



(86) Date de dépôt PCT/PCT Filing Date: 2001/10/12

(87) Date publication PCT/PCT Publication Date: 2002/04/18

(85) Entrée phase nationale/National Entry: 2003/04/11

(86) N° demande PCT/PCT Application No.: US 2001/032127

(87) N° publication PCT/PCT Publication No.: 2002/030465

(30) Priorités/Priorities: 2000/10/12 (60/239,705) US;
2000/10/24 (60/242,812) US

(51) Cl.Int.⁷/Int.Cl.⁷ C07K 14/705, A61K 31/7088,
A61P 35/00, A61K 38/39, A61K 38/17, C12Q 1/68,
G01N 33/566, G01N 33/50

(71) Demandeur/Applicant:
UNIVERSITY OF ROCHESTER, US

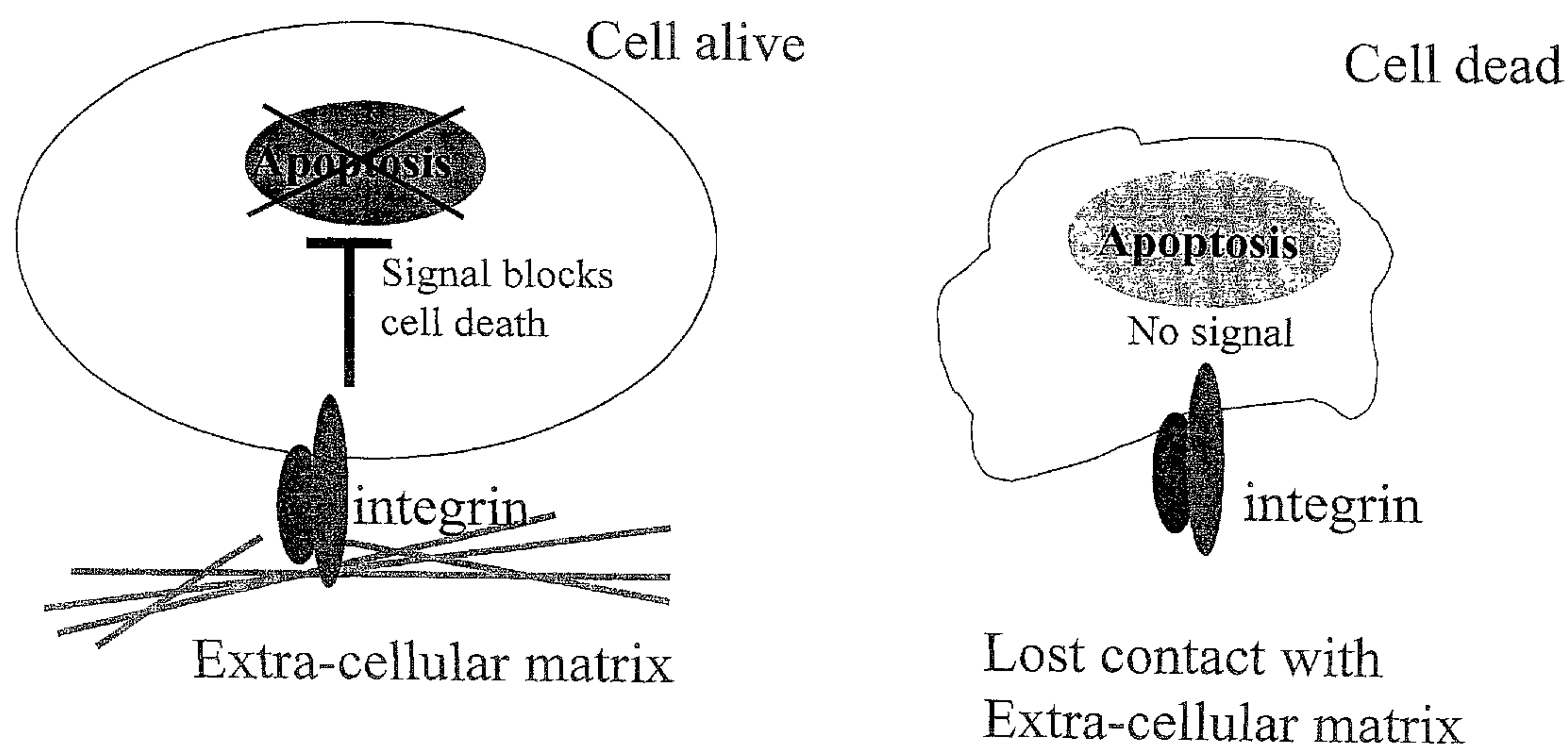
(72) Inventeurs/Inventors:
LAND, HARTMUT, US;
DELEU, LAURENT, US

(74) Agent: GOWLING LAFLEUR HENDERSON LLP

(54) Titre : COMPOSITIONS INHIBANT LA PROLIFERATION DE CELLULES CANCEREUSES

(54) Title: COMPOSITIONS THAT INHIBIT PROLIFERATION OF CANCER CELLS

Normal cells require integrin-matrix interactions for survival



Panel 1

(57) **Abrégé/Abstract:**

Disclosed are compositions and methods for reducing the proliferation of cancer cells through targeted interactions with integrins.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 April 2002 (18.04.2002)

PCT

(10) International Publication Number
WO 02/030465 A3

(51) International Patent Classification⁷: **C07K 14/705**,
A61K 38/17, 31/7088, 38/39, G01N 33/566, 33/50, C12Q
1/68, A61P 35/00

(74) Agents: **SPRATT, Gwendolyn, D.** et al.; Needle &
Rosenberg, P.C., Suite 1200, The Candler Building, 127
Peachtree Street, N.E., Atlanta, GA 30303-1811 (US).

(21) International Application Number: PCT/US01/32127

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI,
SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU,
ZA, ZW.

(22) International Filing Date: 12 October 2001 (12.10.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/239,705 12 October 2000 (12.10.2000) US
60/242,812 24 October 2000 (24.10.2000) US

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,
TG).

(71) Applicant (*for all designated States except US*): **UNI-
VERSITY OF ROCHESTER** [US/US]; 601 Elmwood
Avenue, Box 706, Rochester, NY 14642 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **LAND, Hartmut**
[US/US]; 195 Hollywood Avenue, Rochester, NY 14618
(US). **DELEU, Laurent** [US/US]; 104 Westland Avenue,
Rochester, NY 14618 (US).

Published:

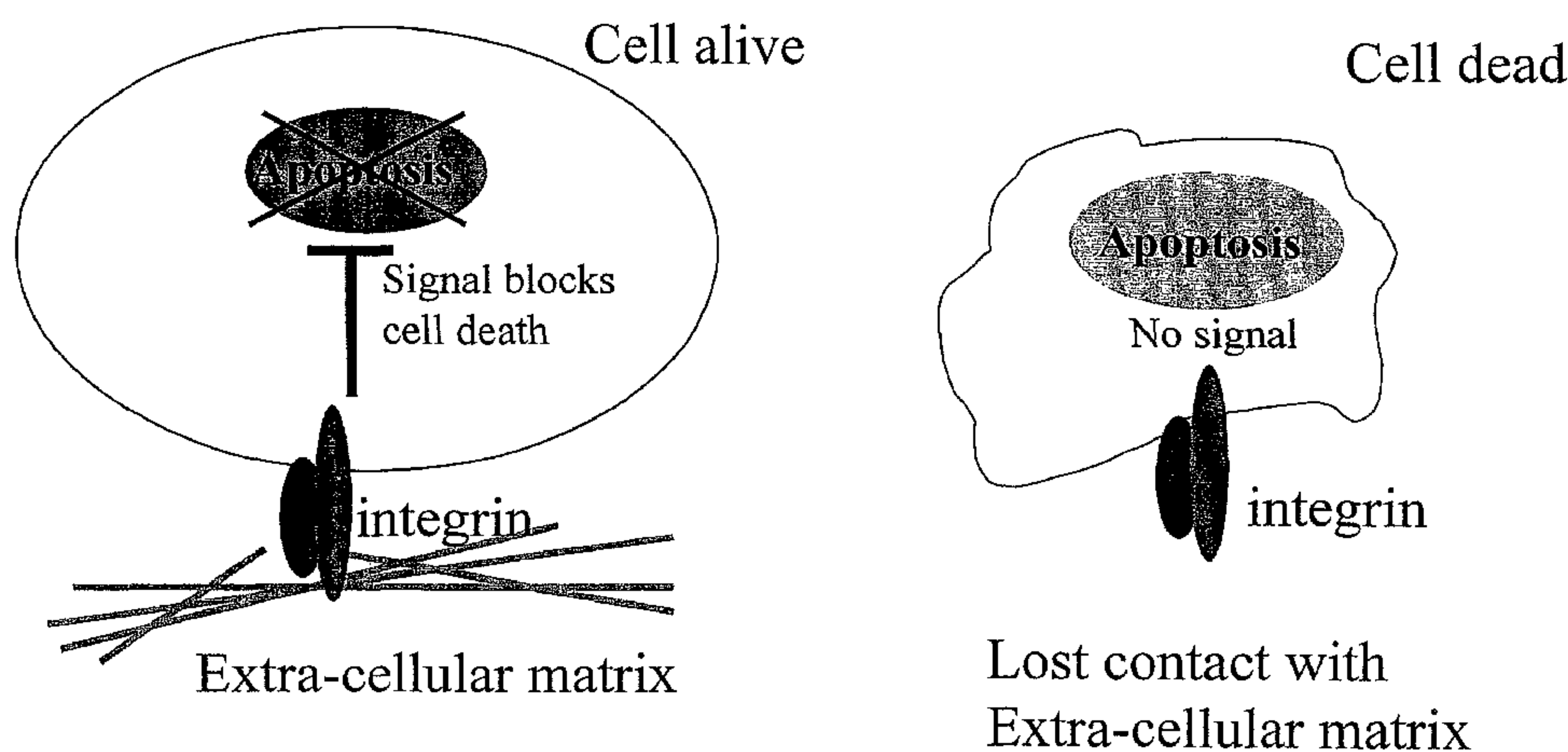
— with international search report

(88) Date of publication of the international search report:
13 March 2003

[Continued on next page]

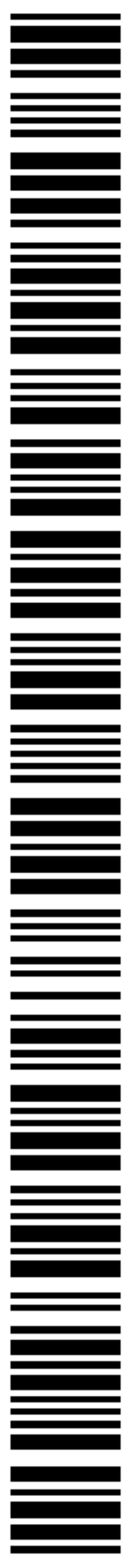
(54) Title: COMPOSITIONS THAT INHIBIT PROLIFERATION OF CANCER CELLS

Normal cells require integrin-matrix interactions for survival



Panel 1

(57) Abstract: Disclosed are compositions and methods for reducing the proliferation of cancer cells through targeted interactions with integrins.



WO 02/030465 A3

WO 02/030465 A3



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

COMPOSITIONS THAT INHIBIT PROLIFERATION OF CANCER CELLS

This application claims priority to United States Provisional Application No. 60/239,705 filed on October 12, 2000, entitled "Agents promoting apoptosis in cancer cells via interruption of oncogene-induced integrin signaling," which application is herein incorporated by reference in its entirety and to United States Provisional Application No. 60/242,812 filed on October 24, 2000 entitled, "Agents promoting apoptosis in cancer cells via interruption of oncogene-induced integrin signaling", and which application is herein incorporated by reference in its entirety.

I. BACKGROUND OF THE INVENTION

10 In cancer cells multiple oncogenic lesions cooperate in malignant transformation. Such cooperation permits survival and proliferation of tumor cells in absence of contact with extra-cellular matrix (ECM), suggesting that tumor cell survival and proliferation have become independent of the engagement of integrin signaling by ECM.

Carcinogenesis is caused by multiple cooperating genetic lesions leading to a progressive deregulation of cellular signaling and cell cycle restriction point control. The mutations involved result in oncogene activation or loss of tumor-suppressor gene function. Typically, single oncogenes are insufficient to cause malignant transformation because they simultaneously induce signals stimulating and inhibiting cell growth. As a result cell proliferation remains restricted. In contrast, cooperating oncogenic lesions act in concert to disable such inhibitory signals while reinforcing the growth-promoting stimuli. The co-operation of oncogenic lesions involves integration of multiple signals converging on the regulation of cell cycle-dependent kinase complexes (Lloyd *et al.*, 1997; Perez-Roger *et al.*, 1999; Roper *et al.*, 2001; Sewing *et al.*, 1997).

Disclosed herein are compositions and methods that show survival of various transformed cell types requires cell-autonomous (autocrine) integrin signaling activity. This activity is induced by cooperating oncogenic lesions and involves induction of integrin receptor and ligand components such as integrin alpha6 and integrin beta4, and laminin5-gamma2 chains. Blocking of integrin or the laminin ligand function induces rapid apoptosis of the transformed cells, even when growing in presence of ECM. In contrast, normal cells remain viable when exposed to the same treatment.

30 The disclosed compositions and methods are related to the cooperation of oncogenic lesions controlling the ability of transformed cells to proliferate in the absence of contact with the extra-cellular matrix (ECM). As taught herein, oncogenes cooperate to promote a cell-autonomous (autocrine) integrin signaling loop that proves essential for the survival of various transformed cell

types. As this signaling loop is not established in corresponding normal cells, the signaling components of this loop constitute attractive targets for cancer therapy.

II. SUMMARY OF THE INVENTION

In accordance with the purposes of this invention, as embodied and broadly described herein, this invention, in one aspect, relates to compositions and methods related to integrin mediated cancer cell growth.

Additional advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

III. BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several embodiments of the invention and together with the description, serve to explain the principles of the invention.

Figure 1 shows a series of schematics representative of the disclosed relationships and compositions. In normal cells integrin receptors signal to suppress programmed cell death (apoptosis) when engaged by appropriate extra-cellular matrix (ECM) ligands. When receptor-ligand interaction is lost, the cells undergo apoptosis due to the lack of survival signals (Figure 1-. Panel 1). In cancer cells multiple oncogenic lesions cooperate to cause malignant transformation. Such cooperation permits survival and proliferation of tumor cells independent of integrin receptor-ECM interactions. This property has been termed anchorage-independence (Panel 2). We have discovered the mechanistic basis of anchorage-independence. The transformed cells replace the requirement for ECM-dependent signaling with a surrogate integrin signaling loop on which they rely for survival. In colonic epithelial cells, activation of Ras in combination with APC (adenomatous polyposis coli) or p53 mutations leads to induction of integrin receptor and ligand components such as integrin alpha6 and laminin gamma2 chains. As a consequence, laminin-dependent activation of alpha6/beta4 integrin receptors signals to inhibit caspase activity and thus to suppress apoptosis (Panel 3). Ablation of integrin alpha6, laminin ligand function or alpha6/beta4 integrin receptor function induces apoptosis of the transformed cells, even when growing in the presence of ECM. In contrast, non-transformed control cells remain viable when exposed to the same treatment, indicating that the dependence of the transformed cells on autocrine integrin signaling may be a particular feature of the cancer cell phenotype. The essential role of alpha6 integrin extends to various transformed cell types including mesenchymal and

SW480 human colon carcinoma cells. Thus inhibition of laminin/alpha6 integrin-mediated signaling is an important method to induce cancer cell-specific death in a variety of cell types (Panel 4).

Figure 2 shows that oncogene cooperation protects cells from apoptosis. Figure 2A shows control, APCm, Ras, APCm+Ras cells that were detached from collagen IV substrates with Trypsin/EDTA and kept in suspension at 2×10^5 cells/ml in RPMI 10%FCS for 12 h at 39°C. Subsequently TUNEL analysis was performed on poly-lysine treated slides. The percentage of tunel-positive cells was determined by immunofluorescence microscopy. Figure 2B shows control, APCm, Ras, APCm Ras, SW480 cells were detached and maintained in suspension as described in (A). SW480 beta4 dn/Gal4VPER cells, express a 4OH-tamoxifen-inducible dominant-negative form of the beta4 integrin. Cells were pelleted and protein extracts were prepared in 300 μ l of 50 mM Tris-HCl, pH 7.4; 1% NP40 ; 0.25% sodium deoxycholate; 150 mM NaCl ; 1 mM EGTA. 200 μ l of extracts were incubated for 10 min with 2 μ l of Caspase 3 fluorometric Substrate (Upstate Biotechnology). Vmax of caspase activity was determined by measuring the fluorescence at 460 nm after excitation at 380 nm for 1 h. Figure 2C shows laminin gamma1 and gamma2-specific peptides were added to APCmin+Ras cells at the concentration of 100 μ g/ml. Caspase activity was measured as in (B). Figure 2D shows caspase 8 and caspase 9 activities were measured as in (B) using caspase 8 and caspase 9-specific fluorimetric substrates (Upstate Biotechnologies).

Figure 3 shows alterations of integrin and laminin expression profiles in malignant cell transformation. Figure 3A shows integrin expression and figure 3B shows laminin expression. The indicated cell populations were cultured on collagen IV-coated dishes at 39°C in RPMI 10% FCS. Total RNA was extracted from 10^6 cells for each sample and used for RT-PCR (laminins, alpha4, gamma2 and GAPDH) or RNase protection. For RT-PCR, cDNA was subjected to 28 cycles (linear range) of PCR amplification. PCR products were analyzed on a 2% agarose gel. For RNase protection, 10 μ g of total RNA was used per reaction. Products were resolved on a 4.5% polyacrylamide/10M urea gel.

Figure 4 shows alpha6/beta4 integrin is engaged by the laminin gamma2 chain to activate Shc (a src homology domain containing protein). Figure 4A shows cells detached from collagen IV coated dishes with 3mM EDTA (in PBS) were incubated on ice with the indicated antibodies for 1 h. Cells were then plated on 96well dishes coated with gamma1 or gamma2-specific peptides and were permitted to attach for 30 min in RPMI medium at 39°C. After incubation, wells were washed with RPMI. The percentage of attached cells per well was measured by hexoaminidase activity after lysis of the cells in the well and incubation with the substrate p-nitrophenol-N-acetyl- β -D-glucosaminide for 5 h at 37°C. Figure 4B shows cells indicated were detached as in (A) and

resuspended at 10^7 cells/ml in PBS. After 1 h of incubation on ice, cells were pelleted by centrifugation 5 min at 900 rpm and resuspended in RPMI containing the phosphatase inhibitor pervanadate at $10\mu\text{M}$. The cells were incubated with beta1 and beta4 integrin antibodies as well as the laminin gamma2-specific peptide for 40 min. Protein extracts were prepared and subjected to
 5 an immuno-precipitation with an anti-Shc antibody. Phospho-tyrosine was detected with a phospho-tyrosine-specific antibody in IP-western-blots (upper panels). The levels of Shc protein were monitored with a Shc-specific antibody reusing the same membrane (lower panels).

Figure 5 shows integrin alpha6/beta4 and Laminin gamma2 chain expression is essential for survival of transformed cells. Figure 5A1 shows the indicated cell populations were infected at
 10 an MOI of 2 with recombinant retroviruses expressing anti-sense RNA for alpha6 integrin, the gamma2 laminin chain or a beta4 integrin dominant-negative mutant together with a puromycin resistance gene. After 2 weeks of selection with puromycin, colonies were stained with Giemsa and counted. APCm+Ras alpha6 and APCm+Ras p35 cells express the alpha6 integrin chain and the anti-apoptotic baculovirus p35, respectively. APCm+Ras cells were also plated on dishes pre-
 15 coated with a laminin gamma2-specific peptide. Figure 5A2 shows APCm+Ras hygro, APCm+Ras Bcl2 and APCm+Ras p35 cells express the hygromycin resistance marker, and the anti-apoptotic proteins Bcl2 or p35, respectively. The cells were infected at an MOI of 2 with retroviruses carrying the beta4 integrin dominant-negative mutant and a puromycin resistance gene, or the puromycin resistance gene alone. Cells (10^5) were maintained in soft agar at 39°C for
 20 two weeks after which macroscopically visible colonies were counted. Figure 5A3 shows the indicated cell populations were infected at an MOI of 2 with recombinant retroviruses, drug-selected and maintained as described in A1. Figure 5A4 shows the indicated cell populations were infected at an MOI of 2 with recombinant retroviruses expressing anti-sense RNA for alpha6 integrin, the beta4 integrin dominant-negative mutant or the puromycin resistance marker. Cells
 25 (10^5) were maintained in soft agar and evaluated as described in A2. Figure 5B shows the effect of the alpha6 anti-sense RNA expression on the cell surface expression of alpha6 integrin was monitored by FACS analysis using an anti-alpha6 rat monoclonal antibody and a FITC conjugated goat anti-rat antiserum as the secondary antibody (upper panel). Expression of the beta4 dominant-negative mutant was confirmed by RNase protection. A probe overlapping the c-
 30 terminal end of the beta4 dominant negative mRNA was used to measure beta4 integrin and beta4 dn expression in the same sample (lower panel). Figure 5C shows arf null mouse embryo fibroblasts (MEFs) that were infected with retroviruses expressing the oncogenes Myc and Ras. Cells were then additionally infected with a retroviruses expressing anti-sense RNA for alpha6 integrin or the beta4 integrin dominant-negative mutant as shown in (A). MEFS
 35 Ras/Myc/Arfnull+alpha6 sense express the alpha6 integrin chain. Figure 4D shows SW480 human

colon carcinoma cells that were infected as described in (A) using VSV pseudo-typed viruses. Infected cells were selected with puromycin in soft agar. Clones were counted 2 weeks after selection. SW480 beta4 dn/Gal4VPER cells, express a 4OH-tamoxifen-inducible dominant-negative form of the beta4 integrin. The cells (10^5) were maintained in soft agar for 2 weeks in
5 presence or absence of 4OH-tamoxifen.

IV. DETAILED DESCRIPTION

The present invention may be understood more readily by reference to the following detailed description of preferred embodiments of the invention and the Examples included therein and to the Figures and their previous and following description.

10 Before the present compounds, compositions, articles, devices, and/or methods are disclosed and described, it is to be understood that this invention is not limited to specific synthetic methods, specific recombinant biotechnology methods unless otherwise specified, or to particular reagents unless otherwise specified, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is
15 not intended to be limiting.

A. Definitions

As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the
20 like.

Ranges may be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment 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 will be understood that the particular value
25 forms another embodiment. It will be 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.

In this specification and in the claims which follow, reference will be made to a number of terms which shall be defined to have the following meanings:

"Optional" or "optionally" means that the subsequently described event or circumstance
30 may or may not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

"Primers" are a subset of probes which are capable of supporting some type of enzymatic manipulation and which can hybridize with a target nucleic acid such that the enzymatic manipulation can occur. A primer can be made from any combination of nucleotides or nucleotide

derivatives or analogs available in the art which do not interfere with the enzymatic manipulation.

“Probes” are molecules capable of interacting with a target nucleic acid, typically in a sequence specific manner, for example through hybridization. The hybridization of nucleic acids is well understood in the art and discussed herein. Typically a probe can be made from any
5 combination of nucleotides or nucleotide derivatives or analogs available in the art.

B. Compositions and methods

Disclosed are compositions and methods related to integrins and integrin signaling. It is shown herein that integrin alpha6, integrin beta4, and laminin5, through at least up regulation of the beta and gamma chains of laminin5, are upregulated in cancer cells. Integrin alpha6 and
10 integrin beta4 interact to form the integrin receptor, A6B4. The integrin receptor A6B4 specifically interacts with laminin5 and laminin5 specifically interacts with A6B4. Furthermore, it is shown that interference with the production or function of alpha6, beta4, or the laminin gamma2 chain not only prevents proliferation of the cancer cells, dependent on the upregulation of alpha6, beta4, and the laminin gamma2 chain, but that this kills the cancer cells as well. Alpha6 and beta4
15 signaling occur through the integrin receptor A6B4. Thus, interference with the formation of A6B4, will interfere with the function of A6B4, for example, the signaling of A6B4. Thus, disclosed are compositions and methods that interfere with the function of alpha6, beta4, laminin5, the laminin gamma2 chain, or A6B4. Also disclosed are compositions and methods that interfere with the function of molecules involved with the signal transduction that is connected to either
20 alpha6, beta4, laminin5, the laminin gamma2 chain, or A6B4. Also disclosed are methods for reducing the proliferation of cancer cells, as well as methods of killing cancer cells that involve using the compositions disclosed herein that interfere, reduce, or eliminate the function or the alpha6, beta4, laminin5, the laminin gamma2 chain, or A6B4 function.

Disclosed herein is a relationship between two types of molecules in a cancer cell. The
25 first type of molecule is an integrin receptor, composed of integrins, and the second type of molecule is a ligand that interacts with the integrin receptor, through the integrins. There are specificities that exist between the integrin receptors and their ligands. One aspect, disclosed herein is that when a cell goes from a non-cancerous state to a cancerous state, there is a co-upregulation of both the ligand (or parts of the ligand, such as subunits) and the cognate integrin
30 receptor. The co-upregulation of both types of molecules creates an autocrine loop situation, wherein the signaling pathways controlled by the integrin receptor become autonomously activated, rather than exogenously activated, as would normally occur. The upregulation of both types of molecules creates a more fully transformed cellular phenotype in which cancer cell survival depends on the autocrine loop. Now therapeutic activities can target both points in the
35 autocrine loop. Specific examples, of this co-upregulation in cancer cells are disclosed herein. For

example, laminin 5 (both the beta and gamma2 chains are upregulated) and integrin receptor alpha6beta4; laminin 10/11 and the integrin receptors alpha6beta1 and alpha3beta1.

As the Examples herein indicate which integrins, which integrin receptor, and which integrin ligand are involved in conferring cancer cells ability to grow in the absence of extra cellular matrix (ECM), also disclosed are methods using these integrins, integrin receptors and ligands to identify molecules that interact with them and/or interfere with their function.

1. Compositions

Disclosed are the components to be used to prepare the disclosed compositions as well as the compositions themselves to be used within the methods disclosed herein. These and other materials are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these materials are disclosed, while specific reference of each various individual and collective permutation of these compounds may not be explicitly disclosed, each is specifically contemplated and described herein. For example, if a particular beta4 or alpha6 is disclosed and discussed and a number of modifications that can be made to a number of molecules including the modifications to beta4 or alpha6 are discussed, specifically contemplated is each and every combination and permutation of these modifications and the modifications that are possible unless specifically indicated to the contrary. Thus, if a class of molecules A, B, and C are disclosed as well as a class of molecules D, E, and F and an example of a combination molecule, A-D is disclosed, then even if each is not individually recited, each is individually and collectively contemplated. Thus, combinations, A-E, A-F, B-D, B-E, B-F, C-D, C-E, and C-F are considered disclosed. Likewise, any subset or combination of these is also disclosed. Thus, for example, the sub-group of A-E, B-F, and C-E would be considered disclosed. This concept applies to all aspects of this application including, but not limited to, steps in methods of making and using the disclosed compositions. Thus, if there are a variety of additional steps that can be performed it is understood that each of these additional steps can be performed with any specific embodiment or combination of embodiments of the disclosed methods.

a) Integrins and their ligands

For proper embryonic development, tissue homeostasis, and wound healing, cell proliferation must be tightly regulated, both in space and over time. In particular, a cell must be able to sense its relationship to other cells and the extra-cellular matrix (ECM) and convert these positional cues into biochemical signals affecting the regulation of proliferation. Because of their ability to couple the recognition of positional cues to the activation of intracellular signaling pathways, adhesion receptors, such as integrins and cadherins, are likely to be necessary to achieve this goal.

The integrins mediate cell adhesion primarily by binding to distinct, although overlapping,

subsets of ECM proteins. Normal cells require contact with serum-derived ECM components for proliferation, differentiation and survival (e.g. Clark and Brugge, 1995; Lin and Bissell, 1993; Parise *et al.*, 2000), a phenomenon called anchorage-dependence. This involves signaling through integrin receptors (Hynes, 1992). Fibronectin and laminin as well as other ECM proteins are
 5 known to act as ligands for integrin receptors (Akiyama *et al.*, 1990). Integrins are transmembrane proteins forming alpha-beta chain heterodimers. Alpha and beta chain integrins are members of distinct gene families. The ligand binding specificity of the hetero dimers is determined by specific combinations of alpha and beta chain gene family members (Hynes, 1992). Ligand binding triggers signaling of integrin receptors through the cytoplasmic tail of the beta chain via
 10 interaction with various signaling components.

Integrins activate common as well as subgroup-specific signaling pathways (Clark and Brugge, 1995; Giancotti and Ruoslahti, 1999). In particular, while most integrins activate focal adhesion kinase (FAK), the $\alpha1\beta1$, $\alpha5\beta1$, $\alpha v\beta3$ and $\alpha6\beta4$ integrins are coupled to the Ras-extracellular signal-regulated kinase (ERK) signaling pathway by Shc (Mainiero *et al.*, 1997;
 15 Mainiero *et al.*, 1995; Wary *et al.*, 1996). Shc is an SH2-PTB domain adapter protein expressed in three forms, p46, p52 and p66, two of which (p46 and p52) link various tyrosine kinases to Ras by recruiting the Grb2/SOS complex to the plasma membrane (Pawson and Scott, 1997). Upon activation by SOS, Ras stimulates a kinase cascade culminating in the activation of the mitogen-activated protein kinase (MAPK) ERK (Marshall, 1995). ERK phosphorylates ternary complex
 20 transcription factors, such as Elk-1 and Sap-1/2, and promotes transcription of the immediate-early gene Fos (Treisman, 1996). In primary endothelial cells and keratinocytes, mitogens and Shc-linked integrins cooperate, in a synergic fashion, to promote transcription from the Fos promoter. Accordingly, ligation of integrins linked to Shc enables these cells to progress through G1 in response to mitogens, whereas ligation of other integrins results in growth arrest, even in the
 25 presence of mitogens (Mainiero *et al.*, 1997; Wary *et al.*, 1996). Shc is like a binary switch controlling cell cycle progression in response to the ECM. Moreover, integrin receptors have been shown to induce intracellular signaling leading to AKT activation supporting cell survival (Lee and Juliano, 2000).

In contrast with normal cells, cancer cells generally are able to survive and proliferate in
 30 the absence of anchorage to ECM (Giancotti and Mainiero, 1994), suggesting that tumor cell survival and proliferation have become independent of the engagement of integrin signaling through ECM.

Proliferation in the absence of anchorage to ECM of secondary rat embryo fibroblasts requires the cooperation of Ras and Myc or Ras and adenovirus E1a oncogenes (Land et al., 1983;
 35 Ruley, 1983). Similarly, murine colonic epithelial cells require both activated Ras and mutation of

the adenomous polyposis coli gene (APC^{min}) (D'Abaco et al., 1996) in order to proliferate in suspension.

Integrins are a large family of cell surface receptor molecules that function to mediate interactions between cells and between cells and the extracellular matrix. Integrin receptors are
5 heterodimers composed of two subunits, an alpha integrin and a beta integrin. The heterodimer forms, is expressed on the cell surface, and acts to transmit signals obtained from interactions with the extracellular matrix or other cells, through the cellular membrane and into the cytosol of the cell. The signal transduction that takes place occurs because of ligand interactions with the receptor. Integrin receptors can have a number of ligands, including collagens, fibronectins, and
10 laminins.

There are currently at least 18 different alpha integrins and at least 8 different beta integrins that have been shown to form at least 24 different alphabeta heterodimers. Certain integrins, such as beta1, interact in a number of different heterodimers, but many subunits only form a single heterodimer, either because of structural constraints on their interactions, or cellular
15 expression patterns that provide only a limited number of potential dimer partners. Disclosed herein are specific relationships that occur between a subset of integrins, integrin receptors, and their ligands. The disclosed relationships, revolve around the alpha6beta4 receptor, formed by the alpha6 and beta4 integrins. Of particular interest is the relationship between the ligand for the alpha6beta4 receptor, laminin5. The laminins are made up of 3 chains, an alpha chain, a beta
20 chain, and a gamma chain. The specificity of the interaction between laminin5 and alpha6beta4 receptor is controlled by the gamma chain. Laminin5 contains a gamma2 chain which only interacts with the alpha6beta4 integrin receptor.

Integrin alpha6 has seven amino-terminal repeating segments that may fold into a seven unit beta-propeller, five n-terminal FG-GAP domains and three divalent cation sites. The
25 transmembrane domain is followed by a short cytoplasmic tail, that is alternatively spliced in A and B forms. The alpha6 integrin chain also shows alternative splicing between repeat units III and IV, resulting in the presence or absence of Exon X2. Integrin alpha6 is processed into a heavy and a light chain that are disulphide linked. A representative allele of the human alpha6 cDNA is set forth in SEQ ID NO:1. It is understood that the disclosed functional domains as well as the
30 others contained within alpha6 are considered separately disclosed as discreet fragments of the alpha6 protein as well as the nucleic acid that encodes them.

Integrin beta4 contains a MIDAS-like motif and four cysteine-rich repeats, three EGF-like domains in the N-terminal extracellular domain, a trans-membrane region and a long cytoplasmic tail containing two pairs of fibronectin Type III repeats. The latter are connected by a variable
35 segment that may undergo alternative splicing. Integrin beta4 also undergoes proteolytic

processing in its cytoplasmic tail, causing the 200kD mature form to be converted to 165 and 130kD fragments. A representative allele of the human beta4 cDNA is set forth in SEQ ID NO:5. It is understood that the disclosed functional domains as well as the others contained within beta4 are considered separately disclosed as discreet fragments of the beta4 protein as well as the nucleic acid that encodes them.

Laminin5 is composed of the laminin chains alpha3, beta3 and gamma2. Laminin5 can may contain either the shorter laminin alpha3A chain or the longer alpha3B chain. Laminin5 can also be trimmed by proteolytic processing of the N-terminal portion of its alpha3A chain and the N-terminal portion of the gamma2 chain. The Laminin gamma2 chain contains at least six laminin EGF-like domains (Domains III and V) with an embedded laminin B domain (Domain IV) within the N-terminal half. The c-terminal tail contains a coiled-coil domain. The N-terminal processed portion of the gamma2 chain is sufficient to bind to and activate the integrin alpha6/beta4 receptor. A representative allele of the human laminin5-gamma2 cDNA is set forth in SEQ ID NO:13. It is understood that the disclosed functional domains as well as the others contained within the laminin5 protein and laminin5-gamma2 protein are considered separately disclosed as discreet fragments of the laminin5 protein and laminin5-gamma2 protein as well as and the nucleic acid that encodes them.

Disclosed are compositions and methods for inhibiting integrin signaling, for example, integrin signaling dependent on alpha6 and beta4 integrins. For example, compositions and methods that inhibit integrin receptor signaling from, for example, the alpha6beta4 integrin receptor are disclosed. It is also understood that the integrin receptor signaling can be affected by, for example, interfering with a molecule, such as a ligand for the integrin receptor, or a downstream signaling molecule of the integrin receptor in a way that prevents the integrin receptor signal from being fully propagated. It is understood that the compositions and methods for inhibition of integrin signaling and function can be any composition or method that ultimately inhibits the cell proliferation in which the integrin is expressed, by for example killing the cell. It is understood that the compositions and methods typically can fall into three basic non-limiting classes of function regulators, which are discussed herein.

(1) Classes

(a) Production regulators

Production regulators is a broad class of integrin function regulators that are directed at the production of the target integrin, by for example, preventing mRNA synthesis or expression of the target integrin, or by causing mRNA degradation of the target integrin which inhibits the translation of the target integrin. While production regulators, can be any type of molecule targeting any point in the integrin production pathway, typically these types of compositions will

target either the mRNA expression or the protein expression of the integrin. For example, if beta4 integrin, alpha6 integrin, or the gamma2 subunit of laminin5, which has been shown herein to be upregulated in cancer cells and which causes the cancer cell to be able to live in the absence of the ECM, was the target integrin, a typical production regulator of beta4 integrin, alpha6 integrin, or the gamma2 subunit of laminin5 would be for example, an antisense molecule that targeted the mRNA of beta4 integrin, alpha6 integrin, or the gamma2 subunit of laminin5. It is also understood that a production regulator could also target any molecule that is disclosed herein, or is within the signaling chain associated with a target integrin or integrin receptor. For example, the inhibition of the production of the ligand for a target integrin receptor is one way of inhibiting integrin function of that receptor. Thus, production regulators can either inhibit or enhance integrin production.

(b) Integrin to integrin regulators

Another type of integrin function regulator is an integrin-integrin regulator. This type of function regulator, typically prevents integrins from interacting to form a functional integrin receptor. For example, an integrin to integrin regulator could be a composition that would interact with beta4 in a way that would prevent beta4 from interacting with alpha6 to form the alpha6beta4 integrin receptor or it could be a composition that would interact with alpha6 in a way that would prevent alpha6 from interacting with beta4 to form the alpha6beta4 integrin receptor. It is also contemplated that the function regulators of the integrin to integrin interaction can affect the signaling pathways dependent on integrin receptors containing alpha6 or beta4 integrins. It is not required that an integrin to integrin regulator prevent an integrin from interacting with all of the possible integrin partners it could interact with, just that it prevent the interaction of the target integrin with another specific integrin. For example, the integrin alpha6 interacts with beta1 integrin and beta4 integrin. In certain embodiments, the compositions interfere with alpha6-beta4 interactions but do not interfere with alpha6-beta1 interactions.

(c) Integrin to other molecule regulators

The third class of function regulators are the integrin to other molecule regulators. These compositions are designed to specifically interfere with molecules such as small molecule ligands or other proteins that interact with the integrin or integrin receptor. For example, an integrin to other molecule regulator might target a ligand for a particular integrin receptor, such as the alpha6beta4 receptor. The ligand for the alpha6beta4 receptor is laminin5 or the laminin gamma2 chain. Compositions that interact with laminin5 such that laminin5 or the laminin gamma2 chain interactions with alpha6beta4 are inhibited or reduced are specifically contemplated herein. Likewise, there are other molecules, such as Shc molecules, that also interact with integrins, such as the alpha6beta4 receptor. Compositions that specifically interact with the Shc molecules such that they prevent the appropriate interactions between the Shc molecule and the alpha6beta4

receptor are disclosed.

(2) Types

Just as there are different general classes of molecules that can regulate (such as by inhibition) the function of the disclosed integrins and integrin receptors, so to there are many different types of molecules that perform that regulation. For example, any molecule that can perform the regulation of for example, the disclosed integrins, integrin receptors, or signaling pathways produced by the disclosed integrins and integrin receptors are contemplated. For example, antibodies or small molecules which inhibit the disclosed compositions are herein disclosed. Also disclosed are, for example, functional nucleic acids, such as ribozymes or antisense molecules that can inhibit the disclosed integrin function in a variety of ways. A non-limiting list of exemplary molecules is discussed herein.

(a) Antibodies

Antibodies can be used to regulate, for example, the function of the disclosed integrins and integrin receptors, molecules that interact with the disclosed integrin receptors, and molecules in the signaling pathways of the disclosed integrin receptors.

As used herein, the term "antibody" encompasses, but is not limited to, whole immunoglobulin (i.e., an intact antibody) of any class. Native antibodies are usually heterotetrameric glycoproteins, composed of two identical light (L) chains and two identical heavy (H) chains. Typically, each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies between the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain (V(H)) followed by a number of constant domains. Each light chain has a variable domain at one end (V(L)) and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain. Particular amino acid residues are believed to form an interface between the light and heavy chain variable domains. The light chains of antibodies from any vertebrate species can be assigned to one of two clearly distinct types, called kappa (k) and lambda (l), based on the amino acid sequences of their constant domains. Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of human immunoglobulins: IgA, IgD, IgE, IgG and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG-1, IgG-2, IgG-3, and IgG-4; IgA-1 and IgA-2. One skilled in the art would recognize the comparable classes for mouse. The heavy chain constant domains that correspond to the different classes of immunoglobulins are called alpha, delta, epsilon, gamma, and mu, respectively.

Antibodies can be either polyclonal or monoclonal. Polyclonal antibodies, typically are derived from the serum of an animal that has been immunogenically challenged, and monoclonal antibodies are derived as discussed herein.

The term “variable” is used herein to describe certain portions of the variable domains that
5 differ in sequence among antibodies and are used in the binding and specificity of each particular antibody for its particular antigen. However, the variability is not usually evenly distributed through the variable domains of antibodies. It is typically concentrated in three segments called complementarity determining regions (CDRs) or hypervariable regions both in the light chain and the heavy chain variable domains. The more highly conserved portions of the variable domains
10 are called the framework (FR). The variable domains of native heavy and light chains each comprise four FR regions, largely adopting a b-sheet configuration, connected by three CDRs, which form loops connecting, and in some cases forming part of, the b-sheet structure. The CDRs in each chain are held together in close proximity by the FR regions and, with the CDRs from the other chain, contribute to the formation of the antigen binding site of antibodies (see Kabat E. A.
15 et al., “Sequences of Proteins of Immunological Interest,” National Institutes of Health, Bethesda, Md. (1987)). 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 toxicity.

As used herein, the term “antibody or fragments thereof” encompasses chimeric antibodies
20 and hybrid antibodies, with dual or multiple antigen or epitope specificities, and fragments, such as F(ab')₂, Fab', Fab and the like, including hybrid fragments. Thus, fragments of the antibodies that retain the ability to bind their specific antigens are provided. For example, fragments of antibodies which maintain EphA2 binding activity are included within the meaning of the term “antibody or fragment thereof.” Such antibodies and fragments can be made by techniques known in the art and
25 can be screened for specificity and activity according to the methods set forth in the Examples and in general methods for producing antibodies and screening antibodies for specificity and activity (See Harlow and Lane. Antibodies, A Laboratory Manual. Cold Spring Harbor Publications, New York, (1988)).

Also included within the meaning of “antibody or fragments thereof” are conjugates of
30 antibody fragments and antigen binding proteins (single chain antibodies) as described, for example, in U.S. Pat. No. 4,704,692, the contents of which are hereby incorporated by reference. Single chain divalent antibodies are also provided.

Optionally, the antibodies are generated in other species and “humanized” for
administration in humans. Humanized forms of non-human (e.g., murine) antibodies are chimeric
35 immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')₂, or

other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or
5 rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or
10 substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin (Jones et al., *Nature*, 321:522-525 (1986); Riechmann et al., *Nature*, 332:323-327 (1988); and Presta, *Curr. Op. Struct. Biol.*, 2:593-
15 596 (1992)).

Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody 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 can be essentially
20 performed following the method of Winter and co-workers (Jones et al., *Nature*, 321:522-525 (1986); Riechmann et al., *Nature*, 332:323-327 (1988); Verhoeyen et al., *Science*, 239:1534-1536 (1988)), by substituting rodent CDRs or CDR 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
25 substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

The choice of human variable domains, both light and heavy, to be used in making the humanized antibodies is very important in order to reduce antigenicity. According to the "best-fit"
30 method, the sequence of the variable domain of a rodent antibody is screened against the entire library of known human variable domain sequences. The human sequence which is closest to that of the rodent is then accepted as the human framework (FR) for the humanized antibody (Sims et al., *J. Immunol.*, 151:2296 (1993) and Chothia et al., *J. Mol. Biol.*, 196:901 (1987)). Another method uses a particular framework derived from the consensus sequence of all human antibodies
35 of a particular subgroup of light or heavy chains. The same framework may be used for several different humanized antibodies (Carter et al., *Proc. Natl. Acad. Sci. USA*, 89:4285 (1992);

Presta et al., J. Immunol., 151:2623 (1993)).

It is further important that antibodies be humanized with retention of high affinity for the antigen and other favorable biological properties. To achieve this goal, according to a preferred method, humanized antibodies are prepared by a process of analysis of the parental sequences and
5 various conceptual humanized products using three dimensional models of the parental and humanized sequences. Three dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the
10 residues in the functioning of the candidate immunoglobulin sequence, i.e., the analysis of residues that influence the ability of the candidate immunoglobulin to bind its antigen. In this way, FR residues can be selected and combined from the consensus and import sequence so that the desired antibody characteristic, such as increased affinity for the target antigen(s), is achieved. In general, the CDR residues are directly and most substantially involved in influencing antigen binding (see,
15 WO 94/04679, published 3 March 1994).

Transgenic animals (e.g., mice) that are capable, upon immunization, of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production can be employed. For example, it has been described that the homozygous deletion of the antibody heavy chain joining region (J(H)) gene in chimeric and germ-line mutant mice results in complete
20 inhibition of endogenous antibody production. Transfer of the human germ-line immunoglobulin gene array in such germ-line mutant mice will result in the production of human antibodies upon antigen challenge (see, e.g., Jakobovits et al., Proc. Natl. Acad. Sci. USA, 90:2551-255 (1993); Jakobovits et al., Nature, 362:255-258 (1993); Bruggemann et al., Year in Immuno., 7:33 (1993)). Human antibodies can also be produced in phage display libraries (Hoogenboom et al., J. Mol.
25 Biol., 227:381 (1991); Marks et al., J. Mol. Biol., 222:581 (1991)). The techniques of Cote et al. and Boerner et al. are also available for the preparation of human monoclonal antibodies (Cole et al., Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, p. 77 (1985); Boerner et al., J. Immunol., 147(1):86-95 (1991)).

The present invention further provides a hybridoma cell that produces the monoclonal
30 antibody of the invention. The term "monoclonal antibody" as used herein refers to an antibody obtained from a substantially homogeneous population of antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. The monoclonal antibodies herein specifically include "chimeric" antibodies in which a portion of the heavy and/or light chain is identical with or homologous to
35 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 activity (See, U.S. Pat. No. 4,816,567 and Morrison et al., Proc. Natl. Acad. Sci. USA, 81:6851-6855 (1984)).

