ccctgggagc cagtcctcca
2221 ctcgacccag aatggagcct gctctccgcg cctacccttc ccgcctccct ctcagaggcc
2281 tgctgccagt gcagccactg gcttggaaca ccttggggtc cctccacccc acagaacctt
2341 caacccagtg ggtctgggat atggctgccc aggagacaga ccacttgcca cgctgttgta
2401 aaaacccaag tccctgtcat ttgaacctgg atccagcact ggtgaactga gctgggcagg
2461 aagggagaac ttgaaacaga ttcaggccag cccagccagg ccaacagcac ctccccgctg
2521 ggaagagaag agggcccagc ccagagccac ctggatctat ccctgcggcc tccacacctg
2581 aacttgccta actaactggc aggggagaca ggagcctagc ggagcccagc ctgggagccc
2641 agagggtggc aagaacagtg ggcgttggga gcctagctcc tgccacatgg agcccctct
2701 gccggtcggg cagccagcag aggggagta gccaagctgc ttgtcctggg cctgcccctg
2761 tgtattcacc accaataaat cagaccatga aaccaaaaaa aaaaaaaaaa aaaaaaaaaa
2821 aaaaaaaaaa
```

An exemplary human Cluster of differentiation 44 (CD44) amino acid sequence is set forth below (SEQ ID NO: 173; GenBank Accession No: ACI46596, Version 1, incorporated herein by reference):

```
  1 mdkfwwhaaw glclvplsla qidlnitcrf agvfhveknq rysisrteaa dlckafnstl
 61 ptmaqmekal sigfetcryg fieghvvipr ihpnsicaan ntgvyiltsn tsqydtycfn
121 asappeedct svtdlpnafd gpititivnr dgtryvqkge yrtnpediyp snptdddvss
181 gsssserssts ggyifytfst vhpipdedsp witdstdrip atrhshgsqe gganttsgpi
241 rtpqipewli ilasllalal ilavciavns rrrcgqkkkl vinsgngave drkpsglnge
301 asksqemvhl vnkessetpd qfmtadetrn lqnvdmkigv
```

An exemplary human *CD44* nucleic acid sequence is set forth below (SEQ ID NO: 174; GenBank Accession No: NM_000610, Version 3, incorporated herein by reference):

```
  1 gagaagaaag ccagtgcgtc tctgggcgca ggggccagtg gggctcggag gcacaggcac
 61 cccgcgacac tccaggttcc ccgacccacg tccctggcag ccccgattat ttacagcctc
```

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 121 agcagagcac ggggcggggg cagaggggcc cgcccgggag ggctgctact tcttaaaacc
 181 tctgcgggct gcttagtcac agccccccct gcttgggtgt gtccttcgct cgctccctcc
 241 ctccgtctta ggtcactgtt ttcaacctcg aataaaaact gcagccaact tccgaggcag
 301 cctcattgcc cagcggaccc cagcctctgc caggttcggt ccgccatcct cgtcccgtcc
 361 tccgccggcc cctgccccgc gcccagggat cctccagctc ctttcgcccg cgccctccgt
 421 tcgctccgga caccatggac aagttttggt ggcacgcagc ctggggactc tgcctcgtgc
 481 cgctgagcct ggcgcagatc gatttgaata taacctgccg ctttgcaggt gtattccacg
 541 tggagaaaaa tggtcgctac agcatctctc ggacggaggc cgctgacctc tgcaaggctt
 601 tcaatagcac cttgcccaca atggcccaga tggagaaagc tctgagcatc ggatttgaga
 661 cctgcaggta tgggttcata gaagggcacg tggtgattcc ccggatccac cccaactcca
 721 tctgtgcagc aaacaacaca ggggtgtaca tcctcacatc caacacctcc cagtatgaca
 781 catattgctt caatgcttca gctccacctg aagaagattg tacatcagtc acagacctgc
 841 ccaatgcctt tgatggacca attaccataa ctattgttaa ccgtgatggc acccgctatg
 901 tccagaaagg agaatacaga acgaatcctg aagacatcta ccccagcaac cctactgatg
 961 atgacgtgag cagcggctcc tccagtgaaa ggagcagcac ttcaggaggt tacatctttt
1021 acacctttc tactgtacac cccatcccag acgaagacag tccctggatc accgacagca
1081 cagacagaat ccctgctacc actttgatga gcactagtgc tacagcaact gagacagcaa
1141 ccaagaggca agaaacctgg gattggtttt catggttgtt tctaccatca gagtcaaaga
1201 atcatcttca cacaacaaca caaatggctg gtacgtcttc aaataccatc tcagcaggct
1261 gggagccaaa tgaagaaaat gaagatgaaa gagacagaca cctcagtttt tctggatcag
1321 gcattgatga tgatgaagat tttatctcca gcaccatttc aaccacacca cgggcttttg
1381 accacacaaa acagaaccag gactggaccc agtggaaccc aagccattca aatccggaag
1441 tgctacttca gacaaccaca aggatgactg atgtagacag aaatggcacc actgcttatg
1501 aaggaaactg gaacccagaa gcacaccctc ccctcattca ccatgagcat catgaggaag
1561 aagagacccc acattctaca agcacaatcc aggcaactcc tagtagtaca acggaagaaa
1621 cagctaccca gaaggaacag tggtttggca acagatggca tgagggatat cgccaaacac
1681 ccaaagaaga ctcccattcg acaacaggga cagctgcagc ctcagctcat accagccatc
1741 caatgcaagg aaggacaaca ccaagcccag aggacagttc ctggactgat ttcttcaacc
1801 caatctcaca ccccatggga cgaggtcatc aagcaggaag aaggatggat atggactcca
1861 gtcatagtat aacgcttcag cctactgcaa atccaaacac aggtttggtg gaagatttgg
1921 acaggacagg acctctttca atgacaacgc agcagagtaa ttctcagagc ttctctacat
1981 cacatgaagg cttggaagaa gataaagacc atccaacaac ttctactctg acatcaagca
2041 ataggaatga tgtcacaggt ggaagaagag acccaaatca ttctgaaggc tcaactactt
2101 tactggaagg ttatacctct cattacccac acacgaagga aagcaggacc ttcatcccag
2161 tgacctcagc taagactggg tcctttggag ttactgcagt tactgttgga gattccaact
2221 ctaatgtcaa tcgttcctta tcaggagacc aagacacatt ccaccccagt ggggggtccc
2281 ataccactca tggatctgaa tcagatggac actcacatgg gagtcaagaa ggtggagcaa
2341 acacaacctc tggtcctata aggacacccc aaattccaga atggctgatc atcttggcat
2401 ccctcttggc cttggctttg attcttgcag tttgcattgc agtcaacagt cgaagaaggt
2461 gtgggcagaa gaaaaagcta gtgatcaaca gtggcaatgg agctgtggag gacagaaagc
2521 caagtggact caacggagag gccagcaagt ctcaggaaat ggtgcatttg gtgaacaagg
2581 agtcgtcaga aactccagac cagtttatga cagctgatga gacaaggaac ctgcagaatg
2641 tggacatgaa gattggggtg taacacctac accattatct tggaaagaaa caaccgttgg
2701 aaacataacc attacaggga gctgggacac ttaacagatg caatgtgcta ctgattgttt
2761 cattgcgaat ctttttttagc ataaaatttt ctactctttt tgtttttttgt gttttgttct
2821 ttaaagtcag gtccaatttg taaaaacagc attgctttct gaaattaggg cccaattaat
2881 aatcagcaag aatttgatcg ttccagttcc cacttggagg cctttcatcc ctcgggtgtg
2941 ctatggatgg cttctaacaa aaactacaca tatgtattcc tgatcgccaa ccttttcccc
3001 accagctaag gacatttccc agggttaata gggcctggtc cctgggagga aatttgaatg
3061 ggtccatttt gcccttccat agcctaatcc ctgggcattg ctttccactg aggttggggg
3121 ttggggtgta ctagttacac atcttcaaca gacccccctct agaaattttt cagatgcttc
3181 tgggagacac ccaaagggtg aagctattta tctgtagtaa actatttatc tgtgtttttg
3241 aaatattaaa ccctggatca gtcctttgat cagtataatt ttttaaagtt actttgtcag
3301 aggcacaaaa gggtttaaac tgattcataa taaatatctg tacttcttcg atcttcacct
3361 tttgtgctgt gattcttcag tttctaaacc agcactgtct gggtccctac aatgtatcag
3421 gaagagctga gaatggtaag gagactcttc taagtcttca tctcagagac cctgagttcc
```

```
3481 cactcagacc cactcagcca aatctcatgg aagaccaagg agggcagcac tgtttttgtt
3541 ttttgttttt tgtttttttt ttttgacact gtccaaaggt tttccatcct gtcctggaat
3601 cagagttgga agctgaggag cttcagcctc ttttatggtt taatggccac ctgttctctc
3661 ctgtgaaagg ctttgcaaag tcacattaag tttgcatgac ctgttatccc tggggcccta
3721 tttcatagag gctggcccta ttagtgattt ccaaaaacaa tatggaagtg ccttttgatg
3781 tcttacaata agagaagaag ccaatggaaa tgaaagagat tggcaaaggg gaaggatgat
3841 gccatgtaga tcctgtttga catttttatg gctgtatttg taaacttaaa cacaccagtg
3901 tctgttcttg atgcagttgc tatttaggat gagttaagtg cctggggagt ccctcaaaag
3961 gttaaaggga ttcccatcat tggaatctta tcaccagata ggcaagttta tgaccaaaca
4021 agagagtact ggctttatcc tctaacctca tattttctcc cacttggcaa gtcctttgtg
4081 gcatttattc atcagtcagg gtgtccgatt ggtcctagaa cttccaaagg ctgcttgtca
4141 tagaagccat tgcatctata aagcaacggc tcctgttaaa tggtatctcc tttctgaggc
4201 tcctactaaa agtcatttgt tacctaaact tatgtgctta acaggcaatg cttctcagac
4261 cacaaagcag aaagaagaag aaaagctcct gactaaatca gggctgggct tagacagagt
4321 tgatctgtag aatatcttta aaggagagat gtcaactttc tgcactattc ccagcctctg
4381 ctcctccctg tctaccctct cccctccctc tctccctcca cttcacccca caatcttgaa
4441 aaacttcctt tctcttctgt gaacatcatt ggccagatcc attttcagtg gtctggattt
4501 ctttttattt tcttttcaac ttgaaagaaa ctggacatta ggccactatg tgttgttact
4561 gccactagtg ttcaagtgcc tcttgttttc ccagagattt cctgggtctg ccagaggccc
4621 agacaggctc actcaagctc tttaactgaa aagcaacaag ccactccagg acaaggttca
4681 aaatggttac aacagcctct acctgtcgcc ccagggagaa aggggtagtg atacaagtct
4741 catagccaga gatggttttc cactccttct agatattccc aaaaagaggc tgagacagga
4801 ggttattttc aattttattt tggaattaaa tacttttttc cctttattac tgttgtagtc
4861 cctcacttgg atatacctct gttttcacga tagaaataag ggaggtctag agcttctatt
4921 ccttggccat tgtcaacgga gagctggcca agtcttcaca aacccttgca acattgcctg
4981 aagtttatgg aataagatgt attctcactc ccttgatctc aagggcgtaa ctctggaagc
5041 acagcttgac tacacgtcat ttttaccaat gattttcagg tgacctgggc taagtcattt
5101 aaactgggtc tttataaaag taaaaggcca acatttaatt attttgcaaa gcaacctaag
5161 agctaaagat gtaatttttc ttgcaattgt aaatcttttg tgtctcctga agacttccct
5221 taaaattagc tctgagtgaa aaatcaaaag agacaaaaga catcttcgaa tccatatttc
5281 aagcctggta gaattggctt ttctagcaga acctttccaa aagttttata ttgagattca
5341 taacaacacc aagaattgat tttgtagcca acattcattc aatactgtta tatcagagga
5401 gtaggagaga ggaaacattt gacttatctg gaaaagcaaa atgtacttaa gaataagaat
5461 aacatggtcc attcaccttt atgttataga tatgtctttg tgtaaatcat ttgttttgag
5521 ttttcaaaga atagcccatt gttcattctt gtgctgtaca atgaccactg ttattgttac
5581 tttgactttt cagagcacac ccttcctctg gtttttgtat atttattgat ggatcaataa
5641 taatgaggaa agcatgatat gtatattgct gagttgaaag cacttattgg aaaatattaa
5701 aaggctaaca ttaaaagact aaaggaaaca gaaaaaaaaa aaaaaaaa
```

An exemplary human Familial adenomatous polyposis (FAP) amino acid sequence is set forth below (SEQ ID NO: 175; GenBank Accession No: Q12884, Version 5, incorporated herein by reference):

```
   1 mktwvkivfg vatsavlall vmcivlrpsr vhnseentmr altlkdilng tfsyktffpn
  61 wisgqeylhq sadnnivlyn ietgqsytil snrtmksvna snyglspdrq fvylesdysk
 121 lwrysytaty yiydlsngef vrgnelprpi qylcwspvgs klayvyqnni ylkqrpgdpp
 181 fqitfngren kifngipdwv yeeemlatky alwwspngkf layaefndtd ipviaysyyg
 241 deqyprtini pypkagaknp vvrifiidtt ypayvgpqev pvpamiassd yyfswltwvt
 301 dervclqwlk rvqnvsvlsi cdfredwqtw dcpktqehie esrtgwaggf fvstpvfsyd
 361 aisyykifsd kdgykhihyi kdtvenaiqi tsgkweaini frvtqdslfy ssnefeeypg
 421 rrniyrisig syppskkcvt chlrkercqy ytasfsdyak yyalvcygpg ipistlhdgr
 481 tdqeikilee nkelenalkn iqlpkeeikk levdeitlwy kmilppqfdr skkyplliqv
 541 yggpcsqsvr svfavnwisy laskegmvia lvdgrgtafq gdkllyavyr klgvyevedq
 601 itavrkfiem gfidekriai wgwsyggyvs slalasgtgl fkcgiavapv ssweyyasvy
```

```
661 terfmglptk ddnlehykns tvmaraeyfr nvdyllihgt addnvhfqns aqiakalvna
721 qvdfqamwys dqnhglsgls tnhlythmth flkqcfslsd
```

An exemplary human *FAP* nucleic acid sequence is set forth below (SEQ ID NO: 176; GenBank Accession No: NM_004460, Version 4, incorporated herein by reference):

```
   1 actcacagtt catttgaggg ccaagaacgc ccccaaaatc tgtttctaat tttacagaaa
  61 tcttttgaaa cttggcacgg tattcaaaag tccgtggaaa gaaaaaaacc ttgtcctggc
 121 ttcagcttcc aactacaaag acagacttgg tccttttcaa cggttttcac agatccagtg
 181 acccacgctc tgaagacaga attagctaac tttcaaaaac atctggaaaa atgaagactt
 241 gggtaaaaat cgtatttgga gttgccacct ctgctgtgct tgccttattg gtgatgtgca
 301 ttgtcttacg cccttcaaga gttcataact ctgaagaaaa tacaatgaga gcactcacac
 361 tgaaggatat tttaaatgga acattttctt ataaaacatt ttttccaaac tggatttcag
 421 gacaagaata tcttcatcaa tctgcagata acaatatagt actttataat attgaaacag
 481 gacaatcata taccattttg agtaatagaa ccatgaaaag tgtgaatgct tcaaattacg
 541 gcttatcacc tgatcggcaa tttgtatatc tagaaagtga ttattcaaag ctttggagat
 601 actcttacac agcaacatat tacatctatg accttagcaa tggagaattt gtaagaggaa
 661 atgagcttcc tcgtccaatt cagtatttat gctggtcgcc tgttgggagt aaattagcat
 721 atgtctatca aaacaatatc tatttgaaac aaagaccagg agatccacct tttcaaataa
 781 catttaatgg aagagaaaat aaaatattta atggaatccc agactgggtt tatgaagagg
 841 aaatgcttgc tacaaaatat gctctctggt ggtctcctaa tggaaaattt ttggcatatg
 901 cggaatttaa tgatacggat ataccagtta ttgcctattc ctattatggc gatgaacaat
 961 atcctagaac aataaatatt ccatacccaa aggctggagc taagaatccc gttgttcgga
1021 tatttattat cgataccact taccctgcgt atgtaggtcc ccaggaagtg cctgttccag
1081 caatgatagc ctcaagtgat tattatttca gttggctcac gtgggttact gatgaacgag
1141 tatgtttgca gtggctaaaa agagtccaga atgtttcggt cctgtctata tgtgacttca
1201 gggaagactg gcagacatgg gattgtccaa agacccagga gcatatagaa gaaagcagaa
1261 ctggatgggc tggtggattc tttgtttcaa caccagtttt cagctatgat gccatttcgt
1321 actacaaaat atttagtgac aaggatggct acaaacatat tcactatatc aaagacactg
1381 tggaaaatgc tattcaaatt acaagtggca agtgggaggc cataaatata ttcagagtaa
1441 cacaggattc actgttttat tctagcaatg aatttgaaga ataccctgga agaagaaaca
1501 tctacagaat tagcattgga agctatcctc caagcaagaa gtgtgttact tgccatctaa
1561 ggaaagaaag gtgccaatat tacacagcaa gtttcagcga ctacgccaag tactatgcac
1621 ttgtctgcta cggcccaggc atccccattt ccacccttca tgatggacgc actgatcaag
1681 aaattaaaat cctggaagaa aacaaggaat tggaaaatgc tttgaaaaat atccagctgc
1741 ctaaagagga aattaagaaa cttgaagtag atgaaattac tttatggtac aagatgattc
1801 ttcctcctca atttgacaga tcaaagaagt atcccttgct aattcaagtg tatggtggtc
1861 cctgcagtca gagtgtaagg tctgtatttg ctgttaattg gatatcttat cttgcaagta
1921 aggaagggat ggtcattgcc ttggtggatg gtcgaggaac agctttccaa ggtgacaaac
1981 tcctctatgc agtgtatcga aagctgggtg tttatgaagt tgaagaccag attacagctg
2041 tcagaaaatt catagaaatg ggtttcattg atgaaaaaag aatagccata tggggctggt
2101 cctatggagg atacgtttca tcactggccc ttgcatctgg aactggtctt ttcaaatgtg
2161 gtatagcagt ggctccagtc tccagctggg aatattacgc gtctgtctac acagagagat
2221 tcatgggtct cccaacaaag gatgataatc ttgagcacta taagaattca actgtgatgg
2281 caagagcaga atatttcaga aatgtagact atcttctcat ccacggaaca gcagatgata
2341 atgtgcactt tcaaaactca gcacagattg ctaaagctct ggttaatgca caagtggatt
2401 tccaggcaat gtggtactct gaccagaacc acggcttatc cggcctgtcc acgaaccact
2461 tatacaccca catgacccac ttcctaaagc agtgtttctc tttgtcagac taaaaacgat
2521 gcagatgcaa gcctgtatca gaatctgaaa accttatata aacccctcag acagtttgct
2581 tattttattt tttatgttgt aaaatgctag tataaacaaa caaattaatg ttgttctaaa
2641 ggctgttaaa aaaaagatga ggactcagaa gttcaagcta aatattgttt acattttctg
2701 gtactctgtg aaagaagaga aaagggagtc atgcattttg ctttggacac agtgttttat
2761 cacctgttca tttgaagaaa aataataaag tcagaagttc aagtgctaaa aaaaaaaaaa
2821 aaaaaaaaaa aaaaaaa
```

An exemplary human Hypoxia-inducible factor 1-alpha (HIF1A) amino acid sequence is set forth below (SEQ ID NO: 177; GenBank Accession No: Q16665, Version 1, incorporated herein by reference):

```
  1 megaggandk kkisserrke ksrdaarsrr skesevfyel ahqlplphnv sshldkasvm
 61 rltisylrvr klldagdldi eddmkaqmnc fylkaldgfv mvltddgdmi yisdnvnkym
121 gltqfeltgh svfdfthpcd heemremlth rnglvkkgke qntqrsfflr mkctltsrgr
181 tmniksatwk vlhctghihv ydtnsnqpqc gykkppmtcl vlicepiphp snieipldsk
241 tflsrhsldm kfsycderit elmgyepeel lgrsiyeyyh aldsdhltkt hhdmftkgqv
301 ttgqyrmlak rggyvwvetq atviyntkns qpqcivcvny vvsgiiqhdl ifslqqtecv
361 lkpvessdmk mtqlftkves edtsslfdkl kkepdaltll apaagdtiis ldfgsndtet
421 ddqqleevpl yndvmlpspn eklqninlam splptaetpk plrssadpal nqevalklep
481 npeslelsft mpqiqdqtps psdgstrqss pepnspseyc fyvdsdmvne fklelveklf
541 aedteaknpf stqdtdldle mlapyipmdd dfqlrsfdql splesssasp esaspqstvt
601 vfqqtqiqep tanattttat tdelktvtkd rmedikilia spspthihke ttsatsspyr
661 dtqsrtaspn ragkgvieqt ekshprspnv lsvalsqrtt vpeeelnpki lalqnaqrkr
721 kmehdgslfq avgigtllqq pddhaattsl swkrvkgcks seqngmeqkt iilipsdlac
781 rllgqsmdes glpqltsydc evnapiqgsr nllqgeellr aldqvn
```

An exemplary human *HIF1A* nucleic acid sequence is set forth below (SEQ ID NO: 178; GenBank Accession No: NM_001530, Version 3, incorporated herein by reference):

```
   1 gcgcgcgccg gcctgggcag gcgagcgggc gcgctcccgc cccctctccc ctccccgcgc
  61 gcccgagcgc gcctccgccc ttgcccgccc cctgacgctg cctcagctcc tcagtgcaca
 121 gtgctgcctc gtctgagggg acaggaggat caccctcttc gtcgcttcgg ccagtgtgtc
 181 gggctgggcc ctgacaagcc acctgaggag aggctcggag ccgggcccgg accccggcga
 241 ttgccgcccg cttctctcta gtctcacgag gggtttcccg cctcgcaccc ccacctctgg
 301 acttgccttt ccttctcttc tccgcgtgtg gagggagcca gcgcttaggc cggagcgagc
 361 ctgggggccg cccgccgtga agacatcgcg gggaccgatt caccatggag ggcgccggcg
 421 gcgcgaacga caagaaaaag ataagttctg aacgtcgaaa agaaaagtct cgagatgcag
 481 ccagatctcg gcgaagtaaa gaatctgaag ttttttatga gcttgctcat cagttgccac
 541 ttccacataa tgtgagttcg catcttgata aggcctctgt gatgaggctt accatcagct
 601 atttgcgtgt gaggaaactt ctggatgctg gtgatttgga tattgaagat gacatgaaag
 661 cacagatgaa ttgcttttat ttgaaagcct tggatggttt tgttatggtt ctcacagatg
 721 atggtgacat gatttacatt tctgataatg tgaacaaata catgggatta actcagtttg
 781 aactaactgg acacagtgtg tttgatttta ctcatccatg tgaccatgag gaaatgagag
 841 aaatgcttac acacagaaat ggccttgtga aaaagggtaa agaacaaaac acacagcgaa
 901 gctttttttct cagaatgaag tgtaccctaa ctagccgagg aagaactatg aacataaagt
 961 ctgcaacatg gaaggtattg cactgcacag gccacattca cgtatatgat accaacagta
1021 accaacctca gtgtgggtat aagaaaccac ctatgacctg cttggtgctg atttgtgaac
1081 ccattcctca cccatcaaat attgaaattc ctttagatag caagactttc ctcagtcgac
1141 acagcctgga tatgaaattt tcttattgtg atgaaagaat taccgaattg atgggatatg
1201 agccagaaga acttttaggc cgctcaattt atgaatatta tcatgctttg gactctgatc
1261 atctgaccaa aactcatcat gatatgttta ctaaaggaca agtcaccaca ggacagtaca
1321 ggatgcttgc caaaagaggt ggatatgtct gggttgaaac tcaagcaact gtcatatata
1381 acaccaagaa ttctcaacca cagtgcattg tatgtgtgaa ttacgttgtg agtggtatta
1441 ttcagcacga cttgattttc tcccttcaac aaacagaatg tgtccttaaa ccggttgaat
1501 cttcagatat gaaaatgact cagctattca ccaaagttga atcagaagat acaagtagcc
1561 tctttgacaa acttaagaag gaacctgatg ctttaacttt gctggcccca gccgctggag
1621 acacaatcat atctttagat tttggcagca acgacacaga aactgatgac cagcaacttg
1681 aggaagtacc attatataat gatgtaatgc tcccctcacc caacgaaaaa ttacagaata
1741 taaatttggc aatgtctcca ttacccaccg ctgaaacgcc aaagccactt cgaagtagtg
1801 ctgaccctgc actcaatcaa gaagttgcat taaaattaga accaaatcca gagtcactgg
```

```
1861 aactttcttt taccatgccc cagattcagg atcagacacc tagtccttcc gatggaagca
1921 ctagacaaag ttcacctgag cctaatagtc ccagtgaata ttgtttttat gtggatagtg
1981 atatggtcaa tgaattcaag ttggaattgg tagaaaaact ttttgctgaa gacacagaag
2041 caaagaaccc attttctact caggacacag atttagactt ggagatgtta gctccctata
2101 tcccaatgga tgatgacttc cagttacgtt ccttcgatca gttgtcacca ttagaaagca
2161 gttccgcaag ccctgaaagc gcaagtcctc aaagcacagt tacagtattc cagcagactc
2221 aaatacaaga acctactgct aatgccacca ctaccactgc caccactgat gaattaaaaa
2281 cagtgacaaa agaccgtatg gaagacatta aaatattgat tgcatctcca tctcctaccc
2341 acatacataa agaaactact agtgccacat catcaccata tagagatact caaagtcgga
2401 cagcctcacc aaacagagca ggaaaaggag tcatagaaca gacagaaaaa tctcatccaa
2461 gaagccctaa cgtgttatct gtcgctttga gtcaaagaac tacagttcct gaggaagaac
2521 taaatccaaa gatactagct ttgcagaatg ctcagagaaa gcgaaaaatg gaacatgatg
2581 gttcactttt tcaagcagta ggaattggaa cattattaca gcagccagac gatcatgcag
2641 ctactacatc actttcttgg aaacgtgtaa aaggatgcaa atctagtgaa cagaatggaa
2701 tggagcaaaa gacaattatt ttaataccct ctgatttagc atgtagactg ctggggcaat
2761 caatggatga aagtggatta ccacagctga ccagttatga ttgtgaagtt aatgctccta
2821 tacaaggcag cagaaaccta ctgcagggtg aagaattact cagagctttg gatcaagtta
2881 actgagcttt ttcttaattt cattcctttt tttggacact ggtggctcat tacctaaagc
2941 agtctattta tattttctac atctaatttt agaagcctgg ctacaatact gcacaaactt
3001 ggttagttca attttgatcc cctttctact taatttacat taatgctctt ttttagtatg
3061 ttctttaatg ctggatcaca gacagctcat tttctcagtt ttttggtatt taaaccattg
3121 cattgcagta gcatcatttt aaaaaatgca ccttttttatt tatttatttt tggctaggga
3181 gtttatccct ttttcgaatt atttttaaga agatgccaat ataatttttg taagaaggca
3241 gtaacctttc atcatgatca taggcagttg aaaaattttt acacctttttt tttcacattt
3301 tacataaata ataatgcttt gccagcagta cgtggtagcc acaattgcac aatatatttt
3361 cttaaaaaat accagcagtt actcatggaa tatattctgc gtttataaaa ctagttttta
3421 agaagaaatt ttttttggcc tatgaaattg ttaaacctgg aacatgacat tgttaatcat
3481 ataataatga ttcttaaatg ctgtatggtt tattatttaa atgggtaaag ccatttacat
3541 aatatagaaa gatatgcata tatctagaag gtatgtggca tttatttgga taaaattctc
3601 aattcagaga aatcatctga tgtttctata gtcactttgc cagctcaaaa gaaaacaata
3661 ccctatgtag ttgtggaagt ttatgctaat attgtgtaac tgatattaaa cctaaatgtt
3721 ctgcctaccc tgttggtata aagatatttt gagcagactg taaacaagaa aaaaaaaatc
3781 atgcattctt agcaaaattg cctagtatgt taatttgctc aaaatacaat gtttgatttt
3841 atgcactttg tcgctattaa catccttttt ttcatgtaga tttcaataat tgagtaattt
3901 tagaagcatt attttaggaa tatatagttg tcacagtaaa tatcttgttt tttctatgta
3961 cattgtacaa atttttcatt ccttttgctc tttgtggttg gatctaacac taactgtatt
4021 gttttgttac atcaaataaa catcttctgt ggaccaggca aaaaaaaaaa aaaaaaaaaa
4081 aa
```

An exemplary human Caveolin-1 (CAV1) amino acid sequence is set forth below (SEQ ID NO: 179; GenBank Accession No: Q03135, Version 4, incorporated herein by reference):

```
  1 msggkyvdse ghlytvpire qgniykpnnk amadelsekq vydahtkeid lvnrdpkhln
 61 ddvvkidfed viaepegths fdgiwkasft tftvtkywfy rllsalfgip maliwgiyfa
121 ilsflhiwav vpciksflie iqcisrvysi yvhtvcdplf eavgkifsnv rinlqkei
```

An exemplary human *CAV1* nucleic acid sequence is set forth below (SEQ ID NO: 180; GenBank Accession No: NM_001753, Version 4, incorporated herein by reference):

```
  1 gggagaaacg ttctcactcg ctctctgctc gctgcgggcg ctccccgccc tctgctgcca
 61 gaaccttggg gatgtgccta gacccggcgc agcacacgtc cgggccaacc gcgagcagaa
121 caaacctttg gcgggcggcc aggaggctcc ctcccagcca ccgccccccct ccagcgcctt
181 tttttccccc catacaatac aagatcttcc ttcctcagtt cccttaaagc acagcccagg
```

```
 241 gaaacctcct cacagttttc atccagccac gggccagcat gtctgggggc aaatacgtag
 301 actcggaggg acatctctac accgttccca tccgggaaca gggcaacatc tacaagccca
 361 acaacaaggc catggcagac gagctgagcg agaagcaagt gtacgacgcg cacaccaagg
 421 agatcgacct ggtcaaccgc gaccctaaac acctcaacga tgacgtggtc aagattgact
 481 ttgaagatgt gattgcagaa ccagaaggga cacacagttt tgacggcatt tggaaggcca
 541 gcttcaccac cttcactgtg acgaaatact ggttttaccg cttgctgtct gccctctttg
 601 gcatcccgat ggcactcatc tggggcattt acttcgccat tctctctttc ctgcacatct
 661 gggcagttgt accatgcatt aagagcttcc tgattgagat tcagtgcatc agccgtgtct
 721 attccatcta cgtccacacc gtctgtgacc cactctttga agctgttggg aaaatattca
 781 gcaatgtccg catcaacttg cagaaagaaa tataaatgac atttcaagga tagaagtata
 841 cctgattttt tttccttta attttcctgg tgccaatttc aagttccaag ttgctaatac
 901 agcaacaatt tatgaattga attatcttgg ttgaaaataa aaagatcact ttctcagttt
 961 tcataagtat tatgtctctt ctgagctatt tcatctattt ttggcagtct gaatttttaa
1021 aacccattta aatttttttc cttacctttt tatttgcatg tggatcaacc atcgctttat
1081 tggctgagat atgaacatat tgttgaaagg taatttgaga gaaatatgaa gaactgagga
1141 ggaaaaaaaa aaaaaagaaa agaaccaaca acctcaactg cctactccaa aatgttggtc
1201 attttatgtt aagggaagaa ttccagggta tggccatgga gtgtacaagt atgtgggcag
1261 attttcagca aactcttttc ccactgttta aggagttagt ggattactgc cattcacttc
1321 ataatccagt aggatccagt gatccttaca agttagaaaa cataatcttc tgccttctca
1381 tgatccaact aatgccttac tcttcttgaa attttaacct atgatatttt ctgtgcctga
1441 atatttgtta tgtagataac aagacctcag tgccttcctg tttttcacat tttccttttc
1501 aaatagggtc taactcagca actcgcttta ggtcagcagc ctccctgaag accaaaatta
1561 gaatatccat gacctagttt tccatgcgtg tttctgactc tgagctacag agtctggtga
1621 agctcacttc tgggcttcat ctggcaacat ctttatccgt agtgggtatg gttgacacta
1681 gcccaatgaa atgaattaaa gtggaccaat agggctgagc tctctgtggg ctggcagtcc
1741 tggaagccag ctttccctgc ctctcatcaa ctgaatgagg tcagcatgtc tattcagctt
1801 cgtttatttt caagaataat cacgctttcc tgaatccaaa ctaatccatc accggggtgg
1861 tttagtggct caacattgtg ttcccatttc agctgatcag tgggcctcca aggaggggct
1921 gtaaaatgga ggccattgtg tgagcctatc agagttgctg caaacctgac ccctgctcag
1981 taaagcactt gcaaccgtct gttatgctgt gacacatggc ccctcccct gccaggagct
2041 ttggacctaa tccaagcatc cctttgccca gaaagaagat gggggaggag gcagtaataa
2101 aaagattgaa gtattttgct ggaataagtt caaattcttc tgaactcaaa ctgaggaatt
2161 tcacctgtaa acctgagtcg tacagaaagc tgcctggtat atccaaaagc tttttattcc
2221 tcctgctcat attgtgattc tgccctttggg gacttttctt aaaccttcag ttatgatttt
2281 tttttcatac acttattgga actctgcttg atttttgcct cttccagtct tcctgacact
2341 ttaattacca acctgttacc tactttgact ttttgcattt aaaacagaca ctggcatgga
2401 tatagtttta cttttaaact gtgtacataa ctgaaaatgt gctatactgc atacttttta
2461 aatgtaaaga tatttttatc tttatatgaa gaaaatcact taggaaatgg ctttgtgatt
2521 caatctgtaa actgtgtatt ccaagacatg tctgttctac atagatgctt agtccctcat
2581 gcaaatcaat tactggtcca aaagattgct gaaattttat atgcttactg atatatttta
2641 caatttttta tcatgcatgt cctgtaaagg ttacaagcct gcacaataaa aatgtttaac
2701 ggttaaacag tcaaaaaaaa aaa
```

An exemplary human Platelet-derived growth factor receptor alpha (PDGFRA) amino acid sequence is set forth below (SEQ ID NO: 181; GenBank Accession No: P16234, Version 1, incorporated herein by reference):

```
   1 mgtshpaflv lgclltglsl ilcqlslpsi lpnenekvvq lnssfslrcf gesevswqyp
  61 mseeessdve irneennsgl fvtvlevssa saahtglytc yynhtqteen elegrhiyiy
 121 vpdpdvafvp lgmtdylviv edddsaiipc rttdpetpvt lhnsegvvpa sydsrqgfng
 181 tftvgpyice atvkgkkfqt ipfnvyalka tseldlemea lktvyksget ivvtcavfnn
 241 evvdlqwtyp gevkgkgitm leeikvpsik lvytltvpea tvkdsgdyec aarqatrevk
 301 emkkvtisvh ekgfieikpt fsqleavnlh evkhfvvevr aypppriswl knnltlienl
 361 teittdveki qeiryrsklk lirakeedsg hytivaqned avksytfell tqvpssildl
```

```
 421 vddhhgstgg qtvrctaegt plpdiewmic kdikkcnnet swtilannvs niiteihsrd
 481 rstvegrvtf akveetiavr claknllgae nrelklvapt lrseltvaaa vlvllvivii
 541 slivlvviwk qkpryeirwr viesispdgh eyiyvdpmql pydsrwefpr dglvlgrvlg
 601 sgafgkvveg tayglsrsqp vmkvavkmlk ptarssekqa lmselkimth lgphlnivnl
 661 lgactksgpi yiiteycfyg dlvnylhknr dsflshhpek pkkeldifgl npadestrsy
 721 vilsfenngd ymdmkqadtt qyvpmlerke vskysdiqrs lydrpasykk ksmldsevkn
 781 llsddnsegl tlldllsfty qvargmefla skncvhrdla arnvllaqgk ivkicdfgla
 841 rdimhdsnyv skgstflpvk wmapesifdn lyttlsdvws ygillweifs lggtpypgmm
 901 vdstfynkik sgyrmakpdh atsevyeimv kcwnsepekr psfyhlseiv enllpgqykk
 961 syekihldfl ksdhpavarm rvdsdnayig vtykneedkl kdweggldeq rlsadsgyii
1021 plpdidpvpe eedlgkrnrh ssqtseesai etgsssstfi kredetiedi dmmddigids
1081 sdlvedsfl
```

An exemplary human *PDGFRA* nucleic acid sequence is set forth below (SEQ ID NO: 182; GenBank Accession No: NM_006206, Version 5, incorporated herein by reference):

```
   1 gattgcgtaa gagcaaaaag cgaaggcgca atctggacac tgggagattc ggagcgcagg
  61 gagtttgaga gaaactttta ttttgaagag accaaggttg agggggggct tatttcctga
 121 cagctattta cttagagcaa atgattagtt ttagaaggat ggactataac attgaatcaa
 181 ttacaaaacg cggtttttga gcccattact gttggagcta cagggagaga aacagaggag
 241 gagactgcaa gagatcattg gaggccgtgg gcacgctctt tactccatgt gtgggacatt
 301 cattgcggaa taacatcgga ggagaagttt cccagagcta tggggacttc ccatccggcg
 361 ttcctggtct taggctgtct tctcacaggg ctgagcctaa tcctctgcca gctttcatta
 421 ccctctatcc ttccaaatga aaatgaaaag gttgtgcagc tgaattcatc cttttctctg
 481 agatgctttg gggagagtga agtgagctgg cagtacccca tgtctgaaga agagagctcc
 541 gatgtggaaa tcagaaatga agaaaacaac agcggccttt ttgtgacggt cttggaagtg
 601 agcagtgcct cggcggccca cacagggttg tacacttgct attacaacca cactcagaca
 661 gaagagaatg agcttgaagg caggcacatt tacatctatg tgccagaccc agatgtagcc
 721 tttgtacctc taggaatgac ggattattta gtcatcgtgg aggatgatga ttctgccatt
 781 ataccttgtc gcacaactga tcccgagact cctgtaacct tacacaacag tgaggggtg
 841 gtacctgcct cctacgacag cagacagggc tttaatggga ccttcactgt agggccctat
 901 atctgtgagg ccaccgtcaa aggaaagaag ttccagacca tcccatttaa tgtttatgct
 961 ttaaaagcaa catcagagct ggatctagaa atggaagctc ttaaaaccgt gtataagtca
1021 ggggaaacga ttgtggtcac ctgtgctgtt tttaacaatg aggtggttga ccttcaatgg
1081 acttaccctg gagaagtgaa aggcaaaggc atcacaatgc tggaagaaat caaagtccca
1141 tccatcaaat tggtgtacac tttgacggtc cccgaggcca cggtgaaaga cagtggagat
1201 tacgaatgtg ctgcccgcca ggctaccagg gaggtcaaag aaatgaagaa agtcactatt
1261 tctgtccatg agaaaggttt cattgaaatc aaacccacct tcagccagtt ggaagctgtc
1321 aacctgcatg aagtcaaaca ttttgttgta gaggtgcggg cctacccacc tcccaggata
1381 tcctggctga aaaacaatct gactctgatt gaaaatctca ctgagatcac cactgatgtg
1441 gaaaagattc aggaaataag gtatcgaagc aaattaaagc tgatccgtgc taaggaagaa
1501 gacagtggcc attatactat tgtagctcaa aatgaagatg ctgtgaagag ctatactttt
1561 gaactgttaa ctcaagttcc ttcatccatt ctggacttgg tcgatgatca ccatggctca
1621 actgggggac agacggtgag gtgcacagct gaaggcacgc cgcttcctga tattgagtgg
1681 atgatatgca aagatattaa gaaatgtaat aatgaaactt cctggactat tttggccaac
1741 aatgtctcaa acatcatcac ggagatccac tcccgagaca ggagtaccgt ggagggccgt
1801 gtgactttcg ccaaagtgga ggagaccatc gccgtgcgat gcctggctaa gaatctcctt
1861 ggagctgaga accgagagct gaagctggtg gctcccaccc tgcgttctga actcacggtg
1921 gctgctgcag tcctggtgct gttggtgatt gtgatcatct cacttattgt cctggttgtc
1981 atttggaaac agaaaccgag gtatgaaatt cgctggaggg tcattgaatc aatcagccca
2041 gatggacatg aatatattta tgtggacccg atgcagctgc cttatgactc aagatgggag
2101 tttccaagag atggactagt gcttggtcgg gtcttggggt ctggagcgtt tgggaaggtg
2161 gttgaaggaa cagcctatgg attaagccgg tcccaacctg tcatgaaagt tgcagtgaag
2221 atgctaaaac ccacggccag atccagtgaa aaacaagctc tcatgtctga actgaagata
2281 atgactcacc tggggccaca tttgaacatt gtaaacttgc tgggagcctg caccaagtca
```

2341 ggccccattt acatcatcac agagtattgc ttctatggag atttggtcaa ctatttgcat
2401 aagaataggg atagcttcct gagccaccac ccagagaagc caaagaaaga gctggatatc
2461 tttggattga accctgctga tgaaagcaca cggagctatg ttatttatc ttttgaaaac
2521 aatggtgact acatggacat gaagcaggct gatactacac agtatgtccc catgctagaa
2581 aggaaagagg tttctaaata ttccgacatc cagagatcac tctatgatcg tccagcctca
2641 tataagaaga aatctatgtt agactcagaa gtcaaaaacc tcctttcaga tgataactca
2701 gaaggcctta ctttattgga tttgttgagc ttcacctatc aagttgcccg aggaatggag
2761 tttttggctt caaaaaattg tgtccaccgt gatctggctg ctcgcaacgt cctcctggca
2821 caaggaaaaa ttgtgaagat ctgtgacttt ggcctggcca gagacatcat gcatgattcg
2881 aactatgtgt cgaaaggcag tacctttctg cccgtgaagt ggatggctcc tgagagcatc
2941 tttgacaacc tctacaccac actgagtgat gtctggtctt atggcattct gctctgggag
3001 atcttttccc ttggtggcac cccttacccc ggcatgatgg tggattctac tttctacaat
3061 aagatcaaga gtgggtaccg gatggccaag cctgaccacg ctaccagtga agtctacgag
3121 atcatggtga aatgctggaa cagtgagccg gagaagagac cctcctttta ccacctgagt
3181 gagattgtgg agaatctgct gcctggacaa tataaaaaga gttatgaaaa aattcacctg
3241 gacttcctga agagtgacca tcctgctgtg gcacgcatgc gtgtggactc agacaatgca
3301 tacattggtg tcacctacaa aaacgaggaa gacaagctga aggactggga gggtggtctg
3361 gatgagcaga gactgagcgc tgacagtggc tacatcattc ctctgcctga cattgaccct
3421 gtccctgagg aggaggacct gggcaagagg aacagacaca gctcgcagac ctctgaagag
3481 agtgccattg agacgggttc cagcagttcc accttcatca agagagagga cgagaccatt
3541 gaagacatcg acatgatgga tgacatcggc atagactctt cagacctggt ggaagacagc
3601 ttcctgtaac tggcggattc gaggggttcc ttccacttct ggggccacct ctggatcccg
3661 ttcagaaaac cactttattg caatgcagag gttgagagga ggacttggtt gatgtttaaa
3721 gagaagttcc cagccaaggg cctcggggag cgttctaaat atgaatgaat gggatatttt
3781 gaaatgaact ttgtcagtgt tgcctcttgc aatgcctcag tagcatctca gtggtgtgtg
3841 aagtttggag atagatggat aagggaataa taggccacag aaggtgaact ttgtgcttca
3901 aggacattgg tgagagtcca acagacacaa tttatactgc gacagaactt cagcattgta
3961 attatgtaaa taactctaac caaggctgtg tttagattgt attaactatc ttctttggac
4021 ttctgaagag accactcaat ccatccatgt acttccctct tgaaacctga tgtcagctgc
4081 tgttgaactt tttaaagaag tgcatgaaaa accatttttg aaccttaaaa ggtactggta
4141 ctatagcatt ttgctatctt ttttagtgtt aaagagataa agaataataa ttaaccaacc
4201 ttgtttaata gatttgggtc atttagaagc ctgacaactc attttcatat tgtaatctat
4261 gtttataata ctactactgt tatcagtaat gctaaatgtg taataatgta acatgatttc
4321 cctccagaga aagcacaatt taaaacaatc cttactaagt aggtgatgag tttgacagtt
4381 tttgacattt atattaaata acatgtttct ctataaagta tggtaatagc tttagtgaat
4441 taaatttagt tgagcataga gaacaaagta aaagtagtgt tgtccaggaa gtcagaattt
4501 ttaactgtac tgaataggtt ccccaatcca tcgtattaaa aaacaattaa ctgccctctg
4561 aaataatggg attagaaaca aacaaaactc ttaagtccta aaagttctca atgtagaggc
4621 ataaacctgt gctgaacata acttctcatg tatattaccc aatggaaaat ataatgatca
4681 gcaaaaagac tggatttgca gaagtttttt ttttttttt cttcatgcct gatgaaagct
4741 ttggcgaccc caatatatgt attttttgaa tctatgaacc tgaaaagggt cagaaggatg
4801 cccagacatc agcctccttc tttcacccct taccccaaag agaaagagtt tgaaactcga
4861 gaccataaag atattcttta gtggaggctg gatgtgcatt agcctggatc ctcagttctc
4921 aaatgtgtgt ggcagccagg atgactagat cctgggtttc catccttgag attctgaagt
4981 atgaagtctg agggaaacca gagtctgtat ttttctaaac tccctggctg ttctgatcgg
5041 ccagttttcg gaaacactga cttaggtttc aggaagttgc catgggaaac aaataatttg
5101 aactttggaa cagggttggc attcaaccac gcaggaagcc tactatttaa atccttggct
5161 tcaggttagt gacatttaat gccatctagc tagcaattgc gaccttaatt taactttcca
5221 gtcttagctg aggctgagaa agctaaagtt tggttttgac aggttttcca aaagtaaaga
5281 tgctacttcc cactgtatgg gggagattga actttccccg tctcccgtct tctgcctccc
5341 actccatacc ccgccaagga aaggcatgta caaaaattat gcaattcagt gttccaagtc
5401 tctgtgtaac cagctcagtg ttttggtgga aaaaacattt taagttttac tgataatttg
5461 aggttagatg ggaggatgaa ttgtcacatc tatccacact gtcaaacagg ttggtgtggg
5521 ttcattggca ttctttgcaa tactgcttaa ttgctgatac catatgaatg aaacatgggc
5581 tgtgattact gcaatcactg tgctatcggc agatgatgct ttggaagatg cagaagcaat
5641 aataaagtac ttgactacct actggtgtaa tctcaatgca agccccaact ttcttatcca