Monoclonal antibodies of the invention may be prepared using hybridoma methods, such as those described by Kohler and Milstein, Nature, 256:495 (1975) or Harlow and Lane. Antibodies, A Laboratory Manual. Cold Spring Harbor Publications, New York, (1988). In a hybridoma method, a mouse or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes may be immunized in vitro. Preferably, the immunizing agent comprises EphA2. Traditionally, the generation of monoclonal antibodies has depended on the availability of purified protein or peptides for use as the immunogen. More recently DNA based immunizations have shown promise as a way to elicit strong immune responses and generate monoclonal antibodies. In this approach, DNA-based immunization can be used, wherein DNA encoding a portion of EphA2 expressed as a fusion protein with human IgG1 is injected into the host animal according to methods known in the art (e.g., Kilpatrick KE, et al. Gene gun delivered DNA-based immunizations mediate rapid production of murine monoclonal antibodies to the Flt-3 receptor. Hybridoma. 1998 Dec;17(6):569-76; Kilpatrick KE et al. High-affinity monoclonal antibodies to PED/PEA-15 generated using 5 microg of DNA. Hybridoma. 2000 Aug;19(4):297-302, which are incorporated herein by referenced in full for the methods of antibody production).

An alternate approach to immunizations with either purified protein or DNA is to use antigen expressed in baculovirus. The advantages to this system include ease of generation, high levels of expression, and post-translational modifications that are highly similar to those seen in mammalian systems. Use of this system involves expressing domains of EphA2 antibody as fusion proteins. The antigen is produced by inserting a gene fragment in-frame between the signal sequence and the mature protein domain of the EphA2 antibody nucleotide sequence. This results in the display of the foreign proteins on the surface of the virion. This method allows immunization with whole virus, eliminating the need for purification of target antigens.

Generally, peripheral blood lymphocytes ("PBLs") are used in methods of producing monoclonal antibodies if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, "Monoclonal Antibodies: Principles and Practice" Academic Press,

(1986) pp. 59-103). Immortalized cell lines are usually transformed mammalian cells, including myeloma cells of rodent, bovine, equine, and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells may be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, 5 immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells. Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing 10 cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San Diego, Calif. and the American Type Culture Collection, Rockville, Md. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor, J. Immunol., 133:3001 (1984); Brodeur et 15 al., "Monoclonal Antibody Production Techniques and Applications" Marcel Dekker, Inc., New York, (1987) pp. 51-63).

The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against EphA2. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or 20 by an in vitro binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art, and are described further in the Examples below or in Harlow and Lane "Antibodies, A Laboratory Manual" Cold Spring Harbor Publications, New York, (1988).

After the desired hybridoma cells are identified, the clones may be subcloned by limiting 25 dilution or FACS sorting procedures and grown by standard methods. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells may be grown in vivo as ascites in a mammal.

The monoclonal antibodies secreted by the subclones may be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, 30 for example, protein A-Sepharose, protein G, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

The monoclonal antibodies may also be made by recombinant DNA methods, such as those described in U.S. Pat. No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (e.g., by using 35 oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and

light chains of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, plasmacytoma cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also may be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences (U.S. Pat. No. 4,816,567) or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Optionally, such a non-immunoglobulin polypeptide is substituted for the constant domains of an antibody of the invention or substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody comprising one antigen-combining site having specificity for EphA2 and another antigen-combining site having specificity for a different antigen.

In vitro methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly, Fab fragments, can be accomplished using routine techniques known in the art. For instance, digestion can be performed using papain. Examples of papain digestion are described in WO 94/29348 published Dec. 22, 1994, U.S. Pat. No. 4,342,566, and Harlow and Lane, *Antibodies, A Laboratory Manual*, Cold Spring Harbor Publications, New York, (1988). Papain digestion of antibodies typically produces two identical antigen binding fragments, called Fab fragments, each with a single antigen binding site, and a residual Fc fragment. Pepsin treatment yields a fragment, called the F(ab')₂ fragment, that has two antigen combining sites and is still capable of cross-linking antigen.

The Fab fragments produced in the antibody digestion also contain the constant domains of the light chain and the first constant domain of the heavy chain. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxy terminus of the heavy chain domain including one or more cysteines from the antibody hinge region. The F(ab')₂ fragment is a bivalent fragment comprising two Fab' fragments linked by a disulfide bridge at the 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. Antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

An isolated immunogenically specific paratope or fragment of the antibody is also provided. A specific immunogenic epitope of the antibody can be isolated from the whole antibody by chemical or mechanical disruption of the molecule. The purified fragments thus obtained are tested to determine their immunogenicity and specificity by the methods taught

herein. Immunoreactive paratopes of the antibody, optionally, are synthesized directly. An immunoreactive fragment is defined as an amino acid sequence of at least about two to five consecutive amino acids derived from the antibody amino acid sequence.

One method of producing proteins comprising the antibodies of the present invention is to link two or more peptides or polypeptides together by protein chemistry techniques. For example, peptides or polypeptides can be chemically synthesized using currently available laboratory equipment using either Fmoc (9-fluorenylmethyloxycarbonyl) or Boc (tert -butyloxycarbonyl) chemistry. (Applied Biosystems, Inc., Foster City, CA). One skilled in the art can readily appreciate that a peptide or polypeptide corresponding to the antibody of the present invention, for example, can be synthesized by standard chemical reactions. For example, a peptide or polypeptide can be synthesized and not cleaved from its synthesis resin whereas the other fragment of an antibody can be synthesized and subsequently cleaved from the resin, thereby exposing a terminal group which is functionally blocked on the other fragment. By peptide condensation reactions, these two fragments can be covalently joined via a peptide bond at their carboxyl and amino termini, respectively, to form an antibody, or fragment thereof. (Grant GA (1992) *Synthetic Peptides: A User Guide*. W.H. Freeman and Co., N.Y. (1992); Bodansky M and Trost B., Ed. (1993) *Principles of Peptide Synthesis*. Springer-Verlag Inc., NY. Alternatively, the peptide or polypeptide is independently synthesized in vivo as described above. Once isolated, these independent peptides or polypeptides may be linked to form an antibody or fragment thereof via similar peptide condensation reactions.

For example, enzymatic ligation of cloned or synthetic peptide segments allow relatively short peptide fragments to be joined to produce larger peptide fragments, polypeptides or whole protein domains (Abrahmsen L et al., *Biochemistry*, 30:4151 (1991)). Alternatively, native chemical ligation of synthetic peptides can be utilized to synthetically construct large peptides or polypeptides from shorter peptide fragments. This method consists of a two step chemical reaction (Dawson et al. *Synthesis of Proteins by Native Chemical Ligation*. *Science*, 266:776-779 (1994)). The first step is the chemoselective reaction of an unprotected synthetic peptide-alpha-thioester with another unprotected peptide segment containing an amino-terminal Cys residue to give a thioester-linked intermediate as the initial covalent product. Without a change in the reaction conditions, this intermediate undergoes spontaneous, rapid intramolecular reaction to form a native peptide bond at the ligation site. Application of this native chemical ligation method to the total synthesis of a protein molecule is illustrated by the preparation of human interleukin 8 (IL-8) (Baggiolini M et al. (1992) *FEBS Lett.* 307:97-101; Clark-Lewis I et al., *J.Biol.Chem.*, 269:16075 (1994); Clark-Lewis I et al., *Biochemistry*, 30:3128 (1991); Rajarathnam K et al., *Biochemistry* 33:6623-30 (1994)).

Alternatively, unprotected peptide segments are chemically linked where the bond formed between the peptide segments as a result of the chemical ligation is an unnatural (non-peptide) bond (Schnolzer, M et al. Science, 256:221 (1992)). This technique has been used to synthesize analogs of protein domains as well as large amounts of relatively pure proteins with full biological activity (deLisle Milton RC et al., Techniques in Protein Chemistry IV. Academic Press, New York, pp. 257-267 (1992)).

The invention also provides fragments of antibodies which have bioactivity. The polypeptide fragments of the present invention can be recombinant proteins obtained by cloning nucleic acids encoding the polypeptide in an expression system capable of producing the polypeptide fragments thereof, such as an adenovirus or baculovirus expression system. For example, one can determine the active domain of an antibody from a specific hybridoma that can cause a biological effect associated with the interaction of the antibody with EphA2. For example, amino acids found to not contribute to either the activity or the binding specificity or affinity of the antibody can be deleted without a loss in the respective activity. For example, in various embodiments, amino or carboxy-terminal amino acids are sequentially removed from either the native or the modified non-immunoglobulin molecule or the immunoglobulin molecule and the respective activity assayed in one of many available assays. In another example, a fragment of an antibody comprises a modified antibody wherein at least one amino acid has been substituted for the naturally occurring amino acid at a specific position, and a portion of either amino terminal or carboxy terminal amino acids, or even an internal region of the antibody, has been replaced with a polypeptide fragment or other moiety, such as biotin, which can facilitate in the purification of the modified antibody. For example, a modified antibody can be fused to a maltose binding protein, through either peptide chemistry or cloning the respective nucleic acids encoding the two polypeptide fragments into an expression vector such that the expression of the coding region results in a hybrid polypeptide. The hybrid polypeptide can be affinity purified by passing it over an amylose affinity solid support, and the modified antibody receptor can then be separated from the maltose binding region by cleaving the hybrid polypeptide with the specific protease factor Xa. (See, for example, New England Biolabs Product Catalog, 1996, pg. 164.). Similar purification procedures are available for isolating hybrid proteins from eukaryotic cells as well.

The fragments, whether attached to other sequences or not, include insertions, deletions, substitutions, or other selected modifications of particular regions or specific amino acids residues, provided the activity of the fragment is not significantly altered or impaired compared to the nonmodified antibody or antibody fragment. These modifications can provide for some additional property, such as to remove or add amino acids capable of disulfide bonding, to increase its bio-longevity, to alter its secretory characteristics, etc. In any case, the fragment must possess a bioactive property, such as binding activity, regulation of binding at the binding domain, etc.

Functional or active regions of the antibody may be identified by mutagenesis of a specific region of the protein, followed by expression and testing of the expressed polypeptide. Such methods are readily apparent to a skilled practitioner in the art and can include site-specific mutagenesis of the nucleic acid encoding the antigen. (Zoller MJ et al. Nucl. Acids Res. 10:6487-500 (1982).

5 A variety of immunoassay formats may be used to select antibodies that selectively bind with a particular protein, variant, or fragment. For example, solid-phase ELISA immunoassays are routinely used to select antibodies selectively immunoreactive with a protein, protein variant, or fragment thereof. See Harlow and Lane. Antibodies, A Laboratory Manual. Cold Spring Harbor Publications, New York, (1988), for a description of immunoassay formats and conditions that
10 could be used to determine selective binding. The binding affinity of a monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson et al., Anal. Biochem., 107:220 (1980).

Also provided is an antibody reagent kit comprising containers of the monoclonal antibody or fragment thereof of the invention and one or more reagents for detecting binding of the antibody
15 or fragment thereof to the EphA2 receptor molecule. The reagents can include, for example, fluorescent tags, enzymatic tags, or other tags. The reagents can also include secondary or tertiary antibodies or reagents for enzymatic reactions, wherein the enzymatic reactions produce a product that can be visualized.

(b) Functional Nucleic Acids

20 Functional nucleic acids can also be used to regulate the , for example, the function of the disclosed integrins, integrin receptors, molecules that interact with the disclosed integrin receptors, and molecules in the signaling pathways of the disclosed integrin receptors.

Functional nucleic acids are nucleic acid molecules that have a specific function, such as binding a target molecule or catalyzing a specific reaction. Functional nucleic acid molecules can
25 be divided into the following categories, which are not meant to be limiting. For example, functional nucleic acids include antisense molecules, aptamers, ribozymes, triplex forming molecules, and external guide sequences. The functional nucleic acid molecules can act as effectors, inhibitors, modulators, and stimulators of a specific activity possessed by a target molecule, or the functional nucleic acid molecules can possess a de novo activity independent of
30 any other molecules.

Functional nucleic acid molecules can interact with any macromolecule, such as DNA, RNA, polypeptides, or carbohydrate chains. Thus, functional nucleic acids can interact with the mRNA of beta4 integrin for example, or the genomic DNA of alpha6 integrin for example, or they can interact with the polypeptide laminin5, or the gamma2 subunit of laminin5. Often functional
35 nucleic acids are designed to interact with other nucleic acids based on sequence homology

between the target molecule and the functional nucleic acid molecule. In other situations, the specific recognition between the functional nucleic acid molecule and the target molecule is not based on sequence homology between the functional nucleic acid molecule and the target molecule, but rather is based on the formation of tertiary structure that allows specific recognition to take place. Antisense molecules are designed to interact with a target nucleic acid molecule through either canonical or non-canonical base pairing. The interaction of the antisense molecule and the target molecule is designed to promote the destruction of the target molecule through, for example, RNaseH mediated RNA-DNA hybrid degradation. Alternatively the antisense molecule is designed to interrupt a processing function that normally would take place on the target molecule, such as transcription or replication. Antisense molecules can be designed based on the sequence of the target molecule. Numerous methods for optimization of antisense efficiency by finding the most accessible regions of the target molecule exist. Exemplary methods would be in vitro selection experiments and DNA modification studies using DMS and DEPC. It is preferred that antisense molecules bind the target molecule with a dissociation constant (k_d) less than 10^{-6} . It is more preferred that antisense molecules bind with a k_d less than 10^{-8} . It is also more preferred that the antisense molecules bind the target molecule with a k_d less than 10^{-10} . It is also preferred that the antisense molecules bind the target molecule with a k_d less than 10^{-12} . A representative sample of methods and techniques which aid in the design and use of antisense molecules can be found in the following non-limiting list of United States patents: 5,135,917, 5,294,533, 5,627,158, 5,641,754, 5,691,317, 5,780,607, 5,786,138, 5,849,903, 5,856,103, 5,919,772, 5,955,590, 5,990,088, 5,994,320, 5,998,602, 6,005,095, 6,007,995, 6,013,522, 6,017,898, 6,018,042, 6,025,198, 6,033,910, 6,040,296, 6,046,004, 6,046,319, and 6,057,437.

Aptamers are molecules that interact with a target molecule, preferably in a specific way. Typically aptamers are small nucleic acids ranging from 15-50 bases in length that fold into defined secondary and tertiary structures, such as stem-loops or G-quartets. Aptamers can bind small molecules, such as ATP (United States patent 5,631,146) and theophiline (United States patent 5,580,737), as well as large molecules, such as reverse transcriptase (United States patent 5,786,462) and thrombin (United States patent 5,543,293). Aptamers can bind very tightly with k_d s from the target molecule of less than 10^{-12} M. It is preferred that the aptamers bind the target molecule with a k_d less than 10^{-6} . It is more preferred that the aptamers bind the target molecule with a k_d less than 10^{-8} . It is also more preferred that the aptamers bind the target molecule with a k_d less than 10^{-10} . It is also preferred that the aptamers bind the target molecule with a k_d less than 10^{-12} . Aptamers can bind the target molecule with a very high degree of specificity. For example, aptamers have been isolated that have greater than a 10000 fold difference in binding affinities between the target molecule and another molecule that differ at only a single position on the molecule (United States patent 5,543,293). It is preferred that the aptamer have a k_d with the target

molecule at least 10 fold lower than the k_d with a background binding molecule. It is more preferred that the aptamer have a k_d with the target molecule at least 100 fold lower than the k_d with a background binding molecule. It is more preferred that the aptamer have a k_d with the target molecule at least 1000 fold lower than the k_d with a background binding molecule. It is preferred that the aptamer have a k_d with the target molecule at least 10000 fold lower than the k_d with a background binding molecule. It is preferred when doing the comparison for a polypeptide for example, that the background molecule be a different polypeptide. For example, when determining the specificity of beta4 integrin aptamers, the background protein could be bovine serum albumin. Representative examples of how to make and use aptamers to bind a variety of different target molecules can be found in the following non-limiting list of United States patents: 5,476,766, 5,503,978, 5,631,146, 5,731,424, 5,780,228, 5,792,613, 5,795,721, 5,846,713, 5,858,660, 5,861,254, 5,864,026, 5,869,641, 5,958,691, 6,001,988, 6,011,020, 6,013,443, 6,020,130, 6,028,186, 6,030,776, and 6,051,698.

Ribozymes are nucleic acid molecules that are capable of catalyzing a chemical reaction, either intramolecularly or intermolecularly. Ribozymes are thus catalytic nucleic acid. It is preferred that the ribozymes catalyze intermolecular reactions. There are a number of different types of ribozymes that catalyze nuclease or nucleic acid polymerase type reactions which are based on ribozymes found in natural systems, such as hammerhead ribozymes, (for example, but not limited to the following United States patents: 5,334,711, 5,436,330, 5,616,466, 5,633,133, 5,646,020, 5,652,094, 5,712,384, 5,770,715, 5,856,463, 5,861,288, 5,891,683, 5,891,684, 5,985,621, 5,989,908, 5,998,193, 5,998,203, WO 9858058 by Ludwig and Sproat, WO 9858057 by Ludwig and Sproat, and WO 9718312 by Ludwig and Sproat) hairpin ribozymes (for example, but not limited to the following United States patents: 5,631,115, 5,646,031, 5,683,902, 5,712,384, 5,856,188, 5,866,701, 5,869,339, and 6,022,962), and tetrahymena ribozymes (for example, but not limited to the following United States patents: 5,595,873 and 5,652,107). There are also a number of ribozymes that are not found in natural systems, but which have been engineered to catalyze specific reactions de novo (for example, but not limited to the following United States patents: 5,580,967, 5,688,670, 5,807,718, and 5,910,408). Preferred ribozymes cleave RNA or DNA substrates, and more preferably cleave RNA substrates. Ribozymes typically cleave nucleic acid substrates through recognition and binding of the target substrate with subsequent cleavage. This recognition is often based mostly on canonical or non-canonical base pair interactions. This property makes ribozymes particularly good candidates for target specific cleavage of nucleic acids because recognition of the target substrate is based on the target substrates sequence. Representative examples of how to make and use ribozymes to catalyze a variety of different reactions can be found in the following non-limiting list of United States patents: 5,646,042, 5,693,535, 5,731,295, 5,811,300, 5,837,855, 5,869,253, 5,877,021, 5,877,022, 5,972,699,

5,972,704, 5,989,906, and 6,017,756.

Triplex forming functional nucleic acid molecules are molecules that can interact with either double-stranded or single-stranded nucleic acid. When triplex molecules interact with a target region, a structure called a triplex is formed, in which there are three strands of DNA forming a complex dependant on both Watson-Crick and Hoogsteen base-pairing. Triplex molecules are preferred because they can bind target regions with high affinity and specificity. It is preferred that the triplex forming molecules bind the target molecule with a k_d less than 10^{-6} . It is more preferred that the triplex forming molecules bind with a k_d less than 10^{-8} . It is also more preferred that the triplex forming molecules bind the target molecule with a k_d less than 10^{-10} . It is also preferred that the triplex forming molecules bind the target molecule with a k_d less than 10^{-12} . Representative examples of how to make and use triplex forming molecules to bind a variety of different target molecules can be found in the following non-limiting list of United States patents: 5,176,996, 5,645,985, 5,650,316, 5,683,874, 5,693,773, 5,834,185, 5,869,246, 5,874,566, and 5,962,426.

External guide sequences (EGSs) are molecules that bind a target nucleic acid molecule forming a complex, and this complex is recognized by RNase P, which cleaves the target molecule. EGSs can be designed to specifically target a RNA molecule of choice. RNase P aids in processing transfer RNA (tRNA) within a cell. Bacterial RNase P can be recruited to cleave virtually any RNA sequence by using an EGS that causes the target RNA:EGS complex to mimic the natural tRNA substrate. (WO 92/03566 by Yale, and Forster and Altman, *Science* 238:407-409 (1990)).

Similarly, eukaryotic EGS/RNase P-directed cleavage of RNA can be utilized to cleave desired targets within eukaryotic cells. (Yuan et al., *Proc. Natl. Acad. Sci. USA* 89:8006-8010 (1992); WO 93/22434 by Yale; WO 95/24489 by Yale; Yuan and Altman, *EMBO J* 14:159-168 (1995), and Carrara et al., *Proc. Natl. Acad. Sci. (USA)* 92:2627-2631 (1995)). Representative examples of how to make and use EGS molecules to facilitate cleavage of a variety of different target molecules be found in the following non-limiting list of United States patents: 5,168,053, 5,624,824, 5,683,873, 5,728,521, 5,869,248, and 5,877,162

(c) Small molecules

Small molecules can also be used to regulate, for example, the function of the disclosed integrins, integrin receptors, molecules that interact with the disclosed integrin receptors, and molecules in the signaling pathways of the disclosed integrin receptors. Those of skill in the art understand how to generate small molecules of this type, and exemplary libraries and methods for isolating small molecule regulators are disclosed herein.

b) Compositions identified by screening with disclosed compositions / combinatorial chemistry

(1) Combinatorial chemistry

The disclosed compositions can be used as targets for any combinatorial technique to
5 identify molecules or macromolecular molecules that interact with the disclosed compositions,
such as beta4 integrin, alpha6 integrin, or the gamma2 subunit of laminin5, in a desired way. The
nucleic acids, peptides, and related molecules disclosed herein can be used as targets for the
combinatorial approaches. Also disclosed are the compositions that are identified through
combinatorial techniques or screening techniques in which the herein disclosed compositions, for
10 example set forth in SEQ ID NOS:1-19 or portions thereof, are used as the target or reagent in a
combinatorial or screening protocol.

It is understood that when using the disclosed compositions in combinatorial techniques or
screening methods, molecules, such as macromolecular molecules, will be identified that have
particular desired properties such as inhibition or stimulation or the target molecule's function.
15 The molecules identified and isolated when using the disclosed compositions, such as, beta4
integrin, alpha6 integrin, or the gamma2 subunit of laminin5, are also disclosed. Thus, the products
produced using the combinatorial or screening approaches that involve the disclosed compositions,
such as, beta4 integrin, alpha6 integrin, or the gamma2 subunit of laminin5, are also considered
herein disclosed.

20 Combinatorial chemistry includes but is not limited to all methods for isolating small
molecules or macromolecules that are capable of binding either a small molecule or another
macromolecule, typically in an iterative process. Proteins, oligonucleotides, and sugars are
examples of macromolecules. For example, oligonucleotide molecules with a given function,
catalytic or ligand-binding, can be isolated from a complex mixture of random oligonucleotides in
25 what has been referred to as "in vitro genetics" (Szostak, TIBS 19:89, 1992). One synthesizes a
large pool of molecules bearing random and defined sequences and subjects that complex mixture,
for example, approximately 10^{15} individual sequences in 100 μ g of a 100 nucleotide RNA, to some
selection and enrichment process. Through repeated cycles of affinity chromatography and PCR
amplification of the molecules bound to the ligand on the solid support, Ellington and Szostak
30 (1990) estimated that 1 in 10^{10} RNA molecules folded in such a way as to bind a small molecule
dyes. DNA molecules with such ligand-binding behavior have been isolated as well (Ellington and
Szostak, 1992; Bock et al, 1992). Techniques aimed at similar goals exist for small organic
molecules, proteins, antibodies and other macromolecules known to those of skill in the art.
Screening sets of molecules for a desired activity whether based on small organic libraries,
35 oligonucleotides, or antibodies is broadly referred to as combinatorial chemistry. Combinatorial
techniques are particularly suited for defining binding interactions between molecules and for

isolating molecules that have a specific binding activity, often called aptamers when the macromolecules are nucleic acids.

There are a number of methods for isolating proteins which either have de novo activity or a modified activity. For example, phage display libraries have been used to isolate numerous
5 peptides that interact with a specific target. (See for example, United States Patent No. 6,031,071; 5,824,520; 5,596,079; and 5,565,332 which are herein incorporated by reference at least for their material related to phage display and methods relate to combinatorial chemistry)

A preferred method for isolating proteins that have a given function is described by Roberts and Szostak (Roberts R.W. and Szostak J.W. Proc. Natl. Acad. Sci. USA,
10 94(23)12997-302 (1997)). This combinatorial chemistry method couples the functional power of proteins and the genetic power of nucleic acids. An RNA molecule is generated in which a puromycin molecule is covalently attached to the 3'-end of the RNA molecule. An *in vitro* translation of this modified RNA molecule causes the correct protein, encoded by the RNA to be translated. In addition, because of the attachment of the puromycin, a peptidyl acceptor which
15 cannot be extended, the growing peptide chain is attached to the puromycin which is attached to the RNA. Thus, the protein molecule is attached to the genetic material that encodes it. Normal *in vitro* selection procedures can now be done to isolate functional peptides. Once the selection procedure for peptide function is complete traditional nucleic acid manipulation procedures are performed to amplify the nucleic acid that codes for the selected functional peptides. After
20 amplification of the genetic material, new RNA is transcribed with puromycin at the 3'-end, new peptide is translated and another functional round of selection is performed. Thus, protein selection can be performed in an iterative manner just like nucleic acid selection techniques. The peptide which is translated is controlled by the sequence of the RNA attached to the puromycin. This sequence can be anything from a random sequence engineered for optimum translation (i.e.
25 no stop codons etc.) or it can be a degenerate sequence of a known RNA molecule to look for improved or altered function of a known peptide. The conditions for nucleic acid amplification and *in vitro* translation are well known to those of ordinary skill in the art and are preferably performed as in Roberts and Szostak (Roberts R.W. and Szostak J.W. Proc. Natl. Acad. Sci. USA, 94(23)12997-302 (1997)).

30 Another preferred method for combinatorial methods designed to isolate peptides is described in Cohen et al. (Cohen B.A., et al., Proc. Natl. Acad. Sci. USA 95(24):14272-7 (1998)). This method utilizes and modifies two-hybrid technology. Yeast two-hybrid systems are useful for the detection and analysis of protein:protein interactions. The two-hybrid system, initially described in the yeast *Saccharomyces cerevisiae*, is a powerful molecular genetic
35 technique for identifying new regulatory molecules, specific to the protein of interest (Fields and

Song, *Nature* 340:245-6 (1989)). Cohen et al., modified this technology so that novel interactions between synthetic or engineered peptide sequences could be identified which bind a molecule of choice. The benefit of this type of technology is that the selection is done in an intracellular environment. The method utilizes a library of peptide molecules that attached to an acidic
 5 activation domain. A peptide of choice, for example a portion of beta4 or alpha6 or gamma2 or laminin5 is attached to a DNA binding domain of a transcriptional activation protein, such as Gal 4. By performing the Two-hybrid technique on this type of system, molecules that bind the portion of beta4 or alpha6 or gamma2 or laminin5 can be identified.

There are molecules that can act like antibodies, in that they can having varying binding
 10 specificities, that are based on a fibronectin motif. The fibronectin type III domain (FN3) is a small autonomous folding unit. This FN3 domain can be found in numerous proteins that bind ligand, such as animal proteins. The beta-sandwich structure of FN3 closely resembles that of immunoglobulin domains. FN3 mutants can be isolated using combinatorial approaches disclosed herein, for example phage display, that bind desired targets. Typically the libraries of FN3
 15 molecules have been randomized in the two surface loops. Thus, FN3 can be used at least as a scaffold for engineering novel binding proteins. (Koide A, Bailey CW, Huang X, Koide S., "The fibronectin type III domain as a scaffold for novel binding proteins." *J Mol Biol* 1998: 284,1141-1151 which is herein incorporated by reference at least for material related to the fibronectin based novel binding proteins).

20 Using methodology well known to those of skill in the art, in combination with various combinatorial libraries, one can isolate and characterize those small molecules or macromolecules, which bind to or interact with the desired target. The relative binding affinity of these compounds can be compared and optimum compounds identified using competitive binding studies, which are well known to those of skill in the art.

25 Techniques for making combinatorial libraries and screening combinatorial libraries to isolate molecules which bind a desired target are well known to those of skill in the art. Representative techniques and methods can be found in but are not limited to United States patents 5,084,824, 5,288,514, 5,449,754, 5,506,337, 5,539,083, 5,545,568, 5,556,762, 5,565,324, 5,565,332, 5,573,905, 5,618,825, 5,619,680, 5,627,210, 5,646,285, 5,663,046, 5,670,326,
 30 5,677,195, 5,683,899, 5,688,696, 5,688,997, 5,698,685, 5,712,146, 5,721,099, 5,723,598, 5,741,713, 5,792,431, 5,807,683, 5,807,754, 5,821,130, 5,831,014, 5,834,195, 5,834,318, 5,834,588, 5,840,500, 5,847,150, 5,856,107, 5,856,496, 5,859,190, 5,864,010, 5,874,443, 5,877,214, 5,880,972, 5,886,126, 5,886,127, 5,891,737, 5,916,899, 5,919,955, 5,925,527, 5,939,268, 5,942,387, 5,945,070, 5,948,696, 5,958,702, 5,958,792, 5,962,337, 5,965,719,
 35 5,972,719, 5,976,894, 5,980,704, 5,985,356, 5,999,086, 6,001,579, 6,004,617, 6,008,321,

6,017,768, 6,025,371, 6,030,917, 6,040,193, 6,045,671, 6,045,755, 6,060,596, and 6,061,636.

Combinatorial libraries can be made from a wide array of molecules using a number of different synthetic techniques. For example, libraries containing fused 2,4-pyrimidinediones (United States patent 6,025,371) dihydrobenzopyrans (United States Patent 6,017,768 and 5 5,821,130), amide alcohols (United States Patent 5,976,894), hydroxy-amino acid amides (United States Patent 5,972,719) carbohydrates (United States patent 5,965,719), 1,4-benzodiazepin-2,5-diones (United States patent 5,962,337), cyclics (United States patent 5,958,792), biaryl amino acid amides (United States patent 5,948,696), thiophenes (United States patent 5,942,387), tricyclic Tetrahydroquinolines (United States patent 5,925,527), benzofurans (United States patent 10 5,919,955), isoquinolines (United States patent 5,916,899), hydantoin and thiohydantoin (United States patent 5,859,190), indoles (United States patent 5,856,496), imidazol-pyrido-indole and imidazol-pyrido-benzothiophenes (United States patent 5,856,107) substituted 2-methylene-2, 3-dihydrothiazoles (United States patent 5,847,150), quinolines (United States patent 5,840,500), PNA (United States patent 5,831,014), containing tags (United States patent 5,721,099), 15 polyketides (United States patent 5,712,146), morpholino-subunits (United States patent 5,698,685 and 5,506,337), sulfamides (United States patent 5,618,825), and benzodiazepines (United States patent 5,288,514).

Screening molecules similar to alpha6 for inhibition of alpha6beta4 formation is a method of identifying and isolating desired compounds that can inhibit the formation of A6B4 receptor. 20 For example, the disclosed compositions, such as alpha6 integrin or beta4 integrin can be used as targets in a selection scheme disclosed herein, and then the counter part integrin could be used as a competitive inhibitor to isolate the desired molecules. For example, a library of molecules could be incubated with beta4 integrin, which is bound to a solid support. The solid support can be washed to remove the unbound molecules and then the solid support can be incubated with, for 25 example, alpha6 integrin at a concentration that will saturate all beta4 binding sites. The molecules which are collected in the flowthrough after washing the solid support will be enriched for molecules that interact with beta4 integrin in a way that is competitive to the alpha6-beta4 interaction. Likewise, the solid support, bound with a target integrin, or more preferably a target integrin receptor, such as alpha6beta4 receptor, could also be washed, with for example, laminin5 30 or the gamma2 subunit of laminin5 at a concentration that will saturate all of the gamma2 binding sites on the beta4 integrin. Collection of the wash under these conditions will yield a population of molecules enriched for molecules that competitively interact with beta4 integrin at the beta4-gamma2 site. Another example, is the following: bind target to solid support on microtiter plate. Incubate with ligand in presence of gridded subset of library members (or single compounds), 35 wash, identify competitor by reduction of ligand binding. It is understood that the exemplary discussions of alpha6beta4 and/or beta4 are equally applicable to alpha6, as well as other

alpha6betax receptors, such alpha6beta1.

Also disclosed are methods of isolating molecules that bind with a target molecule selected from the group consisting, B4 integrin, alpha6 integrin, and the gamma2 subunit of laminin5 comprising 1) contacting a library of molecules with the target molecule and 2)
5 collecting molecules that bind the target molecule producing an enriched population of molecules.

Disclosed are methods, further comprising the step of repeating steps 1 and 2 with the enriched population of molecules, and/or wherein the library comprises a small molecule, peptide, peptide mimetic, or oligonucleotide.

As used herein combinatorial methods and libraries included traditional screening methods
10 and libraries as well as methods and libraries used in iterative processes.

(2) Computer assisted design

The disclosed compositions can be used as targets for any molecular modeling technique to identify either the structure of the disclosed compositions or to identify potential or actual molecules, such as small molecules, which interact in a desired way with the disclosed
15 compositions. The nucleic acids, peptides, and related molecules disclosed herein can be used as targets in any molecular modeling program or approach.

It is understood that when using the disclosed compositions in modeling techniques, molecules, such as macromolecular molecules, will be identified that have particular desired properties such as inhibition or stimulation or the target molecule's function. The molecules
20 identified and isolated when using the disclosed compositions, such as, beta4, are also disclosed. Thus, the products produced using the molecular modeling approaches that involve the disclosed compositions, such as, beta4 integrin, alpha6 integrin, or laminin5, are also considered herein disclosed.

Thus, one way to isolate molecules that bind a molecule of choice is through rational
25 design. This is achieved through structural information and computer modeling. Computer modeling technology allows visualization of the three-dimensional atomic structure of a selected molecule and the rational design of new compounds that will interact with the molecule. The three-dimensional construct typically depends on data from x-ray crystallographic analyses or NMR imaging of the selected molecule. The molecular dynamics require force field data. The
30 computer graphics systems enable prediction of how a new compound will link to the target molecule and allow experimental manipulation of the structures of the compound and target molecule to perfect binding specificity. Prediction of what the molecule-compound interaction will be when small changes are made in one or both requires molecular mechanics software and computationally intensive computers, usually coupled with user-friendly, menu-driven interfaces

between the molecular design program and the user.

Examples of molecular modeling systems are the CHARMM and QUANTA programs, Polygen Corporation, Waltham, MA. CHARMM performs the energy minimization and molecular dynamics functions. QUANTA performs the construction, graphic modeling and analysis of
5 molecular structure. QUANTA allows interactive construction, modification, visualization, and analysis of the behavior of molecules with each other.

A number of articles review computer modeling of drugs interactive with specific proteins, such as Rotivinen, et al., 1988 *Acta Pharmaceutica Fennica* 97, 159-166; Ripka, *New Scientist* 54-57 (June 16, 1988); McKinaly and Rossmann, 1989 *Annu. Rev. Pharmacol. Toxicol.* 29, 111-
10 122; Perry and Davies, QSAR: Quantitative Structure-Activity Relationships in Drug Design pp. 189-193 (Alan R. Liss, Inc. 1989); Lewis and Dean, 1989 *Proc. R. Soc. Lond.* 236, 125-140 and 141-162; and, with respect to a model enzyme for nucleic acid components, Askew, et al., 1989 *J. Am. Chem. Soc.* 111, 1082-1090. Other computer programs that screen and graphically depict chemicals are available from companies such as BioDesign, Inc., Pasadena, CA., Allelix,
15 Inc, Mississauga, Ontario, Canada, and Hypercube, Inc., Cambridge, Ontario. Although these are primarily designed for application to drugs specific to particular proteins, they can be adapted to design of molecules specifically interacting with specific regions of DNA or RNA, once that region is identified.

Although described above with reference to design and generation of compounds which
20 could alter binding, one could also screen libraries of known compounds, including natural products or synthetic chemicals, and biologically active materials, including proteins, for compounds which alter substrate binding or enzymatic activity.

c) Nucleic acids

There are a variety of molecules disclosed herein that are nucleic acid based, including for
25 example the nucleic acids that encode, for example beta4 and the gamma2 subunit of laminin5, as well as various functional nucleic acids. The disclosed nucleic acids are made up of for example, nucleotides, nucleotide analogs, or nucleotide substitutes. Non-limiting examples of these and other molecules are discussed herein. It is understood that for example, when a vector is expressed in a cell, that the expressed mRNA will typically be made up of A, C, G, and U. Likewise, it is
30 understood that if, for example, an antisense molecule is introduced into a cell or cell environment through for example exogenous delivery, it is advantageous that the antisense molecule be made up of nucleotide analogs that reduce the degradation of the antisense molecule in the cellular environment.

(1) Nucleotides and related molecules

35 A nucleotide is a molecule that contains a base moiety, a sugar moiety and a phosphate

moiety. Nucleotides can be linked together through their phosphate moieties and sugar moieties creating an internucleoside linkage. The base moiety of a nucleotide can be adenin-9-yl (A), cytosin-1-yl (C), guanin-9-yl (G), uracil-1-yl (U), and thymine-1-yl (T). The sugar moiety of a nucleotide is a ribose or a deoxyribose. The phosphate moiety of a nucleotide is pentavalent
 5 phosphate. An non-limiting example of a nucleotide would be 3'-AMP (3'-adenosine monophosphate) or 5'-GMP (5'-guanosine monophosphate).

A nucleotide analog is a nucleotide which contains some type of modification to either the base, sugar, or phosphate moieties. Modifications to the base moiety would include natural and synthetic modifications of A, C, G, and T/U as well as different purine or pyrimidine bases, such
 10 as uracil-5-yl (.psi.), hypoxanthin-9-yl (I), and 2-aminoadenin-9-yl. A modified base includes but is not limited to 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-
 15 uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-deazaadenine and 3-deazaguanine and 3-deazaadenine.

Additional base modifications can be found for example in U.S. Pat. No. 3,687,808, Englisch et
 20 al., *Angewandte Chemie, International Edition*, 1991, 30, 613, and Sanghvi, Y. S., Chapter 15, *Antisense Research and Applications*, pages 289-302, Crooke, S. T. and Lebleu, B. ed., CRC Press, 1993. Certain nucleotide analogs, such as 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine can increase the stability of duplex formation. Base
 25 modifications can be combined, for example, with a sugar modification, such as 2'-O-methoxyethyl, to achieve unique properties such as increased duplex stability. There are numerous United States patents such as 4,845,205; 5,130,302; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121, 5,596,091; 5,614,617; and 5,681,941, which detail and describe a range of base
 30 modifications. Each of these patents is herein incorporated by reference.

Nucleotide analogs can also include modifications of the sugar moiety. Modifications to the sugar moiety would include natural modifications of the ribose and deoxy ribose as well as synthetic modifications. Sugar modifications include but are not limited to the following modifications at the 2' position: OH-; F-; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-
 35 alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl may be substituted or unsubstituted C₁ to C₁₀, alkyl or C₂ to C₁₀ alkenyl and alkynyl. 2' sugar modifications also include

but are not limited to $-\text{O}[(\text{CH}_2)_n \text{O}]_m \text{CH}_3$, $-\text{O}(\text{CH}_2)_n \text{OCH}_3$, $-\text{O}(\text{CH}_2)_n \text{NH}_2$, $-\text{O}(\text{CH}_2)_n \text{CH}_3$, $-\text{O}(\text{CH}_2)_n -\text{ONH}_2$, and $-\text{O}(\text{CH}_2)_n \text{ON}[(\text{CH}_2)_n \text{CH}_3]_2$, where n and m are from 1 to about 10.

Other modifications at the 2' position include but are not limited to: C_1 to C_{10} lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH_3 , OCN, Cl, Br, CN, CF_3 , OCF_3 , SOCH_3 , $\text{SO}_2 \text{CH}_3$, ONO_2 , NO_2 , N_3 , NH_2 , heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an oligonucleotide, or a group for improving the pharmacodynamic properties of an oligonucleotide, and other substituents having similar properties. Similar modifications may also be made at other positions on the sugar, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked oligonucleotides and the 5' position of 5' terminal nucleotide. Modified sugars would also include those that contain modifications at the bridging ring oxygen, such as CH_2 and S. Nucleotide sugar analogs may also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. There are numerous United States patents that teach the preparation of such modified sugar structures such as 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; and 5,700,920, each of which is herein incorporated by reference in its entirety.

Nucleotide analogs can also be modified at the phosphate moiety. Modified phosphate moieties include but are not limited to those that can be modified so that the linkage between two nucleotides contains a phosphorothioate, chiral phosphorothioate, phosphorodithioate, phosphotriester, aminoalkylphosphotriester, methyl and other alkyl phosphonates including 3'-alkylene phosphonate and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates. It is understood that these phosphate or modified phosphate linkage between two nucleotides can be through a 3'-5' linkage or a 2'-5' linkage, and the linkage can contain inverted polarity such as 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, mixed salts and free acid forms are also included. Numerous United States patents teach how to make and use nucleotides containing modified phosphates and include but are not limited to, 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5,177,196; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,306; 5,550,111; 5,563,253; 5,571,799; 5,587,361; and 5,625,050, each of which is herein incorporated by reference.

It is understood that nucleotide analogs need only contain a single modification, but may also contain multiple modifications within one of the moieties or between different moieties.

Nucleotide substitutes are molecules having similar functional properties to nucleotides, but which do not contain a phosphate moiety, such as peptide nucleic acid (PNA). Nucleotide substitutes are molecules that will recognize nucleic acids in a Watson-Crick or Hoogsteen manner, but which are linked together through a moiety other than a phosphate moiety.

- 5 Nucleotide substitutes are able to conform to a double helix type structure when interacting with the appropriate target nucleic acid.

Nucleotide substitutes are nucleotides or nucleotide analogs that have had the phosphate moiety and/or sugar moieties replaced. Nucleotide substitutes do not contain a standard phosphorus atom. Substitutes for the phosphate can be for example, short chain alkyl or
 10 cycloalkyl internucleoside linkages, mixed heteroatom and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones;
 15 sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH₂ component parts. Numerous United States patents disclose how to make and use these types of phosphate replacements and include but are not limited to 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,264,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967;
 20 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,610,289; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437; and 5,677,439, each of which is herein incorporated by reference.

It is also understood in a nucleotide substitute that both the sugar and the phosphate moieties of the nucleotide can be replaced, by for example an amide type linkage
 25 (aminoethylglycine) (PNA). United States patents 5,539,082; 5,714,331; and 5,719,262 teach how to make and use PNA molecules, each of which is herein incorporated by reference. (See also Nielsen et al., Science, 1991, 254, 1497-1500).

It is also possible to link other types of molecules (conjugates) to nucleotides or nucleotide analogs to enhance for example, cellular uptake. Conjugates can be chemically linked to the
 30 nucleotide or nucleotide analogs. Such conjugates include but are not limited to lipid moieties such as a cholesterol moiety (Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989,

86, 6553-6556), cholic acid (Manoharan et al., Bioorg. Med. Chem. Let., 1994, 4, 1053-1060), a thioether, e.g., hexyl-S-tritylthiol (Manoharan et al., Ann. N.Y. Acad. Sci., 1992, 660, 306-309; Manoharan et al., Bioorg. Med. Chem. Let., 1993, 3, 2765-2770), a thiocholesterol
 35 (Oberhauser et al., Nucl. Acids Res., 1992, 20, 533-538), an aliphatic chain, e.g., dodecandiol or

undecyl residues (Saison-Behmoaras et al., EMBO J., 1991, 10, 1111-1118; Kabanov et al., FEBS Lett., 1990, 259, 327-330; Svinarchuk et al., Biochimie, 1993, 75, 49-54), a phospholipid, e.g., dihexadecyl-rac-glycerol or triethylammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan et al., Tetrahedron Lett., 1995, 36, 3651-3654; Shea et al., Nucl. Acids Res., 1990, 18, 3777-3783), a polyamine or a polyethylene glycol chain (Manoharan et al., Nucleosides & Nucleotides, 1995, 14, 969-973), or adamantane acetic acid (Manoharan et al., Tetrahedron Lett., 1995, 36, 3651-3654), a palmityl moiety (Mishra et al., Biochim. Biophys. Acta, 1995, 1264, 229-237), or an octadecylamine or hexylamino-carbonyl-oxysterol moiety (Crooke et al., J. Pharmacol. Exp. Ther., 1996, 277, 923-937. Numerous United States patents teach the preparation of such conjugates and include, but are not limited to U.S. Pat. Nos. 4,828,979; 4,948,882; 5,218,105; 5,525,465; 5,541,313; 5,545,730; 5,552,538; 5,578,717, 5,580,731; 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486,603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762,779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241, 5,391,723; 5,416,203, 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5,565,552; 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599,928 and 5,688,941, each of which is herein incorporated by reference.

It is understood that an oligonucleotide can be made from any combination of nucleotides, nucleotide analogs, or nucleotide substitutes disclosed herein or related molecules not specifically recited herein.

A Watson-Crick interaction is at least one interaction with the Watson-Crick face of a nucleotide, nucleotide analog, or nucleotide substitute. The Watson-Crick face of a nucleotide, nucleotide analog, or nucleotide substitute includes the C2, N1, and C6 positions of a purine based nucleotide, nucleotide analog, or nucleotide substitute and the C2, N3, C4 positions of a pyrimidine based nucleotide, nucleotide analog, or nucleotide substitute.

A Hoogsteen interaction is the interaction that takes place on the Hoogsteen face of a nucleotide or nucleotide analog, which is exposed in the major groove of duplex DNA. The Hoogsteen face includes the N7 position and reactive groups (NH₂ or O) at the C6 position of purine nucleotides.

(2) Sequences

There are a variety of sequences related to the beta4 integrin or the laminin5-gamma2 gene or the alpha6 integrin gene having the following Genbank Accession Numbers 6453379, 4557674, and AH006634, respectively. These sequences and others are herein incorporated by reference in their entireties as well as for individual subsequences contained therein.

One particular sequence set forth in SEQ ID NO:1 (beta4 integrin) and having Genbank accession number 6453379 is used herein, at various points, as an example, to exemplify the disclosed compositions and methods (or when another particular sequence is used as an example). It is understood that the description related to this sequence is applicable to any sequence related to
 5 beta4 integrin or any of the other molecules disclosed herein, such as alpha6 integrin, or the subunits of laminin5, such as gamma2, unless specifically indicated otherwise. Those of skill in the art understand how to resolve sequence discrepancies and differences and to adjust the compositions and methods relating to a particular sequence to other related sequences (i.e. sequences of beta4 integrin). Primers and/or probes can be designed for any beta4 integrin
 10 sequence given the information disclosed herein and known in the art.

(3) Primers and probes

Disclosed are compositions including primers and probes, which are capable of interacting with the for example, the alpha6 gene or mRNA, beta4 gene or mRNA, or gamma2 subunit of the laminin5 ligand gene as disclosed herein or mRNA as wells as primers or probes for any of the
 15 sequences or fragments of the sequences, set forth in SEQ ID NOs:1,3,5,7,9,11, and 13. In certain embodiments the primers are used to support DNA amplification reactions. Typically the primers will be capable of being extended in a sequence specific manner. Extension of a primer in a sequence specific manner includes any methods wherein the sequence and/or composition of the nucleic acid molecule to which the primer is hybridized or otherwise associated directs or
 20 influences the composition or sequence of the product produced by the extension of the primer. Extension of the primer in a sequence specific manner therefore includes, but is not limited to, PCR, DNA sequencing, DNA extension, DNA polymerization, RNA transcription, or reverse transcription. Techniques and conditions that amplify the primer in a sequence specific manner are preferred. In certain embodiments the primers are used for the DNA amplification reactions,
 25 such as PCR or direct sequencing. It is understood that in certain embodiments the primers can also be extended using non-enzymatic techniques, where for example, the nucleotides or oligonucleotides used to extend the primer are modified such that they will chemically react to extend the primer in a sequence specific manner. Typically the disclosed primers hybridize with the beta4 gene, alpha6 gene, or laminin5-gamma2 subunit gene, for example, or region of the
 30 beta4 gene, alpha6 gene, or laminin5-gamma2 subunit gene, for example, or they hybridize with the complement of the beta4 gene, alpha6 gene, or laminin5-gamma2 subunit gene, for example, or complement of a region of the beta4 gene, alpha6 gene, or laminin5-gamma2 subunit gene, or any of the sequences or fragments of the sequences, set forth in SEQ ID NOs:1,3,5,7,9,11, and 13, for example.

35 The size of the primers or probes for interaction with the beta4 gene, alpha6 gene, or laminin5-gamma2 subunit gene, for example, in certain embodiments can be any size that supports

the desired enzymatic manipulation of the primer, such as DNA amplification or the simple hybridization of the probe or primer. A typical primer or probe for beta4 gene, alpha6 gene, or laminin5-gamma2 subunit gene, for example, or primer or probe for any of the sequences or fragments of the sequences, set forth in SEQ ID NOs:1,3,5,7,9,11, and 13 would be at least about

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, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1250,

10 1500, 1750, 2000, 2250, 2500, 2750, 3000, 3500, or 4000 nucleotides long.

In other embodiments a primer or probe for beta4 gene, alpha6 gene, or laminin5-gamma2 subunit gene, for example, primer or probe or a primer or probe for any of the sequences or fragments of the sequences, set forth in SEQ ID NOs:1,3,5,7,9,11, and 13 can be less than or equal to about 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,

15 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1250, 1500, 1750, 2000, 2250, 2500, 2750, 3000, 3500, or 4000 nucleotides long.

20 The primers for the beta4 gene, alpha6 gene, or laminin5-gamma2 subunit gene, or any of the sequences or fragments of the sequences, set forth in SEQ ID NOs:1,3,5,7,9,11, and 13, for example, typically will be used to produce an amplified DNA product that contains a desired region. In general, typically the size of the product will be such that the size can be accurately determined to within 3, or 2 or 1 nucleotides.

25 In certain embodiments this product is at least about 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, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950,

30 1000, 1250, 1500, 1750, 2000, 2250, 2500, 2750, 3000, 3500, or 4000 nucleotides long.

In other embodiments the product is less than or equal to about 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, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 125, 150, 175,

35 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 550, 600, 650, 700, 750, 800, 850,

900, 950, 1000, 1250, 1500, 1750, 2000, 2250, 2500, 2750, 3000, 3500, or 4000 nucleotides long.

d) Sequence similarities

It is understood that as discussed herein the use of the terms homology and identity mean the same thing as similarity. Thus, for example, if the word homology is used between two non-
5 natural sequences it is understood that this is not necessarily indicating an evolutionary relationship between these two sequences, but rather is looking at the similarity or relatedness between their nucleic acid sequences. Many of the methods for determining homology between two evolutionarily related molecules are routinely applied to any two or more nucleic acids or proteins for the purpose of measuring sequence similarity regardless of whether or not they are
10 evolutionarily related.

In general, it is understood that one way to define any known variants and derivatives or those that might arise, of the disclosed genes and proteins herein, is through defining the variants and derivatives in terms of homology to specific known sequences. This identity of particular sequences disclosed herein is also discussed elsewhere herein. In general, variants of genes and
15 proteins herein disclosed typically have at least, about 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 percent homology to the stated sequence or the native sequence. Those of skill in the art readily understand how to determine the homology of two proteins or nucleic acids, such as genes. For example, the homology can be calculated after aligning the two sequences so that the homology is at its highest
20 level.

Another way of calculating homology can be performed by published algorithms. Optimal alignment of sequences for comparison may be conducted by the local homology algorithm of Smith and Waterman Adv. Appl. Math. 2: 482 (1981), by the homology alignment algorithm of Needleman and Wunsch, J. Mol Biol. 48: 443 (1970), by the search for similarity method of
25 Pearson and Lipman, Proc. Natl. Acad. Sci. U.S.A. 85: 2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by inspection.

The same types of homology can be obtained for nucleic acids by for example the
30 algorithms disclosed in Zuker, M. *Science* 244:48-52, 1989, Jaeger et al. *Proc. Natl. Acad. Sci. USA* 86:7706-7710, 1989, Jaeger et al. *Methods Enzymol.* 183:281-306, 1989 which are herein incorporated by reference for at least material related to nucleic acid alignment. It is understood that any of the methods typically can be used and that in certain instances the results of these various methods may differ, but the skilled artisan understands if identity is found with at least one
35 of these methods, the sequences would be said to have the stated identity, and be disclosed herein.

For example, as used herein, a sequence recited as having a particular percent homology to another sequence refers to sequences that have the recited homology as calculated by any one or more of the calculation methods described above. For example, a first sequence has 80 percent homology, as defined herein, to a second sequence if the first sequence is calculated to have 80 percent homology to the second sequence using the Zuker calculation method even if the first sequence does not have 80 percent homology to the second sequence as calculated by any of the other calculation methods. As another example, a first sequence has 80 percent homology, as defined herein, to a second sequence if the first sequence is calculated to have 80 percent homology to the second sequence using both the Zuker calculation method and the Pearson and Lipman calculation method even if the first sequence does not have 80 percent homology to the second sequence as calculated by the Smith and Waterman calculation method, the Needleman and Wunsch calculation method, the Jaeger calculation methods, or any of the other calculation methods. As yet another example, a first sequence has 80 percent homology, as defined herein, to a second sequence if the first sequence is calculated to have 80 percent homology to the second sequence using each of calculation methods (although, in practice, the different calculation methods will often result in different calculated homology percentages).

It is also understood that functional fragments as well as antigenic fragments as well as fragments that can be used in selection protocols of the disclosed compositions are also disclosed. For example, integrins have domains that interact with the other integrins. It may be advantageous in certain embodiments to utilize just the integrin binding domain fragment of, for example, the beta4 integrin, in a selection protocol disclosed herein. By using this domain of the beta4 integrin as the selection target, for example, the selection protocol will be biased for molecules binding this domain of beta4 integrin.

e) Hybridization/selective hybridization

The term hybridization typically means a sequence driven interaction between at least two nucleic acid molecules, such as a primer or a probe and a gene. Sequence driven interaction means an interaction that occurs between two nucleotides or nucleotide analogs or nucleotide derivatives in a nucleotide specific manner. For example, G interacting with C or A interacting with T are sequence driven interactions. Typically sequence driven interactions occur on the Watson-Crick face or Hoogsteen face of the nucleotide. The hybridization of two nucleic acids is affected by a number of conditions and parameters known to those of skill in the art. For example, the salt concentrations, pH, and temperature of the reaction all affect whether two nucleic acid molecules will hybridize.

Parameters for selective hybridization between two nucleic acid molecules are well known to those of skill in the art. For example, in some embodiments selective hybridization conditions

can be defined as stringent hybridization conditions. For example, stringency of hybridization is controlled by both temperature and salt concentration of either or both of the hybridization and washing steps. For example, the conditions of hybridization to achieve selective hybridization may involve hybridization in high ionic strength solution (6X SSC or 6X SSPE) at a temperature
5 that is about 12-25°C below the T_m (the melting temperature at which half of the molecules dissociate from their hybridization partners) followed by washing at a combination of temperature and salt concentration chosen so that the washing temperature is about 5°C to 20°C below the T_m . The temperature and salt conditions are readily determined empirically in preliminary experiments in which samples of reference DNA immobilized on filters are hybridized to a labeled
10 nucleic acid of interest and then washed under conditions of different stringencies. Hybridization temperatures are typically higher for DNA-RNA and RNA-RNA hybridizations. The conditions can be used as described above to achieve stringency, or as is known in the art. (Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, 1989; Kunkel et al. Methods Enzymol. 1987:154:367, 1987 which is herein
15 incorporated by reference for material at least related to hybridization of nucleic acids). A preferable stringent hybridization condition for a DNA:DNA hybridization can be at about 68°C (in aqueous solution) in 6X SSC or 6X SSPE followed by washing at 68°C. Stringency of hybridization and washing, if desired, can be reduced accordingly as the degree of complementarity desired is decreased, and further, depending upon the G-C or A-T richness of any
20 area wherein variability is searched for. Likewise, stringency of hybridization and washing, if desired, can be increased accordingly as homology desired is increased, and further, depending upon the G-C or A-T richness of any area wherein high homology is desired, all as known in the art.

Another way to define selective hybridization is by looking at the amount (percentage) of
25 one of the nucleic acids bound to the other nucleic acid. For example, in some embodiments selective hybridization conditions would be when at least about, 60, 65, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 percent of the limiting nucleic acid is bound to the non-limiting nucleic acid. Typically, the non-limiting primer is in for example, 10 or 100 or 1000 fold excess. This type of assay can be performed at
30 under conditions where both the limiting and non-limiting primer are for example, 10 fold or 100 fold or 1000 fold below their k_d , or where only one of the nucleic acid molecules is 10 fold or 100 fold or 1000 fold or where one or both nucleic acid molecules are above their k_d .

Another way to define selective hybridization is by looking at the percentage of primer that gets enzymatically manipulated under conditions where hybridization is required to promote
35 the desired enzymatic manipulation. For example, in some embodiments selective hybridization conditions would be when at least about, 60, 65, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82,

83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 percent of the primer is enzymatically manipulated under conditions which promote the enzymatic manipulation, for example if the enzymatic manipulation is DNA extension, then selective hybridization conditions would be when at least about 60, 65, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 5 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 percent of the primer molecules are extended. Preferred conditions also include those suggested by the manufacturer or indicated in the art as being appropriate for the enzyme performing the manipulation.

Just as with homology, it is understood that there are a variety of methods herein disclosed for determining the level of hybridization between two nucleic acid molecules. It is understood 10 that these methods and conditions may provide different percentages of hybridization between two nucleic acid molecules, but unless otherwise indicated meeting the parameters of any of the methods would be sufficient. For example if 80% hybridization was required and as long as hybridization occurs within the required parameters in any one of these methods it is considered disclosed herein.

15 It is understood that those of skill in the art understand that if a composition or method meets any one of these criteria for determining hybridization either collectively or singly it is a composition or method that is disclosed herein.

f) Delivery of the compositions to cells

The disclosed compositions and methods often entail delivery of the compositions to cells. 20 For example, antisense molecules directed to alpha6 mRNA or gamma2 mRNA can be delivered to cells via any method. A number of exemplary methods are disclosed herein. It is also understood that in certain embodiments, non-nucleic acid molecules will be and can be delivered to cells, for example an antibody to beta4 integrin, alpha6 integrin or, gamma2, or a small molecule, or a peptide. Delivery of these molecules can occur by any means, and exemplary 25 compositions and methods for such delivery are disclosed herein.

There are a number of compositions and methods which can be used to deliver nucleic acids to cells, either in vitro or in vivo. These methods and compositions can largely be broken down into two classes: viral based delivery systems and non-viral based delivery systems. For example, the nucleic acids can be delivered through a number of direct delivery systems such as, 30 electroporation, lipofection, calcium phosphate precipitation, plasmids, viral vectors, viral nucleic acids, phage nucleic acids, phages, cosmids, or via transfer of genetic material in cells or carriers such as cationic liposomes. Appropriate means for transfection, including viral vectors, chemical transfectants, or physico-mechanical methods such as electroporation and direct diffusion of DNA, are described by, for example, Wolff, J. A., et al., Science, 247, 1465-1468, (1990); and Wolff, J. 35 A. Nature, 352, 815-818, (1991). Such methods are well known in the art and readily adaptable for

use with the compositions and methods described herein. In certain cases, the methods will be modified to specifically function with large DNA molecules. Further, these methods can be used to target certain diseases and cell populations by using the targeting characteristics of the carrier.

(1) Nucleic acid based delivery systems

5 Transfer vectors can be any nucleotide construction used to deliver genes into cells (e.g., a plasmid), or as part of a general strategy to deliver genes, e.g., as part of recombinant retrovirus or adenovirus (Ram et al. Cancer Res. 53:83-88, (1993)).

As used herein, plasmid or viral vectors are agents that transport the disclosed nucleic acids, such as gamma2 antisense producing molecules into the cell without degradation and
10 include a promoter yielding expression of the gene in the cells into which it is delivered. In some embodiments the delivery vectors are derived from either a virus or a retrovirus. Viral vectors are, for example, Adenovirus, Adeno-associated virus, Herpes virus, Vaccinia virus, Polio virus, AIDS virus, neuronal trophic virus, Sindbis and other RNA viruses, including these viruses with the HIV backbone. Also preferred are any viral families which share the properties of these viruses which
15 make them suitable for use as vectors. Retroviruses include Murine Moloney Leukemia virus, MMLV, and retroviruses that express the desirable properties of MMLV as a vector. Retroviral vectors are able to carry a larger genetic payload, i.e., a transgene or marker gene, than other viral vectors, and for this reason are a commonly used vector. However, other than Lentivirus vectors, they are typically not as useful in non-proliferating cells. Adenovirus vectors are relatively stable
20 and easy to work with, have high titers, and can be delivered in aerosol formulation, and can transfect non-dividing cells. Pox viral vectors are large and have several sites for inserting genes, they are thermostable and can be stored at room temperature. A preferred embodiment is a viral vector which has been engineered so as to suppress the immune response of the host organism, elicited by the viral antigens. Preferred vectors of this type will carry coding regions for
25 Interleukin 8 or 10.

Viral vectors can have higher transaction (ability to introduce genes) abilities than chemical or physical methods to introduce genes into cells. Typically, viral vectors contain, nonstructural early genes, structural late genes, an RNA polymerase III transcript, inverted terminal repeats necessary for replication and encapsidation, and promoters to control the
30 transcription and replication of the viral genome. When engineered as vectors, viruses typically have one or more of the early genes removed and a gene or gene/promoter cassette is inserted into the viral genome in place of the removed viral DNA. Constructs of this type can carry up to about 8 kb of foreign genetic material. The necessary functions of the removed early genes are typically supplied by cell lines which have been engineered to express the gene products of the early genes
35 in trans.

(a) Retroviral Vectors

A retrovirus is an animal virus belonging to the virus family of Retroviridae, including any types, subfamilies, genus, or tropisms. Retroviral vectors, in general, are described by Verma, I.M., Retroviral vectors for gene transfer. In Microbiology-1985, American Society for
5 Microbiology, pp. 229-232, Washington, (1985), which is incorporated by reference herein. Examples of methods for using retroviral vectors for gene therapy are described in U.S. Patent Nos. 4,868,116 and 4,980,286; PCT applications WO 90/02806 and WO 89/07136; and Mulligan, (Science 260:926-932 (1993)); the teachings of which are incorporated herein by reference.

A retrovirus is essentially a package which has packed into it nucleic acid cargo. The
10 nucleic acid cargo carries with it a packaging signal, which ensures that the replicated daughter molecules will be efficiently packaged within the package coat. In addition to the package signal, there are a number of molecules which are needed in cis, for the replication, and packaging of the replicated virus. Typically a retroviral genome, contains the gag, pol, and env genes which are involved in the making of the protein coat. It is the gag, pol, and env genes which are typically
15 replaced by the foreign DNA that it is to be transferred to the target cell. Retrovirus vectors typically contain a packaging signal for incorporation into the package coat, a sequence which signals the start of the gag transcription unit, elements necessary for reverse transcription, including a primer binding site to bind the tRNA primer of reverse transcription, terminal repeat sequences that guide the switch of RNA strands during DNA synthesis, a purine rich sequence 5' to
20 the 3' LTR that serve as the priming site for the synthesis of the second strand of DNA synthesis, and specific sequences near the ends of the LTRs that enable the insertion of the DNA state of the retrovirus to insert into the host genome. The removal of the gag, pol, and env genes allows for about 8 kb of foreign sequence to be inserted into the viral genome, become reverse transcribed, and upon replication be packaged into a new retroviral particle. This amount of nucleic acid is
25 sufficient for the delivery of a one to many genes depending on the size of each transcript. It is preferable to include either positive or negative selectable markers along with other genes in the insert.

Since the replication machinery and packaging proteins in most retroviral vectors have been removed (gag, pol, and env), the vectors are typically generated by placing them into a
30 packaging cell line. A packaging cell line is a cell line which has been transfected or transformed with a retrovirus that contains the replication and packaging machinery, but lacks any packaging signal. When the vector carrying the DNA of choice is transfected into these cell lines, the vector containing the gene of interest is replicated and packaged into new retroviral particles, by the machinery provided in cis by the helper cell. The genomes for the machinery are not packaged
35 because they lack the necessary signals.

(b) Adenoviral Vectors

The construction of replication-defective adenoviruses has been described (Berkner et al., J. Virology 61:1213-1220 (1987); Massie et al., Mol. Cell. Biol. 6:2872-2883 (1986); Haj-Ahmad et al., J. Virology 57:267-274 (1986); Davidson et al., J. Virology 61:1226-1239 (1987);

5 Zhang "Generation and identification of recombinant adenovirus by liposome-mediated transfection and PCR analysis" BioTechniques 15:868-872 (1993)). The benefit of the use of these viruses as vectors is that they are limited in the extent to which they can spread to other cell types, since they can replicate within an initial infected cell, but are unable to form new infectious viral particles. Recombinant adenoviruses have been shown to achieve high efficiency gene

10 transfer after direct, in vivo delivery to airway epithelium, hepatocytes, vascular endothelium, CNS parenchyma and a number of other tissue sites (Morsy, J. Clin. Invest. 92:1580-1586 (1993); Kirshenbaum, J. Clin. Invest. 92:381-387 (1993); Roessler, J. Clin. Invest. 92:1085-1092 (1993); Moullier, Nature Genetics 4:154-159 (1993); La Salle, Science 259:988-990 (1993); Gomez-Foix, J. Biol. Chem. 267:25129-25134 (1992); Rich, Human Gene Therapy 4:461-476

15 (1993); Zabner, Nature Genetics 6:75-83 (1994); Guzman, Circulation Research 73:1201-1207 (1993); Bout, Human Gene Therapy 5:3-10 (1994); Zabner, Cell 75:207-216 (1993); Caillaud, Eur. J. Neuroscience 5:1287-1291 (1993); and Ragot, J. Gen. Virology 74:501-507 (1993)). Recombinant adenoviruses achieve gene transduction by binding to specific cell surface receptors, after which the virus is internalized by receptor-mediated endocytosis, in the same manner as wild

20 type or replication-defective adenovirus (Chardonnet and Dales, Virology 40:462-477 (1970); Brown and Burlingham, J. Virology 12:386-396 (1973); Svensson and Persson, J. Virology 55:442-449 (1985); Seth, et al., J. Virol. 51:650-655 (1984); Seth, et al., Mol. Cell. Biol. 4:1528-1533 (1984); Varga et al., J. Virology 65:6061-6070 (1991); Wickham et al., Cell 73:309-319 (1993)).

25 A viral vector can be one based on an adenovirus which has had the E1 gene removed and these virions are generated in a cell line such as the human 293 cell line. In another preferred embodiment both the E1 and E3 genes are removed from the adenovirus genome.

(c) Adeno-associated viral vectors

Another type of viral vector is based on an adeno-associated virus (AAV). This defective

30 parvovirus is a preferred vector because it can infect many cell types and is nonpathogenic to humans. AAV type vectors can transport about 4 to 5 kb and wild type AAV is known to stably insert into chromosome 19. Vectors which contain this site specific integration property are preferred. An especially preferred embodiment of this type of vector is the P4.1 C vector produced by Avigen, San Francisco, CA, which can contain the herpes simplex virus thymidine kinase gene,

35 HSV-tk, and/or a marker gene, such as the gene encoding the green fluorescent protein, GFP.

In another type of AAV virus, the AAV contains a pair of inverted terminal repeats (ITRs) which flank at least one cassette containing a promoter which directs cell-specific expression operably linked to a heterologous gene. Heterologous in this context refers to any nucleotide sequence or gene which is not native to the AAV or B19 parvovirus.

5 Typically the AAV and B19 coding regions have been deleted, resulting in a safe, noncytotoxic vector. The AAV ITRs, or modifications thereof, confer infectivity and site-specific integration, but not cytotoxicity, and the promoter directs cell-specific expression. United states Patent No. 6,261,834 is herein incorporated by reference for material related to the AAV vector.

The vectors of the present invention thus provide DNA molecules which are capable of
10 integration into a mammalian chromosome without substantial toxicity.

The inserted genes in viral and retroviral usually contain promoters, and/or enhancers to help control the expression of the desired gene product. A promoter is generally a sequence or sequences of DNA that function when in a relatively fixed location in regard to the transcription start site. A promoter contains core elements required for basic interaction of RNA polymerase
15 and transcription factors, and may contain upstream elements and response elements.

(d) Large payload viral vectors

Molecular genetic experiments with large human herpesviruses have provided a means whereby large heterologous DNA fragments can be cloned, propagated and established in cells permissive for infection with herpesviruses (Sun et al., Nature genetics 8: 33-41, 1994; Cotter and
20 Robertson, Curr Opin Mol Ther 5: 633-644, 1999). These large DNA viruses (herpes simplex virus (HSV) and Epstein-Barr virus (EBV), have the potential to deliver fragments of human heterologous DNA > 150 kb to specific cells. EBV recombinants can maintain large pieces of DNA in the infected B-cells as episomal DNA. Individual clones carried human genomic inserts up to 330 kb appeared genetically stable. The maintenance of these episomes requires a specific
25 EBV nuclear protein, EBNA1, constitutively expressed during infection with EBV. Additionally, these vectors can be used for transfection, where large amounts of protein can be generated transiently in vitro. Herpesvirus amplicon systems are also being used to package pieces of DNA > 220 kb and to infect cells that can stably maintain DNA as episomes.

Other useful systems include, for example, replicating and host-restricted non-replicating
30 vaccinia virus vectors.

(2) Non-nucleic acid based systems

The disclosed compositions can be delivered to the target cells in a variety of ways. For example, the compositions can be delivered through electroporation, or through lipofection, or through calcium phosphate precipitation. The delivery mechanism chosen will depend in part on

the type of cell targeted and whether the delivery is occurring for example *in vivo* or *in vitro*.

Thus, the compositions can comprise, in addition to the disclosed nucleic acids and proteins or vectors for example, lipids such as liposomes, such as cationic liposomes (e.g., DOTMA, DOPE, DC-cholesterol) or anionic liposomes. Liposomes can further comprise proteins
5 to facilitate targeting a particular cell, if desired. Administration of a composition comprising a compound and a cationic liposome can be administered to the blood afferent to a target organ or inhaled into the respiratory tract to target cells of the respiratory tract. Regarding liposomes, see, e.g., Brigham et al. *Am. J. Resp. Cell. Mol. Biol.* 1:95-100 (1989); Felgner et al. *Proc. Natl. Acad. Sci USA* 84:7413-7417 (1987); U.S. Pat. No.4,897,355. Furthermore, the compound can
10 be administered as a component of a microcapsule that can be targeted to specific cell types, such as macrophages, or where the diffusion of the compound or delivery of the compound from the microcapsule is designed for a specific rate or dosage.

In the methods described above which include the administration and uptake of exogenous DNA into the cells of a subject (i.e., gene transduction or transfection), delivery of the
15 compositions to cells can be via a variety of mechanisms. As one example, delivery can be via a liposome, using commercially available liposome preparations such as LIPOFECTIN, LIPOFECTAMINE (GIBCO-BRL, Inc., Gaithersburg, MD), SUPERFECT (Qiagen, Inc. Hilden, Germany) and TRANSFECTAM (Promega Biotec, Inc., Madison, WI), as well as other liposomes developed according to procedures standard in the art. In addition, the nucleic acid or vector of
20 this invention can be delivered *in vivo* by electroporation, the technology for which is available from Genetronics, Inc. (San Diego, CA) as well as by means of a SONOPORATION machine (ImaRx Pharmaceutical Corp., Tucson, AZ).

The materials may be in solution or suspension (for example, incorporated into microparticles, liposomes, or cells). These may be targeted to a particular cell type via antibodies,
25 receptors, or receptor ligands. The following references are examples of the use of this technology to target specific proteins to tumor tissue (Senter, et al., Bioconjugate Chem., 2:447-451, (1991); Bagshawe, K.D., Br. J. Cancer, 60:275-281, (1989); Bagshawe, et al., Br. J. Cancer, 58:700-703, (1988); Senter, et al., Bioconjugate Chem., 4:3-9, (1993); Battelli, et al., Cancer Immunol. Immunother., 35:421-425, (1992); Pietersz and McKenzie, Immunolog. Reviews, 129:57-80,
30 (1992); and Roffler, et al., Biochem. Pharmacol, 42:2062-2065, (1991)). These techniques can be used for a variety of other specific cell types. Vehicles, among others, include "stealth" and other antibody conjugated liposomes (including lipid mediated drug targeting to colonic carcinoma), receptor mediated targeting of DNA through cell specific ligands, lymphocyte directed tumor targeting, and highly specific therapeutic retroviral targeting of murine glioma cells *in vivo*. The
35 following references are examples of the use of this technology to target specific proteins to tumor

tissue (Hughes et al., Cancer Research, 49:6214-6220, (1989); and Litzinger and Huang, Biochimica et Biophysica Acta, 1104:179-187, (1992)). In general, receptors are involved in pathways of endocytosis, either constitutive or ligand induced. These receptors cluster in clathrin-coated pits, enter the cell via clathrin-coated vesicles, pass through an acidified endosome in which
 5 the receptors are sorted, and then either recycle to the cell surface, become stored intracellularly, or are degraded in lysosomes. The internalization pathways serve a variety of functions, such as nutrient uptake, removal of activated proteins, clearance of macromolecules, opportunistic entry of viruses and toxins, dissociation and degradation of ligand, and receptor-level regulation. Many receptors follow more than one intracellular pathway, depending on the cell type, receptor
 10 concentration, type of ligand, ligand valency, and ligand concentration. Molecular and cellular mechanisms of receptor-mediated endocytosis has been reviewed (Brown and Greene, DNA and Cell Biology 10:6, 399-409 (1991)).

Nucleic acids that are delivered to cells which are to be integrated into the host cell genome, typically contain integration sequences. These sequences are often viral related
 15 sequences, particularly when viral based systems are used. These viral integration systems can also be incorporated into nucleic acids which are to be delivered using a non-nucleic acid based system of deliver, such as a liposome, so that the nucleic acid contained in the delivery system can be come integrated into the host genome.

Other general techniques for integration into the host genome include, for example,
 20 systems designed to promote homologous recombination with the host genome. These systems typically rely on sequence flanking the nucleic acid to be expressed that has enough homology with a target sequence within the host cell genome that recombination between the vector nucleic acid and the target nucleic acid takes place, causing the delivered nucleic acid to be integrated into the host genome. These systems and the methods necessary to promote homologous
 25 recombination are known to those of skill in the art.

(3) In vivo/ex vivo

As described above, the compositions can be administered in a pharmaceutically acceptable carrier and can be delivered to the subject's cells *in vivo* and/or *ex vivo* by a variety of mechanisms well known in the art (e.g., uptake of naked DNA, liposome fusion, intramuscular
 30 injection of DNA via a gene gun, endocytosis and the like).

If *ex vivo* methods are employed, cells or tissues can be removed and maintained outside the body according to standard protocols well known in the art. The compositions can be introduced into the cells via any gene transfer mechanism, such as, for example, calcium phosphate mediated gene delivery, electroporation, microinjection or proteoliposomes. The
 35 transduced cells can then be infused (e.g., in a pharmaceutically acceptable carrier) or

homotopically transplanted back into the subject per standard methods for the cell or tissue type. Standard methods are known for transplantation or infusion of various cells into a subject.

It is understood that in certain embodiments, constructs which produce an integrin signal transduction inhibitor are driven by inducible promoters, rather than constitutive promoters.

5 inducible systems provide certain advantages, to the expression of the disclosed constructs. Any inducible system can be used. Also disclosed are cells containing the inducible systems, described herein, and in the Examples. These cells, can be used as model systems in a wide variety of assays, as well as in vivo settings.

g) Expression systems

10 The nucleic acids that are delivered to cells typically contain expression controlling systems. For example, the inserted genes in viral and retroviral systems usually contain promoters, and/or enhancers to help control the expression of the desired gene product. A promoter is generally a sequence or sequences of DNA that function when in a relatively fixed location in regard to the transcription start site. A promoter contains core elements required for basic
15 interaction of RNA polymerase and transcription factors, and may contain upstream elements and response elements.

(1) Viral Promoters and Enhancers

Preferred promoters controlling transcription from vectors in mammalian host cells may be obtained from various sources, for example, the genomes of viruses such as: polyoma, Simian
20 Virus 40 (SV40), adenovirus, retroviruses, hepatitis-B virus and most preferably cytomegalovirus, or from heterologous mammalian promoters, e.g. beta actin promoter. The early and late promoters of the SV40 virus are conveniently obtained as an SV40 restriction fragment which also contains the SV40 viral origin of replication (Fiers et al., Nature, 273: 113 (1978)). The immediate early promoter of the human cytomegalovirus is conveniently obtained as a HindIII E
25 restriction fragment (Greenway, P.J. et al., Gene 18: 355-360 (1982)). Of course, promoters from the host cell or related species also are useful herein.

Enhancer generally refers to a sequence of DNA that functions at no fixed distance from the transcription start site and can be either 5' (Laimins, L. et al., Proc. Natl. Acad. Sci. 78: 993 (1981)) or 3' (Lusky, M.L., et al., Mol. Cell Bio. 3: 1108 (1983)) to the transcription unit.
30 Furthermore, enhancers can be within an intron (Banerji, J.L. et al., Cell 33: 729 (1983)) as well as within the coding sequence itself (Osborne, T.F., et al., Mol. Cell Bio. 4: 1293 (1984)). They are usually between 10 and 300 bp in length, and they function in cis. Enhancers function to increase transcription from nearby promoters. Enhancers also often contain response elements that mediate the regulation of transcription. Promoters can also contain response elements that mediate
35 the regulation of transcription. Enhancers often determine the regulation of expression of a gene.

While many enhancer sequences are now known from mammalian genes (globin, elastase, albumin, α -fetoprotein and insulin), typically one will use an enhancer from a eukaryotic cell virus for general expression. Preferred examples are the SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma
5 enhancer on the late side of the replication origin, and adenovirus enhancers.

The promoter and/or enhancer may be specifically activated either by light or specific chemical events which trigger their function. Systems can be regulated by reagents such as tetracycline and dexamethasone. There are also ways to enhance viral vector gene expression by exposure to irradiation, such as gamma irradiation, or alkylating chemotherapy drugs.

10 In certain embodiments the promoter and/or enhancer region can act as a constitutive promoter and/or enhancer to maximize expression of the region of the transcription unit to be transcribed. In certain constructs the promoter and/or enhancer region be active in all eukaryotic cell types, even if it is only expressed in a particular type of cell at a particular time. A preferred promoter of this type is the CMV promoter (650 bases). Other preferred promoters are SV40
15 promoters, cytomegalovirus (full length promoter), and retroviral vector LTR.

It has been shown that all specific regulatory elements can be cloned and used to construct expression vectors that are selectively expressed in specific cell types such as melanoma cells. The glial fibrillary acidic protein (GFAP) promoter has been used to selectively express genes in cells of glial origin.

20 Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human or nucleated cells) may also contain sequences necessary for the termination of transcription which may affect mRNA expression. These regions are transcribed as polyadenylated segments in the untranslated portion of the mRNA encoding tissue factor protein. The 3' untranslated regions also include transcription termination sites. It is preferred that the transcription unit also contain a
25 polyadenylation region. One benefit of this region is that it increases the likelihood that the transcribed unit will be processed and transported like mRNA. The identification and use of polyadenylation signals in expression constructs is well established. It is preferred that homologous polyadenylation signals be used in the transgene constructs. In certain transcription units, the polyadenylation region is derived from the SV40 early polyadenylation signal and
30 consists of about 400 bases. It is also preferred that the transcribed units contain other standard sequences alone or in combination with the above sequences improve expression from, or stability of, the construct.

(2) Markers

The viral vectors can include nucleic acid sequence encoding a marker product. This
35 marker product is used to determine if the gene has been delivered to the cell and once delivered is

being expressed. Preferred marker genes are the *E. Coli* lacZ gene, which encodes β -galactosidase, and green fluorescent protein.

In some embodiments the marker may be a selectable marker. Examples of suitable selectable markers for mammalian cells are dihydrofolate reductase (DHFR), thymidine kinase, 5 neomycin, neomycin analog G418, hydromycin, and puromycin. When such selectable markers are successfully transferred into a mammalian host cell, the transformed mammalian host cell can survive if placed under selective pressure. There are two widely used distinct categories of selective regimes. The first category is based on a cell's metabolism and the use of a mutant cell line which lacks the ability to grow independent of a supplemented media. Two examples are: 10 CHO DHFR- cells and mouse LTK- cells. These cells lack the ability to grow without the addition of such nutrients as thymidine or hypoxanthine. Because these cells lack certain genes necessary for a complete nucleotide synthesis pathway, they cannot survive unless the missing nucleotides are provided in a supplemented media. An alternative to supplementing the media is to introduce an intact DHFR or TK gene into cells lacking the respective genes, thus altering their 15 growth requirements. Individual cells which were not transformed with the DHFR or TK gene will not be capable of survival in non-supplemented media.

The second category is dominant selection which refers to a selection scheme used in any cell type and does not require the use of a mutant cell line. These schemes typically use a drug to arrest growth of a host cell. Those cells which have a novel gene would express a protein 20 conveying drug resistance and would survive the selection. Examples of such dominant selection use the drugs neomycin, (Southern P. and Berg, P., *J. Molec. Appl. Genet.* 1: 327 (1982)), mycophenolic acid, (Mulligan, R.C. and Berg, P. *Science* 209: 1422 (1980)) or hygromycin, (Sugden, B. et al., *Mol. Cell. Biol.* 5: 410-413 (1985)). The three examples employ bacterial genes under eukaryotic control to convey resistance to the appropriate drug G418 or neomycin 25 (geneticin), xgpt (mycophenolic acid) or hygromycin, respectively. Others include the neomycin analog G418 and puromycin.

h) Peptides

(1) Protein variants

As discussed herein there are numerous variants of the beta4 integrin protein, alpha6 30 integrin protein, and gamma2 laminin5 protein, for example, that are known and herein contemplated. In addition, to the known functional homologue variants there are derivatives of the beta4, alpha6, and gamma2, and other disclosed proteins which also function in the disclosed methods and compositions. Protein variants and derivatives are well understood to those of skill in the art and in can involve amino acid sequence modifications. For example, amino acid sequence 35 modifications typically fall into one or more of three classes: substitutional, insertional or

deletional variants. Insertions include amino and/or carboxyl terminal fusions as well as intrasequence insertions of single or multiple amino acid residues. Insertions ordinarily will be smaller insertions than those of amino or carboxyl terminal fusions, for example, on the order of one to four residues. Immunogenic fusion protein derivatives are made by fusing a polypeptide sufficiently large to confer immunogenicity to the target sequence by cross-linking in vitro or by recombinant cell culture transformed with DNA encoding the fusion. Deletions are characterized by the removal of one or more amino acid residues from the protein sequence. Typically, no more than about from 2 to 6 residues are deleted at any one site within the protein molecule. These variants ordinarily are prepared by site specific mutagenesis of nucleotides in the DNA encoding the protein, thereby producing DNA encoding the variant, and thereafter expressing the DNA in recombinant cell culture. Techniques for making substitution mutations at predetermined sites in DNA having a known sequence are well known, for example M13 primer mutagenesis and PCR mutagenesis. Amino acid substitutions are typically of single residues, but can occur at a number of different locations at once; insertions usually will be on the order of about from 1 to 10 amino acid residues; and deletions will range about from 1 to 30 residues. Deletions or insertions preferably are made in adjacent pairs, i.e. a deletion of 2 residues or insertion of 2 residues. Substitutions, deletions, insertions or any combination thereof may be combined to arrive at a final construct. The mutations must not place the sequence out of reading frame and preferably will not create complementary regions that could produce secondary mRNA structure. Substitutional variants are those in which at least one residue has been removed and a different residue inserted in its place. Such substitutions generally are made in accordance with the following Tables 1 and 2 and are referred to as conservative substitutions.

TABLE 1: Amino Acid Abbreviations

Amino Acid	Abbreviations	
alanine	Ala	A
allosoleucine	AlIe	
arginine	Arg	R
asparagine	Asn	N
aspartic acid	Asp	D
cysteine	Cys	C
glutamic acid	Glu	E
glutamine	Gln	K
glycine	Gly	G
histidine	His	H
isoleucine	Ile	I
leucine	Leu	L
lysine	Lys	K
phenylalanine	Phe	F
proline	Pro	P
pyroglutamic acid	pGlu	
serine	Ser	S
threonine	Thr	T

tyrosine	Tyr	Y	
tryptophan		Trp	W
valine		Val	V

5 TABLE 2: Amino Acid Substitutions

Original Residue Exemplary Conservative Substitutions, others are known in the art.

	Ala	ser
	Arg	lys, gln
	Asn	gln; his
10	Asp	glu
	Cys	ser
	Gln	asn, lys
	Glu	asp
	Gly	pro
15	His	asn;gln
	Ile	leu; val
	Leu	ile; val
	Lys	arg; gln;
	Met	Leu; ile
20	Phe	met; leu; tyr
	Ser	thr
	Thr	ser
	Trp	tyr
	Tyr	trp; phe
25	Val	ile; leu

Substantial changes in function or immunological identity are made by selecting substitutions that are less conservative than those in Table 2, i.e., selecting residues that differ more significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site or (c) the bulk of the side chain. The substitutions which in general are expected to produce the greatest changes in the protein properties will be those in which (a) a hydrophilic residue, e.g. seryl or threonyl, is substituted for (or by) a hydrophobic residue, e.g. leucyl, isoleucyl, phenylalanyl, valyl or alanyl; (b) a cysteine or proline is substituted for (or by) any other residue; (c) a residue having an electropositive side chain, e.g., lysyl, arginyl, or histidyl, is substituted for (or by) an electronegative residue, e.g., glutamyl or aspartyl; or (d) a residue having a bulky side chain, e.g., phenylalanine, is substituted for (or by) one not having a side chain, e.g., glycine, in this case, (e) by increasing the number of sites for sulfation and/or glycosylation.

For example, the replacement of one amino acid residue with another that is biologically and/or chemically similar is known to those skilled in the art as a conservative substitution. For example, a conservative substitution would be replacing one hydrophobic residue for another, or one polar residue for another. The substitutions include combinations such as, for example, Gly, Ala; Val, Ile, Leu; Asp, Glu; Asn, Gln; Ser, Thr; Lys, Arg; and Phe, Tyr. Such conservatively substituted variations of each explicitly disclosed sequence are included within the mosaic

polypeptides provided herein.

Substitutional or deletional mutagenesis can be employed to insert sites for N-glycosylation (Asn-X-Thr/Ser) or O-glycosylation (Ser or Thr). Deletions of cysteine or other labile residues also may be desirable. Deletions or substitutions of potential proteolysis sites, e.g. Arg, is accomplished for example by deleting one of the basic residues or substituting one by glutaminyl or histidyl residues.

Certain post-translational derivatizations are the result of the action of recombinant host cells on the expressed polypeptide. Glutaminyl and asparaginyl residues are frequently post-translationally deamidated to the corresponding glutamyl and asparyl residues. Alternatively, these residues are deamidated under mildly acidic conditions. Other post-translational modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the o-amino groups of lysine, arginine, and histidine side chains (T.E. Creighton, *Proteins: Structure and Molecular Properties*, W. H. Freeman & Co., San Francisco pp 79-86 [1983]), acetylation of the N-terminal amine and, in some instances, amidation of the C-terminal carboxyl.

It is understood that one way to define the variants and derivatives of the disclosed proteins herein is through defining the variants and derivatives in terms of homology/identity to specific known sequences. For example, SEQ ID NO:5 sets forth a particular sequence of beta4 integrin cDNA and SEQ ID NO:6 sets forth a particular sequence of a beta4 integrin protein. Specifically disclosed are variants of these and other proteins herein disclosed which have at least, 70% or 75% or 80% or 85% or 90% or 95% homology to the stated sequence. Those of skill in the art readily understand how to determine the homology of two proteins. For example, the homology can be calculated after aligning the two sequences so that the homology is at its highest level.

Another way of calculating homology can be performed by published algorithms. Optimal alignment of sequences for comparison may be conducted by the local homology algorithm of Smith and Waterman *Adv. Appl. Math.* 2: 482 (1981), by the homology alignment algorithm of Needleman and Wunsch, *J. Mol. Biol.* 48: 443 (1970), by the search for similarity method of Pearson and Lipman, *Proc. Natl. Acad. Sci. U.S.A.* 85: 2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by inspection.

The same types of homology can be obtained for nucleic acids by for example the algorithms disclosed in Zuker, M. *Science* 244:48-52, 1989, Jaeger et al. *Proc. Natl. Acad. Sci. USA* 86:7706-7710, 1989, Jaeger et al. *Methods Enzymol.* 183:281-306, 1989 which are herein

incorporated by reference for at least material related to nucleic acid alignment.

It is understood that the description of conservative mutations and homology can be combined together in any combination, such as embodiments that have at least 70% homology to a particular sequence wherein the variants are conservative mutations.

5 As this specification discusses various proteins and protein sequences it is understood that the nucleic acids that can encode those protein sequences are also disclosed. This would include all degenerate sequences related to a specific protein sequence, i.e. all nucleic acids having a sequence that encodes one particular protein sequence as well as all nucleic acids, including degenerate nucleic acids, encoding the disclosed variants and derivatives of the protein sequences.

10 Thus, while each particular nucleic acid sequence may not be written out herein, it is understood that each and every sequence is in fact disclosed and described herein through the disclosed protein sequence. For example, one of the many nucleic acid sequences that can encode the protein sequence set forth in SEQ ID NO:6 is set forth in SEQ ID NO:5. Another nucleic acid sequence that encodes the same protein sequence set forth in SEQ ID NO:6 is set forth in SEQ ID

15 NO:16. In addition, for example, a disclosed conservative derivative of SEQ ID NO:2 is shown in SEQ ID NO: 17, where the valine (V) at position 34 is changed to a isoleucine (I). It is understood that for this mutation all of the nucleic acid sequences that encode this particular derivative of the beta4 integrin are also disclosed including for example SEQ ID NO:18 and SEQ ID NO:19 which set forth two of the degenerate nucleic acid sequences that encode the particular polypeptide set

20 forth in SEQ ID NO:17. It is also understood that while no amino acid sequence indicates what particular DNA sequence encodes that protein within an organism, where particular variants of a disclosed protein are disclosed herein, the known nucleic acid sequence that encodes that protein in the particular organism from which that protein arises is also known and herein disclosed and described.

25 i) Pharmaceutical carriers/Delivery of pharmaceutical products

As described above, the compositions, for example, compositions that inhibit alpha6 function, beta4 function, or gamma2 function can also be administered *in vivo* in a pharmaceutically acceptable carrier. By "pharmaceutically acceptable" is meant a material that is not biologically or otherwise undesirable, i.e., the material may be administered to a subject, along

30 with the nucleic acid or vector, without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained. The carrier would naturally be selected to minimize any degradation of the active ingredient and to minimize any adverse side effects in the subject, as would be well known to one of skill in the art.

35 The compositions may be administered orally, parenterally (e.g., intravenously), by

intramuscular injection, by intraperitoneal injection, transdermally, extracorporeally, topically or the like, although topical intranasal administration or administration by inhalant is typically preferred. As used herein, "topical intranasal administration" means delivery of the compositions into the nose and nasal passages through one or both of the nares and can comprise delivery by a spraying mechanism or droplet mechanism, or through aerosolization of the nucleic acid or vector. The latter may be effective when a large number of animals is to be treated simultaneously. Administration of the compositions by inhalant can be through the nose or mouth via delivery by a spraying or droplet mechanism. Delivery can also be directly to any area of the respiratory system (e.g., lungs) via intubation. The exact amount of the compositions required will vary from subject to subject, depending on the species, age, weight and general condition of the subject, the severity of the allergic disorder being treated, the particular nucleic acid or vector used, its mode of administration and the like. Thus, it is not possible to specify an exact amount for every composition. However, an appropriate amount can be determined by one of ordinary skill in the art using only routine experimentation given the teachings herein.