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5701 acttttttcat agtaagtgcg aagactgagc cagattggcc aattaaaaac gaaaacctga
5761 ctaggttctg tagagccaat tagacttgaa atacgtttgt gtttctagaa tcacagctca
5821 agcattctgt ttatcgctca ctctcccttg tacagcctta ttttgttggt gctttgcatt
5881 ttgatattgc tgtgagcctt gcatgacatc atgaggccgg atgaaacttc tcagtccagc
5941 agtttccagt cctaacaaat gctcccacct gaatttgtat atgactgcat ttgtgtgtgt
6001 gtgtgtgttt tcagcaaatt ccagatttgt ttccttttgg cctcctgcaa agtctccaga
6061 agaaaatttg ccaatctttc ctactttcta tttttatgat gacaatcaaa gccggcctga
6121 gaaacactat ttgtgacttt ttaaacgatt agtgatgtcc ttaaaatgtg gtctgccaat
6181 ctgtacaaaa tggtcctatt tttgtgaaga gggacataag ataaaatgat gttatacatc
6241 aatatgtata tatgtatttc tatatagact tggagaatac tgccaaaaca tttatgacaa
6301 gctgtatcac tgccttcgtt tatatttttt taactgtgat aatccccaca ggcacattaa
6361 ctgttgcact tttgaatgtc caaaatttat attttagaaa taataaaaag aaagatactt
6421 acatgttccc aaaacaatgg tgtggtgaat gtgtgagaaa aactaacttg atagggtcta
6481 ccaatacaaa atgtattacg aatgcccctg ttcatgtttt tgttttaaaa cgtgtaaatg
6541 aagatcttta tatttcaata aatgatatat aatttaaagt tataaaaaaa
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An exemplary human Platelet-derived growth factor receptor beta (PDGFRB) amino acid sequence is set forth below (SEQ ID NO: 183; GenBank Accession No: P09619, Version 1, incorporated herein by reference):

```
   1 mrlpgampal alkgellls llllepqis qglvvtppgp elvlnvsstf vltcsgsapv
  61 vwermsqepp qemakaqdgt fssvltltnl tgldtgeyfc thndsrglet derkrlyifv
 121 pdptvgflpn daeelfiflt eiteitipcr vtdpqlvvtl hekkgdvalp vpydhqrgfs
 181 gifedrsyic kttigdrevd sdayyvyrlq vssinvsvna vqtvvrqgen itlmcivign
 241 evvnfewtyp rkesgrlvep vtdflldmpy hirsilhips aeledsgtyt cnvtesvndh
 301 qdekainitv vesgyvrllg evgtlqfael hrsrtlqvvf eayppptvlw fkdnrtlgds
 361 sageialstr nvsetryvse ltlvrvkvae aghytmrafh edaevqlsfq lqinvpvrvl
 421 elseshpdsg eqtvrcrgrg mpqpniiwsa crdlkrcpre lpptllgnss eeesqletnv
 481 tyweeeqefe vvstlrlqhv drplsvrctl rnavgqdtqe vivvphslpf kvvvisaila
 541 lvvltiisli ilimlwqkkp ryeirwkvie svssdgheyi yvdpmqlpyd stwelprdql
 601 vlgrtlgsga fgqvveatah glshsqatmk vavkmlksta rssekqalms elkimshlgp
 661 hlnvvnllga ctkggpiyii teycrygdlv dylhrnkhtf lqhhsdkrrp psaelysnal
 721 pvglplpshv sltgesdggy mdmskdesvd yvpmldmkgd vkyadiessn ymapydnyvp
 781 sapertcrat linespvlsy mdlvgfsyqv angmeflask ncvhrdlaar nvlicegklv
 841 kicdfglard imrdsnyisk gstflplkwm apesifnsly ttlsdvwsfg illweiftlg
 901 gtpypelpmn eqfynaikrg yrmaqpahas deiyeimqkc weekfeirpp fsqlvlller
 961 llgegykkky qqvdeeflrs dhpailrsqa rlpgfhglrs pldtssvlyt avqpnegdnd
1021 yiiplpdpkp evadegpleg spslasstln evntsstisc dsplepqdep epepqlelqv
1081 epepeleqlp dsgcpaprae aedsfl
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An exemplary human *PDGFRB* nucleic acid sequence is set forth below (SEQ ID NO: 184; GenBank Accession No: NM_002609, Version 3, incorporated herein by reference):

```
   1 ctcctgaggc tgccagcagc cagcagtgac tgcccgccct atctgggacc caggatcgct
  61 ctgtgagcaa cttggagcca gagaggagat caacaaggag gaggagagag ccggcccctc
 121 agccctgctg cccagcagca gcctgtgctc gccctgccca acgcagacag ccagacccag
 181 ggcggccccc ctggcggctc tgctcctccc gaaggatgct tggggagtga ggcgaagctg
 241 ggccgctcct ctcccctaca gcagcccccc tcctccatcc ctctgttctc ctgagccttc
 301 aggagcctgc accagtcctg cctgtccttc tactcagctg ttacccactc tgggaccagc
 361 agtctttctg ataactggga gagggcagta aggaggactt cctggagggg gtgactgtcc
 421 agagcctgga actgtgccca caccagaagc catcagcagc aaggacacca tgcggcttcc
 481 gggtgcgatg ccagctctgg ccctcaaagg cgagctgctg ttgctgtctc tcctgttact
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 541 tctggaacca cagatctctc agggcctggt cgtcacaccc ccggggccag agcttgtcct
 601 caatgtctcc agcaccttcg ttctgacctg ctcgggttca gctccggtgg tgtgggaacg
 661 gatgtcccag gagcccccac aggaaatggc caaggcccag gatggcacct tctccagcgt
 721 gctcacactg accaacctca ctgggctaga cacgggagaa tacttttgca cccacaatga
 781 ctcccgtgga ctggagaccg atgagcggaa acggctctac atctttgtgc cagatcccac
 841 cgtgggcttc ctccctaatg atgccgagga actattcatc tttctcacgg aaataactga
 901 gatcaccatt ccatgccgag taacagaccc acagctggtg gtgacactgc acgagaagaa
 961 aggggacgtt gcactgcctg tcccctatga tcaccaacgt ggcttttctg gtatctttga
1021 ggacagaagc tacatctgca aaaccaccat tggggacagg gaggtggatt ctgatgccta
1081 ctatgtctac agactccagg tgtcatccat caacgtctct gtgaacgcag tgcagactgt
1141 ggtccgccag ggtgagaaca tcaccctcat gtgcattgtg atcgggaatg aggtggtcaa
1201 cttcgagtgg acatacccccc gcaaagaaag tgggcggctg gtggagccgg tgactgactt
1261 cctcttggat atgccttacc acatccgctc catcctgcac atccccagtg ccgagttaga
1321 agactcgggg acctacacct gcaatgtgac ggagagtgtg aatgaccatc aggatgaaaa
1381 ggccatcaac atcaccgtgg ttgagagcgg ctacgtgcgg ctcctgggag aggtgggcac
1441 actacaattt gctgagctgc atcggagccg gacactgcag gtagtgttcg aggcctaccc
1501 accgcccact gtcctgtggt tcaaagacaa ccgcaccctg ggcgactcca gcgctggcga
1561 aatcgccctg tccacgcgca acgtgtcgga gacccggtat gtgtcagagc tgacactggt
1621 tcgcgtgaag gtggcagagg ctggccacta caccatgcgg gccttccatg aggatgctga
1681 ggtccagctc tccttccagc tacagatcaa tgtccctgtc cgagtgctgg agctaagtga
1741 gagccaccct gacagtgggg aacagacagt ccgctgtcgt ggccggggca tgccccagcc
1801 gaacatcatc tggtctgcct gcagagacct caaaaggtgt ccacgtgagc tgccgcccac
1861 gctgctgggg aacagttccg aagaggagag ccagctggag actaacgtga cgtactggga
1921 ggaggagcag gagtttgagg tggtgagcac actgcgtctg cagcacgtgg atcggccact
1981 gtcggtgcgc tgcacgctgc gcaacgctgt gggccaggac acgcaggagg tcatcgtggt
2041 gccacactcc ttgcccttta aggtggtggt gatctcagcc atcctggccc tggtggtgct
2101 caccatcatc tcccttatca tcctcatcat gctttggcag aagaagccac gttacgagat
2161 ccgatggaag gtgattgagt ctgtgagctc tgacggccat gagtacatct acgtggaccc
2221 catgcagctg ccctatgact ccacgtggga gctgccgcgg gaccagcttg tgctgggacg
2281 caccctcggc tctggggcct ttgggcaggt ggtggaggcc acggctcatg gcctgagcca
2341 ttctcaggcc acgatgaaag tggccgtcaa gatgcttaaa tccacagccc gcagcagtga
2401 gaagcaagcc cttatgtcgg agctgaagat catgagtcac cttgggcccc acctgaacgt
2461 ggtcaacctg ttgggggcct gcaccaaagg aggacccatc tatatcatca ctgagtactg
2521 ccgctacgga gacctggtgg actacctgca ccgcaacaaa cacaccttcc tgcagcacca
2581 ctccgacaag cgccgcccgc ccagcgcgga gctctacagc aatgctctgc ccgttgggct
2641 ccccctgccc agccatgtgt ccttgaccgg ggagagcgac ggtggctaca tggacatgag
2701 caaggacgag tcggtggact atgtgcccat gctggacatg aaaggagacg tcaaatatgc
2761 agacatcgag tcctccaact acatggcccc ttacgataac tacgttccct ctgcccctga
2821 gaggacctgc cgagcaactt tgatcaacga gtctccagtg ctaagctaca tggacctcgt
2881 gggcttcagc taccaggtgg ccaatggcat ggagtttctg gcctccaaga actgcgtcca
2941 cagagacctg gcggctagga acgtgctcat ctgtgaaggc aagctggtca agatctgtga
3001 ctttggcctg gctcgagaca tcatgcggga ctcgaattac atctccaaag gcagcacctt
3061 tttgccttta aagtggatgg ctccggagag catcttcaac agcctctaca ccaccctgag
3121 cgacgtgtgg tccttcggga tcctgctctg ggagatcttc accttgggtg gcaccccttа
3181 cccagagctg cccatgaacg agcagttcta caatgccatc aaacggggtt accgcatggc
3241 ccagcctgcc catgcctccg acgagatcta tgagatcatg cagaagtgct gggaagagaa
3301 gtttgagatt cggccccccc tctcccagct ggtgctgctt ctcgagagac tgttgggcga
3361 aggttacaaa aagaagtacc agcaggtgga tgaggagttt ctgaggagtg accacccagc
3421 catccttcgg tcccaggccc gcttgcctgg gttccatggc ctccgatctc ccctggacac
3481 cagctccgtc ctctatactg ccgtgcagcc caatgagggt gacaacgact atatcatccc
3541 cctgcctgac cccaaacccg aggttgctga cgagggccca ctggagggtt cccccagcct
3601 agccagctcc accctgaatg aagtcaacac ctcctcaacc atctcctgtg acagcccccc
3661 ggagccccag gacgaaccag agccagagcc ccagcttgag ctccaggtgg agccggagcc
3721 agagctggaa cagttgccgg attcggggtg ccctgcgcct cgggcggaag cagaggatag
3781 cttcctgtag ggggctggcc cctaccctgc cctgcctgaa gctccccccc tgccagcacc
3841 cagcatctcc tggcctggcc tgaccgggct tcctgtcagc caggctgccc ttatcagctg
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3901 tccccttctg gaagctttct gctcctgacg tgttgtgccc caaaccctgg ggctggctta
3961 ggaggcaaga aaactgcagg ggccgtgacc agccctctgc ctccagggag gccaactgac
4021 tctgagccag ggttccccca gggaactcag ttttcccata tgtaagatgg gaaagttagg
4081 cttgatgacc cagaatctag gattctctcc ctggctgaca ggtggggaga ccgaatccct
4141 ccctgggaag attcttggag ttactgaggt ggtaaattaa ctttttttctg ttcagccagc
4201 tacccctcaa ggaatcatag ctctctcctc gcacttttat ccacccagga gctagggaag
4261 agaccctagc ctccctggct gctggctgag ctagggccta gccttgagca gtgttgcctc
4321 atccagaaga aagccagtct cctccctatg atgccagtcc ctgcgttccc tggcccgagc
4381 tggtctgggg ccattaggca gcctaattaa tgctggaggc tgagccaagt acaggacacc
4441 cccagcctgc agcccttgcc cagggcactt ggagcacacg cagccatagc aagtgcctgt
4501 gtccctgtcc ttcaggccca tcagtcctgg ggctttttct ttatcaccct cagtcttaat
4561 ccatccacca gagtctagaa ggccagacgg gccccgcatc tgtgatgaga atgtaaatgt
4621 gccagtgtgg agtggccacg tgtgtgtgcc agtatatggc cctggctctg cattggacct
4681 gctatgaggc tttggaggaa tccctcaccc tctctgggcc tcagtttccc cttcaaaaaa
4741 tgaataagtc ggacttatta actctgagtg ccttgccagc actaacattc tagagtattc
4801 caggtggttg cacatttgtc cagatgaagc aaggccatat accctaaact tccatcctgg
4861 gggtcagctg ggctcctggg agattccaga tcacacatca cactctgggg actcaggaac
4921 catgcccctt ccccaggccc ccagcaagtc tcaagaacac agctgcacag gccttgactt
4981 agagtgacag ccggtgtcct ggaaagcccc cagcagctgc cccagggaca tgggaagacc
5041 acgggacctc tttcactacc cacgatgacc tccgggggta tcctgggcaa aagggacaaa
5101 gagggcaaat gagatcacct cctgcagccc accactccag cacctgtgcc gaggtctgcg
5161 tcgaagacag aatggacagt gaggacagtt atgtcttgta aaagacaaga agcttcagat
5221 gggtacccca agaaggatgt gagaggtggg cgctttggag gtttgcccct cacccaccag
5281 ctgccccatc cctgaggcag cgctccatgg gggtatggtt ttgtcactgc ccagacctag
5341 cagtgacatc tcattgtccc cagcccagtg ggcattggag gtgccagggg agtcagggtt
5401 gtagccaaga cgcccccgca cggggagggt tgggaagggg gtgcaggaag ctcaacccct
5461 ctgggcacca accctgcatt gcaggttggc accttacttc cctgggatcc ccagagttgg
5521 tccaaggagg gagagtgggt tctcaatacg gtaccaaaga tataatcacc taggtttaca
5581 aatattttta ggactcacgt taactcacat ttatacagca gaaatgctat tttgtatgct
5641 gttaagtttt tctatctgtg tacttttttt taagggaaag attttaatat taaacctggt
5701 gcttctcact cacaaaaa
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An exemplary human Neuregulin 1 (NRG1) amino acid sequence is set forth below (SEQ ID NO: 185; GenBank Accession No: Q02297, Version 3, incorporated herein by reference):

```
   1 mserkegrgk gkgkkkergs gkkpesaags qspalpprlk emksqesaag sklvlrcets
  61 seysslrfkw fkngnelnrk nkpqnikiqk kpgkselrin kasladsgey mckvisklgn
 121 dsasanitiv esneiitgmp astegayvss espirisvst egantsssts tsttgtshlv
 181 kcaekektfc vnggecfmvk dlsnpsrylc kcqpgftgar ctenvpmkvq nqekaeelyq
 241 krvltitgic iallvvgimc vvaycktkkq rkklhdrlrq slrsernnmm niangphhpn
 301 pppenvqlvn qyvsknviss ehivereaet sfstshytst ahhsttvtqt pshswsnght
 361 esilseshsv ivmssvensr hssptggprg rlngtggpre cnsflrhare tpdsyrdsph
 421 seryvsamtt parmspvdfh tpsspkspps emsppvssmt vsmpsmavsp fmeeerplll
 481 vtpprlrekk fdhhpqqfss fhhnpahdsn slpasplriv edeeyettqe yepaqepvkk
 541 lansrrakrt kpnghianrl evdsntssqs snsesetede rvgedtpflg iqnplaasle
 601 atpafrlads rtnpagrfst qeeiqarlss vianqdpiav
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An exemplary human *NRG1* nucleic acid sequence is set forth below (SEQ ID NO: 186; GenBank Accession No: NM_013960, Version 4, incorporated herein by reference):

```
   1 gaggccaggg gagggtgcga aggaggcgcc tgcctccaac ctgcgggcgg gaggtgggtg
  61 gctgcggggc aattgaaaaa gagccggcga ggagttcccc gaaacttgtt ggaactccgg
 121 gctcgcgcgg aggccaggag ctgagcggcg gcggctgccg gacgatggga gcgtgagcag
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 181 gacggtgata acctctcccc gatcgggttg cgagggcgcc gggcagaggc caggacgcga
 241 gccgccagcg gtgggaccca tcgacgactt cccggggcga caggagcagc cccgagagcc
 301 agggcgagcg cccgttccag gtggccggac cgcccgccgc gtccgcgccg cgctccctgc
 361 aggcaacggg agacgccccc gcgcagcgcg agcgcctcag cgcggccgct cgctctcccc
 421 ctcgagggac aaacttttcc caaacccgat ccgagccctt ggaccaaact cgcctgcgcc
 481 gagagccgtc cgcgtagagc gctccgtctc cggcgagatg tccgagcgca aagaaggcag
 541 aggcaaaggg aagggcaaga agaaggagcg aggctccggc aagaagccgg agtccgcggc
 601 gggcagccag agcccagcct tgcctccccg attgaaagag atgaaaagcc aggaatcggc
 661 tgcaggttcc aaactagtcc ttcggtgtga aaccagttct gaatactcct ctctcagatt
 721 caagtggttc aagaatggga atgaattgaa tcgaaaaaac aaaccacaaa atatcaagat
 781 acaaaaaaag ccagggaagt cagaacttcg cattaacaaa gcatcactgg ctgattctgg
 841 agagtatatg tgcaaagtga tcagcaaatt aggaaatgac agtgcctctg ccaatatcac
 901 catcgtggaa tcaaacgaga tcatcactgg tatgccagcc tcaactgaag gagcatatgt
 961 gtcttcagag tctcccatta gaatatcagt atccacagaa ggagcaaata cttcttcatc
1021 tacatctaca tccaccactg ggacaagcca tcttgtaaaa tgtgcggaga aggagaaaac
1081 tttctgtgtg aatggagggg agtgcttcat ggtgaaagac ctttcaaacc cctcgagata
1141 cttgtgcaag tgccaacctg gattcactgg agcaagatgt actgagaatg tgcccatgaa
1201 agtccaaaac caagaaaagg cggaggagct gtaccagaag agagtgctga ccataaccgg
1261 catctgcatc gccctccttg tggtcggcat catgtgtgtg gtggcctact gcaaaaccaa
1321 gaaacagcgg aaaaagctgc atgaccgtct tcggcagagc cttcggtctg aacgaaacaa
1381 tatgatgaac attgccaatg ggcctcacca tcctaaccca ccccccgaga atgtccagct
1441 ggtgaatcaa tacgtatcta aaaacgtcat ctccagtgag catattgttg agagagaagc
1501 agagacatcc ttttccacca gtcactatac ttccacagcc catcactcca ctactgtcac
1561 ccagactcct agccacagct ggagcaacgg acacactgaa agcatccttt ccgaaagcca
1621 ctctgtaatc gtgatgtcat ccgtagaaaa cagtaggcac agcagcccaa ctgggggccc
1681 aagaggacgt cttaatggca caggaggccc tcgtgaatgt aacagcttcc tcaggcatgc
1741 cagagaaacc cctgattcct accgagactc tcctcatagt gaaagacata accttatagc
1801 tgagctaagg agaaacaagg cacacagatc caaatgcatg cagatccagc tatcagcaac
1861 tcatcttaga tcttcttcca ttccccattt gggcttcatt ctctaagacc ccttggcctt
1921 taggaaggta tgtgtcagcc atgaccaccc cggctcgtat gtcacctgta gatttccaca
1981 cgccaagctc ccccaaatcg ccccccttcgg aaatgtctcc acccgtgtcc agcatgacgg
2041 tgtccatgcc ttccatggcg gtcagcccct tcatggaaga agagagacct ctacttctcg
2101 tgacaccacc aaggctgcgg gagaagaagt ttgaccatca ccctcagcag ttcagctcct
2161 tccaccacaa ccccgcgcat gacagtaaca gcctccctgc tagccccttg aggatagtgg
2221 aggatgagga gtatgaaacg acccaagagt acgagccagc ccaagagcct gttaagaaac
2281 tcgccaatag ccggcgggcc aaaagaacca agcccaatgg ccacattgct aacagattgg
2341 aagtggacag caacacaagc tcccagagca gtaactcaga gagtgaaaca gaagatgaaa
2401 gagtaggtga agatacgcct ttcctgggca tacagaaccc cctggcagcc agtcttgagg
2461 caacacctgc cttccgcctg gctgacagca ggactaaccc agcaggccgc ttctcgacac
2521 aggaagaaat ccaggccagg ctgtctagtg taattgctaa ccaagaccct attgctgtat
2581 aaaacctaaa taaacacata gattcacctg taaaacttta ttttatataa taaagtattc
2641 caccttaaat taaacaattt attttatttt agcagttctg caaatagaaa acaggaaaaa
2701 aacttttata aattaaatat atgtatgtaa aaatgtgtta tgtgccatat gtagcaattt
2761 tttacagtat ttcaaaacga gaaagatatc aatggtgcct ttatgttatg ttatgtcgag
2821 agcaagtttt gtacagttac agtgattgct tttccacagt atttctgcaa aacctctcat
2881 agattcagtt tttgctggct tcttgtgcat tgcattatga tgttgactgg atgtatgatt
2941 tgcaagactt gcaactgtcc ctctgtttgc ttgtagtagc acccgatcag tatgtcttgt
3001 aatggcacat ccatccagat atgcctctct tgtgtatgaa gttttctttg ctttcagaat
3061 atgaaatgag ttgtgtctac tctgccagcc aaaggtttgc ctcattgggc tctgagataa
3121 tagtagatcc aacagcatgc tactattaaa tacagcaaga aactgcatta agtaatgtta
3181 aatattagga agaaagtaat actgtgattt aaaaaaaact atattattaa tcagaagaca
3241 gcttgctctt actaaaagga gctctcattt actttatttg attttatttt tcttgacaaa
3301 aagcaacagt tttagggata gcttagaaaa tgggttctgg cttgctatca gggtaaatct
3361 aacaccttac aagaggactg agtgtcactt tctctctggg ggaatgatcc agcagcttat
3421 ctagttgaca atcaaaacac ggctgataaa ggtgcaatca tttctgacat gtatttttca
3481 ctgattttga agctagtgat tggttgtgtc ttcttggctc aaaaagaagc atattacggc
```

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3541 acaaaaagcc cagcccagac agcacatgca gcattttgtc tgaaatactt ctagagtcaa
3601 acgtgcctgc tgtacatagc gatgacttgt catcataggg aagtatttcc atcgtagagt
3661 gttcagaagg agtgactgta taggtggaga gaagcttagt gactccgttg aaattttaaa
3721 atgtggatga ccaccccttt ctccccctta tttttctttt atctttccat gttgccttga
3781 tcaggtcata actatgcatg aacatttttt atcaggaatg gccgatgtgt atgtgatttg
3841 taatcacaag taatgattca tcaggaaatg tcaatcctgt tggaaagatt gcacctttac
3901 ttgcagaagt gacccccacc tgtgtcctga cctctccatt tacaggctct ctcacccatt
3961 tcccccacct cctttaattt ttgctttact gtcataaagt aggactaaga ttggtctaag
4021 cattgcatgt tcttttgtga tggtaaatcc aaaggaaggc ctataagtat taacatttga
4081 aataactgct aattcaggaa aatggaagaa aaaaaattat ttgaaacaca gaacccattt
4141 catggcctgc ctgatatctg tgaaatcagg gctggagctt tacttaggat tcacatggcc
4201 tcctaggaac catgggacaa atgggaaaca ggttatcggg ggattcatga agtcagtgag
4261 agtaattgct tctttttgc gggtgaactg aatgtatttc ttcaccaaat cttgatgtta
4321 acaattaaaa agaagaaatg acatgcaagt aggtcttagc agaaaaatgc aggctgggca
4381 tgagtcatgt tgttaccctc ccacatgctc ctacaatcca cagagatgcc tgtctgcagg
4441 ttcttgaagt tattgttagt atttggtatc tcaaattttt cgtcactgtt cacatgccac
4501 tttctctgtg cacagtggta tcctcatttg ctttttaacc tacactgagg agtctttgtc
4561 aggttgcact gattttccaa ttctgcagta atgagtaagc tcacggcatg gggaagaaga
4621 cagtcagtcc aatgaagttc tctaaattat tttaacattg cctttgaagg ccttgactca
4681 tccttagcta tttcaatgaa gaaattccta ccatgaattt aaaaccctaa aaattctgtt
4741 tcaaattctt tgggcattgg ggtactcaga tatcccattg tggaagaatt ttaagaataa
4801 atagaagttt ctgttgagaa ccatgagcaa catgtttctt acaatgagaa ttgctatgca
4861 ttttaaaatt gcaaatatat atgaaaattg aagacaagag gaaattgtat ttctaacttg
4921 attctgatca ctcacagagg tggcatatta ttatagttgg gacatccttt gcacccttca
4981 taaaaaaggc cagctgactg ctcagcatca cctgccaagg ccactagatt tgtgtttaca
5041 ggggtatctc tgtgatgctt gtcacatcac tcttgaccac ctctgttaat aaattccgac
5101 agtgcagtgg cgatcggagt gtgaacttat gttcccagca tatggaaagc tatcttaggt
5161 tttaaggtag tagaaattgc ccaggagttt gacagcaact ttgtttcccg ggtctaaaat
5221 cgtatcccac tgaggtgtat gcagtggagc ataatacatg caaatacatg caaaactcct
5281 tttgtttcac ctaagattca ctttctatct tactttccct tcctgcctag tgtgactttt
5341 gcccccaaga gtgcctggac agcattctag tttctacaaa atggtcctct gtgtaggtga
5401 atgtgtccca aacctgctat cactttcttg tttcagtgtg actgtcttgt tagaggtgaa
5461 gtttatccag ggtaacttgc tcactaacta ttccttttta tggcctgggg ttaaagggcg
5521 catggctcac actggtgaaa ataaggaagg cctggtctta tcttgtatta ataatactgg
5581 ctgcattcca ccagccagag atttctatct gcgaagacct atgaaacact gaagagaaat
5641 gtaggcagaa ggaaatggcc acatatcaca agttctatta tatattcttt tgtaaataca
5701 tattgtatat tacttggatg ttttcttata tcatttactg tctttttgag ttaatgtcag
5761 tttttactct ctcaacttac tatgtaacat tgtaaataac ataatgtcct ttattattta
5821 tatttaagca tctaacatat agagttgttt tcatataagt ttaagataaa tgtcaaaaat
5881 atatgttctt ttgtttttct ttgctttaaa attatgtatc ttttcctttt ctttttttta
5941 agaataattt attgttcagg agaaagaatg tatatgtaac tgaaactatc tgaagaatgc
6001 acattgaagg ccgtgaggta ctgataaact aaagaattta ttattcaaaa tactaagcaa
6061 taagtaattg tgatttattt aaagttttgt ccattttcca tgaaagacat actgcaataa
6121 aaatgctact ctgtggaaaa aaaaaaaaaa aaaa
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An exemplary human Tenascin C (TNC) amino acid sequence is set forth below (SEQ ID NO: 187; GenBank Accession No: P24821, Version 3, incorporated herein by reference):

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  1 mgamtqllag vflaflalat eggvlkkvir hkrqsgvnat lpeenqpvvf nhvyniklpv
 61 gsqcsvdles asgekdlapp sepsesfqeh tvdgenqivf thriniprra cgcaaapdvk
121 ellsrleele nlvsslreqc tagagcclqp atgrldtrpf csgrgnfste gcgcvcepgw
181 kgpncsepec pgnchlrgrc idgqcicddg ftgedcsqla cpsdcndqgk cvngvcicfe
241 gyagadcsre icpvpcseeh gtcvdglcvc hdgfagddcn kplclnncyn rgrcvenecv
301 cdegftgedc selicpndcf drgrcingtc yceegftged cgkptcphac htqgrceegq
361 cvcdegfagv dcsekrcpad chnrgrcvdg rcecddgftg adcgelkcpn gcsghgrcvn
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 421 gqcvcdegyt gedcsqlrcp ndchsrgrcv egkcvceqgf kgydcsdmsc pndchqhgrc
 481 vngmcvcddg ytgedcrdrq cprdcsnrgl cvdgqcvced gftgpdcael scpndchgqg
 541 rcvngqcvch egfmgkdcke qrcpsdchgq grcvdgqcic hegftgldcg qhscpsdcnn
 601 lgqcvsgrci cnegysgedc sevsppkdlv vtevteetvn lawdnemrvt eylvvytpth
 661 egglemqfrv pgdqtstiiq elepgveyfi rvfailenkk sipvsarvat ylpapeglkf
 721 ksiketsvev ewdpldiafe tweiifrnmn kedegeitks lrrpetsyrq tglapgqeye
 781 islhivknnt rgpglkrvtt trldapsqie vkdvtdttal itwfkplaei dgieltygik
 841 dvpgdrttid ltedenqysi gnlkpdteye vslisrrgdm ssnpaketft tgldaprnlr
 901 rvsqtdnsit lewrngkaai dsyrikyapi sggdhaevdv pksqqattkt tltglrpgte
 961 ygigvsavke dkesnpatin aateldtpkd lqvsetaets ltllwktpla kfdryrlnys
1021 lptgqwvgvq lprnttsyvl rglepgqeyn vlltaekgrh kskparvkas teqapelenl
1081 tvtevgwdgl rlnwtaadqa yehfiiqvqe ankveaarnl tvpgslravd ipglkaatpy
1141 tvsiygviqg yrtpvlsaea stgetpnlge vvvaevgwda lklnwtapeg ayeyffiqvq
1201 eadtveaaqn ltvpgglrst dlpglkaath ytitirgvtq dfsttplsve vlteevpdmg
1261 nltvtevswd alrlnwttpd gtydqftiqv qeadqveeah nltvpgslrs meipglragt
1321 pytvtlhgev rghstrplav evvtedlpql gdlavsevgw dglrlnwtaa dnayehfviq
1381 vqevnkveaa qnltlpgslr avdipgleaa tpyrvsiygv irgyrtpvls aeastakepe
1441 ignlnvsdit pesfnlswma tdgifetfti eiidsnrlle tveynisgae rtahisglpp
1501 stdfivylsg lapsirtkti satattealp llenltisdi npygftvswm asenafdsfl
1561 vtvvdsgkll dpqeftlsgt qrklelrgli tgigyevmvs gftqghqtkp lraeivteae
1621 pevdnllvsd atpdgfrlsw tadegvfdnf vlkirdtkkq sepleitlla pertrditgl
1681 reateyeiel ygiskgrrsq tvsaiattam gspkevifsd itensatvsw raptaqvesf
1741 rityvpitgg tpsmvtvdgt ktqtrlvkli pgveylvsii amkgfeesep vsgsfttald
1801 gpsglvtani tdsealarwq paiatvdsyv isytgekvpe itrtvsgntv eyaltdlepa
1861 teytlrifae kgpqksstit akfttdldsp rdltatevqs etalltwrpp rasvtgyllv
1921 yesvdgtvke vivgpdttsy sladlspsth ytakiqalng plrsnmiqti fttigllypf
1981 pkdcsqamln gdttsglyti ylngdkaeal evfcdmtsdg ggwivflrrk ngrenfyqnw
2041 kayaagfgdr reefwlgldn lnkitaqgqy elrvdlrdhg etafavydkf svgdaktryk
2101 lkvegysgta gdsmayhngr sfstfdkdtd saitncalsy kgafwyrnch rvnlmgrygd
2161 nnhsqgvnwf hwkghehsiq faemklrpsn frnlegrrkr a
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An exemplary human *TNC* nucleic acid sequence is set forth below (SEQ ID NO: 188; GenBank Accession No: NM_002160, Version 3, incorporated herein by reference):

```
   1 aattcgccaa ctgaaaaagt gggaaaggat gtctggaggc gaggcgtccc attacagagg
  61 aaggagctcg ctatataagc cagccaaagt tggctgcacc ggccacagcc tgcctactgt
 121 cacccgcctc tcccgcgcgc agatacacgc ccccgcctcc gtgggcacaa aggcagcgct
 181 gctggggaac tcgggggaac gcgcacgtgg gaaccgccgc agctccacac tccaggtact
 241 tcttccaagg acctaggtct ctcgcccatc ggaaagaaaa taattctttc aagaagatca
 301 gggacaactg atttgaagtc tactctgtgc ttctaaatcc ccaattctgc tgaaagtgag
 361 ataccctaga gccctagagc cccagcagca cccagccaaa cccacctcca ccatgggggc
 421 catgactcag ctgttggcag gtgtctttct tgctttcctt gccctcgcta ccgaaggtgg
 481 ggtcctcaag aaagtcatcc ggcacaagcg acagagtggg gtgaacgcca ccctgccaga
 541 agagaaccag ccagtggtgt ttaaccacgt ttacaacatc aagctgccag tgggatccca
 601 gtgttcggtg gatctggagt cagccagtgg ggagaaagac ctggcaccgc cttcagagcc
 661 cagcgaaagc tttcaggagc acacagtgga tggggaaaac cagattgtct tcacacatcg
 721 catcaacatc ccccgccggg cctgtggctg tgccgcagcc cctgatgtta aggagctgct
 781 gagcagactg gaggagctgg agaacctggt gtcttccctg agggagcaat gtactgcagg
 841 agcaggctgc tgtctccagc ctgccacagg ccgcttggac accaggccct tctgtagcgg
 901 tcggggcaac ttcagcactg aaggatgtgg ctgtgtctgc gaacctggct ggaaaggccc
 961 caactgctct gagcccgaat gtccaggcaa ctgtcacctt cgaggccggt gcattgatgg
1021 gcagtgcatc tgtgacgacg gcttcacggg cgaggactgc agccagctgg cttgccccag
1081 cgactgcaat gaccagggca agtgcgtaaa tggagtctgc atctgtttcg aaggctacgc
1141 cggggctgac tgcagccgtg aaatctgccc agtgccctgc agtgaggagc acggcacatg
1201 tgtagatggc ttgtgtgtgt gccacgatgg ctttgcaggc gatgactgca acaagcctct
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1261 gtgtctcaac aattgctaca accgtggacg atgcgtggag aatgagtgcg tgtgtgatga
1321 gggtttcacg ggcgaagact gcagtgagct catctgcccc aatgactgct tcgaccgggg
1381 ccgctgcatc aatggcacct gctactgcga agaaggcttc acaggtgaag actgcgggaa
1441 acccacctgc ccacatgcct gccacaccca gggccggtgt gaggaggggc agtgtgtatg
1501 tgatgagggc tttgccggtg tggactgcag cgagaagagg tgtcctgctg actgtcacaa
1561 tcgtggccgc tgtgtagacg ggcggtgtga gtgtgatgat ggtttcactg gagctgactg
1621 tggggagctc aagtgtccca atggctgcag tggccatggc cgctgtgtca atgggcagtg
1681 tgtgtgtgat gagggctata ctggggagga ctgcagccag ctacggtgcc ccaatgactg
1741 tcacagtcgg ggccgctgtg tcgagggcaa atgtgtatgt gagcaaggct tcaagggcta
1801 tgactgcagt gacatgagct gccctaatga ctgtcaccag cacggccgct gtgtgaatgg
1861 catgtgtgtt tgtgatgacg gctacacagg ggaagactgc cgggatcgcc aatgccccag
1921 ggactgcagc aacaggggcc tctgtgtgga cggacagtgc gtctgtgagg acggcttcac
1981 cggccctgac tgtgcagaac tctcctgtcc aaatgactgc catggccagg gtcgctgtgt
2041 gaatgggcag tgcgtgtgcc atgaaggatt tatgggcaaa gactgcaagg agcaaagatg
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2221 atgcgtctcg ggccgctgca tctgcaacga gggctacagc ggagaagact gctcagaggt
2281 gtctcctccc aaagacctcg ttgtgacaga agtgacggaa gagacggtca acctggcctg
2341 ggacaatgag atgcgggtca cagagtacct tgtcgtgtac acgcccaccc acgagggtgg
2401 tctggaaatg cagttccgtg tgcctgggga ccagacgtcc accatcatcc aggagctgga
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2701 gccagagacc tcttaccggc aaactggtct agctcctggg caagagtatg agatatctct
2761 gcacatagtg aaaaacaata cccggggccc tggcctgaag agggtgacca ccacacgctt
2821 ggatgccccc agccagatcg aggtgaaaga tgtcacagac accactgcct tgatcacctg
2881 gttcaagccc ctggctgaga tcgatggcat tgagctgacc tacggcatca aagacgtgcc
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3061 cccagccaaa gagaccttca caacaggcct cgatgctccc aggaatcttc gacgtgtttc
3121 ccagacagat aacagcatca ccctggaatg gaggaatggc aaggcagcta ttgacagtta
3181 cagaattaag tatgccccca tctctggagg ggaccacgct gaggttgatg ttccaaagag
3241 ccaacaagcc acaaccaaaa ccacactcac aggtctgagg ccgggaactg aatatgggat
3301 tggagtttct gctgtgaagg aagacaagga gagcaatcca gcgaccatca acgcagccac
3361 agagttggac acgcccaagg accttcaggt ttctgaaact gcagagacca gcctgaccct
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3481 aggccagtgg gtgggagtgc agcttccaag aaacaccact tcctatgtcc tgagaggcct
3541 ggaaccagga caggagtaca atgtcctcct gacagccgag aaaggcagac acaagagcaa
3601 gcccgcacgt gtgaaggcat ccactgaaca agcccctgag ctggaaaacc tcaccgtgac
3661 tgaggttggc tgggatggcc tcagactcaa ctggaccgca gctgaccagg cctatgagca
3721 ctttatcatt caggtgcagg aggccaacaa ggtggaggca gctcggaacc tcaccgtgcc
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6061 cacaacagac ctcgattctc caagagactt gactgctact gaggttcagt cggaaactgc
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6241 agacctgagc ccatccaccc actacacagc caagatccag gcactcaatg ggcccctgag
6301 gagcaatatg atccagacca tcttcaccac aattggactc ctgtacccct tccccaagga
6361 ctgctcccaa gcaatgctga atggagacac gacctctggc ctctacacca tttatctgaa
6421 tggtgataag gctgaggcgc tggaagtctt ctgtgacatg acctctgatg ggggtggatg
6481 gattgtgttc ctgagacgca aaaacggacg cgagaacttc taccaaaact ggaaggcata
6541 tgctgctgga tttggggacc gcagagaaga attctggctt gggctggaca acctgaacaa
6601 aatcacagcc caggggcagt acgagctccg ggtggacctg cgggaccatg gggagacagc
6661 ctttgctgtc tatgacaagt tcagcgtggg agatgccaag actcgctaca agctgaaggt
6721 ggaggggtac agtgggacag caggtgactc catggcctac cacaatggca gatccttctc
6781 cacctttgac aaggacacag attcagccat caccaactgt gctctgtcct acaaaggggc
6841 tttctggtac aggaactgtc accgtgtcaa cctgatgggg agatatgggg acaataacca
6901 cagtcagggc gttaactggt tccactggaa gggccacgaa cactcaatcc agtttgctga
6961 gatgaagctg agaccaagca acttcagaaa tcttgaaggc aggcgcaaac gggcataaat
7021 tccagggacc actgggtgag agaggaataa ggcccagagc gaggaaagga ttttaccaaa
7081 gcatcaatac aaccagccca accatcggtc cacacctggg catttggtga gagtcaaagc
7141 tgaccatgga tccctggggc caacggcaac agcatgggcc tcacctcctc tgtgatttct
7201 ttctttgcac caaagacatc agtctccaac atgtttctgt tttgttgttt gattcagcaa
7261 aaatctccca gtgacaacat cgcaatagtt ttttacttct cttaggtggc tctgggaatg
7321 ggagaggggt aggatgtaca ggggtagttt gttttagaac cagccgtatt ttacatgaag
7381 ctgtataatt aattgtcatt atttttgtta gcaaagatta aatgtgtcat tggaagccat
7441 ccctttttttt acatttcata caacagaaac cagaaaagca atactgtttc cattttaagg
7501 atatgattaa tattattaat ataataatga tgatgatgat gatgaaaact aaggatttttt
7561 caagagatct ttctttccaa aacatttctg gacagtacct gattgtattt ttttttaaaa
7621 taaaagcaca agtacttttg agtttgttat tttgctttga attgttgagt ctgaatttca
7681 ccaaagccaa tcatttgaac aaagcgggga atgttgggat aggaaaggta agtagggata
7741 gtggtcaagt gggaggggtg gaaaggagac taaagactgg gagagaggga agcacttttt
7801 ttaaataaag ttgaacacac ttgggaaaag cttacaggcc aggcctgtaa tcccaacact
7861 ttgggaggcc aaggtgggag gatagcttaa ccccaggagt ttgagaccag cctgagcaac
7921 atagtgagaa cttgtctcta cagaaaaaaa aaaaaaaaaa aatttaatta ggcaagcgtg

```
7981 gtagtgcgca cctgtcgtcc cagctactca ggaggctgag gtaggaaaat cactggagcc
8041 caggagttag aggttacagt gagctatgat cacactactg cactccagcc tgggcaacag
8101 agggagaccc tgtctctaaa taaaaaaaga aaagaaaaaa aaagcttaca acttgagatt
8161 cagcatcttg ctcagtattt ccaagactaa tagattatgg tttaaaagat gcttttatac
8221 tcattttcta atgcaactcc tagaaactct atgatatagt tgaggtaagt attgttacca
8281 cacatgggct aagatcccca gaggcagact gcctgagttc aattcttggc tccaccattc
8341 ccaagttccc taacctctct atgcctcagt ttcctcttct gtaaagtagg gacactcata
8401 cttctcattt cagaacattt ttgtgaagaa taaattatgt tatccatttg aggcccttag
8461 aatggtaccc ggtgtatatt aagtgctagt acatgttagc tatcatcatt atcactttat
8521 atgagatgga ctggggttca tagaaaccca atgacttgat tgtggctact actcaataaa
8581 taatagaatt tggatttaaa aaaaa
```

An exemplary human Periostin (POSTN) amino acid sequence is set forth below (SEQ ID NO: 189; GenBank Accession No: AAI06710, Version 1, incorporated herein by reference):

```
   1 mipflpmfsl llllivnpin annhydkila hsrirgrdqg pnvcalqqil gtkkkyfstc
  61 knwykksicg qkttvlyecc pgymrmegmk gcpavlpidh vygtlgivga tttqrysdas
 121 klreeiegkg sftyfapsne awdnldsdir rglesnvnve llnalhshmi nkrmltkdlk
 181 ngmiipsmyn nlglfinhyp ngvvtvncar iihgnqiatn gvvhvidrvl tqigtsiqdf
 241 ieaeddlssf raaaitsdil ealgrdghft lfaptneafe klprgvleri mgdkvaseal
 301 mkyhilntlq csesimggav fetlegntie igcdgdsitv ngikmvnkkd ivtnngvihl
 361 idqvlipdsa kqvielagkq qttftdlvaq lglasalrpd geytllapvn nafsddtlsm
 421 dqrllklilq nhilkvkvgl nelyngqile tiggkqlrvf vyrtavcien scmekgskqg
 481 rngaihifre iikpaekslh eklkqdkrfs tflslleaad lkelltqpgd wtlfvptnda
 541 fkgmtseeke ilirdknalq niilyhltpg vfigkgfepg vtnilkttqg skiflkevnd
 601 tllvnelksk esdimttngv ihvvdkllyp adtpvgndql leilnkliky iqikfvrgst
 661 fkeipvtvyk piikkytkii dgvpveitek etreeriitg peikytrist gggeteetlk
 721 kllqeevtkv tkfieggdgh lfedeeikrl lqgdtpvrkl qankkvqgsr rrlregrsq
```

An exemplary human *POSTN* nucleic acid sequence is set forth below (SEQ ID NO: 190; GenBank Accession No: NM_006475, Version 2, incorporated herein by reference):

```
   1 agactctcag gttgatgcag tgttccctcc cacaactctg acatgtatat aaattctgag
  61 ctctccaaag cccactgcca gttctcttcg gggactaact gcaacggaga gactcaagat
 121 gattcccttt ttacccatgt tttctctact attgctgctt attgttaacc ctataaacgc
 181 caacaatcat tatgacaaga tcttggctca tagtcgtatc aggggtcggg accaaggccc
 241 aaatgtctgt gcccttcaac agattttggg caccaaaaag aaatacttca gcacttgtaa
 301 gaactggtat aaaaagtcca tctgtggaca gaaaacgact gtgttatatg aatgttgccc
 361 tggttatatg agaatggaag gaatgaaagg ctgcccagca gttttgccca ttgaccatgt
 421 ttatggcact ctgggcatcg tgggagccac cacaacgcag cgctattctg acgcctcaaa
 481 actgagggag gagatcgagg gaaagggatc cttcacttac tttgcaccga gtaatgaggc
 541 ttgggacaac ttggattctg atatccgtag aggtttggag agcaacgtga atgttgaatt
 601 actgaatgct ttacatagtc acatgattaa taagagaatg ttgaccaagg acttaaaaaa
 661 tggcatgatt attccttcaa tgtataacaa tttggggctt ttcattaacc attatcctaa
 721 tggggttgtc actgttaatt gtgctcgaat catccatggg aaccagattg caacaaatgg
 781 tgttgtccat gtcattgacc gtgtgcttac acaaattggt acctcaattc aagacttcat
 841 tgaagcagaa gatgaccttt catcttttag agcagctgcc atcacatcgg acatattgga
 901 ggcccttgga agagacggtc acttcacact ctttgctccc accaatgagg cttttgagaa
 961 acttccacga ggtgtcctag aaaggatcat gggagacaaa gtggcttccg aagctcttat
1021 gaagtaccac atcttaaata ctctccagtg ttctgagtct attatgggag gagcagtctt
1081 tgagacgctg gaaggaaata caattgagat aggatgtgac ggtgacagta taacagtaaa
1141 tggaatcaaa atggtgaaca aaaaggatat tgtgacaaat aatggtgtga tccatttgat
1201 tgatcaggtc ctaattcctg attctgccaa acaagttatt gagctggctg gaaaacagca
```

```
1261 aaccaccttc acggatcttg tggcccaatt aggcttggca tctgctctga ggccagatgg
1321 agaatacact ttgctggcac ctgtgaataa tgcattttct gatgatactc tcagcatgga
1381 tcagcgcctc cttaaattaa ttctgcagaa tcacatattg aaagtaaaag ttggccttaa
1441 tgagctttac aacgggcaaa tactggaaac catcggaggc aaacagctca gagtcttcgt
1501 atatcgtaca gctgtctgca ttgaaaattc atgcatggag aaagggagta agcaagggag
1561 aaacggtgcg attcacatat tccgcgagat catcaagcca gcagagaaat ccctccatga
1621 aaagttaaaa caagataagc gctttagcac cttcctcagc ctacttgaag ctgcagactt
1681 gaaagagctc ctgacacaac ctggagactg gacattattt gtgccaacca atgatgcttt
1741 taagggaatg actagtgaag aaaaagaaat tctgatacgg gacaaaaatg ctcttcaaaa
1801 catcattctt tatcacctga caccaggagt tttcattgga aaaggatttg aacctggtgt
1861 tactaacatt ttaaagacca cacaaggaag caaaatcttt ctgaaagaag taaatgatac
1921 acttctggtg aatgaattga aatcaaaaga atctgacatc atgacaacaa atggtgtaat
1981 tcatgttgta gataaactcc tctatccagc agacacacct gttggaaatg atcaactgct
2041 ggaaatactt aataaattaa tcaaatacat ccaaattaag tttgttcgtg gtagcacctt
2101 caaagaaatc cccgtgactg tctatacaac taaaattata accaaagttg tggaaccaaa
2161 aattaaagtg attgaaggca gtcttcagcc tattatcaaa actgaaggac ccacactaac
2221 aaaagtcaaa attgaaggtg aacctgaatt cagactgatt aaagaaggtg aaacaataac
2281 tgaagtgatc catggagagc caattattaa aaaatacacc aaaatcattg atggagtgcc
2341 tgtggaaata actgaaaaag agacacgaga agaacgaatc attacaggtc ctgaaataaa
2401 atacactagg atttctactg gaggtggaga aacagaagaa actctgaaga aattgttaca
2461 agaagaggtc accaaggtca ccaaattcat tgaaggtggt gatggtcatt tatttgaaga
2521 tgaagaaatt aaaagactgc ttcagggaga cacacccgtg aggaagttgc aagccaacaa
2581 aaaagttcaa ggatctagaa gacgattaag ggaaggtcgt tctcagtgaa aatccaaaaa
2641 ccagaaaaaa atgtttatac aaccctaagt caataacctg accttagaaa attgtgagag
2701 ccaagttgac ttcaggaact gaaacatcag cacaaagaag caatcatcaa ataattctga
2761 acacaaattt aatatttttt tttctgaatg agaaacatga gggaaattgt ggagttagcc
2821 tcctgtggta aaggaattga agaaaatata acaccttaca ccctttttca tcttgacatt
2881 aaaagttctg gctaactttg gaatccatta gagaaaaatc cttgtcacca gattcattac
2941 aattcaaatc gaagagttgt gaactgttat cccattgaaa agaccgagcc ttgtatgtat
3001 gttatggata cataaaatgc acgcaagcca ttatctctcc atgggaagct aagttataaa
3061 aataggtgct tggtgtacaa aacttttat atcaaaaggc tttgcacatt tctatatgag
3121 tgggtttact ggtaaattat gttatttttt acaactaatt ttgtactctc agaatgtttg
3181 tcatatgctt cttgcaatgc atatttttta atctcaaacg tttcaataaa accatttttc
3241 agatataaag agaattactt caaattgagt aattcagaaa aactcaagat ttaagttaaa
3301 aagtggtttg gacttgggaa caggacttta tacctctttt actgtaacaa gtactcatta
3361 aaggaaattg aatgaaatta aaaaaaaaaa
```

An exemplary human Alpha-actin-2 (ACTA2) amino acid sequence is set forth below (SEQ ID NO: 191; GenBank Accession No: P62736, Version 1, incorporated herein by reference):

```
   1 mceeedstal vcdngsglck agfagddapr avfpsivgrp rhqgvmvgmg qkdsyvgdea
  61 qskrgiltlk ypiehgiitn wddmekiwhh sfynelrvap eehptlltea plnpkanrek
 121 mtqimfetfn vpamyvaiqa vlslyasgrt tgivldsgdg vthnvpiyeg yalphaimrl
 181 dlagrdltdy lmkiltergy sfvttaerei vrdikeklcy valdfenema taasssslek
 241 syelpdgqvi tignerfrcp etlfqpsfig mesagihett ynsimkcdid irkdlyannv
 301 lsggttmypg iadrmqkeit alapstmkik iiapperkys vwiggsilas lstfqqmwis
 361 kqeydeagps ivhrkcf
```

An exemplary human *ACTA2* nucleic acid sequence is set forth below (SEQ ID NO: 192; GenBank Accession No: NM_001141945, Version 2, incorporated herein by reference):

```
   1 gcaggctctc tccccgcccc cgcggggcgg cgcgcactca cccacccgcg ccggagcgga
  61 cctttggctt ggcttgtcag ggcttgtcca ggagttccgc tcctctctcc aaccggggtc
 121 cccctccagc gaccctaaag cttcccagac ttccgcttca attcctgtcc gcaccccacg
 181 cccacctcaa cgtggagcgc agtggtctcc gaggagcgcc ggagctgccc cgcctgccca
 241 gcggggtcag cacttcgcat caaggcccaa gaaaagcaag tcctccagcg ttctgagcac
 301 ccgggcctga gggaaggtcc taacagcccc cgggagccag tctccaacgc ctcccgcagc
 361 agcccgccgc tcccaggtgc ccgcgtgcgc cgctgccgcc gcaatcccgc acgcgtcccg
 421 cgcccgcccc actttgccta tccccgggac taagacggga atcctgtgaa gcagctccag
 481 ctatgtgtga agaagaggac agcactgcct tggtgtgtga caatggctct gggctctgta
 541 aggccggctt tgctggggac gatgctccca gggctgtttt cccatccatt gtgggacgtc
 601 ccagacatca gggggtgatg gtgggaatgg gacaaaaaga cagctacgtg ggtgacgaag
 661 cacagagcaa aagaggaatc ctgaccctga agtacccgat agaacatggc atcatcacca
 721 actgggacga catggaaaag atctggcacc actctttcta caatgagctt cgtgttgccc
 781 ctgaagagca tcccaccctg ctcacggagg cacccctgaa ccccaaggcc aaccgggaga
 841 aaatgactca aattatgttt gagactttca atgtcccagc catgtatgtg gctatccagg
 901 cggtgctgtc tctctatgcc tctggacgca caactggcat cgtgctggac tctggagatg
 961 gtgtcaccca caatgtcccc atctatgagg gctatgcctt gccccatgcc atcatgcgtc
1021 tggatctggc tggccgagat ctcactgact acctcatgaa gatcctgact gagcgtggct
1081 attccttcgt tactactgct gagcgtgaga ttgtccggga catcaaggag aaactgtgtt
1141 atgtagctct ggactttgaa aatgagatgg ccactgccgc atcctcatcc tcccttgaga
1201 agagttacga gttgcctgat gggcaagtga tcaccatcgg aaatgaacgt ttccgctgcc
1261 cagagaccct gttccagcca tccttcatcg ggatggagtc tgctggcatc catgaaacca
1321 cctacaacag catcatgaag tgtgatattg acatcaggaa ggacctctat gctaacaatg
1381 tcctatcagg gggcaccact atgtaccctg gcattgccga ccgaatgcag aaggagatca
1441 cggccctagc acccagcacc atgaagatca agatcattgc ccctccggag cgcaaatact
1501 ctgtctggat cggtggctcc atcctggcct ctctgtccac cttccagcag atgtggatca
1561 gcaaacagga atacgatgaa gccgggcctt ccattgtcca ccgcaaatgc ttctaaaaca
1621 ctttcctgct cctctctgtc tctagcacac aactgtgaat gtcctgtgga attatgcctt
1681 cagttctttt ccaaatcatt cctagccaaa gctctgactc gttacctatg tgtttttaa
1741 taaatctgaa ataggctact ggtaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa
1801 aaaaa
```

An exemplary human Prolyl 4-hydroxylase subunit alpha-1 (P4HA1) amino acid sequence is set forth below (SEQ ID NO: 193; GenBank Accession No: P13674, Version 2, incorporated herein by reference):

```
   1 miwyiliigi llpqslahpg fftsigqmtd lihtekdlvt slkdyikaee dkleqikkwa
  61 ekldrltsta tkdpegfvgh pvnafklmkr lntewselen lvlkdmsdgf isnltiqrqy
 121 fpndedqvga akallrlqdt ynldtdtisk gnlpgvkhks fltaedcfel gkvayteady
 181 yhtelwmeqa lrqldegeis tidkvsvldy lsyavyqqgd ldkallltkk lleldpehqr
 241 angnlkyfey imakekdvnk sasddqsdqk ttpkkkgvav dylperqkye mlcrgegikm
 301 tprrqkklfc ryhdgnrnpk filapakqed ewdkpriirf hdiisdaeie ivkdlakprl
 361 rratisnpit gdletvhyri sksawlsgye npvvsrinmr iqdltgldvs taeelqvany
 421 gvggqyephf dfarkdepda fkelgtgnri atwlfymsdv saggatvfpe vgasvwpkkg
 481 tavfwynlfa sgegdystrh aacpvlvgnk wvsnkwlher gqefrrpctl sele
```

An exemplary human *P4HA1* nucleic acid sequence is set forth below (SEQ ID NO: 194; GenBank Accession No: NM_000917, Version 3, incorporated herein by reference):

```
   1 ggggcgctgg tgtgatcgag ctcacgtagc gagggctgca gtcgcctcct ccctggcgct
  61 gccatcgcgg cctagaggtt ataaaagggc taacgggctc cctctgctgc ccagtcgcgc
 121 cgccagcggg ctgagggtag gaagtagccg ctccgagtgg aggcgactgg gggctgaaga
 181 gcgcgccgcc ctctcgtccc actttccagg tgtgtgatcc tgtaaaatta aatcttccaa
 241 gatgatctgg tatatattaa ttataggaat tctgcttccc cagtctttgg ctcatccagg
 301 ctttttttact tcaattggtc agatgactga tttgatccat actgagaaag atctggtgac
 361 ttctctgaaa gattatatta aggcagaaga ggacaagtta gaacaaataa aaaaatgggc
 421 agagaagtta gatcggctaa ctagtacagc gacaaaagat ccagaaggat ttgttgggca
 481 tccagtaaat gcattcaaat taatgaaacg tctgaatact gagtggagtg agttggagaa
 541 tctggtcctt aaggatatgt cagatggctt tatctctaac ctaaccattc agagacagta
 601 ctttcctaat gatgaagatc aggttggggc agccaaagct ctgttacgtc tccaggatac
 661 ctacaatttg gatacagata ccatctcaaa gggtaatctt ccaggagtga aacacaaatc
 721 ttttctaacg gctgaggact gctttgagtt gggcaaagtg gcctatacag aagcagatta
 781 ttaccatacg gaactgtgga tggaacaagc cctaaggcaa ctggatgaag gcgagatttc
 841 taccatagat aaagtctctg ttctagatta tttgagctat gcggtatatc agcagggaga
 901 cctggataag gcacttttgc tcacaaagaa gcttcttgaa ctagatcctg aacatcagag
 961 agctaatggt aacttaaaat attttgagta tataatggct aaagaaaaag atgtcaataa
1021 gtctgcttca gatgaccaat ctgatcagaa aactacacca aagaaaaaag gggttgctgt
1081 ggattacctg ccagagagac agaagtacga aatgctgtgc cgtggggagg gtatcaaaat
1141 gacccctcgg agacagaaaa aactcttttg ccgctaccat gatggaaacc gtaatcctaa
1201 atttattctg gctccagcta aacaggagga tgaatgggac aagcctcgta ttattcgctt
1261 ccatgatatt atttctgatg cagaaattga aatcgtcaaa gacctagcaa aaccaaggct
1321 gagccgagct acagtacatg accctgagac tggaaaattg accacagcac agtacagagt
1381 atctaagagt gcctggctct ctggctatga aaatcctgtg gtgtctcgaa ttaatatgag
1441 aatacaagat ctaacaggac tagatgtttc cacagcagag gaattacagg tagcaaatta
1501 tggagttgga ggacagtatg aaccccattt tgactttgca cggaaagatg agccagatgc
1561 tttcaaagag ctggggacag gaaatagaat tgctacatgg ctgttttata tgagtgatgt
1621 gtctgcagga ggagccactg tttttcctga agttggagct agtgtttggc ccaaaaaagg
1681 aactgctgtt ttctggtata atctgtttgc cagtggagaa ggagattata gtacacggca
1741 tgcagcctgt ccagtgctag ttggcaacaa atgggtatcc aataaatggc tccatgaacg
1801 tggacaagaa tttcgaagac cttgtacgtt gtcagaattg gaatgacaaa caggcttccc
1861 tttttctcct attgttgtac tcttatgtgt ctgatataca catttcctag tcttaacttt
1921 caggagttta caattgacta acactccatg attgattcag tcatgaacct catcccatgt
1981 ttcatctgtg gacaattgct tactttgtgg gttcttttaa aagtaacacg aaatcatcat
2041 attgcataaa accttaaagt tctgttggta tcacagaaga caaggcagag tttaaagtga
2101 ggaattttat atttaaagaa ctttttggtt ggataaaaac ataatttgag catccagttt
2161 tagtatttca ctacatctca gttggtgggt gttaagctag aatgggctgt gtgataggaa
2221 acaaatgcct tacagatgtg cctaggtgtt ctgtttacct agtgtcttac tctgttttct
2281 ggatctgaag actagtaata aactaggaca ctaactgggt tccatgtgat tgccctttca
2341 tatgatcttc taagttgatt tttttcctcc caagtctttt ttaaagaaag tatactgtat
2401 tttaccaacc ccctctcttt tcttttagct cctctgtggt gaattaaacg tacttgagtt
2461 aaaatatttc gatttttttt tttttttaa tggaaagtcc tgcataacaa cactgggcct
2521 tcttaactaa aatgctcacc acttagcctg tttttttatc ccttttttaa aatgacagat
2581 gattttgttc aggaattttg ctgtttttct tagtgctaat accttgcctc ttattcctgc
2641 tacagcaggg tggtaatatt ggcattctga ttaaatactg tgccttagga gactggaagt
2701 ttaaaaatgt acaagtcctt tcagtgatga gggaattgat ttttttaaa agtctttttc
2761 ttagaaagcc aaaatgtttg tttttttaag attctgaaat gtgttgtgac aacaatgacc
2821 tatttatgat cttaaatctt ttttaaaaaa aaaaaaaaaa
```

An exemplary human Prolyl 4-hydroxylase subunit beta (P4HB) amino acid sequence is set forth below (SEQ ID NO: 195; GenBank Accession No: P07237, Version 3, incorporated herein by reference):

```
  1 mlrrallcla vaalvradap eeedhvlvlr ksnfaealaa hkyllvefya pwcghckala
 61 peyakaagkl kaegseirla kvdateesdl aqqygvrgyp tikffrngdt aspkeytagr
121 eaddivnwlk krtgpaattl pdgaaaeslv essevavigf fkdvesdsak qflqaaeaid
181 dipfgitsns dvfskyqldk dgvvlfkkfd egrnnfegev tkenlldfik hnqlplvief
241 teqtapkifg geikthillf lpksvsdydg klsnfktaae sfkgkilfif idsdhtdnqr
301 ileffglkke ecpavrlitl eeemtkykpe seeltaerit efchrflegk ikphlmsqel
361 pedwdkqpvk vlvgknfedv afdekknvfv efyapwcghc kqlapiwdkl getykdheni
421 viakmdstan eveavkvhsf ptlkffpasa drtvidynge rtldgfkkfl esggqdgagd
481 dddledleea eepdmeeddd qkavkdel
```

An exemplary human *P4HB* nucleic acid sequence is set forth below (SEQ ID NO: 196; GenBank Accession No: NM_000918, Version 3, incorporated herein by reference):

```
   1 gagcctcgaa gtccgccggc caatcgaagg cgggccccag cggcgcgtgc gcgccgcggc
  61 cagcgcgcgc gggcgggggg gcaggcgcgc cccggaccca ggatttataa aggcgaggcc
 121 gggaccggcg cgcgctctcg tcgcccccgc tgtcccggcg gcgccaaccg aagcgccccg
 181 cctgatccgt gtccgacatg ctgcgccgcg ctctgctgtg cctggccgtg gccgccctgg
 241 tgcgcgccga cgcccccgag gaggaggacc acgtcctggt gctgcggaaa agcaacttcg
 301 cggaggcgct ggcggcccac aagtacctgc tggtggagtt ctatgccccc tggtgtggcc
 361 actgcaaggc tctggccccc gagtatgcca aagccgctgg gaagctgaag gcagaaggtt
 421 ccgagatcag gttggccaag gtggacgcca cggaggagtc tgacctggcc cagcagtacg
 481 gcgtgcgcgg ctatcccacc atcaagttct tcaggaatgg agacacggct tcccccaagg
 541 aatatacagc tggcagagag gctgatgaca tcgtgaactg gctgaagaag cgcacgggcc
 601 cggctgccac caccctgcct gacggcgcag ctgcagagtc cttggtggag tccagcgagg
 661 tggctgtcat cggcttcttc aaggacgtgg agtcggactc tgccaagcag tttttgcagg
 721 cagcagaggc catcgatgac ataccatttg ggatcacttc caacagtgac gtgttctcca
 781 aataccagct cgacaaagat ggggttgtcc tctttaagaa gtttgatgaa ggccggaaca
 841 actttgaagg ggaggtcacc aaggagaacc tgctggactt tatcaaacac aaccagctgc
 901 cccttgtcat cgagttcacc gagcagacag ccccgaagat ttttggaggt gaaatcaaga
 961 ctcacatcct gctgttcttg cccaagagtg tgtctgacta tgacggcaaa ctgagcaact
1021 tcaaaacagc agccgagagc ttcaagggca agatcctgtt catcttcatc gacagcgacc
1081 acaccgacaa ccagcgcatc ctcgagttct ttggcctgaa gaaggaagag tgcccggccg
1141 tgcgcctcat caccctggag gaggagatga ccaagtacaa gcccgaatcg gaggagctga
1201 cggcagagag gatcacagag ttctgccacc gcttcctgga gggcaaaatc aagccccacc
1261 tgatgagcca ggagctgccg gaggactggg acaagcagcc tgtcaaggtg cttgttggga
1321 agaactttga agacgtggct tttgatgaga aaaaaaacgt ctttgtggag ttctatgccc
1381 catggtgtgg tcactgcaaa cagttggctc ccatttggga taaactggga gagacgtaca
1441 aggaccatga gaacatcgtc atcgccaaga tggactcgac tgccaacgag gtggaggccg
1501 tcaaagtgca cagcttcccc acactcaagt tctttcctgc cagtgccgac aggacggtca
1561 ttgattacaa cggggaacgc acgctggatg gttttaagaa attcctggag agcggtggcc
1621 aggatggggc aggggatgat gacgatctcg aggacctgga agaagcagag gagccagaca
1681 tggaggaaga cgatgatcag aaagctgtga aagatgaact gtaatacgca aagccagacc
1741 cgggcgctgc cgagacccct cgggggctgc acacccagca gcagcgcacg cctccgaagc
1801 ctgcggcctc gcttgaagga gggcgtcgcc ggaaacccag ggaacctctc tgaagtgaca
1861 cctcaccccc acacaccgtc cgttcacccc cgtctcttcc ttctgctttt cggtttttgg
1921 aaagggatcc atctccaggc agcccaccct ggtggggctt gtttcctgaa accatgatgt
1981 acttttttcat acatgagtct gtccagagtg cttgctaccg tgttcggagt ctcgctgcct
2041 ccctcccgcg ggaggtttct cctctttttg aaaattccgt ctgtgggatt tttagacatt
2101 tttcgacatc agggtatttg ttccaccttg gccaggcctc ctcggagaag cttgtccccc
```

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2161 gtgtgggagg gacggagccg gactggacat ggtcactcag taccgcctgc agtgtcgcca
2221 tgactgatca tggctcttgc atttttgggt aaatggagac ttccggatcc tgtcagggtg
2281 tcccccatgc ctggaagagg agctggtggc tgccagccct ggggcccggc acaggcctgg
2341 gccttccccc tccctcaagc cagggctcct cctcctgtcg tgggctcatt gtgaccactg
2401 gcctctctac agcacggcct gtggcctgtt caaggcagaa ccacgaccct tgactcccgg
2461 gtggggaggt ggccaaggat gctggagctg aatcagacgc tgacagttct tcaggcattt
2521 ctatttcaca atcgaattga acacattggc caaataaagt tgaaatttta ccacctgtaa
2581 aaaaaaaaaa aaaaaa
```

An exemplary human vimentin (VIM) amino acid sequence is set forth below (SEQ ID NO: 197; GenBank Accession No: NP_003371, Version 2, incorporated herein by reference):

```
   1 mstrsvssss yrrmfggpgt asrpsssrsy vttstrtysl gsalrpstsr slyasspggv
  61 yatrssavrl rssvpgvrll qdsvdfslad aintefkntr tnekvelqel ndrfanyidk
 121 vrfleqqnki llaeleqlkg qgksrlgdly eeemrelrrq vdqltndkar veverdnlae
 181 dimrlreklq eemlqreeae ntlqsfrqdv dnaslarldl erkveslqee iaflkklhee
 241 eiqelqaqiq eqhvqidvdv skpdltaalr dvrqqyesva aknlqeaeew ykskfadlse
 301 aanrnndalr qakqesteyr rqvqsltcev dalkgtnesl erqmremeen faveaanyqd
 361 tigrlqdeiq nmkeemarhl reyqdllnvk maldieiaty rkllegeesr islplpnfss
 421 lnlretnlds lplvdthskr tlliktvetr dgqvinetsq hhddle
```

An exemplary human *VIM* nucleic acid sequence is set forth below (SEQ ID NO: 198; GenBank Accession No: XM_006717500, Version 1, incorporated herein by reference):

```
   1 tttgtgttac ataattgcct ttcatttgaa ctcattaatc aaattggggt ttttaagcaa
  61 cacctaatta attctttaac tggctcatat tataccttta atgacttcca ccagggtaaa
 121 aaccactgat cactgagttc tattttgaaa ctacggacgt cgagtttcct ctttcaccca
 181 gaattttcag atcttgttta aaaagttggg tgtggtttca tgggggggagg gggaagagcg
 241 agaggagacc agagggacgg gggcggggac tctgcaagaa aaaccttccc ggtgcaatcg
 301 tgatctggga ggcccacgta tggcgcctct ccaaaggctg cagaagtttc ttgctaacaa
 361 aaagtccgca cattcgagca aagacaggct ttagcgagtt attaaaaact taggggcgct
 421 cttgtccccc acagggcccg accgcacaca gcaaggcgat ggcccagctg taagttggta
 481 gcactgagaa ctagcagcgc gcgcggagcc cgctgagact tgaatcaatc tggtctaacg
 541 gtttccccta aaccgctagg agccctcaat cggcgggaca gcagggcgcg gtgagtcacc
 601 gccggtgact aagcgacccc acccctctcc ctcgggcttt cctctgccac cgccgtctcg
 661 caactcccgc cgtccgaagc tggactgagc ccgttaggtc cctcgacaga acctcccctc
 721 cccccaacat ctctccgcca aggcaagtcg atggacagag gcgcgggccg gagcagcccc
 781 cctttccaag cgggcggcgc gcgaggctgc ggcgaggcct gagccctgcg ttcctgcgct
 841 gtgcgcgccc ccaccccgcg ttccaatctc aggcgctctt tgtttctttc tccgcgactt
 901 cagatctgag ggattcctta ctctttcctc ttcccgctcc tttgcccgcg ggtctccccg
 961 cctgaccgca gccccgagac cgccgcgcac ctcctcccac gccccttttgg cgtggtgcca
1021 ccggacccct ctggttcagt cccaggcgga ccccccccctc accgcgcgac cccgcctttt
1081 tcagcacccc agggtgagcc cagctcagac tatcatccgg aaagccccca aaagtcccag
1141 cccagcgctg aagtaacggg accatgccca gtcccaggcc ccggagcagg aaggctcgag
1201 ggcgccccca ccccacccgc ccaccctccc cgcttctcgc taggtcccta ttggctggcg
1261 cgctccgcgg ctgggatggc agtgggaggg gaccctcttt cctaacgggg ttataaaaac
1321 agcgccctcg gcggggtcca gtcctctgcc actctcgctc cgaggtcccc gcgccagaga
1381 cgcagccgcg ctcccaccac ccacacccac cgcgccctcg ttcgcctctt ctccgggagc
1441 cagtccgcgc caccgccgcc gcccaggcca tcgccaccct ccgcagccat gtccaccagg
1501 tccgtgtcct cgtcctccta ccgcaggatg ttcggcggcc cgggcaccgc gagccggccg
1561 agctccagcc ggagctacgt gactacgtcc acccgcacct acagcctggg cagcgcgctg
1621 cgccccagca ccagccgcag cctctacgcc tcgtccccgg gcggcgtgta tgccacgcgc
1681 tcctctgccg tgcgcctgcg gagcagcgtg cccggggtgc ggctcctgca ggactcggtg
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1741 gacttctcgc tggccgacgc catcaacacc gagttcaaga acacccgcac caacgagaag
1801 gtggagctgc aggagctgaa tgaccgcttc gccaactaca tcgacaaggt gcgcttcctg
1861 gagcagcaga ataagatcct gctggccgag ctcgagcagc tcaagggcca aggcaagtcg
1921 cgcctggggg acctctacga ggaggagatg cgggagctgc gccggcaggt ggaccagcta
1981 accaacgaca aagcccgcgt cgaggtggag cgcgacaacc tggccgagga catcatgcgc
2041 ctccgggaga aattgcagga ggagatgctt cagagagagg aagccgaaaa caccctgcaa
2101 tctttcagac aggatgttga caatgcgtct ctggcacgtc ttgaccttga acgcaaagtg
2161 gaatctttgc aagaagagat tgccttttg aagaaactcc acgaagagga aatccaggag
2221 ctgcaggctc agattcagga acagcatgtc caaatcgatg tggatgtttc caagcctgac
2281 ctcacggctg ccctgcgtga cgtacgtcag caatatgaaa gtgtggctgc caagaacctg
2341 caggaggcag aagaatggta caaatccaag tttgctgacc tctctgaggc tgccaaccgg
2401 aacaatgacg ccctgcgcca ggcaaagcag gagtccactg agtaccggag acaggtgcag
2461 tccctcacct gtgaagtgga tgcccttaaa ggaaccaatg agtccctgga acgccagatg
2521 cgtgaaatgg aagagaactt tgccgttgaa gctgctaact accaagacac tattggccgc
2581 ctgcaggatg agattcagaa tatgaaggag gaaatggctc gtcaccttcg tgaataccaa
2641 gacctgctca atgttaagat ggcccttgac attgagattg ccacctacag gaagctgctg
2701 gaaggcgagg agagcaggat ttctctgcct cttccaaact tttcctccct gaacctgagg
2761 gaaactaatc tggattcact ccctctggtt gatacccact caaaaaggac acttctgatt
2821 aagacggttg aaactagaga tggacaggtt atcaacgaaa cttctcagca tcacgatgac
2881 cttgaataaa aattgcacac actcagtgca gcaatatatt accagcaaga ataaaaaaga
2941 aatccatatc ttaaagaaac agctttcaag tgcctttctg cagtttttca ggagcgcaag
3001 atagatttgg aataggaata agctctagtt cttaacaacc gacactccta caagatttag
3061 aaaaaagttt acaacataat ctagtttaca gaaaaatctt gtgctagaat acttttttaaa
3121 aggtattttg aataccatta aaactgcttt ttttttttcca gcaagtatcc aaccaacttg
3181 gttctgcttc aataaatctt tggaaaaact c
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Pharmaceutical Therapeutics

For therapeutic uses, the compositions or agents described herein may be administered systemically, for example, formulated in a pharmaceutically-acceptable buffer such as physiological saline. Preferable routes of administration include, for example, subcutaneous, intravenous, interperitoneally, intramuscular, or intradermal injections that provide continuous, sustained levels of the drug in the patient. Treatment of human patients or other animals will be carried out using a therapeutically effective amount of a therapeutic identified herein in a physiologically-acceptable carrier. Suitable carriers and their formulation are described, for example, in Remington's Pharmaceutical Sciences by E. W. Martin. The amount of the therapeutic agent to be administered varies depending upon the manner of administration, the age and body weight of the patient, and with the clinical symptoms of the neoplasia, i.e., the SINET. Generally, amounts will be in the range of those used for other agents used in the treatment of other diseases associated with neoplasia, although in certain instances lower amounts will be needed because of the increased specificity of the compound. For example, a therapeutic compound is administered at a dosage that is cytotoxic to a neoplastic cell.

Formulation of Pharmaceutical Compositions

The administration of a compound or a combination of compounds for the treatment of a neoplasia, e.g., a SINET, may be by any suitable means that results in a concentration of the therapeutic that, combined with other components, is effective in ameliorating, reducing, or stabilizing a neoplasia. The compound may be contained in any appropriate amount in any suitable carrier substance, and is generally present in an amount of 1-95% by weight of the total weight of the composition. The composition may be provided in a dosage form that is suitable for parenteral (e.g., subcutaneously, intravenously, intramuscularly, or intraperitoneally) administration route. The pharmaceutical compositions may be formulated according to conventional pharmaceutical practice (see, e.g., Remington: The Science and Practice of Pharmacy (20th ed.), ed. A. R. Gennaro, Lippincott Williams & Wilkins, 2000 and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York).

Human dosage amounts can initially be determined by extrapolating from the amount of compound used in mice, as a skilled artisan recognizes it is routine in the art to modify the dosage for humans compared to animal models. In certain embodiments it is envisioned that the dosage may vary from between about 1 μg compound/Kg body weight to about 5000 mg compound/Kg body weight; or from about 5 mg/Kg body weight to about 4000 mg/Kg body weight or from about 10 mg/Kg body weight to about 3000 mg/Kg body weight; or from about 50 mg/Kg body weight to about 2000 mg/Kg body weight; or from about 100 mg/Kg body weight to about 1000 mg/Kg body weight; or from about 150 mg/Kg body weight to about 500 mg/Kg body weight. In other cases, this dose may be about 1, 5, 10, 25, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1050, 1100, 1150, 1200, 1250, 1300, 1350, 1400, 1450, 1500, 1600, 1700, 1800, 1900, 2000, 2500, 3000, 3500, 4000, 4500, or 5000 mg/Kg body weight. In other aspects, it is envisaged that doses may be in the range of about 5 mg compound/Kg body to about 20 mg compound/Kg body. In other embodiments, the doses may be about 8, 10, 12, 14, 16 or 18 mg/Kg body weight. Of course, this dosage amount may be adjusted upward or downward, as is routinely done in such treatment protocols, depending on the results of the initial clinical trials and the needs of a particular patient.

Pharmaceutical compositions according to the invention may be formulated to release the active compound substantially immediately upon administration or at any predetermined time or time period after administration. The latter types of compositions are generally known as controlled release formulations, which include (i) formulations that create a substantially constant concentration of the drug within the body over an extended period of time; (ii) formulations that after a predetermined lag time create a substantially constant concentration of the drug within the body over an extended period of time; (iii) formulations that sustain action during a predetermined time period by maintaining a relatively, constant, effective level in the body with concomitant minimization of undesirable side effects associated with fluctuations in the plasma level of the active substance (sawtooth kinetic pattern); (iv) formulations that localize action by, e.g., spatial placement of a controlled release composition adjacent to or in contact with the thymus; (v) formulations that allow for convenient dosing, such that doses are administered, for example, once every one or two weeks; and (vi) formulations that target a neoplasia by using carriers or chemical derivatives to deliver the therapeutic agent to a particular cell type (e.g., neoplastic cell). For some applications, controlled release formulations obviate the need for frequent dosing during the day to sustain the plasma level at a therapeutic level.

Any of a number of strategies can be pursued in order to obtain controlled release in which the rate of release outweighs the rate of metabolism of the compound in question. In one example, controlled release is obtained by appropriate selection of various formulation parameters and ingredients, including, e.g., various types of controlled release compositions and coatings. Thus, the therapeutic is formulated with appropriate excipients into a pharmaceutical composition that, upon administration, releases the therapeutic in a controlled manner. Examples include single or multiple unit tablet or capsule compositions, oil solutions, suspensions, emulsions, microcapsules, microspheres, molecular complexes, nanoparticles, patches, and liposomes.

Parenteral Compositions

The pharmaceutical composition may be administered parenterally by injection, infusion or implantation (subcutaneous, intravenous, intramuscular, intraperitoneal, or the like) in dosage forms, formulations, or via suitable delivery devices or implants containing conventional, non-toxic pharmaceutically acceptable carriers and adjuvants. The formulation and preparation of

such compositions are well known to those skilled in the art of pharmaceutical formulation. Formulations can be found in Remington: The Science and Practice of Pharmacy, supra.

Compositions for parenteral use may be provided in unit dosage forms (e.g., in single-dose ampoules), or in vials containing several doses and in which a suitable preservative may be added (see below). The composition may be in the form of a solution, a suspension, an emulsion, an infusion device, or a delivery device for implantation, or it may be presented as a dry powder to be reconstituted with water or another suitable vehicle before use. Apart from the active agent that reduces or ameliorates a neoplasia, the composition may include suitable parenterally acceptable carriers and/or excipients. The active therapeutic agent(s) may be incorporated into microspheres, microcapsules, nanoparticles, liposomes, or the like for controlled release. Furthermore, the composition may include suspending, solubilizing, stabilizing, pH-adjusting agents, tonicity adjusting agents, and/or dispersing, agents.

As indicated above, the pharmaceutical compositions according to the invention may be in the form suitable for sterile injection. To prepare such a composition, the suitable active antineoplastic therapeutic(s) are dissolved or suspended in a parenterally acceptable liquid vehicle. Among acceptable vehicles and solvents that may be employed are water, water adjusted to a suitable pH by addition of an appropriate amount of hydrochloric acid, sodium hydroxide or a suitable buffer, 1,3-butanediol, Ringer's solution, and isotonic sodium chloride solution and dextrose solution. The aqueous formulation may also contain one or more preservatives (e.g., methyl, ethyl or n-propyl p-hydroxybenzoate). In cases where one of the compounds is only sparingly or slightly soluble in water, a dissolution enhancing or solubilizing agent can be added, or the solvent may include 10-60% w/w of propylene glycol.

Controlled Release Parenteral Compositions

Controlled release parenteral compositions may be in form of aqueous suspensions, microspheres, microcapsules, magnetic microspheres, oil solutions, oil suspensions, or emulsions. Alternatively, the active drug may be incorporated in biocompatible carriers, liposomes, nanoparticles, implants, or infusion devices.

Materials for use in the preparation of microspheres and/or microcapsules are, e.g., biodegradable/bioerodible polymers such as polygalactin, poly-(isobutyl cyanoacrylate), poly(2-hydroxyethyl-L-glutam- nine) and, poly(lactic acid). Biocompatible carriers that may be used when formulating a controlled release parenteral formulation are carbohydrates (e.g., dextrans),

proteins (e.g., albumin), lipoproteins, or antibodies. Materials for use in implants can be non-biodegradable (e.g., polydimethyl siloxane) or biodegradable (e.g., poly(caprolactone), poly(lactic acid), poly(glycolic acid) or poly(ortho esters) or combinations thereof).

Kits or Pharmaceutical Systems

The present compositions may be assembled into kits or pharmaceutical systems for use in ameliorating a neoplasia (e.g., SINET). Kits or pharmaceutical systems according to this aspect of the invention comprise a carrier means, such as a box, carton, tube or the like, having in close confinement therein one or more container means, such as vials, tubes, ampoules, or bottles. The kits or pharmaceutical systems of the invention may also comprise associated instructions for using the agents of the invention.

The practice of the present invention employs, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, biochemistry and immunology, which are well within the purview of the skilled artisan. Such techniques are explained fully in the literature, such as, "Molecular Cloning: A Laboratory Manual", second edition (Sambrook, 1989); "Oligonucleotide Synthesis" (Gait, 1984); "Animal Cell Culture" (Freshney, 1987); "Methods in Enzymology" "Handbook of Experimental Immunology" (Weir, 1996); "Gene Transfer Vectors for Mammalian Cells" (Miller and Calos, 1987); "Current Protocols in Molecular Biology" (Ausubel, 1987); "PCR: The Polymerase Chain Reaction", (Mullis, 1994); "Current Protocols in Immunology" (Coligan, 1991). These techniques are applicable to the production of the polynucleotides and polypeptides of the invention, and, as such, may be considered in making and practicing the invention. Particularly useful techniques for particular embodiments will be discussed in the sections that follow.

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the assay, screening, and therapeutic methods of the invention, and are not intended to limit the scope of what the inventors regard as their invention.

## EXAMPLES

Example 1: Understanding the Role of Carcinoid Associated Fibroblasts in the Neuroendocrine Tumor Microenvironment

Prior to the invention described herein, a lack of cell lines and animal models had been an

obstacle in developing therapeutic agents for advanced carcinoid tumors. Described herein is the development of a collection of short term carcinoid cell lines. Carcinoid cells in culture grow slowly and are importantly attached to stromal fibroblasts, referred to as CAF (Carcinoid Associated Fibroblasts). As described herein, CAF cell culture supernatants have been collected from 22 of the short-term primary cell lines, and the secreted levels of proteins have been measured utilizing a multiplexed bead-based approach to develop a secretion gene signature.

The carcinoid tumorj-stroma microenvironment was investigated to shed light on tumor-stromal interactions that might point to potential biomarkers of clinical utility. Described herein is (1) the development of short-term primary CAF cell cultures from carcinoid patient tumors; (2) the optimization of a culturing protocol for collecting CAF supernatants, whereby sufficient concentration of secreted proteins would be detectable in vitro; and (3) the performance of multiplexed analysis of secreted proteins on supernatants to investigate whether there is a secreted gene signature profile for well-differentiated tumors.

As shown in FIG. 1, primary tumor tissue was minced in culture medium and disaggregated by overnight incubation in collagenase (100U/ml at 37°C). 50,000 cells were seeded and cultured in 2 ml Dulbecco's modified eagle's / F12 (50:50) medium containing 10% fetal bovine serum and antibiotic-antimycotic and glutamax.

Cell culture supernatants were collected after 24, 48, and 72 hours and centrifuged at 12,300 rpm for 10 min (4°C). A Bioplex 200 platform was utilized for multiplex analysis. Cell culture supernatant concentration levels [pg/ml] of each protein were derived from 5-parameter curve fitting models. All concentrations were normalized to total protein concentration. Fold changes relative to normal human fibroblasts (BJ and HFF1 lines) were calculated.

Table 1: Primary tumor banked an short-term cell lines developed

| | |
|---|---|
| Primary Carcinoid Tumors | 32 |
| Carcinoid Associated Fibroblasts | 22 |

Short-term culures were generated for all but 1 primary tumor received. The collection comprises mostly mixed tumor/CAF cultures of varying tumor composition and pure CAF cultures, of which there are 22 (Table 1). Carcinoid cells stain positively for Chromogranin A, CgA, a marker of neuroendocrine phenotype. Carcinoid-associated fibroblasts stain positively for Vimentin, a mesenchymal marker. A unique library of frozen and FFPE primary tumors,

short-term cell cultures and exnograft models, was developed (Figure 2). In particular, note the CAF cells in the xenograft models were of human and not host origin (2H).

56 target proteins were measured across 3 multiplex assays utilizing a Bioplex platform, including IL-1β, IL-1RA, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, Eotaxin, FGF Basic, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1 (MCAF), MIP-1α, PDGF-BB, MIP-1β, RANTES, TNF-α, VEGF, sEGFR, Folastatin, sHER2 neu, HGF, sIL-6Ra, Leptin, Osteopontin, PDGF-AA BB, PECAM1, Prolactin, SCF, sTIE-2, sVEGFR1, sVEGFR2, Angiopoietin, sCD40L, EGF, Endoglin, sFASL, HB-EGF, IGFBP-1, IL-18, PAI-1, PLGF, TGFa, uPA, VEGF-A, VEGF-C and VEGF-D. Target proteins with a concentration below the lower limit of quantitation (LLOQ) or which were detected in less than 50% of the supernatants were eliminated from the data set. Fold changes for all target proteins remaining where calculated for each time point and trends evaluated.

Fold expression trends across the time course, 24 – 72hr were calculated. Within the CAF cohort, the secretion levels varied widely. This underlines the complexity of not only protein secretion within each tumor microenvironment but also the timing and mechanistic process by which these proteins are shed or secreted from CAF's. However an 8 marker signature, comprised of IL-6, IL-12, IL-13, RANTES, sEGFR, sVEGFR2, sTIE-2 and SCF, was identified (3B).

A multiplexed bead-based suspension assay was conducted with the cell library to investigate the protein secretion profile of carcinoid associated fibroblasts in cell supernatants derived from short-term primary cultures. Next, the 8 marker signature is validated in the plasma from patients with metastatic disease to establish their value in early diagnosis and/or assessing progression and prognosis.

Example 2: Secretion Profiling Identifies Biomarkers of Metastatic Small Bowel Neuroendocrine Tumors in Short-Term Neuroendocrnie-Associatd Fibroblast Primary Cultures

The following materials and methods were utilized in this example.

Clinical specimens

Neuroendocrine tumor tissue and plasma samples were obtained from the Dana-Farber Cancer Institute Neuroendocrine Tumor Biospecimen database, under an IRB-approved protocol (IRB# 02-314) in which patients provide informed consent for collection of tissue specimens and

blood obtained during routine clinical care. Blood/plasma was also collected from consenting spousal/friend as healthy controls. Briefly, blood (up to 10ml) was collected into tubes containing EDTA, and the separation procedure was carried out within 3hr of venipuncture. The samples were spun at 3000rpm for 15min resulting in approximately 3-6ml plasma. The plasma was aliquoted and stored at -80°C for preservation.

Patient-derived CAF cultures and supernatant collection

A portion of each tumor tissue specimen was minced in culture medium and disaggregated by overnight incubation in collagenase (100 U/ml at 37°C). Cells were initially cultured in Dulbecco's modified eagle's / F12 (50:50) medium containing 10% fetal bovine serum, antibiotic-antimycotic and glutamax. 50k cells were seeded in 2ml media in 6-well plates. Cell culture supernatants and cell pellets were collected at 24, 48 and 72hr. 1.5 ml of cell culture supernatant was centrifuged at 12300rpm for 10 min at 4°C and stored at -80°C. Cell were trypsinized, washed in PBS, and lysed for total protein extraction. Total proteins were quantitated by Bradford assay (Biorad cat #500-0002). Normal human fibroblast cell lines, BJ and HFF1 (ATCC cat# CRL-2522 and SCRC-1041) were cultured under the same conditions.

Clinical characteristics of patient-derived CAFs

Tumors from 20 SINET patients (55%/45% female to male ration) were collected for the generation of short-term cultures of patient-derived fibroblasts (Table 2). The median age of the patients was 58.5 years of age. 50% were of grade 1 and 25% of grade 2. 65% of patients were treated with Octreotide, of which almost half of these patients also had additional treatment(s) at the time of surgery.

Table 2: Clinical characteristics of SINET specimens utilized in creation of short-term cultures

| Sample | Age | Gender | Disease | Tissue collected | Grade | Octreotide | Other Treatment |
|---|---|---|---|---|---|---|---|
| CAR1 | 44 | F | Small Intestine | mesenteric mass | 1 | No | No |
| CAR3 | 67 | F | Small Intestine | mesenteric mass | 2 | Yes | Yes |
| CAR4 | 57 | M | Small Intestine | mesenteric mass | 1 | No | No |
| CAR6 | 78 | F | UNK Primary | mesenteric mass | 1 | Yes | Yes |
| CAR8 | 56 | M | Small Intestine | mesenteric mass | NA | Yes | No |
| CAR13 | 81 | M | Small Intestine | mesenteric mass | 2 | No | No |
| CAR15 | 55 | M | Small Intestine | small bowel | 1 | Yes | No |
| CAR16 | 62 | F | UNK Primary | peritoneal tu | 2 | No | No |
| CAR17 | 47 | F | UNK Primary | small bowel | 1 | Yes | Yes |
| CAR20 | 72 | F | Small Intestine | small bowel | 1 | Yes | No |
| CAR21 | 70 | F | Small Intestine | mesenteric mass | 2 | Yes | No |
| CAR23 | 49 | M | Small Intestine | mesenteric mass | 1 | Yes | Yes |
| CAR24 | 74 | M | Small Intestine | mesenteric mass | 2 | No | No |
| CAR26 | 68 | F | Small Intestine | small bowel | 1 | Yes | No |
| CAR27 | 60 | M | Small Intestine | mesenteric mass | 1 | Yes | No |
| CAR2 | 57 | F | Small Intestine | ovary | 1 | Yes | Yes |
| CAR5 | 47 | F | UNK Primary | ovary | NA | Yes | Yes |
| CAR10 | 73 | M | Small Intestine | liver | NA | Yes | No |
| CAR11 | 49 | F | Small Intestine | liver | 1 | No | No |
| CAR18 | 57 | M | Small Intestine | liver | 2 | No | No |

***NOTE**: NA: All tumors were well-differentiated*

Short-term NAF cultures

A portion of each tissue sample was frozen and evaluated to confirm histological features and rule out the presence of significant hemorrhagic/necrotic areas, not suitable for

experimentation. Additional portions of each tissue were snap frozen and banked, and also formalin-fixed and processed for paraffin-embedding (FFPE). Tumor tissue was then minced in culture medium and disaggregated by overnight incubation in collagenase (100 U/ml at 37°C). Cells were initially cultured in Dulbecco's modified eagle's / F12 (50:50) medium containing 10% fetal bovine serum, antibiotic-antimycotic and glutamax.

Cell Culture Supernatant Collection

50k cells were seeded in 2ml DMEM F12 supplemented with 10% FBS and 1% P/S in 6-well plates. Cell culture supernatants and cell pellets were collected at 24, 48, and 72hr. 1.5 ml of cell culture supernatant was centrifuged at 12,300rpm for 10 min at 4°C and aliquoted (3 x 500 µl aliquots) for storage at -80 °C. The remaining cells were then washed in PBS, and lysed for total proteins extraction. Total Proteins were quantitated by Bradford assay (Biorad cat #500-0002).

Multiplex Secretion profiling

Multiplex assays were performed utilizing a bead-based immunoassay approach, namely the Bio-Plex Pro™ Human Cytokine 27-plex Assay (Cat# M500KNAF0Y), Bio-Plex Pro™ Human Cancer Biomarker Panel 1, 16-plex (Cat#171AC500M) and Bio-Plex Pro™ Human Cancer Biomarker Panel 2, 18-plex (Cat# 171AC600M) on a Bio-plex 200 system (Cat# 171000201). Manufacturer guidelines were followed without deviation or amendments. Briefly, capture antibodies for each protein were coupled to a uniquely encoded bead. A sandwich ELISA in suspension ensues incorporating a dual detection system that identifies the encoded bead and measures the fluorescent intensity of the associated protein in the cell culture supernatant. Plasma and cell culture supernatant concentration levels [pg/ml] of each protein were derived from 5-parameter curve fitting models. All concentrations were normalized to total protein concentration. Normalized secreted protein levels in the carcinoid associated fibroblasts NAF's supernatant were compared to normal human fibroblast cell lines, BJ and HFF1 (ATCC cat# CRL-2522 and SCRC-1041). Fold changes relative to the mean of these normal human fibroblasts (NHF's) were calculated and two-tailed student t-tests performed, where p-values $<0.05$ were considered significant. Hierarchical clustering utilized Gene Cluster 3.0 employing Euclidean distance and average linkage for clustering of secreted proteins and time points. Java Treeview (Version 1.1.5) software was used to plot the heatmap from hierarchical clustering results.

RNA Extraction and Quantification

CAF/NAF and normal human fibroblasts (NHF) cells were trypsinized, scraped and transferred to an RNase-/DNase-free 2ml eppendorf tube. Cells were pelleted by centrifugation and washed in 1 ml PBS in triplicate. RNA was extracted from the cell pellets utilizing the AllPrep mini kit [Qiagen cat# 80204], as described by the manufacturers protocol. RNA isolates were eluted in a 14µl volume of RNase/DNase-free H2O. All RNA was stored at -80°C. RNA isolates were quantified utilizing the Quant-iT RiboGreen assay (Life Technologies – cat# R11490). 1µl of RNA is required for quantification. Concentration was measured as ng/µl. For RNA quantification, isolates were excited at 485 ± 10 nm and the fluorescence emission intensity was measured at 530 ± 12 nm using a Victor X3 spectrophotometer (Perkin Elmer cat# 2030-0030). Fluorescence intensity was plotted versus RNA concentration over the calibration range, 0 -100 ng/µl.

qRT-PCR

RT-PCR was employed to interrogate list all genes studied (Life Technologies, High Capacity cDNA Reverse Transcription Kit [Cat# 4368814], TaqMan® Gene Expression Master Mix [Cat# 4369016], see Table 3 for probe id information) 20ng RNA input was utilized in the reverse transcription reaction (High-Capacity cDNA Reverse Transcription Kit Life Technologies) and 2µl of the subsequent cDNA product was transferred to the PCR assay (Taqman Gene Expression Mastermix, Cat # 4369510, Life Technologies). Triplicate reactions were prepared using Taqman assay probes for for IL-6 (Hs00174131_m1), MCP-1 (CCL2; Hs00234140_m1) and VEGFA (Hs00900055_m1) for each sample. GAPDH (Taqman cat #: Hs 02758991_g1, Life Technologies) was utilized as the reference housekeeping gene and subsequent differential expression was assessed by comparative CT analysis as previously described (Schmittgen TD, Livak KJ. Analyzing real-time PCR data by the comparative $C_T$ method (Schmittgen TD and Livak KJ, Nature Protocols, 3:1101-1108 (2008)).