Parenteral administration of the composition, if used, is generally characterized by injection. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. A more recently revised approach for parenteral administration involves use of a slow release or sustained release system such that a constant dosage is maintained. See, e.g., U.S. Patent No. 3,610,795, which is incorporated by reference herein.

The materials may be in solution, suspension (for example, incorporated into microparticles, liposomes, or cells). These may be targeted to a particular cell type via antibodies, receptors, or receptor ligands. The following references are examples of the use of this technology to target specific proteins to tumor tissue (Senter, et al., Bioconjugate Chem., 2:447-451, (1991); Bagshawe, K.D., Br. J. Cancer, 60:275-281, (1989); Bagshawe, et al., Br. J. Cancer, 58:700-703, (1988); Senter, et al., Bioconjugate Chem., 4:3-9, (1993); Battelli, et al., Cancer Immunol. Immunother., 35:421-425, (1992); Pietersz and McKenzie, Immunolog. Reviews, 129:57-80, (1992); and Roffler, et al., Biochem. Pharmacol, 42:2062-2065, (1991)). Vehicles such as "stealth" and other antibody conjugated liposomes (including lipid mediated drug targeting to colonic carcinoma), receptor mediated targeting of DNA through cell specific ligands, lymphocyte directed tumor targeting, and highly specific therapeutic retroviral targeting of murine glioma cells *in vivo*. The following references are examples of the use of this technology to target specific proteins to tumor tissue (Hughes et al., Cancer Research, 49:6214-6220, (1989); and Litzinger and Huang, Biochimica et Biophysica Acta, 1104:179-187, (1992)). In general, receptors are involved in pathways of endocytosis, either constitutive or ligand induced. These receptors cluster in clathrin-coated pits, enter the cell via clathrin-coated vesicles, pass through an acidified endosome

in which the receptors are sorted, and then either recycle to the cell surface, become stored intracellularly, or are degraded in lysosomes. The internalization pathways serve a variety of functions, such as nutrient uptake, removal of activated proteins, clearance of macromolecules, opportunistic entry of viruses and toxins, dissociation and degradation of ligand, and receptor-level
 5 regulation. Many receptors follow more than one intracellular pathway, depending on the cell type, receptor concentration, type of ligand, ligand valency, and ligand concentration. Molecular and cellular mechanisms of receptor-mediated endocytosis has been reviewed (Brown and Greene, DNA and Cell Biology 10:6, 399-409 (1991)).

(1) Pharmaceutically Acceptable Carriers

10 The compositions, including antibodies, can be used therapeutically in combination with a pharmaceutically acceptable carrier.

Pharmaceutical carriers are known to those skilled in the art. These most typically would be standard carriers for administration of drugs to humans, including solutions such as sterile water, saline, and buffered solutions at physiological pH. The compositions can be administered
 15 intramuscularly or subcutaneously. Other compounds will be administered according to standard procedures used by those skilled in the art.

Pharmaceutical compositions may include carriers, thickeners, diluents, buffers, preservatives, surface active agents and the like in addition to the molecule of choice.

Pharmaceutical compositions may also include one or more active ingredients such as antimicrobial
 20 agents, anti-inflammatory agents, anesthetics, and the like.

The pharmaceutical composition may be administered in a number of ways depending on whether local or systemic treatment is desired, and on the area to be treated. Administration may be topically (including ophthalmically, vaginally, rectally, intranasally), orally, by inhalation, or parenterally, for example by intravenous drip, subcutaneous, intraperitoneal or intramuscular
 25 injection. The disclosed antibodies can be administered intravenously, intraperitoneally, intramuscularly, subcutaneously, intracavity, or transdermally.

Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl
 30 oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives may also be present such as, for

example, antimicrobials, anti-oxidants, chelating agents, and inert gases and the like.

Formulations for topical administration may include ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

- 5 Compositions for oral administration include powders or granules, suspensions or solutions in water or non-aqueous media, capsules, sachets, or tablets. Thickeners, flavorings, diluents, emulsifiers, dispersing aids or binders may be desirable.

Some of the compositions may potentially be administered as a pharmaceutically acceptable acid- or base- addition salt, formed by reaction with inorganic acids such as
10 hydrochloric acid, hydrobromic acid, perchloric acid, nitric acid, thiocyanic acid, sulfuric acid, and phosphoric acid, and organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, maleic acid, and fumaric acid, or by reaction with an inorganic base such as sodium hydroxide, ammonium hydroxide, potassium hydroxide, and organic bases such as mono-, di-, trialkyl and aryl amines and substituted
15 ethanolamines.

(2) Therapeutic Uses

The dosage ranges for the administration of the compositions are those large enough to produce the desired effect in which the symptoms disorder are effected. The dosage should not be so large as to cause adverse side effects, such as unwanted cross-reactions, anaphylactic reactions,
20 and the like. Generally, the dosage will vary with the age, condition, sex and extent of the disease in the patient and can be determined by one of skill in the art. The dosage can be adjusted by the individual physician in the event of any counterindications. Dosage can vary, and can be administered in one or more dose administrations daily, for one or several days.

Other compositions which do not have a specific pharmaceutical function, but which may
25 be used for tracking changes within cellular chromosomes or for the delivery of diagnostic tools for example can be delivered in ways similar to those described for the pharmaceutical products.

j) Chips and micro arrays

Disclosed are chips where at least one address is the sequences or part of the sequences set forth in any of the nucleic acid sequences disclosed herein. Also disclosed are chips where at least
30 one address is the sequences or portion of sequences set forth in any of the peptide sequences disclosed herein.

Also disclosed are chips where at least one address is a variant of the sequences or part of the sequences set forth in any of the nucleic acid sequences disclosed herein. Also disclosed are chips where at least one address is a variant of the sequences or portion of sequences set forth in

any of the peptide sequences disclosed herein.

k) Computer readable mediums

It is understood that the disclosed nucleic acids and proteins can be represented as a sequence consisting of the nucleotides of amino acids. There are a variety of ways to display these sequences, for example the nucleotide guanosine can be represented by G or g. Likewise the amino acid valine can be represented by Val or V. Those of skill in the art understand how to display and express any nucleic acid or protein sequence in any of the variety of ways that exist, each of which is considered herein disclosed. Specifically contemplated herein is the display of these sequences on computer readable mediums, such as, commercially available floppy disks, tapes, chips, hard drives, compact disks, and video disks, or other computer readable mediums. Also disclosed are the binary code representations of the disclosed sequences. Those of skill in the art understand what computer readable mediums. Thus, computer readable mediums on which the nucleic acids or protein sequences are recorded, stored, or saved.

Disclosed are computer readable mediums comprising the sequences and information regarding the sequences set forth herein. Also disclosed are computer readable mediums comprising the sequences and information regarding the sequences set forth herein wherein the sequences do not include SEQ ID NOs: SEQ ID NOs:1-19.

l) Kits

Disclosed herein are kits that are drawn to reagents that can be used in practicing the methods disclosed herein. The kits can include any reagent or combination of reagent discussed herein or that would be understood to be required or beneficial in the practice of the disclosed methods. For example, the kits could include primers to perform the amplification reactions discussed in certain embodiments of the methods, as well as the buffers and enzymes required to use the primers as intended. For example, disclosed is a kit for assessing a subject's risk for acquiring cancer, such as colon cancer, comprising the primers or probes that hybridize to the sequences set forth in SEQ ID NOs: 1, 3, 5, 7, 9, 11, and 13, for example.

m) Compositions with similar functions

It is understood that the compositions disclosed herein have certain functions, such as inhibiting gamma2 function or binding alpha6 integrin or inhibiting beta4 function. Disclosed herein are certain structural requirements for performing the disclosed functions, and it is understood that there are a variety of structures which can perform the same function which are related to the disclosed structures, and that these structures will ultimately achieve the same result, for example stimulation or inhibition alpha6beta4 signaling or interruption of the alpha6beta4 signaling pathway.

2. Methods of making the compositions

The compositions disclosed herein and the compositions necessary to perform the disclosed methods can be made using any method known to those of skill in the art for that particular reagent or compound unless otherwise specifically noted.

5 a) Nucleic acid synthesis

For example, the nucleic acids, such as, the oligonucleotides to be used as primers can be made using standard chemical synthesis methods or can be produced using enzymatic methods or any other known method. Such methods can range from standard enzymatic digestion followed by nucleotide fragment isolation (see for example, Sambrook *et al.*, *Molecular Cloning: A Laboratory*
10 *Manual*, 2nd Edition (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989) Chapters 5, 6) to purely synthetic methods, for example, by the cyanoethyl phosphoramidite method using a Milligen or Beckman System 1Plus DNA synthesizer (for example, Model 8700 automated synthesizer of Milligen-Bioscience, Burlington, MA or ABI Model 380B). Synthetic methods useful for making oligonucleotides are also described by Ikuta *et al.*, *Ann. Rev. Biochem.*
15 53:323-356 (1984), (phosphotriester and phosphite-triester methods), and Narang *et al.*, *Methods Enzymol.*, 65:610-620 (1980), (phosphotriester method). Protein nucleic acid molecules can be made using known methods such as those described by Nielsen *et al.*, *Bioconjug. Chem.* 5:3-7 (1994).

b) Peptide synthesis

20 One method of producing the disclosed proteins, or fragments of the disclosed proteins, such as a fragment of SEQ ID NO:6, is to link two or more peptides or polypeptides together by protein chemistry techniques. For example, peptides or polypeptides can be chemically synthesized using currently available laboratory equipment using either Fmoc (9-fluorenylmethyloxycarbonyl) or Boc (*tert*-butyloxycarbonyl) chemistry. (Applied Biosystems,
25 Inc., Foster City, CA). One skilled in the art can readily appreciate that a peptide or polypeptide corresponding to the disclosed proteins, for example, can be synthesized by standard chemical reactions. For example, a peptide or polypeptide can be synthesized and not cleaved from its synthesis resin whereas the other fragment of a peptide or protein can be synthesized and subsequently cleaved from the resin, thereby exposing a terminal group which is functionally
30 blocked on the other fragment. By peptide condensation reactions, these two fragments can be covalently joined via a peptide bond at their carboxyl and amino termini, respectively, to form an antibody, or fragment thereof. (Grant GA (1992) *Synthetic Peptides: A User Guide*. W.H. Freeman and Co., N.Y. (1992); Bodansky M and Trost B., Ed. (1993) *Principles of Peptide Synthesis*. Springer-Verlag Inc., NY (which is herein incorporated by reference at least for
35 material related to peptide synthesis). Alternatively, the peptide or polypeptide is independently synthesized *in vivo* as described herein. Once isolated, these independent peptides or polypeptides

may be linked to form a peptide or fragment thereof via similar peptide condensation reactions.

For example, enzymatic ligation of cloned or synthetic peptide segments allow relatively short peptide fragments to be joined to produce larger peptide fragments, polypeptides or whole protein domains (Abrahmsen L et al., *Biochemistry*, 30:4151 (1991)). Alternatively, native
 5 chemical ligation of synthetic peptides can be utilized to synthetically construct large peptides or polypeptides from shorter peptide fragments. This method consists of a two step chemical reaction (Dawson et al. *Synthesis of Proteins by Native Chemical Ligation*. *Science*, 266:776-779 (1994)).

The first step is the chemoselective reaction of an unprotected synthetic peptide--thioester with another unprotected peptide segment containing an amino-terminal Cys residue to give a thioester-
 10 linked intermediate as the initial covalent product. Without a change in the reaction conditions, this intermediate undergoes spontaneous, rapid intramolecular reaction to form a native peptide bond at the ligation site (Baggiolini M et al. (1992) *FEBS Lett.* 307:97-101; Clark-Lewis I et al., *J.Biol.Chem.*, 269:16075 (1994); Clark-Lewis I et al., *Biochemistry*, 30:3128 (1991); Rajarathnam K et al., *Biochemistry* 33:6623-30 (1994)).

15 Alternatively, unprotected peptide segments are chemically linked where the bond formed between the peptide segments as a result of the chemical ligation is an unnatural (non-peptide) bond (Schnolzer, M et al. *Science*, 256:221 (1992)). This technique has been used to synthesize analogs of protein domains as well as large amounts of relatively pure proteins with full biological activity (deLisle Milton RC et al., *Techniques in Protein Chemistry IV*. Academic Press, New
 20 York, pp. 257-267 (1992)).

The disclosed proteins and polypeptides such as that for SEQ ID NO:6, beta4 integrin, can be made using any traditional recombinant biotechnology method. Examples of such methods can be found in Sambrook et al. which is herein incorporated by reference at least for material related to production of proteins and antibodies.

25 c) Processes for making the compositions

Disclosed are processes for making the compositions as well as making the intermediates leading to the compositions. For example, disclosed are nucleic acids in SEQ ID NOs:1, 3, 5, 7, 9, 11, and 13. There are a variety of methods that can be used for making these compositions, such as synthetic chemical methods and standard molecular biology methods. It is understood that the
 30 methods of making these and the other disclosed compositions are specifically disclosed.

Disclosed are nucleic acid molecules produced by the process comprising linking in an operative way a nucleic acid molecule comprising the sequence set forth in SEQ ID Nos:1, 3, 5, 7, 9, 11, or 13 or a fragment thereof, and a sequence controlling the expression of the nucleic acid.

Also disclosed are nucleic acid molecules produced by the process comprising linking in

an operative way a nucleic acid molecule comprising a sequence having at least 80% identity to a sequence set forth in SEQ ID Nos:1, 3, 5, 7, 9, 11, or 13 or a fragment thereof, and a sequence controlling the expression of the nucleic acid.

Disclosed are nucleic acid molecules produced by the process comprising linking in an
5 operative way a nucleic acid molecule comprising a sequence that hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising the sequence set forth in SEQ ID Nos:1, 3, 5, 7, 9, 11, or 13 or a fragment thereof, and a sequence controlling the expression of the nucleic acid.

Disclosed are nucleic acid molecules produced by the process comprising linking in an
10 operative way a nucleic acid molecule comprising a sequence encoding a peptide set forth in SEQ ID Nos:2, 4, 6, 8, 10, 12, or 14 or a fragment thereof, and a sequence controlling an expression of the nucleic acid molecule.

Disclosed are nucleic acid molecules produced by the process comprising linking in an
operative way a nucleic acid molecule comprising a sequence encoding a peptide having 80%
15 identity to a peptide set forth in SEQ ID Nos:2, 4, 6, 8, 10, 12, or 14 or a fragment thereof and a sequence controlling an expression of the nucleic acid molecule.

Disclosed are nucleic acids produced by the process comprising linking in an operative
way a nucleic acid molecule comprising a sequence encoding a peptide having 80% identity to a
peptide set forth in SEQ ID Nos:2, 4, 6, 8, 10, 12, or 14 or a fragment thereof, wherein any change
20 from the sequences set forth in SEQ ID Nos:2, 4, 6, 8, 10, 12, or 14 or a fragment thereof are conservative changes and a sequence controlling an expression of the nucleic acid molecule.

Disclosed are cells produced by the process of transforming the cell with any of the
disclosed nucleic acids. Disclosed are cells produced by the process of transforming the cell with
any of the non-naturally occurring disclosed nucleic acids.

25 Disclosed are any of the disclosed peptides produced by the process of expressing any of the disclosed nucleic acids. Disclosed are any of the non-naturally occurring disclosed peptides produced by the process of expressing any of the disclosed nucleic acids. Disclosed are any of the disclosed peptides produced by the process of expressing any of the non-naturally disclosed nucleic acids.

30 Disclosed are animals produced by the process of transfecting a cell within the animal with any of the nucleic acid molecules disclosed herein. Disclosed are animals produced by the process of transfecting a cell within the animal any of the nucleic acid molecules disclosed herein, wherein the animal is a mammal. Also disclosed are animals produced by the process of transfecting a cell within the animal any of the nucleic acid molecules disclosed herein, wherein the mammal is

mouse, rat, rabbit, cow, sheep, pig, or primate.

Also disclosed are animals produced by the process of adding to the animal any of the cells disclosed herein.

d) Products produced from selection protocols

5 Also disclosed are methods of obtaining molecules that act as functional regulators of integrin function, integrin receptor function, and functional regulators of signaling pathways related to integrin receptors, in particular integrin alpha6beta4.

Disclosed are methods for isolating molecules that interact with the proteins set forth in SEQ ID Nos:2, 4, 6, 8, 10, 12, or 14 or a fragment thereof comprising, interacting a library of
10 molecules with the proteins set forth in SEQ ID Nos:2, 4, 6, 8, 10, 12, or 14 or a fragment thereof, removing the unbound molecules, and collecting the molecules that are bound to at least one of the proteins set forth in SEQ ID Nos:2, 4, 6, 8, 10, 12, or 14 or a fragment thereof.

3. Methods of using the compositions

a) Methods of using the compositions as research tools

15 The compositions can be used for example as targets in combinatorial chemistry protocols or other screening protocols to isolate molecules that possess desired functional properties related to A6B4 and A6B1 signaling pathways.

The disclosed compositions can also be used diagnostic tools related to diseases such as cancer, such as colon cancer.

20 The disclosed compositions can be used as discussed herein as either reagents in micro arrays or as reagents to probe or analyze existing microarrays. The disclosed compositions can be used in any known method for isolating or identifying single nucleotide polymorphisms. The compositions can also be used in any method for determining allelic analysis of for example, beta4 alleles having varying function, particularly allelic analysis as it relates to beta4 signaling and
25 functions. The compositions can also be used in any known method of screening assays, related to chip/micro arrays. The compositions can also be used in any known way of using the computer readable embodiments of the disclosed compositions, for example, to study relatedness or to perform molecular modeling analysis related to the disclosed compositions.

b) Methods for affecting cancer

30 The disclosed compositions can be used to affect the growth of cancer cells because as disclosed herein, the disclosed relationships are fundamental to the ability of cancer cells to continue growing. The disclosed compositions, such as antisense constructs that will inhibit the production of either alpha6, beta4, or the gamma2 chain of laminin5 reduce the proliferation of cancer cells. In fact, the compositions cannot only reduce the proliferation of the cancer cells, but

the compositions can kill the cancer cells, as shown herein.

It is understood that cancer is caused by a variety of cellular events, of which certain events related to alpha6 integrin (up regulated), beta4 integrin (upregulated) and gamma2 (upregulated) allow the continued viability of cancer cells, and that interference of these upregulated molecules inhibits the growth and kills the cancer cells. However, there are other known events that can cause non-cancerous cells to become oncogenic. For example, Abl, Ras, EGF receptor, ErbB-2, APC, beta-catenin, Arf, Mdm2, p53, Rb, Myc are known to be involved in oncogenesis, and some of these molecules (For example, Ras, APC loss, p53 loss) are directly related to the disclosed target signal transduction pathways mediated by the alpha6beta4 receptor. Just as the presently disclosed compositions can be used as therapeutics targeting the disclosed relationships, so there are other targets (For example, Abl, ErbB-2) for which pharmaceutical compositions have been developed (For example, Glivec, Herceptin, respectively).

It is understood that the disclosed anti-cancer compositions can be used in combination with other anti-cancer compositions. Great benefits can be obtained from using anti-cancer compositions that target different molecules, in the same signal transduction pathway as well as, or in addition to, targeting molecules in different signal transduction pathways than those disclosed herein. Thus, the disclosed compositions which can affect the growth of cancer cells, indeed kill cancer cells, can be used in conjunction with any other chemotherapy, radiation, or any other anti-cancer therapy.

Disclosed are methods of reducing the proliferation of a cancer cell which comprises inhibiting ligand binding to an integrin receptor on the cancer cell, wherein the integrin receptor comprises an integrin.

Also disclosed are methods of reducing the proliferation of a cancer cell which comprises reducing integrin-integrin interaction, integrin receptor clustering interaction, or integrin-non-integrin protein interaction.

Also disclosed are methods of selectively reducing the proliferation of cancer cells which comprises reducing integrins from interacting with one another, integrins from clustering, or integrins from interacting with other proteins associated with cancer cells.

Disclosed are methods of reducing the proliferation of a cancer cell which comprises reducing the production of an integrin by the cancer cell.

Also disclosed are methods of reducing the proliferation of a cancer cell which comprises reducing the production of an integrin receptor ligand by the cancer cell.

Disclosed are methods of reducing the proliferation of a cancer cell which comprises

interfering with an integrin signaling pathway.

Also disclosed are methods of selectively killing or reducing the proliferation of cancer cells which comprises inhibiting ligand binding to integrin receptors on the cancer cells, wherein the integrin receptor comprises a B4 integrin.

5 Disclosed are methods of selectively killing or reducing the proliferation of cancer cells which comprises inhibiting ligand binding to integrin receptors on the cancer cells, wherein the ligand comprises a laminin5.

Also disclosed are methods of selectively killing or reducing the proliferation of cancer cells which comprises inhibiting ligand binding to integrin receptors on the cancer cells, wherein
10 the ligand comprises the gamma2 subunit of the laminin L5.

Disclosed are methods of selectively killing or reducing the proliferation of cancer cells which comprises inhibiting ligand binding to integrin receptors on the cancer cells, wherein the integrin receptor comprises an alpha6 integrin.

Further disclosed are methods of selectively killing or reducing the proliferation of cancer
15 cells which comprises preventing integrin receptor subunits from interacting with one another, preventing integrin clustering, or preventing integrin receptor subunits from interacting with other proteins on cancer cells, wherein the integrin receptor comprises a B4 integrin.

Disclosed are methods of selectively killing or reducing the proliferation of cancer cells which comprises reducing the production of laminin by the cancer cells, wherein the laminin
20 comprises laminin5, and/or any of the subunits of laminin5, such as gamma2.

Also disclosed is a method of selectively killing or reducing the proliferation of cancer cells which comprises interfering with an integrin signaling pathway, wherein the integrin signaling pathway comprises a B4 integrin or an alpha6 integrin or a beta1 integrin or a laminin or a laminin5 or the gamma2 subunit of laminin5.

25 Also disclosed are methods, wherein the integrin receptor comprises integrin B4 and/or wherein the integrin receptor comprises integrin A6, and/or wherein the ligand that binds to the integrin receptor is laminin5, and/or wherein the integrin receptor is A6B4, and/or wherein the ligand comprises laminin5, and/or wherein the ligand comprises the gamma-2 subunit of laminin5, and/or wherein inhibiting ligand binding to an integrin receptor does not occur by using an
30 antisense molecule to A6, and/or wherein inhibiting ligand binding to an integrin receptor comprises contacting a A6 integrin with a composition that inhibits ligand binding, and/or wherein inhibiting ligand binding to an integrin receptor comprises contacting a B4 integrin with a composition that inhibits ligand binding, and/or wherein inhibiting ligand binding to an integrin receptor comprises contacting a laminin5 with a composition that inhibits ligand binding, and/or

wherein inhibiting ligand binding to an integrin receptor comprises contacting a gamma-2 subunit with a composition that inhibits ligand binding, and/or wherein reducing integrin-integrin interaction, integrin receptor clustering interaction, or integrin-non-integrin protein interaction does not occur by using a B4-delta-cyt, and/or wherein reducing integrin-integrin interaction,

5 integrin receptor clustering interaction, or integrin-non-integrin protein interaction does not occur by using an antisense molecule to A6, and/or wherein reducing integrin-integrin interaction, integrin receptor clustering interaction, or integrin-non-integrin protein interaction comprises contacting a A6 integrin with a composition that inhibits an interaction between the B4 integrin and another integrin or protein molecule, and/or wherein reducing integrin-integrin interaction,

10 integrin receptor clustering interaction, or integrin-non-integrin protein interaction comprises contacting a B4 integrin with a composition that inhibits the interaction between the B4 integrin and another integrin or protein molecule, and/or wherein reducing integrin-integrin interaction, integrin receptor clustering interaction, or integrin-non-integrin protein interaction comprises contacting a laminin5 with a composition that inhibits ligand binding, and/or wherein reducing

15 integrin-integrin interaction, integrin receptor clustering interaction, or integrin-non-integrin protein interaction comprises contacting a gamma2 subunit with a composition that inhibits ligand binding, and/or wherein the non-integrin protein comprises a growth factor receptor, and/or wherein the non-integrin protein comprises a hemi-desmosome junction, and/or wherein the non-integrin protein comprises a SH2 domain, and/or wherein the non-integrin protein comprises a Shc

20 protein, and/or wherein the non-integrin protein comprises a IRS-1 protein, and/or wherein the non-integrin protein comprises a IRS-2 protein, and/or wherein reducing the production of an integrin does not occur by using an antisense molecule to A6, and/or wherein the production of an integrin is reduced by inhibiting signaling leading to induction of expression of an integrin, and/or wherein reducing the production of an integrin comprises inhibiting alpha6 production, and/or

25 wherein inhibiting alpha6 production further comprises using antisense molecules to alpha6 mRNA, and/or wherein reducing the production of an integrin comprises inhibiting beta4 production, and/or wherein inhibiting beta4 production further comprises using antisense molecules to beta4 mRNA, and/or wherein reducing the production of an integrin receptor ligand comprises inhibiting gamma2 production, and/or wherein reducing the production of an integrin

30 receptor ligand comprises inhibiting laminin production, and/or wherein reducing the production of an integrin receptor ligand comprises inhibiting laminin5 production, and/or wherein interfering with an integrin signaling pathway does not occur by using a B4-delta-cyt, and/or wherein interfering with an integrin signaling pathway does not occur by using an antisense molecule to A6, and/or wherein interfering with an integrin signaling pathway comprises contacting an A6

35 integrin in the cell with a composition that inhibits ligand binding, and/or wherein interfering with an integrin signaling pathway comprises contacting a B4 integrin with a composition that inhibits

ligand binding, and/or wherein interfering with an integrin signaling pathway comprises contacting a laminin5 with a composition that inhibits ligand binding, and/or wherein interfering with an integrin signaling pathway comprises contacting a gamma2 subunit with a composition that inhibits ligand binding, and/or wherein interfering with an integrin signaling pathway comprises
 5 contacting the cancer cell with a molecule that interferes with at least one of talin, paxillin, vinculin, a CAS family protein, CRX, NCK, FAK, ILK, Src, Fyn, Shc, Grb-2, Guanine nucleotide exchange factors, SOS, DOCK 180, Vav, Syk, P-1-3 kinase, AKT, Bad, Bid, Caspase 9, Cdc42, PAK, Rac, Rho, Rho kinase, Ras, Caveolin, Tetraspan, Receptor-type protein tyrosine phosphatase, SHP-2, Alpha-actinin, Filamin, Cytohesin, Beta3-endonexin, ICAP-1, RACK-1, CIB,
 10 actin, receptor tyrosine kinase, IRS-1 or IRS-2, and/or wherein interfering with an integrin signaling pathway comprises contacting the cancer cell with an agent that interferes with post-translational modification of integrins, and/or wherein the post translational modification is glycosylation or phosphorylation.

Also disclosed are methods, wherein the integrin comprises an A6 integrin, and/or wherein
 15 the integrin comprises a B4 integrin, and/or further comprising reducing a laminin5-integrin interaction, and/or further comprising reducing a laminin5 gamma2 integrin interaction, and/or wherein the cancer cell comprises normal p53, and/or wherein the proliferation of the cancer cells is not dependent on AKT/PKB, and/or wherein reducing the proliferation of the cancer cells is selective, and/or wherein the cancer cell is not an MDA-MB-435 cell, and/or wherein the cancer
 20 cell is not an HMT-3522 cell, and/or wherein the cancer cell is not an RKO colon carcinoma line, and/or wherein the cancer cell does not express exogenous B4 integrin, and/or further comprising contacting the cancer cells with a small molecule, peptide, peptide mimetic, or oligonucleotide or synthetic analog thereof, and/or wherein the cancer cells are contacted with dominant-negative beta 4 integrin, and/or wherein the cancer cell is contacted with an antisense molecule, and/or
 25 wherein the antisense molecule is linked to a leader sequence which enables translocation across a cell membrane, and/or wherein the leader sequence binds to a cell surface protein which facilitates internalization, and/or wherein the leader sequence is TAT or antennapedia, or fragment thereof, and/or wherein the antisense molecule is an alpha6 RNA antisense molecule, and/or wherein the small molecule peptide, peptide mimetic, or oligonucleotide or synthetic analog thereof is linked
 30 to a carrier, and/or wherein the carrier is at least one of a lipidic carrier, charged carrier, retroviral carrier, TAT or fragment thereof, antennapedia or fragment thereof, or polyethylene glycol, and/or further comprising contacting the cancer cell with another agent which modulates cell signaling, a chemotherapeutic drug, or treated with radiation or angiogenesis inhibitor, and/or wherein reducing the proliferation of cancer cell is *in vitro*, and/or wherein reducing the proliferation of the
 35 cancer cell is *in vivo*, and/or wherein the cancer cell is selected from the group consisting of melanoma, adenoma, lymphoma, myeloma, carcinoma, plasmocytoma, sarcoma, glioma, thymoma,

leukemia, skin cancer, retinal cancer, breast cancer, prostate cancer, colon cancer, esophageal cancer, stomach cancer, pancreas cancer, brain tumors, lung cancer, ovarian cancer, cervical cancer, hepatic cancer, gastrointestinal cancer, and head and neck cancer cells, and/or wherein the cancer cell is killed, and/or wherein the cancer cell expresses a mutated Ras, and/or wherein the cancer
 5 cell expresses a mutated Ras and a mutated p53, and/or wherein the cancer cell expresses a mutated Ras and activates the AKT/PKB protein, and/or wherein the cancer cell expresses a mutated Ras, a mutated p53, and activates the AKT/PKB protein, and/or wherein the cancer cell expresses a mutated APC, and/or wherein the cancer cell expresses a mutated Ras and mutated APC.

10 Disclosed are methods of reducing the proliferation of a cancer cell in a patient which comprises administering to the patient a composition which inhibits ligand binding to an integrin receptor on the cancer cell, wherein the integrin receptor comprises an integrin.

Also disclosed are methods of reducing the proliferation of a cancer cell in a patient which comprises administering to the patient a composition which reduces integrin-integrin interaction,
 15 integrin receptor clustering interaction, or integrin-non-integrin protein interaction.

Also disclosed are methods of reducing the proliferation of a cancer cell in a patient which comprises administering to the patient a composition which reduces the production of an integrin or laminin by the cancer cell.

Further disclosed are methods of reducing the proliferation of a cancer cell in a patient
 20 which comprises administering to the patient a composition which interferes with an integrin signaling pathway.

Also disclosed are methods, wherein the reduction in cancer cell proliferation is selective, and/or wherein the administering is local or systemic, and/or wherein the patient is additionally administered an agent which modulates cell signaling, a chemotherapeutic drug, or treated with
 25 radiation or angiogenesis inhibitor, and/or wherein the additional agent is administered serially or in combination, and/or wherein the local administering is direct application to cancer cells, and/or wherein the direct application to cancer cells is performed during surgery, and/or wherein the direct application to cancer cells is performed topically to cancerous tissue, and/or wherein the systemic administration is by subcutaneous, intraperitoneal, intra-arterial, intravenous, or bolus
 30 administration, or by application through a catheter or similar apparatus, and/or wherein the systemic administration comprises a long-term release formulation, and/or wherein the systemic administration is by oral administration, and/or wherein the oral administration comprises administering a pill, capsule, tablet, liquid or suspension.

Disclosed are methods of reducing the proliferation of a cancer cell in a patient which

comprises administering to a patient a vector comprising coding sequence for a protein or peptide which inhibits ligand binding to integrin receptors on cancer cells wherein the coding sequence is under the control of a promoter which functions in mammalian cells.

Also disclosed are methods of reducing the proliferation of a cancer cell in a patient which
 5 comprises administering to a patient a vector comprising coding sequence for a protein or peptide which prevents integrin receptor subunits from interacting with one another, prevents integrin receptor clustering interaction, or prevents integrin receptor subunits from interacting with other proteins on cancer cells wherein the coding sequence is under the control of a promoter which functions in mammalian cells.

10 Further disclosed are methods of reducing the proliferation of a cancer cell in a patient which comprises administering to a patient a vector comprising coding sequence for a protein or peptide which prevents integrin receptor subunits from interacting with one another, prevents integrin receptor clustering interaction, or prevents integrin receptor subunits from interacting with other proteins in cancer cells wherein the coding sequence is under the control of a promoter which
 15 functions in mammalian cells.

Also disclosed are method of reducing the proliferation of a cancer cell in a patient which comprises administering to a patient a vector comprising coding sequence for a protein or peptide which interferes with integrin subunit or laminin production wherein the coding sequence is under the control of a promoter which functions in mammalian cells.

20 Further disclosed are methods of reducing the proliferation of a cancer cell in a patient which comprises administering to a patient a vector comprising coding sequence for a protein or peptide which interferes with an integrin signaling pathway of cells wherein the coding sequence is under the control of a promoter which functions in mammalian cells.

Also disclosed are methods, wherein the reduction in cancer cell proliferation is selective,
 25 and/or wherein the vector is administered directly to a cancer cell, and/or wherein the vector is administered directly to a normal cell, and/or wherein the vector is packaged in a viral vector or liposome, and/or wherein the vector is a retroviral vector, and/or wherein the vector is administered systemically, and/or wherein the direct administration is by topical application, and/or wherein the direct administration is by topical application, and/or wherein the direct
 30 administration is performed during surgery, and/or wherein the direct administration is performed during surgery, and/or wherein the patient is an animal, such as a mammal, mouse, rabbit, primate, chimp, ape, goriilla, and human, and/or wherein the cancer cells are selected from the group consisting of melanoma, adenoma, lymphoma, myeloma, carcinoma, plasmocytoma, sarcoma, glioma, thyoma, leukemia, skin cancer, retinal cancer, breast cancer, prostate cancer, colon cancer,
 35 esophageal cancer, stomach cancer, pancreas cancer, brain tumors, lung cancer, ovarian cancer,

cervical cancer, hepatic cancer, gastrointestinal cancer, and head and neck cancer cells, and/or wherein the patient is additionally administered at least one of another agent which modulates cell signaling, a chemotherapeutic drug, an angiogenesis inhibitor or treated with radiation, and/or wherein the other agent which modifies cell signaling, chemotherapeutic drug, angiogenesis
5 inhibitor or radiation treatment is administered serially or in combination.

c) Methods of gene modification and gene disruption

The disclosed compositions and methods can be used in targeted gene disruption and modification in any animal that can undergo these events. Gene modification and gene disruption refer to the methods, techniques, and compositions that surround the selective removal or
10 alteration of a gene or stretch of chromosome in an animal, such as a mammal, in a way that propagates the modification through the germ line of the mammal. In general, a cell is transformed with a vector which is designed to homologously recombine with a region of a particular chromosome contained within the cell, as for example, described herein. This homologous recombination event can produce a chromosome which has exogenous DNA
15 introduced, for example in frame, with the surrounding DNA. This type of protocol allows for very specific mutations, such as point mutations, to be introduced into the genome contained within the cell. Methods for performing this type of homologous recombination are disclosed herein.

One of the preferred characteristics of performing homologous recombination in
20 mammalian cells is that the cells should be able to be cultured, because the desired recombination event occur at a low frequency.

Once the cell is produced through the methods described herein, an animal can be produced from this cell through either stem cell technology or cloning technology. For example, if the cell into which the nucleic acid was transfected was a stem cell for the organism, then this cell,
25 after transfection and culturing, can be used to produce an organism which will contain the gene modification or disruption in germ line cells, which can then in turn be used to produce another animal that possesses the gene modification or disruption in all of its cells. In other methods for production of an animal containing the gene modification or disruption in all of its cells, cloning technologies can be used. These technologies generally take the nucleus of the transfected cell and
30 either through fusion or replacement fuse the transfected nucleus with an oocyte which can then be manipulated to produce an animal. The advantage of procedures that use cloning instead of ES technology is that cells other than ES cells can be transfected. For example, a fibroblast cell, which is very easy to culture can be used as the cell which is transfected and has a gene modification or disruption event take place, and then cells derived from this cell can be used to
35 clone a whole animal. Conditional knockouts can also be made which will conditionally delete

expression of the desired molecule, for example, an A6 or integrin or the gamma2 chain of laminin5.

d) Methods of diagnosing cancer

Methods of diagnosing cancer using the disclosed information and the disclosed
5 molecules. In particular disclosed are methods of diagnoses that rely on the combined upregulation of both the ligand and the cognate integrin receptor or cognate integrins. It is understood that all of the methods of diagnosis disclosed herein, can be used with any of the disclosed compositions, but they also can be used in conjunction, where for example, both the ligand and the integrin receptor are monitored and correlated with cancer developing.

10 Disclosed are methods of assessing a subject's risk of developing cancer comprising determining the amount of A6 present in a target cell obtained from the subject, wherein a determination of increased levels of A6 correlates with an increased risk of cancer.

Disclosed are methods of assessing a subject's risk of acquiring cancer comprising determining the amount of B4 present in a target cell obtained from the subject, wherein a
15 determination of increased levels of B4 correlates with an increased risk of cancer.

Disclosed are methods of assessing a subject's risk of acquiring cancer comprising determining the amount of laminin5 present in a target cell obtained from the subject, wherein a determination of increased levels of laminin5 correlates with an increased risk of cancer.

Disclosed are methods of assessing a subject's risk of acquiring cancer comprising
20 determining the amount of gamma2 subunit present in a target cell obtained from the subject, wherein a determination of increased levels of gamma2 subunit correlates with an increased risk of cancer.

Also disclosed are methods, further comprising comparing the amount A6 present to the amount in a control cell, and wherein determining the amount of A6 present in the target cell
25 comprises assaying the amount of A6 mRNA in the cell, and/or wherein the assaying the amount of mRNA in the cell comprises hybridizing a A6 probe to a sample of the subject's mRNA, and/or wherein the assaying the amount of mRNA in the cell comprises hybridizing a A6 primer to a sample of the subject's mRNA, and/or wherein the assaying the amount of mRNA further comprises performing an nucleic acid amplification reaction involving the primer, and/or wherein
30 the nucleic acid amplification reaction comprises reverse transcription, producing a cDNA, and/or wherein the nucleic acid amplification reaction further comprises performing a polymerase chain reaction on the cDNA, and/or wherein determining the amount of A6 present in the target cell comprises assaying the amount of A6 protein in the cell, and/or further comprising comparing the amount B4 present to the amount in a control cell, and/or further comprising comparing the

amount laminin5 present to the amount in a control cell, and/or further comprising comparing the amount gamma2 subunit present to the amount in a control cell.

C. Examples

Throughout this application, various publications are referenced. The disclosures of these
5 publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains. The references disclosed are also individually and specifically incorporated by reference herein for the material contained in them that is discussed in the sentence in which the reference is relied upon.

It will be apparent to those skilled in the art that various modifications and variations can
10 be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

15 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 the compounds, compositions, articles, devices and/or methods claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts,
20 temperature, etc.), but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in °C or is at ambient temperature, and pressure is at or near atmospheric.

1. Example 1 Colonic epithelial cells dependent on alpha6beta4 receptor signal transduction for growth in the absence of ECM

25 Integrin alpha6 and integrin beta4 and laminin gamma2 chains are essential for tumor cell survival in vivo. The data disclosed herein indicate that interfering with integrin alpha6-mediated signaling, integrin beta 4signaling, and laminin gamma2 signaling can constitute an effective approach to induce programmed cell death in cancer cells without damaging normal cells. Ablation of integrin alpha6-dependent signaling, integrin beta4-dependent signaling, and laminin
30 gamma2- dependent signaling in human cancer cell lines supports this.

The murine colonic epithelial transformation system introduced by D'Abaco et al. (1996) was used. In this system, control cells (control), cells containing an activated ras oncogene (Ras), a deletion in the APC gene (APCmin) or both alterations together (Ras+APCmin) can be compared with regard to their proliferation characteristics in tissue culture. The cells were derived from
35 transgenic mice containing a temperature-sensitive allele of SV40 large T under the control of a

gamma interferon-inducible promoter permitting conditional immortalization (Jat *et al.*, 1991). All experiments were carried out with the cells being kept at non-permissive temperature in the absence of gamma interferon. As shown previously (D'Abaco *et al.*, 1996), only the cells carrying activated Ras and the APCmin mutation were able to form colonies in soft agar in the absence of anchorage to a substratum. All other cell populations did not give rise to colonies under these conditions.

The frequency of tunel-staining cells (Fig. 2A) and caspase 3 activity (Fig. 2B) in control, Ras, APCmin and Ras+APCmin colonic epithelial cells (D'Abaco *et al.*, 1996) in suspension was measured. Both assays show a strong suppression of apoptosis in Ras-APCmin cells, indicating that Ras and APCmin co-operate in preventing cell death in the absence of apparent ECM contacts. Activated Ras can protect cells from apoptosis via activation of the serine-threonine kinase AKT (Kauffmann-Zeh *et al.*, 1997; Khwaja *et al.*, 1997). However, both Ras and Ras+APCmin cells show equivalent levels of AKT phosphorylation (not shown), eliminating AKT as the relevant target of Ras+APCmin cooperation.

Although cancer cells have been thought to survive independently of integrin signaling, they frequently express high levels of alpha3 or alpha6 integrin receptors and/or their ligands (Dedhar *et al.*, 1993; Kennel *et al.*, 1989; Koshikawa *et al.*, 1999; Lohi *et al.*, 2000; Nejjari *et al.*, 1999; Van Waes and Carey, 1992). These integrins are suspected to play a role in invasion and metastasis (Mukhopadhyay *et al.*, 1999; Shaw *et al.*, 1997). Ras and APCmin mutations would induce alterations in the mRNA expression patterns of integrin and ECM components. Induction of alpha6 integrin alone, was specific to Ras+APCmin cells (Fig. 3A). In addition, we found elevated expression of the laminin alpha5, gamma2 and beta2 chains induced in Ras and Ras+APCmin cells (Fig. 3B). These chains are components of laminins 5, 10 and 11 (Malinda and Kleinman, 1996), which are ligands of integrin receptors alpha6/beta4 and alpha3/beta1 (Kikkawa *et al.*, 2000; Niessen *et al.*, 1994). These results indicate that Ras and APCmin mutations can cooperate to induce autocrine activation of integrin receptors.

Alpha6 integrin can form functional receptors together with either beta1 or beta4 integrins (Clark and Brugge, 1995), leading to signaling through downstream effectors such as focal adhesion kinase (FAK) or the SH2 domain adapter Shc (Giancotti and Ruoslahti, 1999). Conversely, beta4 integrin only binds to alpha6 integrin (Clark and Brugge, 1995). In transformed colonic epithelial cells alpha6 integrin functions in conjunction with integrin beta4 and is engaged by the laminin gamma2 chain to activate Shc (see Fig. 4). Consistent with alpha6 integrin induction, only Ras+APCmin cells can bind a laminin gamma2-specific peptide in an alpha6 and beta4 integrin-specific manner. In contrast, an alpha3/beta1 and alpha6/beta1-specific peptide derived from the laminin gamma1 chain, only binds to control cells (Fig. 4A). In addition, only in

Ras+APCmin cells is Shc phosphorylated in response to clustering of the integrin alpha6/beta4 receptor by beta4-specific antibodies (Mainiero *et al.*, 1995) and by the laminin gamma2-specific peptide (Fig. 4B). In both cases p52^{Shc} is the major phosphorylated form. Moreover, alpha6 integrin is required for Shc activation, as Shc phosphorylation is inhibited in response to
 5 expression of a dominant-negative beta4 integrin mutant. This mutant lacks the cytoplasmic signaling domain but selectively binds to alpha6 integrin to form a ligand binding, yet signaling-defective alpha6/beta4 integrin (Spinardi *et al.*, 1993) (Fig. 4B)

Anti-sense RNAs specific for alpha6 integrin and gamma2 laminin, as well as dominant-negative beta4 integrin, were expressed and results indicated that integrin alpha6, integrin beta4,
 10 and laminin gamma2 expression are relevant for the survival of Ras+APCmin cells in Ras+APCmin, Ras, APC and control cells. All three constructs efficiently inhibit the growth of Ras+APCmin cells in soft agar (not shown) and when attached to plastic (Fig. 5A1). In contrast, the proliferation of wt, Ras and APCmin cells is not affected by this treatment (Fig. 5A1). Importantly, the colony formation of Ras+APC cells exposed to any of the three inhibitory
 15 constructs can be rescued by co-expression of baculovirus p35, a potent inhibitor of caspase activity and of apoptosis (Resnicoff *et al.*, 1998) (Fig. 5A1). Similarly, co-expression of exogenous integrin alpha6 mRNA efficiently rescues Ras-APCmin cell proliferation inhibited by alpha6 anti-sense RNA (Fig. 5A1). This is mirrored by a rescue of alpha6 integrin expression on the cell surface of alpha6 anti-sense RNA expressing cells (Fig. 5B). Moreover, ectopic alpha6
 20 integrin expression also rescues apoptosis induced by dominant-negative beta4 integrin (Fig. 5A1). The latter is expressed at constant levels (Fig. 5B). As one would expect, the cells expressing laminin gamma2 antisense RNA could not be rescued by integrin alpha6 over-expression, but showed significant rescue when plated on dishes coated with laminin gamma2 peptide (Fig. 5A1). Similarly, this peptide increases the survival of Ras+APCmin cells in
 25 suspension, as indicated by lower caspase 3 activity (Fig. 2C). In summary, the survival of Ras-APCmin cells depends on the expression of alpha6/beta4 integrin and the laminin gamma2 chain. Conversely, the inhibition of these gene activities leads to selective killing of transformed cells.

Data also indicate that cell death due to lack of alpha6/beta4 integrin receptor signaling in Ras-APCmin cells is independent of the death signaling pathway involving the induction of
 30 mitochondrial damage and caspase 9 activity. Instead, the data indicate an involvement of the Fas/TNF receptor/death domain protein/caspase8 pathway (Kruidering and Evan, 2000) in the control of tumor cell survival by alpha6 integrin-containing integrin receptors.