Table 3

| Gene Name | Hs ID | Amplicon Length | Entrez Gene ID | NCBI Chromosomal Location |
|---|---|---|---|---|
| IL6 | 00985639_m1 | 66 | 3569 | Chr.7: 22766766 - 22771621 |
| IL8 | 00174103_m1 | 101 | 3576 | Chr.4: 74606223 - 74609433 |
| VEGFA | 00900055_m1 | 59 | 7422 | Chr.6: 43737946 - 43754224 |
| CCL5 (alias RANTES) | 00982282_m1 | 70 | 6352 | Chr.17: 34198495 - 34207377 |
| FST | 00246256_m1 | 108 | 10468 | Chr.5: 52776264 - 52782304 |
| BIRC5 | 04194392_s1 | 102 | 332 | Chr.17: 76210277 - 76221716 |
| PLAU (alias uPA) | 01547054_m1 | 61 | 5328 | Chr.10: 75670862 - 75677259 |
| FGF2 (alias FGF basic) | 00266645_m1 | 82 | 2247 | Chr.4: 123747863 - 123819390 |
| CXCL10 (alias IP-10) | 01124252_g1 | 83 | 3627 | Chr.4: 76942269 - 76944689 |
| SPP1 | 00959010_m1 | 84 | 6696 | Chr.4: 88896802 - 88904563 |

Cell Viability Assay

The ATP activity was assessed by CellTiter-Glo® Luminescent Cell Viability Assay (Promega cat # G7571) to determine cell viability in NAF cell cultures. Briefly, 200µl of CellTiter-Glo® Reagent was added directly to cells, resulting in cell lysis and generation of a luminescent signal proportional to the amount of ATP present. Luminescent intensity was measured using a Victor X3 spectrophotometer (Perkin Elmer cat# 2030-0030) after 10min incubation at room temperature and 2min shaking at 600rpm on an orbital shaker (IKA, MTS 2/4 digital microtiter shaker, cat # 0003208001).

Automated Library Preparation and RNA Sequencing

A total of 50ng of RNA was utilized as input for RNA-Seq library preparation utilizing the TruSeq Stranded RNA Access Library Prep Kit (cat# RS-301-2001). The method was automated on the Biomek® FXP Laboratory Automation Workstation (Beckman Coulter). This method facilitates enrichment of the coding regions of the transcriptome that are captured using sequence-specific probes to create the final library. cDNA libraries were quantified utilizing the Quanti-iT PicoGreen assay (Life Technologies – cat# P7589). 1µl of cDNA was required for quantification. Concentration is measured as ng/ul. Libraries were excited at 480 nm and the fluorescence emission intensity was measured at 520 nm using a Victor X3 spectrophotometer (Perkin Elmer cat# 2030-0030). Fluorescence intensity was plotted versus concentration over the low calibration range, 0–50ng/µl. Libraries were also quality checked by Agilent Bioanalyzer using the High Sensitivity DNA kit (cat# 5067-4626). cDNA libraries were then sequenced on the Illumina NextSeq500 platform as 75bp paired end reads. Data was streamed in real-time to

the Illumina BaseSpace cloud tool. The STAR RNA sequencing alignment tool (Spliced Transcripts Alignment to a Reference) aligner [STAR_2.5.0a]) was utilized to align the data to the genome, Homo sapiens UCSC hg19 (RefSeq gene annotations). DeSeq2 (Love et al., Genome Biol, 15:550 (2014)) was utilized to perform differential expression analysis (±2-fold, P value<0.05). Overlaps between the DE gene set and the annotated Hallmark gene sets in the Molecular Signature DataBase, MSigDB (FDR q-value<0.05, Subramanian et al., Proc Natl Acad Sci USA, 102:15545-50 (2005)), were computed. Gene Cluster 3.0 was utilized to perform hierarchical clustering and subsequent plotting of the resulting heatmap was completed in Java TreeView.

Immunohistochemistry

A portion of each primary tissue was formalin-fixed and paraffin-embedded (FFPE) to confirm histological features and assess hemorrhagic / necrotic areas. Single immunohistochemical staining for Chromogranin A, CgA, and Vimentin, Vim, was performed on 4μm sections cut from primary tissue FFPE blocks. Immunostaining was performed on tissue sections following deparaffinization in for 5 min in xylene and rehydration through graded alcohols to distilled water. After blocking endogenous peroxidase activity, sections were subjected to heat-induced epitope retrieval in citrate buffer (pH 6.1) for 5 min. Following heat-induced epitope retrieval, the primary mouse monoclonal antibody for Chromogranin A (Ms mAb, Clone LK2H10, MS-324-PABX, NeoMarkers) and the primary mouse monoclonal antibody Vim (Ms mAb, Clone V9, MUO74-UC, Biogenex) was applied to the sections. Protein levels were examined using a dilution of 1:4000 for CgA and 1:500 for Vim respectively for 1 hour at room temperature. Incubation with the biotinylated universal secondary antibody was then performed. Visualization was performed with 3,3'-diaminobenzidine (DAB) as the chromogenic substrate.

Exclusion Criteria

In experiments, 61 target proteins were measured across 3 multiplex assays utilizing a Bioplex platform (See FIG. 18A- FIG. 18C as a referece), including IL-1b, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, Eotaxin, FGF Basic, G-CSF, GM-CSF, IFNg, IP-10, MCP-1 (MCAF), MIP-1a, PDGF-bb, MIP-1b, RANTES, TNFa, VEGF, sEGFR, Folastatin, sHER2 neu, HGF, sIL-6Ra, Leptin, Osteopontin, PDGF-AA BB, PECAM1, Prolactin, SCF, sTIE-2, sVEGFR1, sVEGFR2, Angiopoietin, sCD40L, EGF, Endoglin, sFASL,

HB-EGF, IGFBP-1, IL-18, PAI-1, PLGF, TGFa, uPA, VEGF-A, VEGF-C and VEGF-D. Target proteins with a concentration below the lower limit of quantitation (LLOQ) or which were detected in less than 75% of the supernatants were eliminated from the data set. Secretion levels were assessed as being low (<100pg/ml), moderate (100-1000pg/ml) and high (>1000pg/ml) expressing. To account for increasing levels of secretion associated with cell growth all protein concentrations were normalized to total protein levels in the cell lysate from which the supernatant was collected. These normalized levels of secreted protein were utilized for all subsequent analysis.

The results of the experiments described above are presented below.

Basic characterization of SINET tissue and short-term NAF cultures

A portion of each primary SINET tumor was fixed and embedded in paraffin for histopathological confirmation of the presence of tumor cells by H&E and IHC (FIG. 2A). SINET cells stain positively for Chromogranin A, CgA, a marker of neuroendocrine phenotype (FIG. 2B). NAFs stain positively for Vimentin, a mesenchymal marker in the stroma indicative of an activated fibroblastic phenotype (FIG. 2C).

The short-term cultures comprise mixed tumor/NAF cultures of varying tumor composition (FIG. 2D), and pure NAF cultures, where tumor cells stain for CgA (FIG. 2E) and NAFs for VIM (FIG. 2F). SINET patient-derived xenografts (PDX) in mice remain viable for months; however, their growth rate is almost negligible, which means that even though they replicate the tumor biology, they are unsuitable as surrogate *in vivo* models to study the disease biology. Basic histological characterization of PDX's generated herein revealed morphology that is almost identical to the primary tumors (FIG. 2G). In the PDX models, it was identified that SINET cells grow in close association with fibroblasts (termed NAFs), and that the fibroblasts from the original tumor specimen are preserved (FIG. 2G) and grow in association with tumors in implanted xenografts. In particular, it was noteworthy that the NAF cells in the xenograft models where of human and not host origin (FIG. 2H and FIG. 2I). These observations suggest that tumor-stromal interactions play a critical, underappreciated role in driving and maintaining neuroendocrine tumor growth.

Stromal cells form a significant component of the xenografts. This is consistent with observations in primary tumors, and suggests that tumor-stromal interactions may play a key role in SINET growth, particularly in light of the relatively silent mutational landscape of these

tumors (Francis et al., 2013 Nat Genet., 45(12):1483-6; Jiao Y et al., 2011 Science, 331(6021):1199-203). With the development of this resource of short-term primary cell lines and control normal cultured fibroblast cell lines, teasing apart the tumor-stroma relationship is feasible via collection of cell culture supernatants and *in vitro* screening of secreted proteins. A single protein is insufficient to fully reflect this complex relationship. Accordingly, it was envisaged that a panel of secreted proteins would be more informative. Because the commonly used single ELISA assays in standardized 96-well plates are cumbersome and both sample exhaustive and labor-intensive, a bead-based multiplexing approach was utlized to screen for potential biomarkers of metastatic SINET disease. It is increasingly evident that biomarker signatures have a higher probability of being prognostic or predictive than any single biomarker on its own.

Establishment of cancer-associated fibroblast cultures from SINET tissue

The basic histopathology of SINETs comprise islands of neuroendocrine tumors cells (FIG. 2A), which stain positively for chromogranin A, CgA, the neuroendocrine tumor-specific markers (FIG. 2B), with surrounding dense regions of stroma that stain positively for the fibroblast-specific marker, Vimentin, VIM (FIG. 2C). A portion of each tumor was disaggregated in culture. Experiments allowed for in vitro observation that SINET cells grow in clusters and appear to adhere to a scaffold of adjacent fibroblasts (FIG. 2D). In culture tumor cells were quickly overgrown by fibroblasts and the prohibitive rate of tumor to fibroblast cell growth resulted in loss of tumor cells completely from the culture within several passages. As in the primary tumor, the neuroendocrine tumor cells stain for CgA (FIG. 2E) and fibroblasts for VIM (FIG. 2F). Experiments created a total of 20 CAF cultures, and then utilized these patient-derived CAF cultures for subsequent studies. Table 4 displays secretion levels as measured by multiplex assays for 24 healthy donors versus 16 metastatic SINET patients. Differences in expression were considered significant, where p-value $< 0.05$. For plasma analysis, $\log_2$(fold change) differences between the metastatic patients and healthy controls were reported and two-tailed student t-tests were performed, where p-values $<0.05$ were considered significant.

Table 4: Secretion levels as measured by multiplex assays for 24 healthy donors versus 16 metastatic SINET patients

| Secreted Protein [pg/ml] | Control [n=24] % | mean±sd | 95% CI | SINET [n=16] % | mean±sd | 95% CI | Ctrl v SINET p-value |
|---|---|---|---|---|---|---|---|
| Angiopoietin | 1.0 | 1119.5 ± 532.9 | [906.3, 1332.7] | 1.0 | 1975.2 ± 1463.5 | [1258.6, 2691.9] | 0.012 |
| EGF | 1.0 | 88.5 ± 47.5 | [69.1, 107.9] | 1.0 | 117.2 ± 55.3 | [90.1, 144.3] | 0.091 |
| Endoglin | 1.0 | 1967.5 ± 1011.2 | [1562.9, 2372.0] | 1.0 | 2762.5 ± 1217.4 | [2166.0, 3359.0] | 0.031 |
| Eotaxin | 1.0 | 55.0 ± 33.9 | [41.4, 68.6] | 0.9 | 64.1 ± 41.1 | [43.3, 84.9] | 0.457 |
| FGF basic* | 1.0 | 311.4 ± 110.4 | [267.2, 355.6] | 1.0 | 276.4 ± 56.0 | [249.0, 303.9] | 0.250 |
| Folastatin | 1.0 | 1370.9 ± 474.0 | [1181.3, 1560.5] | 1.0 | 1101.0 ± 367.4 | [921.0, 1281.1] | 0.062 |
| G-CSF* | 1.0 | 517.1 ± 402.4 | [356.1, 678.1] | 1.0 | 465.8 ± 360.7 | [289.0, 642.6] | 0.683 |
| GM-CSF | 0.8 | 137.5 ± 52.0 | [113.4, 161.5] | 0.9 | 154.3 ± 78.0 | [114.8, 193.8] | 0.465 |
| HB-EGF | 1.0 | 69.5 ± 32.5 | [56.5, 82.5] | 1.0 | 92.2 ± 41.7 | [71.7, 112.6] | 0.061 |
| HGF | 1.0 | 1416.7 ± 479.1 | [1225.0, 1608.4] | 1.0 | 1169.6 ± 374.0 | [986.3, 1352.8] | 0.090 |
| IFNg | 1.0 | 202.5 ± 127.3 | [151.5, 253.4] | 1.0 | 397.7 ± 341.0 | [230.7, 564.6] | 0.014 |
| IGFBP-1 | 1.0 | 3470.9 ± 3523.4 | [2061.7, 4880.1] | 1.0 | 6275.5 ± 7431.5 | [2634.1, 9916.9] | 0.117 |
| IL-10 | 0.8 | 16.8 ± 8.9 | [12.7, 20.9] | 0.9 | 28.4 ± 21.4 | [17.6, 39.3] | 0.045 |
| IL-12(p70) | 1.0 | 27.1 ± 12.7 | [22.0, 32.2] | 1.0 | 42.2 ± 31.9 | [26.6, 57.8] | 0.043 |
| IL-13 | 1.0 | 23.2 ± 15.9 | [16.8, 29.5] | 1.0 | 33.7 ± 32.2 | [18.0, 49.5] | 0.175 |
| IL-17 | 0.8 | 27.0 ± 17.7 | [19.0, 34.9] | 0.9 | 56.4 ± 53.5 | [28.4, 84.4] | 0.032 |
| IL-18 | 1.0 | 282.6 ± 101.0 | [242.3, 323.0] | 1.0 | 320.2 ± 82.7 | [279.7, 360.6] | 0.224 |
| IL-1b | 0.9 | 4.1 ± 2.0 | [3.3, 4.9] | 0.8 | 7.7 ± 5.4 | [4.8, 10.6] | 0.008 |
| IL-1ra | 1.0 | 177.3 ± 128.1 | [126.0, 228.5] | 1.0 | 360.0 ± 351.2 | [187.9, 532.1] | 0.025 |
| IL-2 | 0.7 | 11.6 ± 6.4 | [8.6, 14.6] | 0.9 | 23.9 ± 22.1 | [12.3, 35.5] | 0.037 |
| IL-4 | 1.0 | 4.0 ± 2.1 | [3.2, 4.9] | 1.0 | 6.4 ± 4.5 | [4.2, 8.6] | 0.031 |
| IL-5 | 0.9 | 9.3 ± 3.9 | [7.6, 11.0] | 0.9 | 15.8 ± 10.3 | [10.4, 21.2] | 0.012 |
| IL-6* | 1.0 | 143.0 ± 78.7 | [111.5, 174.4] | 1.0 | 206.9 ± 96.6 | [159.5, 254.3] | 0.027 |
| IL-7 | 1.0 | 17.0 ± 7.4 | [14.1, 20.0] | 1.0 | 24.6 ± 14.9 | [17.3, 31.9] | 0.038 |
| IL-8* | 1.0 | 30.8 ± 19.6 | [23.0, 38.7] | 1.0 | 39.9 ± 19.7 | [30.3, 49.6] | 0.159 |
| IL-9 | 0.8 | 13.4 ± 7.2 | [10.2, 16.6] | 0.9 | 23.2 ± 18.9 | [13.6, 32.8] | 0.045 |
| IP-10 | 1.0 | 665.3 ± 529.5 | [453.5, 877.2] | 1.0 | 598.9 ± 355.3 | [424.8, 773.0] | 0.663 |
| Leptin | 1.0 | 6428.2 ± 5424.7 | [4257.9, 8598.4] | 1.0 | 3462.0 ± 2957.3 | [2012.9, 4911.0] | 0.053 |
| MCP-1 (MCAF) | 1.0 | 57.2 ± 19.0 | [49.6, 64.9] | 1.0 | 80.6 ± 43.5 | [59.2, 101.9] | 0.026 |
| MIP-1a | 1.0 | 5.2 ± 2.4 | [4.2, 6.1] | 1.0 | 8.1 ± 5.1 | [5.6, 10.6] | 0.021 |
| MIP-1b | 1.0 | 52.9 ± 49.3 | [33.1, 72.6] | 1.0 | 41.2 ± 6.2 | [38.2, 44.3] | 0.355 |
| Osteopontin | 1.0 | 46143.1 ± 12307.2 | [41259.3, 51026.9] | 1.0 | 50885.3 ± 43614.6 | [29514.6, 72256.1] | 0.615 |
| PAI-1 | 1.0 | 15527.9 ± 9041.0 | [11910.8, 19145.0] | 1.0 | 17488.0 ± 8169.1 | [13485.2, 21490.8] | 0.490 |
| PDGF-AA BB | 1.0 | 618.6 ± 682.2 | [345.7, 891.5] | 1.0 | 652.6 ± 441.1 | [436.5, 868.7] | 0.861 |
| PDGF-bb | 1.0 | 499.4 ± 520.5 | [291.2, 707.7] | 1.0 | 709.7 ± 479.2 | [474.8, 944.5] | 0.205 |
| PECAM1 | 1.0 | 3784.6 ± 854.4 | [3442.7, 4126.4] | 1.0 | 3599.2 ± 1211.6 | [3005.5, 4192.9] | 0.573 |
| PLGF | 1.0 | 159.5 ± 84.5 | [125.7, 193.3] | 1.0 | 219.4 ± 101.4 | [169.7, 269.1] | 0.050 |
| Prolactin | 1.0 | 5287.9 ± 2307.5 | [4364.7, 6211.1] | 1.0 | 5897.4 ± 6070.9 | [2922.7, 8872.1] | 0.657 |
| RANTES | 1.0 | 7104.6 ± 2222.0 | [6215.7, 7993.6] | 1.0 | 5938.0 ± 2318.2 | [4802.1, 7073.9] | 0.118 |
| sCD40L | 1.0 | 415.7 ± 198.8 | [336.2, 495.2] | 1.0 | 542.6 ± 262.8 | [413.8, 671.4] | 0.090 |
| SCF | 1.0 | 259.0 ± 57.9 | [235.9, 282.2] | 1.0 | 213.5 ± 57.5 | [185.3, 241.6] | 0.019 |
| sEGFR | 1.0 | 15889.4 ± 4791.1 | [13972.6, 17806.2] | 1.0 | 10982.3 ± 4427.9 | [8812.6, 13151.9] | 0.002 |
| sFASL | 1.0 | 808.7 ± 314.9 | [680.0, 937.3] | 1.0 | 1032.6 ± 407.5 | [833.0, 1232.3] | 0.060 |
| sHER2 neu | 1.0 | 3236.1 ± 1092.2 | [2799.1, 3673.1] | 1.0 | 2350.1 ± 1264.4 | [1730.6, 2969.6] | 0.024 |
| sIL-6Ra | 1.0 | 6858.9 ± 3369.2 | [5511.0, 8206.9] | 1.0 | 4935.9 ± 3279.8 | [3328.8, 6542.9] | 0.082 |
| sTIE-2 | 1.0 | 8684.2 ± 2760.2 | [7579.9, 9788.8] | 1.0 | 7657.8 ± 2909.0 | [6232.4, 9083.2] | 0.266 |
| sVEGFR1 | 1.0 | 531.6 ± 253.8 | [430.1, 633.1] | 1.0 | 591.7 ± 369.1 | [410.8, 772.5] | 0.545 |
| sVEGFR2 | 1.0 | 4019.9 ± 1104.1 | [3578.1, 4461.6] | 1.0 | 3179.2 ± 928.7 | [2724.2, 3634.3] | 0.017 |
| TGFa | 1.0 | 134.5 ± 79.4 | [102.7, 166.3] | 1.0 | 181.7 ± 98.8 | [133.3, 230.1] | 0.103 |
| TNFa* | 1.0 | 110.9 ± 55.9 | [88.6, 133.3] | 1.0 | 145.7 ± 70.0 | [111.4, 180.0] | 0.090 |
| uPA | 1.0 | 476.4 ± 146.2 | [417.9, 534.9] | 1.0 | 561.8 ± 208.9 | [459.5, 664.2] | 0.136 |
| VEGF | 1.0 | 37.6 ± 17.9 | [30.4, 44.7] | 1.0 | 63.7 ± 87.5 | [20.9, 106.6] | 0.161 |
| VEGF-A | 1.0 | 569.8 ± 280.7 | [457.5, 682.1] | 1.0 | 804.3 ± 377.1 | [619.5, 989.1] | 0.030 |
| VEGF-C | 1.0 | 901.3 ± 375.7 | [751.0, 1051.6] | 1.0 | 1175.6 ± 500.9 | [930.1, 1421.0] | 0.055 |
| VEGF-D | 1.0 | 1166.2 ± 392.5 | [1009.2, 1323.2] | 1.0 | 1447.6 ± 462.0 | [1221.2, 1674.0] | 0.045 |

*In-vitro* NAFs/CAFs have a distinct secretion profile relative to normal human fibroblasts

First the secreted protein profiles of CAFs were examined, and it was determined whether these profiles differed from normal human fibroblasts. A total of 61 target proteins were measured across 3 multiplex assays utilizing a Bioplex platform (FIG. 4A), including IL-1b, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, Eotaxin, FGF Basic, G-CSF, GM-CSF, IFNg, IP-10, MCP-1 (MNAF), MIP-1a, PDGF-bb, MIP-1b, RANTES, TNFa, VEGF, sEGFR, Folastatin, sHER2 neu, HGF, sIL-6Ra, Leptin, Osteopontin, PDGF-AA BB, PECAM1, Prolactin, SCF, sTIE-2, sVEGFR1, sVEGFR2, Angiopoietin, sCD40L, EGF, Endoglin, sFASL, HB-EGF, IGFBP-1, IL-18, PAI-1, PLGF, TGFa, uPA, VEGF-A, VEGF-C and VEGF-D. Target proteins with a concentration below the lower limit of quantitation (LLOQ) or which were detected in less than 75% of the supernatants were eliminated from the data set (FIG. 4B), resulting in a total of 47 secreted proteins of interest: Angiopoietin, EGF, Endoglin, Eotaxin, FGF Basic, Follistatin, GM-CSF, HB-EGF, HGF, IFNg, IGFBP-1, IL-10, IL-12 (p70), IL-13, IL-18, IL-1ra, IL-2, IL-4, IL-6, IL-7, IL-8, IL-9, IP-10, Leptin, MCP-1 (MCAF), MIP-1b, Osteopontin, PAI-1, PDGF-AA BB, PDGF-bb, PLGF, RANTES, sCD40L, SCF, sEGFR, sFASL, sHER2 neu, sIL-6Ra, sTIE-2, sVEGFR1, sVEGFR2, TGFa, uPA, VEGF, VEGF-A, VEGF-C and VEGF-D. Secretion levels were assessed as being low (<100pg/ml), moderate (100-1000pg/ml) and high (>1000pg/ml) expressing, the distribution for each time point is shown by pie chart (FIG. 4C), where increasing expression of secreted proteins are observed over the time course 24-72hr, resulting in a doubling of the number of high expressing proteins being detected after 72hr. To account for increasing levels of secretion associated with cell growth all protein concentrations were normalized to total protein levels in the cell lysate from which the supernatant was collected. These normalized levels of secreted protein were utilized for all subsequent analysis.

Within the NAF cohort, the secretion levels varied widely. This underscores the biological diversity of these well differentiated tumors and the complexity of secretion feedback loops within the tumor microenvironment with respect to the kinetics of activation and inactivation and mechanistic process by which these proteins are shed or secreted from NAF's. NAF supernatants were compared to supernatants collected from 2 normal human fibroblast cell lines, BJ and HFF1 (NHF's). Mean expression levels for NAF versus NHF were utilized to calculate fold changes for each target protein for each time point and trends were evaluated

across the time course, 24 – 72hr. Multiplex bead-based evaluation of a panel of cytokines, chemokines, hormones and growth factors in culture supernatants collected at 24hr, 48hr and 72hr time points from the patient-derived CAF cells grown in vitro were performed. Fold changes were $log_2$ transformed and plotted versus time point. Hierarchical clustering of the secreted proteins versus time point, are represented by the heatmap shown in FIG. 5A. Fold changes that were greater than ±1.5 fold and/or where the differential expression levels were sustained over the entire time course, where noted. At the mean expression level, either sustained trends of higher secretion levels over the entire time course or increasing secretion over the time course were observed for the majority of secreted proteins evaluated in the CAFs relative to NHFs. For example, a group of 16 proteins had sustained higher secretion levels over the time course of 72hr. However, when evaluating the individual tumors, it is evident that not all SINET samples secrete similar profiles. Among the secreted proteins that were profiled, IL-6, MCP-1, VEGF, IL-12, IFNg, IL-1ra and IL-10 (FIG. 5B-FIG. 5E and FIG. 5H- FIG. 5J), showed marked trends of overexpression (>2-fold induction of the mean expression level) in the CAF's relative to the NHFs. Representative bar charts of NAF's and NHF's plotting secreted levels of over-expressing uPA, IL-6, MCP-1 and VEGF are shown in FIG. 5B-FIG. 5E. IL-6, MCP-1, IL-12 and VEGF, along with IL-2 and IL-13 share a more common pattern across the majority of NAF's showing substantially higher secretion levels than the NHF's. Inversely, there were several protein secretion levels that were suppressed in CAFs/NAF's relative to the NHF's, such as SCF and sEGFR (>1.5-fold suppression of the mean expression level, FIG. 5F-FIG. 5G). FIG. 5F is a graph of SCF concentration for CAF and NHG, and FIG. 5G is a graph of sEGFR concentration in CAF and NHG further supporting the aforementioned results.

Secreted proteins measured in plasma from matched SINET patients with metastatic disease correlate with the short-term NAF supernatants

40 plasma samples (16 matched tumors and 24 healthy controls) were screened for the 61 proteins across the 3 multiplex assays as described for the cell culture supernatants. 59/61 proteins were measured in >75% of both the healthy donor and metastatic patient groups. The results of which are shown in Table 5, where mean expression, standard deviation, lower and upper confidence levels are provided for the control and CAR groups. The control and tumor groups were compared and statistical significance was determined to be a p-value $< 0.05$.

35 targets, i.e., sEGFR, IL-1b, Angiopoietin, IL-5, IFNg, sVEGFR2, SCF, MIP-1a, sHER2 neu, IL-1ra, MCP-1 (MCAF), IL-6, VEGF-A, IL-4, Endoglin, IL-17, IL-2, IL-7, IL-12(p70), IL-10, VEGF-D, IL-9, PLGF, Leptin, VEGF-C, sFASL, HB-EGF, Follistatin, sIL-6Ra, TNFa, sCD40L, HGF, EGF, TGFa and IGFBP-1, across the 3 panels were differentially expressed between the control and tumor group, which suggest that there is a diagnostic, prognostic, and/or predictive association of clinical utility.

Table 5: Secretion levels as measured by multiplex assay for 24 healthy donors versus 16 metastatic patients. Differences in expression were considered significant, where p-value < 0.05.

| Secreted Protein [pg/ml] | Control [n=24] | | | SINET [n=16] | | | Ctrl v SINET |
|---|---|---|---|---|---|---|---|
| | % | mean±sd | 95% CI | % | mean±sd | 95% CI | p-value |
| Angiopoietin | 1.0 | 1119.5 ± 532.9 | [906.3, 1332.7] | 1.0 | 1975.2 ± 1462.5 | [1258.6, 2691.9] | 0.012 |
| EGF | 1.0 | 88.5 ± 47.5 | [69.1, 107.9] | 1.0 | 117.2 ± 55.3 | [90.1, 144.3] | 0.091 |
| Endoglin | 1.0 | 1967.5 ± 1011.2 | [1562.9, 2372.0] | 1.0 | 2762.5 ± 1217.4 | [2166.0, 3359.0] | 0.031 |
| Eotaxin | 1.0 | 55.0 ± 33.9 | [41.4, 68.6] | 0.9 | 64.1 ± 41.1 | [43.3, 84.9] | 0.457 |
| FGF basic* | 1.0 | 311.4 ± 110.4 | [267.2, 355.6] | 1.0 | 276.4 ± 56.0 | [249.0, 303.9] | 0.250 |
| Folastatin | 1.0 | 1370.9 ± 474.0 | [1181.3, 1560.5] | 1.0 | 1101.0 ± 367.4 | [921.0, 1281.1] | 0.062 |
| G-CSF* | 1.0 | 517.1 ± 402.4 | [356.1, 678.1] | 1.0 | 465.8 ± 360.7 | [289.0, 642.6] | 0.683 |
| GM-CSF | 0.8 | 137.5 ± 52.0 | [113.4, 161.5] | 0.9 | 154.3 ± 78.0 | [114.8, 193.8] | 0.465 |
| HB-EGF | 1.0 | 69.5 ± 32.5 | [56.5, 82.5] | 1.0 | 92.2 ± 41.7 | [71.7, 112.6] | 0.061 |
| HGF | 1.0 | 1416.7 ± 479.1 | [1225.0, 1608.4] | 1.0 | 1169.6 ± 374.0 | [986.3, 1352.8] | 0.090 |
| IFNg | 1.0 | 202.5 ± 127.3 | [151.5, 253.4] | 1.0 | 397.7 ± 341.0 | [230.7, 564.8] | 0.014 |
| IGFBP-1 | 1.0 | 3470.9 ± 3522.4 | [2061.7, 4880.1] | 1.0 | 6275.5 ± 7431.5 | [2634.1, 9916.9] | 0.117 |
| IL-10 | 0.8 | 16.8 ± 8.9 | [12.7, 20.9] | 0.9 | 28.4 ± 21.4 | [17.6, 39.3] | 0.045 |
| IL-12(p70) | 1.0 | 27.1 ± 12.7 | [22.0, 32.2] | 1.0 | 42.2 ± 31.9 | [26.6, 57.8] | 0.043 |
| IL-13 | 1.0 | 23.2 ± 15.9 | [16.8, 29.5] | 1.0 | 33.7 ± 32.2 | [18.0, 49.5] | 0.175 |
| IL-17 | 0.8 | 27.0 ± 17.7 | [19.0, 34.9] | 0.9 | 56.4 ± 53.5 | [28.4, 84.4] | 0.032 |
| IL-18 | 1.0 | 282.6 ± 101.0 | [242.2, 323.0] | 1.0 | 320.2 ± 82.7 | [279.7, 360.8] | 0.224 |
| IL-1b | 0.9 | 4.1 ± 2.0 | [3.2, 4.9] | 0.8 | 7.7 ± 5.4 | [4.8, 10.6] | 0.008 |
| IL-1ra | 1.0 | 177.3 ± 128.1 | [126.0, 228.5] | 1.0 | 360.0 ± 351.2 | [187.9, 532.1] | 0.025 |
| IL-2 | 0.7 | 11.6 ± 6.4 | [8.6, 14.6] | 0.9 | 23.9 ± 22.1 | [12.3, 35.5] | 0.037 |
| IL-4 | 1.0 | 4.0 ± 2.1 | [3.2, 4.9] | 1.0 | 6.4 ± 4.5 | [4.2, 8.6] | 0.031 |
| IL-5 | 0.9 | 9.3 ± 3.9 | [7.6, 11.0] | 0.9 | 15.8 ± 10.3 | [10.4, 21.2] | 0.012 |
| IL-6* | 1.0 | 143.0 ± 78.7 | [111.5, 174.4] | 1.0 | 206.9 ± 96.6 | [159.5, 254.3] | 0.027 |
| IL-7 | 1.0 | 17.0 ± 7.4 | [14.1, 20.0] | 1.0 | 24.6 ± 14.9 | [17.3, 31.9] | 0.038 |
| IL-8* | 1.0 | 30.8 ± 19.6 | [23.0, 38.7] | 1.0 | 39.9 ± 19.7 | [30.3, 49.6] | 0.159 |
| IL-9 | 0.8 | 13.4 ± 7.2 | [10.2, 16.6] | 0.9 | 23.2 ± 18.9 | [13.6, 32.8] | 0.045 |
| IP-10 | 1.0 | 665.3 ± 529.5 | [453.5, 877.2] | 1.0 | 598.9 ± 355.3 | [424.8, 773.0] | 0.663 |
| Leptin | 1.0 | 6428.2 ± 5424.7 | [4257.9, 8598.4] | 1.0 | 3462.0 ± 2957.3 | [2012.9, 4911.0] | 0.053 |
| MCP-1 (MCAF) | 1.0 | 57.2 ± 19.0 | [49.6, 64.9] | 1.0 | 80.6 ± 43.5 | [59.2, 101.9] | 0.026 |
| MIP-1a | 1.0 | 5.2 ± 2.4 | [4.2, 6.1] | 1.0 | 8.1 ± 5.1 | [5.6, 10.6] | 0.021 |
| MIP-1b | 1.0 | 52.9 ± 49.3 | [33.1, 72.6] | 1.0 | 41.2 ± 6.2 | [38.2, 44.3] | 0.355 |
| Osteopontin | 1.0 | 46143.1 ± 12207.2 | [41259.3, 51026.9] | 1.0 | 50885.3 ± 43614.6 | [29514.6, 72256.1] | 0.615 |
| PAI-1 | 1.0 | 15527.9 ± 9041.0 | [11910.8, 19145.0] | 1.0 | 17488.0 ± 8169.1 | [13485.2, 21490.8] | 0.490 |
| PDGF-AA BB | 1.0 | 618.6 ± 682.2 | [345.7, 891.5] | 1.0 | 652.6 ± 441.1 | [436.5, 868.7] | 0.861 |
| PDGF-bb | 1.0 | 499.4 ± 520.5 | [291.2, 707.7] | 1.0 | 709.7 ± 479.2 | [474.8, 944.5] | 0.205 |
| PECAM1 | 1.0 | 3784.6 ± 854.4 | [3442.7, 4126.4] | 1.0 | 3599.2 ± 1211.6 | [3005.5, 4192.9] | 0.573 |
| PLGF | 1.0 | 159.5 ± 84.5 | [125.7, 193.3] | 1.0 | 219.4 ± 101.4 | [169.7, 269.1] | 0.050 |
| Prolactin | 1.0 | 5287.9 ± 2307.5 | [4364.7, 6211.1] | 1.0 | 5897.4 ± 6070.9 | [2922.7, 8872.1] | 0.657 |
| RANTES | 1.0 | 7104.6 ± 2222.0 | [6215.7, 7993.6] | 1.0 | 5938.0 ± 2318.2 | [4802.1, 7073.9] | 0.118 |
| sCD40L | 1.0 | 415.7 ± 198.8 | [336.2, 495.2] | 1.0 | 542.6 ± 262.8 | [413.8, 671.4] | 0.090 |
| SCF | 1.0 | 259.0 ± 57.9 | [235.9, 282.2] | 1.0 | 213.5 ± 57.5 | [185.3, 241.6] | 0.019 |
| sEGFR | 1.0 | 15889.4 ± 4791.1 | [13972.6, 17806.2] | 1.0 | 10982.3 ± 4427.9 | [8812.6, 13151.9] | 0.002 |
| sFASL | 1.0 | 808.7 ± 314.9 | [680.0, 937.3] | 1.0 | 1032.6 ± 407.5 | [833.0, 1232.3] | 0.060 |
| sHER2 neu | 1.0 | 3236.1 ± 1092.2 | [2799.1, 3673.1] | 1.0 | 2350.1 ± 1264.4 | [1730.6, 2969.6] | 0.024 |
| sIL-6Ra | 1.0 | 6858.9 ± 3369.2 | [5511.0, 8206.9] | 1.0 | 4935.9 ± 3279.8 | [3328.8, 6542.9] | 0.082 |
| sTIE-2 | 1.0 | 8684.2 ± 2760.2 | [7579.9, 9788.8] | 1.0 | 7657.8 ± 2909.0 | [6232.4, 9083.2] | 0.266 |
| sVEGFR1 | 1.0 | 531.6 ± 253.8 | [430.1, 633.1] | 1.0 | 591.7 ± 369.1 | [410.8, 772.5] | 0.545 |
| sVEGFR2 | 1.0 | 4019.9 ± 1104.1 | [3578.1, 4461.6] | 1.0 | 3179.2 ± 928.7 | [2724.2, 3634.3] | 0.017 |
| TGFa | 1.0 | 134.5 ± 79.4 | [102.7, 166.3] | 1.0 | 181.7 ± 98.8 | [133.3, 230.1] | 0.103 |
| TNFa* | 1.0 | 110.9 ± 55.9 | [88.6, 133.3] | 1.0 | 145.7 ± 70.0 | [111.4, 180.0] | 0.090 |
| uPA | 1.0 | 476.4 ± 146.2 | [417.9, 534.9] | 1.0 | 561.8 ± 208.9 | [459.5, 664.2] | 0.136 |
| VEGF | 1.0 | 37.6 ± 17.9 | [30.4, 44.7] | 1.0 | 63.7 ± 87.5 | [20.9, 106.6] | 0.161 |
| VEGF-A | 1.0 | 569.8 ± 280.7 | [457.5, 682.1] | 1.0 | 804.3 ± 377.1 | [619.5, 989.1] | 0.030 |
| VEGF-C | 1.0 | 901.3 ± 375.7 | [751.0, 1051.6] | 1.0 | 1175.6 ± 500.9 | [930.1, 1421.0] | 0.055 |
| VEGF-D | 1.0 | 1166.2 ± 392.5 | [1009.2, 1323.2] | 1.0 | 1447.6 ± 462.0 | [1221.2, 1674.0] | 0.045 |

The CAF secretion signature is recapitulated in plasma from matched SINET patients with metastatic disease

To validate the findings in vivo, evaluation of whether the CAF secreted protein signatures identified in vitro would also be present in the plasma of the matched patients was performed. Plasma samples from the same 16 patients from whom the cultures had been derived were compared to 24 control samples derived from spousal and friend controls. Using the same assay utilized to evaluate the CAF supernatants, it was found that in the patient plasma samples IL-6, MCP-1, VEGF, IL-12, IFNg, IL-1ra and IL-10 (FIG. 6A- FIG. 6B and FIG. 6E- FIG. 6I) were over-expressed and SCF (FIG. 6D) and sEGFR (FIG. 6C) were suppressed in plasma derived from the SINET patients relative to the normal controls, mirroring the secretion patterns observed in the CAFs relative to the NHFs. Specifically, this result mimicked the short-term culture supernatant findings (FIG. 5B, FIG. 5D, FIG. 5F and FIG. 5G). Global comparison of the mean $\log_2$[mets/ctrl] in the metastatic plasma samples to the supernatant results found high concordance (FIG. 6J). Comparing the global $\log_2$ transformed fold differences in expression in the metastatic plasma samples relative to the normal controls, to those in the CAF's/NAF's relative to the NHF's, resulted in 75% concordance of the secreted proteins in terms of trend observed, as shown in FIG. 6J. The correlation is shown in FIG. 6K as a scatterplot, where the Pearson correlation coefficient was calculated to be 0.5427 ($P<0.001$).

Genes expressed in CAFs harbor characteristics of an aggressive tumor-associated stromal cell phenotype

Prior to the invention described herein, no single marker of tumor-associated stromal cells has been identified, rather a combination of a panel of markers aid CAF characterization. Studies found that, consistent with the IHC results (FIG. 12), CAR24 and CAR26, two representative CAFs, did not express CgA but strongly expressed VIM. Tumor-associated stromal cells do not have epithelial or endothelial characteristics and therefore do not express cell surface markers such as CD34, CD31 (PECAM1) and MUC16, as well as cytokeratins, such as KRT5, KRT6 and others, which is observed replicated in the CAF gene expression data (FIG. 11E, Table 6). In contrast, αSmooth muscle actin (ACTA2) and fibroblast activation protein (FAP), along with a panel of general markers of tumor-associated stromal cells, including tenascin-C (TNC), Periostin (POSTN), Neuron-glial antigen-2 (NRG2) and platelet-derived growth factor receptors (PDGFRA,-B) were highly expressed in CAFs. E-cadherin (CDH1)

expression was very low in the CAFs, a feature known to be associated with tumor invasiveness and transformation via epithelial mesenchymal transition (EMT). EMT is also regulated by exogenous stimulating factors released by the microenvironment including Matrix Metallopeptidase (MMP-1,-2), integrin (ITGA-1,-2,-3,-5,-7,-11) and TGF-β (-1,-induced) factors, which were found to be highly expressed in the representative CAFs, CAR24 and CAR26.

Table 6: Genes that aid characterization of stromal-associated stromal fibroblasts

| NET-specific | CGA | Chromogranin A | References |
|---|---|---|---|
| Cell surface epithelial-specific | CD34 | Hematopoietic progenitor cell antigen CD34 | |
| | PECAM1 | Platelet and Endothelial Cell Adhesion Molecule 1 | Xing et al., Front. Biosci, 15: 166-179 (2010); Sukowati et al., BMC Cancer, 15: 188 (2015) |
| | MUC16 | Mucin 16, cell surface associated | |
| | KRT5 | Keratin 5 | Xing et al., Front. Biosci, 15: 166-179 (2010); Sukowati et al., BMC Cancer, 15: 188 (2015) |
| | KRT6A | Keratin 6A | Xing et al., Front. Biosci, 15: 166-179 (2010); Sukowati et al., BMC Cancer, 15: 188 (2015) |
| | KRT6B | Keratin 6B | Xing et al., Front. Biosci, 15: 166-179 (2010); Sukowati et al., BMC Cancer, 15: 188 (2015) |
| | KRT17 | Keratin 17 | Xing et al., Front. Biosci, 15: 166-179 (2010); Sukowati et al., BMC Cancer, 15: 188 (2015) |
| Stimulants of malignant cell proliferation | EGFR | Epidermal growth factor receptor | |
| | FGF2 | Fibroblast growth factor 2 | Jung et al., Int J Cancer, 127: 332-344 (2010); Acloque et al., J Clin Invest, 109: 1438-1449 (2009) |
| | HGF | Hepatocyte growth factor | De Wever et al. FASEB J, 18: 1061-1018 (2004); Vermeulen et al. Nat Cell Biol, 12: 468-476 (2010) |
| | CXCL12 | C-X-C Motif Chemokine Ligand 12 | Du et al., Cancer Cell, 13: 206-220 (2008) |
| | CDH1 | Cadherin 1 | Chen et al., J Clin Invest, 120: 1178-1191 (2010) |

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|---|---|---|---|
| epithelial-mesenchymal transition | CDH2 | Cadherin 2 | Thiery JP, Curr Opin Biol, 15: 740-746 (2003) |
| | MMP1 | Matrix Metallopeptidase 1 | Boire et al., Cell, 120: 303-313 (2005) |
| | MMP2 | Matrix Metallopeptidase 2 | Mueller MM and Fusenig NE, Nat Rev Cancer, 4: 839-849 (2004) |
| | ITGA1 | Integrin Subunit Alpha 1 | Mueller MM and Fusenig NE, Nat Rev Cancer, 4: 839-849 (2004) |
| | ITGA2 | Integrin Subunit Alpha 2 | Mueller MM and Fusenig NE, Nat Rev Cancer, 4: 839-849 (2004) |
| | ITGA3 | Integrin Subunit Alpha 3 | Mueller MM and Fusenig NE, Nat Rev Cancer, 4: 839-849 (2004) |
| | ITGA5 | Integrin Subunit Alpha 5 | Mueller MM and Fusenig NE, Nat Rev Cancer, 4: 839-849 (2004) |
| | ITGA7 | Integrin Subunit Alpha 7 | Mueller MM and Fusenig NE, Nat Rev Cancer, 4: 839-849 (2004) |
| | ITGA11 | Integrin Subunit Alpha 11 | Mueller MM and Fusenig NE, Nat Rev Cancer, 4: 839-849 (2004) |
| | TGFB1 | Transforming growth factor beta 1 | Costea et al., Cancer Res, 73: 3888-3901 (2013) |
| | TGFBI | Transforming growth factor beta induced | Costea et al., Cancer Res, 73: 3888-3901 (2013) |
| metastatic transition | YAP1 | Yes associated protein 1 | Calvo et al., Nat Cell Biol, 15: 637-646 (2013) |
| | HAS2 | Hyaluronan Synthase 2 | Kobayashi et al., Cancer Res, 70:7073-7083 (2010) |
| | LOX | Lysyl Oxidase | Erler et al., Cancer Cell, 15: 35-44 (2009); Barry-Hamilton et al., Nat Med, 16: 1009-1017 (2010) |
| | S100A4 | S100 Calcium Binding Protein A4 | Yan et al., Hepatology 57: 2274-2286 (2013) |

| | | | |
|---|---|---|---|
| | GSTP1 | Glutathione S-Transferase Pi 1 | Chaiwun et al., Br J Cancer, 105: 1224-1229 (2011) |
| | CD81 | CD81 molecule | Luga et al., Cell, 151: 1542-1556 (2012) |
| mesenchymal-like | THY1 | Thy-1 Cell Surface Antigen | Nazarethet al., J Immunol, 178; 5552-5562 (2007) |
| | NT5E | 5'-Nucleotidase Ecto | Turcotte et al., Cancer Res, 75: 4494-4503 (2015) |
| | ENG | Endoglin | Martinez et al., PLoS One, 10: e121421 (2015) |
| | CD44 | CD44 antigen | Sukowati et al., BMC Cancer, 15: 188 (2015) |
| matrix-remodeling | FAP | Fibroblast Activation Protein Alpha | Lee et al., Cancer Res, 75:73-85 (2015); Cheng et al., Cancer Res, 62: 4767-4772 (2002); Kraman et al., Science, 330: 827-830 (2010) |
| Hypoxia and Angiogenesis | VEGFA | Vascular endothelial growth factor A | De Francesca et al., Breast Cancer Res, 15: R64 (2013) |
| | VEGFC | Vascular endothelial growth factor C | De Francesca et al., Breast Cancer Res, 15: R64 (2013) |
| | HIF1A | Hypoxia Inducible Factor 1 Alpha Subunit | Du et al., Cancer Cell, 13: 206-220 (2008); De Francesca et al., Breast Cancer Res, 15: R64 (2013); Del Rey et al., Arthritis Rheum, 60: 2926-2934 (2009) |
| | CAV1 | Caveolin 1 | Shimizu et al., J Cancer Res Clin Oncol, 143: 321-328 (2017) |
| tumor-associated stromal cell and myofibroblasts | PDGFRA | Platelet-derived growth factor receptor A | Strutz et al., J Cell Biol, 130: 393-405 (1995); Togo et al., Cancers, 5:149-169 (2013) |
| | PDGFRB | Platelet-derived growth factor receptor B | Strutz et al., J Cell Biol, 130: 393-405 (1995); Togo et al., Cancers, 5:149-169 (2013); Shinagawa et al., Int J Cancer, 127: 2323-2333 (2010) |
| | NRG1 | Neuregulin 1 | Han et al., Gastroenterol, 50: 645-56 (2015) |

| | | | |
|---|---|---|---|
| | TNC | Tenascin C | Saupe et al., Cell Rep, 5: 482-492 (2013) |
| | POSTN | Periostin | Ratajczak-Wielgomas et al., Oncol Rep, 36: 2745-4754 (2016) |
| | ACTA2 | Actin, Alpha 2, Smooth Muscle, Aorta | Sappino et al., Int J Cancer, 41: 707-712 (1988); Orimo A and Weinberg RA, Cancer Biol Ther, 6: 618-619 (2007); Tomasek et al., Nat Rev Mol Cell Biol, 3: 349-363 (2002) |
| stromal-specific | P4HA1 | Prolyl 4-Hydroxylase Subunit Alpha 1 | Lou et al., J Cell Mol Med, doi: 10.1111/jcmm.13208 (2017) |
| | P4HB | Prolyl 4-Hydroxylase Subunit Beta | Zhang et al., Neoplasma, doi: 10.4149/neo_2018_101 (2017) |
| | VIM | Vimentin | |

NAF/CAFs short term cultures are highly sensitive to inhibition of the NFkB pathway

From the initial NAF screening, a set of secreted proteins including, IL-6, MCP-1, VEGF, IL-2, IL-12 and IL-13 that were upregulated in the supernatants was identified. Since all of these proteins are related to NFκB signaling, the NAF short term cultures were treated with a small molecule inhibitor, Withaferin A (WFA) that potently prevents NFκB activation by inhibiting activation of IKKβ, displaying anti-inflammatory, antitumor and antiangiogenic activity. Withaferin A is also known to bind directly to vimentin and disrupts the cytoskeleton (Stevens et at., 2013 Gut, 62(5):695-707; Bargagna-Mohan et al., 2015 PLoS One, 10(7):e0133399).

CAR24 and CAR26 were selected as representative NAF cultures. Since it was anticipated that NAF's would be sensitive to $NF_KB$ inactivation, it was determined to treat CAR24 and CAR26 for 24hr with Withaferin A (WFA), a potent inhibitor of NFκB activation, over the concentration range, 10 – 1000nM (10, 25, 50, 100, 250, 500 and 1000nM), to establish a dose curve response and evaluate dysregulation of the secreted protein profile.

Secretion profiling fold changes between the WFA treated supernatants and those treated with dimethyl sulfoxide (DMSO) as the vehicle were converted to $\log_2$(Fold Change) for

generating the heatmap as shown in FIG. 7A. A dose dependent suppression of the pro-oncogenic secretion profile (approximately 30 of the soluble proteins measured) was observed in the CAFs/NAFs treated with increasing concentrations of WFA (FIG. 17A) over the concentration range, 50-1000nM. The WFA-treated NAF secretion profiles for CAR24 and CAR26 were compared at the 50uM dose resulting in a Pearson correlation coefficient of 0.7217 ($P<0.0001$). This suggests that even though secretion profiles vary across NAFs derived from SINET patient tumors as demonstrated in FIG. 7A-FIG. 7G, NFkB inactivation with a 50nM concentration of WFA induces a common suppression signature of secreted proteins as measured in supernatants derived from treated short-term NAF cultures. Inversely, sEGFR was induced in the NAFs in response to increasing concentration of WFA, which mirrors the statistically significant higher plasma concentration of sEGFR observed in controls (FIG. 6C, $P=0.002$) and the observation that normal human fibroblasts secrete larger amounts of sEGFR with respect to NAFs derived from SINET tumors (FIG. 5G).

Cell viability decreased in a dose dependent manner (FIG. 7B), where both CAR24 and CAR26 NAF were sensitive to WFA inhibition with greater than 70% cell death observed at 24hr post-treatment with a 250nM single dose. The suppression of secreted proteins associated with NFkB signaling closely trends with the decrease in cell viability with increasing WFA concentration.

In parallel, mRNA was extracted to assess transcriptional regulation of VEGF-A, MCP-1 and IL-6 in response to a single potent dose of 100uM WFA treatment, as shown in FIG. 7C. Fold change due to WFA treatment was plotted as $-1/2^{-\Delta\Delta CT}$. The mRNA expression of VEGF-A, IL-6 and MCP-1 in CAR24 NAF was reduced 1.45-fold, 16.82-fold and 36.92-fold, respectively, due to treatment with 100nM WFA for 24hr. The mRNA expression of VEGF-A, IL-6 and MCP-1 in CAR26 NAF was reduced 2.18-fold, 9.01-fold and 3.32-fold, respectively, due to treatment with 100nM WFA for 24hr. The transcriptional downregulation of mRNA levels of VEGF-A, IL-6 and MCP-1 in response to NFkB inactivation by 100nM WFA treatment (FIG. 7C) was observed and mirrored the suppression observed in the supernatant secretion levels measured for VEGF-A, IL-6 and MCP-1 (2.57-fold, 6.99-fold and 4.95-fold for CAR24; 1.72-fold, 4.13-fold and 1.57-fold for CAR26), respectively. In FIG. 7C, fold change due to WFA treatment was plotted as $-1/2^{-\Delta\Delta CT}$. Overall, trends show that these 3 genes were

transcriptionally downregulated and correlate with the suppression of VEGF-a, IL-6 and MCP-1 secretion levels in response to inhibition of $NF_KB$ activation by WFA.

Transcriptional changes in response to NFκB inactivation results in blockade of EMT

Whole transcriptome sequencing on the representative CAFs, CAR24 and CAR26 evaluated transcriptional differences in gene expression in response to a single 100nM dose of WFA. RNA-Seq was utilized for transcriptional profiling on total RNA extracted from both CAR24 and CAR26 NAFs treated with 100nM WFA or DMSO as the control. In total, 3825 genes were differentially expressed between the WFA treated CAFs and the untreated controls (AdjP<0.05, $log_2FC\pm0.6$). A total of 156 genes (Table 7) in the NAFs showed a $log_2(FC)$ of 3.5 increase or reduction compared with the control, as shown in the Volcano plot (FIG. 11A). Of these, 106 genes had a biological significance of $log_2(FC)$ of ±3.5, as shown in the Volcano plot (FIG. 11E, full DE genes list, see Table 8). Gene sets were evaluated using the MSigDB tool (software.broadinstitute.org/gsea/msigdb/annotate.jsp) to determine which were most associated with the differentially expressed genes. Separating the differentially expressed genes into 2 groups; those that were upregulated (n=1832) and those that were downregulated (n=1993),, the top 10 Hallmark gene sets for each (FIG. 11B/FIG. 11G and FIG. 11C/FIG. 11H, respectively, full enrichment results, see Table 9 and Table 10) were identified. The upregulated genes were enriched for MTOR signaling, a pathway known to be active in NET biology and hypoxia pathways, a stress response typical of the TME. The downregulated genes were predominantly enriched for proliferation-related gene sets, mostly cell cycle-related and notably EMT (FIG. 11C/FIG. 11H). NFkB-related signaling was enriched in both groups, indicated as the blue bar with black border on both plots.

Specifically, the 10 hallmark gene sets include a NET specific marker set: CGA, a cell surface speithelial specific markers set: CD34, PECAM1, MUC16, KRT5, KRT6A, KRT6B, and KRT17, a stimulants of malignant cell proliferation set: EGFR, FGF-2, HGF, and CXCL12, an epithelial-mesenchymal transition set: CDH1, CDH2, MMP1, MMP2, ITGA1, ITGA2, ITGA3 ITGA5, ITGA7, ITGA11, TGFB1, and TGFBI, a metastatic transition set: YAP1, HAS2, LOX, S100A4, GSTP1, and CD81, a mesenchymal-like set: THY1, NT5E, ENG, and CD44; a matrix-remodeling set: FAP, a hypoxia and angiogenesis set: VEGFA, VEGFC, HIF1A, and CAV1, a tumor-associated stromal cells and myofibroblasts set: PDGFRA, PDGFRB, NRG1, TNC, POSTN, and ACTA2, and a stromal-specific set: P4HA1, P4HB, and VIM.

Unsurprisingly, NFkB signaling was identified in both groups as being one of the most statistically significant enriched data sets, indicated as white shaded bar on both plots. Next, the MSigDB Hallmark set of genes regulated by NF-kB in response to TNF in CAR24 and CAR26 NAFs data [HALLMARK_TNFA_SIGNALING_VIA_NFKB - M5890] was explored. Genes comprising the EMT signature were selected and plotted as a heatmap (FIG. 11I/FIG. 11D), evaluating transcriptional changes pre- and post-treatment with Withaferin. In FIG. 11D, the heatmap representing supervised hierarchical clustering shows clear distinction between the treated and untreated NAFs. The saturation of either color (scale from green to red) reflects the magnitude of the difference on gene expression level. As noted above, VEGF-A and IL-6, were downregulated post-treatment with 100nM WFA, consistent with the secretion profiling and qRT-PCR results (FIG. 7A and FIG. 7C). Many other genes in the EMT signature are known to characterize tumor-associated stromal fibroblasts (FIG. 11E), including NT5E, CXCL12, POSTN, PDGFRB, LOX, ACTA2, FGF2, ITGA2, VEGFC, CHD2 and TNC. These were also downregulated in response to WFA treatment, consistent with a role of NFkB pathway activation in inducing EMT in the CAFs.

Table 7: 156 Genes in the NAFs analyzed by RNA-Seq

| in treated NAF cell lines, CAR24 and CAR26 | |
|---|---|
| up | down |
| RASD1 | HIST1H2AJ |
| HSPA6 | ANK3 |
| ZCCHC12 | PTX3 |
| CDKN1C | HTR2B |
| TNFSF9 | CDK1 |
| DHRS2 | HIST1H2AL |
| ATP1B2 | ESCO2 |
| GADD45G | OSR1 |
| MAFB | TRIP13 |
| AMIGO3 | NDC80 |
| RFPL4A | CCDC81 |
| ULBP1 | TOP2A |
| FAM222A | HIST1H4I |
| FOS | PLK1 |
| KCNC3 | KIF2C |
| HSPA1A | DEPTOR |
| MT1G | HIST1H3B |
| TRIM36 | ASPM |
| HSPA1B | HJURP |
| PEG10 | BDNF |
| BAIAP2 | SPC24 |
| NKX3-1 | UHRF1 |
| DUSP5 | GBP1 |
| MIR22HG | ERCC6L |
| PCDH19 | TYMS |
| HSPA2 | HIST1H2AI |
| SERPINB9 | UBE2C |
| EGR3 | FAM65B |
| MAFA | LDB2 |
| IL10RA | CCDC8 |
| CCDC64 | GDF5 |
| CHRNA7 | HIST1H3C |
| HMOX1 | SERTAD4 |
| RELT | RRM2 |
| KRT16 | LRRN3 |
| SLCO4A1 | SPC25 |
| BCL2L11 | HIST1H1B |
| CEBPA | VCAM1 |
| MT1X | MN1 |
| MKNK2 | HAS2 |
| NPTX2 | KRT19 |
| DNAJA4 | TXNIP |
| ARC | CKAP2L |
| ZFP36 | SDPR |
| RASL11A | DKK1 |
| SLCO5A1 | IQGAP3 |
| SAT1 | TNFRSF11B |
| CCL7 | BUB1B |
| ERN1 | EDN1 |
| FAM46C | DLGAP5 |
| | PBK |
| | HIST1H4L |
| | IL6 |
| | KIT |
| | FOXS1 |
| | HIST1H2BM |

Table 8: 106 differentially expressed genes associated with WFA treatment on CAR24 and CAR26, where biological and statistical significance thresholds were $log_2$FC+/-3.5 and AdjP<0.05, respectivel

| GeneName | baseMean | log2FoldChange | lfcSE | stat | pvalue | padj |
|---|---|---|---|---|---|---|
| RASD1 | 793.05 | 7.22 | 0.42 | 17.29 | 5.27E-67 | 1.32E-63 |
| HSPA6 | 259.61 | 6.33 | 0.49 | 13.01 | 1.11E-38 | 3.98E-36 |
| ZCCHC12 | 129.82 | 6.23 | 0.59 | 10.55 | 5.28E-26 | 6.23E-24 |
| CDKN1C | 169.20 | 5.62 | 0.52 | 10.87 | 1.64E-27 | 2.22E-25 |
| TNFSF9 | 227.36 | 5.53 | 0.45 | 12.38 | 3.29E-35 | 8.76E-33 |
| DHRS2 | 374.03 | 5.46 | 0.37 | 14.89 | 3.63E-50 | 2.84E-47 |
| ATP1B2 | 173.64 | 5.29 | 0.51 | 10.28 | 8.25E-25 | 9.30E-23 |
| GADD45G | 177.25 | 5.04 | 0.44 | 11.34 | 8.35E-30 | 1.36E-27 |
| MAFB | 240.34 | 4.98 | 0.41 | 12.05 | 2.00E-33 | 4.54E-31 |
| AMIGO3 | 511.73 | 4.83 | 0.36 | 13.27 | 3.54E-40 | 1.38E-37 |
| RFPL4A | 42.58 | 4.82 | 0.68 | 7.11 | 1.13E-12 | 3.55E-11 |
| ULBP1 | 567.91 | 4.75 | 0.30 | 15.62 | 5.68E-55 | 5.92E-52 |
| FAM222A | 61.45 | 4.72 | 0.60 | 7.82 | 5.44E-15 | 2.25E-13 |
| FOS | 864.90 | 4.70 | 0.63 | 7.45 | 9.61E-14 | 3.47E-12 |
| KCNC3 | 257.49 | 4.70 | 0.37 | 12.74 | 3.70E-37 | 1.13E-34 |
| HSPA1A | 6824.18 | 4.69 | 0.20 | 23.33 | 2.09E-120 | 2.61E-116 |
| MT1G | 188.10 | 4.68 | 0.41 | 11.38 | 5.00E-30 | 8.46E-28 |
| TRIM36 | 171.74 | 4.66 | 0.44 | 10.65 | 1.69E-26 | 2.09E-24 |
| HSPA1B | 5176.06 | 4.46 | 0.20 | 21.92 | 1.84E-106 | 1.15E-102 |
| PEG10 | 3009.86 | 4.33 | 0.24 | 18.13 | 1.89E-73 | 7.87E-70 |
| BAIAP2 | 1887.22 | 4.27 | 0.25 | 17.40 | 7.80E-68 | 2.44E-64 |
| NKX3-1 | 79.24 | 4.23 | 0.56 | 7.61 | 2.73E-14 | 1.06E-12 |
| DUSP5 | 211.96 | 4.18 | 0.37 | 11.18 | 5.11E-29 | 7.69E-27 |
| MIR22HG | 147.48 | 4.14 | 0.42 | 9.85 | 7.06E-23 | 6.69E-21 |
| PCDH19 | 235.31 | 4.06 | 0.38 | 10.74 | 6.93E-27 | 9.02E-25 |
| HSPA2 | 1320.83 | 4.04 | 0.23 | 17.21 | 2.40E-66 | 5.01E-63 |
| SERPINB9 | 266.47 | 4.04 | 0.35 | 11.55 | 7.52E-31 | 1.40E-28 |
| EGR3 | 52.46 | 4.02 | 0.61 | 6.54 | 5.98E-11 | 1.46E-09 |
| MAFA | 29.70 | 3.99 | 0.69 | 5.81 | 6.39E-09 | 1.15E-07 |
| IL10RA | 33.44 | 3.97 | 0.69 | 5.76 | 8.36E-09 | 1.46E-07 |
| CCDC64 | 34.28 | 3.94 | 0.67 | 5.92 | 3.13E-09 | 5.89E-08 |
| CHRNA7 | 68.25 | 3.92 | 0.61 | 6.46 | 1.02E-10 | 2.40E-09 |
| HMOX1 | 11263.77 | 3.89 | 0.27 | 14.54 | 6.70E-48 | 3.81E-45 |
| RELT | 546.81 | 3.87 | 0.31 | 12.61 | 1.89E-36 | 5.62E-34 |
| KRT16 | 306.08 | 3.86 | 0.33 | 11.74 | 7.71E-32 | 1.61E-29 |
| SLCO4A1 | 35.12 | 3.82 | 0.68 | 5.62 | 1.92E-08 | 3.15E-07 |
| BCL2L11 | 52.67 | 3.76 | 0.58 | 6.53 | 6.46E-11 | 1.57E-09 |
| CEBPA | 25.05 | 3.72 | 0.70 | 5.32 | 1.06E-07 | 1.52E-06 |
| MT1X | 978.35 | 3.70 | 0.24 | 15.44 | 8.18E-54 | 7.31E-51 |
| MKNK2 | 4895.05 | 3.68 | 0.25 | 14.89 | 4.01E-50 | 2.95E-47 |
| NPTX2 | 116.27 | 3.67 | 0.48 | 7.57 | 3.69E-14 | 1.40E-12 |
| DNAJA4 | 540.32 | 3.66 | 0.27 | 13.44 | 3.70E-41 | 1.54E-38 |
| ARC | 790.76 | 3.65 | 0.74 | 4.90 | 9.48E-07 | 1.10E-05 |
| ZFP36 | 570.78 | 3.64 | 0.28 | 12.87 | 6.71E-38 | 2.15E-35 |
| RASL11A | 181.26 | 3.63 | 0.38 | 9.53 | 1.54E-21 | 1.21E-19 |
| SLCO5A1 | 50.80 | 3.60 | 0.58 | 6.21 | 5.44E-10 | 1.16E-08 |

| | | | | | | |
|---|---|---|---|---|---|---|
| SAT1 | 2959.81 | 3.59 | 0.24 | 14.87 | 4.94E-50 | 3.43E-47 |
| CCL7 | 34.61 | 3.59 | 0.66 | 5.42 | 5.85E-08 | 8.93E-07 |
| ERN1 | 962.63 | 3.59 | 0.25 | 14.13 | 2.53E-45 | 1.32E-42 |
| FAM46C | 93.55 | 3.51 | 0.49 | 7.21 | 5.41E-13 | 1.81E-11 |
| HIST1H2AJ | 111.12 | -3.51 | 0.51 | -6.83 | 8.56E-12 | 2.38E-10 |
| ANK3 | 1148.48 | -3.54 | 0.24 | -14.74 | 3.63E-49 | 2.39E-46 |
| PTX3 | 3458.54 | -3.54 | 0.22 | -16.44 | 1.06E-60 | 1.33E-57 |
| HTR2B | 60.86 | -3.54 | 0.55 | -6.41 | 1.43E-10 | 3.31E-09 |
| CDK1 | 174.77 | -3.56 | 0.39 | -9.13 | 6.81E-20 | 4.55E-18 |
| HIST1H2AL | 233.76 | -3.56 | 0.37 | -9.71 | 2.77E-22 | 2.41E-20 |
| ESCO2 | 56.54 | -3.58 | 0.56 | -6.41 | 1.41E-10 | 3.26E-09 |
| OSR1 | 210.19 | -3.65 | 0.36 | -10.23 | 1.51E-24 | 1.67E-22 |
| TRIP13 | 139.22 | -3.66 | 0.41 | -8.91 | 5.22E-19 | 3.30E-17 |
| NDC80 | 177.17 | -3.67 | 0.40 | -9.15 | 5.70E-20 | 3.92E-18 |
| CCDC81 | 34.71 | -3.67 | 0.64 | -5.79 | 1.21E-08 | 2.06E-07 |
| TOP2A | 1882.19 | -3.68 | 0.22 | -16.85 | 1.03E-63 | 1.81E-60 |
| HIST1H4I | 38.85 | -3.70 | 0.63 | -5.88 | 4.06E-09 | 7.55E-08 |
| PLK1 | 132.78 | -3.72 | 0.43 | -8.74 | 2.26E-18 | 1.33E-16 |
| KIF2C | 175.86 | -3.78 | 0.39 | -9.71 | 2.62E-22 | 2.29E-20 |
| DEPTOR | 434.80 | -3.80 | 0.30 | -12.57 | 3.20E-36 | 8.90E-34 |
| HIST1H3B | 162.23 | -3.80 | 0.48 | -8.00 | 1.23E-15 | 5.44E-14 |
| ASPM | 797.42 | -3.82 | 0.27 | -14.39 | 6.28E-47 | 3.42E-44 |
| HJURP | 241.03 | -3.82 | 0.35 | -10.84 | 2.18E-27 | 2.93E-25 |
| BDNF | 259.34 | -3.85 | 0.40 | -9.54 | 1.37E-21 | 1.10E-19 |
| SPC24 | 38.65 | -3.87 | 0.66 | -5.83 | 5.43E-09 | 9.93E-08 |
| UHRF1 | 134.59 | -3.90 | 0.42 | -9.20 | 3.73E-20 | 2.62E-18 |
| GBP1 | 489.41 | -3.91 | 0.28 | -13.86 | 1.05E-43 | 5.04E-41 |
| ERCC6L | 44.77 | -3.92 | 0.61 | -6.39 | 1.64E-10 | 3.73E-09 |
| TYMS | 201.34 | -3.94 | 0.37 | -10.70 | 1.02E-26 | 1.30E-24 |
| HIST1H2AI | 139.10 | -3.97 | 0.43 | -9.12 | 7.53E-20 | 5.01E-18 |
| UBE2C | 120.29 | -3.97 | 0.44 | -8.97 | 2.86E-19 | 1.85E-17 |
| FAM65B | 33.29 | -3.97 | 0.67 | -5.97 | 2.43E-09 | 4.65E-08 |
| LDB2 | 140.63 | -3.99 | 0.44 | -9.15 | 5.85E-20 | 4.00E-18 |
| CCDC8 | 76.84 | -4.00 | 0.60 | -6.69 | 2.27E-11 | 5.90E-10 |
| GDF5 | 66.01 | -4.03 | 0.59 | -6.81 | 9.94E-12 | 2.72E-10 |
| HIST1H3C | 177.53 | -4.04 | 0.41 | -9.84 | 7.74E-23 | 7.28E-21 |
| SERTAD4 | 37.99 | -4.07 | 0.66 | -6.13 | 9.00E-10 | 1.84E-08 |
| RRM2 | 259.38 | -4.16 | 0.40 | -10.48 | 1.07E-25 | 1.25E-23 |
| LRRN3 | 57.32 | -4.16 | 0.58 | -7.20 | 5.82E-13 | 1.95E-11 |
| SPC25 | 32.61 | -4.20 | 0.68 | -6.17 | 6.91E-10 | 1.44E-08 |
| HIST1H1B | 234.71 | -4.26 | 0.38 | -11.19 | 4.44E-29 | 6.86E-27 |
| VCAM1 | 70.84 | -4.26 | 0.61 | -6.94 | 3.90E-12 | 1.14E-10 |
| MN1 | 188.20 | -4.28 | 0.41 | -10.38 | 3.02E-25 | 3.47E-23 |
| HAS2 | 513.58 | -4.36 | 0.32 | -13.82 | 1.89E-43 | 8.75E-41 |
| KRT19 | 428.64 | -4.41 | 0.34 | -12.91 | 3.85E-38 | 1.27E-35 |
| TXNIP | 767.74 | -4.46 | 0.26 | -16.84 | 1.16E-63 | 1.81E-60 |
| CKAP2L | 131.09 | -4.46 | 0.48 | -9.27 | 1.79E-20 | 1.30E-18 |
| SDPR | 251.14 | -4.49 | 0.40 | -11.30 | 1.28E-29 | 2.03E-27 |
| DKK1 | 603.89 | -4.55 | 0.29 | -15.59 | 8.49E-55 | 8.17E-52 |
| IQGAP3 | 211.54 | -4.60 | 0.40 | -11.53 | 9.24E-31 | 1.70E-28 |

| | | | | | | |
|---|---|---|---|---|---|---|
| TNFRSF11B | 556.64 | -4.63 | 0.32 | -14.66 | 1.19E-48 | 7.12E-46 |
| BUB1B | 294.31 | -4.63 | 0.36 | -12.93 | 3.19E-38 | 1.08E-35 |
| EDN1 | 85.41 | -4.64 | 0.55 | -8.36 | 6.10E-17 | 3.04E-15 |
| DLGAP5 | 240.66 | -4.70 | 0.38 | -12.35 | 4.70E-35 | 1.23E-32 |
| PBK | 94.58 | -4.71 | 0.53 | -8.90 | 5.50E-19 | 3.44E-17 |
| HIST1H4L | 88.93 | -4.72 | 0.53 | -8.82 | 1.13E-18 | 6.86E-17 |
| IL6 | 221.07 | -4.89 | 0.41 | -12.03 | 2.41E-33 | 5.38E-31 |
| KIT | 256.47 | -4.98 | 0.42 | -11.73 | 8.65E-32 | 1.77E-29 |
| FOXS1 | 195.49 | -5.16 | 0.48 | -10.77 | 4.61E-27 | 6.07E-25 |
| HIST1H2BM | 186.74 | -5.19 | 0.46 | -11.36 | 6.62E-30 | 1.09E-27 |

Table 9: Hallmark enrichment gent set analysis associated with upregulated genes in the WFA-treated CAFs using MSigDB tool

| Gene Set Name | # Genes in Gene Set (K) | Description | # Genes in Overlap (k) | k/K | p-value | FDR q-value |
|---|---|---|---|---|---|---|
| HALLMARK_TNFA_SIGNALING_VIA_NFKB | 200 | Genes regulated by NF-kB in response to TNF [GeneID=7124]. | 58 | 0.29 | 5.13E-35 | 2.56E-33 |
| HALLMARK_P53_PATHWAY | 200 | Genes involved in p53 pathways and networks. | 57 | 0.285 | 5.53E-34 | 1.38E-32 |
| HALLMARK_UV_RESPONSE_UP | 158 | Genes up-regulated in response to ultraviolet (UV) radiation. | 43 | 0.2722 | 4.37E-25 | 7.29E-24 |
| HALLMARK_MTORC1_SIGNALING | 200 | Genes up-regulated through activation of mTORC1 complex. | 47 | 0.235 | 2.83E-24 | 3.54E-23 |
| HALLMARK_HEME_METABOLISM | 200 | Genes involved in metabolism of heme (a cofactor consisting of iron and porphyrin) and erythroblast differentiation. | 40 | 0.2 | 3.40E-18 | 3.40E-17 |
| HALLMARK_UNFOLDED_PROTEIN_RESPONSE | 113 | Genes up-regulated during unfolded protein response, a cellular stress response related to the endoplasmic reticulum. | 28 | 0.2478 | 1.10E-15 | 9.18E-15 |
| HALLMARK_APOPTOSIS | 161 | Genes mediating programmed cell death (apoptosis) by activation of caspases. | 29 | 0.1801 | 2.19E-12 | 1.56E-11 |
| HALLMARK_HYPOXIA | 200 | Genes up-regulated in response to low oxygen levels (hypoxia). | 32 | 0.16 | 4.54E-12 | 2.84E-11 |
| HALLMARK_ANDROGEN_RESPONSE | 101 | Genes defining response to androgens. | 22 | 0.2178 | 1.93E-11 | 1.10E-10 |
| HALLMARK_ESTROGEN_RESPONSE_LATE | 200 | Genes defining late response to estrogen. | 31 | 0.155 | 2.36E-11 | 1.18E-10 |
| HALLMARK_IL2_STAT5_SIGNALING | 200 | Genes up-regulated by STAT5 in response to IL2 stimulation. | 30 | 0.15 | 1.09E-10 | 4.94E-10 |

| | | | | | | |
|---|---|---|---|---|---|---|
| HALLMARK_PI3K_AKT_MTOR_SIGNALING | 105 | Genes up-regulated by activation of the PI3K/AKT/mTOR pathway. | 21 | 0.2 | 3.07E-10 | 1.28E-09 |
| HALLMARK_REACTIVE_OXIGEN_SPECIES_PATHWAY | 49 | Genes up-regulated by reactive oxigen species (ROS). | 14 | 0.2857 | 2.00E-09 | 7.68E-09 |
| HALLMARK_ESTROGEN_RESPONSE_EARLY | 200 | Genes defining early response to estrogen. | 27 | 0.135 | 9.48E-09 | 2.96E-08 |
| HALLMARK_KRAS_SIGNALING_UP | 200 | Genes up-regulated by KRAS activation. | 27 | 0.135 | 9.48E-09 | 2.96E-08 |
| HALLMARK_XENOBIOTIC_METABOLISM | 200 | Genes encoding proteins involved in processing of drugs and other xenobiotics. | 27 | 0.135 | 9.48E-09 | 2.96E-08 |
| HALLMARK_DNA_REPAIR | 150 | Genes involved in DNA repair. | 23 | 0.1533 | 1.02E-08 | 3.01E-08 |
| HALLMARK_COMPLEMENT | 200 | Genes encoding components of the complement system, which is part of the innate immune system. | 26 | 0.13 | 3.88E-08 | 1.02E-07 |
| HALLMARK_MYOGENESIS | 200 | Genes involved in development of skeletal muscle (myogenesis). | 26 | 0.13 | 3.88E-08 | 1.02E-07 |
| HALLMARK_CHOLESTEROL_HOMEOSTASIS | 74 | Genes involved in cholesterol homeostasis. | 15 | 0.2027 | 8.56E-08 | 2.14E-07 |
| HALLMARK_ADIPOGENESIS | 200 | Genes up-regulated during adipocyte differentiation (adipogenesis). | 25 | 0.125 | 1.52E-07 | 3.45E-07 |
| HALLMARK_MITOTIC_SPINDLE | 200 | Genes important for mitotic spindle assembly. | 25 | 0.125 | 1.52E-07 | 3.45E-07 |
| HALLMARK_INTERFERON_GAMMA_RESPONSE | 200 | Genes up-regulated in response to IFNG [GeneID=3458]. | 23 | 0.115 | 2.03E-06 | 4.42E-06 |
| HALLMARK_INFLAMMATORY_RESPONSE | 200 | Genes defining inflammatory response. | 22 | 0.11 | 6.95E-06 | 1.45E-05 |
| HALLMARK_FATTY_ACID_METABOLISM | 158 | Genes encoding proteins involved in metabolism of fatty acids. | 19 | 0.1203 | 8.01E-06 | 1.60E-05 |

| | | | | | | |
|---|---|---|---|---|---|---|
| HALLMARK_PEROXISOME | 104 | Genes encoding components of peroxisome. | 13 | 0.125 | 1.40E-04 | 2.67E-04 |
| HALLMARK_WNT_BETA_CATENIN_SIGNALING | 42 | Genes up-regulated by activation of WNT signaling through accumulation of beta catenin CTNNB1 [GeneID=1499]. | 8 | 0.1905 | 1.44E-04 | 2.67E-04 |
| HALLMARK_TGF_BETA_SIGNALING | 54 | Genes up-regulated in response to TGFB1 [GeneID=7040]. | 9 | 0.1667 | 1.65E-04 | 2.94E-04 |
| HALLMARK_SPERMATOGENESIS | 135 | Genes up-regulated during production of male gametes (sperm), as in spermatogenesis. | 15 | 0.1111 | 1.71E-04 | 2.95E-04 |
| HALLMARK_G2M_CHECKPOINT | 200 | Genes involved in the G2/M checkpoint, as in progression through the cell division cycle. | 19 | 0.095 | 2.05E-04 | 3.42E-04 |
| HALLMARK_PROTEIN_SECRETION | 96 | Genes involved in protein secretion pathway. | 12 | 0.125 | 2.50E-04 | 4.03E-04 |
| HALLMARK_UV_RESPONSE_DN | 144 | Genes down-regulated in response to ultraviolet (UV) radiation. | 15 | 0.1042 | 3.48E-04 | 5.43E-04 |
| HALLMARK_IL6_JAK_STAT3_SIGNALING | 87 | Genes up-regulated by IL6 [GeneID=3569] via STAT3 [GeneID=6774], e.g., during acute phase response. | 11 | 0.1264 | 4.05E-04 | 6.13E-04 |
| HALLMARK_BILE_ACID_METABOLISM | 112 | Genes involve in metabolism of bile acids and salts. | 12 | 0.1071 | 1.02E-03 | 1.51E-03 |
| HALLMARK_APICAL_JUNCTION | 200 | Genes encoding components of apical junction complex. | 16 | 0.08 | 3.72E-03 | 5.31E-03 |
| HALLMARK_NOTCH_SIGNALING | 32 | Genes up-regulated by activation of Notch signaling. | 5 | 0.1562 | 6.35E-03 | 8.82E-03 |
| HALLMARK_GLYCOLYSIS | 200 | Genes encoding proteins involved in glycolysis and gluconeogenesis. | 15 | 0.075 | 8.67E-03 | 1.17E-02 |
| HALLMARK_ANGIOGENESIS | 36 | Genes up-regulated during formation of blood vessels (angiogenesis). | 5 | 0.1389 | 1.05E-02 | 1.38E-02 |

| | | | | | | |
|---|---|---|---|---|---|---|
| HALLMARK_MYC_TARGETS_V1 | 200 | A subgroup of genes regulated by MYC - version 1 (v1). | 14 | 0.07 | 1.90E-02 | 2.37E-02 |
| HALLMARK_OXIDATIVE_PHOSPHORYLATION | 200 | Genes encoding proteins involved in oxidative phosphorylation. | 14 | 0.07 | 1.90E-02 | 2.37E-02 |
| HALLMARK_ALLOGRAFT_REJECTION | 200 | Genes up-regulated during transplant rejection. | 13 | 0.065 | 3.89E-02 | 4.74E-02 |

Table 10: Hallmark enrichment gent set analysis associated with downregulated genes in the WFA-treated CAFs using MSigDB tool

| Gene Set Name | # Genes in Gene Set (K) | Description | # Genes in Overlap (k) | k/K | p-value | FDR q-value |
|---|---|---|---|---|---|---|
| HALLMARK_E2F_TARGETS | 200 | Genes encoding cell cycle related targets of E2F transcription factors. | 97 | 0.485 | 1.36E-78 | 6.78E-77 |
| HALLMARK_G2M_CHECKPOINT | 200 | Genes involved in the G2/M checkpoint, as in progression through the cell division cycle. | 85 | 0.425 | 6.20E-69 | 1.55E-61 |
| HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION | 200 | Genes defining epithelial-mesenchymal transition, as in wound healing, fibrosis and metastasis. | 68 | 0.34 | 5.26E-48 | 8.76E-42 |
| HALLMARK_MYC_TARGETS_V1 | 200 | A subgroup of genes regulated by MYC - version 1 (v1). | 63 | 0.315 | 1.13E-37 | 1.41E-36 |
| HALLMARK_MITOTIC_SPINDLE | 200 | Genes important for mitotic spindle assembly. | 61 | 0.305 | 1.30E-35 | 1.30E-34 |
| HALLMARK_UV_RESPONSE_DN | 144 | Genes down-regulated in response to ultraviolet (UV) radiation. | 46 | 0.3194 | 3.51E-28 | 2.93E-27 |
| HALLMARK_MYC_TARGETS_V2 | 58 | A subgroup of genes regulated by MYC - version 2 (v2). | 28 | 0.4828 | 1.53E-23 | 1.09E-22 |
| HALLMARK_INTERFERON_GAMMA_RESPONSE | 200 | Genes up-regulated in response to IFNG [GeneID=3458]. | 44 | 0.22 | 7.50E-20 | 4.69E-19 |
| HALLMARK_ESTROGEN_RESPONSE_EARLY | 200 | Genes defining early response to estrogen. | 42 | 0.21 | 3.19E-18 | 1.77E-17 |
| HALLMARK_TNFA_SIGNALING_VIA_NFKB | 200 | Genes regulated by NF-kB in response to TNF [GeneID=7124]. | 41 | 0.205 | 1.99E-17 | 9.94E-17 |
| HALLMARK_APICAL_JUNCTION | 200 | Genes encoding components of apical junction complex. | 40 | 0.2 | 1.20E-16 | 5.46E-16 |

| | | | | | | |
|---|---|---|---|---|---|---|
| HALLMARK_INTERFERON_ALPHA_RESPONSE | 97 | Genes up-regulated in response to alpha interferon proteins. | 28 | 0.2887 | 2.01E-16 | 8.38E-16 |
| HALLMARK_MYOGENESIS | 200 | Genes involved in development of skeletal muscle (myogenesis). | 39 | 0.195 | 7.05E-16 | 2.71E-15 |
| HALLMARK_GLYCOLYSIS | 200 | Genes encoding proteins involved in glycolysis and gluconeogenesis. | 38 | 0.19 | 4.00E-15 | 1.43E-14 |
| HALLMARK_ESTROGEN_RESPONSE_LATE | 200 | Genes defining late response to estrogen. | 37 | 0.185 | 2.20E-14 | 7.33E-14 |
| HALLMARK_OXIDATIVE_PHOSPHORYLATION | 200 | Genes encoding proteins involved in oxidative phosphorylation. | 35 | 0.175 | 6.02E-13 | 1.77E-12 |
| HALLMARK_P53_PATHWAY | 200 | Genes involved in p53 pathways and networks. | 35 | 0.175 | 6.02E-13 | 1.77E-12 |
| HALLMARK_DNA_REPAIR | 150 | Genes involved in DNA repair. | 30 | 0.2 | 7.51E-13 | 2.09E-12 |
| HALLMARK_MTORC1_SIGNALING | 200 | Genes up-regulated through activation of mTORC1 complex. | 34 | 0.17 | 2.99E-12 | 7.87E-12 |
| HALLMARK_HYPOXIA | 200 | Genes up-regulated in response to low oxygen levels (hypoxia). | 33 | 0.165 | 1.44E-11 | 3.59E-11 |
| HALLMARK_KRAS_SIGNALING_UP | 200 | Genes up-regulated by KRAS activation. | 32 | 0.16 | 6.65E-11 | 1.58E-10 |
| HALLMARK_UNFOLDED_PROTEIN_RESPONSE | 113 | Genes up-regulated during unfolded protein response, a cellular stress response related to the endoplasmic reticulum. | 22 | 0.1947 | 1.42E-09 | 3.22E-09 |
| HALLMARK_APOPTOSIS | 161 | Genes mediating programmed cell death (apoptosis) by activation of caspases. | 26 | 0.1615 | 3.23E-09 | 7.01E-09 |
| HALLMARK_IL2_STAT5_SIGNALING | 200 | Genes up-regulated by STAT5 in response to IL2 stimulation. | 29 | 0.145 | 5.29E-09 | 1.10E-08 |
| HALLMARK_ADIPOGENESIS | 200 | Genes up-regulated during adipocyte | 28 | 0.14 | 2.10E-08 | 4.21E-08 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | differentiation (adipogenesis). | | | | |
| HALLMARK_ALLOGRAFT_REJECTION | 200 | Genes up-regulated during transplant rejection. | 27 | 0.135 | 8.04E-08 | 1.49E-07 |
| HALLMARK_INFLAMMATORY_RESPONSE | 200 | Genes defining inflammatory response. | 27 | 0.135 | 8.04E-08 | 1.49E-07 |
| HALLMARK_ANGIOGENESIS | 36 | Genes up-regulated during formation of blood vessels (angiogenesis). | 11 | 0.3056 | 1.43E-07 | 2.56E-07 |
| HALLMARK_ANDROGEN_RESPONSE | 101 | Genes defining response to androgens. | 17 | 0.1683 | 8.98E-07 | 1.55E-06 |
| HALLMARK_COAGULATION | 138 | Genes encoding components of blood coagulation system; also up-regulated in platelets. | 20 | 0.1449 | 1.20E-06 | 2.01E-06 |
| HALLMARK_PI3K_AKT_MTOR_SIGNALING | 105 | Genes up-regulated by activation of the PI3K/AKT/mTOR pathway. | 16 | 0.1524 | 7.10E-06 | 1.14E-05 |
| HALLMARK_FATTY_ACID_METABOLISM | 158 | Genes encoding proteins involved in metabolism of fatty acids. | 20 | 0.1266 | 9.92E-06 | 1.55E-05 |
| HALLMARK_COMPLEMENT | 200 | Genes encoding components of the complement system, which is part of the innate immune system. | 22 | 0.11 | 3.43E-05 | 5.20E-05 |
| HALLMARK_WNT_BETA_CATENIN_SIGNALING | 42 | Genes up-regulated by activation of WNT signaling through accumulation of beta catenin CTNNB1 [GeneID=1499]. | 9 | 0.2143 | 4.69E-05 | 6.89E-05 |
| HALLMARK_HEDGEHOG_SIGNALING | 36 | Genes up-regulated by activation of hedgehog signaling. | 8 | 0.2222 | 9.40E-05 | 1.34E-04 |
| HALLMARK_IL6_JAK_STAT3_SIGNALING | 87 | Genes up-regulated by IL6 [GeneID=3569] via STAT3 [GeneID=6774], e.g., during acute phase response. | 12 | 0.1379 | 2.55E-04 | 3.54E-04 |

| | | | | | | |
|---|---|---|---|---|---|---|
| HALLMARK_TGF_BETA_SIGNALING | 54 | Genes up-regulated in response to TGFB1 [GeneID=7040]. | 9 | 0.1667 | 3.57E-04 | 4.83E-04 |
| HALLMARK_PROTEIN_SECRETION | 96 | Genes involved in protein secretion pathway. | 12 | 0.125 | 6.37E-04 | 8.38E-04 |
| HALLMARK_BILE_ACID_METABOLISM | 112 | Genes involve in metabolism of bile acids and salts. | 13 | 0.1161 | 7.88E-04 | 1.01E-03 |
| HALLMARK_PEROXISOME | 104 | Genes encoding components of peroxisome. | 12 | 0.1154 | 1.30E-03 | 1.63E-03 |
| HALLMARK_XENOBIOTIC_METABOLISM | 200 | Genes encoding proteins involved in processing of drugs and other xenobiotics. | 18 | 0.09 | 1.84E-03 | 2.25E-03 |
| HALLMARK_CHOLESTEROL_HOMEOSTASIS | 74 | Genes involved in cholesterol homeostasis. | 9 | 0.1216 | 3.54E-03 | 4.21E-03 |
| HALLMARK_REACTIVE_OXIGEN_SPECIES_PATHWAY | 49 | Genes up-regulated by reactive oxigen species (ROS). | 7 | 0.1429 | 3.95E-03 | 4.60E-03 |
| HALLMARK_UV_RESPONSE_UP | 158 | Genes up-regulated in response to ultraviolet (UV) radiation. | 14 | 0.0886 | 6.42E-03 | 7.29E-03 |
| HALLMARK_HEME_METABOLISM | 200 | Genes involved in metabolism of heme (a cofactor consisting of iron and porphyrin) and erythroblast differentiation. | 16 | 0.08 | 9.76E-03 | 1.06E-02 |
| HALLMARK_NOTCH_SIGNALING | 32 | Genes up-regulated by activation of Notch signaling. | 5 | 0.1562 | 9.77E-03 | 1.06E-02 |
| HALLMARK_APICAL_SURFACE | 44 | Genes encoding proteins over-represented on the apical surface of epithelial cells, e.g., important for cell polarity (apical area). | 5 | 0.1136 | 3.51E-02 | 3.73E-02 |

Differential gene expression analysis

The focus on NAF's was initially influenced by the fact that SINET patient-derived xenografts (PDX) do not grow. During initial histological characterization of the PDX tissue, the NAF cells were observed to be of human and not host origin, which led to full consideration of the importance and role of fibroblasts in neuroendocrine tumor biology. As described herein, short-term NAF cultures were developed to study secretion patterns that differentiated these activated fibroblasts from quiescent normal human fibroblasts. An enhanced secretory signature comprised of induced IL-6, IL-10, VEGF and MCP-1 was identified. HGF, uPA and RANTES were also found to be enhanced in the NAFs. These 3 secreted proteins coupled with positive vimentin expression have been implicated as markers of an activated fibroblast phenotype (Kalluri R., 2016 Nat Rev Cancer, 16:582-98).

In 2011, Hanahan and Weinberg included tumor-promoting inflammation and avoidance of immune destruction in their reassessment of the hallmarks of cancer (Hanahan D, Weinberg RA., 2011 Cell., 144: 646-674). Hanahan and Weinberg described the inadvertent corruption of the innate immune cell inflammatory response being consequential in promoting tumor growth. IL-6, IL-10, and MCP-1 are key components of a CAF-mediated pro-inflammatory signature (Harper J and Sainson RCA, 2014 Semin Cancer Biol, 25:69-77). MCP-1 is a well-characterized chemokine involved in attracting macrophages into the tumor microenvironment driving invasion and metastasis (Roca H et al. 2009 J Biol Chem, 284:34342-54). MCP-1 has also been shown to be involved in the recruitment of macrophages and monocytes to the site of inflammation IL-6, IL-10 VEGF (angiogenesis).

Crosstalk between various cell components within the tumor microenvironment facilitates the development of an activated fibroblastic phenotype. Under these conditions, an NFkB-mediated release of chemokines and cytokines into the stromal environment is initated.

Plasma matched studies and potential

Additionally, mechanistic elucidation of the corresponding signaling pathways involved in neuroendocrine tumor microenvironments and functional characterization of these mechanisms could lead to a more targeted approach to current patient treatment options. Current trends indicate that a more thorough investigation of the tumor microenvironment results in more sophisticated combinatorial drug approaches. As described herein, it is determined whether combining tumor targeting drugs in conjunction with repressing cytokine signaling in the stromal

environment provides the narrative for a new paradigm in the treatment of advanced small intestinal neuroendocrine tumors.

The identification and validation of biomarkers for neuroendocrine tumors enhances the use of currently available therapies and provides a path to identify therapeutic targets.

Targeting NFkB suppresses secretion and gene expression signatures in cancer-associated fibroblasts derived from metastatic small intestine neuroendocrine tumors

The focus on cancer-associated fibroblasts was based on observations that SINET patient-derived xenografts do not grow in vivo, coupled with the lack of tumor cells and the prevalence of fibroblast growth in vitro. CAFs have been established as playing a prominent role in cancer progression and metastasis, as well in tumor-stroma crosstalk (Huang et al., World J Gastroenterol, 20:17804-17818 (2014)). This study demonstrates for the first time that CAFs from SINETS are capable of being independently cultured and have pro-oncogenic properties as measured by both secretion profiling and transcriptional expression. Studies further demonstrate that these properties are inhibited with Withaferin A, a potent inhibitor of the NFkB pathway.

In other malignancies, CAFs have been shown to contribute to tumor proliferation, invasion, and metastasis via secretion of growth factors, cytokines, chemokines and degradation of extracellular matrix (ECM) proteins (Yamamura et al., Cancer Res, 75:813-823 (2015), Ben-Baruch A, Cancer Met. Rev, 25:357-371 (2006). Observations that IL-6, MCP-1 and VEGF were upregulated in the CAFs relative to normal human fibroblast, and moreover that these proteins were also identified in the plasma of patients compared to normal controls, is consistent with the hypothesis that CAFs may play a key role in promoting the growth of SINETS. MCP-1 is involved in attracting macrophages into the tumor microenvironment driving invasion and metastasis (Roca et al., J Biol Chem, 284:34342-54 (2009)) and also has been shown to recruiting the macrophages and monocytes to sites of inflammation (Roca et al., J Biol Chem, 284:34342-54 (2009)). Observation that CAFs in SINETS also secrete VEGF is consistent with an established role CAFs in other settings in modulating angiogenesis to expand the tumor mass and facilitate metastasis (Vong S and Kalluri R, Genes Cancer 2:1139-1145 (2011)). VEGF is secreted by many cancers and is associated with poor outcome, such as, gastric and esophageal cancers (Salvatore et al., Oncotarget, 8:9608-9616 (2017); Chen et al., Tumour Biol, 35:2513-2519 (2014); Kozłowski et al., Adv Med Sci, 58:227-234 (2013)). VEGF correlated with increased angiogenesis and decreased progression-free survival among patients with low-grade

NETs (Zhang et al., Cancer, 190:1478-1486 (2007)). VEGF secretion by CAFs has, in turn, been shown to be induced by IL-6 (Adachi et al., Int J Cancer, 119:1303-11(2006); Zhu et al., World J Gastroenterol, 17:2315-2325 (2011), Nagasaki et al., Br J Cancer, 110:469–478 (2014)). IL-6 is a multifunctional cytokine integral to inflammation and immune regulatory responses that is known to promote migration and EMT in the TME (Osuala et al., BMC Cancer, 15:584 (2015); Giannoni et al., Cancer Res, 70:6945-6956 (2010)). High IL-6 expression in many cancers, such as bladder cancer, cervical cancer and NSCLC has been associated with a worse outcome (Chen et al., PLoS ONE, 8:e61901 (2013); Song et al., Inter Med J Exp Clin Res, 22:4475-4481 (2016); Silva et al., PLoS One, 12:e0181125 (2017)).

Observations are further suggestive that CAFs in SINETs are driven by activation of the NFkB pathway. This observation is consistent with studies in other malignancies that CAFs are activated by tumor and immune-cell derived factors in the early stages of tumorigenesis to express pro-inflammatory genes such as IL-6, in an NFκB-dependent manner (Subramanian et al., Proc Natl Acad Sci USA, 102:15545-50 (2005)), Kozłowski et al., Adv Med Sci, 58:227-234 (2013); Bhowmick et al., Nature, 432:332-337 (2004)). Along with IL-6, MCP-1 and VEGF, RANTES, IL-2, IFNg, IL-2, IL-10, IL-12 and IL-13 were found to have higher secretion levels in the CAFs relative to normal human fibroblasts. These secreted proteins form part of the cytokine signaling that is associated with the NFkB-dependent inflammatory response in the TME (Katanov et al., Stem Cell & Ther, 6:87 (2015); Schauer et al., Neoplasia, 15:409-420 (2013)). CAFs were treated with Withaferin A, an agent that prevents NFkB activation by inhibiting activation of IKKβ (Kaileh et al., J Biol Chem, 282:4253-64 (2007)). WFA also had a potent effect on cell viability at low concentrations (FIG. 4B) and suppressed mRNA expression of IL-6, MCP-1 and VEGF.

A role for NFkB signaling in SINET CAFs is further supported by the Enrichment analysis, which revealed that WFA treatment suppressed transcription of genes associated with MTOR signaling, a pathway known to be activated in NET, and EMT, a process related to NFkB signaling and a more invasive tumor microenvironment. EMT is co-opted by tumor cells to facilitate an invasive-metastatic cascade that relies on the plasticity of the stromal fibroblasts in the microenvironment (Wu et al., Oncotarget, 8:20741-20750 (2017)).