Control, APCmin and Ras cells, which lack alpha6/beta4 integrin receptor signaling activity, show high levels of caspase 8 activity when kept in suspension, while at the same time
 35 caspase 9 activity cannot be detected (Fig. 2D).

Although Ras-APCmin cells can be rescued from apoptosis by caspase inhibitor baculovirus p35 (Fig. 5 A1, A2 and text above), cell death induced by expression of dominant-negative beta4 integrin cannot be prevented by expression of the survival factor Bcl2 (see Fig. 5 A2). Bcl2 binds to and neutralizes BH3-domain killer proteins that cause mitochondrial damage, cytochrome C release and caspase 9 activation (Luo *et al.*, 1998).

Ras cells which lack alpha6/beta4 integrin receptor signaling activity and cannot survive in the absence of ECM contacts, and Ras+APCmin cells which depend on alpha6/beta4 integrin receptor signaling for survival, show equivalent levels of AKT phosphorylation (data not shown). This indicates that AKT does not serve as the key target for alpha6/beta4 integrin receptor signaling. AKT has been described to promote cell survival via phosphorylation and inactivation of Bad, a BH3-domain killer protein (Datta *et al.*, 1999).

2. Example 2 Other cancer cells dependent on alpha6beta4 receptor signal transduction for growth in the absence of ECM

The survival of highly transformed primary mouse embryo fibroblasts expressing Ras and Myc oncoproteins in conjunction with a homozygous ARF null mutation (Kamijo *et al.*, 1997) depends on expression and function of alpha6 integrin (Fig. 5C), thus demonstrating that this principle also may apply to transformed mesenchymal cells. Moreover, the human colon cancer cell line SW480 carrying multiple oncogenic mutations such as activated Ras (Fujita *et al.*, 1988), amplified c-Myc (Cherif *et al.*, 1988), a mutated APC allele (Munemitsu *et al.*, 1995) and a p53 mutation (Abarzua *et al.*, 1995) is effectively killed by anti-sense integrin alpha6 and laminin gamma2 RNAs as well as dominant-negative beta4 integrin (Fig. 4D). Similarly, integrin alpha6 ablation even leads to apoptosis of Ras/APCmin cells in the presence of active SV40 large T (not shown). Thus the survival of different types of highly transformed cells depends on alpha6 integrin expression, beta4 integrin expression and laminin5 expression irrespective of the status of major tumor suppressor genes, such as arf, p53 or rb, and for at least sw480 cells, murine colon epithelial cells, and the ras/APCmin cells, alpha6, beta4, and laminin5/gamma2 are required. The sensitivity of transformed cells to ablation of integrin signaling, for example, A6B4 integrin receptor signaling, is thus quite remarkable in its apparent generality.

Oncogenic mutations co-operate to engage autocrine integrin signaling. Importantly, this signaling mechanism, involving alpha6 integrin, beta4 integrin and the laminin gamma2 chain, becomes an essential component of the survival mechanism in transformed colonic epithelial cells. In addition, fibroblasts and human colon cancer cells also rely on integrin alpha6 for survival. In contrast, normal and partially transformed cells that express alpha6 integrin at low levels do not require this polypeptide for survival. Thus, integrin signaling inhibition can lead to selective killing of cancer cells.

The laminin-integrin receptor signaling loop is also relevant to the survival of cells transformed by other combinations of oncogenic lesions. Introduction of activated Ras together with dominant-negative p53 (Lloyd et al., 1997) into murine colonic epithelial cells (D'Abaco *et al.*, 1996; see also above) via retroviral infection supports this. Four distinct polyclonal pools of
 5 infected cells were derived by drug selection: 1) Control (bleo/neo) cells, infected with two retroviruses carrying neomycin (neo) or bleomycin (bleo) drug resistance markers, respectively; 2) Ras cells, infected with a Ras/neo virus and a virus with the bleo marker; 3) DNp53 cells, infected with a DNp53/bleo virus and a virus with the neo marker; and 4) Ras/DNp53 cells, infected with a Ras/neo virus and a DNp53/bleo virus.

10 As the colon epithelial cells contain temperature-sensitive SV40 large T under control of the gamma interferon promoter, all cell populations were drug-selected at the permissive temperature (33°C) in the presence of gamma interferon. All further experiments were carried out at the non-permissive temperature for SV40 large T in the absence of gamma interferon, as described above for Ras+APCmin cells.

15 Similar to Ras+APCmin cells, only Ras/DNp53 cells but neither bleo/neo, Ras/bleo or DNp53/neo cells were able to grow in the absence of ECM contact in soft agar (not shown). Moreover, Ras and DNp53 cooperate in the suppression of caspase 3 activity in suspension (Fig. 2B), and in the induction of alpha6 integrin expression (Fig. 4A). In Ras/DNp53 cells passaged through a single round of soft agar growth, alpha6 integrin is expressed at even higher levels,
 20 demonstrating a correlation between the ability of the cells to survive in the absence of ECM contact and alpha6 integrin expression. In Ras/DNp53 cells beta4 integrin expression levels are also increased, when compared to controls (Fig. 4A). As expected expression of the laminin gamma2 chain is induced in Ras/bleo and Ras/DNp53 cells (Fig. 4B).

Anti-sense RNAs specific for alpha6 integrin and gamma2 laminin, as well as dominant-
 25 negative beta4 integrin were expressed in Ras/DNp53, Ras/bleo, DNp53/neo and neo/bleo cells. All three constructs efficiently inhibit the growth of Ras/DNp53 cells when attached to plastic. In contrast, the proliferation of neo/bleo, Ras/bleo and DNp53/neo cells is not affected by this treatment (Fig. 5A3). Anti-sense alpha6 integrin or dominant-negative beta4 integrin also inhibit the growth of Ras/DNp53 cells in soft agar (Fig. 5A4).

30 Integrin alpha6 expression can also be induced by activated Ras and DNp53 in primary murine colon crypt epithelial cells (not shown). Furthermore introduction of Ras and Myc oncoproteins into our control colon epithelial cells also leads to an induction of alpha6 expression (not shown), suggesting that induction of alpha6 integrin expression may be an integral component of distinct oncogene cooperation paradigms

a) Cell types to be tested

As described herein, there are a variety of cancer and transformed cell types that express alpha6 integrin and laminins at high levels (Dedhar *et al.*, 1993; Koshikawa *et al.*, 1999; Lohi *et al.*, 2000; Van Waes and Carey, 1992). As disclosed herein the following cell lines other than the
 5 fibroblasts require alpha6 and beta4 integrin expression, as well as laminin gamma2 chain expression: (1) the human colon carcinoma cell line SW480 (data not shown), (2) Ras+APCmin-transformed murine colon epithelial cells (see Fig. 3A) Murine fibroblasts transformed by activated Ras and Myc in conjunction with homozygous Arf null mutation require alpha6 expression for their survival. These cells do not express integrin beta4, but express beta1 integrin,
 10 indicating the importance of alpha6/beta1 receptors in the transformed fibroblasts.

b) Inducible expression of inhibitors

To interrupt alpha6 integrin and laminin gamma2 chain-dependent signaling in tumors regulatable alpha6 integrin and laminin gamma2 antisense mRNA expression as well as regulatable expression of the beta4 integrin the dominant-negative polypeptide described in
 15 Section C were used. Constitutive expression of these inhibitors leads to rapid cell death in tissue culture. In contrast, the establishment of clonal cell lines with inducible expression of anti-sense mRNAs or dominant-negative beta4 integrin minimize such limitations.

The doxycycline (dox)-inducible reverse tetracycline transactivator (rtTA) is frequently used to overexpress transgenes in a temporally regulated fashion in vitro and in vivo (Efrat *et al.*,
 20 1995; Gossen *et al.*, 1995; Ray *et al.*, 1997). These systems are, however, often compromised by the levels of gene expression in the absence of dox administration. The tetracycline controlled transcriptional silencer (tTS), a fusion protein containing the tet repressor and the KRAB-AB domain of the kid-1 transcriptional repressor, is inhibited by doxycycline. As shown in tissue culture (Freundlieb *et al.*, 1999) and in transgenic mice (Zhu *et al.*, 2001), tTS tightens the control
 25 of transgene expression in rtTA-based systems, i.e. tTS effectively eliminates leaky baseline expression without altering the inducibility of rtTA-regulated genes. Thus optimal "off/on" regulation of gene expression can be accomplished with the combined use of tTS and rtTA. The complete expression system is commercially available from CLONTECH. This system can be used for the preparation of all inducible cell lines.

30 Another regulatable system comprising the estrogen-dependent transactivator GalER-VP16 and a promoter under the control of Gal4 DNA binding sites (Brasemann *et al.*, 1993) can be used. (Perez-Roger *et al.*, 1997). This particular experimental set up, was used herein to show that the induction of the beta4 integrin dominant-negative mutant in SW480 colon cancer cells induces apoptosis in vitro, as measured by caspase 3 activation (Fig. 2B). For in vivo use,
 35 however, a point mutation has to be introduced into the GalER-VP16 transactivator that eliminates

its sensitivity to estrogen while retaining its response to the anti-estrogen 4OH-tamoxifen (Littlewood *et al.*, 1995). 4OH-tamoxifen has been demonstrated to reversibly regulate in vivo the activity of another regulatable transactivator, the MycER chimera (Pelengaris *et al.*, 1999).

Typically, inducible cell lines are first stably transfected with the anti-sense or dominant-negative constructs coupled to the regulatable promoters into the four test cell lines. Subsequently, the activator is introduced and the repressor, such as rtTA and tTS (see above) via infection using recombinant retroviruses with different selectable markers

D. References

- Abarzua, P., LoSardo, J.E., Gubler, M.L. and Neri, A. (1995) Microinjection of monoclonal antibody PAb421 into human SW480 colorectal carcinoma cells restores the transcription activation function to mutant p53. *Cancer Res*, **55**, 3490-4.
- Akiyama, S.K., Nagata, K. and Yamada, K.M. (1990) Cell surface receptors for extracellular matrix components. *Biochim Biophys Acta*, **1031**, 91-110.
- Brasemann, S., Graninger, P. and Busslinger, M. (1993) A selective transcriptional induction system for mammalian cells based on Gal4-estrogen receptor fusion proteins. *Proc Natl Acad Sci U S A*, **90**, 1657-61.
- Cherif, D., Le Coniat, M., Suarez, H.G., Bernheim, A. and Berger, R. (1988) Chromosomal localization of amplified c-myc in a human colon adenocarcinoma cell line with a biotinylated probe. *Cancer Genet Cytogenet*, **33**, 245-9.
- Clark, E.A. and Brugge, J.S. (1995) Integrins and signal transduction pathways: the road taken. *Science*, **268**, 233-9.
- D'Abaco, G.M., Whitehead, R.H. and Burgess, A.W. (1996) Synergy between Apc min and an activated ras mutation is sufficient to induce colon carcinomas. *Mol Cell Biol*, **16**, 884-91.
- Dedhar, S., Saulnier, R., Nagle, R. and Overall, C.M. (1993) Specific alterations in the expression of alpha 3 beta 1 and alpha 6 beta 4 integrins in highly invasive and metastatic variants of human prostate carcinoma cells selected by in vitro invasion through reconstituted basement membrane. *Clin Exp Metastasis*, **11**, 391-400.
- Efrat, S., Fusco-DeMane, D., Lemberg, H., al Emran, O. and Wang, X. (1995) Conditional transformation of a pancreatic beta-cell line derived from transgenic mice expressing a tetracycline-regulated oncogene. *Proc Natl Acad Sci U S A*, **92**, 3576-80.
- Freundlieb, S., Schirra-Muller, C. and Bujard, H. (1999) A tetracycline controlled activation/repression system with increased potential for gene transfer into mammalian cells. *J Gene Med*, **1**, 4-12.
- Fujita, J., Yoshida, O., Ebi, Y., Nakayama, H., Onoue, H., Rhim, J.S. and Kitamura, Y. (1988) Detection of ras oncogenes by analysis of p21 proteins in human tumor cell lines. *Urol Res*, **16**, 415-8.
- Giancotti, F.G. and Mainiero, F. (1994) Integrin-mediated adhesion and signaling in tumorigenesis. *Biochim Biophys Acta*, **1198**, 47-64.
- Giancotti, F.G. and Ruoslahti, E. (1999) Integrin signaling. *Science*, **285**, 1028-32.
- Gossen, M., Freundlieb, S., Bender, G., Muller, G., Hillen, W. and Bujard, H. (1995) Transcriptional activation by tetracyclines in mammalian cells. *Science*, **268**, 1766-9.
- He, T.C., Sparks, A.B., Rago, C., Hermeking, H., Zawel, L., da Costa, L.T., Morin, P.J., Vogelstein, B. and Kinzler, K.W. (1998) Identification of c-MYC as a target of the APC pathway. *Science*, **281**, 1509-12.
- Hynes, R.O. (1992) Integrins: versatility, modulation, and signaling in cell adhesion. *Cell*, **69**, 11-25.
- Jat, P.S., Noble, M.D., Ataliotis, P., Tanaka, Y., Yannoutsos, N., Larsen, L. and Kioussis, D. (1991) Direct derivation of conditionally immortal cell lines from an H-2Kb-tsA58 transgenic mouse. *Proc Natl Acad Sci U S A*, **88**, 5096-100.
- Kamijo, T., Zindy, F., Roussel, M.F., Quelle, D.E., Downing, J.R., Ashmun, R.A., Grosveld, G. and Sherr, C.J. (1997) Tumor suppression at the mouse INK4a locus mediated by the

- alternative reading frame product p19ARF. *Cell*, **91**, 649-59.
- Kauffmann-Zeh, A., Rodriguez-Viciana, P., Ulrich, E., Gilbert, C., Coffey, P., Downward, J. and Evan, G. (1997) Suppression of c-Myc-induced apoptosis by Ras signalling through PI(3)K and PKB. *Nature*, **385**, 544-8.
- 5 Kennel, S.J., Foote, L.J., Falcioni, R., Sonnenberg, A., Stringer, C.D., Crouse, C. and Hemler, M.E. (1989) Analysis of the tumor-associated antigen TSP-180. Identity with alpha 6-beta 4 in the integrin superfamily. *J Biol Chem*, **264**, 15515-21.
- Khwaja, A., Rodriguez-Viciana, P., Wennstrom, S., Warne, P.H. and Downward, J. (1997) Matrix adhesion and Ras transformation both activate a phosphoinositide 3-OH kinase and protein kinase B/Akt cellular survival pathway. *Embo J*, **16**, 2783-93.
- 10 Kikkawa, Y., Sanzen, N., Fujiwara, H., Sonnenberg, A. and Sekiguchi, K. (2000) Integrin binding specificity of laminin-10/11: laminin-10/11 are recognized by alpha 3 beta 1, alpha 6 beta 1 and alpha 6 beta 4 integrins. *J Cell Sci*, **113**, 869-76.
- Koshikawa, N., Moriyama, K., Takamura, H., Mizushima, H., Nagashima, Y., Yanoma, S. and Miyazaki, K. (1999) Overexpression of laminin gamma2 chain monomer in invading gastric carcinoma cells. *Cancer Res*, **59**, 5596-601.
- 15 Land, H., Parada, L.F. and Weinberg, R.A. (1983) Tumorigenic conversion of primary embryo fibroblasts requires at least two cooperating oncogenes. *Nature*, **304**, 596-602.
- Lee, J.W. and Juliano, R.L. (2000) alpha5beta1 integrin protects intestinal epithelial cells from apoptosis through a phosphatidylinositol 3-kinase and protein kinase B- dependent pathway. *Mol Biol Cell*, **11**, 1973-87.
- 20 Lin, C.Q. and Bissell, M.J. (1993) Multi-faceted regulation of cell differentiation by extracellular matrix. *Faseb J*, **7**, 737-43.
- Littlewood, T.D., Hancock, D.C., Danielian, P.S., Parker, M.G. and Evan, G.I. (1995) A modified oestrogen receptor ligand-binding domain as an improved switch for the regulation of heterologous proteins. *Nucleic Acids Res*, **23**, 1686-90.
- Lloyd, A.C., Obermuller, F., Staddon, S., Barth, C.F., McMahon, M. and Land, H. (1997) Cooperating oncogenes converge to regulate cyclin/cdk complexes. *Genes Dev*, **11**, 663-77.
- 30 Lohi, J., Oivula, J., Kivilaakso, E., Kiviluoto, T., Frojman, K., Yamada, Y., Burgeson, R.E., Leivo, I. and Virtanen, I. (2000) Basement membrane laminin-5 is deposited in colorectal adenomas and carcinomas and serves as a ligand for alpha3beta1 integrin. *Apms*, **108**, 161-72.
- Mainiero, F., Murgia, C., Wary, K.K., Curatola, A.M., Pepe, A., Blumberg, M., Westwick, J.K., Der, C.J. and Giancotti, F.G. (1997) The coupling of alpha6beta4 integrin to Ras-MAP kinase pathways mediated by Shc controls keratinocyte proliferation. *Embo J*, **16**, 2365-75.
- 35 Mainiero, F., Pepe, A., Wary, K.K., Spinardi, L., Mohammadi, M., Schlessinger, J. and Giancotti, F.G. (1995) Signal transduction by the alpha 6 beta 4 integrin: distinct beta 4 subunit sites mediate recruitment of Shc/Grb2 and association with the cytoskeleton of hemidesmosomes. *Embo J*, **14**, 4470-81.
- 40 Malinda, K.M. and Kleinman, H.K. (1996) The laminins. *Int J Biochem Cell Biol*, **28**, 957-9.
- Marshall, M.S. (1995) Ras target proteins in eukaryotic cells. *Faseb J*, **9**, 1311-8.
- Morgenstern, J.P. and Land, H. (1990) Advanced mammalian gene transfer: high titre retroviral vectors with multiple drug selection markers and a complementary helper-free packaging cell line. *Nucleic Acids Res*, **18**, 3587-96.
- 45 Mukhopadhyay, R., Theriault, R.L. and Price, J.E. (1999) Increased levels of alpha6 integrins are associated with the metastatic phenotype of human breast cancer cells. *Clin Exp Metastasis*, **17**, 325-32.
- 50 Munemitsu, S., Albert, I., Souza, B., Rubinfeld, B. and Polakis, P. (1995) Regulation of intracellular beta-catenin levels by the adenomatous polyposis coli (APC) tumor-suppressor protein. *Proc Natl Acad Sci U S A*, **92**, 3046-50.
- Nejjari, M., Hafdi, Z., Dumortier, J., Bringuier, A.F., Feldmann, G. and Scoazec, J.Y. (1999) alpha6beta1 integrin expression in hepatocarcinoma cells: regulation and role in cell adhesion and migration. *Int J Cancer*, **83**, 518-25.
- 55 Niessen, C.M., Hogervorst, F., Jaspars, L.H., de Melker, A.A., Delwel, G.O., Hulsman, E.H., Kuikman, I. and Sonnenberg, A. (1994) The alpha 6 beta 4 integrin is a receptor for both

- laminin and kalinin. *Exp Cell Res*, **211**, 360-7.
- Parise, L.V., Lee, J. and Juliano, R.L. (2000) New aspects of integrin signaling in cancer. *Semin Cancer Biol*, **10**, 407-14.
- Pawson, T. and Scott, J.D. (1997) Signaling through scaffold, anchoring, and adaptor proteins. *Science*, **278**, 2075-80.
- Pelengaris, S., Littlewood, T., Khan, M., Elia, G. and Evan, G. (1999) Reversible activation of c-Myc in skin: induction of a complex neoplastic phenotype by a single oncogenic lesion. *Mol Cell*, **3**, 565-77.
- Perez-Roger, I., Kim, S.H., Griffiths, B., Sewing, A. and Land, H. (1999) Cyclins D1 and D2 mediate myc-induced proliferation via sequestration of p27(Kip1) and p21(Cip1). *Embo J*, **18**, 5310-20.
- Perez-Roger, I., Solomon, D.L., Sewing, A. and Land, H. (1997) Myc activation of cyclin E/Cdk2 kinase involves induction of cyclin E gene transcription and inhibition of p27(Kip1) binding to newly formed complexes. *Oncogene*, **14**, 2373-81.
- Ray, P., Tang, W., Wang, P., Homer, R., Kuhn, C., 3rd, Flavell, R.A. and Elias, J.A. (1997) Regulated overexpression of interleukin 11 in the lung. Use to dissociate development-dependent and -independent phenotypes. *J Clin Invest*, **100**, 2501-11.
- Resnicoff, M., Valentinis, B., Herbert, D., Abraham, D., Friesen, P.D., Alnemri, E.S. and Baserga, R. (1998) The baculovirus anti-apoptotic p35 protein promotes transformation of mouse embryo fibroblasts. *J Biol Chem*, **273**, 10376-80.
- Roper, E., Weinberg, W., Watt, F.M. and Land, H. (2001) p19ARF-independent induction of p53 and cell cycle arrest by Raf in murine keratinocytes. *EMBO Rep*, **2**, 145-50.
- Ruley, H.E. (1983) Adenovirus early region 1A enables viral and cellular transforming genes to transform primary cells in culture. *Nature*, **304**, 602-6.
- Sewing, A., Wiseman, B., Lloyd, A.C. and Land, H. (1997) High-intensity Raf signal causes cell cycle arrest mediated by p21Cip1. *Mol Cell Biol*, **17**, 5588-97.
- Shaw, L.M., Rabinovitz, I., Wang, H.H., Toker, A. and Mercurio, A.M. (1997) Activation of phosphoinositide 3-OH kinase by the alpha6beta4 integrin promotes carcinoma invasion. *Cell*, **91**, 949-60.
- Sonnenberg, A., Linders, C.J., Daams, J.H. and Kennel, S.J. (1990) The alpha 6 beta 1 (VLA-6) and alpha 6 beta 4 protein complexes: tissue distribution and biochemical properties. *J Cell Sci*, **96**, 207-17.
- Spinardi, L., Ren, Y.L., Sanders, R. and Giancotti, F.G. (1993) The beta 4 subunit cytoplasmic domain mediates the interaction of alpha 6 beta 4 integrin with the cytoskeleton of hemidesmosomes. *Mol Biol Cell*, **4**, 871-84.
- Thompson, T.C., Southgate, J., Kitchener, G. and Land, H. (1989) Multistage carcinogenesis induced by ras and myc oncogenes in a reconstituted organ. *Cell*, **56**, 917-30.
- Treisman, R. (1996) Regulation of transcription by MAP kinase cascades. *Curr Opin Cell Biol*, **8**, 205-15.
- Van Waes, C. and Carey, T.E. (1992) Overexpression of the A9 antigen/alpha 6 beta 4 integrin in head and neck cancer. *Otolaryngol Clin North Am*, **25**, 1117-39.
- Wary, K.K., Mainiero, F., Isakoff, S.J., Marcantonio, E.E. and Giancotti, F.G. (1996) The adaptor protein Shc couples a class of integrins to the control of cell cycle progression. *Cell*, **87**, 733-43.
- Zhu, Z., Ma, B., Homer, R.J., Zheng, T. and Elias, J.A. (2001) Use of the tetracycline controlled transcriptional silencer (tTS) to eliminate transgene leak in inducible overexpression transgenic mice. *J Biol Chem*, **30**, 30.

E. Sequences

1. SEQ ID NO:1 Human alpha6 integrin cds (acc# 4557674)

50 atggccgcccgcgggcagctgtgcttgcctacctgtcggcggggctcctgtcccggtcggcgcagccttcaacttggac
actcgggaggacaacgtgatccggaaatatggagacccgggagcctcttcggcttctcgcctggccatgcactggcaactg
cagcccaggacaagcggctgttgcctcgtgggggccccgcgcggagaagcgttccactgcagagagccaacagaacggga
gggctgtacagctgcgacatcacgcgccgggggccaatgcacgcggatcgagtttgataacgatgctgacccacgtcagaa
agcaaggaagatcagtgatgggggtcaccgtccagagccaaggtccagggggcaaggtcgtgacatgtgctcacccatat
55 gaaaaaaggcagcatgttaatacgaagcaggaatccccgagacatcttggggcgggtgttatgtcctgagtcagaatctcagg

attgaagacgatatggatgggggagattggagcttttgtgatgggagattgagaggccatgagaaatttggctcttgccag
 caaggtgtagcagctacttttactaaagacttttcattacattgtatttggagccccgggtacttataactggaaagggatt
 gttcgtgtagagcaaaagaataaacactttttttgacatgaacatctttgaagatgggcttatgaagttggtggagagact
 gagcatgatgaaagtctcgttccctgttccctgctaacagttacttaggtttttcttggactcagggaaaggtattgtttct
 5 aaagatgagatcacttttgtatctggtgctcccagagccaatcacagtggagccgtgggttttgcctgaagagagacatgaag
 tctgcacatctcctccctgagcacatattcgatggagaaggtctggcctcttcatttggctatgatgtggcgggtggaggac
 ctcaacaaggatgggtggcaagatatagttatttggagccccacagtattttgatagagatggagaagttggaggtgcagtg
 tatgtctacatgaaccagcaaggcagatggaataatgtgaagccaattcgtcttaatggaaccaaagattctatgtttggc
 attgcagtaaaaaatattggagatattaatcaagatggctacccagatattgcagttggagctccgtatgatgacttggga
 10 aaggtttttatctatcatggatctgcaaatggaataaataccaaaccaacacaggttctcaagggatatcaccttatttt
 ggatattcaattgctggaaacatggaccttgatcgaaattcctaccctgatgttgcctggttccctctcagattcagta
 actattttcagatcccgccctgtgattaatattcagaaaaccatcacagtaactcctaacagaattgacctccgccagaaa
 acagcgtgtggggcgccctagtggttatgctccaggttaaattcctgttttgaaataactgctaaccctcggttataat
 ccttcaatatcaattgtgggcacacttgaagctgaaaaagaaagaagaaaatctgggctatcctcaagagttcagtttca
 15 aaccaaggttctgagcccaaatatactcaagaactaactctgaagaggcagaaacagaaagtggtgcagtgaggaaaccctg
 tggctacaggataatatcagagataaactgcgtcccattcccataactgcctcagtgagatccaagagccaagctctcgt
 aggcgagtgaattcacttccagaagttcttccaattctgaattcagatgaaccaagacagctcatattgatgttcaacttc
 ttaaaagagggtatgtggagacgacaatgtatgtaacagcaaccttaactagaatataaattttgcacccgagaaggaaat
 caagacaaattttcttattttaccaattcaaaaaggtgtaccagaactagttctaaaagatcagaaggatattgctttagaa
 20 ataacagtgcacaaacagcccttccaacccaaggaatcccacaaaagatggcgatgacgcccattgaggctaaactgattgca
 acgtttccagacactttaacctattctgcataatagagaactgagggctttccctgagaaacagttgagttgtgttgccaac
 cagaatggctcgcaagctgactgtgagctcggaatccttttaaaagaaattcaaatgtcactttttatttggttttaagt
 acaactgaagtcacctttgacaccccatatctggatattaatctgaagttagaacaacaagcaatcaagataatttggct
 ccaattacagctaaagcaaaagtgggttattgaactgcttttatcggtctcgggagttgctaaccctcccaggtgtatttt
 25 ggaggtacagttgttggcgagcaagctatgaaatctgaagatgaagtgggaagtttaatatagagtatgaattcagggttaata
 aacttaggtaaacctcttacaacacctcggcacagcaaccttgaaacattcagtgggccaaaagaaattagcaatgggaaatgg
 ttgctttatttgggtgaaagtagaatccaaaggattggaaaaggtaacttgtgagccacaaaaggagataaactccctgaac
 ctaacggagttctcacaactcaagaaagaaacgggaaattactgaaaaacagatagatgataacagaaaattttctttattt
 gctgaaagaaaataccagactcttaactgtagcgtgaacgtgaactgtgtgaacatcagatgcccgctgccccgggctggac
 30 agcaaggcgtctcttatttttgcgctcgaggttatggaacagcacatttctagaggaatattccaaactgaactacttggac
 attctcatgagcagccttcattgatgtgactgctgctgccgaaaatatcaggctgccaaatgcaggcactcaggttcgagtg
 actgtgtttccctcaaagactgtagctcagttatcggtgagttaccttgggtggatcatcctagtggttattctcgttgggac
 ttgatgcttgcctttattagtggtttatactatggaagtgtggtttcttcaagagaaataagaaagatcattatgatgccaca
 tatcacaaggctgagatccatgctcagccatctgataaagagaggcttacttctgatgcatag

35 **2. SEQ ID NO:2 Human integrin alpha6 protein sequence (acc# NP_000201):**

1 maaaggllcll ylsagllsrll gaafnldtre dnvirkygdp gslfgfslam hwqlqpedkr
 61 lllvgaprge alplqranrt gglyscdita rgpctriefd ndadptsesk edqwmgvvtvq
 121 sqgpggkvvt cahryekrqh vntkqesrdi fgrcyvlsgn lrieddmdgg dwsfcdgrlr
 40 181 ghekfgscqg gvaatftkdf hyivfgapgt ynwkgivrve qknnffdmn ifedgpyevg
 241 getehdeslv pvpansylgf sldsgkgivs kdeitfvsga pranhsgavv llkrdmksah
 301 llpehifdge glassfgydv avvdlnkdgw qdivigapgy fdrdgevga vyvymnqggr
 361 wnnvkpirln gtdksmfia vknigdingd gypdiavgap yddlkvfiy hgsangintk
 421 ptqvlkgisp yfgysiagnm dldrnsypdv avgsldsdt ifrsrpvini qktitvtpr
 45 481 idlrqktacg apsgiclqv kscfeytanpa gynpsisivg tleaekerrk sglssrvqfr
 541 nqgsepkytq eltlkrqkqk vcmeetlwlq dnirdklrpi pitasveiqe pssrrrvnsl
 601 pevlpilnsd epkthidvh flkegcgddn vcnsnlkley kfctregnd kfsylpiqkg
 661 vpevlkdqk dialeltvtn spsnprnptk dgddaheakl iatfpdltly sayrelrafp
 721 ekqlscvanq ngsqadcelg npfkrnsnvt fylvlsttev tfdtpyldin lklettsnq
 50 781 nlapitakak vvielllsvs gvakpsqvyf ggtvvegam ksdevgsli eyefrvnl
 841 kpltnlgtat lniqwpkeis ngkwllylvk veskglekvt cepqkeinsl nlteshnsrk
 901 kreitekqid dnrkfslfae rkyqtlncsv nvncvnirp lrgldskasl ilrsrlwnst
 961 fleysklly ldilmrafid vtaaaenirl pnagtqvrvt vfpsktvaqy sgvpwwiilv
 1021 ailagilmla llvfilwkcg ffkrnkhdhy datyhkaeh aqpsdkerlt sda

55 **3. SEQ ID NO:3 Mus musculus alpha6 integrin cds (acc# 7110658):**

atggccgtcgcgggccagttgtgctgctctacctgtccgcggggcttctagcccggtgggtacagccttcaacctggac
 acccgcgaggacaacgtgatccggaatcggggatcccgggagcctcttcggcttctcgtcgcctatgcactggcagttg
 cagccggaggacaagcggctgttgccttgtgggggacacctcgggcagaagcactcccgctgcagagggcgaacagaacaggg
 ggctgtacagctgtgacatcacctcccgaggaccttgtaacggattgaatttgataatgacgctgatcctatgtcagaa
 60 agcaaggaagaccagtggtggagtcactgtccagagccaaggtccagggggcgaagtgggtgacgtgtgcacatcgatat
 gagaaacggcagcagctcaacacgaagcaggagtcgcgggatatcttggaaagtgttatgtcctgagtcagaatctcaga
 attgaagatgatattggacggaggagactggagtttctgcgatggccggttgagaggccatgaaaagtttggctcctgtcag
 caaggagttagcggctactttcactaaggactttcattacattgtttttggagccccagggacttacaactggaaagggatc
 gtcctgttagaacaagaataaacactttttttgacatgaacatcttgaagatgggcccctatgaagttggtggagagaca
 65 gatcatgatgaaagtctcgtgcccgttccctgctaacagttacctaggttttctgctggactcagggaaaggtattgtttct

aaagatgacatcacttttbtgtcttggtgctccaagagccaatcacagtggggctgtagtggttgctaaaaagagacatgaag
 tccgcacatctgctccctgagtatatatttgacggagaaggcctggcttctcgtttggctatgatgtggcagtggtggac
 ctcaatgcagatgggtggcaagacatcgttatcggagctccacagtattttgatagggttggtgaagtcgggggtgcagtt
 tacgtctacattaaccagcaaggcaaatggagtaattgtgaagccgattcgtctaaatgggaccaagactcgatgtttgga
 5 atctctgtgaaaaatataggtgatattaaccaagatggctatccagatatgtgttggtgagctccctatgatgatctgggg
 aaggtttttatctatcatggatccccgactggcataattaccaagccaacacaggttctcgaggggacatcgcttacttc
 ggctattcaatcgctgggaatatggacctggatcggaattcctaccccgaccttgctgtgggctccctctcagactcgggtc
 actattttcagatccccggccagtgattaacattctaaaaaccatcacagtgactcctaacagaattgacctccgccagaag
 tccatgtgtggctcacctagcgggatatgcctcaagggttaaagcctgttttgaaataactgcgaaaccttccgggttataac
 10 cctccaatatcaattttgggtatttcttgaaagctgaaaaagaaagaaagaaatcaggggtgtcatcgagagttcagtttcga
 aaccaaggttccgagccaaagtatactcaggagctgacctgaatcggcagaagcagcgggctgcatggaggagaccttc
 tggctgcaggagaacatcagagacaagctgcgtcccatccccatcaaggcttctgtggagatccaggagcccacgtctcgc
 cggcgggtgaactcactccccgaagttcttcccatcctgaattcaaatgaagccaaaacgggtccagacagatgtccacttc
 ttaaaggaaggatgtggagacgacaatgtctgtaacagcaaccttaagctagagtataaatttggtacccgagaaggaaat
 15 caagacaaattctcttaccttccaattcaaaaaggcatcccagaatttagtctaaaagatcagaaagatatagctctggaa
 ataacggtgaccaacagcccttcggatccaaggaatccccggaaagatggcgacgatgcccatgaagccaaactcatcgcc
 acgtttccagacactctgacataattccgcttacagagaactgagggttttccctgagaagcagctgagctgtgtggccaac
 cagaatgggtcccaagccgactgtgagctcggaaatcctttcaagagaaattccagtggttactttctatctgattttaagt
 acaaccgaggtcacctttgacaccacagatctggatattaatctgaagttggaaacaacaagcaatcaggataaattgggt
 20 ccaattacagcgaaggcaaaagtgggttattgaattgcttttatccctctccggagtcgctaagccttcgcaggtgtatttt
 ggaggtacagttgttgggtgagcaagctatgaaatctgaagatgaagtaggaagtttaatatagagtatgaatttaggggtgatt
 aacttaggcaagcctcttaaaaacctcggcacagcaaccttgaatatcacagtggcccaaggagattagcaatggcaaatgg
 ttgctttattttgatgaaagtgaatccaaaggtttggagcagattgtttgtgagccacacaatgaaataaactacctgaag
 ctgaaggagttctcacaactcaagaaagaaacgggaacttctgaaaaacagatagatgacagcaggaaattttctttattt
 25 cctgaaagaaaataaccagactctcaactgcagcgtcaacgtcaggtgtgtgaacatcaggtgcccactgcgagggctggac
 acgaaggcctctctcgttctgtgttccaggttggtggaacagcacatttctagaggaatattccaaactgaactacttggac
 attctcgtgagggcttccatagatgtcacccgtgctgctcagaatatcaagctccctcacgcgggcactcaggttcgagtg
 acggtgttttccctcaaagactgtagctcagttatcaggagtagcttggtggatcatcctcctggctgttcttgcgggatt
 ctgatgctggctctattagtggtttttactgtggaagtgtggcttcttcaagagaaataagaaagatcattacgatgccacc
 30 tatcacaaggctgagatccatactcagccgtctgataaagagaggcttacttccgatgcatag

4. SEQ ID NO:4 Mus musculus alpha6 integrin protein sequence (acc# NP_032423)

1 mavagqlcll ylsagllarl gtafnldtre dnvirksgdp gslfgfslam hwqlqpedkr
 61 lllvgaprae alplqranrt gglyscdits rgpctriefd ndadpmsesk edqwmgtvtg
 35 121 sqgpggkvvt cahryekrqh vntkqesrdi fgrcyvlsqn lrieddmdgg dwsfcdgrlr
 181 ghekfgscqq gvaatftkdf hyivfgapgt ynwkgivrve qknntffdmn ifedgpyevg
 241 getdhdeslv pvpansylgf sldsgkgivs kdditfvsga pranhsgavv llkrdmksah
 301 llpeyifdge glassfgydv avvdlnadgw qdivigapqy fdrdgevsga vyvyinqggk
 361 wsnvkpirln gtkdsmfgis vknigdingd gypdiavgap yddlqkvfiy hgsptgiitk
 40 421 ptqvlegts yfgysiagnm dldrnsypdl avgsldsdtv ifrsrpvini lktitvtpr
 481 idlrqksmcg spsgiclkvk acfeytakps gynppisilg ileaekerrk sglssrvqfr
 541 nqgsepkytq eltlnrqkqr acmeetlwlq enirdklrpi pitasveiqe ptsrrrvnsl
 601 pevlpilnsn eaktvqtdvh flkegcgddn vcnsnlkley kfgtregnd kfslpqiqlg
 661 ipelvlkdqk dialeltvtn spsdprnprk dgddaheakl iatfpdtlty sayrelrafp
 45 721 ekqlscvanq ngsqadcelg npfkrnssvt fylilsttev tfdttdldin lklettsnqd
 781 klapitakak vviellllsls gvakpsqvyf ggtvvgeqam ksedevgsli eyefrvnlg
 841 kplknlgat lniqwpkeis ngkwlllylmk veskglegiv cepheinyll klkeshnsrk
 901 krelpekqid dsrkfslfpe rkyqtlncsv nvrcvnircp lrgldtkasl vlcsrlwnst
 961 fleeysklly ldilvrasid vtaaaqnikl phagtqvrvt vfpsktvaqy sgvawwiill
 50 1021 avlagilmla llvflwkcg ffkrnkdkdhy datyhkaeih tqpsdkerlt sda

5. SEQ ID NO:5 Human integrin beta4 subunit cds (acc# 6453379):

atggcagggccacgccccagccccatgggcccaggctgctcctggcagccttgatcagcgtcagcctctctgggaccttgaac
 cgctgcaagaaggccccagtgaaagagctgcacggagtggtgctcgtgtggataaggactgcgcctactgcacagacgagatg
 ttcagggaccggcgctgcaacaccagggcgagctgctggccgcgggctgccagcgggagagcatcgtggtcatggagagc
 55 agcttccaaatcacagaggagaccagattgacaccacctgcgggcgcagccagatgtcccccaaggcctgcgggtccgt
 ctgcccggcgggtgaggagcggcattttgagctggaggtgtttgagccactggagagccccgtggacctgtacatcctcatg
 gacttctccaaactccatgtccgatgatctggacaacctcaagaagatggggcagaacctgggtcgggtcctgagccagctc
 accagcgaactacactatttggttttggaagtgttggtggacaaagtcagcgtcccgccagacggacatgaggcctgagaagctg
 aaggagccttggcccaacagtgaccccccttctccttcaagaacgtcatcagcctgacagaagatgtggatgagttccgg
 60 aataaactgcagggagagcggatctcaggcaacctggatgctcctgagggcggttcgatgccatcctgcagacagctgtg
 tgcacgagggacattgggtggcgcccgagcaccacctgctgggtcttctccaccgagtcagccttccactatgaggct
 gatggcgccaacgtgctggctggcatcatgagccgcaacgatgaacggtggccacctggacaccacgggcaacctacaccag
 tacaggacacaggactaccgctcgggtgccaccctgggtgcgcctgctcgccaagcacaacatcatccccatcttctgtgtc
 accaactactcctatagctactacgagaagcttcacacctatttccctgtctcctcactgggggtgctgcaggaggactcg
 65 tccaacatcgtggagctgctggaggaggccttcaatcggatccgctccaacctggacatccggggccttagacagccccga

6. SEQ ID NO:6 Human beta4 integrin protein sequence (acc# CAB61345):

81

541 qcprtsqgflc ndrgrcsmgq cvcepgwtgp scdcpisnat cidsnggicn grghcecgrc
 601 hchqgslytd ticeinysas trasartyap acsarrgapa rrrgarvrna tsrsrwtsl
 661 rearrrwcaa psgtrmttap tatpwkvtap lgptalswct rrrdcppgsf wwliplllll
 721 lp11a11111 cwkycaccka clallpccnr ghmvgfkedh ymlrenlmas dhldtpmlrs
 5 781 gnlkgrdvvr wkvtnnmqrp gfathaasin ptelvpysls lrlarlcten llkpdtreca
 841 qlrqveeenl nevyrqisgv hklqqtkfrq qpnaqkkqdh tivdtvlmap rsakpallkl
 901 tekqveqraf hdlkvapgyy tltadqdarg mvefgegvel vdvrplfir pedddekql
 961 veaidvpagt atlgrrlvni tiikegardv vsfeqqefsv srgdqvarip virrvldggk
 1021 sqvsyrtqdg taggnrdyip vegellfqpg eawkelqvkl lelqevdsll rgrqvrrfhv
 10 1081 qlsnpkfgah lgqphstti iirdpeldrs ftsqmlssqp pphgdlgapq npnakaagsr
 1141 kihfnwlpss gkpmgyrvky wiqgdsesea hlldskvpsv eltnlypycd yemkvcaiga
 1201 qgegpysslv scrthqevps epgrlafnv sstvtqlswa epaetngeit ayevcyglvn
 1261 ddnrpigpmk kvldvnpknr mllienlres qpyrytvkar ngagwgpere aiinlatqpk
 1321 rpmsipiipd ipivdaqsg dydsflmysd dvlrspgsq rpsvsddtgc gwkfepllge
 15 1381 eldlrrvtwr lppeliprls assgrssdae aphgppddgg agggkgsllpr satpgppgeh
 1441 lvngrmdfaf pgstnsllhm tttsaaaygt hlsphvphrv ltsstltdr ynsltrsehs
 1501 hsttlprdis tltsvsshgl ppiwehgrsr lplswalgsr sraqmkgfpp srgprdsiil
 1561 agrpaapswg pdsrltagvp dtptrlvlsa lgptslrvsw qeprcerplq gysveyqln
 1621 ggelhrlnip npaqtsvvve dllpnhsyvf rvraqsqegw greregviti esqvhpgspl
 20 1681 cplpgsaftl stpsagplv ftalspdsll lswprprpn gdivgylvtc emaggggpat
 1741 afrvdgdspe srltvpglse nvpkyfkvga rttegfger egiitiesqd ggpfpqlgsr
 1801 aglfqhplqs eyssistttht satepflvgp tlgaqhleag gsltrhvtqe fvsrtlttsq
 1861 tltshmdqqf fqt