As part of this study, patient-derived cancer-associated fibroblast cultures were developed and characterized. CAFs harbor a signature that is different from normal human

fibroblasts and are shown to express genes that characterize an aggressive tumor-associated stromal fibroblast phenotype. CAFs exhibit a pro-malignant secretion profile that is distinct from normal human fibroblasts, where IL-6, MCP-1 and VEGF are upregulated. SINET associated CAFs are further characterized by a gene expression profile that reflects an aggressive tumor-associated stromal fibroblast phenotype associated with EMT. Treatment with Withaferin A, resulted in downregulation of secreted IL-6, MCP-1 and VEGF, and suppressed transcription of genes associated with EMT. Further studies evaluating the therapeutic potential of targeting the tumor microenvironment in SINETS are warranted.

Example 3: Development of an Ex-Vivo Model of Neuroendocrine Tumors and Exploration of Therapeutics

Prior to the invention described herein, a lack of cell lines and animal models of neuroendocrine tumors has been a challenge in the development of new therapeutic agents for this disease. As described herein, in the past two years, a program has been initiated to develop such models. Initial attempts have focused on the development of short-term cell lines and xenografts. Over 50 fresh tumor specimens have been collected from consented patients undergoing surgical resection of neuroendocrine tumors at Brigham and Women's Hospital. In an unexpected observation, it was identified that carcinoid cells grow in close association with fibroblasts (termed CAFs), and that carcinoid associated fibroblasts from the original tumor specimen are preserved and grow in association with carcinoid tumors in implanted xenografts (FIG. 8). These findings suggest that tumor-stromal interactions may play a critical role in driving neuroendocrine tumor growth.

The Center for Molecular Pathology at Dana-Farber Cancer Institute has recently developed an ex-vivo tissue slice model appropriate for evaluating the biological effects of therapeutics on specific malignancies (Vairo et al, 2010 PNAS, 107: 8352-8356, incorporated herein by reference). The ability to rapidly section and culture tissue from specimens immediately after surgical excision allows for the preservation of morphological tissue integrity, including general epithelial architecture, which can be retained up to 72-96 hours. This technique has been widely used in a range of tumor types at Dana-Farber since the initially reported by the Dana-Farber group in 2010. Representative organotypic human prostate tissue culture H&E and immunohistochemical (IHC) images are shown in FIG. 9. The preservation of tissue antigenicity

is demonstrated through AMACR IHC. Mitotic activity is preserved through 72 hours in this experiment.

As described herein, this technique is extended to neuroendocrine tumors. Approximately one neuroendocrine tumor surgical specimens are collected per month, through an IRB approved protocol. As described in detail below, ex-vivo organotypic neuroendocrine tumor tissue slice cultures are be established. At baseline (T0), cultures are processed for histology and IHC staining, while additional PCa tissue slice cultures are treated with therapeutic agents of interest.

Study of neuroendocrine tumor tissue slices

First, the feasibility of using NET slices for evaluation of therapeutics is assessed and conditions are optimized for these experiments.

As an initial proof of principle, the effect of Rapamycin (100 nM, demonstrated effective in NIH/3T3 cells and known to be active in neuroendocrine tumors) is evaluated on tissue slices. For each of the treatments, two neuroendocrine tumor slices are used. Each culture is subjected to drug treatment and corresponding vehicle control on alternate slices, harvested 48 or 72 hours and fixed in FFPE. For each time point, pathology review is conducted using H&E slides of FFPE material to assess the morphological integrity of tissue samples and to evaluate neuroendocrine tumor morphology. Incorporation of BrDU is evaluated to assess cell proliferation following exposure to rapamycin. Expression of downstream targets of mTOR is evaluated using IHC. Targets include normal and phosphorylated 4EBP1 and s6K1.

Use of tissue slices to evaluate potential therapeutic effects of agents

Following optimization of the protocol above, tissue slices are utilized to explore the potential antitumor and antisecretory effects of therapeutic agents, in collaboration with Ipsen. Potential antitumor effects are evaluated using BrDU cell proliferation assays, together with measurement of drug-specific targets in treated and untreated tumor tissue. Potential antisecretory effects are evaluated by measuring levels of the validated secretory markers chromogranin A (CGA) and neuron specific enolase (NSE) in the supernatant of the tissue slices prior to and after treatment.

Example 4: Patient-derived *ex vivo* tissue slice cultures as models to characterize treatment response in GI malignancies

Prior to the invention described herein, there was a great need for models that replicate the tumor environment and are predictive of in vivo efficacy in patients with neuroendocrine tumors. The use of tumor tissue slices that incorporate not only tumor cells, but also 3D tissue architecture and the tumor microenvironment, provides a new opportunity to identify drugs and treatment targets (Grosso et al., 2013 Cell Tissue Res., 352(3):671-84, incorporated herein by reference). As described herein, this technology is developed for neuroendocrine tumors, where prior to the invention described herein, a lack of cell lines and animal models has been a particularly acute problem in identifying new therapeutic agents. mTOR inhibitors are known to be active in neuroendocrine tumors, and as an initial proof of principle, the response to treatment in neuroendocrine tumors treated with the mTOR inhibitor rapamycin was evaluated.

Tissue Collection

To date 12 tumor specimens have been collected to conduct ex vivo tissue slice culture [xTSC] studies to investigate their response to MTOR inhibition. Patients are identified pre-operatively in clinic, and consented to the tissue banking protocol. Clinical information including demographics, diagnosis, staging, treatment and survival data is also collected.

xTSC

This is an organotypic culture method where fresh tissues are rapidly sectioned and cultured immediately after surgical excision. Morphological tissue integrity, including general epithelial architecture is preserved. As schematically represented in FIG. 10, briefly, tissues are mounted and cut into 300 μM thick slices on a vibrotome instrument. Single slices are placed in individual wells in a 6-well plate format and supplemented with with modified eagle's / F12 (50:50) medium supplemented with 10% FBS and antibiotics/antimycotics and Glutamax. Slices are treated with DMSO, as control or 100 nM rapamycin for 24hr. The xTSC supernatant is collected. Tissue is preserved in OCT and/or FFPE.

The histologic response to mTOR inhibitors in neuroendocrine tumors has been evaluated using a tissue slice model. Differentially expressed secreted proteins have been identified before and after mTOR inhibition. IL-6, IL-8, VEGF, MCP-1, Osteopontin, Angiopoietin-2, sTIE-2, uPA, PAI-1, Follistatin, PECAM-1 are strongly secreted from SINET tissue slices in culture for 24hr. The secretion profile from xTSC is not dissimilar from the NAF observations. Post-

treatment with a single 100 nM dose of rapamycin, significant reduction in secretion of Osteopontin, IL-6, VEGF, MCP-1, IL-10, MIP-1a, MIP-1b, IP-10, IL-8 and uPA is observed. Library preparation and RNA-Seq on RNA isolated from sections derived from the tissue slice model have been completed to identify differentially expressed genes and pathways enriched for these differentially expressed genes in neuroendocrine tumors prior to and following MTOR inhibition.

These methods are utilized to evaluate drugs targeting the neuroendocrine tumors and neuroendocrine associated fibroblasts (NAFs).

Example 5: Protocol for NAF models and short-term culture generation

A protocol for NAF models and short-term culture generation is provided below.

1. A portion of each tissue sample is frozen in OCT and evaluated to confirm histological features and rule out the presence of significant hemorrhagic / necrotic areas, not suitable for experimentation.
2. Additional portions of each tissue are snap frozen and banked, and also processed for FFPE.
3. Remaining tissue is cut in to small pieces.
4. Add medium and collagenase II at a final concentration 2mg/ml.
5. Overnight incubation in 5% $CO_2$ at 37°C.
6. Mechanical disaggregation with 18-gauge needle and syringe.
7. Cells are filtered through a cell strainer, pore size 70 microns.
8. Cells are spun in centrifuge at 1000rpm for 5min.
9. The supernatant is removed and cells are washed with 10ml 1x PBS.
10. The cells are spun a second time, same centrifuge settings.
11. If the pellet is bloody the cells are hemolyzed using ACK lysis buffer.
12. Then, the cells are plated into 5-15cm tissue culture plates (polymer, not glass) with modified eagle's / F12 (50:50) medium supplemented with 10% FBS and antibiotics/antimycotics and Glutamax. This particular culture is referred to as the "cells" population.
13. Remaining tissue pieces from the strainer are added to the dish, where collagenization took place.

14. This population is refered to as "cuts and pieces", which is supplemented with the same media as described above.
15. After 3 – 10 days of culture, when cells have attached and start to grow (varies from tumor to tumor), a fraction of the cells are cryopreserved as PO and the rest is passaged and re-plated.
16. P0 is the first short-term culture population that most resembles the cell composition of the tumor and includes both tumor and stromal cell populations.
17. Subsequently, cells are passage 2-4 times and cryopreserved each passage.
18. For each cryopreserved passage, the composition of tumor to stroma cells present is annotated.
19. Pure NAF cultures are generated for all fresh tumors received. For the majority of tumors, a mixed tumor/NAF culture is also generated.
20. Cells are seeded at 50k per well in 6-well plate format for 24hr. Then, the media is replenished, and 24hr later cell culture supernatants are collected.
21. Cell culture supernatants are centrifuged at 1200rpm for 10min (at RT) to remove debris and aliquoted in 65ul vials and stored at -80°C.
22. The remaining cells are then washed in PBS and scraped.
23. Cells are lyzed to collect total proteins extracted using the ELB lysis buffer with a proteinase inhibitor.

Example 6: uPA secretion in a subset of short term NAF cultures

Additionally, in a subset of short term NAF cultures, uPA secretion was extremely high. Preliminary analysis was performed on an example NAF cell line, CAR15. Specifically, an invasion migration assay was performed in vitro in culture over a 5 day time period. CAR15 was treated with an anti-uPA inhibitor, which did not result in cell killing; however, migration of cells was impeded in the short-term cultures as compared with the untreated CAR15 culture. uPA secretion levels were not shut down, since no cell death occured. However, uPA is important for migration of NAFs. This study was repeated with an alternate compound also known to impair uPA activity, an anti-Survivin inhibitor. The same impeded migration was observed in the treated short term NAF culture. The results are presented in FIG. 12, which shows images of untreated CAR15 NAFs in vitro in 6-well plates at time 0hr, 72hr and Day 5

(top panel), of CAR15 NAF's treated with 100uM uPA inhibitor or 100nM Survivin at 72hrs and Day 5 (middle panel). Inset: uPA concentration [pg/ml] measured in cell culture supernatant from CAR15 treated with either uPA or survivin inhibitor. Gene expression knockdown and secretion levels relative to untreated control for CAR15 treated with either 100nM of uPA or survivin inhibitor (bottom panel).

## OTHER EMBODIMENTS

While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

The patent and scientific literature referred to herein establishes the knowledge that is available to those with skill in the art. All United States patents and published or unpublished United States patent applications cited herein are incorporated by reference. All published foreign patents and patent applications cited herein are hereby incorporated by reference. Genbank and NCBI submissions indicated by accession number cited herein are hereby incorporated by reference. All other published references, documents, manuscripts and scientific literature cited herein are hereby incorporated by reference.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

**What is claimed is:**

1. A method of determining whether a small bowel neuroendocrine tumor (SINET) in a subject will metastasize comprising:

obtaining a test sample from a subject having or at risk of developing SINET;

determining the expression level of at least one SINET-associated gene in the test sample;

comparing the expression level of the SINET-associated gene in the test sample with the expression level of the SINET-associated gene in a reference sample; and

determining that the SINET in the subject will metastasize if the expression level of the SINET-associated gene in the test sample is differentially expressed as compared to the level of the SINET-associated gene in the reference sample.

2. The method of claim 1, wherein the test sample is obtained from resected SINET tissue.

3. The method of claim 1, wherein the test sample is obtained from blood or plasma.

4. The method of claim 1, wherein said sample comprises circulating tumor cells.

5. The method of claim 1, wherein the reference sample is obtained from immortalized healthy normal control fibroblastic cell lines or cancerous SINET tissue.

6. The method of claim 1, wherein the reference sample is obtained from healthy normal tissue from the same individual as the test sample or one or more healthy normal tissues from different individuals.

7. The method of claim 1, wherein said sample comprises deoxyribonucleic acid (DNA) or ribonucleic acid (RNA).

8. The method of claim 1, wherein the SINET-associated gene comprises interleukin-2 (IL-2), IL-6, IL-12, IL-13, vascular endothelial growth factor (VEGF), monocyte

chemoattractant protein-1 (MCP-1), urinary plasminogen activator (uPA), hepatocyte growth factor (HGF), RANTES (regulated on activation, normal T cell expressed and secreted, alternatively, chemokine (C-C motif) ligand 5; alternatively CCL5), and Eotaxin; and

determining that the SINET in the subject will metastasize if the expression level of the SINET-associated gene in the test sample is higher than the level of the SINET-associated gene in the reference sample.

9. The method of claim 1, wherein the SINET-associated gene comprises stem cell factor (SCF), soluble epidermal growth factor receptor (sEGFR), granulocyte macrophage colony stimulating factor (GM-CSF), soluble vascular endothelial growth factor receptor 2 (sVEGFR2), and soluble interleukin 6 receptor, alpha (sIL-6RA); and

determining that the SINET in the subject will metastasize if the expression level of the SINET-associated gene in the test sample is lower than the level of the SINET-associated gene in the reference sample.

10. The method of claim 1, wherein the SINET-associated gene comprises a NET-specific gene set where the gene comprises CGA; and

determining that the SINET in the subject will metastasize if the expression level of the SINET-associated gene in the test sample is lower than the level of the SINET-associated gene in the reference sample.

11. The method of claim 1, wherein the SINET-associated gene comprises a cell surface epithelial-specific gene set selected from the group consisting of CD34, PECAM1, MUC16, KRT5, KRT6A, KRT6B, and KRT17; and

determining that the SINET in the subject will metastasize if the expression level of the SINET-associated gene in the test sample is lower than the level of the SINET-associated gene in the reference sample.

12. The method of claim 1, wherein the SINET-associated gene comprises a stimulants of malignant cell proliferation gene set selected from the group consisting of EGFR, FGF-2, HGF, and CXCL12; and

determining that the SINET in the subject will metastasize if the expression level of the SINET-associated gene in the test sample is higher than the level of the SINET-associated gene in the reference sample.

13. The method of claim 1, wherein the SINET-associated gene comprises an epithelial-mesenchymal transition gene set where the gene comprises CDH1; and

determining that the SINET in the subject will metastasize if the expression level of the SINET-associated gene in the test sample is lower than the level of the SINET-associated gene in the reference sample.

14. The method of claim 1, wherein the SINET-associated gene comprises an epithelial-mesenchymal transition gene set selected from the group consisting of CDH2, MMP1, MMP2, ITGA1, ITGA2, ITGA3 ITGA5, ITGA7, ITGA11, TGFB1, and TGFBI; and

determining that the SINET in the subject will metastasize if the expression level of the SINET-associated gene in the test sample is higher than the level of the SINET-associated gene in the reference sample.

15. The method of claim 1, wherein the SINET-associated gene comprises a metastatic transition gene set selected from the group consisting of YAP1, HAS2, LOX, S100A4, GSTP1, and CD81; and

determining that the SINET in the subject will metastasize if the expression level of the SINET-associated gene in the test sample is higher than the level of the SINET-associated gene in the reference sample.

16. The method of claim 1, wherein the SINET-associated gene comprises a mesenchymal-like gene set selected from the group consisting of THY1, NT5E, ENG, and CD44; and

determining that the SINET in the subject will metastasize if the expression level of the SINET-associated gene in the test sample is higher than the level of the SINET-associated gene in the reference sample.

17. The method of claim 1, wherein the SINET-associated gene comprises a matrix-remodeling gene set where the gene comprises FAP; and

determining that the SINET in the subject will metastasize if the expression level of the SINET-associated gene in the test sample is higher than the level of the SINET-associated gene in the reference sample.

18. The method of claim 1, wherein the SINET-associated gene comprises a hypoxia and angiogenesis gene set selected from the group consisting of VEGFA, VEGFC, HIF1A, and CAV1; and

determining that the SINET in the subject will metastasize if the expression level of the SINET-associated gene in the test sample is higher than the level of the SINET-associated gene in the reference sample.

19. The method of claim 1, wherein the SINET-associated gene comprises a tumor-associated stromal cells and myofibroblasts gene set selected from the group consisting of PDGFRA, PDGFRB, NRG1, TNC, POSTN, and ACTA2; and

determining that the SINET in the subject will metastasize if the expression level of the SINET-associated gene in the test sample is higher than the level of the SINET-associated gene in the reference sample.

20. The method of claim 1, wherein the SINET-associated gene comprises a stromal-specific gene set selected from the group consisting of P4HA1, P4HB, and VIM; and

determining that the SINET in the subject will metastasize if the expression level of the SINET-associated gene in the test sample is higher than the level of the SINET-associated gene in the reference sample.

21. The method of claim 1, wherein the expression level of the SINET-associated gene is detected via an Affymetrix Gene Array hybridization, next generation sequencing, ribonucleic acid sequencing (RNA-seq), a real time reverse transcriptase polymerase chain reaction (real time RT-PCR) assay, immunohistochemistry (IHC), immunofluorescence, methylation-specific PCR, or a bead-based multiplex assay.

22. The method of claim 1, wherein said subject is a human.

23. The method of claim 1, further comprising treating the subject with a chemotherapeutic agent, radiation therapy, cryotherapy, hormone therapy, or immunotherapy.

24. The method of claim 23, wherein the chemotherapeutic agent comprises a somatostatin analog, wherein the somatostatin analogue comprises octreotide long-acting repeatable (LAR).

25. The method of claim 24, further comprising administering an inhibitor of the SINET-associated gene with a higher level of expression compared to the level of the SINET-associated gene in the reference sample, thereby treating the SINET.

26. The method of claim 25, wherein the inhibitor comprises a tumor-specific inhibitor selected from the group consisting of Rapamycin, Cabozantinib, and Erlotinib.

27. The method of claim 25, wherein the inhibitor comprises a polypeptide, a small molecule inhibitor, RNA interference (RNAi), an antibody, or any fragment or combination thereof.

28. The method of claim 27, wherein the antibody or antibody fragment is partially humanized, fully humanized, or chimeric.

29. The method of claim 27, wherein the antibody or antibody fragment comprises a nanobody, an Fab, an Fab', an (Fab')2, an Fv, a single-chain variable fragment (ScFv), a diabody, a triabody,a tetrabody, a Bis-scFv, a minibody, an Fab2, an Fab3 fragment, or any combination thereof.

30. The method of claim 27, wherein the small molecule inhibitor comprises an inhibitor of NFκB activity.

31. The method of claim 30, wherein the inhibitor of NFκB activity comprises Withaferin A (WFA).

32. The method of claim 25, wherein the inhibitor comprises Ruxolitinib or Momelotinib.

33. The method of claim 31, wherein WFA is administered at a concentration of 10-1000 nM.

34. The method of claim 33, wherein expression levels of VEGF, IL-6, and MCP-1 are increased following administration of WFA.

35. The method of claim 1, further comprising administering an agonist of the SINET-associated gene with a lower level of expression compared to the level of the SINET-associated gene in the reference sample, thereby treating the SINET.

36. A composition for predicting whether a SINET will metastasize comprising a SINET-associated gene, wherein the SINET-associated gene comprises IL-2, IL-6, IL-12, IL-13, VEGF, MCP-1, uPA, HGF, RANTES, Eotaxin, GM-CSF, sVEGFR2, and sIL-6RA synthesized complementary deoxyribonucleic acid (cDNA).

37. A composition for predicting whether a SINET will metastasize comprising a SINET-associated gene, wherein the SINET-associated gene comprises a neuroendocrine tumor (NET) specific gene, a cell surface eithelial gene, a stimulants of malignant cell proliferation gene, an epithelial-mesenchymal transition gene, a metastatic transition gene, a mesenchymal-like gene, a matrix-remodeling gene, a hypoxia and angiogenesis gene, a tumor-associated stromal cells and myofibroblasts gene, and a stromal-specific gene, wherein the NET-specific gene comprises CGA, the cell surface eithelial gene is selected from the group consisting of CD34, PECAM1, MUC16, KRT5, KRT6A, KRT6B, and KRT17, the stimulants of malignant cell proliferation gene is selected from the group consisting of EGFR, FGF-2, HGF, and CXCL12, the epithelial-mesenchymal gene is selected from the group consisting of CDH1, CDH2, MMP1, MMP2, ITGA1, ITGA2, ITGA3 ITGA5, ITGA7, ITGA11, TGFB1, and TGFBI, the metastatic transition

gene is selected from the group consisting of YAP1, HAS2, LOX, S100A4, GSTP1, and CD81, the mesenchymal-like gene is selected from the group consisting of THY1, NT5E, ENG, and CD44; the matrix-remodeling gene comprising FAP, the hypoxia and angiogenesis gene is selected from the group consisting of VEGFA, VEGFC, HIF1A, and CAV1, the tumor-associated stromal cells and myofibroblasts gene is selected from the group consisting of PDGFRA, PDGFRB, NRG1, TNC, POSTN, and ACTA2, and the stromal-specific gene is selected from the group consisting of P4HA1, P4HB, and VIM.

38. The composition of claim 36, wherein said composition further comprises SCF and sEGFR, GM-CSF, sVEGFR2, and sIL-6RA synthesized cDNA.

39. The composition of claim 36, wherein the SINET-associated gene is immobilized on a solid support.

40. The composition of claim 36, wherein the SINET-associated gene is linked to a detectable label.

41. The composition of claim 40, wherein the detectable label comprises a fluorescent label, a luminescent label, a chemiluminescent label, a radiolabel, a SYBR Green label, or a Cy3-label.

42. A kit comprising a package with a SINET-associated gene, wherein the SINET-associated gene comprises IL-2, IL-6, IL-12, IL-13, VEGF, MCP-1, uPA, HGF, RANTES, Eotaxin, GM-CSF, sVEGFR2, and sIL-6RA and instructions for use thereof in the evaluation of SINET progression and metastasis.

43. A kit comprising a package with a SINET-associated gene, wherein the SINET-associated gene comprises a neuroendocrine tumor (NET) specific gene, a cell surface eithelial gene, a stimulants of malignant cell proliferation gene, an epithelial-mesenchymal transition gene, a metastatic transition gene, a mesenchymal-like gene, a matrix-remodeling gene, a hypoxia and angiogenesis gene, a tumor-associated stromal cells and myofibroblasts gene, and a stromal-specific gene, wherein the NET-specific gene comprises CGA, the cell surface eithelial

gene is selected from the group consisting of CD34, PECAM1, MUC16, KRT5, KRT6A, KRT6B, and KRT17, the stimulants of malignant cell proliferation gene is selected from the group consisting of EGFR, FGF-2, HGF, and CXCL12, the epithelial-mesenchymal gene is selected from the group consisting of CDH1, CDH2, MMP1, MMP2, ITGA1, ITGA2, ITGA3 ITGA5, ITGA7, ITGA11, TGFB1, and TGFBI, the metastatic transition gene is selected from the group consisting of YAP1, HAS2, LOX, S100A4, GSTP1, and CD81, the mesenchymal-like gene is selected from the group consisting of THY1, NT5E, ENG, and CD44; the matrix-remodeling gene comprising FAP, the hypoxia and angiogenesis gene is selected from the group consisting of VEGFA, VEGFC, HIF1A, and CAV1, the tumor-associated stromal cells and myofibroblasts gene is selected from the group consisting of PDGFRA, PDGFRB, NRG1, TNC, POSTN, and ACTA2, and the stromal-specific gene is selected from the group consisting of P4HA1, P4HB, and VIM.

44. An ex vivo method of screening therapeutic agents for a neuroendocrine tumor comprising:

establishing an ex vivo organotypic neuroendocrine tumor tissue slice culture;

administering a candidate compound to the culture; and

determining that the candidate compound is a therapeutic agent for a neuroendocrine tumor if the candidate compound inhibits the neuroendocrine tumor.

45. The ex vivo method of claim 44, wherein proliferation of the neuroendocrine tumor is inhibited.

46. The ex vivo method of claim 45, wherein proliferation is evaluated using a bromodeoxyuridine (BrDU) cell proliferation assay.

47. The ex vivo method of claim 44, further comprising detecting a level of a candidate compound-specific target.

48. The ex vivo method of claim 44, further comprising detecting a level of a secretory protein in supernatant of the tissue slices prior to and following administration of the candidate compound.

49. The ex vivo method of claim 48, wherein the secretory protein comprises chromogranin A (CGA) or neuron specific enolsase (NSE).

50. The ex vivo method of claim 44, wherein said candidate compound comprises a mechanistic target of rapamycin (mTOR) inhibitor comprising Rapamycin.

51. The ex vivo method of claim 44, wherein said candidate compound comprises Cabozantinib, Erlotinib, a histone deacetylase (HDAC) inhibitor, or a cyclin-dependendt kinase (CDK) 4/6 inhibitor.

52. The ex vivo method of claim 49, wherein the Rapamycin is administered at a dose of 100 nM.

53. The ex vivo method of claim 50, wherein administration of Rapamycin results in a reduction of secretion of osteoponin, IL-16, VEGF, MCP-1, IL-10, macrophage inflammatory protein-1a (MIP-1a), MIP-1b, interferon-γ-inducible protein-10 (IP-10), IL-8, and urinary plasminogen activator (uPA) from the culture.

54. A method of generating a neuroendocrine-associated fibroblast culture comprising:

obtaining a tissue sample from a patient;

dissecting the tissue sample into pieces;

enzymatically disaggregating the tissue sample;

mechanically disaggregating the tissue sample;

filtering and centrifuging the cells;

plating the cells on polymer tissue culture plates; and

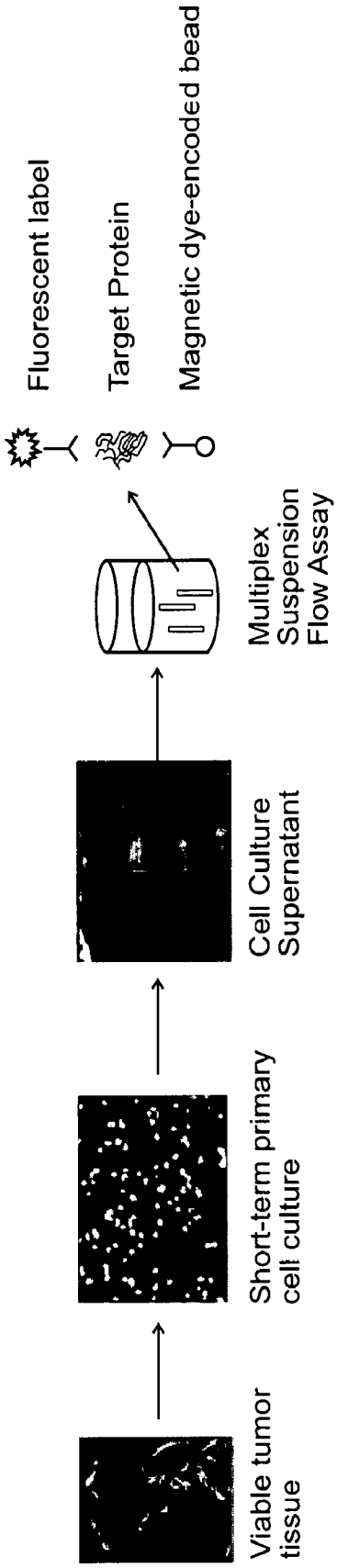
culturing the cells,

thereby generating a neuroendocrine-associated fibroblast culture.

55. The method of claim 54, wherein the tissue sample is enzymatically disaggregated with collagenase II at 2 mg/ml.

56. The method of claim 54, wherein the tissue sample is mechanically disaggregated with an 18-guage needle and syringe.

FIG. 1


Fluorescent label
Target Protein
Magnetic dye-encoded bead
Multiplex Suspension Flow Assay
Cell Culture Supernatant
Short-term primary cell culture
Viable tumor tissue

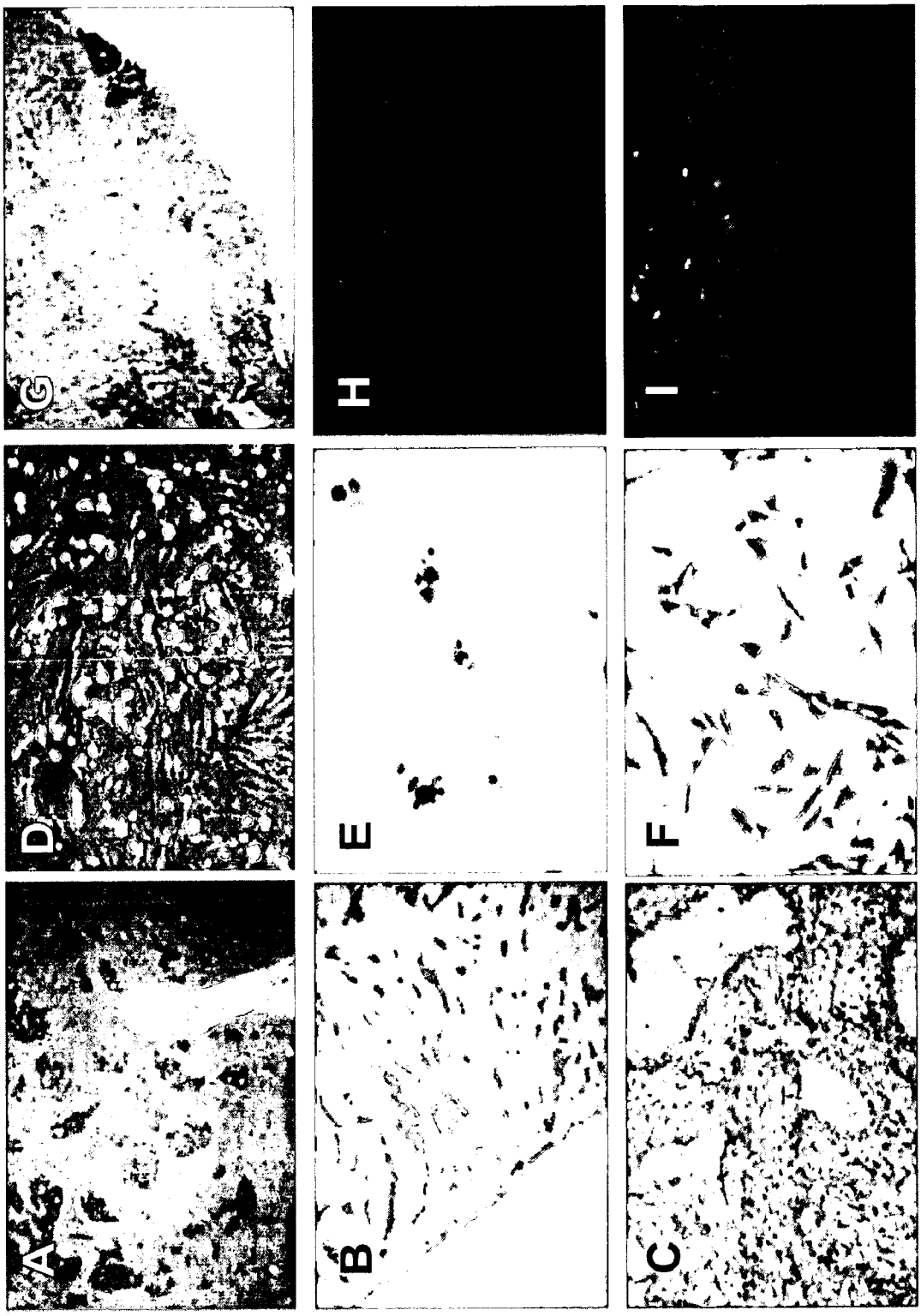
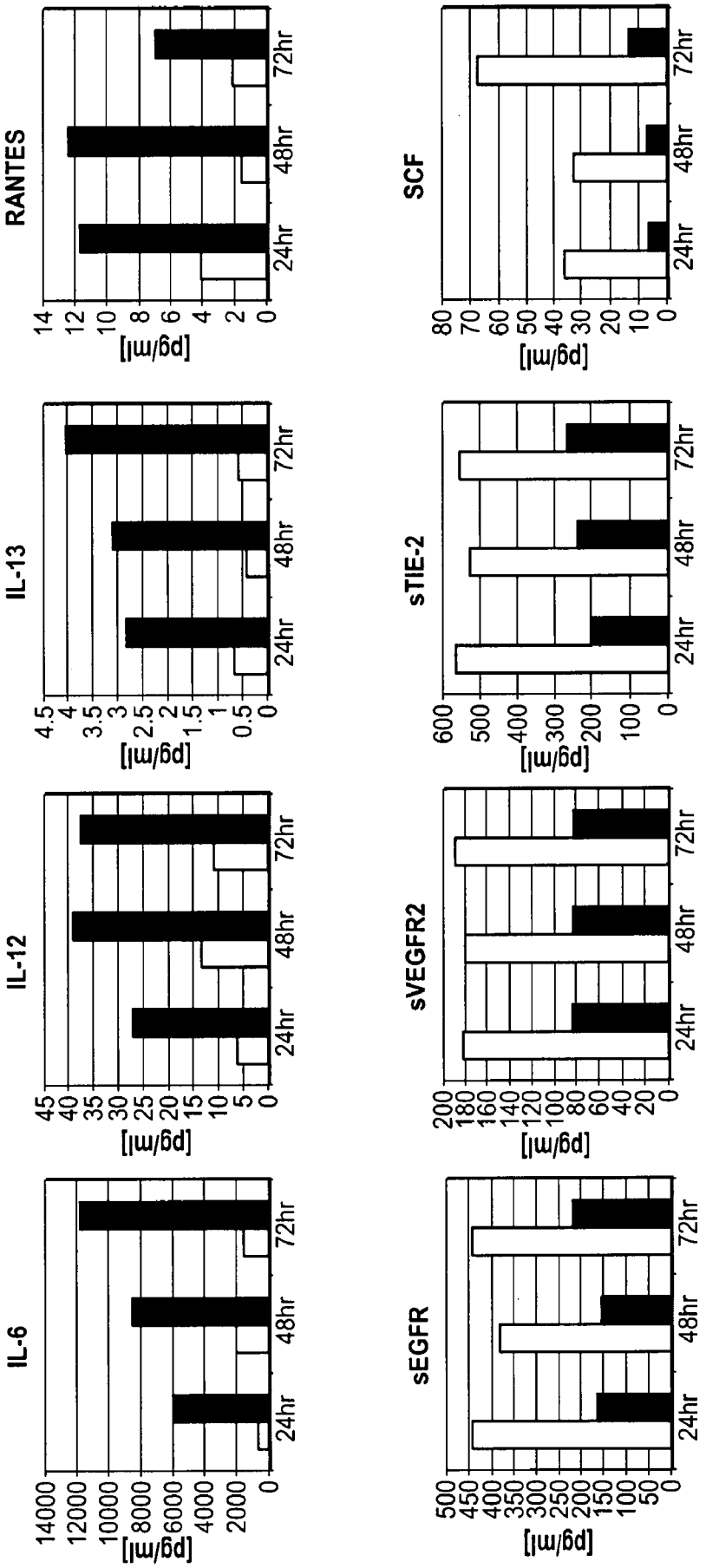



FIG. 2

FIG. 3A


RANTES
[pg/ml]
24hr
48hr
72hr
SCF
IL-13
sTIE-2
IL-12
sVEGFR2
IL-6
sEGFR

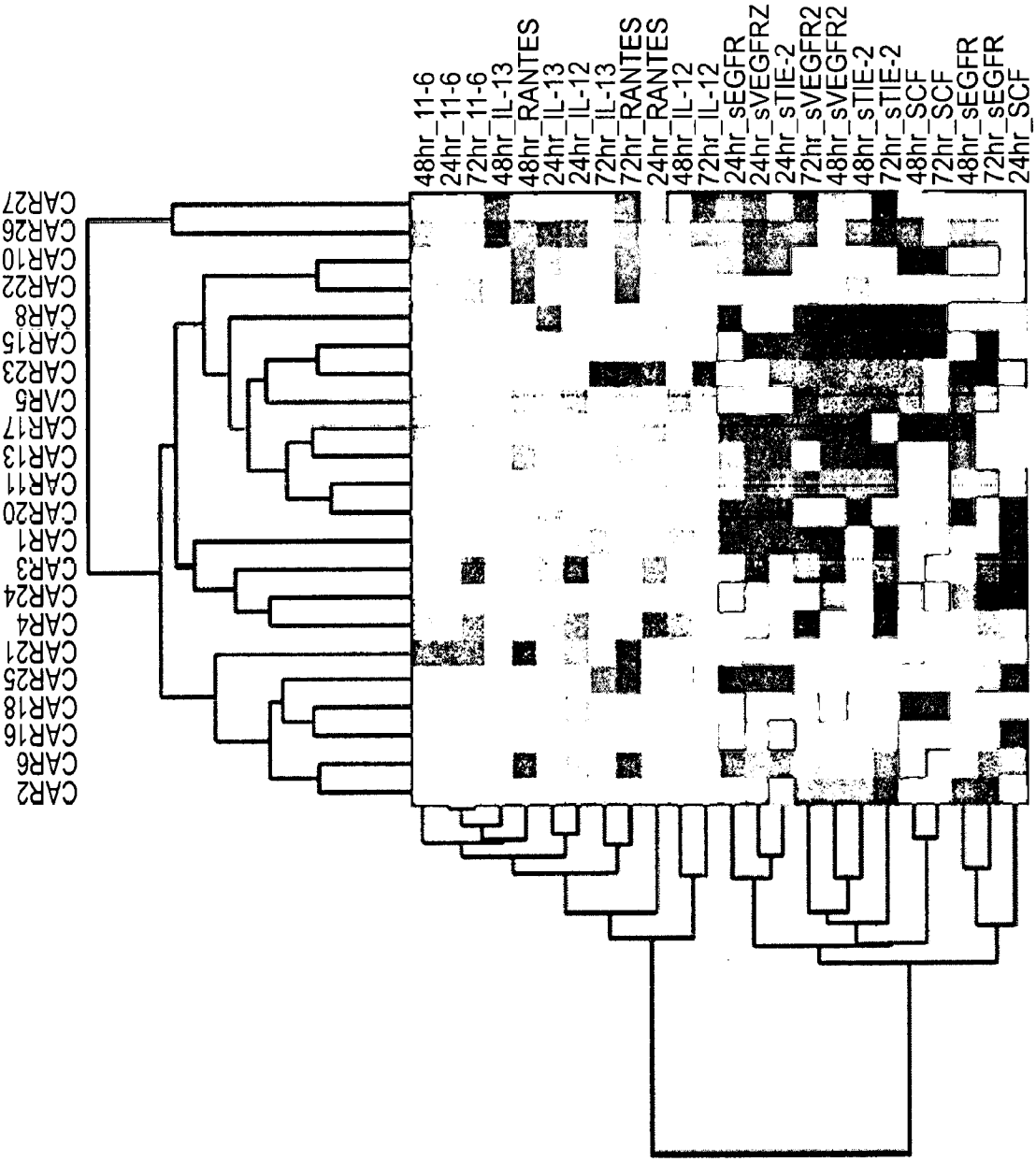

48hr_11-6
24hr_11-6
72hr_11-6
48hr_IL-13
48hr_RANTES
24hr_IL-13
24hr_IL-12
72hr_IL-13
72hr_RANTES
24hr_RANTES
48hr_IL-12
72hr_IL-12
24hr_sEGFR
24hr_sVEGFRZ
24hr_sTIE-2
72hr_sVEGFR2
48hr_sVEGFR2
48hr_sTIE-2
72hr_sTIE-2
48hr_SCF
72hr_SCF
48hr_sEGFR
72hr_sEGFR
24hr_SCF
CAR27
CAR26
CAR10
CAR22
CAR8
CAR15
CAR23
CAR5
CAR17
CAR13
CAR11
CAR20
CAR1
CAR3
CAR24
CAR4
CAR21
CAR25
CAR18
CAR16
CAR6
CAR2

FIG. 3B

FIG. 4A

3 multiplex panels----------→61 targets
5 duplicates across panels---→56 targets
2/5 duplicates undetected-→54 targets
7 < LLOQ----------→47 targets

FIG. 4B

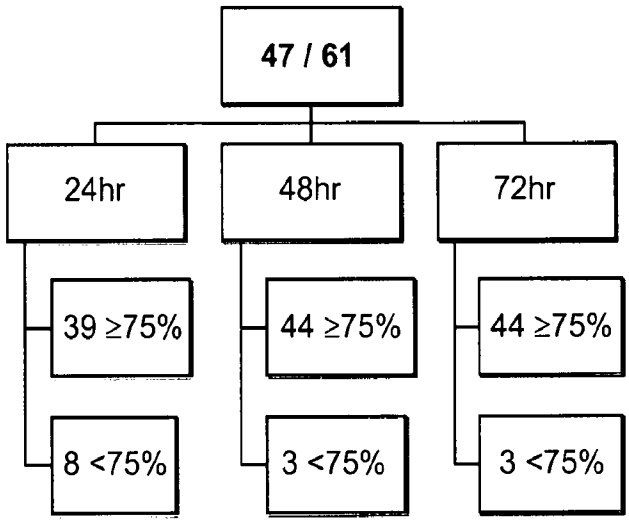


FIG. 4C


low [<100pg/ml]
mod [<100-˙000pg/ml]
high [>1000pg/ml]
24hr time point
12%
31%
57%
48hr time point
20%
27%
53%
72hr time point
24%
25%
51%

FIG. 5A

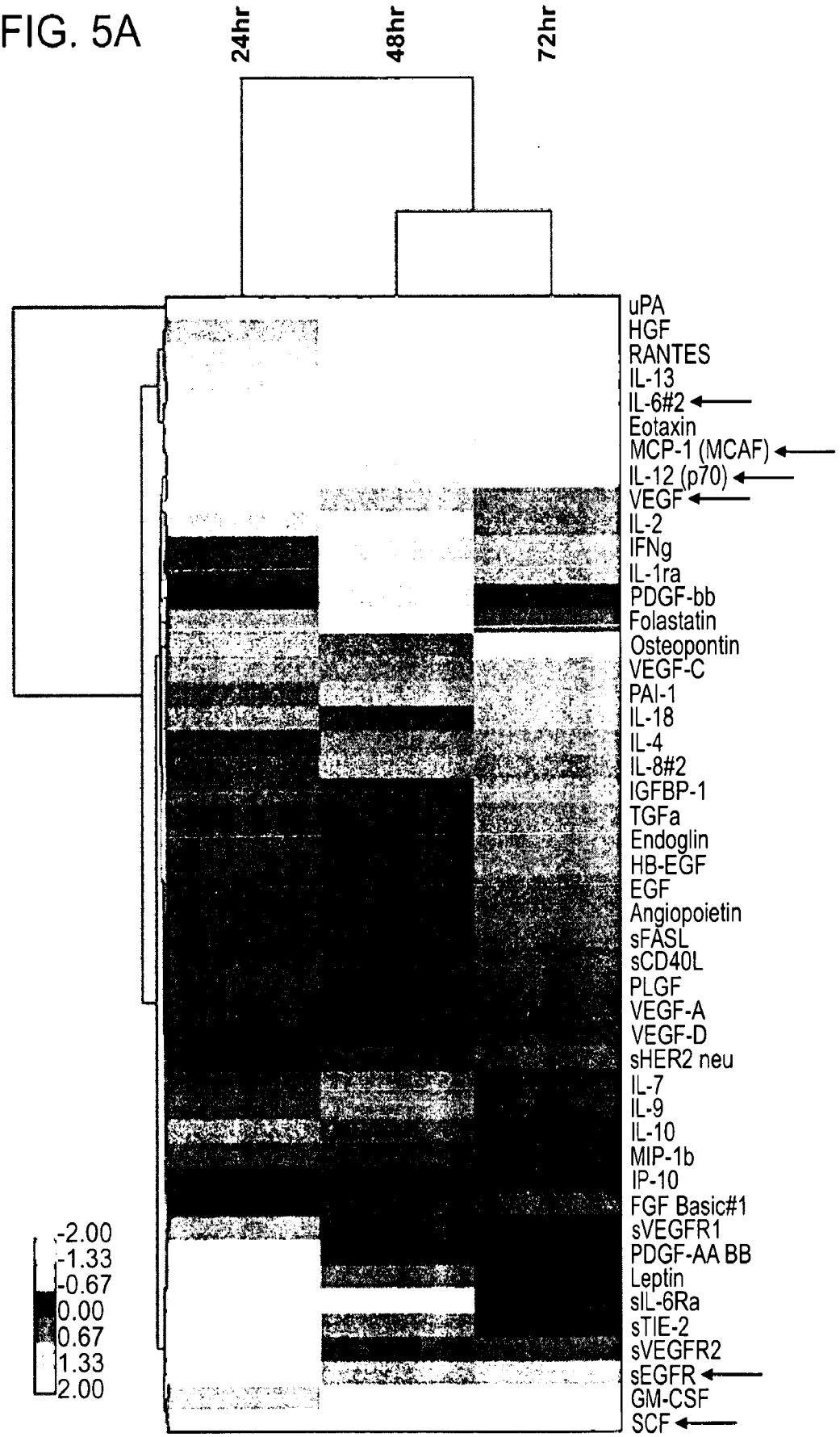

24hr
48hr
72hr
uPA
HGF
RANTES
IL-13
IL-6#2
Eotaxin
MCP-1 (MCAF)
IL-12 (p70)
VEGF
IL-2
IFNg
IL-1ra
PDGF-bb
Folastatin
Osteopontin
VEGF-C
PAI-1
IL-18
IL-4
IL-8#2
IGFBP-1
TGFa
Endoglin
HB-EGF
EGF
Angiopoietin
sFASL
sCD40L
PLGF
VEGF-A
VEGF-D
sHER2 neu
IL-7
IL-9
IL-10
MIP-1b
IP-10
FGF Basic#1
sVEGFR1
PDGF-AA BB
Leptin
sIL-6Ra
sTIE-2
sVEGFR2
sEGFR
GM-CSF
SCF
-2.00
-1.33
-0.67
0.00
0.67
1.33
2.00

FIG. 5B

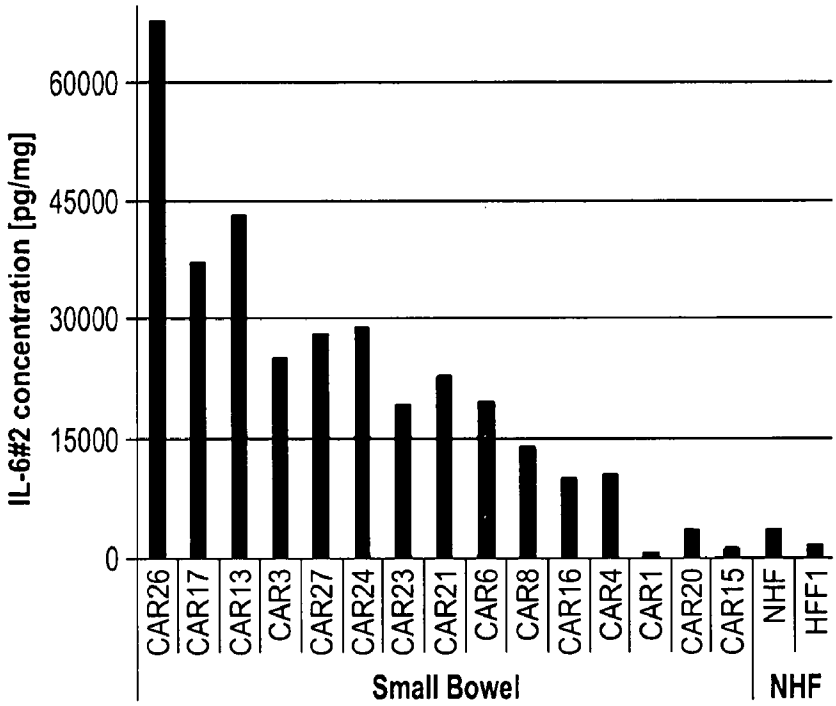

IL-6#2 concentration [pg/mg]
60000
45000
30000
15000
0
CAR26
CAR17
CAR13
CAR3
CAR27
CAR24
CAR23
CAR21
CAR6
CAR8
CAR16
CAR4
CAR1
CAR20
CAR15
NHF
HFF1
Small Bowel
NHF

FIG. 5C

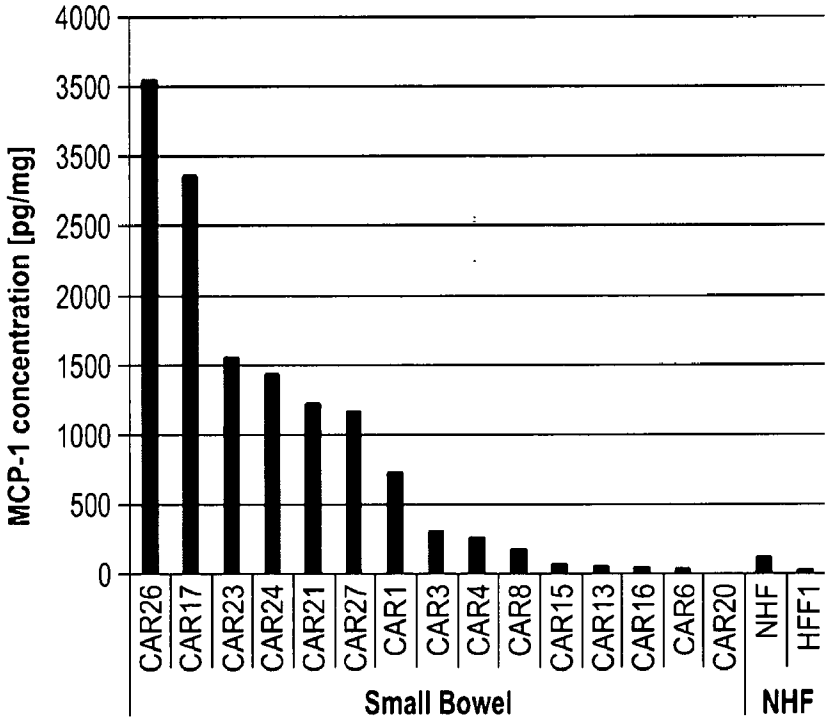

MCP-1 concentration [pg/mg]
4000
3500
3500
2500
2000
1500
1000
500
0
CAR26
CAR17
CAR23
CAR24
CAR21
CAR27
CAR1
CAR3
CAR4
CAR8
CAR15
CAR13
CAR16
CAR6
CAR20
NHF
HFF1
Small Bowel
NHF

FIG. 5D

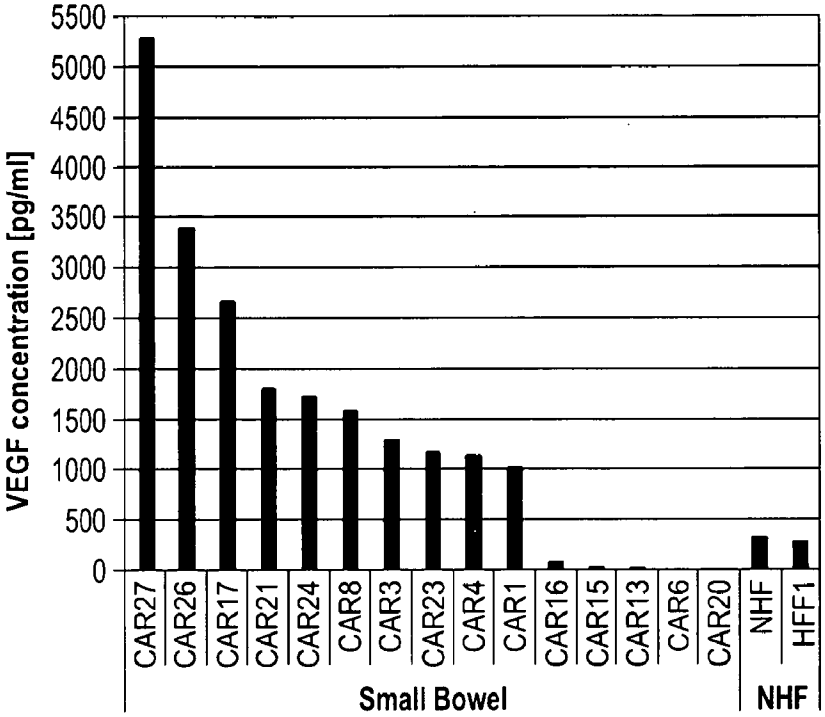

VEGF concentration [pg/ml]
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
CAR27
CAR26
CAR17
CAR21
CAR24
CAR8
CAR3
CAR23
CAR4
CAR1
CAR16
CAR15
CAR13
CAR6
CAR20
NHF
HFF1
Small Bowel
NHF

FIG. 5E

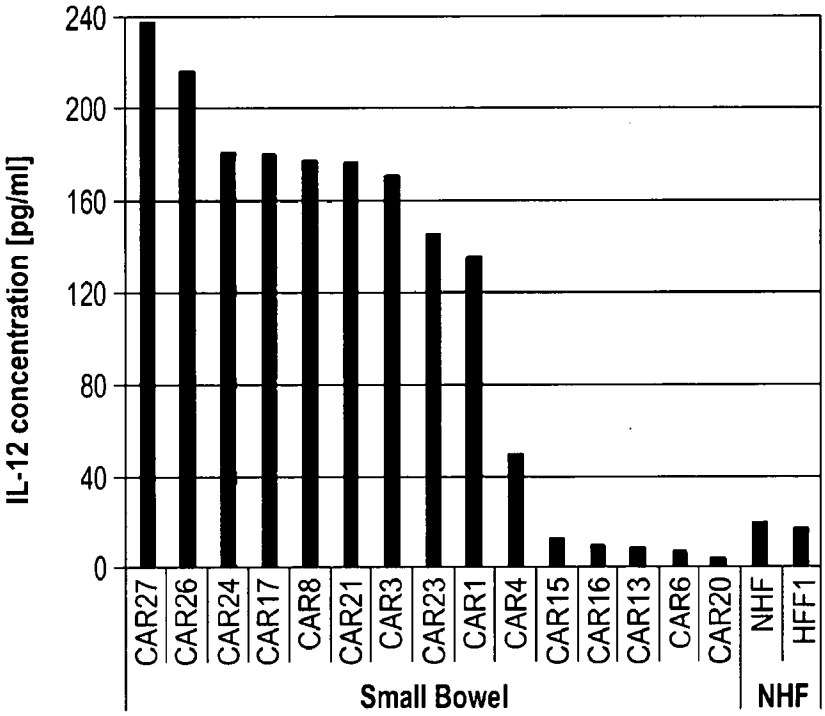

IL-12 concentration [pg/ml]
240
200
160
120
80
40
0
CAR27
CAR26
CAR24
CAR17
CAR8
CAR21
CAR3
CAR23
CAR1
CAR4
CAR15
CAR16
CAR13
CAR6
CAR20
NHF
HFF1
Small Bowel
NHF

FIG. 5F

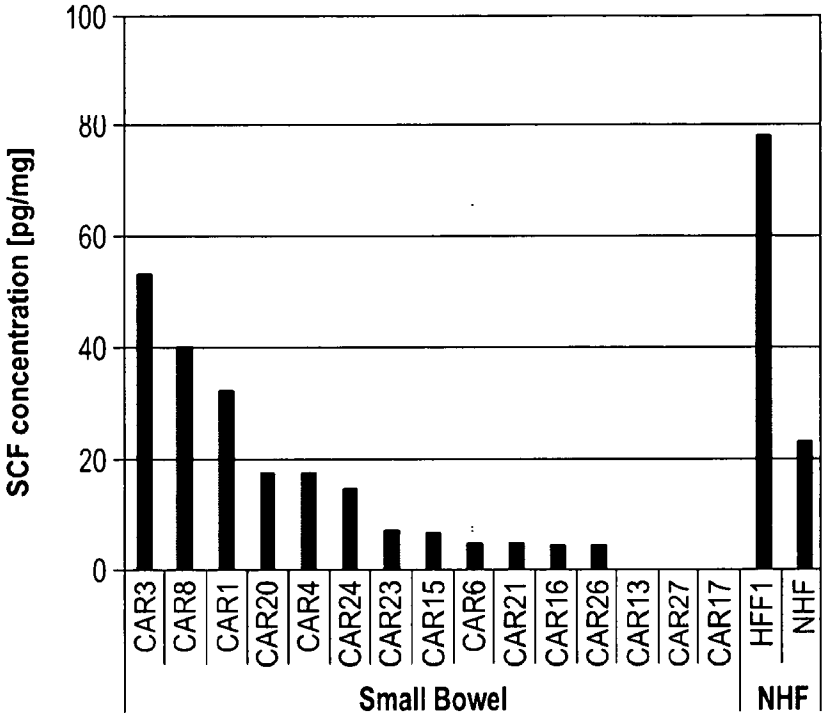

SCF concentration [pg/mg]
100
80
60
40
20
0
CAR3
CAR8
CAR1
CAR20
CAR4
CAR24
CAR23
CAR15
CAR6
CAR21
CAR16
CAR26
CAR13
CAR27
CAR17
HFF1
NHF
Small Bowel
NHF

FIG. 5G

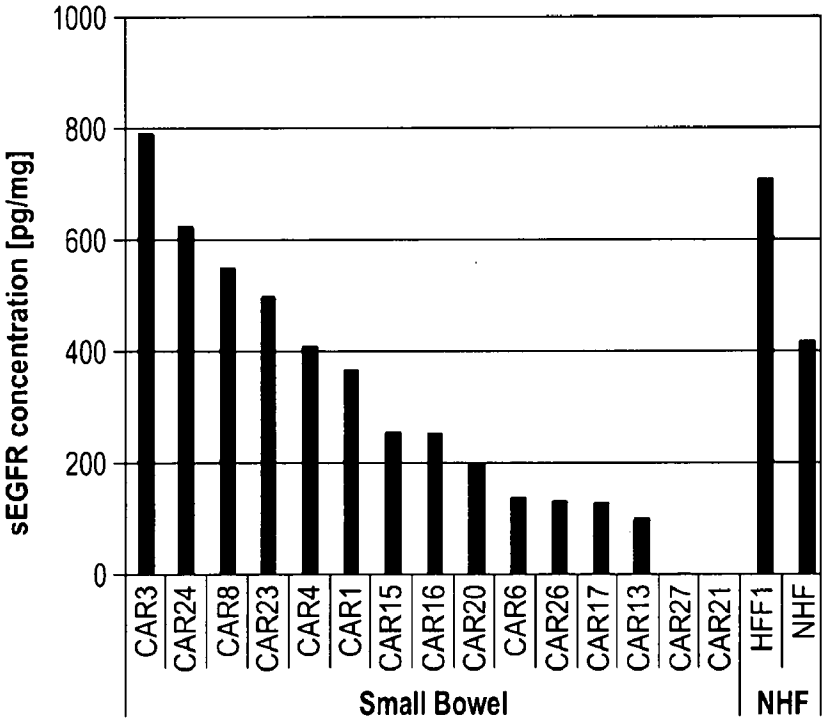

sEGFR concentration [pg/mg]
1000
800
600
400
200
0
CAR3
CAR24
CAR8
CAR23
CAR4
CAR1
CAR15
CAR16
CAR20
CAR6
CAR26
CAR17
CAR13
CAR27
CAR21
HFF1
NHF
Small Bowel
NHF

FIG. 5H

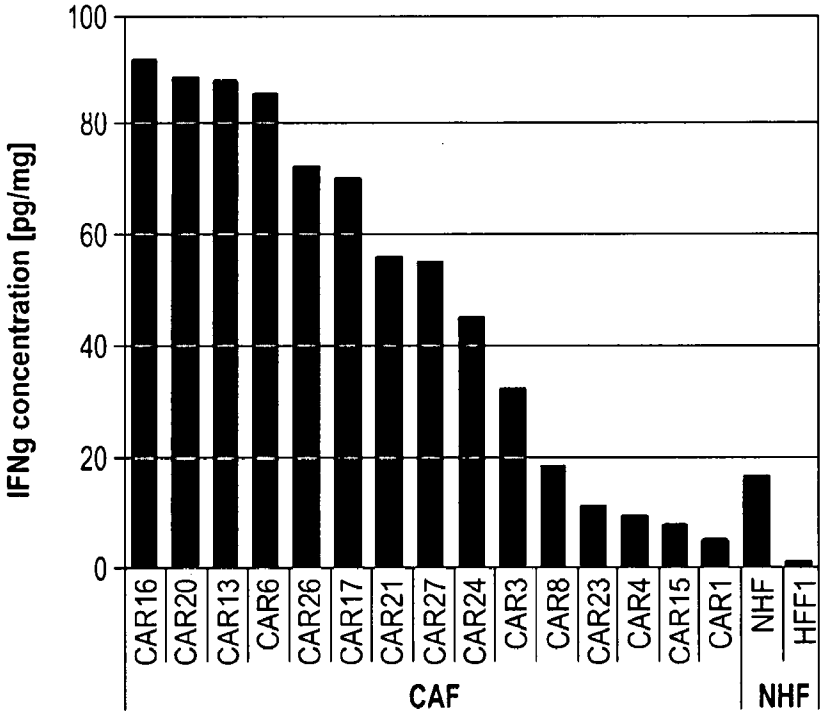

IFNg concentration [pg/mg]
100
80
60
40
20
0
CAR16
CAR20
CAR13
CAR6
CAR26
CAR17
CAR21
CAR27
CAR24
CAR3
CAR8
CAR23
CAR4
CAR15
CAR1
NHF
HFF1
CAF
NHF

FIG. 5I

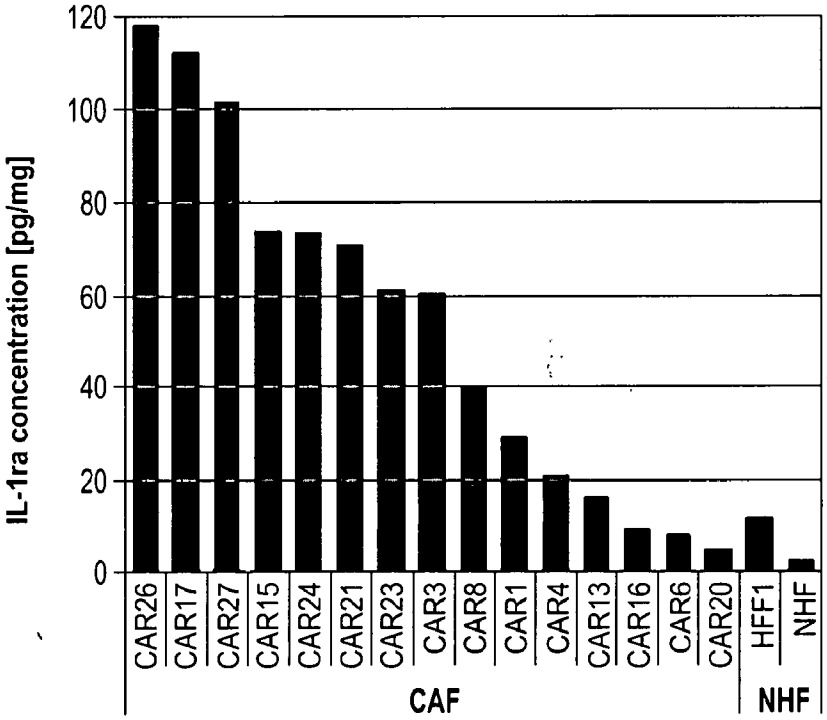

IL-1ra concentration [pg/mg]
120
100
80
60
40
20
0
CAR26
CAR17
CAR27
CAR15
CAR24
CAR21
CAR23
CAR3
CAR8
CAR1
CAR4
CAR13
CAR16
CAR6
CAR20
HFF1
NHF
CAF
NHF

FIG. 5J

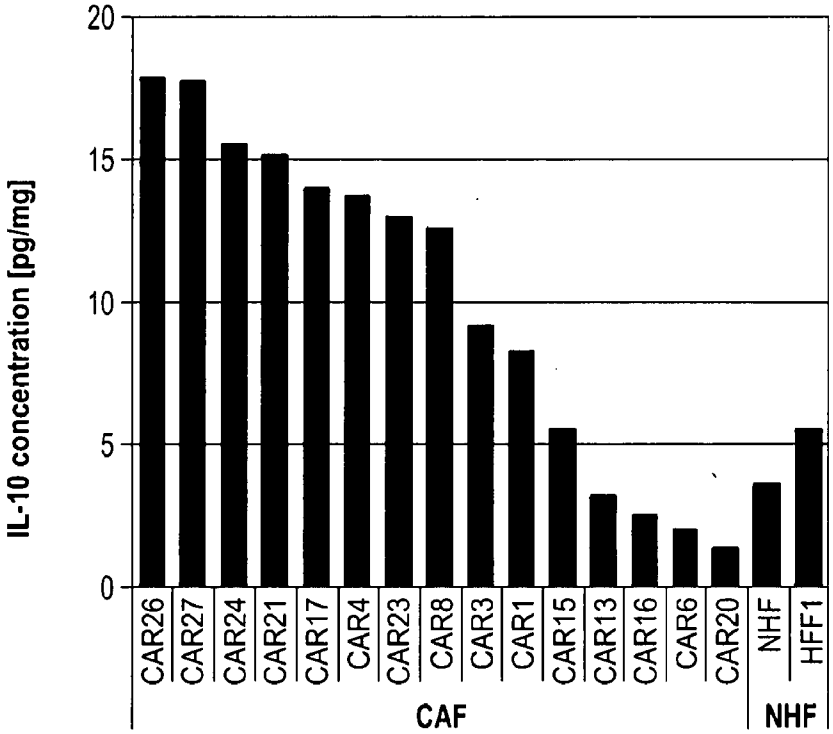

IL-10 concentration [pg/mg]
20
15
10
5
0
CAR26
CAR27
CAR24
CAR21
CAR17
CAR4
CAR23
CAR8
CAR3
CAR1
CAR15
CAR13
CAR16
CAR6
CAR20
NHF
HFF1
CAF
NHF

FIG. 6A

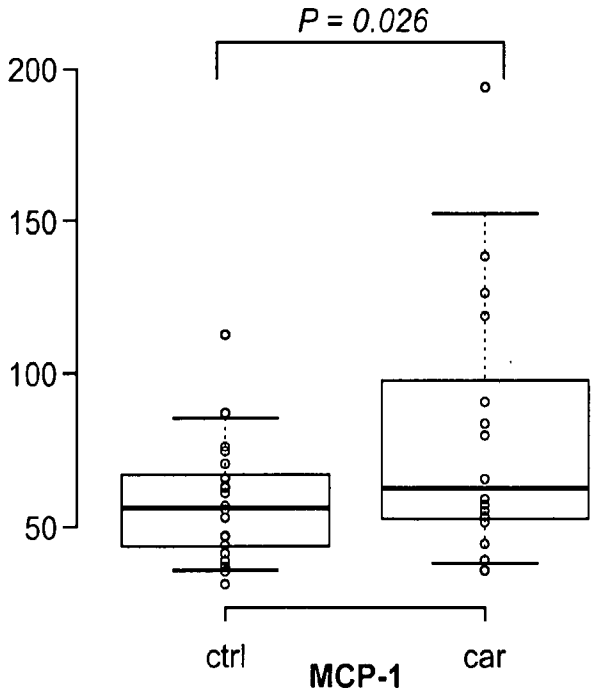

P = 0.026
200
150
100
50
ctrl
car
MCP-1

FIG. 6B

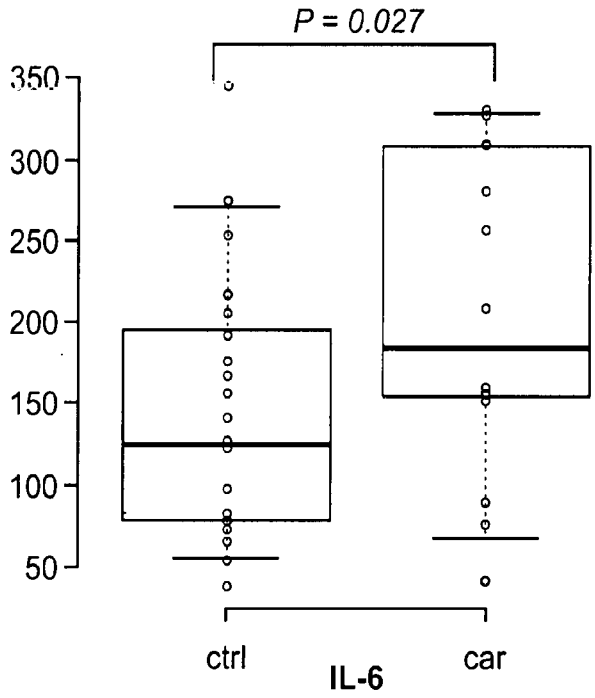

P = 0.027
350
300
250
200
150
100
50
ctrl
car
IL-6

FIG. 6C

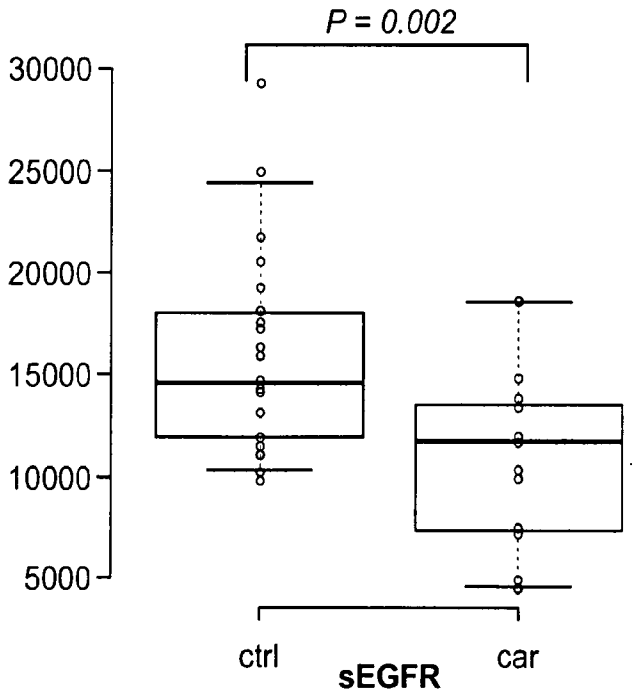

P = 0.002
30000
25000
20000
15000
10000
5000
ctrl
car
sEGFR

FIG. 6D

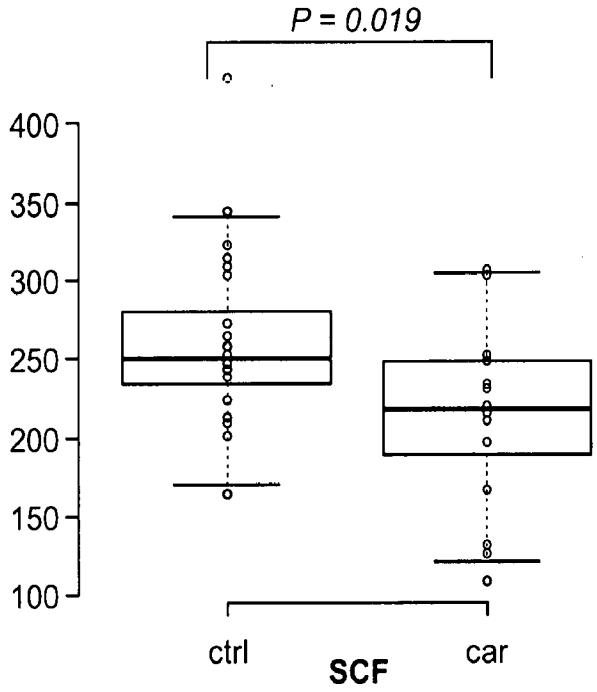

P = 0.019
400
350
300
250
200
150
100
ctrl
car
SCF

FIG. 6E

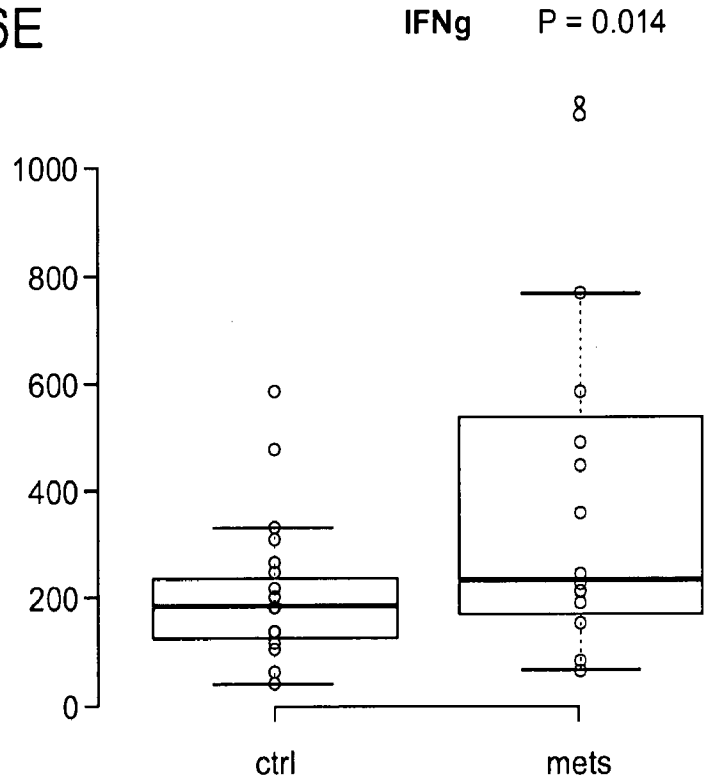

IFNg
P = 0.014
1000
800
600
400
200
0
ctrl
mets

FIG. 6F

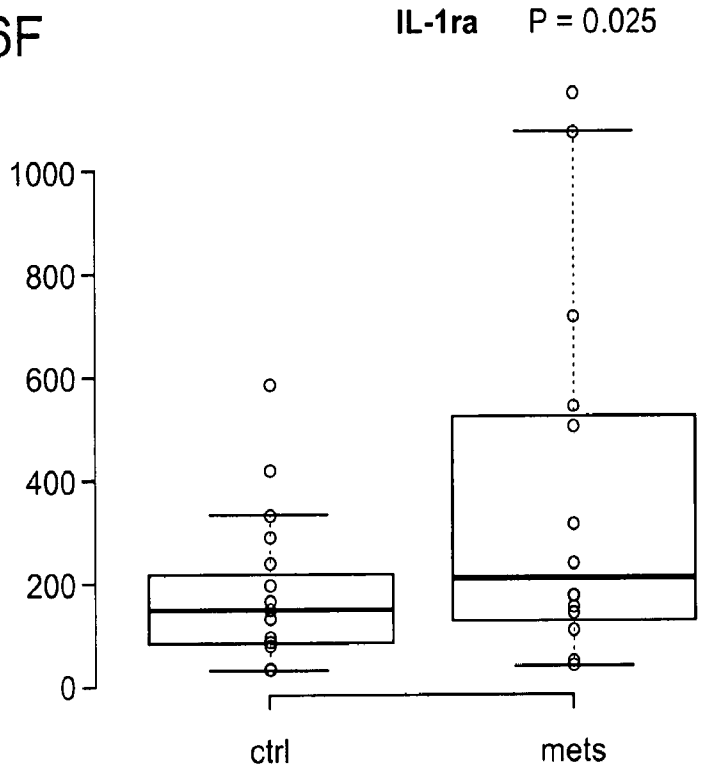

IL-1ra P = 0.025
1000
800
600
400
200
0
ctrl
mets

FIG. 6G

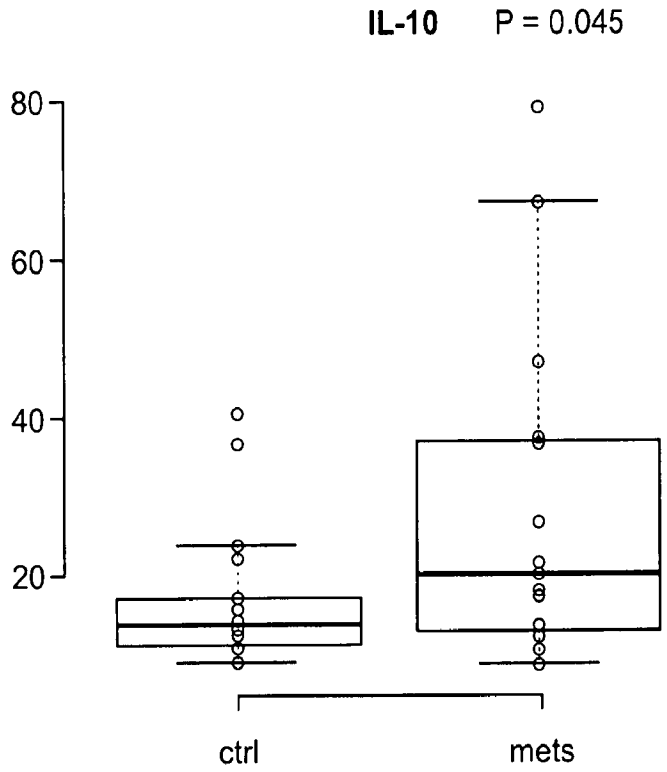

IL-10 P = 0.045
80
60
40
20
ctrl
mets

FIG. 6H

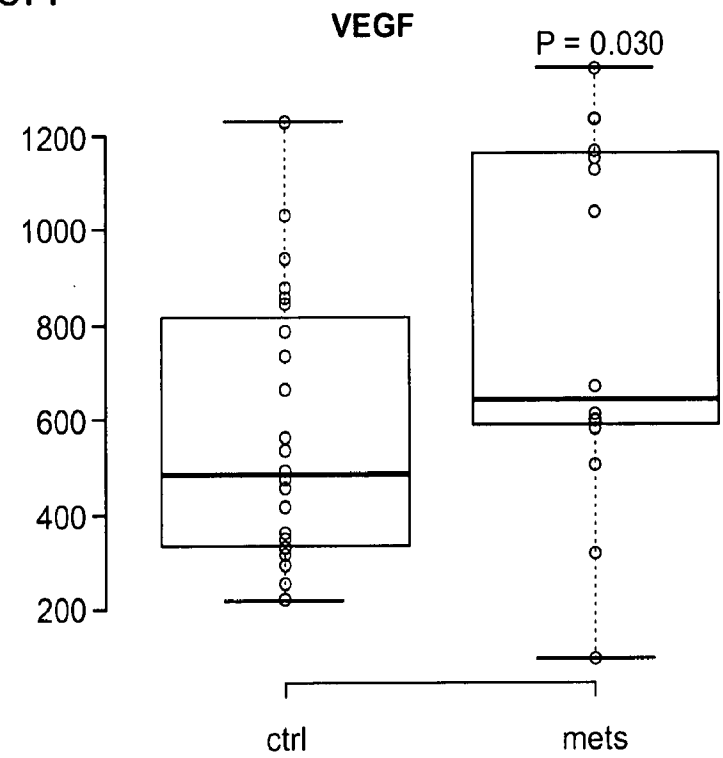

VEGF
P = 0.030
1200
1000
800
600
400
200
ctrl
mets

FIG. 6I

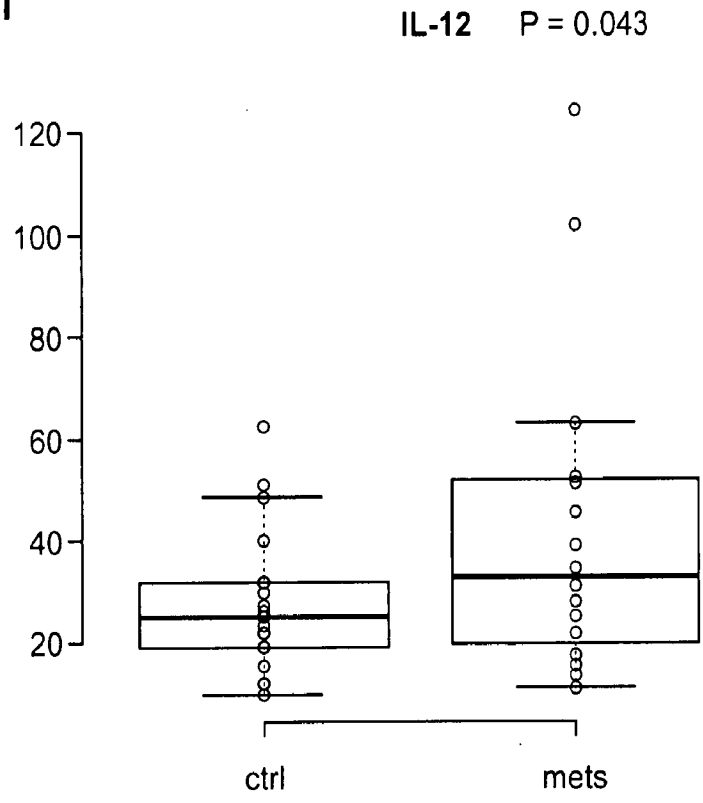

IL-12 P = 0.043
120
100
80
60
40
20
ctrl
mets

FIG. 6J

Supernatant NAF/NHF

| Plasma Mets/Control | *up* | *down* | *Concordance (total)* |
|---|---|---|---|
| ***up*** | 31 | 3 | 91% (34) |
| ***down*** | 7 | 6 | 46% (13) |
| *Concordance (total)* | 82% (38) | 66% (9) | |

FIG. 6K

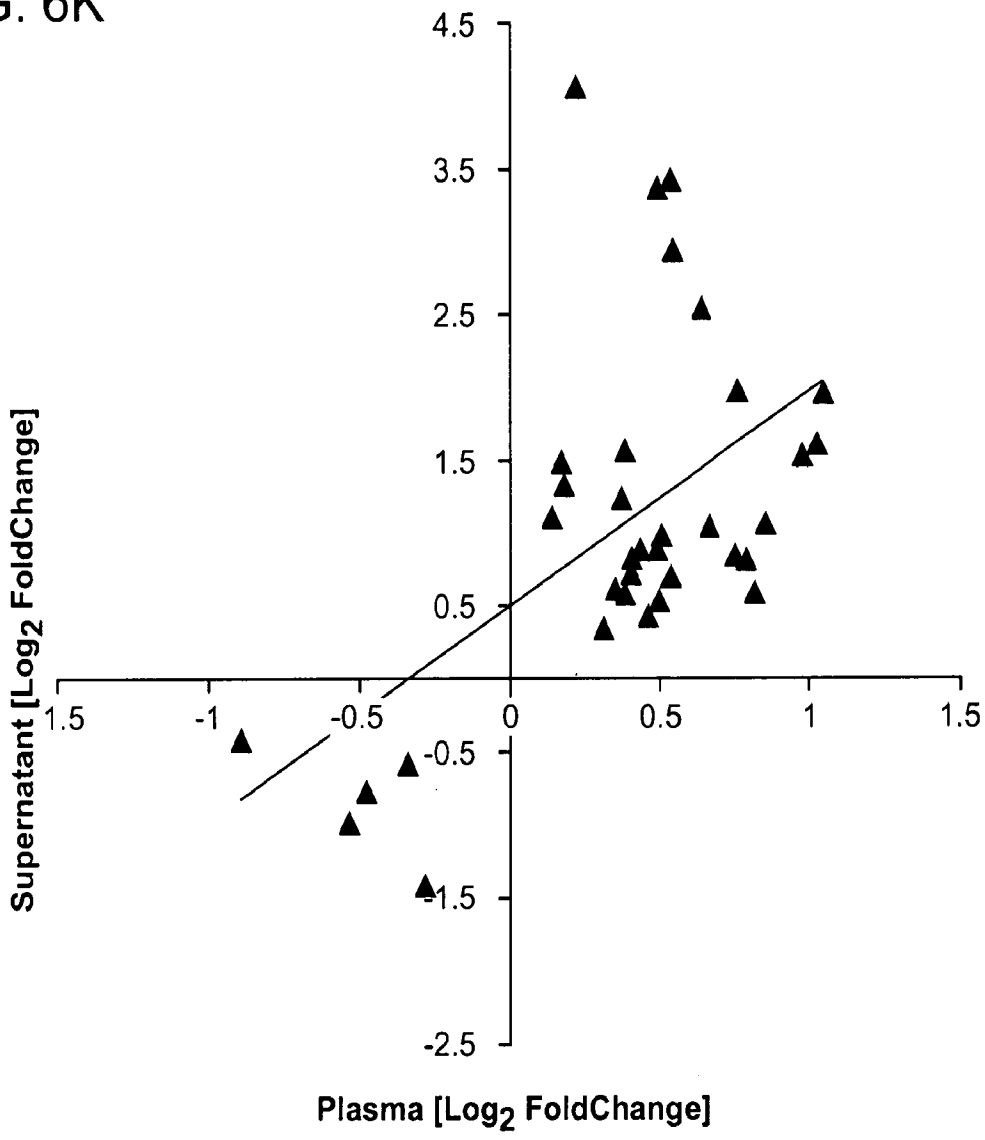


FIG. 7A

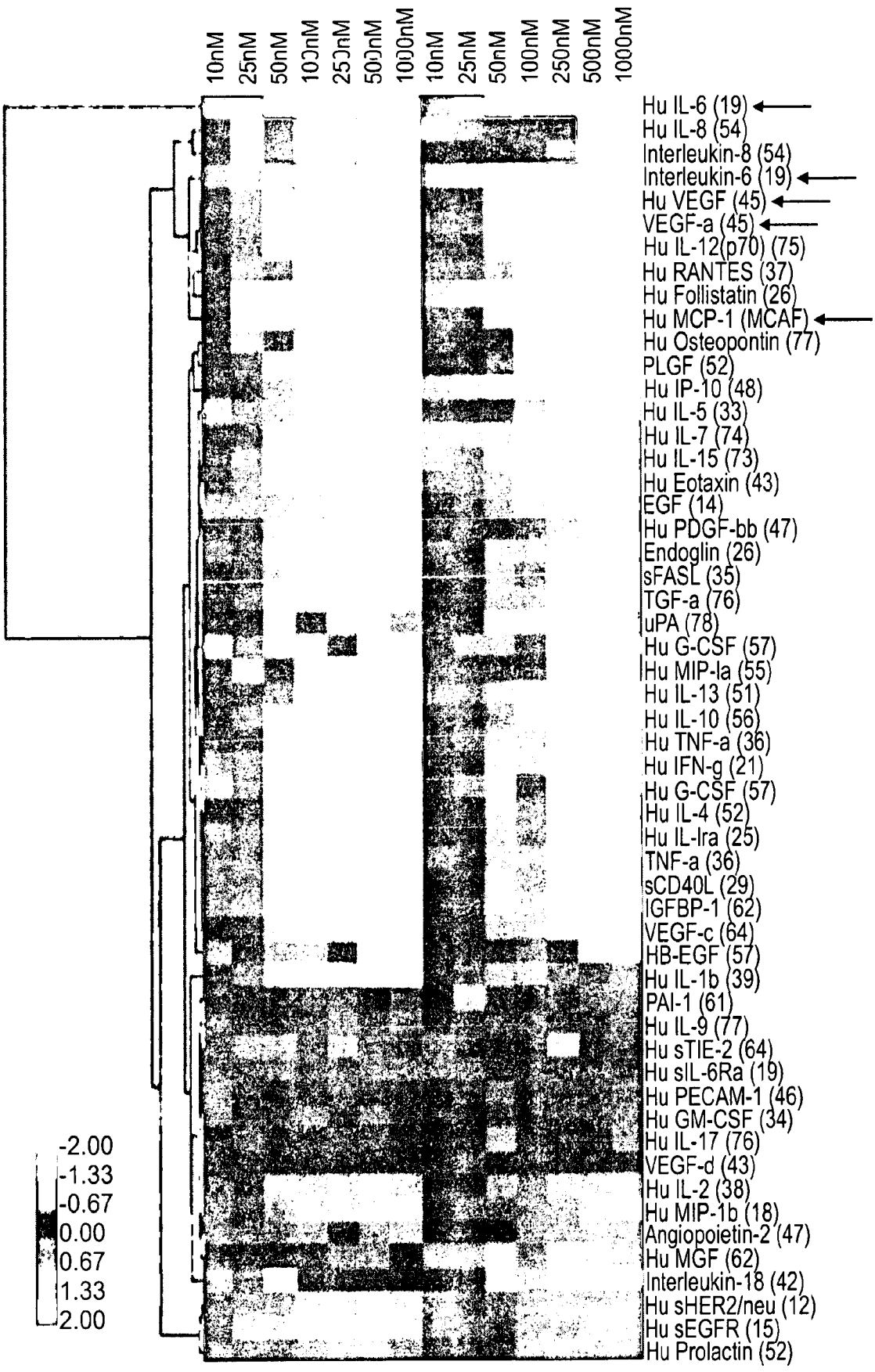

CAR24
CAR26
10nM
25nM
50nM
100nM
250nM
500nM
1000nM
Hu IL-6 (19)
Hu IL-8 (54)
Interleukin-8 (54)
Interleukin-6 (19)
Hu VEGF (45)
VEGF-a (45)
Hu IL-12(p70) (75)
Hu RANTES (37)
Hu Follistatin (26)
Hu MCP-1 (MCAF)
Hu Osteopontin (77)
PLGF (52)
Hu IP-10 (48)
Hu IL-5 (33)
Hu IL-7 (74)
Hu IL-15 (73)
Hu Eotaxin (43)
EGF (14)
Hu PDGF-bb (47)
Endoglin (26)
sFASL (35)
TGF-a (76)
uPA (78)
Hu G-CSF (57)
Hu MIP-la (55)
Hu IL-13 (51)
Hu IL-10 (56)
Hu TNF-a (36)
Hu IFN-g (21)
Hu G-CSF (57)
Hu IL-4 (52)
Hu IL-lra (25)
TNF-a (36)
sCD40L (29)
IGFBP-1 (62)
VEGF-c (64)
HB-EGF (57)
Hu IL-1b (39)
PAI-1 (61)
Hu IL-9 (77)
Hu sTIE-2 (64)
Hu sIL-6Ra (19)
Hu PECAM-1 (46)
Hu GM-CSF (34)
Hu IL-17 (76)
VEGF-d (43)
Hu IL-2 (38)
Hu MIP-1b (18)
Angiopoietin-2 (47)
Hu MGF (62)
Interleukin-18 (42)
Hu sHER2/neu (12)
Hu sEGFR (15)
Hu Prolactin (52)
-2.00
-1.33
-0.67
0.00
0.67
1.33
2.00

FIG. 7B

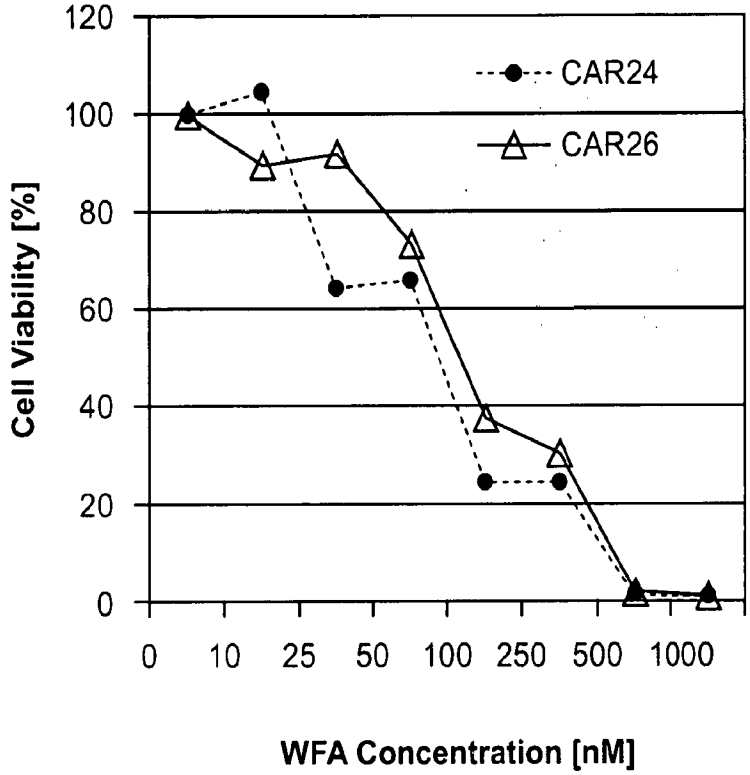
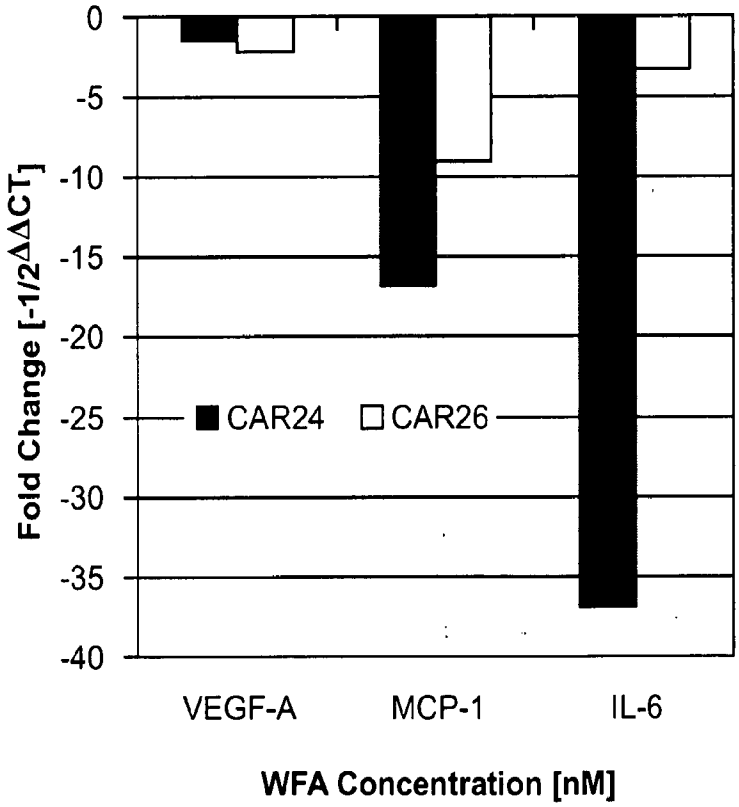

120
100
80
60
40
20
0
Cell Viability [%]
CAR24
CAR26
0
10
25
50
100
250
500
1000
WFA Concentration [nM]

FIG. 7C


0
-5
-10
-15
-20
-25
-30
-35
-40
Fold Change [-1/2ΔΔCT]
CAR24
CAR26
VEGF-A
MCP-1
IL-6
WFA Concentration [nM]