7. SEQ ID NO:7 Mouse integrin beta4 subunit mRNA (not only cds) (acc# L04678):

25 ggaccgtcgaggcagcgggactgacccagctgggctcactgtattaagaagcggacccgcgacccggagcgcgggggacc
 cgatctgggagcctggacgggtgcagcgcgcaggaatgcagtcgcctgactcaccagcgcctccttctacctgcgcgc
 ccgtccataaagcgtgctcgtcccgccgcgcgcgcgcgcctgctgtcccgccgggctcgccgcgcgctcagctcgacc
 caacgcagcccaagtcgaggtagtctcactaaggaggaggaggatggcagggccctgttgagcccatgggtgaagctgc
 30 tgctgctggcacgaatgctgagtgccagcctccctggagacctggccaaccgctgcaagaaggctcaggtgaagagctgta
 ccgagtgcatccgggtggacaagagctgtgcctactgcacagacgagctgttcaaggagaggcgtgcaacaccagggcgg
 acgttctggctgcaggctgcaggggagagagcatcctggctcatggagagcagccttgaaatcacagagaacaccagatcg
 tcaccagcctgcaccgcagccaggtatctcccaaggcctgcaagtcgggctgcggcggggtgaggagcgcacgtttgtgt
 tccaggtctttgagccctggagagcccgctggatctgtatatcctcatggacttctccaactccatgtctgacgatctgg
 35 acaacctcaagcagatggggcagaacctggccaagatcctgcgccagctcaccagcgactacaccattggatttggaaagt
 ttgtggacaaagtcagcgtcccacagacagacatgaggccccgagaaactgaaggagccctggcccaacagtgatccccgt
 tctccttcaagaacgttatcagcttaacggagaatgtggaagaattctggaacaaactgcaaggagaacgcctctcaggca
 acctggacgctcctgaaggggctttgatgccatcctgcagacagctgtgtgcacaaggacattggctggagggtgaca
 gcacccacctgctgggtgttctccaccagctgtgccttccactacgaggtgatgggtgccaacgttctggccggcatcatga
 40 accgcaatgatgagaaatgccacctggacgcctcgggcgcctacacccaatacagacacaggactacccatcagtgccca
 cgctgggttcgctgcttgccaagcataacatcatcccatctttgctgtcaccaactactcttacagctactatgagaagc
 tccataagtatctcccgctctctctctctgggcgtcctgcaggaggattcatccaacatcgtggagctgctggaggaggcct
 tctatcgaattcgcctccaacctggacatccgggctctggacagccccagaggcctgagaacagaggtcacctccgatactc
 tccagaagacggagactgggtcctttcacatcaagcggggggaagtgggcacatacaatgtgcatctccgggcagtgagg
 45 acatagatgggacacatgtgtgccagctggctaaagaagaccaagggggcaacatccacctgaaacctccttctctgatg
 gcctccggatggacgcgagtgatctgtgacgtgtgcccctgtgagctgcaaaaggaagtccgatcagctcgctgtcact
 tcagaggagacttcatgtgtggacactgtgtgtgcaatgagggtggagtgggcaaaacctgcaactgctccaccggctctc
 tgagtgacacacagccctgcctgcgtgagggtgaggacaaacctgctcgggccacggcgagtgccagtgccggacgctgtg
 tgtgctatgggtgaaggccgctacgagggtcacttctgcgagtatgacaacttccagtgctccccggacctctggattcctgt
 50 gcaatgaccggggacgctgttctatgggagagtgtgtgtgtgagcctgggtggacagggcgcagctgcgactgtccctca
 gcaatgccacctgcatcgatagcaacgggggcatctgcaacggccgaggctactgtgagtggtggcgtgtgactgcaacc
 agcagtcgctctacacggacaccacctgtgagatcaactactctgcgatactgggtctctgtgaggatctccgctcctgcg
 tacagtgccaggcctggggcaccgggggagaagaaagggcgcgctgtgacgattgccccctttaaagtcaagatggtagacg
 agcttaagaagaagaggtgggtggagtactgtccttccgggatgaggatgacgactgcacttacagctacaacgtggagg
 55 gcgacggcagccctgggcccacagcagctcctgggtccacaaaaagaaagactgcctcccggtccttccctgggtggctca
 tccccctgctcatcttctcctgttgcctcctggcggttgccttctgctgctctgctggaaatactgtgcctgctgcaagcct
 gcctggggcttcttctccttgcctgcaaccgaggtcacatgggtgggctttaaaggaagatcactatatgcttcgggagaacctga
 tggcctctgaccacctggacacgcccctgctacgaagcgggaacctcaaggagcagagacacagtcgctggaagatcacca
 acaatgtgacgcgcctggctttggcaccatgcccgcagcaccagccccacggagctcgtacctacgggctgtccctgc
 60 gccttggccgctctgactgagaaccttatgaagccggggcaccagagagtgtagcagctacgccaggaggtggaggaaa
 atctgaatgaggtgtatagacaggtcagcggcgacacacaagctccagcagacgaagtccgacagcagcccaacgcggga
 aaaagcaagaccacaccattgtggacacagtggtgctggcgccccgctccgccaagcagatgctgctgaagctgacagaga
 agcaggtggagcaggggtccttccatgaactgaaggtggccccctggctactacactgtcacggcagagcaggatgcccggg
 gcatgggtggagttccaggagggcggtggagctgggtggatgtgcgagtgccccctcttcatccggcctgaggatgatgaga
 65 agcagctgctgggtggaggccattgatgtcctgtgagcactgccaccttgggtcgccgtctggtaaacatcaccattatca
 aggaacaagctagtggggtagtgtccttcgagcagcctgaatactcggtgagtcgtggagaccaggtggcccgcatccctg

tcattccggcacatcctggacaatggcaagbtcccaggtctcctatagcacacaggataatacagcacacggacacccgggatt
 atgttcccgtggaggagagctgctgttccatcctggggaaacctggaaggagttgcaggtgaagctactggagctgcagg
 aggttgactccctcctgctggtggccgaggtccgcttccaagtccaactcagcaaccccaagttcggagcccgctgg
 gccagcccagcacaaccacggttattctcgatgaaacggacaggagttcataaatcaaacactttcatcgccctccgccac
 5 cccatggagacctggggcgccccacagaaccccaatgccaaggctgccgatccaggaagatccatttcaactggctgcccc
 ctcttggaagccaatggggtacaggggtgaagtactggatccagggcgactctgaatctgaagcccaccttctagatagca
 aggtgccctcagtggaaactcaccaacctgtatccctattgctgactacgaaatgaaggtgtgtgcctatggggccaagggtg
 aggggcccctatagctcactggtgtcctgcccacccaccaggaagtacccagtgagccaggaggctggctttcaatgtag
 tctcttctacgggtgactcagctgagctgggcagagccagctgagaccaatggcgagatcacagcctacgaggtctgctatg
 10 gactggtcaatgaggacaacagacccattggacctatgaagaagggtgctcgtggacaaccccaagaaccggatgctgctca
 ttgagaatctgagagattcccagccataccgatacacggttaaggcgcgcaatggggcaggatggggacccgagagagagg
 ctatcatcaacctgggtacacagcccaagcgcccatgtccatccctatcatcccagacatccccatagtgagcgccagg
 gtggagaagactacgaaaacttccttatgtacagtgtgacgtcctgcggtccccagccagcagccagaggcccagcgttt
 ctgatgacactgagcacctggtgaatggccggatggactttgcctatccaggcagcgccaactccctgcacagaatgactg
 15 cagccaatgtggcctatggcacgcatctgagcccacacctgtcccaccagagtgtgagcacgtcctccacccttaccggg
 actaccactctctgacacgcacagagcactccactcaggcacacttcccagggactactccaccctcacttccctttcct
 cccaagcctccctcctatctgggaagatgggaggagcaggcttccgctgtcctggactcttgggtccttgagccgggtca
 catgaagggtgtgcccgcattccagggttccaccagactctataatcctggccgggagtcagcagcaccctcctgggttac
 aggatccccgtggggctgtgggtgtgcctgacacacccactcggtgtgttctctgcccctggggcgacgtcttgaagg
 20 tgagctggcaggagccacagtgtgatcggaagctgtgtgggtacagtggtgaataccagctactaacgtgcgtcgagatgc
 atcggctcaacatccctaacctggccaaacctcggtggtggttagaggatctcctgcctaactactctcatgtgttccggg
 tacgggcacagagccaggagggtgggtcgagagcgagagggtgtcatcccatcgagtcaccaggtgcacccgcagagcc
 ctctctgccccctgcccaggctcagccttcaactctgagcacccccagcgccccaggaccactgggtgttcaactgccctaagcc
 cagactccccgcagctcagctgggagcgccgaggagccgcaatggagatataccttggttacctgggtgacctgtgagatgg
 25 cccaaggaggagcaccagccaggaccttccgggtggacggagacaacctgagagccggttgactgtacctggcctcagtg
 agaaggttccctacaagttcaaggttcaggccaggacgaccgagggttggggccagagcgtgagggtatcatcaccatcg
 agtctcagggttgagggtcccttcccacagctgggcagcaattctgggtcttccagaaccagtgcaaagcgagttcagca
 gcgtgaccagcacgcacagcaccacgactgagcccttctcatggatgggtctaaacctggggacccagcgcttgaagcag
 gaggctccctcaccggcatgtgaccagggaattcgtgaccggaccttaacggccagtggtctctcagcactcataatgg
 30 accaacagttcttccaaacctgaacctcccccgcgccccagccacctggggccccctccttgccctcctctcctagcgcccttct
 tccctctgctgctctacccacagagcttgctgaccacagagccagccctgtagtcagagagcaggggtagggtgctgtccagg
 aaccataaagtgggttagaggtgatacaaggtcttcttctgactgcattccaccctgggtccaatccacatgtaacc

8. SEQ ID NO:8 Murine integrin beta4 protein sequence:

MAGPCCSPWV KLLLLARMLS ASLPGDLANR CKKAQVKST ECIRVDKSCA YCTDELFKERRCNTQADVLA
 35 AGCRGESILV MESSLEITEN TQIVTSLHRS QVSPQGLQVR LRRGEERTFVFQVFEPLESP VDLIYLMDFS
 NSMSDDLNL KQMGQNLAKI LRQLTSDYTI GFGKFVDKVSVPQTDMRPEK LKEPWPNSDP PFSFKNVISL
 TENVEEFWNK LQGERISGNL DAPEGGFDAILLQTAVCTRDI GWRADSTHLL VFSTESAFHY EADGANVLG
 IMNRNDEKCH LDASGAYTQY
 KTQDYPSPVT LVRLLAKHNI IPIFAVTNYS YSYEKLHKY FPVSSLGVLQ EDSSNIVELLEAFYRIRSN
 40 LDIRALDSPR GLRTEVTSdT LQKTETGSFH IKRGEVGTYN VHLRAVEDIDGTHVCQLAKE DQGGNIHLKP
 SFSDGLRMDA SVICDVCPCE LQKEVRSARC HFRGDFMCGHCVCNEGWSGK TCNCSTGSLS DTQPCLREGE
 DKPCS GHGEC QCGRCVCYGE GRYEGHFCEYDNFQCPRTSF FLCNDRGRCS MGEVCCEPGW TGRSCDCPLS
 NATCIDSNGG ICNNGRYCEC
 GRCHCNQQLS YDITTCEINY SAILGLCEDL RSCVQCQAWG TGEKKGRACD DCPFKVKMVDLKKEEVVEY
 45 CSFRDEDDDC TSYNVEGDG SPGNSTVLV HKKKDCLPAP SWWLIPLLIIFLLLLALLLL LCWKYCACCK
 ACLGLLPCCN RGHMVGFKED HYMLRENLMA SDHLDTPMLRSGNLKGRDTV RWKITNNVQR PGFATHAAS
 SPTELVPYGL SLRLGRLCTE NLMKPGTRECDQLRQEVEEN LNEVYRQVSG AHKLQQTFR QPNAGKKQD
 HTIVDTVLLA PRSAQMLLK
 LTEKQVEQGS FHELKVAPGY YTVTAEQDAR GMVEFQEGVE LVDVRVPLFI RPEDDDEKQLLVEAIDVPVS
 50 TATLGRRLVN ITIIKEQASG VVSFEQPEYS VSRGDQVARI PVIRHILDNGKSQVSYSTQD NTAHGHRDYV
 PVEGELLFHP GETWKELQVK LLELQEVDSL LRGRQVRRFQVQLSNPKFGA RLGQPSTTTV ILDETDRSLI
 NQTLSSPPPP HGDLGAPQNP NAKAAGSRKIHFNLPPPGK PMGYRVKYWI QGDSESEAH LSKVPSVEL
 TNLYPYCDYE MKVCAYGAKG
 EGPYSSLVSC RTHQEVSEF GRFAFNVVSS TVTQLSWAEP AETNGEITAY EVCYGLVNEDNRPFGPMKKV
 55 LVDNPKNRML LIENLRDSQP YRYTVKARNG AGWGPEREAI INLATQPKRPMSPPIPDIP IVDAQGGEDY
 ENFLMYSDDV LRSPASSQR SVSDDTEHLV NGRMDFAYPGSANSLHRMTA ANVAYGTHLS PHLSHRVLST
 SSTLTRDYHS LTRTEHSHG TLPRDYSTLTLSSQASLLS GKMGGAGFRC PGLLGP

9. SEQ ID NO:9 Mouse beta4 dominant negative cds:

atggcagggccctgttgacagccatgggtgaagctgctgctgctggcagcaatgctgagtgccagcctccctggagacctg
 60 gccaaccgctgcaagaaggctcaggtgaagagctgtaccgagtgcatccgggtggacaagagctgtgcctactgcacagac
 gagctgttcaaggagaggcgctgcaacacccaggcgagcttctggctgacggctgacggggagagagcatcctggtcatg
 gagagcagccttgaaatcacagagaacacccagatcgtcaccagcctgcaccgcagccaggtatctccccaaggcctgcaa
 gtccggctgcgccggggtgaggagcgacgtttgtgttccaggtctttagacccctggagagcccgctggatctgtatct
 ctcatggacttctccaactccatgtctgacgatctggacaacctcaagcagatggggcagaacctggccaagatcctgcgc
 65 cagctcaccagcgactacaccattggatttggaaagtgtgtggacaaagtcagcgtcccacagacagacatgaggcccgag

10. SEQ ID NO:10 Mouse beta4 dominant negative protein sequence:

11. SEQ ID NO:11 Murine laminin gamma2 chain complete cds (acc# U43327):

84

ggccctgggtttcaaaggctcaggggtgggtgggtgggtgggtacagtcccagtgcagctggaaggcaggatcgag
 caggctgagcaggcccttcaggacattctgggagaagctcagatttcagaaggggcaatgagagccgttgctg
 tccggctggccaaggcaaggagccaagagaacgactacaagaccgcctggatgacctcaagatgactgcaga
 aaggatccgggcccctgggcagtcagcatcagaacagagttcaggatacgagcagactcatctctcagatgcgc
 5 ctgagctctggcaggaagcgaagctctcttggaaaacactaatatccattcttctgagcactacgtggggccga
 atgatttttaaagctctggctcaggaggctacaagaaaggcagacagccacgctgagtcagctaacgcaatgaa
 gcaactagcaagggaactgaggactactccaaacaagcactttcattggcccgcgaagctcttgagtggagga
 ggccgaagtggctcttgggacagctccgtgggtacaaggtcttatgggaaaattagagaaaaccaagtccctga
 gccagcagctgtcattggagggcaccgaagccgacattgaagctgataggctcgtatcagcacagctctccgcct
 10 cctggattctgcctctcagcttcaggagtcagtgatctgtcctttcagggtggaagcaaagaggatcagacaa
 aaggctgattctctctcaaacctgggtgaccagacaaacggatgcattcacgcgtgtgcgaaacaatctgggga
 actgggaaaaagaaacacggcagcttttacagactggaaaggataggagacagacttcagatcagctgctttc
 ccgtgccaaccttgctaaaaacagagcccaagaagcgctaagtatgggcaatgccactttttatgaagttgag
 aacatcctgaagaacctccgagagtttgatctgcaggttgaaagacagaaaagcagaggctgaagaggccatga
 15 agagactctcctctattagccagaaggttgccgatgccagtgacaagaccagcaagcagaaaacggccctggg
 gagcgccactgccgacaccaacgggcaaagaacgcagctagggaggccctggagatcagcagcgagatagag
 ctggagatagggagctctgaacttggaagctaattgtgacagcagatggggcccttgccatggagaaagggactg
 ccactctgaagagcgagatgagagagatgattgagctggccagaaaggagctggagtttgacacgggataagga
 cacggtgcagctgggtgattactgaagcccagcaagctgatgccagagccacgagtgccggagttaccatccaa
 20 gacacrtcaacacattggacggcatcctacacctcatagaccagcctggcagtggtgatgaagaagggatga
 tgctattagaacaagggtttttccaagccaagaccagatcaacagtcgacttcggcccttgatgtctgacct
 ggaggagaggggtgcgtcggcagaggaaccacctccatctgctggagactagcatagatggaattcttgctgat
 gtgaagaacctggagaacattcgagacaacctgccccaggctgctacaataaccaagctcttgagcaacagt
 ga

25 **12. SEQ ID NO:12 Murine laminin gamma2 chain protein sequence (acc# AAA85256)**

1 mpalwlsccl gvalllpasq atsrrevcdc ngksrqcvfd qelhrqagsg frclncndnt
 61 agvhcersre gfyqhqsksr clpcnchskg slsagcdnsg qcrckpgvtg qrcdqcpqgf
 121 hmltdagctr dggqldskcd cdpagisgpc dsgrcvckpa vtgercdrcr prdyhldran
 30 181 pegctqcfcy ghsaschasa dfsvokitst fsqdvdgwka vqrngapakl hwsqrhrdvf
 241 ssarrsdpyv fvapakflgn qqvsyqgsls fdyrvdrgr qpsaydvile gaglqirapl
 301 mapgktilpcg itktytfrln ehpsshwspq lsyfeyrll rnlallmir atygeystgy
 361 idnvtlvsar pvlgapapwv ercvcllyk gqfcqecag ykrdsarlga fgacvpcncq
 421 gegacdpdtg dcysgdenpd iecadcpigf yndphdprsc kpcpchnghfs csvmpeteev
 35 481 vcnnpppgvt garcelcadg ffgdpfgeh pvrpcqrcqc nnnvdpnasg ncdqltgrcl
 541 kciyntagvy cdqckagyfg dplapnpadk cracncspmg aepgecrdg scvckpgfga
 601 fncdhaalts cpacynqvki qmdqftqqlq slealvskaq ggggggtvpv qlegriegae
 661 qalqdilgea qisegamrav avrlakarsq endyktrldd lkmtaerira lgsqhqnrvq
 721 dtsrlisqmr lslagseall entnihsseh yvgpndfksl ageatrakads haesanamkq
 40 781 laretedysk qalslarkll sggggsgswd ssvvqglmgk lektkslsqg lslegtqadi
 841 eadrsyqhsr rlldsasqlq gvsdlfque akrirkads lsnlvtrqtd aftrvrnrlg
 901 nweketrqll qtgkdrqts dqlslranla knragealsm gnatfyeven ilknlrefdl
 961 qvedrkaeae eamkrllsis qkvadasdk qgaetalgsa tadtqrakna arealeisse
 1021 ieleigslnl eanvtadgal amekgtatl semremiela rkelefddtk dtvqlvitea
 45 1081 qqadaratsa gvtiqdtlnt ldgilhlidq pgsvdeegmm lleqglfqak tqinsrlrpl
 1141 msdleervrr qrnhlhllet sidgiladvk nlenirdnlp pgcyntqale qq

13. SEQ ID NO:13 Human laminin gamma2 chain complete cds (acc# AH006634)

atgectgegetctggctgggctgctgectctgcttctegctcctcctgccgcagcccgggccacctccaggagggaagtc
 50 tgtgattgcaatgggaagtccaggcagtgatctttgatcggaacttcacagacaaactggtaatggattccgctgectc
 aactgcaatgacaacactgatggcattcactgcgagaagtgcagaatggcttttaccggcacagagaaaggaccgctgt
 ttgccctgcaattgtaactccaaaggttctcttagtgctcgatgtgacaactctggacggtgcagctgtaaaccaggtgtg
 acaggagccagatgcgaccgatgtctgccaggcttccacatgctcacggatgcggggtgcacccaagaccagagactgcta
 gactccaagtgtgactgtgaccagctggcatcgaggggccctgtgacgcgggcccgtgtgtctgcaagccagctgttact
 55 ggagaacgctgtgataggtgtcgatcaggttactataatctggatggggggaaccctgagggtgtaccaggtgtttctgc
 tatgggcattcagccagctgcgcagctctgcagaatacagtggtccataagatcacctctacctttcatcaagatgttgat
 ggctggaaggctgtccaacgaaatgggtctcctgcaaagctccaatgggtcacagcgccatcaagatgtgtttagctcagcc
 caacgactagacctgtctattttggtggctcctgcccatttcttgggaatcaacaggtgagctatgggcaaagcctgtcc
 tttgactaccgtgtggacagaggaggcagacacctatctgccatgatgtgattctggaaggtgctgggtctacggatcaca
 60 gctcccttgatgccacttggaagacactgccttgtgggctcaccaagacttacacattcaggttaaatgagcatccaagc
 aataattggagccccagctgagttactttgagtatcgaaggttactgcggaatctcacagccctccgcatccgagctaca
 tatggagaatacagtactgggtacattgacaatgtgacctgatttcagcccgcctgtctctggagccccagcacctgg

ggtgaacagtgatatgtcctgttgggtacaaggggcaattctgccaggattgtgcttctggctacaagagagattcagcg
 agactggggccttttggcacctgtattccttgtaactgtcaagggggaggggctgtgatccagacacaggagattgttat
 tcaggggatgagaatcctgacattgagtgctgactgcccatttggtttctacaacgatccgcacgacccccgcagctgc
 aagccatgtccctgtcataacgggttcagctgctcagtgatgccggagacggaggaggtggtgtgcaataactgccctccc
 5 ggggtcaccgggtgcccgtgtgagctctgtgctgatggctactttggggacccctttggtgaacatggcccagtgaggcct
 tgtcagccctgtcaatgcaacaacaatgtggaccccagtgccctctgggaattgtgaccggctgacaggcaggtgtttgaag
 tgtatccacaacacagccggcatctactgcgaccagtgcaaagcaggetacttcggggacccattggctcccaaccagca
 gacaagtgtcgagcttgcaactgtaaccccatgggctcagagcctgtaggatgtcgaagtgtggcacctgtgtttgcaag
 ccaggatttgggtggccccaactgtgagcatggagcattcagctgtccagcttgctataatcaagtgaagattcagatggat
 10 cagtttatgcagcagcttcagagaatggaggccctgatttcaaaggctcaggggtggtgatggagtagtacctgatacagag
 ctggaaggcaggatgcagcaggctgagcaggcccttcaggacattctgagagatgccagatttcagaaggtgctagcaga
 tcccttgggtctccagttggccaaggtgaggagccaagagaacagctaccagagccgcctggatgacctcaagatgactgtg
 gaaagagttcgggctctgggaagtcagtaccagaaccgagttcgggatactcacaggctcatcactcagatgcagctgagc
 ctggcagaaaagtgaagcttccttgggaaacactaacattcctgcctcagaccactacgtggggccaaatggctttaaaagt
 15 ctggctcaggaggccacaagattagcagaaaagccacgttgagtacagccagtaacatggagcaactgacaagggaaactgag
 gactattccaaacaagccctctcactgggtgctgcaagggccctgcatgaaggagtcggaagcggagcggtagcccgagcgg
 gctgtggtgcaagggcttgtggaaaaattggagaaaaccaagtccttggcccagcagttgacaagggaggccactcaagcg
 gaaattgaagcagataggtcttatcagcacagtctccgcctcctggattcagtgctctcggcttcaggagtgatgacag
 tcctttcaggtggaagaagcaaagaggatcaaacaaaaagcggattcactctcaacgctggtaaccaggcatatggatgag
 20 ttcaagcgtacacaaaagaatctgggaaactggaaagaagaagcacagcagctcttacagaatggaaaaagtgggagagag
 aaatcagatcagctgctttcccgtgccaatcttgctaaaagcagagcacagaagcactgagtatgggcaatgccactttt
 tatgaagttgagagcatccttaaaaacctcagagagtttgacctgcagggtggacaacagaaaagcagaagctgaagaagcc
 atgaagagactctcctacatcagccagaaggtttcagatgccagtgcagacaccagcaagcagaaagagccctggggagc
 gctgctgctgatgcacagagggcaaagaatggggccggggaggccctggaaaatctccagtgagattgaacaggagattggg
 25 agtctgaacttgaagccaatgtgacagcagatggagccttggccatggaaaagggactggcctctctgaagagtgagatg
 aggggaagtggaggagagctggaaaggaaggagctggagtttgacacgaatatggatgcagtacagatgggtgattacagaa
 gccagaaggttgataccagagccaagaacgctgggggttacaatccaagacacactcaacacattagacggcctcctgcac
 ctgatggaccagcctctcagtgtagatgaagaggggctgggtcttactggagcagaagctttcccgagccaagaccagatc
 aacagccaactgcggcccatgatgtcagagctggaagagagggcacgtcagcagagggggccacotccatttgctggagaca
 30 agcatagatgggattctggctgatgtgaagaacttggaagaacattagggacaacctgccccaggctgctacaataccag
 gctcttgagcaacagtga

14. SEQ ID NO:14 Human laminin gamma2 chain protein sequence (acc# AAC50457) Alternative splice form

1 mpalwlgccl cfslllpaa atsrrevcdc ngksrqcifd relhrqtgng frclncndnt
 35 61 dgihecekcn gfyrhrerdr clpcncnsg slsarcnsg rcsckpgvtg arcdrcclpgf
 121 hmltdagctq dqrllldskcd cdpagiagpc dagrcvckpa vtgercdrcr sgyynldggn
 181 pegctqcfcy ghsascrssa eysvokitst fhqdvdgwka vqrngspakl qwsqrhgdvf
 241 ssagrldpvy fvapakflgn qqvsyqsls fdyrvdrgr hpsahdvile gaglritapl
 301 mplgkltlpcg ltktytfrln ehpsnnwspq lsyfeyrrll rnlalrira tygeystgyi
 40 361 dnvtilisarp vsgapapwve qcicpvgykg qfcqdcasgy krdsarlpgf gtcipncqg
 421 ggacdptgd cysgdenpdi ecadcpigfy ndphdprck pcpchngfsc svmpeteevv
 481 cncpppgvtg arcelcadgy fgdpfgehgp vrpcqpcqn nnvdpsasgn cdriltgrclk
 541 cihntagiyc dqckagyfgd plapnpadkc racncnmpgs epvgcrsdgt cvckpgfggp
 601 ncehgafscp acynqvkiqm dqfmqqlqrm ealiskaagg dgvpdtele grmqqaegal
 45 661 qdilrdaqis egasrslglq lakvrsqens yqsrlddlkm tvervralgs qyqnrvrldth
 721 rlitqmqsls aeseaslgnt nipasdhvvg pngfkslage atrlaeshve sasnmegltr
 781 etedyskqal slvrkalheg vsgsgspdg avvqglvekl ektkslaqqi treatgaeie
 841 adrsyqhsrlr lldsvsrlqg vsdqsfqvee akrikqkads lstlvtrhmd efkrtqknlg
 901 nwkeeaqql qngksgreks dqllsranla ksraqealsm gnatfyeyes ilknlrefdl
 50 961 qvdnrkaeae eamkrlyis qkvdsasdk qqaeralgsa aadaqrakng agealeisse
 1021 ieqeigslnl eanvtadgal amekglaslk semrevegele erkelefdtn mdavqmvite
 1081 aqkvdtrakn agvtiqdtln tldgllhlmd qplsvdeegl vlleqklsra ktqinsqlrp
 1141 mmseleerar qqrghlhlle tsidgiladv knlenirdnl ppgcyntqal eqq

15. SEQ ID NO:15 Human laminin gamma2 chain protein sequence (acc# AAC50456) Alternative splice form

1 mpalwlgccl cfslllpaa atsrrevcdc ngksrqcifd relhrqtgng frclncndnt
 61 dgihecekcn gfyrhrerdr clpcncnsg slsarcnsg rcsckpgvtg arcdrcclpgf
 121 hmltdagctq dqrllldskcd cdpagiagpc dagrcvckpa vtgercdrcr sgyynldggn
 181 pegctqcfcy ghsascrssa eysvokitst fhqdvdgwka vqrngspakl qwsqrhgdvf
 60 241 ssagrldpvy fvapakflgn qqvsyqsls fdyrvdrgr hpsahdvile gaglritapl
 301 mplgkltlpcg ltktytfrln ehpsnnwspq lsyfeyrrll rnlalrira tygeystgyi
 361 dnvtilisarp vsgapapwve qcicpvgykg qfcqdcasgy krdsarlpgf gtcipncqg
 421 ggacdptgd cysgdenpdi ecadcpigfy ndphdprck pcpchngfsc svmpeteevv
 481 cncpppgvtg arcelcadgy fgdpfgehgp vrpcqpcqn nnvdpsasgn cdriltgrclk
 65 541 cihntagiyc dqckagyfgd plapnpadkc racncnmpgs epvgcrsdgt cvckpgfggp

601 ncehgafscp acynqvkiqm dqfmqqlqrm ealiskaagg dgvpdpdtele grmqqaegal
 661 qdilirdaqis egasrslglq lakvrsqens yqsrlddlkm tvervralgs qyqnrvrdrh
 721 rlitqmqlsl aeseaslgnt nipasdhvvg pngfkslage atrlaeshve sasnmeqltr
 781 etedyskgal slvrkalheg vsgsgspdg avvqglvekl ektkslagql treatqaeie
 5 841 adrsyqhsrlr lldsvsrlgg vsdqsfgvee akrikqkads lstlvtrhmd efkrtqknlg
 901 nwkeeagqll qngksgreks dqllsranla ksraqealsm gnatfyeves ilknlfrefdl
 961 qvdnrkaeae eamkrlysis qkvsdasdkt qqaeralgsa aadaqrakng agealeisse
 1021 ieqeigslnl eanvtadgal amekglaslk semrevegele erkelefdtn mdavqmvite
 1081 aqkvdtrakn agvtiqdtln tldgllhlmg m

10 16. Degenerate Human integrin beta4 subunit cds

atg gca gCg cca cgc ccc agc cca tgg gcc agg ctg ctc ctg gca gcc ttg atc agc gtc
 agc ctc tct ggg acc ttg aac cgc tgc aag aag gcc cca gtg aag agc tgc acg gag tgt
 gtc cgt gtg gat aag gac tgc gcc tac tgc aca gac gag atg ttc agg
 gaccggcgctgcaacacccaggcgagctgctggccgcgggctgccagcgggagagcatcgtgggtcatggagagcagcttc
 15 caaatcacagaggagacccagattgacaccacccctgcccgcagccagatgtcccccaaggcctgcccgtctctgccc
 cccggtgaggagcggcatttttgagctggaggtgtttgagccactggagagccccgtggacctgtacatcctcatggacttc
 tccaactccatgtccgatgatctggacaacctcaagaagatggggcagaacctgggtcctgagccagctcaccagc
 gactacactattggatttggcaagtgttggaacaaagtacgctcccgcagacggacatgaggcctgagaagctgaaggag
 ccttggcccaacagtgaccccccttctccttcaagaacgtcatcagcctgacagaagatgtggatgagttccggaataaa
 20 ctgcagggagagcggatctcaggcaacctggatgctcctgagggcggtcttcgatgccatcctgcagacagctgtgtgcacg
 agggacattggctggcgcccgacagcaccacccctgctgggtcttctccaccagctcagccttccactatgaggctgatggc
 gccaacgtgctggctggcatcatgagccgcaacgatgaacgggtgccacccctggacaccacgggcacctacacccagtacagg
 acacaggactaccgctcggtgccacccctgggtgcgcctgctcgcgaagcacaacatcatccccatcttctgtgtcaccaac
 tactcctatagctactacgagaagcttcacacctatttccctgtctcctcactgggggtgctgcaggaggactcgtccaac
 25 atcgtggagctgctggaggaggccttcaatcggtacgctccaacctggacatccgggcccctagacagccccgaggcctt
 cggacagaggtcacctccaagatgttccagaagacgaggactgggtcctttcacatccggcggggggaagtgggtatatac
 caggtgcagctgcgggccccttgagcacgtggatgggacgcacgtgtgccagctgccggaggaccagaagggaacatccat
 ctgaaaccttcttctccgacggcctcaagatggacgcgggcatcatctgtgatgtgtgcacctgcgagctgcaaaaagag
 gtgcggctcagctcgctgcagcttcaacgggagacttcgtgtgcggacagtggtgtgtgcagcagagggtggagtgccagacc
 30 tgcaactgctccaccggctctctgagtgcattcagccctgcttgcgggagggcgaggacaagccgtgctccggcctggtg
 gagggtgcagtgccggcactgtgtgtgtgtacggcgaaggccgctacgagggtcagttctgcgagtatgacaacttccagtg
 ccccgcaacttccgggttctctgcaatgaccgaggacgctgctccatggggcagtggtgtgtgtgagcctggttgacagggc
 ccaagctgtgactgtccctcagcaatgccacctgcacgcagcaatgggggcatctgtaattggacgtggccactgtgag
 tgtggcgcgtgccactgccaccagcagtcgctctacacggacaccatctgcgagatcaactactcggcgctccaccggggcc
 35 tctgcgaggacctacgctcctgctgcagtgccaggcggtggggcaccggcgagaagaagggggcgacgtgtgaggaatgca
 acttcaagggtcaagatgggtggacgagcttaagagaggcgaggaggtgggtgggtgcgctgctccttccgggacgaggatgacg
 actgcacctacagctacaccatggaagggtgacggcgcccctgggcccacagcactgtcctgggtgcacaagaagaaggac
 tggcctccgggctccttctgggtgggtcatccccctgctcctcctcctcctgcgctcctggccctgctactgctgctatgc
 tggaaagtactgtgctgctgcaaggcctgctggcacttctcccggtgctgcaaccgagggtcacatgggtgggctttaaggaa
 40 gaccactacatgctgcgggagaacctgatggcctctgaccacttggacacgcccctgctgcgcagcgggaacctcaagggc
 cgtgacgtgggtccgctggaagggtcaccaacaacatgcagcggcctggccttggccactcatgcccgcagcatcaaccccaca
 gagctgggtgccctacgggctgtccttgccgctggcccgccttggcaccgagaacctgctgaagcctgacactcgggagtg
 gccagctgcgcacaggaggtggaggagaacctgaacgaggtctacaggcagatctccgggtgtacacaagctccagcagacc
 aagttccggcagcagcccaatgcccgggaaaaagcaagaccacaccattgtggacacagtgctgatggcgccccgctcggcc
 45 aagccggcccctgctgaagcttacagagaagcaggtggaacagagggccttccacgacctcaagggtggcccccggtactac
 accctcactgcagaccaggacgcccggggcatgggtggagttccaggaggcggtggagctgggtggacgtacgggtgcccctc
 tttatccggcctgaggatgacgacgagaagcagctgctgggtggaggccatgcagctgcccgcaggcactgccacctcggc
 cggcgccctggtaaacatcaccatcatcaaggagcaagccagagacgtgggtgtcctttgagcagcctgagttctcggtcagc
 cgcggggaccagggtggcccgcatccctgtcatccggcggtgtcctggacggcggggaagtcaccaggtctcctaccgcacacag
 50 gatggcaccgcgcagggcaaccgggactacatccccgtggagggtgagctgctgttccagcctggggaggcctggaaagag
 ctgcaggtgaagctcctggagctgcaagaagttgactccctcctgcccgggcccaggtccgcccgtttccacgtccagctc
 agcaaccctaagtbtggggcccacctggggcagccccactccaccacccatcatcatcagggaaccagatgaactggaccgg
 agcttcacgagtcagatgtgtcatcacagccacccccctcagggcgacctggggcgccccgcagaaccccaatgctaaggcc
 gctgggtccaggaagatccatttcaactgggtgcccccttctggcaagccaatgggggtacagggtaaagtactggattcag
 55 ggtgactccgaatccgaagcccacctgctgcagacgaagggtgccctcagtgaggctcaccaacctgtaccctgattgcgac
 tatgagatgaagggtgtgcgcctacgggggtcagggcgagggaacctacagctccctgggtgtcctgcccacccaccaggaa
 gtgcccagcgcagccagggtgtgtggccttcaatgtcgtctcctccacgggtgacctcagctgagctgggtgagccggctgag
 accaacgggtgagatcacagcctacgaggtctgctatggcctgggtcaacgatgacaaccgacctattggggcccatgaagaaa
 gtgctgggttgacaaccctaagaaccggatgctgcttattgagaaccttcgggaggtcccagccctaccgctacacgggtgaag
 60 gcgcgcaacggggcggtggtggggcctgagcgggaggccatcatcaacctggccacccagcccaaggaggcccatgtccatc
 cccatcatccctgacatccctatcgtggacgcccagagcggggaggactacgacagcttcccttatgtacagcgatgacgtt
 ctacgctctccatcgggcagccagaggcccagcgtctccgatgacactgggtgcggctggaagttcgagccccctgctgggg
 gaggagctggacctgcggcgctcagctggcggtgcccccgagctcatcccgcgctgtcgccagcagcggcgctcc
 tccgacgcccaggcgccccacgggcccccgacgagcggcgggcggggaaggcgggcagcctgccccgcagtgcgaca
 65 cccgggccccccggagagcacctggatgaatggccggatggactttgccttccggggcagcaccacccctcctgcacaggatg
 accacgaccagtgctgctgcctatggcaccacccctgagcccacacgtgccccacccgctgctaagcacatcctccacctc

acacgggactacaactcactgacccgctcagaacactcacactcgaccacactgccgagggactactccaccctcacctcc
gtctcctcccacggcctccctcccatctgggaacacgggaggagcaggcttccgctgtcctgggcccctggggctcccgagt
cgggctcagatgaaaggggtcccccttccaggggcccacgagactctataatcctggctgggaggccagcagcgccctcc
tggggcccagactctcgcctgactgctgggtgtgcccgacacgcccaccgcctgggtgttctctgccctggggcccacatct
5 ctcagagttagctggcaggagccgcgggtgcgagcggccgctgcagggtacagtgtggagtaccagctgctgaacggcggt
gagctgcatcggctcaacatccccaaccctgccagacctcgggtgggtgggaagacctcctgccaaccactcctacgtg
ttccgctgcgggcccagagccaggaaggctggggccgagagcgtgaggggtgtcatcaccattgaatcccaggtgcaccgc
cagagcccactgtgtccctgccaggctccgccttctactttgagcactcccagtgccccaggccccgctgggtgttactgcc
ctgagcccagactcgctgcagctgagctgggagcggccacggaggcccaatggggatatcgtcgggtacctgggtgacctgt
10 gagatggcccaaggaggaggtccagccaccgcattccgggtggatggagacagccccgagagccggctgacctgcccggc
ctcagcgagaacgtgccctacaagttcaaggtgcaggccaggaccactgagggcttcggggccagagcgcgagggcatcatc
accatagagtcccaggatggagggtcccttcccgcagctgggcagccgtgccgggctcttccagcaccgcctgcaaagcgag
tacagcagcatctccaccacccacaccagcgcacccagaccccttctagtgggtccgacctggggggcccagcacttgag
gcaggcggtccctcaccggcatgtgacctaggagtttgtgagccggacactgaccaccagcggaacccttagcaccac
15 atggaccaacagttcttccaaacttga

17. SEQ ID NO:17 Human beta4 integrin protein sequence Variant V at 34 to I:

1 magprpspwa rlllaalisv slsgtlrck kapIksctec vrvdkdcayc tдемfdrirc
61 ntqaellaag cgresivvme ssfqiteetq idttlrrsqm spqglrvlr pgeerhfele
20 121 vfeplespvd lyilmdfsns msddlndlkk mgqlarvls qltsdytigf gkfvdksvsv
181 qtdmrpekkl epwpnsdpff sfknvislte dvdefrnklq gerisgnlda peggfdaillq
241 tavctrdigw rpdsthllvf stesafhyea dganvlagim srnderchld ttgtytqyrt
301 qdypsvptlv rllakhniip ifavtnsys yyeklhtyfp vsslglvqed ssnivellee
361 afnrirsnl d iraldsprgl rtevtskmfq ktrtgsfhir rgevgiyqvq lrlehdvgt
25 421 hvcqlpedqk gnihlkpsfs dglkmdagii cdvctcelqk evrsarcsfn gdfvcgqcvc
481 segwsgqtcn cstgslsdiq pclregedkp csgrgecqcg hcvcygegry egqfceydnf
541 qcprtsgflc ndrgrcsmgq cvcepgwtgp scdclsnat cidsnggicn grghcecgrc
601 hchqqslytd ticeinysas trasartyap acsarrgapa rrrgarvrna tsrsrwtsl
661 rearrrwcaa psgtrmttap tatpwkvtap lgptalswct rrrdcpqgsf wwliplllll
30 721 lp11all111 cwkycaccka clallpccnr ghmvgfkedh ymlrenlmas dhldtpmlrs
781 gnlkgrdvvr wkvtnnmqrp gfathaasin ptelvpysls lrlarlcten llkpdtreca
841 qlrqevenl nevyrgisgv hklqgtkfrq qpnagkkqdh tivdtvlmap rsakpallkl
901 tekqvegraf hdlkvapgyy tltadqdarg mvefgegvel vdvrplfir pedddekqll
961 veaidvpagt atlgrrlvni tiikeqardv vsfeqpefsv srgdqvarip virrvldggk
35 1021 sqvsyrtqdg taqgnrdyip vegellfqpg eawkelqvkl lelgevdsll rgrqvrfrh
1081 qlsnpkfgah lgqphsttii irdpdeldrs ftsqmlssqp pphgdldgapq npnakaagsr
1141 kihfnwlpss gkpmgyrvky wiqgdsesea hlldskvpsv eltnlypycd yemkvcaiga
1201 qgegpysslv scrthqevps epgrlafnvv sstvtqlswa epaetngeit ayevcyglvn
1261 ddnrpigmk kvlvdnpknr mllienlres qpyrytvkar ngagwgpere aiinlatqpk
40 1321 rpmsipiipd ipivdaqsg dydsflmysd dvlrpspsq rpsvsddtgc gwkfepllge
1381 eldlrrvtwr lppeliprls assgrssdae aphgppddgg aggkgsllpr satpgppgeh
1441 lvngrmdfaf pgstnslhrm ttttaaaygt hlsphvphrv ltsstltd ynsltrsehs
1501 hsttlprdis tltsvsshgl ppiwehgrsr lplswalgsr sraqmkgfpp srgprdsiil
1561 agrpaapswg pdsrltagvp dtptrlvfa lgptslrvsw qeprcerplq gysveyqln
45 1621 ggelhrlnip npaqtssvve dllpnhsyvf rvraqsqegw greregvti esqvhpqsp
1681 cplpgsaftl stpsagplv ftalspdsll lswprrrpn gdivgylvtc emaggggpat
1741 afrvdgdspe srltvpglse nvpkyfkva rttegfger egiitiesqd ggpfpqlgsr
1801 aglfqhplqs eyssistht satepflvgt tlgaqhleag gsltrhvtqe fvsrtltts
1861 tlsthmdqf fqt

18. SEQ ID NO:18 Human integrin beta4 subunit cds Variant at 34 V to I:

atg gca ggg cca cgc ccc agc cca tgg gcc agg ctg ctc ctg gca gcc ttg atc agc gtc
agc ctc tct ggg acc ttg aac cgc tgc aag aag gcc cca AtA aag agc tgc acg gag tgt
gtc cgt gtg gat aag gac tgc gcc tac tgc aca gac gag atg ttc agg
gaccggcgtgcaacacccaggcggagctgctggccgagggtgccagcgggagagcatcgtgggtcatggagagcagcttc
55 caaatcacagaggagacccagattgacaccacctgcggcgagccagatgtcccccaaggcctgcgggtccgtctgcgg
cccggtgaggagcggcattttgagctggagggtgtttgagccactggagagccccgtggacctgtacatcctcatggacttc
tccaactccatgtccgatgatctggacaacctcaagaagatggggcagaacctgggtcctgagccagctcaccagc
gactacactattggatttggcaagtttgtggacaaagtcagcgtcccgcagacggacatgaggcctgagaagctgaaggag
ccttggccccacagtgaccccccttctccttcaagaacgtcatcagcctgacagaagatgtggatgagttccggaataaa
60 ctgcaggagagcggatctcaggcaacctggatgctcctgaggcggttcgatgccatcctgcagacagctgtgtgcacg
agggacattggctggcgcccggacagcaccacctgctgggtcttctccacagagtcagccttccactatgaggctgatggc
gccaacgtgctggctggcatcatgagccgcaacgatgaacgggtgccacctggacaccacgggcacctacaccagtagg
acacaggactaccgctcggtgcccacctgggtgcgctgctcgccaagcacaacatcatccccatctttgctgtcaccac
tactcctatagctactacgagaagcttcacacctatcttccctgtctcctcactgggggtgctgcaggaggactcgtccaac
65 atcgtggagctgctggaggaggccttcaatcgatccgctccaacctggacatccgggcccctagacagccccaggcctt

cggacagaggtcacctccaagatgttccagaagacgaggactgggtcctttcacatccggcggggggaagtgggtatatac
 caggtgcagctgcgggcccttgagcacgtggatgggacgcacgtgtgcccagctgcccggaggaccagaagggcaacatccat
 ctgaaaccttcccttctccgacggcctcaagatggacgcgggcatcatctgtgatgtgtgcacctgcgagctgcaaaaagag
 gtgcgggtcagctcgctgcagcttcaacggagacttcgtgtgcggacagtgtgtgtgcagcgagggtggagtggccagacc
 5 tgcaactgctccaccggctctctgagtgacattcagccctgcctgcgggagggcgaggacaagccgtgctccggccgtggg
 gagtgcagtgcgggcactgtgtgtgtgtacggcggaaggccgctacgaggggtcagttctgcgagtatgacaacttccagtgt
 ccccgcaacttccgggttccctctgcaatgaccgaggacgctgctccatggggccagtgtgtgtgtgagcctgggtggacaggc
 ccaagctgtgactgtccctcagcaatgcccactgcctcgacagcaatgggggcatctgtaatggacgtggccactgtgag
 tgtggccgctgccactgccaccagcagtcgctctacacggacaccatctgcgagatcaactactcggcgtccaccggggcc
 10 tctgcgaggacctacgctcctgcgtgcagtgccaggcgtggggcaccggcgagaagaagggcgcacgtgtgaggaatgca
 acttcaaggtcaagatgggtggacgagcttaagagaggcgaggaggtgggtgggtgcgtgctccttccgggacgaggatgacg
 actgcacctacagctacaccatggaaggtgacggcgccctggggcccaacagcactgtcctgggtgcacaagaagaagggac
 tgccttccgggctccttctgggtgggtcatccccctgctcctcctcctcctgcgcgtcctggccctgctactgctgctatgc
 tggaaagtactgtgcctgctgcaaggcctgcctggcacttctcccgctgctgcaaccgaggtcacatgggtgggtttaaaggaa
 15 gaccactacatgctgcgggagaacctgatggcctctgaccacttggacacgcccattgctgcgcagcgggaaacctcaagggc
 cgtgacgtgggtccgctggaaggtcaccaacaacatgcagcgccctggctttgccactcatgccgccagcatcaaccccaca
 gagctgggtgccctacgggctgtccttgcgcctggcccgctttgcaccgagaacctgctgaagcctgacactcgggagtgc
 gccagctgcgccaggaggtggaggagaacctgaacgaggtctacaggcagatctccggtgtacacaagctccagcagacc
 aagttccggcgagcagcccaatgccgggaaaaagcaagaccacaccattgtggacacagtgtgatggcgccccgctcggcc
 20 aagccggccctgctgaagcttacagagaagcaggtggaacagagggccttccacgacctcaaggtggcccccggtactac
 accctcactgcagaccaggacgcccggggcatgggtggagtccaggagggcgctggagctgggtggacgtacgggtgcccctc
 tttatccggcctgaggatgacgacgagaagcagctgctgggtggaggccatcgacgtgcccgagggcactgccaccctcggc
 cgccgctggtaaacatcaccatcatcaaggagcaagccagagacgtgggtgctcctttgagcagcctgagttctcgggtcagc
 cgccgggaccagggtggcccgcatccctgtcatccggcgtgtcctggacggcggggaagteccagggtctcctaccgcacacag
 25 gatggcaccgcgcaggggcaaccgggactacatccccgtggaggggtgagctgctgttccagcctggggaggcctggaaagag
 ctgcagggtgaagctcctggagctgcaagaagttgactccctcctgcggggcgccaggtccgcgcttccacgtccagctc
 agcaaccctaagtttggggcccacctggggccagccccactccaccacctcatcatcagggaccagatgaactggaccgg
 agcttcacgagtcagatgttgtcatcacagccacccctcacggcgacctggggcgccccgcagaaccccaatgctaaggcc
 gctgggtccaggaagatccatttcaactggctgcccccttctggcaagccaatgggggtacagggtaaagtactggattcag
 30 ggtgactccgaatccgaagcccacctgctcgacagcaaggtgcccctcagtgagctcaccaacctgtaccggtatttgcgac
 tatgagatgaaggtgtgcgcctacgggggtcagggcgagggaacctacagctccctgggtgtcctgcgcacccaccaggaa
 gtgccccagcgagccaggcgctgtggccttcaatgtcgtctcctccacgggtgaccagctgagctgggctgagccggctgag
 accaaccggtgagatcacagcctacgaggtctgtatggcctgggtcaacgatgacaaccgacctattggggccatgaagaaa
 gtgctgggttgacaaccctaagaaccggatgctgcttatttgagaaccttcgggagtcaccagccctaccgctacacgggtgaag
 35 gcgcgcaaccggggccggctgggggctgagcgggaggccatcatcaacctggccaccagcccaagaggcccatgtccatc
 cccatcatccctgacatccctatcgtggacgcccagagcggggaggactacgacagcttcccttatgtacagcagtgacgtt
 ctacgctctccatcgggcagccagaggccagcgtctccgatgacactggctgcggctggaagttcgagccctgctgggg
 gaggagctggacctgcggcgctcacgtggcggtgcccccgagctcatcccgcgctgtcggccagcagcggggcgctcc
 tccgacgcccaggcgccccacggggcccccgagcagcgggcgggcggggaagggcggcagcctgccccgcagtgcgaca
 40 cccggggcccccgagagcacctgggtgaatggccggatggactttgccttcccgggcagcaccactccctgcacaggatg
 accacgaccagtgtgtgtgcttatggcaccacctgagcccacacgtgccccaccgctgctaagcacatcctccaccctc
 acacgggactacaactcactgaccgctcagaacactcacactcgaccacactgcccaggggactactccaccctcacctcc
 gtctcctccacggcctccctcccatctgggaacacgggaggagcaggcttccgctgtcctggggccctgggggtcccgaggt
 cgggctcagatgaaagggttcccccttccaggggcccacgagactctataatcctgggtgggaggccagcagcgccctcc
 45 tggggcccagactctcgctgactgctgggtgtgcccgcacgccccaccgctgggtgttctctgccttggggcccacatct
 ctgagagtgtgctggcaggagcccggtgtgcgagcgggcgctgcaggggtacagtggtggagtaccagctgctgaacggcggt
 gagctgcatcggtcaacatcccccaacctgcccagacctcggtgggtgggtggaagacctcctgcccaccactcctacgtg
 ttccgctgtcggggccagagccaggaaggctggggccgagagcgtgaggggtgtcatcaccattgaatcccagggtgcaccg
 cagagcccactgtgtccctgcccaggctccgcttccctttgagcactcccagtgccccaggcccgctgggtgttccactgcc
 50 ctgagcccagactcgctgcagctgagctgggagcgggccacggaggcccaatggggatctcgtcggtacctgggtgacctgt
 gagatggcccaaggaggaggtccagccaccgcatttccgggtggatggagacagccccgagagccggctgaccgtgcccgggc
 ctgagcgagaacgtgcccatacaagttcaaggtgcaggccaggaccactgagggcttccgggcccagagcgcgagggtcatc
 accatagagtcccaggatggaggtcccttcccgagctgggcagccgtgcccgggctcttccagcaccgctgcaaaagcgag
 tacagcagcatctccaccaccacaccagcgccaccgagcccttccctagtgggtccgacctggggggccagcaccctggag
 55 gcaggcggtccctcaccggcatgtgacccaggagtttgtgagccggacactgaccaccagcggaaaccttagcaccac
 atggaccaacagttcttccaaacttga