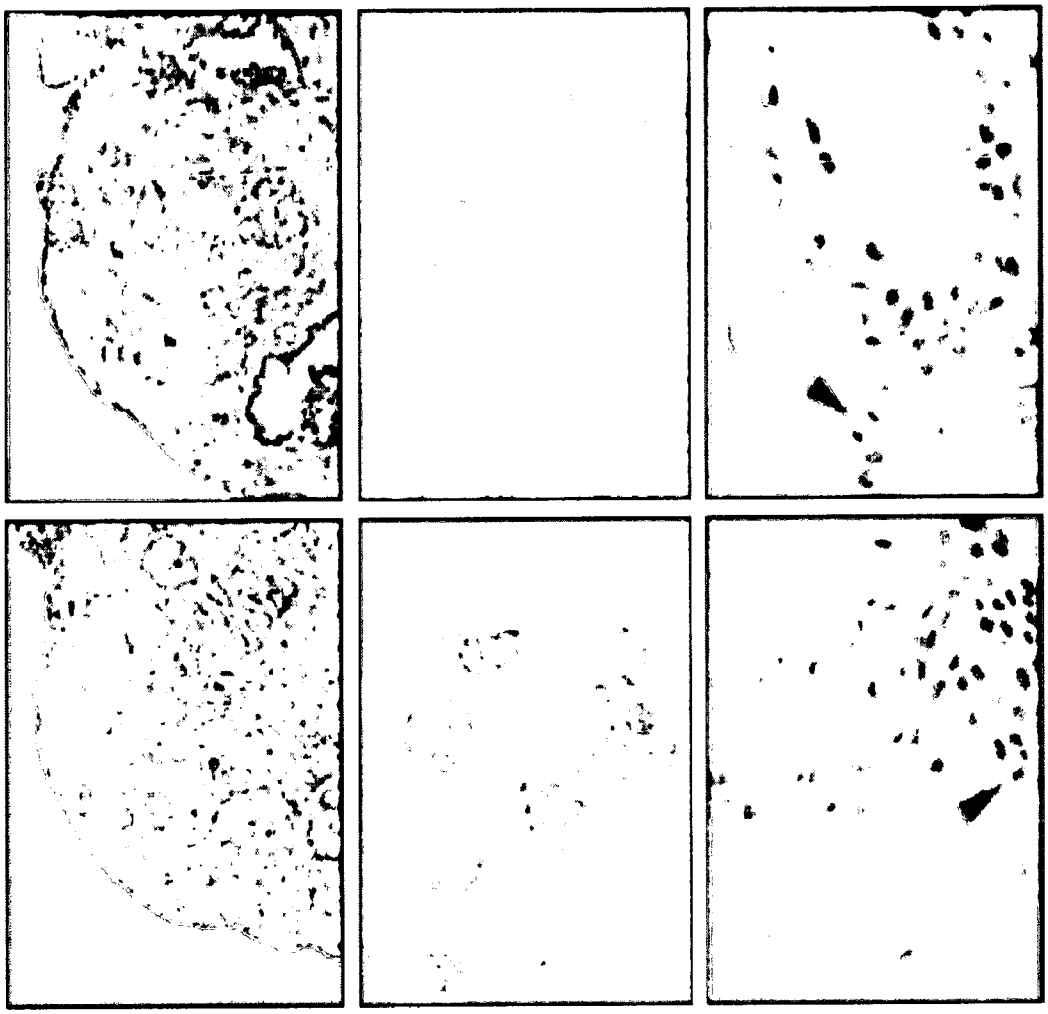


FIG. 9

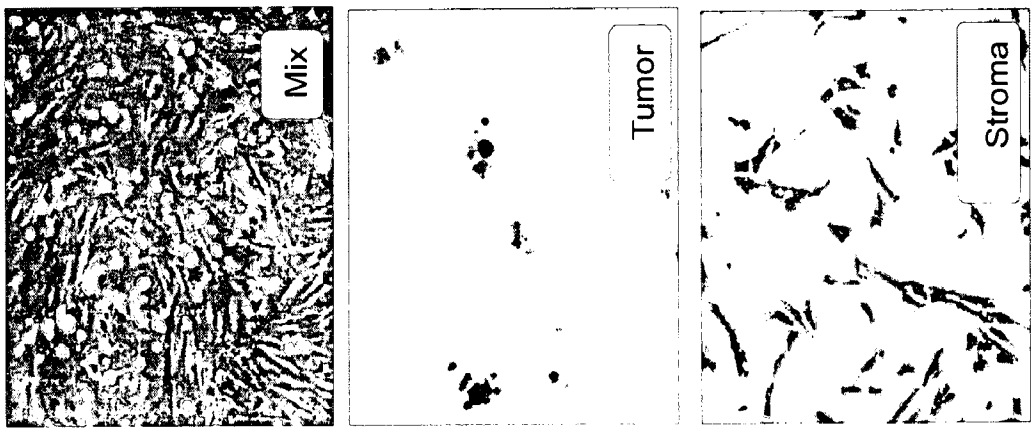



FIG. 8

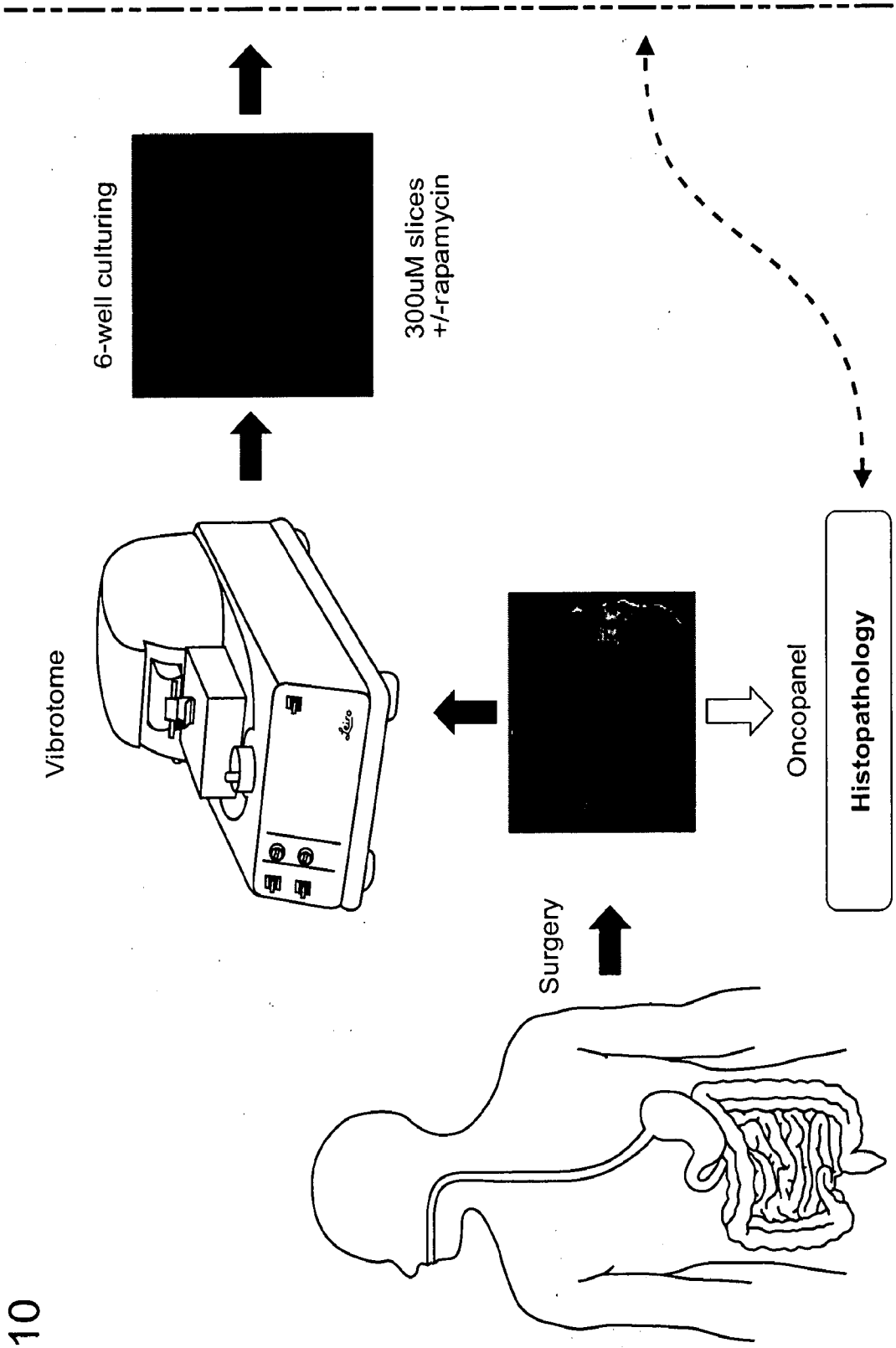
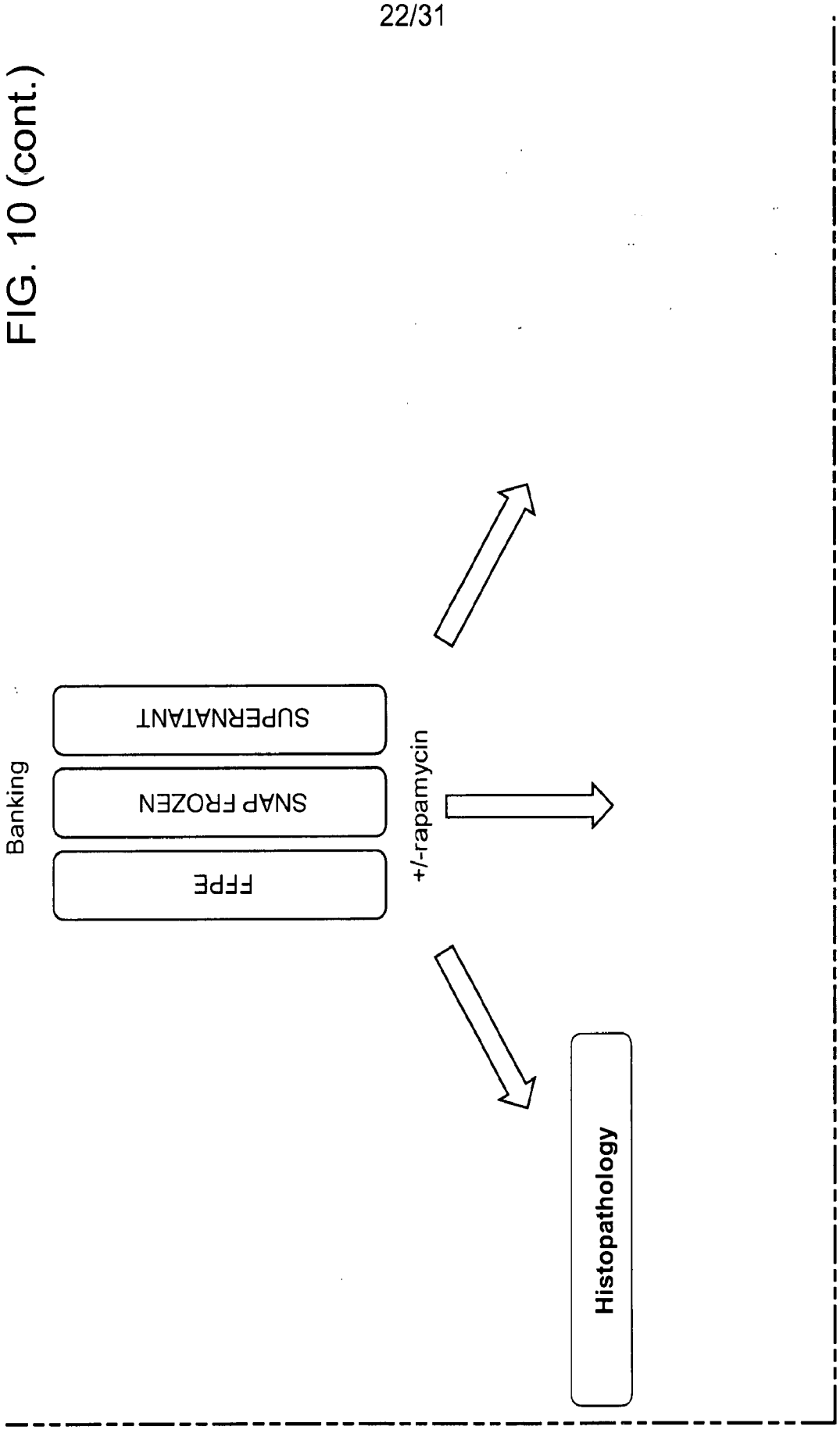

6-well culturing
300uM slices
+/-rapamycin
Vibrotome
Oncopanel
Histopathology
Surgery

FIG. 10

FIG. 10 (cont.)


Banking
SUPERNATANT
SNAP FROZEN
FFPE
+/-rapamycin
Histopathology

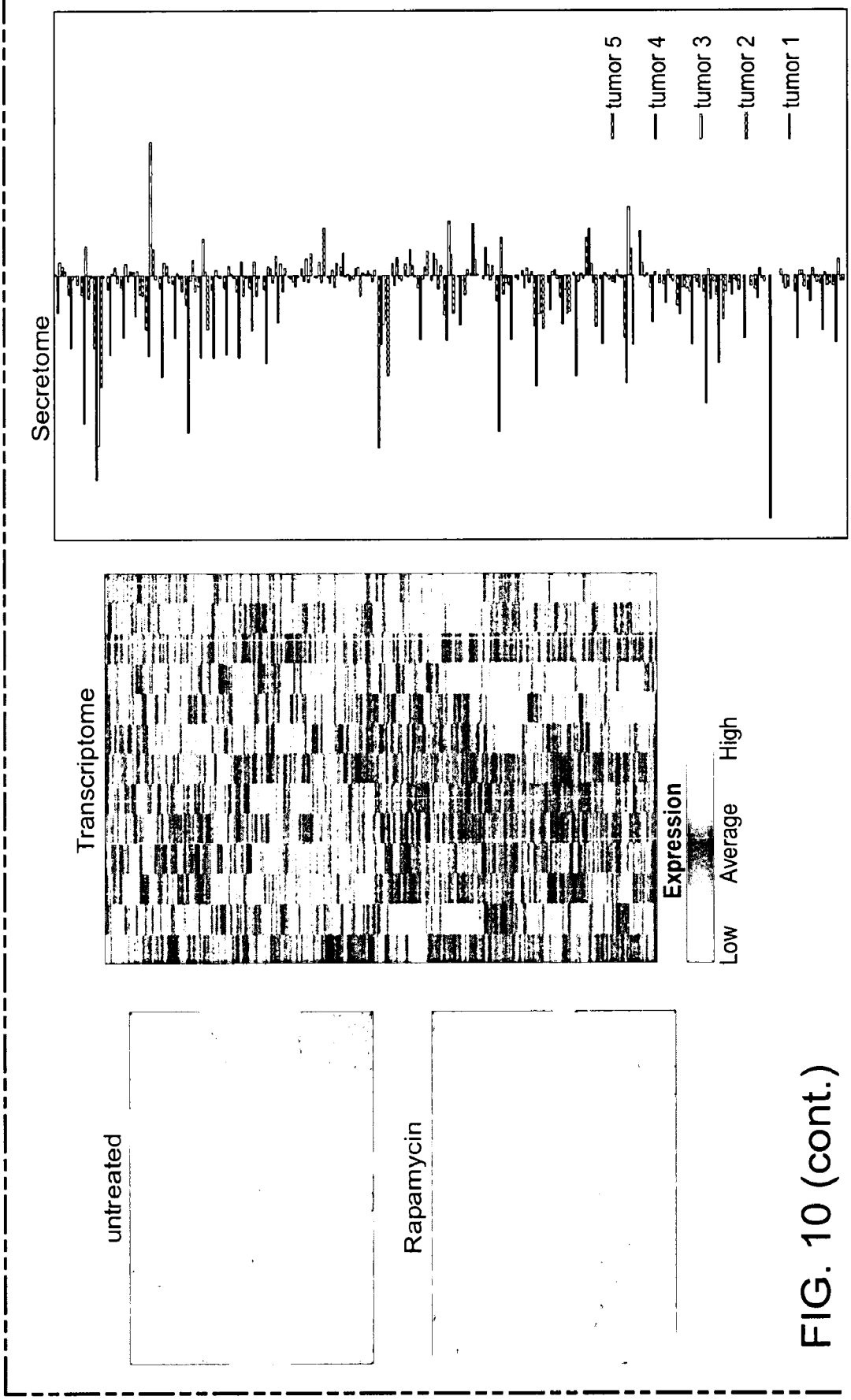

Secretome
tumor 5
tumor 4
tumor 3
tumor 2
tumor 1
Transcriptome
Expression
High
Average
Low
untreated
Rapamycin

FIG. 10 (cont.)

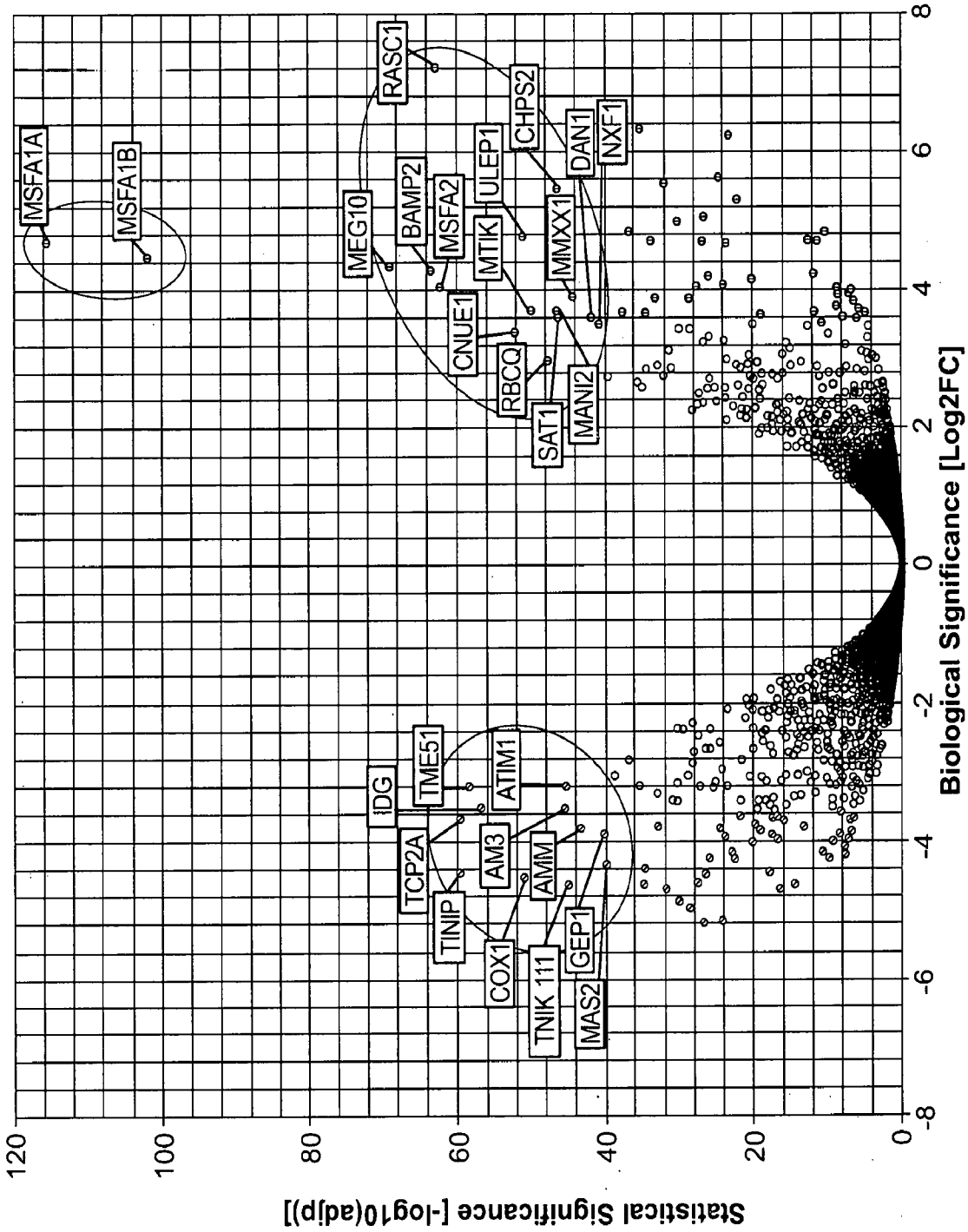

Statistical Significance [-log10(adjp)]
Biological Significance [Log2FC]
120
100
80
60
40
20
0
8
6
4
2
0
-2
-4
-6
-8
MSFA1A
MSFA1B
RASC1
CHPS2
DAN1
NXF1
MEG10
BAMP2
MSFA2
ULEP1
MTIK
MMXX1
CNUE1
RBCQ
SAT1
MANI2
iDG
TME51
ATIM1
TCP2A
AM3
AMM
TINIP
COX1
GEP1
TNIK 111
MAS2

FIG. 11A

FIG. 11B

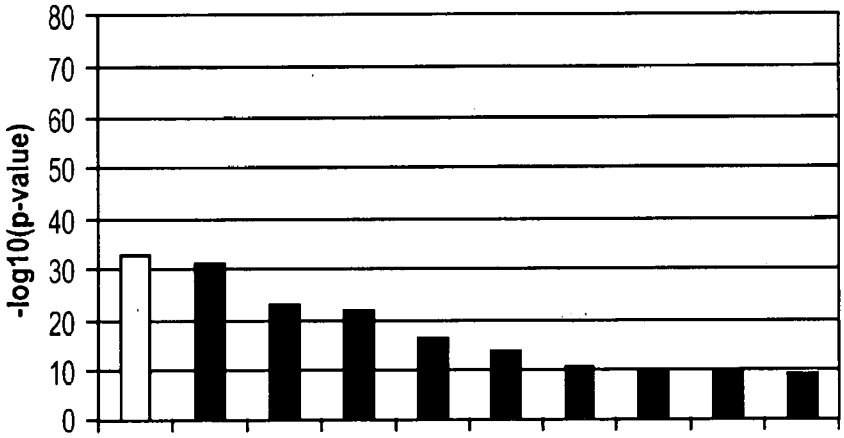



FIG. 11C

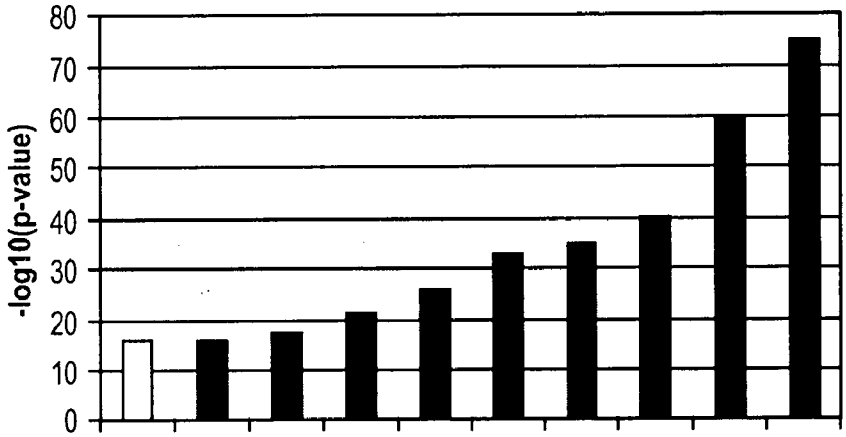


FIG. 11D

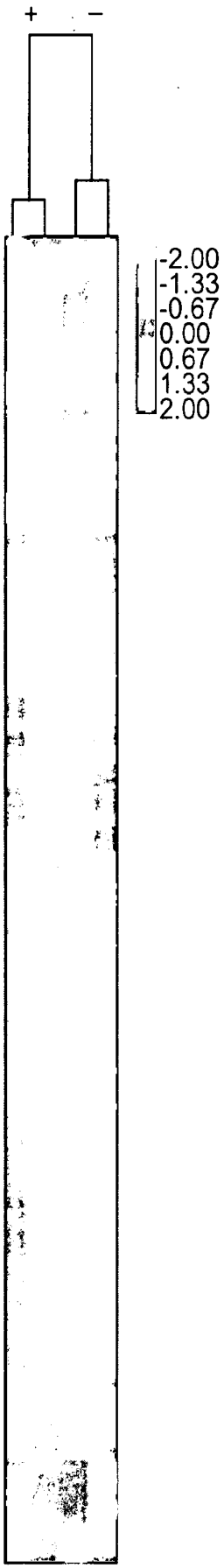
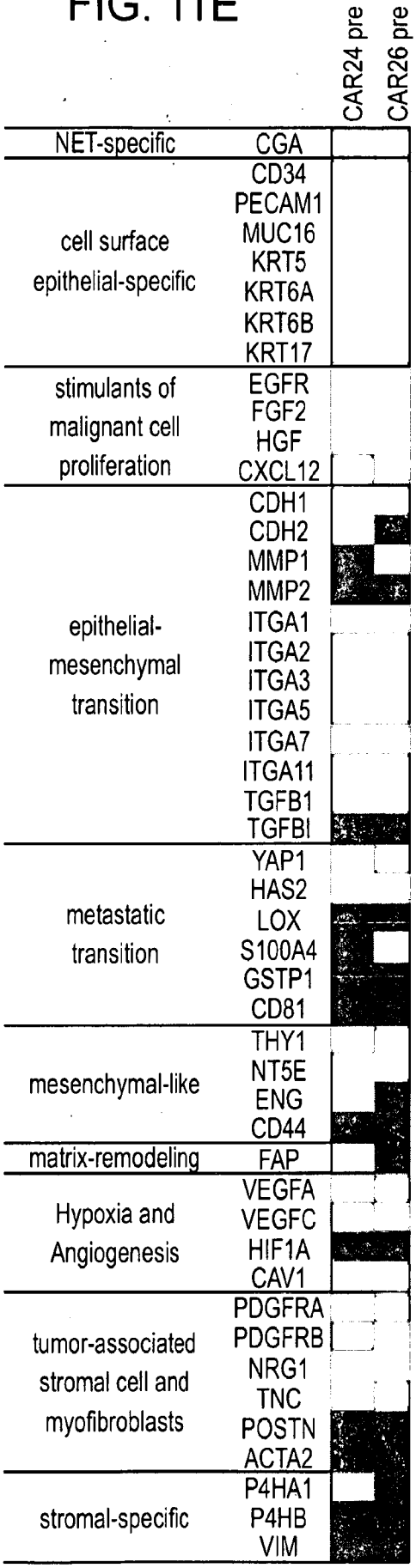



FIG. 11E



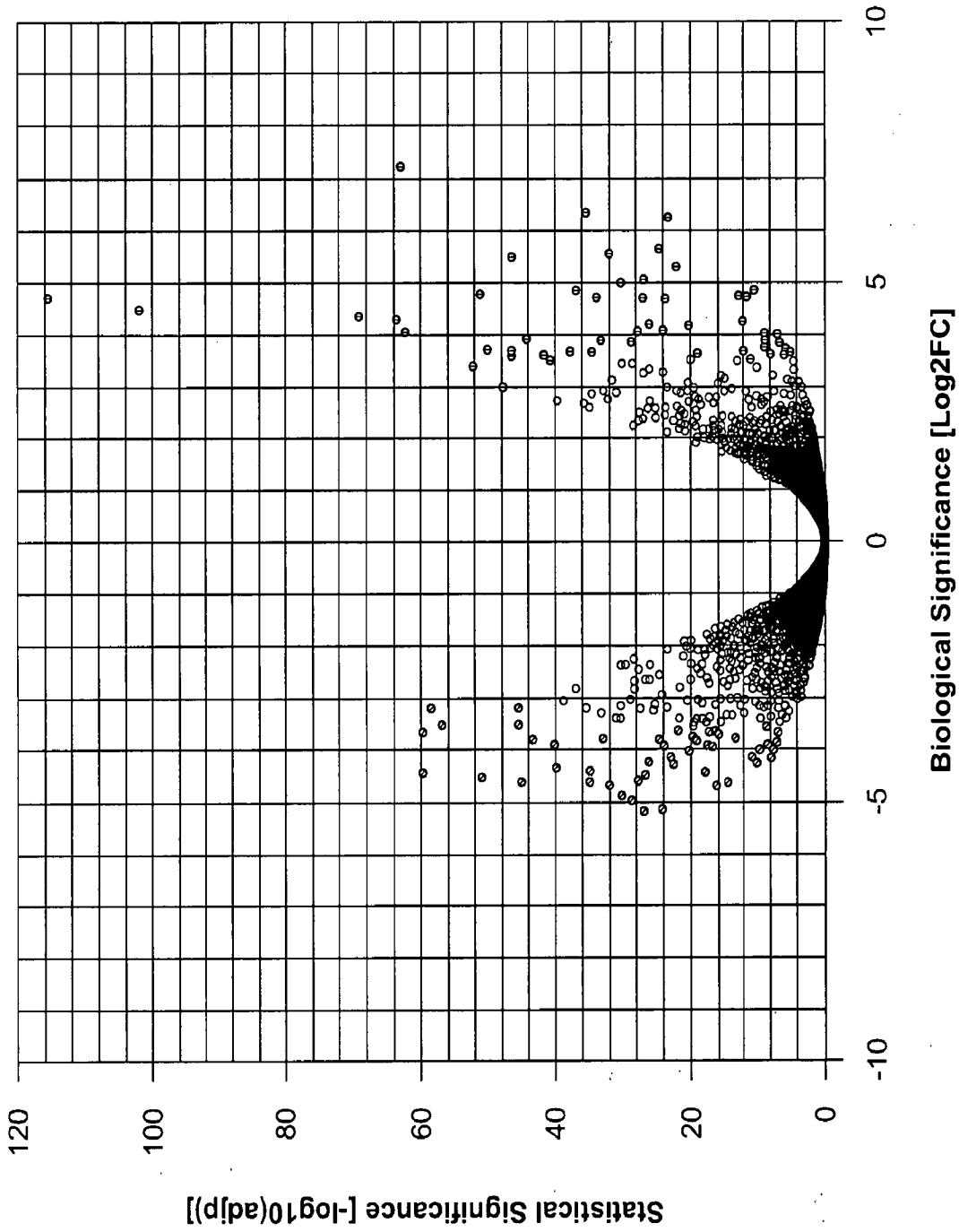

Biological Significance [Log2FC]
10
5
0
-5
-10
Statistical Significance [-log10(adjp)]
120
100
80
60
40
20
0

FIG. 11F

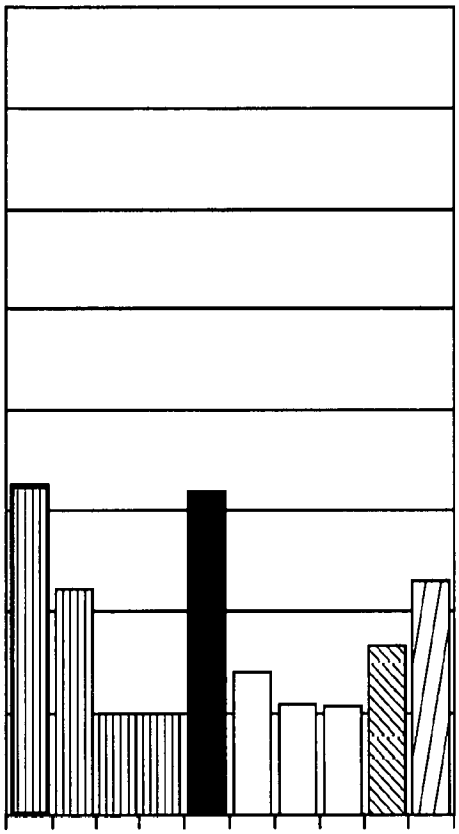



FIG. 11G

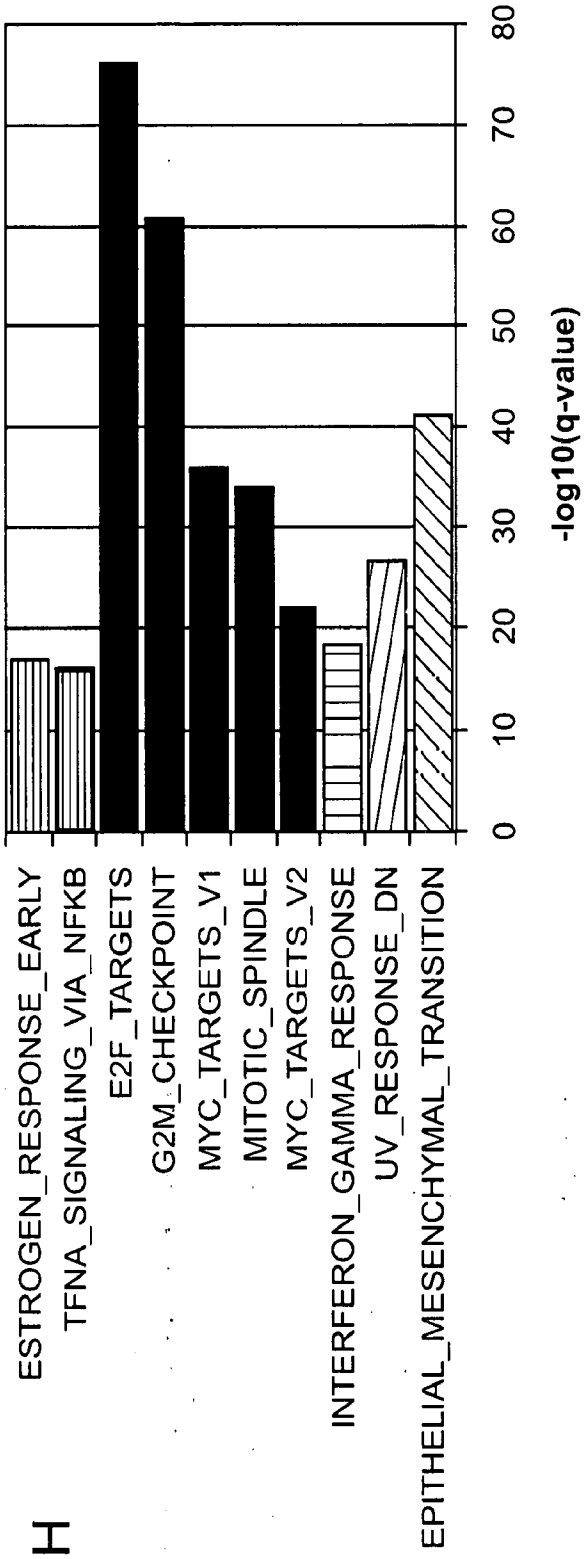



FIG. 11H

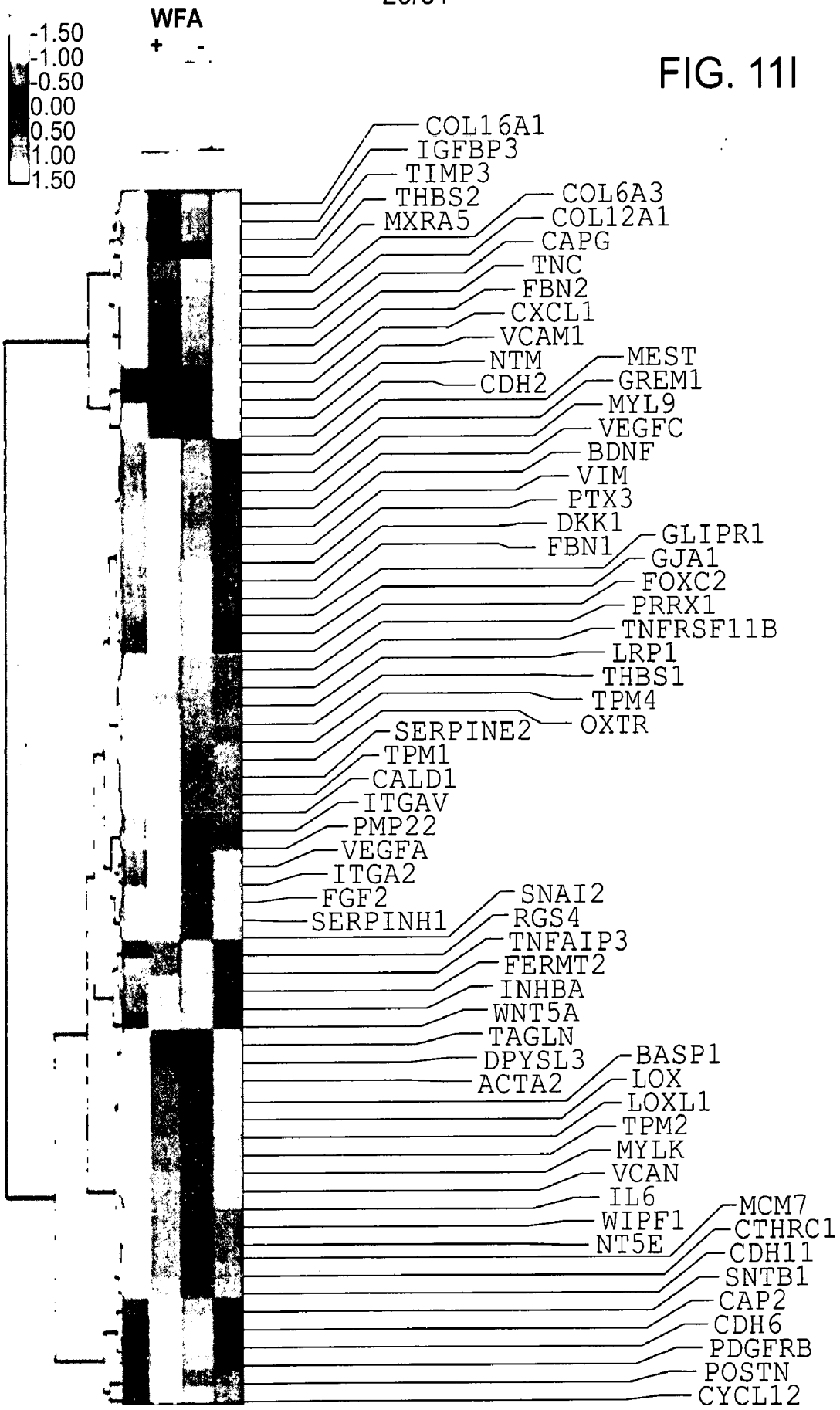

WFA
+ -
-1.50
-1.00
-0.50
0.00
0.50
1.00
1.50
COL16A1
IGFBP3
TIMP3
THBS2
MXRA5
COL6A3
COL12A1
CAPG
TNC
FBN2
CXCL1
VCAM1
NTM
CDH2
MEST
GREM1
MYL9
VEGFC
BDNF
VIM
PTX3
DKK1
FBN1
GLIPR1
GJA1
FOXC2
PRRX1
TNFRSF11B
LRP1
THBS1
TPM4
OXTR
SERPINE2
TPM1
CALD1
ITGAV
PMP22
VEGFA
ITGA2
FGF2
SERPINH1
SNAI2
RGS4
TNFAIP3
FERMT2
INHBA
WNT5A
TAGLN
DPYSL3
ACTA2
BASP1
LOX
LOXL1
TPM2
MYLK
VCAN
IL6
WIPF1
NT5E
MCM7
CTHRC1
CDH11
SNTB1
CAP2
CDH6
PDGFRB
POSTN
CYCL12

FIG. 11I

FIG. 12

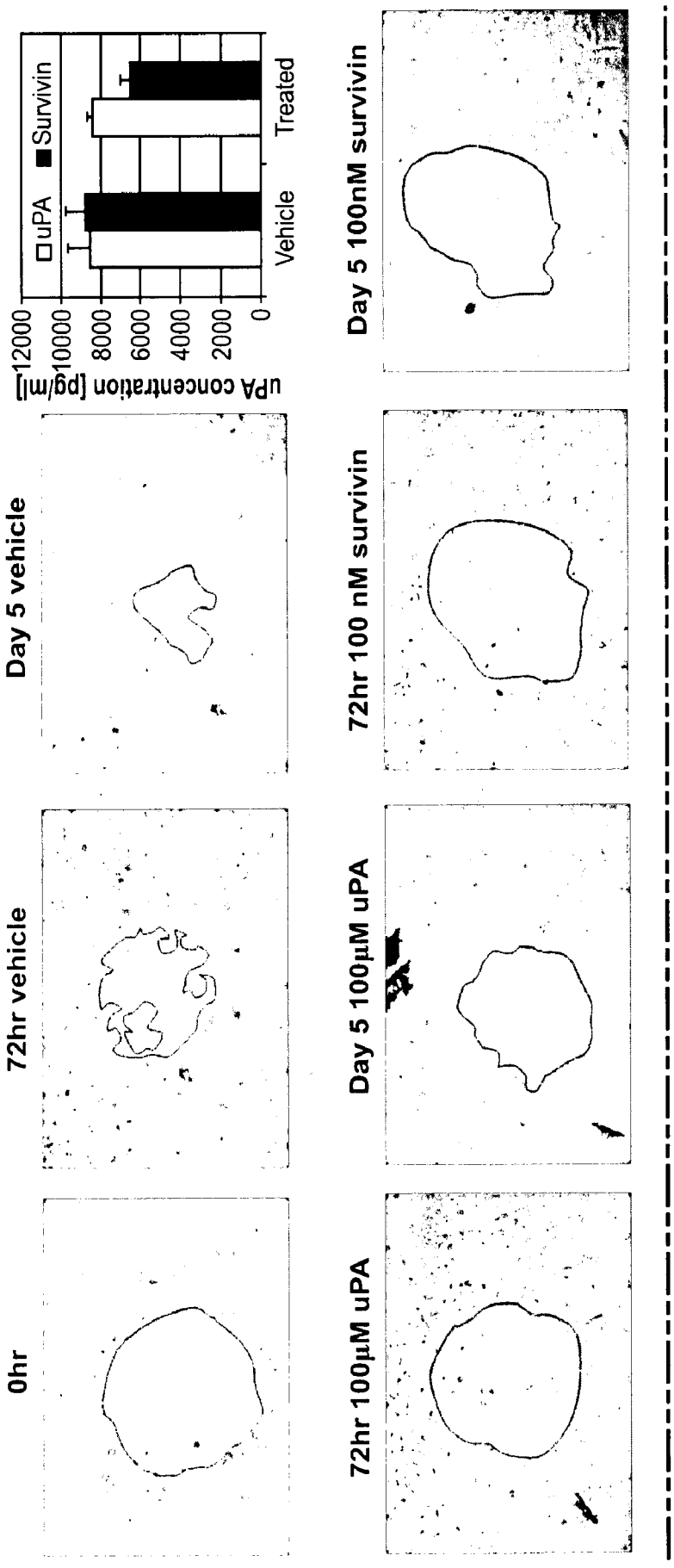
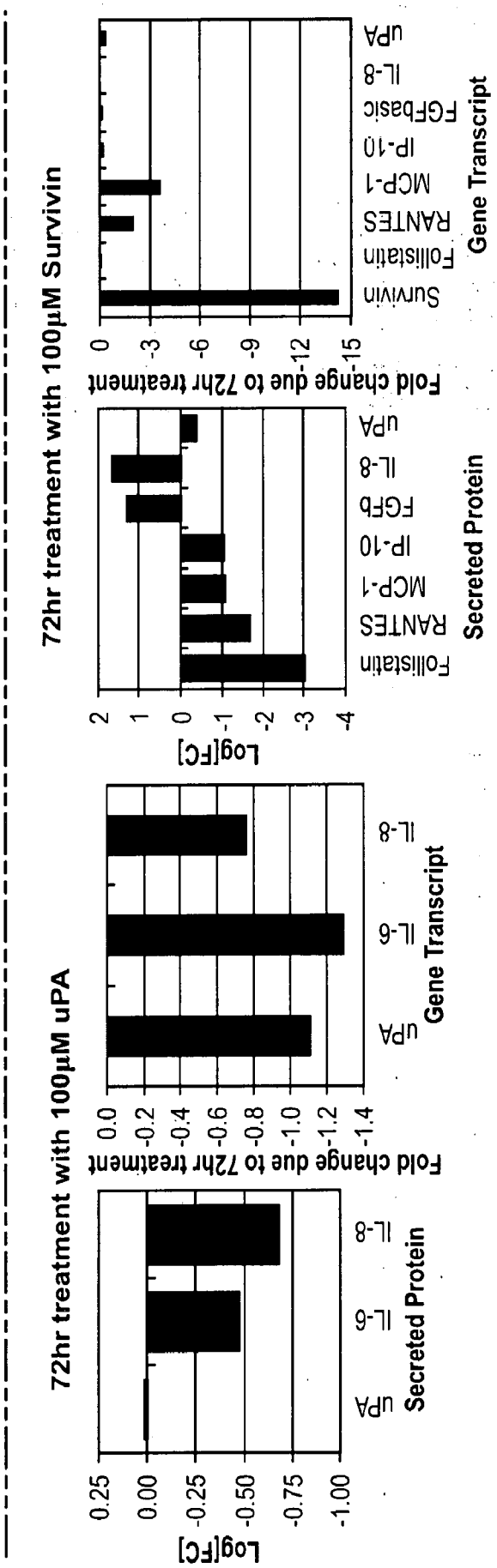

0hr
72hr vehicle
Day 5 vehicle
uPA concentration [pg/ml]
12000
10000
8000
6000
4000
2000
0
uPA
Survivin
Vehicle
Treated
72hr 100µM uPA
Day 5 100µM uPA
72hr 100 nM survivin
Day 5 100nM survivin

FIG. 12 (cont.)


72hr treatment with 100µM Survivin
Fold change due to 72hr treatment
0
-3
-6
-9
-12
-15
Survivin
Follistatin
RANTES
MCP-1
IP-10
FGFbasic
IL-8
uPA
Gene Transcript
Log[FC]
2
1
0
-1
-2
-3
-4
Follistatin
RANTES
MCP-1
IP-10
FGFb
IL-8
uPA
Secreted Protein
72hr treatment with 100µM uPA
Fold change due to 72hr treatment
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.4
uPA
IL-6
IL-8
Gene Transcript
Log[FC]
0.25
0.00
-0.25
-0.50
-0.75
-1.00
uPA
IL-6
IL-8
Secreted Protein

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/043028

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/6886
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, Sequence Search, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | MILLER HELEN C ET AL: "MicroRNAs associated with small bowel neuroendocrine tumours and their metastases.", ENDOCRINE-RELATED CANCER 09 2016, vol. 23, no. 9, September 2016 (2016-09), pages 711-726, XP002785111, ISSN: 1479-6821 the whole document<br>-----<br>-/-- | 1-7,22 |

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 26 September 2018 | 10/10/2018 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Botz, Jürgen |

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | Michaela Bowden: "Profiling of metastatic small intestine neuroendocrine tumors reveals characteristic miRNAs detectable in plasma", , 7 April 2017 (2017-04-07), XP055509581, Retrieved from the Internet: URL:file:///C:/Users/JB03843/AppData/Local/Temp/16908-248016-8-PB.pdf [retrieved on 2018-09-25] the whole document | 1-7,22 |
| X | JOY ES ARDILL ET AL: "Raised circulating Neurokinin A predicts prognosis in metastatic small bowel neuroendocrine tumours. Lowering Neurokinin A indicates improved prognosis", ANNALS OF CLINICAL BIOCHEMISTRY., vol. 53, no. 2, 1 March 2016 (2016-03-01), pages 259-264, XP055509476, GB ISSN: 0004-5632, DOI: 10.1177/0004563215592021 the whole document | 1-7,22 |
| X | SHERMAN SCOTT K ET AL: "Gene expression accurately distinguishes liver metastases of small bowel and pancreas neuroendocrine tumors", CLINICAL AND EXPERIMENTAL METASTASIS, SPRINGER NETHERLANDS, NL, vol. 31, no. 8, 21 September 2014 (2014-09-21), pages 935-944, XP035409360, ISSN: 0262-0898, DOI: 10.1007/S10585-014-9681-2 [retrieved on 2014-09-21] the whole document | 1-7,22 |
| X | MAXWELL JESSICA E ET AL: "Somatic alterations ofCDKN1Bare associated with small bowel neuroendocrine tumors", CANCER GENETICS, ELSEVIER, AMSTERDAM, NL, vol. 208, no. 11, 15 September 2015 (2015-09-15), pages 564-570, XP029306813, ISSN: 2210-7762, DOI: 10.1016/J.CANCERGEN.2015.08.003 the whole document | 1-7,22 |

-/--

1

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | KECK KENDALL J ET AL: "Changes in gene expression in small bowel neuroendocrine tumors associated with progression to metastases", SURGERY, MOSBY, INC, US, vol. 163, no. 1, 2 April 2017 (2017-04-02) , pages 232-239, XP085309008, ISSN: 0039-6060, DOI: 10.1016/J.SURG.2017.07.031 the whole document | 1-7,22 |
| X | DIEBOLD ANNE E ET AL: "Neurokinin A levels predict survival in patients with stage IV well differentiated small bowel neuroendocrine neoplasms", SURGERY (ST LOUIS), vol. 152, no. 6, December 2012 (2012-12), pages 1172-1176, XP002785112, ISSN: 0039-6060 the whole document | 1-7,22 |
| X | SCOTT K. SHERMAN ET AL: "Pancreastatin Predicts Survival in Neuroendocrine Tumors", ANNALS OF SURGICAL ONCOLOGY., vol. 21, no. 9, 22 April 2014 (2014-04-22) , pages 2971-2980, XP055509492, US ISSN: 1068-9265, DOI: 10.1245/s10434-014-3728-0 the whole document | 1-7,22 |
| A | Anonymous: "Abstract 168: Understanding the role of the carcinoid associated fibroblasts in the neuroendocrine tumor microenvironment ¦ Cancer Research", , 1 October 2014 (2014-10-01), XP055509988, Retrieved from the Internet: URL:http://cancerres.aacrjournals.org/content/74/19_Supplement/168 [retrieved on 2018-09-26] the whole document | 1-56 |

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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