**19. SEQ ID NO:19 Degenerate Human integrin beta4 subunit cds variant at
 34 Vto I:**

atg gca ggg cca cgG ccc agc cca tgg gcc agg ctg ctc ctg gca gcc ttg atc agc gtc
 60 agc ctc tct ggg acc ttg aac cgc tgc aag aag gcc cca AtA aag agc tgc acg gag tgt
 gtc cgt gtg gat aag gac tgc gcc tac tgc aca gac gag atg ttc agg
 gaccggcgctgcaacacccaggcgagctgtgtggcgcgggctgccagcgggagagcatcgtgggtcatggagagcagcttc
 caaatcacagaggagaccagattgacaccacctgcggcgagccagatgtcccccaaggcctgcgggtccgtctgcgg
 cccgggtgaggagcggcatttttgagctggaggtgttttgagccactggagagccccgtggacctgtacatcctcatggacttc
 65 tccaactccatgtccgatgatctggacaacctcaagaagatggggcgagaacctggctcgggtcctgagccagctcaccagc
 gactacactattggatttggcaagtttgtggacaaagtacgctcccgagacggacatgaggcctgagaagctgaaggag

ccttggcccaacagtgaccccccttctccttcaagaacgtcatcagcctgacagaagatgtggatgagttccggaataaa
 ctgcaggagagcggatctcaggcaacctggatgctcctgagggcggttcgatgccatcctgcagacagctgtgtgcacg
 agggacattggctggcgcccgacagcaccacctgctgggtcttctccaccgagtcagccttccactatgaggctgatggc
 gccaacgtgctggctggcatcatgagccgcaacgatgaacgggtgccacctggacaccacgggcacctacaccagtacagg
 5 acacaggactacccgtcggtgccaccctgggtgcgcctgctcgccaagcacaacatcatccccatcttctgtgtcaccaac
 tactcctatagctactacgagaagcttcacacctatttccctgtctcctcactgggggtgctgcaggaggactcgtccaac
 atcgtggagctgctggaggaggccttcaatcggatccgctccaacctggacatccgggcccctagacagcccccgaggcctt
 cggacagagggtcacctccaagatgttccagaagacgaggactgggtcctttcacatccggcggggggaagtgggtatatac
 caggtgcagctgcgggccccttgagcacgtggatgggacgcacgtgtgccagctgccggaggaccagaagggaacatccat
 10 ctgaaaccttcccttctccgacggcctcaagatggacgcgggcacatctgtgatgtgtgcacctgcgagctgcaaaaagag
 gtgcggctcagctcgctgcagcttcaacggagacttcgtgtgcggacagtggtgtgtgcagcgagggtggagtggccagacc
 tgcaactgctccaccggctctctgagtgacattcagccctgctgcgggaggcgaggacaagccgtgctccggccgtggg
 gagtgccagtgccggcactgtgtgtgtgtacggcggaaggccgctacgagggtcagttctgcgagtatgacaacttccagtgt
 ccccgacttccgggttccctctgcaatgaccgaggacgctgctccatggggccagtgtgtgtgtgagcctgggtggacaggc
 15 ccaagctgtgactgtccccctcagcaatgccacctgcatcgacagcaatgggggcacatctgtaatggacgtggccactgtgag
 tgtggccgctgccactgccaccagcagtcgctctacacggacaccatctgcgagatcaactactcggcgctccaccgggccc
 tctgcgaggacctacgctcctgcgtgcagtgccaggcgtggggcaccggcgagaagaaggggcgacgtgtgaggaatgca
 acttcaagggtcaagatgggtggacgagcttaagagaggcgaggaggtgggtgggtgcgctgctccttccgggacgaggatgacg
 actgcacctacagctacaccatggaagggtgacggcgcccctggggcccaacagcactgtcctgggtgcacaagaagaagggac
 20 tggcctccgggctccttctgggtggctcatccccctgctcctcctcctcctcctgcgctcctggccctgctactgctgctatgc
 tgggaagtactgtgcctgctgcaaggcctgcctggcacttctcccgctgctgcaaccgagggtcacatgggtgggctttaaggaa
 gaccactacatgctgcgggagaacctgatggcctctgaccacttggacacgcccacatgctgcgcagcgggaacctcaagggc
 cgtgacgtgggtccgctggaagggtcaccaacaacatgcagcggcctggcttggccactcatgccgccagcatcaaccccaca
 gagctgggtgcccctacgggctgtccttgcgcctggccccgcttggcaccgagaacctgctgaagcctgacactcgggagtg
 25 gcccagctgcgcccaggagggtggaggagaacctgaacgagggtctacaggcagatctccgggtgtacacaagctccagcagacc
 aagttccggcgacgagcccaatgccgggaaaaagcaagaccacacacatgtgtggacacagtgctgatggcgccccgctcggcc
 aagccggcccctgctgaagcttacagagaagcagggtggaacagagggccttccacgacctcaagggtggcccccggtactac
 accctcactgcagaccaggacgccccggggcatgggtggagtccaggaggcggtggagctgggtggacgtacgggtgccccctc
 tttatccggcctgaggatgacgacgagaagcagctgctgggtggaggccatcgacgtgcccgaggcactgccaccctcggc
 30 cgccgctgggtaaacatcacatcatcaaggagcaagccagagacgtgggtgtccttggagcagcctgagttctcggtcagc
 cgccggggaccagggtggccccgcacccctgtcatccggcggtgctcctggacggcggggaagtcccagggtctcctaccgcacacag
 gatggccaccgcgcaggggcaaccgggactacatccccgtggagggtgagctgctgttccagcctggggaggcctggaaagag
 ctgcagggtgaagctcctggagctgcaagaagtgtactccctcctgcggggcgccagggtccgcccgttccacgtccagctc
 agcaaccctaagtgtggggccacacctggggccagccccactccaccacctcatcatcagggaaccagatgaactggaccgg
 35 agcttcacgagtcagatgttgtcatcacagccacccccctcagggcgacctggggcgccccgcagaaccccaatgctaaggcc
 gctgggtccaggaagatccatttcaactggctgcccccttctggcaagccaatgggggtacagggtaaagtactggattcag
 ggtgactccgaatccgaagcccacctgctcgacagcaagggtgcccctcagtgaggctcaccaacctgtaccggtattgagac
 tatgagatgaagggtgtgcgcctacgggggtcaggggcgagggaacctacagctccctgggtgtcctgcgcacccaccaggaa
 gtgcccagcagaccaggcgctgtggccttcaatgtcgtctcctccacgggtgacccagctgagctgggctgagccggctgag
 40 accaacgggtgagatcacagcctacgagggtctgctatggcctgggtcaacgatgacaaccgacctattggggcccatgaagaaa
 gtgctgggttgacaacctaaagaaccggatgctgcttattgagaaccttcgggagtcaccagccctaccgctacacgggtgaag
 gcgcgcaacggggccggctggggggcctgagcgggaggccatcatcaacctggccacccagcccaagaggcccatgtccatc
 cccatcatccctgacatccctatcgtggacgcccagagcggggaggactacgacagcttcccttatgtacagcgatgacgtt
 ctacgctctccatcgggcagccagaggccagcgtctccgatgacactggctgcggctggaagtccgagccctgctgggg
 45 gaggagctggacctgcggcgctcacgtggcggtgcccccgagctcatcccgcgctgtcgggccagcagcggcgctcc
 tccgacgcccaggcgccccacgggcccccgagcagcggcgcgggcggggaaggggcgagcctgcccccgagtgcgaca
 cccggggcccccgagagcacctgggtgaatggccggatggacttgccttcccgggcagcaccacacccctgcacaggatg
 accacgaccagtgtgtgctgctatggcaccacctgagcccacacgtgccccaccgctgttaagcacatcctccacctc
 acacgggactacaactcactgacctgctcagaacactcacactcgaccacactgcccagggaactactccacctcacctcc
 50 gtctcctccacggcctccctcccatctgggaacacgggaggagcaggcttccgctgtcctgggcccctgggggtcccgaggt
 cggggtcagatgaaagggttcccccttccaggggcccacgagactctataatcctgggtgggaggccagcagcgcctcc
 tggggcccagactctcgctgactgctgggtgtgcccgcacgcgccaccccgctgggtgttctctgcccctggggcccacatct
 ctgagagtgagctggcaggagccgcggtgcgagcggccgctgcagggtacagtggtggagtaccagctgctgaacggcggt
 gagctgcatcggtcaacatccccacacctgcccagacctcggtgggtgggtggaagacctcctgcccacacctcctacgtg
 55 tcccgctgcgggcccagagccaggaaggctggggccgagagcgtgagggtgtcatcaccattgaatcccagggtgcacccg
 cagagcccactgtgtccccctgcccaggctccgcttccacttggagcactcccagtgccccaggcccgctgggtgttccactg
 ctgagcccagactcgctgcagctgagctgggagcggccacggaggcccaatggggatatcgtcggtacctgggtgacctgt
 gagatggcccaaggaggagggtccagccaccgcatccgggtggatggagacagccccgagagccggctgaccgtgcccgggc
 ctcagcgagaacgtgcccatacaagttcaagggtgcaggccaggaccactgagggttccgggcccagagcgcgagggtcatc
 60 accatagagtcccaggatggagggtcccttcccgcagctgggcagccgtgcgggctcttccagcaccgctgcaaagcgag
 tacagcagcatctccaccaccacaccagcggccaccgagcccttccctagtgggtccgacccctggggggcccagcaccctggag
 gcaggcggtccctcaccggcatgtgacccaggaggttgggtgagccggacactgaccaccagcgaacctttagcaccac
 atggaccaacagttcttccaaacttga

SEQUENCE LISTING

<110> University of Rochester Medical Center

Deleu, Laurent
Land, Hartmut

<120> COMPOSITIONS THAT INHIBIT PROLIFERATION
OF CANCER CELLS

<130> 21108.0005P1

<150> 60/239,705

<151> 2000-10-12

<150> 60/242,812

<151> 2000-10-24

<160> 19

<170> FastSEQ for Windows Version 4.0

<210> 1

<211> 3222

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence; Note =
synthetic construct

<400> 1

atggccgcgcg	ccgggcagct	gtgcttgctc	tacctgtcgg	cggggctcct	gtcccggctc	60
ggcgcagcct	tcaacttgga	cactcgggag	gacaacgtga	tccggaaata	tggagacccc	120
gggagcctct	tcggcttctc	gctggccatg	cactggcaac	tgcagcccga	ggacaagcgg	180
ctgttgctcg	tgggggcccc	gcgcggagaa	gcgcttccac	tgcagagagc	caacagaacg	240
ggagggctgt	acagctgcga	catcaccgcc	cgggggccat	gcacgcggat	cgagtttgat	300
aacgatgctg	acccacgctc	agaaagcaag	gaagatcagt	ggatgggggt	caccgtccag	360
agccaaggtc	cagggggcaa	ggtcgtgaca	tgtgctcacc	gatatgaaaa	aaggcagcat	420
gttaatacga	agcaggaatc	ccgagacatc	tttgggcggt	gttatgtcct	gagtcagaat	480
ctcaggattg	aagacgatat	ggatggggga	gattggagct	tttgtgatgg	gcgattgaga	540
ggccatgaga	aatttggtc	ttgccagcaa	ggtgtagcag	ctacttttac	taaagacttt	600
cattacattg	tatttgagc	cccgggtact	tataactgga	aagggtattg	tcgtgtagag	660
caaaagaata	acactttttt	tgacatgaac	atctttgaag	atgggcctta	tgaagttggt	720
ggagagactg	agcatgatga	aagtctcggt	cctgttcctg	ctaacagtta	cttaggtttt	780
tctttggact	cagggaaagg	tattgtttct	aaagatgaga	tcacttttgt	atctggtgct	840
cccagagcca	atcacagtgg	agccgtgggt	ttgctgaaga	gagacatgaa	gtctgcacat	900
ctcctccctg	agcacatatt	cgatggagaa	ggtctggcct	cttcatttgg	ctatgatgtg	960
gcggtggtgg	acctcaacaa	ggatgggtgg	caagatatag	ttattggagc	cccacagtat	1020
tttgatagag	atggagaagt	tggagggtga	gtgtatgtct	acatgaacca	gcaaggcaga	1080
tggaaataatg	tgaagccaat	tcgtcttaat	ggaaccaaag	attctatgtt	tggcattgca	1140
gtaaaaaata	ttggagatat	taatcaagat	ggctacccag	atattgcagt	tggagctccg	1200
tatgatgact	tgggaaagg	ttttatctat	catggatctg	caaatggaat	aaataccaaa	1260
ccaacacagg	ttctcaagg	tatatcacct	tatttttgat	attcaattgc	tggaaacatg	1320
gaccttgatc	gaaattccta	ccctgatgtt	gctgttggtt	ccctctcaga	ttcagtaact	1380
attttccagat	cccggcctgt	gattaatatt	cagaaaacca	tcacagtaac	tcctaacaga	1440
attgacctcc	gccagaaaac	agcgtgtggg	gcgcctagt	ggatatgcct	ccagggttaa	1500
tcctgttttg	aatatactgc	taaccccgct	ggttataatc	cttcaatatc	aattgtgggc	1560
acacttgaag	ctgaaaaaga	aagaagaaaa	tctgggctat	cctcaagagt	tcagtttcga	1620
aaccaagggt	ctgagcccaa	atatactcaa	gaactaactc	tgaagaggca	gaaacagaaa	1680
gtgtgcatgg	aggaaaccct	gtggctacag	gataatatca	gagataaact	gcgtcccat	1740

```

cccataactg cctcagtggg gatccaagag ccaagctctc gtaggcgagt gaattcactt 1800
ccagaagttc ttccaattct gaattcagat gaaccaaga cagctcatat tgatgttcac 1860
ttctttaaag agggatgtgg agacgacaat gtatgtaaca gcaaccttaa actagaatat 1920
aaatttttgca cccgagaagg aaatcaagac aaattttctt atttaccaat tcaaaaagggt 1980
gtaccagaac tagttctaaa agatcagaag gatattgctt tagaaataac agtgacaaac 2040
agcccttcca acccaaggaa tcccacaaaa gatggcgatg acgcccataa ggctaaactg 2100
attgcaacgt ttccagacac tttaacctat tctgcatata gagaactgag ggctttccct 2160
gagaaacagt tgagtttgtt tgccaaccag aatggctcgc aagctgactg tgagctcggg 2220
aatcctttta aaagaaattc aaatgtcact ttttatttgg ttttaagtac aactgaagtc 2280
acctttgaca ccccatatct ggatattaat ctgaagttag aaacaacaag caatcaagat 2340
aatttggctc caattacagc taaagcaaaa gtggttattg aactgctttt atcggtctcg 2400
ggagttgcta aaccttccca ggtgtatttt ggaggtacag ttggtggcga gcaagctatg 2460
aaatctgaag atgaagtggg aagtttaata gagtatgaat tcagggtaat aaacttaggt 2520
aaacctctta caaacctcgg cacagcaacc ttgaacattc agtggccaaa agaaattagc 2580
aatgggaaat ggttgcttta tttggtgaaa gtagaatcca aaggattgga aaaggtaact 2640
tgtgagccac aaaaggagat aaactccctg aacctaacgg agtctcacia ctcaagaaag 2700
aaacgggaaa ttactgaaaa acagatagat gataacagaa aattttcttt atttgctgaa 2760
agaaaatacc agactcttaa ctgtagcgtg aacgtgaact gtgtgaacat cagatgcccg 2820
ctgcggggggc tggacagcaa ggcgtctctt attttgcgct cgaggttatg gaacagcaca 2880
tttctagagg aatattccaa actgaactac ttggacattc tcatgcgagc cttcattgat 2940
gtgactgctg ctgccgaaaa tatcaggctg ccaaatgcag gcactcaggt tcgagtgact 3000
gtgtttccct caaagactgt agctcagtat tcgggagtac cttggtggat catcctagtg 3060
gctattctcg ctgggatctt gatgcttgct ttattagtgt ttatactatg gaagtgtggt 3120
ttcttcaaga gaaataagaa agatcattat gatgccacat atcacaaggc tgagatccat 3180
gctcagccat ctgataaaga gaggcttact tctgatgcat ag 3222

```

<210> 2

<211> 1072

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence; Note =
synthetic construct

<400> 2

```

Met Ala Ala Ala Gly Gln Leu Cys Leu Leu Tyr Leu Ser Ala Gly Leu
 1          5          10          15
Leu Ser Arg Leu Gly Ala Ala Phe Asn Leu Asp Thr Arg Glu Asp Asn
          20          25          30
Val Ile Arg Lys Tyr Gly Asp Pro Gly Ser Leu Phe Gly Phe Ser Leu
          35          40          45
Ala Met His Trp Gln Leu Gln Pro Glu Asp Lys Arg Leu Leu Val Gly
          50          55          60
Ala Pro Arg Gly Glu Ala Leu Pro Leu Gln Arg Ala Asn Arg Thr Gly
          65          70          75          80
Gly Leu Tyr Ser Cys Asp Ile Thr Ala Arg Gly Pro Cys Thr Arg Ile
          85          90          95
Glu Phe Asp Asn Asp Ala Asp Pro Thr Ser Glu Ser Lys Glu Asp Gln
          100          105          110
Trp Met Gly Val Thr Val Gln Ser Gln Gly Pro Gly Gly Lys Val Val
          115          120          125
Thr Cys Ala His Arg Tyr Glu Lys Arg Gln His Val Asn Thr Lys Gln
          130          135          140
Glu Ser Arg Asp Ile Phe Gly Arg Cys Tyr Val Leu Ser Gln Asn Leu
          145          150          155          160
Arg Ile Glu Asp Asp Met Asp Gly Gly Asp Trp Ser Phe Cys Asp Gly
          165          170          175
Arg Leu Arg Gly His Glu Lys Phe Gly Ser Cys Gln Gln Gly Val Ala
          180          185          190
Ala Thr Phe Thr Lys Asp Phe His Tyr Ile Val Phe Gly Ala Pro Gly
          195          200          205

```

Thr	Tyr	Asn	Trp	Lys	Gly	Ile	Val	Arg	Val	Glu	Gln	Lys	Asn	Asn	Thr
	210					215					220				
Phe	Phe	Asp	Met	Asn	Ile	Phe	Glu	Asp	Gly	Pro	Tyr	Glu	Val	Gly	Gly
225					230					235					240
Glu	Thr	Glu	His	Asp	Glu	Ser	Leu	Val	Pro	Val	Pro	Ala	Asn	Ser	Tyr
				245					250					255	
Leu	Gly	Phe	Ser	Leu	Asp	Ser	Gly	Lys	Gly	Ile	Val	Ser	Lys	Asp	Glu
			260					265					270		
Ile	Thr	Phe	Val	Ser	Gly	Ala	Pro	Arg	Ala	Asn	His	Ser	Gly	Ala	Val
		275					280					285			
Val	Leu	Leu	Lys	Arg	Asp	Met	Lys	Ser	Ala	His	Leu	Leu	Pro	Glu	His
	290					295					300				
Ile	Phe	Asp	Gly	Glu	Gly	Leu	Ala	Ser	Ser	Phe	Gly	Tyr	Asp	Val	Ala
305					310					315					320
Val	Val	Asp	Leu	Asn	Lys	Asp	Gly	Trp	Gln	Asp	Ile	Val	Ile	Gly	Ala
				325					330					335	
Pro	Gln	Tyr	Phe	Asp	Arg	Asp	Gly	Glu	Val	Gly	Gly	Ala	Val	Tyr	Val
			340					345					350		
Tyr	Met	Asn	Gln	Gln	Gly	Arg	Trp	Asn	Asn	Val	Lys	Pro	Ile	Arg	Leu
		355					360					365			
Asn	Gly	Thr	Lys	Asp	Ser	Met	Phe	Gly	Ile	Ala	Val	Lys	Asn	Ile	Gly
	370					375					380				
Asp	Ile	Asn	Gln	Asp	Gly	Tyr	Pro	Asp	Ile	Ala	Val	Gly	Ala	Pro	Tyr
385					390					395					400
Asp	Asp	Leu	Gly	Lys	Val	Phe	Ile	Tyr	His	Gly	Ser	Ala	Asn	Gly	Ile
				405					410					415	
Asn	Thr	Lys	Pro	Thr	Gln	Val	Leu	Lys	Gly	Ile	Ser	Pro	Tyr	Phe	Gly
			420					425					430		
Tyr	Ser	Ile	Ala	Gly	Asn	Met	Asp	Leu	Asp	Arg	Asn	Ser	Tyr	Pro	Asp
		435					440					445			
Val	Ala	Val	Gly	Ser	Leu	Ser	Asp	Ser	Val	Thr	Ile	Phe	Arg	Ser	Arg
	450					455					460				
Pro	Val	Ile	Asn	Ile	Gln	Lys	Thr	Ile	Thr	Val	Thr	Pro	Asn	Arg	Ile
465					470					475					480
Asp	Leu	Arg	Gln	Lys	Thr	Ala	Cys	Gly	Ala	Pro	Ser	Gly	Ile	Cys	Leu
				485					490					495	
Gln	Val	Lys	Ser	Cys	Phe	Glu	Tyr	Thr	Ala	Asn	Pro	Ala	Gly	Tyr	Asn
			500					505					510		
Pro	Ser	Ile	Ser	Ile	Val	Gly	Thr	Leu	Glu	Ala	Glu	Lys	Glu	Arg	Arg
		515					520						525		
Lys	Ser	Gly	Leu	Ser	Ser	Arg	Val	Gln	Phe	Arg	Asn	Gln	Gly	Ser	Glu
	530					535					540				
Pro	Lys	Tyr	Thr	Gln	Glu	Leu	Thr	Leu	Lys	Arg	Gln	Lys	Gln	Lys	Val
545					550					555					560
Cys	Met	Glu	Glu	Thr	Leu	Trp	Leu	Gln	Asp	Asn	Ile	Arg	Asp	Lys	Leu
				565					570					575	
Arg	Pro	Ile	Pro	Ile	Thr	Ala	Ser	Val	Glu	Ile	Gln	Glu	Pro	Ser	Ser
			580					585					590		
Arg	Arg	Arg	Val	Asn	Ser	Leu	Pro	Glu	Val	Leu	Pro	Ile	Leu	Asn	Ser
		595					600					605			
Asp	Glu	Pro	Lys	Thr	Ala	His	Ile	Asp	Val	His	Phe	Leu	Lys	Glu	Gly
	610					615					620				
Cys	Gly	Asp	Asp	Asn	Val	Cys	Asn	Ser	Asn	Leu	Lys	Leu	Glu	Tyr	Lys
625					630					635					640
Phe	Cys	Thr	Arg	Glu	Gly	Asn	Gln	Asp	Lys	Phe	Ser	Tyr	Leu	Pro	Ile
				645					650					655	
Gln	Lys	Gly	Val	Pro	Glu	Leu	Val	Leu	Lys	Asp	Gln	Lys	Asp	Ile	Ala
			660					665					670		
Leu	Glu	Ile	Thr	Val	Thr	Asn	Ser	Pro	Ser	Asn	Pro	Arg	Asn	Pro	Thr
		675					680					685			
Lys	Asp	Gly	Asp	Asp	Ala	His	Glu	Ala	Lys	Leu	Ile	Ala	Thr	Phe	Pro
	690					695					700				

Asp Thr Leu Thr Tyr Ser Ala Tyr Arg Glu Leu Arg Ala Phe Pro Glu
 705 710 715 720
 Lys Gln Leu Ser Cys Val Ala Asn Gln Asn Gly Ser Gln Ala Asp Cys
 725 730 735
 Glu Leu Gly Asn Pro Phe Lys Arg Asn Ser Asn Val Thr Phe Tyr Leu
 740 745 750
 Val Leu Ser Thr Thr Glu Val Thr Phe Asp Thr Pro Tyr Leu Asp Ile
 755 760 765
 Asn Leu Lys Leu Glu Thr Thr Ser Asn Gln Asp Asn Leu Ala Pro Ile
 770 775 780
 Thr Ala Lys Ala Lys Val Val Ile Glu Leu Leu Leu Ser Val Ser Gly
 785 790 795 800
 Val Ala Lys Pro Ser Gln Val Tyr Phe Gly Gly Thr Val Val Gly Glu
 805 810 815
 Gln Ala Met Lys Ser Glu Asp Glu Val Gly Ser Leu Ile Glu Tyr Glu
 820 825 830
 Phe Arg Val Ile Asn Leu Gly Lys Pro Leu Thr Asn Leu Gly Thr Ala
 835 840 845
 Thr Leu Asn Ile Gln Trp Pro Lys Glu Ile Ser Asn Gly Lys Trp Leu
 850 855 860
 Leu Tyr Leu Val Lys Val Glu Ser Lys Gly Leu Glu Lys Val Thr Cys
 865 870 875 880
 Glu Pro Gln Lys Glu Ile Asn Ser Leu Asn Leu Thr Glu Ser His Asn
 885 890 895
 Ser Arg Lys Lys Arg Glu Ile Thr Glu Lys Gln Ile Asp Asp Asn Arg
 900 905 910
 Lys Phe Ser Leu Phe Ala Glu Arg Lys Tyr Gln Thr Leu Asn Cys Ser
 915 920 925
 Val Asn Val Asn Cys Val Asn Ile Arg Cys Pro Leu Arg Gly Leu Asp
 930 935 940
 Ser Lys Ala Ser Leu Ile Leu Arg Ser Arg Leu Trp Asn Ser Thr Phe
 945 950 955 960
 Leu Glu Glu Tyr Ser Lys Leu Asn Tyr Leu Asp Ile Leu Met Arg Ala
 965 970 975
 Phe Ile Asp Val Thr Ala Ala Ala Glu Asn Ile Arg Leu Pro Asn Ala
 980 985 990
 Gly Thr Gln Val Arg Val Thr Val Phe Pro Ser Lys Thr Val Ala Gln
 995 1000 1005
 Tyr Ser Gly Val Pro Trp Trp Ile Ile Leu Val Ala Ile Leu Ala Gly
 1010 1015 1020
 Ile Leu Met Leu Ala Leu Leu Val Phe Ile Leu Trp Lys Cys Gly Phe
 1025 1030 1035 1040
 Phe Lys Arg Asn Lys Lys Asp His Tyr Asp Ala Thr Tyr His Lys Ala
 1045 1050 1055
 Glu Ile His Ala Gln Pro Ser Asp Lys Glu Arg Leu Thr Ser Asp Ala
 1060 1065 1070

<210> 3
 <211> 3222
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence; Note =
 synthetic construct

<400> 3
 atggccgctcg cgggccagtt gtgcctgctc tacctgtccg cggggccttct agcccggctg 60
 ggtacagcct tcaacctgga caccgcgcag gacaacgtga tccggaaatc gggggatccc 120
 gggagcctct tcggcttctc gctcgccatg cactggcagt tgcagccgga ggacaagcgg 180
 ctgttgcttg tgggggcacc tcgggcagaa gcactccgc tgcagagggc gaacagaaca 240
 gggggcctgt acagctgtga catcacctcc cgaggacctt gtacacggat tgaatttgat 300

```

aatgacgctg atcctatgtc agaaagcaag gaagaccagt ggatgggagt cactgtccag 360
agccaaggtc cagggggcaa agtgggtgacg tgtgcacatc gatatgagaa acggcagcac 420
gtcaacacga agcaggagtc gcgggatatc tttggaagat gttatgtcct gagtcagaat 480
ctcagaattg aagatgatat ggacggagga gactggagtt tctgcgatgg ccggttgaga 540
ggccatgaaa agtttggctc ctgtcagcaa ggagtagcgg ctactttcac taaggacttt 600
cattacattg tttttggagc cccaggggact tacaactgga aagggatcgt ccgtgtagaa 660
caaaagaata acactttttt tgacatgaac atctttgaag atgggcccta tgaagttggt 720
ggagagacag atcatgatga aagtctcgtg ccggttcctg ctaacagtta cctaggcctt 780
tcgctggact caggggaaggg tattgtttct aaagatgaca tcacttttgt gtctggtgct 840
ccaagagcca atcacagtgg ggctgtagtg ttgctaaaaa gagacatgaa gtccgcacat 900
ctgctccctg agtatatat ttgacggagaa ggctgggctt cctcgttttg ctatgatgtg 960
gcagtgggtg acctcaatgc agatgggtgg caagacatcg ttatcggagc tccacagtat 1020
tttgataggg atggtgaagt cgggggtgca gtttacgtct acattaacca gcaaggcaaa 1080
tggagtaatg tgaagccgat tcgtctaaat gggaccaaaag actcgatgtt tggaatctct 1140
gtgaaaaata taggtgatat taaccaagat ggctatccag atattgctgt tggagctccc 1200
tatgatgatc tggggaagggt ttttatctat catggatccc cgactggcat aattaccaag 1260
ccaacacagg ttctcgaggg gacatcgctt tacttcggct attcaatcgc tgggaatatg 1320
gacctggatc ggaattccta ccccgacctt gctgtgggct ccctctcaga ctcggtcact 1380
attttcagat cccggccagt gattaacatt ctaaaaacca tcacagtgaac tcctaacaga 1440
attgacctcc gccagaagtc catgtgtggc tcacctagcg ggatatgcct caaggttaaa 1500
gcctgttttg aatatactgc gaaaccttcc gggtataacc ctccaatatc aattttgggt 1560
attcttgaag ctgaaaaaga aagaagaaaa tcagggttgt catcgagagt tcagtttcga 1620
aaccaagggt ccgagccaaa gtatactcag gagctgacct tgaatcggca gaagcagcgg 1680
gcgtgcatgg aggagacct ctggctgcag gagaacatca gagacaagct gcgtcccatc 1740
cccatcacgg cttctgtgga gatccaggag cccacgtctc gccggcgggt gaactcactc 1800
cccgaaagttc ttcccatcct gaattcaaat gaagccaaaa cgggtccagac agatgtccac 1860
ttcttaaagg aaggatgtgg agacgacaat gtctgttaaca gcaaccttaa gctagagtat 1920
aaatttggtg cccgagaagg aaatcaagac aaattctctt accttccaat tcaaaaaggc 1980
atcccagaat tagtcctaaa agatcagaaa gatatagctc tggaaataac ggtgaccaac 2040
agcccttcgg atccaaggaa tccccggaaa gatggcgacg atgcccatga agccaaactc 2100
atcgccacgt ttccagacac tctgacatat tccgcttaca gagaactgag ggctttccct 2160
gagaagcagc tgagctgtgt ggccaaccag aatggctccc aagccgactg tgagctcgga 2220
aatcctttca agagaaattc cagtgttact ttctatctga ttttaagtac aaccgaggtc 2280
acctttgaca ccacagatct ggatattaat ctgaagttgg aaacaacaag caatcaggat 2340
aaattggctc caattacagc gaaggcaaaa gtggttattg aattgctttt atccctctcc 2400
ggagtcgcta agccttcgca ggtgtatttt ggaggtacag ttggttggtg gcaagctatg 2460
aaatctgaag atgaagtagg aagtttaata gagtatgaat ttaggggtgat taacttaggc 2520
aagcctctta aaaacctcgg cacagcaacc ttgaatatat agtggcccaa ggagattagc 2580
aatggcaaat ggttgcttta tttgatgaaa gttgaatcca aaggtttgga gcagattggt 2640
tgtgagccac acaatgaaat aaactacctg aagctgaagg agtctcacia ctcaagaaag 2700
aaacgggaac ttctgaaaa acagatagat gacagcagga aattttcttt atttcctgaa 2760
agaaaatacc agactctcaa ctgcagcgtc aacgtcaggt gtgtgaacat caggtgccca 2820
ctgcgagggc tggacacgaa ggcctctctc gttctgtgtt ccaggttgtg gaacagcaca 2880
tttctagagg aatattccaa actgaactac ttggacattc tcgtgagggc ttccatagat 2940
gtcaccgctg ctgctcagaa tatcaagctc cctcacgcgg gcactcaggt tcgagtgaag 3000
gtgtttccct caaagactgt agctcagtat tcaggagtag cttggtggat catcctcctg 3060
gctgttcttg ccgggattct gatgctggct ctattagtgt ttttactgtg gaagtgtggc 3120
ttcttcaaga gaaataagaa agatcattac gatgccacct atcacaaggc tgagatccat 3180
actcagccgt ctgataaaga gaggcttact tccgatgcat ag 3222

```

<210> 4

<211> 1073

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence; Note =
synthetic construct

<400> 4

Met Ala Val Ala Gly Gln Leu Cys Leu Leu Tyr Leu Ser Ala Gly Leu
1 5 10 15

Leu	Ala	Arg	Leu	Gly	Thr	Ala	Phe	Asn	Leu	Asp	Thr	Arg	Glu	Asp	Asn
			20					25					30		
Val	Ile	Arg	Lys	Ser	Gly	Asp	Pro	Gly	Ser	Leu	Phe	Gly	Phe	Ser	Leu
		35					40					45			
Ala	Met	His	Trp	Gln	Leu	Gln	Pro	Glu	Asp	Lys	Arg	Leu	Leu	Leu	Val
	50					55					60				
Gly	Ala	Pro	Arg	Ala	Glu	Ala	Leu	Pro	Leu	Gln	Arg	Ala	Asn	Arg	Thr
65					70					75					80
Gly	Gly	Leu	Tyr	Ser	Cys	Asp	Ile	Thr	Ser	Arg	Gly	Pro	Cys	Thr	Arg
			85					90						95	
Ile	Glu	Phe	Asp	Asn	Asp	Ala	Asp	Pro	Met	Ser	Glu	Ser	Lys	Glu	Asp
			100					105					110		
Gln	Trp	Met	Gly	Val	Thr	Val	Gln	Ser	Gln	Gly	Pro	Gly	Gly	Lys	Val
		115					120					125			
Val	Thr	Cys	Ala	His	Arg	Tyr	Glu	Lys	Arg	Gln	His	Val	Asn	Thr	Lys
	130					135					140				
Gln	Glu	Ser	Arg	Asp	Ile	Phe	Gly	Arg	Cys	Tyr	Val	Leu	Ser	Gln	Asn
145					150					155					160
Leu	Arg	Ile	Glu	Asp	Asp	Met	Asp	Gly	Gly	Asp	Trp	Ser	Phe	Cys	Asp
			165					170						175	
Gly	Arg	Leu	Arg	Gly	His	Glu	Lys	Phe	Gly	Ser	Cys	Gln	Gln	Gly	Val
			180					185					190		
Ala	Ala	Thr	Phe	Thr	Lys	Asp	Phe	His	Tyr	Ile	Val	Phe	Gly	Ala	Pro
		195					200					205			
Gly	Thr	Tyr	Asn	Trp	Lys	Gly	Ile	Val	Arg	Val	Glu	Gln	Lys	Asn	Asn
	210					215					220				
Thr	Phe	Phe	Asp	Met	Asn	Ile	Phe	Glu	Asp	Gly	Pro	Tyr	Glu	Val	Gly
225					230					235					240
Gly	Glu	Thr	Asp	His	Asp	Glu	Ser	Leu	Val	Pro	Val	Pro	Ala	Asn	Ser
			245						250					255	
Tyr	Leu	Gly	Phe	Ser	Leu	Asp	Ser	Gly	Lys	Gly	Ile	Val	Ser	Lys	Asp
		260						265					270		
Asp	Ile	Thr	Phe	Val	Ser	Gly	Ala	Pro	Arg	Ala	Asn	His	Ser	Gly	Ala
		275					280					285			
Val	Val	Leu	Leu	Lys	Arg	Asp	Met	Lys	Ser	Ala	His	Leu	Leu	Pro	Glu
	290					295					300				
Tyr	Ile	Phe	Asp	Gly	Glu	Gly	Leu	Ala	Ser	Ser	Phe	Gly	Tyr	Asp	Val
305					310					315					320
Ala	Val	Val	Asp	Leu	Asn	Ala	Asp	Gly	Trp	Gln	Asp	Ile	Val	Ile	Gly
			325						330					335	
Ala	Pro	Gln	Tyr	Phe	Asp	Arg	Asp	Gly	Glu	Val	Gly	Gly	Ala	Val	Tyr
		340						345					350		
Val	Tyr	Ile	Asn	Gln	Gln	Gly	Lys	Trp	Ser	Asn	Val	Lys	Pro	Ile	Arg
		355					360					365			
Leu	Asn	Gly	Thr	Lys	Asp	Ser	Met	Phe	Gly	Ile	Ser	Val	Lys	Asn	Ile
	370					375					380				
Gly	Asp	Ile	Asn	Gln	Asp	Gly	Tyr	Pro	Asp	Ile	Ala	Val	Gly	Ala	Pro
385					390					395					400
Tyr	Asp	Asp	Leu	Gly	Lys	Val	Phe	Ile	Tyr	His	Gly	Ser	Pro	Thr	Gly
			405						410					415	
Ile	Ile	Thr	Lys	Pro	Thr	Gln	Val	Leu	Glu	Gly	Thr	Ser	Pro	Tyr	Phe
		420						425					430		
Gly	Tyr	Ser	Ile	Ala	Gly	Asn	Met	Asp	Leu	Asp	Arg	Asn	Ser	Tyr	Pro
		435					440					445			
Asp	Leu	Ala	Val	Gly	Ser	Leu	Ser	Asp	Ser	Val	Thr	Ile	Phe	Arg	Ser
	450					455					460				
Arg	Pro	Val	Ile	Asn	Ile	Leu	Lys	Thr	Ile	Thr	Val	Thr	Pro	Asn	Arg
465					470					475					480
Ile	Asp	Leu	Arg	Gln	Lys	Ser	Met	Cys	Gly	Ser	Pro	Ser	Gly	Ile	Cys
			485						490					495	
Leu	Lys	Val	Lys	Ala	Cys	Phe	Glu	Tyr	Thr	Ala	Lys	Pro	Ser	Gly	Tyr
			500					505					510		

Asn	Pro	Pro	Ile	Ser	Ile	Leu	Gly	Ile	Leu	Glu	Ala	Glu	Lys	Glu	Arg
		515					520					525			
Arg	Lys	Ser	Gly	Leu	Ser	Ser	Arg	Val	Gln	Phe	Arg	Asn	Gln	Gly	Ser
	530					535					540				
Glu	Pro	Lys	Tyr	Thr	Gln	Glu	Leu	Thr	Leu	Asn	Arg	Gln	Lys	Gln	Arg
545					550					555					560
Ala	Cys	Met	Glu	Glu	Thr	Leu	Trp	Leu	Gln	Glu	Asn	Ile	Arg	Asp	Lys
				565					570					575	
Leu	Arg	Pro	Ile	Pro	Ile	Thr	Ala	Ser	Val	Glu	Ile	Gln	Glu	Pro	Thr
			580					585						590	
Ser	Arg	Arg	Arg	Val	Asn	Ser	Leu	Pro	Glu	Val	Leu	Pro	Ile	Leu	Asn
		595					600					605			
Ser	Asn	Glu	Ala	Lys	Thr	Val	Gln	Thr	Asp	Val	His	Phe	Leu	Lys	Glu
	610					615					620				
Gly	Cys	Gly	Asp	Asp	Asn	Val	Cys	Asn	Ser	Asn	Leu	Lys	Leu	Glu	Tyr
625					630					635					640
Lys	Phe	Gly	Thr	Arg	Glu	Gly	Asn	Gln	Asp	Lys	Phe	Ser	Tyr	Leu	Pro
				645					650					655	
Ile	Gln	Lys	Gly	Ile	Pro	Glu	Leu	Val	Leu	Lys	Asp	Gln	Lys	Asp	Ile
			660					665						670	
Ala	Leu	Glu	Ile	Thr	Val	Thr	Asn	Ser	Pro	Ser	Asp	Pro	Arg	Asn	Pro
		675					680							685	
Arg	Lys	Asp	Gly	Asp	Asp	Ala	His	Glu	Ala	Lys	Leu	Ile	Ala	Thr	Phe
	690					695					700				
Pro	Asp	Thr	Leu	Thr	Tyr	Ser	Ala	Tyr	Arg	Glu	Leu	Arg	Ala	Phe	Pro
705					710					715					720
Glu	Lys	Gln	Leu	Ser	Cys	Val	Ala	Asn	Gln	Asn	Gly	Ser	Gln	Ala	Asp
				725					730					735	
Cys	Glu	Leu	Gly	Asn	Pro	Phe	Lys	Arg	Asn	Ser	Ser	Val	Thr	Phe	Tyr
		740					745						750		
Leu	Ile	Leu	Ser	Thr	Thr	Glu	Val	Thr	Phe	Asp	Thr	Thr	Asp	Leu	Asp
		755				760						765			
Ile	Asn	Leu	Lys	Leu	Glu	Thr	Thr	Ser	Asn	Gln	Asp	Lys	Leu	Ala	Pro
	770					775					780				
Ile	Thr	Ala	Lys	Ala	Lys	Val	Val	Ile	Glu	Leu	Leu	Leu	Ser	Leu	Ser
785					790					795					800
Gly	Val	Ala	Lys	Pro	Ser	Gln	Val	Tyr	Phe	Gly	Gly	Thr	Val	Val	Gly
				805					810					815	
Glu	Gln	Ala	Met	Lys	Ser	Glu	Asp	Glu	Val	Gly	Ser	Leu	Ile	Glu	Tyr
			820					825					830		
Glu	Phe	Arg	Val	Ile	Asn	Leu	Gly	Lys	Pro	Leu	Lys	Asn	Leu	Gly	Thr
	835					840						845			
Ala	Thr	Leu	Asn	Ile	Gln	Trp	Pro	Lys	Glu	Ile	Ser	Asn	Gly	Lys	Trp
	850					855					860				
Leu	Leu	Tyr	Leu	Met	Lys	Val	Glu	Ser	Lys	Gly	Leu	Glu	Gln	Ile	Val
865					870					875					880
Cys	Glu	Pro	His	Asn	Glu	Ile	Asn	Tyr	Leu	Lys	Leu	Lys	Glu	Ser	His
			885					890						895	
Asn	Ser	Arg	Lys	Lys	Arg	Glu	Leu	Pro	Glu	Lys	Gln	Ile	Asp	Asp	Ser
			900					905					910		
Arg	Lys	Phe	Ser	Leu	Phe	Pro	Glu	Arg	Lys	Tyr	Gln	Thr	Leu	Asn	Cys
	915						920					925			
Ser	Val	Asn	Val	Arg	Cys	Val	Asn	Ile	Arg	Cys	Pro	Leu	Arg	Gly	Leu
	930					935					940				
Asp	Thr	Lys	Ala	Ser	Leu	Val	Leu	Cys	Ser	Arg	Leu	Trp	Asn	Ser	Thr
945					950					955					960
Phe	Leu	Glu	Glu	Tyr	Ser	Lys	Leu	Asn	Tyr	Leu	Asp	Ile	Leu	Val	Arg
				965					970					975	
Ala	Ser	Ile	Asp	Val	Thr	Ala	Ala	Ala	Gln	Asn	Ile	Lys	Leu	Pro	His
			980					985						990	
Ala	Gly	Thr	Gln	Val	Arg	Val	Thr	Val	Phe	Pro	Ser	Lys	Thr	Val	Ala
		995					1000						1005		

Gln Tyr Ser Gly Val Ala Trp Trp Ile Ile Leu Leu Ala Val Leu Ala
 1010 1015 1020
 Gly Ile Leu Met Leu Ala Leu Leu Val Phe Leu Leu Trp Lys Cys Gly
 1025 1030 1035 1040
 Phe Phe Lys Arg Asn Lys Lys Asp His Tyr Asp Ala Thr Tyr His Lys
 1045 1050 1055
 Ala Glu Ile His Thr Gln Pro Ser Asp Lys Glu Arg Leu Thr Ser Asp
 1060 1065 1070
 Ala

<210> 5
 <211> 5622
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence; Note =
 synthetic construct

<400> 5
 atggcagggc cacgccccag cccatggggc aggctgctcc tggcagcctt gatcagcgtc 60
 agcctctctg ggaccttgaa ccgctgcaag aaggccccag tgaagagctg cacggagtgt 120
 gtccgtgtgg ataaggactg cgcctactgc acagacgaga tgttcaggga ccggcgctgc 180
 aacacccagg cggagctgct ggccgcgggc tgccagcggg agagcatcgt ggtcatggag 240
 agcagcttcc aaatcacaga ggagacccag attgacacca ccctgcggcg cagccagatg 300
 tccccccaag gcttgccggg cctgtctgcg cccgggtgagg agcggcattt tgagctggag 360
 gtgtttgagc cactggagag ccccggtggac ctgtacatcc tcatggactt ctccaactcc 420
 atgtccgatg atctggacaa cctcaagaag atggggcaga acctggctcg ggtcctgagc 480
 cagctcacca gcgactacac tattggattt ggcaagtttg tggacaaagt cagcgtcccc 540
 cagacggaca tgaggcctga gaagctgaag gagccttggc ccaacagtga ccccccttc 600
 tccttcaaga acgtcatcag cctgacagaa gatgtggatg agttccggaa taaactgcag 660
 ggagagcgga tctcaggcaa cctggatgct cctgagggcg gcttcgatgc catcctgcag 720
 acagctgtgt gcacgagggg cattggctgg cgcccgaca gcacccacct gctggtcttc 780
 tccaccgagt cagccttcca ctatgaggct gatggcgcca acgtgctggc tggcatcatg 840
 agccgcaacg atgaacggtg ccacctggac accacgggca cctacacca gtacaggaca 900
 caggactacc cgtcgggtgc caccctggtg cgcctgctcg ccaagcaca catcatcccc 960
 atctttgctg tcaccaacta ctctatagc tactacgaga agcttcacac ctatttccct 1020
 gtctcctcac tgggggtgct gcaggaggac tcgtccaaca tcgtggagct gctggaggag 1080
 gccttcaatc ggatccgctc caacctggac atccgggccc tagacagccc ccgaggcctt 1140
 cggacagagg tcacctcaa gatgttccag aagacgagga ctgggtcctt tcacatccgg 1200
 cggggggaag tgggtatata ccagggtgcag ctgcgggccc ttgagcacgt ggatgggacg 1260
 cacgtgtgcc agctgccgga ggaccagaag ggcaacatcc atctgaaacc ttccttctcc 1320
 gacggcctca agatggacgc gggcatcatc tgtgatgtgt gcacctgcga gctgcaaaaa 1380
 gaggtgcggt cagctcgctg cagcttcaac ggagacttcg tgtgcggaca gtgtgtgtgc 1440
 agcgagggct ggagtggcca gacctgcaac tgctccaccg gctctctgag tgacattcag 1500
 ccctgcctgc gggagggcga ggacaagccg tgctccggcc gtggggagtg ccagtgcggg 1560
 cactgtgtgt gctacggcga aggcgctac gagggtcagt tctgcgagta tgacaacttc 1620
 cagtgtcccc gcacttccgg gtctctctgc aatgaccgag gacgtgctc catgggccag 1680
 tgtgtgtgtg agcctgggtg gacaggecca agctgtgact gtccccctcag caatgccacc 1740
 tgcattcgaca gcaatggggg catctgtaat ggacgtggcc actgtgagtg tggccgctgc 1800
 cactgccacc agcagtcgct ctacacggac accatctgcg agatcaacta ctcggcgtcc 1860
 acccgggcct ctgcgaggac ctacgctcct gcgtgcagtg ccaggcgtgg ggcaccggcg 1920
 agaagaaggg gcgcacgtgt gaggaatgca acttcaaggt caagatggtg gacgagctta 1980
 agagaggcga ggaggtggtg gtgcgctgct ccttccggga cgaggatgac gactgcacct 2040
 acagctacac catggaaggt gacggcgccc ctgggcccga cagcactgtc ctggtgcaca 2100
 agaagaaggg actgccctcc gggctccttc tgggtggctca tccccctgct cctcctcctc 2160
 ctgccgctcc tggccctgct actgctgcta tgctggaagt actgtgctg ctgcaaggcc 2220
 tgcctggcac ttctcccgtg ctgcaaccga ggtcacatgg tgggctttaa ggaagaccac 2280
 tacatgctgc gggagaacct gatggcctct gaccacttgg acacgcccac gctgcgcagc 2340
 gggaaacctca agggccgtga cgtggctcgc tgggaaggtc ccaacaacat gcagcggcct 2400
 ggctttgcca ctcatgccgc cagcatcaac cccacagagc tgggtgcccta cgggctgtcc 2460

ttgcgcctgg	cccgcctttg	caccgagaac	ctgctgaagc	ctgacactcg	ggagtgcgcc	2520
cagctgcgcc	aggaggtgga	ggagaacctg	aacgaggtct	acaggcagat	ctccggtgta	2580
cacaagctcc	agcagaccaa	gttccggcag	cagcccaatg	ccgggaaaaa	gcaagaccac	2640
accatttgtg	acacagtgtc	gatggcgccc	cgctcggcca	agccggccct	gctgaagctt	2700
acagagaagc	aggtggaaca	gagggccttc	cacgacctca	aggtggcccc	cggctactac	2760
accctcactg	cagaccagga	cgcccggggc	atggtggagt	tccaggaggg	cgtggagctg	2820
gtggacgtac	gggtgcccct	ctttatccgg	cctgaggatg	acgacgagaa	gcagctgctg	2880
gtggaggcca	tcgacgtgcc	cgcaggcact	gccaccctcg	gccgcgcgct	ggtaaaccatc	2940
accatcatca	aggagcaagc	cagagacgtg	gtgtcctttg	agcagcctga	gttctcggtc	3000
agccgcgggg	accaggtggc	ccgcatccct	gtcatccggc	gtgtcctgga	cggcgggaag	3060
tcccaggtct	cctaccgcac	acaggatggc	accgcgcagg	gcaaccggga	ctacatcccc	3120
gtggaggggtg	agctgctgtt	ccagcctggg	gaggcctgga	aagagctgca	ggtgaagctc	3180
ctggagctgc	aagaagttga	ctccctcctg	cggggccgcc	aggtccgccc	tttccacgtc	3240
cagctcagca	accctaagtt	tggggcccac	ctggggccagc	cccactccac	caccatcacc	3300
atcagggacc	cagatgaact	ggaccgggagc	ttcacgagtc	agatgttgtc	atcacagcca	3360
ccccctcacg	gcgacctggg	cgccccgcag	aaccccaatg	ctaaggccgc	tgggtccagg	3420
aagatccatt	tcaactggct	gcccccttct	ggcaagccaa	tggggtacag	ggtaaagtac	3480
tggatttcagg	gtgactccga	atccgaagcc	cacctgctcg	acagcaaggt	gccctcagtg	3540
gagctcacca	acctgtaccc	gtattgcgac	tatgagatga	aggtgtgcgc	ctacggggct	3600
cagggcgagg	gacctacag	ctccctgggtg	tcctgccgca	cccaccagga	agtgccccagc	3660
gagccagggc	gtctggcctt	caatgtcgtc	tcctccacgg	tgaccagct	gagctgggct	3720
gagccggctg	agaccaacgg	tgagatcaca	gcctacgagg	tctgctatgg	cctgggtcaac	3780
gatgacaacc	gacctattgg	gcccattgaag	aaagtgtctg	ttgacaaccc	taagaaccgg	3840
atgctgctta	ttgagaacct	tcgggagtc	cagccctacc	gctacacggt	gaaggcgcgc	3900
aacggggccg	gctggggggc	tgagcgggag	gccatcatca	acctggccac	ccagcccaag	3960
aggcccatgt	ccatccccat	catccctgac	atccctatcg	tggacgcccc	gagcggggag	4020
gactacgaca	gcttccttat	gtacagcgat	gacgttctac	gctctccatc	gggcagccag	4080
aggcccagcg	tctccgatga	cactggctgc	ggctggaagt	tcgagccccc	gctgggggag	4140
gagctggacc	tgcggcgcg	cacgtggcgg	ctgcccccg	agctcatccc	gcgctgtcg	4200
gccagcagcg	ggcgctcctc	cgacgcgcag	gcgccccacg	ggcccccgga	cgacggcggc	4260
gcggggcgga	agggcggcag	cctgccccgc	agtgcgacac	ccggggcccc	cggagagcac	4320
ctggtgaatg	gccggatgga	ctttgccttc	ccgggcagca	ccaactccct	gcacaggatg	4380
accacgacca	gtgctgctgc	ctatggcacc	cacctgagcc	cacacgtgcc	ccaccgcgtg	4440
ctaagcacat	cctccaccct	cacacgggac	tacaactcac	tgaccgcgtc	agaacactca	4500
cactcgacca	cactgccgag	ggactactcc	accctcacct	ccgtctcctc	ccacggcctc	4560
cctcccatct	gggaacacgg	gaggagcagg	cttccgctgt	cctgggcccct	ggggtcccgg	4620
agtcgggctc	agatgaaagg	gttccccctt	tccagggggc	cacgagactc	tataatcctg	4680
gctgggaggc	cagcagcgcc	ctcctggggc	ccagactctc	gcctgactgc	tgggtgtgcc	4740
gacacgcccc	ccgcctgggt	gttctctgcc	ctggggccca	catctctcag	agtgagctgg	4800
caggagccgc	ggtgcgagcg	gccgctgcag	ggctacagtg	tggagtacca	gctgctgaac	4860
ggcggtgagc	tgcctcggct	caacatcccc	aacctgccc	agacctcggt	ggtgggtgga	4920
gacctcctgc	ccaaccactc	ctacgtgttc	cgcgtgcggg	cccagagcca	ggaaggctgg	4980
ggccgagagc	gtgagggtgt	catcaccatt	gaatcccagg	tgcaccgcga	gagcccactg	5040
tgtccccctg	caggctccgc	cttcactttg	agcactccca	gtgccccagg	cccgtggtg	5100
ttcactgccc	tgagcccaga	ctcgctgcag	ctgagctggg	agcggccacg	gaggcccaat	5160
ggggatatcg	tcggctacct	ggtgacctgt	gagatggccc	aaggaggagg	tccagccacc	5220
gcattccggg	tggatggaga	cagccccgag	agccggctga	ccgtgccggg	cctcagcgag	5280
aacgtgccct	acaagttcaa	ggtgcaggcc	aggaccactg	agggcttcgg	gccagagcgc	5340
gagggcatca	tcaccataga	gtcccaggat	ggaggtccct	tcccgagct	gggcagccgt	5400
gccgggctct	tccagcacc	gctgcaaagc	gagtacagca	gcattctccac	caccacacac	5460
agcgcaccgc	agcccttctt	agtgggtccg	accctggggg	cccagcacct	ggaggcaggc	5520
ggctccctca	cccggcatgt	gaccagggag	tttgtgagcc	ggacactgac	caccagcgga	5580
acccttagca	cccacatgga	ccaacagttc	ttccaaactt	ga		5622

<210> 6

<211> 1873

<212> PRT

<213> Artificial Sequence

<220>

10

<223> Description of Artificial Sequence; Note =
synthetic construct

<400> 6

Met	Ala	Gly	Pro	Arg	Pro	Ser	Pro	Trp	Ala	Arg	Leu	Leu	Leu	Ala	Ala			
1				5					10					15				
Leu	Ile	Ser	Val	Ser	Leu	Ser	Gly	Thr	Leu	Asn	Arg	Cys	Lys	Lys	Ala			
			20					25					30					
Pro	Val	Lys	Ser	Cys	Thr	Glu	Cys	Val	Arg	Val	Asp	Lys	Asp	Cys	Ala			
		35					40					45						
Tyr	Cys	Thr	Asp	Glu	Met	Phe	Arg	Asp	Arg	Arg	Cys	Asn	Thr	Gln	Ala			
	50					55					60							
Glu	Leu	Leu	Ala	Ala	Gly	Cys	Gln	Arg	Glu	Ser	Ile	Val	Val	Met	Glu			
65					70					75					80			
Ser	Ser	Phe	Gln	Ile	Thr	Glu	Glu	Thr	Gln	Ile	Asp	Thr	Thr	Leu	Arg			
				85					90					95				
Arg	Ser	Gln	Met	Ser	Pro	Gln	Gly	Leu	Arg	Val	Arg	Leu	Arg	Pro	Gly			
			100					105					110					
Glu	Glu	Arg	His	Phe	Glu	Leu	Glu	Val	Phe	Glu	Pro	Leu	Glu	Ser	Pro			
		115					120					125						
Val	Asp	Leu	Tyr	Ile	Leu	Met	Asp	Phe	Ser	Asn	Ser	Met	Ser	Asp	Asp			
	130					135					140							
Leu	Asp	Asn	Leu	Lys	Lys	Met	Gly	Gln	Asn	Leu	Ala	Arg	Val	Leu	Ser			
145				150					155						160			
Gln	Leu	Thr	Ser	Asp	Tyr	Thr	Ile	Gly	Phe	Gly	Lys	Phe	Val	Asp	Lys			
				165					170					175				
Val	Ser	Val	Pro	Gln	Thr	Asp	Met	Arg	Pro	Glu	Lys	Leu	Lys	Glu	Pro			
			180					185					190					
Trp	Pro	Asn	Ser	Asp	Pro	Pro	Phe	Ser	Phe	Lys	Asn	Val	Ile	Ser	Leu			
		195					200					205						
Thr	Glu	Asp	Val	Asp	Glu	Phe	Arg	Asn	Lys	Leu	Gln	Gly	Glu	Arg	Ile			
	210					215					220							
Ser	Gly	Asn	Leu	Asp	Ala	Pro	Glu	Gly	Gly	Phe	Asp	Ala	Ile	Leu	Gln			
225					230					235					240			
Thr	Ala	Val	Cys	Thr	Arg	Asp	Ile	Gly	Trp	Arg	Pro	Asp	Ser	Thr	His			
				245					250					255				
Leu	Leu	Val	Phe	Ser	Thr	Glu	Ser	Ala	Phe	His	Tyr	Glu	Ala	Asp	Gly			
			260					265					270					
Ala	Asn	Val	Leu	Ala	Gly	Ile	Met	Ser	Arg	Asn	Asp	Glu	Arg	Cys	His			
		275					280					285						
Leu	Asp	Thr	Thr	Gly	Thr	Tyr	Thr	Gln	Tyr	Arg	Thr	Gln	Asp	Tyr	Pro			
	290					295					300							
Ser	Val	Pro	Thr	Leu	Val	Arg	Leu	Leu	Ala	Lys	His	Asn	Ile	Ile	Pro			
305					310					315					320			
Ile	Phe	Ala	Val	Thr	Asn	Tyr	Ser	Tyr	Ser	Tyr	Tyr	Glu	Lys	Leu	His			
				325					330					335				
Thr	Tyr	Phe	Pro	Val	Ser	Ser	Leu	Gly	Val	Leu	Gln	Glu	Asp	Ser	Ser			
			340					345					350					
Asn	Ile	Val	Glu	Leu	Leu	Glu	Glu	Ala	Phe	Asn	Arg	Ile	Arg	Ser	Asn			
		355					360					365						
Leu	Asp	Ile	Arg	Ala	Leu	Asp	Ser	Pro	Arg	Gly	Leu	Arg	Thr	Glu	Val			
	370					375					380							
Thr	Ser	Lys	Met	Phe	Gln	Lys	Thr	Arg	Thr	Gly	Ser	Phe	His	Ile	Arg			
385					390					395					400			
Arg	Gly	Glu	Val	Gly	Ile	Tyr	Gln	Val	Gln	Leu	Arg	Ala	Leu	Glu	His			
				405					410					415				
Val	Asp	Gly	Thr	His	Val	Cys	Gln	Leu	Pro	Glu	Asp	Gln	Lys	Gly	Asn			
			420					425					430					
Ile	His	Leu	Lys	Pro	Ser	Phe	Ser	Asp	Gly	Leu	Lys	Met	Asp	Ala	Gly			
		435				440						445						
Ile	Ile	Cys	Asp	Val	Cys	Thr	Cys	Glu	Leu	Gln	Lys	Glu	Val	Arg	Ser			
	450					455					460							

Ala	Arg	Cys	Ser	Phe	Asn	Gly	Asp	Phe	Val	Cys	Gly	Gln	Cys	Val	Cys	465	470	475	480
Ser	Glu	Gly	Trp	Ser	Gly	Gln	Thr	Cys	Asn	Cys	Ser	Thr	Gly	Ser	Leu	485	490		495
Ser	Asp	Ile	Gln	Pro	Cys	Leu	Arg	Glu	Gly	Glu	Asp	Lys	Pro	Cys	Ser	500	505		510
Gly	Arg	Gly	Glu	Cys	Gln	Cys	Gly	His	Cys	Val	Cys	Tyr	Gly	Glu	Gly	515	520	525	
Arg	Tyr	Glu	Gly	Gln	Phe	Cys	Glu	Tyr	Asp	Asn	Phe	Gln	Cys	Pro	Arg	530	535	540	
Thr	Ser	Gly	Phe	Leu	Cys	Asn	Asp	Arg	Gly	Arg	Cys	Ser	Met	Gly	Gln	545	550	555	560
Cys	Val	Cys	Glu	Pro	Gly	Trp	Thr	Gly	Pro	Ser	Cys	Asp	Cys	Pro	Leu	565	570		575
Ser	Asn	Ala	Thr	Cys	Ile	Asp	Ser	Asn	Gly	Gly	Ile	Cys	Asn	Gly	Arg	580	585		590
Gly	His	Cys	Glu	Cys	Gly	Arg	Cys	His	Cys	His	Gln	Gln	Ser	Leu	Tyr	595	600	605	
Thr	Asp	Thr	Ile	Cys	Glu	Ile	Asn	Tyr	Ser	Ala	Ser	Thr	Arg	Ala	Ser	610	615	620	
Ala	Arg	Thr	Tyr	Ala	Pro	Ala	Cys	Ser	Ala	Arg	Arg	Gly	Ala	Pro	Ala	625	630	635	640
Arg	Arg	Arg	Gly	Ala	Arg	Val	Arg	Asn	Ala	Thr	Ser	Arg	Ser	Arg	Trp	645	650		655
Trp	Thr	Ser	Leu	Arg	Glu	Ala	Arg	Arg	Trp	Trp	Cys	Ala	Ala	Pro	Ser	660	665		670
Gly	Thr	Arg	Met	Thr	Thr	Ala	Pro	Thr	Ala	Thr	Pro	Trp	Lys	Val	Thr	675	680	685	
Ala	Pro	Leu	Gly	Pro	Thr	Ala	Leu	Ser	Trp	Cys	Thr	Arg	Arg	Arg	Asp	690	695	700	
Cys	Pro	Pro	Gly	Ser	Phe	Trp	Trp	Leu	Ile	Pro	Leu	Leu	Leu	Leu	Leu	705	710	715	720
Leu	Pro	Leu	Leu	Ala	Leu	Leu	Leu	Leu	Leu	Cys	Trp	Lys	Tyr	Cys	Ala	725	730		735
Cys	Cys	Lys	Ala	Cys	Leu	Ala	Leu	Leu	Pro	Cys	Cys	Asn	Arg	Gly	His	740	745		750
Met	Val	Gly	Phe	Lys	Glu	Asp	His	Tyr	Met	Leu	Arg	Glu	Asn	Leu	Met	755	760	765	
Ala	Ser	Asp	His	Leu	Asp	Thr	Pro	Met	Leu	Arg	Ser	Gly	Asn	Leu	Lys	770	775	780	
Gly	Arg	Asp	Val	Val	Arg	Trp	Lys	Val	Thr	Asn	Asn	Met	Gln	Arg	Pro	785	790	795	800
Gly	Phe	Ala	Thr	His	Ala	Ala	Ser	Ile	Asn	Pro	Thr	Glu	Leu	Val	Pro	805	810		815
Tyr	Gly	Leu	Ser	Leu	Arg	Leu	Ala	Arg	Leu	Cys	Thr	Glu	Asn	Leu	Leu	820	825		830
Lys	Pro	Asp	Thr	Arg	Glu	Cys	Ala	Gln	Leu	Arg	Gln	Glu	Val	Glu	Glu	835	840	845	
Asn	Leu	Asn	Glu	Val	Tyr	Arg	Gln	Ile	Ser	Gly	Val	His	Lys	Leu	Gln	850	855	860	
Gln	Thr	Lys	Phe	Arg	Gln	Gln	Pro	Asn	Ala	Gly	Lys	Lys	Gln	Asp	His	865	870	875	880
Thr	Ile	Val	Asp	Thr	Val	Leu	Met	Ala	Pro	Arg	Ser	Ala	Lys	Pro	Ala	885	890		895
Leu	Leu	Lys	Leu	Thr	Glu	Lys	Gln	Val	Glu	Gln	Arg	Ala	Phe	His	Asp	900	905		910
Leu	Lys	Val	Ala	Pro	Gly	Tyr	Tyr	Thr	Leu	Thr	Ala	Asp	Gln	Asp	Ala	915	920	925	
Arg	Gly	Met	Val	Glu	Phe	Gln	Glu	Gly	Val	Glu	Leu	Val	Asp	Val	Arg	930	935	940	
Val	Pro	Leu	Phe	Ile	Arg	Pro	Glu	Asp	Asp	Asp	Glu	Lys	Gln	Leu	Leu	945	950	955	960

12

Val	Glu	Ala	Ile	Asp	Val	Pro	Ala	Gly	Thr	Ala	Thr	Leu	Gly	Arg	Arg	
				965					970					975		
Leu	Val	Asn	Ile	Thr	Ile	Ile	Lys	Glu	Gln	Ala	Arg	Asp	Val	Val	Ser	
			980					985					990			
Phe	Glu	Gln	Pro	Glu	Phe	Ser	Val	Ser	Arg	Gly	Asp	Gln	Val	Ala	Arg	
		995					1000					1005				
Ile	Pro	Val	Ile	Arg	Arg	Val	Leu	Asp	Gly	Gly	Lys	Ser	Gln	Val	Ser	
	1010					1015					1020					
Tyr	Arg	Thr	Gln	Asp	Gly	Thr	Ala	Gln	Gly	Asn	Arg	Asp	Tyr	Ile	Pro	
1025					1030					1035					1040	
Val	Glu	Gly	Glu	Leu	Leu	Phe	Gln	Pro	Gly	Glu	Ala	Trp	Lys	Glu	Leu	
				1045					1050					1055		
Gln	Val	Lys	Leu	Leu	Glu	Leu	Gln	Glu	Val	Asp	Ser	Leu	Leu	Arg	Gly	
			1060					1065					1070			
Arg	Gln	Val	Arg	Arg	Phe	His	Val	Gln	Leu	Ser	Asn	Pro	Lys	Phe	Gly	
		1075					1080					1085				
Ala	His	Leu	Gly	Gln	Pro	His	Ser	Thr	Thr	Ile	Ile	Ile	Arg	Asp	Pro	
	1090					1095					1100					
Asp	Glu	Leu	Asp	Arg	Ser	Phe	Thr	Ser	Gln	Met	Leu	Ser	Ser	Gln	Pro	
1105					1110				1115						1120	
Pro	Pro	His	Gly	Asp	Leu	Gly	Ala	Pro	Gln	Asn	Pro	Asn	Ala	Lys	Ala	
			1125						1130					1135		
Ala	Gly	Ser	Arg	Lys	Ile	His	Phe	Asn	Trp	Leu	Pro	Pro	Ser	Gly	Lys	
		1140						1145					1150			
Pro	Met	Gly	Tyr	Arg	Val	Lys	Tyr	Trp	Ile	Gln	Gly	Asp	Ser	Glu	Ser	
	1155					1160						1165				
Glu	Ala	His	Leu	Leu	Asp	Ser	Lys	Val	Pro	Ser	Val	Glu	Leu	Thr	Asn	
	1170					1175					1180					
Leu	Tyr	Pro	Tyr	Cys	Asp	Tyr	Glu	Met	Lys	Val	Cys	Ala	Tyr	Gly	Ala	
1185					1190				1195						1200	
Gln	Gly	Glu	Gly	Pro	Tyr	Ser	Ser	Leu	Val	Ser	Cys	Arg	Thr	His	Gln	
			1205						1210					1215		
Glu	Val	Pro	Ser	Glu	Pro	Gly	Arg	Leu	Ala	Phe	Asn	Val	Val	Ser	Ser	
		1220						1225					1230			
Thr	Val	Thr	Gln	Leu	Ser	Trp	Ala	Glu	Pro	Ala	Glu	Thr	Asn	Gly	Glu	
	1235						1240					1245				
Ile	Thr	Ala	Tyr	Glu	Val	Cys	Tyr	Gly	Leu	Val	Asn	Asp	Asp	Asn	Arg	
	1250					1255					1260					
Pro	Ile	Gly	Pro	Met	Lys	Lys	Val	Leu	Val	Asp	Asn	Pro	Lys	Asn	Arg	
1265					1270					1275					1280	
Met	Leu	Leu	Ile	Glu	Asn	Leu	Arg	Glu	Ser	Gln	Pro	Tyr	Arg	Tyr	Thr	
			1285					1290					1295			
Val	Lys	Ala	Arg	Asn	Gly	Ala	Gly	Trp	Gly	Pro	Glu	Arg	Glu	Ala	Ile	
		1300						1305					1310			
Ile	Asn	Leu	Ala	Thr	Gln	Pro	Lys	Arg	Pro	Met	Ser	Ile	Pro	Ile	Ile	
	1315						1320					1325				
Pro	Asp	Ile	Pro	Ile	Val	Asp	Ala	Gln	Ser	Gly	Glu	Asp	Tyr	Asp	Ser	
	1330					1335					1340					
Phe	Leu	Met	Tyr	Ser	Asp	Asp	Val	Leu	Arg	Ser	Pro	Ser	Gly	Ser	Gln	
1345					1350				1355						1360	
Arg	Pro	Ser	Val	Ser	Asp	Asp	Thr	Gly	Cys	Gly	Trp	Lys	Phe	Glu	Pro	
			1365					1370						1375		
Leu	Leu	Gly	Glu	Glu	Leu	Asp	Leu	Arg	Arg	Val	Thr	Trp	Arg	Leu	Pro	
		1380						1385					1390			
Pro	Glu	Leu	Ile	Pro	Arg	Leu	Ser	Ala	Ser	Ser	Gly	Arg	Ser	Ser	Asp	
	1395					1400						1405				
Ala	Glu	Ala	Pro	His	Gly	Pro	Pro	Asp	Asp	Gly	Gly	Ala	Gly	Gly	Lys	
	1410					1415					1420					
Gly	Gly	Ser	Leu	Pro	Arg	Ser	Ala	Thr	Pro	Gly	Pro	Pro	Gly	Glu	His	
1425					1430					1435					1440	
Leu	Val	Asn	Gly	Arg	Met	Asp	Phe	Ala	Phe	Pro	Gly	Ser	Thr	Asn	Ser	
			1445						1450					1455		

13

Leu His Arg Met Thr Thr Thr Ser Ala Ala Ala Tyr Gly Thr His Leu
 1460 1465 1470
 Ser Pro His Val Pro His Arg Val Leu Ser Thr Ser Ser Thr Leu Thr
 1475 1480 1485
 Arg Asp Tyr Asn Ser Leu Thr Arg Ser Glu His Ser His Ser Thr Thr
 1490 1495 1500
 Leu Pro Arg Asp Tyr Ser Thr Leu Thr Ser Val Ser Ser His Gly Leu
 1505 1510 1515 1520
 Pro Pro Ile Trp Glu His Gly Arg Ser Arg Leu Pro Leu Ser Trp Ala
 1525 1530 1535
 Leu Gly Ser Arg Ser Arg Ala Gln Met Lys Gly Phe Pro Pro Ser Arg
 1540 1545 1550
 Gly Pro Arg Asp Ser Ile Ile Leu Ala Gly Arg Pro Ala Ala Pro Ser
 1555 1560 1565
 Trp Gly Pro Asp Ser Arg Leu Thr Ala Gly Val Pro Asp Thr Pro Thr
 1570 1575 1580
 Arg Leu Val Phe Ser Ala Leu Gly Pro Thr Ser Leu Arg Val Ser Trp
 1585 1590 1595 1600
 Gln Glu Pro Arg Cys Glu Arg Pro Leu Gln Gly Tyr Ser Val Glu Tyr
 1605 1610 1615
 Gln Leu Leu Asn Gly Gly Glu Leu His Arg Leu Asn Ile Pro Asn Pro
 1620 1625 1630
 Ala Gln Thr Ser Val Val Val Glu Asp Leu Leu Pro Asn His Ser Tyr
 1635 1640 1645
 Val Phe Arg Val Arg Ala Gln Ser Gln Glu Gly Trp Gly Arg Glu Arg
 1650 1655 1660
 Glu Gly Val Ile Thr Ile Glu Ser Gln Val His Pro Gln Ser Pro Leu
 1665 1670 1675 1680
 Cys Pro Leu Pro Gly Ser Ala Phe Thr Leu Ser Thr Pro Ser Ala Pro
 1685 1690 1695
 Gly Pro Leu Val Phe Thr Ala Leu Ser Pro Asp Ser Leu Gln Leu Ser
 1700 1705 1710
 Trp Glu Arg Pro Arg Arg Pro Asn Gly Asp Ile Val Gly Tyr Leu Val
 1715 1720 1725
 Thr Cys Glu Met Ala Gln Gly Gly Gly Pro Ala Thr Ala Phe Arg Val
 1730 1735 1740
 Asp Gly Asp Ser Pro Glu Ser Arg Leu Thr Val Pro Gly Leu Ser Glu
 1745 1750 1755 1760
 Asn Val Pro Tyr Lys Phe Lys Val Gln Ala Arg Thr Thr Glu Gly Phe
 1765 1770 1775
 Gly Pro Glu Arg Glu Gly Ile Ile Thr Ile Glu Ser Gln Asp Gly Gly
 1780 1785 1790
 Pro Phe Pro Gln Leu Gly Ser Arg Ala Gly Leu Phe Gln His Pro Leu
 1795 1800 1805
 Gln Ser Glu Tyr Ser Ser Ile Ser Thr Thr His Thr Ser Ala Thr Glu
 1810 1815 1820
 Pro Phe Leu Val Gly Pro Thr Leu Gly Ala Gln His Leu Glu Ala Gly
 1825 1830 1835 1840
 Gly Ser Leu Thr Arg His Val Thr Gln Glu Phe Val Ser Arg Thr Leu
 1845 1850 1855
 Thr Thr Ser Gly Thr Leu Ser Thr His Met Asp Gln Gln Phe Phe Gln
 1860 1865 1870
 Thr

<210> 7

<211> 5907

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence; Note =

synthetic construct

<400> 7

ggaccgctcga	ggcagcggga	ctgacccagc	tgggctcact	gtattaagaa	gcggacccgc	60
gacccggagc	gcccggggac	ccgatctggg	agcctggacg	ggtgcagcgc	gcagggaatgc	120
agtcgcctg	actcaccagc	gcctccttcc	tacctgcgcc	gcccgtccat	aaagcgctgc	180
tcgtcccgc	cgccgcgcgc	gccctgctgt	cccgcgggc	tcgcccgcgc	gctcagctcg	240
acccaacgca	gccaagtc	gaggtagtct	cactaaggag	gaggaggatg	gcagggccct	300
gttgcagccc	atgggtgaag	ctgctgctgc	tggcacgaat	gctgagtgcc	agcctccctg	360
gagacctggc	caaccgctgc	aagaaggctc	aggtgaagag	ctgtaccgag	tgcattccggg	420
tggacaagag	ctgtgcctac	tgcacagacg	agctgttcaa	ggagaggcgc	tgcaacaccc	480
aggcggacgt	tctggctgca	ggctgcaggg	gagagagcat	cctgggtcatg	gagagcagcc	540
ttgaaatcac	agagaacacc	cagatcgtca	ccagcctgca	ccgcagccag	gtatctcccc	600
aaggcctgca	agtccggctg	cgccgggggtg	aggagcgcac	gtttgtgttc	caggtctttg	660
agcccctgga	gagccccgtg	gatctgtata	tcctcatgga	cttctccaac	tccatgtctg	720
acgatctgga	caacctcaag	cagatggggc	agaacctggc	caagatcctg	cgccagctca	780
ccagcgacta	caccattgga	tttggaaggt	ttgtggacaa	agtcagcgtc	ccacagacag	840
acatgaggcc	cgagaaactg	aaggagccct	ggcccaacag	tgatcccccg	ttctccttca	900
agaacgttat	cagcttaacg	gagaatgtgg	aagaattctg	gaacaaactg	caaggagaac	960
gcattctcagg	caacctggac	gctcctgaag	ggggctttga	tgccatcctg	cagacagctg	1020
tgtgcacaag	ggacattggc	tggaggggctg	acagcaccca	cctgctgggtg	ttctccaccg	1080
agtctgcctt	ccactacgag	gctgatgggtg	ccaacgttct	ggccggcatc	atgaaccgca	1140
atgatgagaa	atgccacctg	gacgcctcgg	gcgcctacac	ccaatacaag	acacaggact	1200
acccatcagt	gcccacgctg	gttcgcctgc	ttgccaagca	taacatcatc	cccatctttg	1260
ctgtcaccaa	ctactcttac	agctactatg	agaagctcca	taagtatttc	ccgtctcct	1320
ctctgggcgt	cctgcaggag	gattcatcca	acatcgtgga	gctgctggag	gaggccttct	1380
atcgaattcg	ctccaacctg	gacatccggg	ctctggacag	ccccagaggc	ctgagaacag	1440
aggtcacctc	cgatactctc	cagaagacgg	agactgggtc	ctttcacatc	aagcgggggg	1500
aagtgggcac	atacaatgtg	catctccggg	cagtggagga	catagatggg	acacatgtgt	1560
gccagctggc	taaagaagac	caagggggca	acatccacct	gaaacctcc	ttctctgatg	1620
gcctccggat	ggacgcgagt	gtgatctgtg	acgtgtgccc	ctgtgagctg	caaaaggaag	1680
ttcgatcagc	tcgctgtcac	ttcagaggag	acttcatgtg	tggacactgt	gtgtgcaatg	1740
agggctggag	tggcaaaacc	tgcaactgct	ccaccggctc	tctgagtgc	acacagccct	1800
gcctgcgtga	gggtgaggac	aaaccgtgct	cgggccacgg	cgagtgccag	tgccgacgct	1860
gtgtgtgcta	tgggtgaaggc	cgctacgagg	gtcacttctg	cgagtatgac	aacttccagt	1920
gtccccggac	ctctggattc	ctgtgcaatg	accggggacg	ctgttctatg	ggagagtgtg	1980
tgtgtgagcc	tgggttgga	ggccgcagct	gcgactgtcc	cctcagcaat	gccacctgca	2040
tcgatagcaa	cgggggcatc	tgcaacggcc	gaggctactg	tgagtgtggc	cgttgtcact	2100
gcaaccagca	gtcgtcttac	acggacacca	cctgtgagat	caactactct	gcgatactgg	2160
gtctctgtga	ggatctccgc	tcctgcgtac	agtgccaggc	ctggggcacc	ggggagaaga	2220
aagggcgcg	gtgtgacgat	tgccccctta	aagtcaagat	ggtagacgag	cttaagaaag	2280
aagagggtgg	ggagtactgc	tccttccggg	atgaggatga	cgactgcact	tacagctaca	2340
acgtggaggg	cgacggcagc	cctggggcca	acagcacagt	cctgggtccac	aaaaagaaag	2400
actgcctccc	ggctccttcc	tgggtggctca	tccccctgct	catcttctct	ctgttgctcc	2460
tggcgttgct	tctgctgctc	tgctggaaat	actgtgcctg	ctgcaaagcc	tgccctggggc	2520
ttcttccctg	ctgcaaccga	ggtcacatgg	tgggctttaa	ggaagatcac	tatatgcttc	2580
gggagaacct	gatggcctct	gaccacctgg	acacgcccac	gctacgaagc	gggaacctca	2640
agggacgaga	cacagtccgc	tgggaagatca	ccaacaatgt	gcagcgcctt	ggcttttgcca	2700
cccatgccgc	cagcaccagc	cccacggagc	tcgtacccta	cgggctgtcc	ctgcgccttg	2760
gcccctctg	cactgagaac	cttatgaagc	cgggcacccg	agagtgtgac	cagctacgcc	2820
aggagggtgga	ggaaaatctg	aatgagggtgt	atagacagggt	cagcggcgca	cacaagctcc	2880
agcagacgaa	gttccgacag	cagcccaacg	ccgggaaaaa	gcaagaccac	accattgttg	2940
acacagtgtt	gctggcgccc	cgctccgcca	agcagatgct	gctgaagctg	acagagaagc	3000
aggtggagca	ggggtccttc	catgaactga	aggtggcccc	tggctactac	actgtcacgg	3060
cagagcagga	tgcccggggc	atgggtggagt	tccaggaggg	cgtggagctg	gtggatgtgc	3120
gagtgcctct	cttcatccgg	cctgaggatg	atgatgagaa	gcagctgctg	gtggaggcca	3180
ttgatgtccc	tgtgagcact	gccaccttgc	gtcgccgtct	ggtaaacatc	accattatca	3240
aggaacaagc	tagtggggta	gtgtccttcg	agcagcctga	atactcgggtg	agtcgtggag	3300
accagggtggc	ccgcatccct	gtcatccggc	acatcctgga	caatggcaag	tcccagggtct	3360
cctatagcac	acaggataat	acagcacacg	gacaccggga	ttatgttccc	gtggaggggag	3420
agctgctgtt	ccatcctggg	gaaacctgga	aggagtgtga	ggtgaagcta	ctggagctgc	3480
aggagggtga	ctccctcctg	cgtggccgcg	aggtccgcgc	cttccaagtc	caactcagca	3540

15

```

acccaagtt cggagccgc ctgggccagc ccagcacaac caccgttatt ctcgatgaaa 3600
cggacaggag tctcataaat caaacacttt catcgccctcc gccaccccat ggagacctgg 3660
gcgccccaca gaaccccaat gccaaaggctg ccggatccag gaagatccat ttcaactggc 3720
tgccccctcc tggcaagcca atgggggtaca ggggtgaagta ctggatccag ggcgactctg 3780
aatctgaagc ccaccttcta gatagcaagg tgccctcagt ggaactcacc aacctgtatc 3840
cctattgcga ctacgaaatg aagggtgtgtg cctatggggc caaggggtgag gggccctata 3900
gctcactggg gtccctgccgc acccaccagg aagtaccacag tgagccaggg aggctggctt 3960
tcaatgtagt ctcttctacg gtgactcagc tgagctgggc agagccagct gagaccaatg 4020
gcgagatcac agcctacgag gtctgctatg gactgggtcaa tgaggacaac agaccattg 4080
gacctatgaa gaagggtgctc gtggacaacc ccaagaaccg gatgctgctc attgagaatc 4140
tgcgagattc ccagccatac cgatacacgg ttaaggcgcg caatggggca ggatggggac 4200
ccgagagaga ggctatcatc aacctggcta cacagcccaa gcggcccatg tccatcccta 4260
tcatcccaga catcccata gtggacgccc aggggtggaga agactacgaa aacttcctta 4320
tgtacagtga tgacgtcctg cgggtccccag ccagcagcca gaggcccagc gtttctgatg 4380
acactgagca cctgggtgaat ggccggatgg actttgccta tccaggcagc gccaaactccc 4440
tgcacagaat gactgcagcc aatgtggcct atggcacgca tctgagccca cacctgtccc 4500
accgagtgtc gagcacgtcc tccaccctta cccgggacta ccactctctg acacgcacag 4560
agcactccca ctcaggcaca cttcccaggg actactccac cctcacttcc ctttcctccc 4620
aagcctccct cctatctggg aagatgggag gagcaggctt ccgctgtcct ggactcttgg 4680
gtccttgagc cgggctcaca tgaagggtgt gcccgcatcc aggggttcac cagactctat 4740
aatcctggcc gggcagtcag cagcacctc ctgggggtaca ggattcccgt ggggctgtgg 4800
gtgtgcctga cacaccact cggtgtgtgt tctctgcctt ggggcgcacg tctttgaagg 4860
tgagctggca ggagccacag tgtgatcgga cgctgctggg ctacagtgtg gaataccagc 4920
tactaacgtg cgtcgagatg catcggtca acatccctaa ccctggccaa acctcggtgg 4980
tggtagagga tctcctgcct aactactctc atgtgttccg ggtacgggca cagagccagg 5040
agggctgggg tcgagagcga gaggggtgtc tcaccatcga gtcccagggt caccgcaga 5100
gccctctctg cccctgccca ggctcagcct tcaactctgag cacccccagc gcccaggac 5160
cactgggtgt cactgcccta agcccagact ccccgagct cagctgggag cggccgagga 5220
gccgcaatgg agatatcctt ggctacctgg tgacctgtga gatggcccaa ggaggagcac 5280
cagccaggac cttccgggtg gacggagaca accctgagag ccggttgact gtacctggcc 5340
tcagtgagaa cgttccttac aagttcaagg ttcaggccag gacgaccgag ggctttgggc 5400
cagagcgtga gggatatcat accatcgagt ctcagggttg agggcccttc ccacagctgg 5460
gcagcaattc tgggctcttc cagaaccag tgcaaagcga gttcagcagc gtgaccagca 5520
cgcacagcac cagactgag cccttcctca tggatggtct aacctgggg acccagcgcc 5580
tggaagcagg aggtccctc acccgcatg tgaccagga attcgtgacc cggaccttaa 5640
cggccagtgg ctctctcagc actcatatgg accaacagtt cttccaaacc tgaacctccc 5700
ccgcgccccca gccacctggg cccctccttg cctcctctcc tagcgcttc ttcctctgct 5760
gctctaccca cgagcttgct gaccacagag ccagcccctg tagtcagaga gcaggggtag 5820
gtgctgtcca ggaaccataa agtgggtaga ggtgatacaa ggtctttctg actgcatccc 5880
accctgggtc caatcccaca tgtaacc 5907

```

<210> 8

<211> 1466

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence; Note =
synthetic construct

<400> 8

```

Met Ala Gly Pro Cys Cys Ser Pro Trp Val Lys Leu Leu Leu Ala
 1             5             10             15
Arg Met Leu Ser Ala Ser Leu Pro Gly Asp Leu Ala Asn Arg Cys Lys
          20             25             30
Lys Ala Gln Val Lys Ser Cys Thr Glu Cys Ile Arg Val Asp Lys Ser
          35             40             45
Cys Ala Tyr Cys Thr Asp Glu Leu Phe Lys Glu Arg Arg Cys Asn Thr
          50             55             60

```

16

Gln	Ala	Asp	Val	Leu	Ala	Ala	Gly	Cys	Arg	Gly	Glu	Ser	Ile	Leu	Val
65					70					75					80
Met	Glu	Ser	Ser	Leu	Glu	Ile	Thr	Glu	Asn	Thr	Gln	Ile	Val	Thr	Ser
				85					90					95	
Leu	His	Arg	Ser	Gln	Val	Ser	Pro	Gln	Gly	Leu	Gln	Val	Arg	Leu	Arg
			100					105					110		
Arg	Gly	Glu	Glu	Arg	Thr	Phe	Val	Phe	Gln	Val	Phe	Glu	Pro	Leu	Glu
	115						120					125			
Ser	Pro	Val	Asp	Leu	Tyr	Ile	Leu	Met	Asp	Phe	Ser	Asn	Ser	Met	Ser
	130					135					140				
Asp	Asp	Leu	Asp	Asn	Leu	Lys	Gln	Met	Gly	Gln	Asn	Leu	Ala	Lys	Ile
145				150						155					160
Leu	Arg	Gln	Leu	Thr	Ser	Asp	Tyr	Thr	Ile	Gly	Phe	Gly	Lys	Phe	Val
				165					170					175	
Asp	Lys	Val	Ser	Val	Pro	Gln	Thr	Asp	Met	Arg	Pro	Glu	Lys	Leu	Lys
			180					185					190		
Glu	Pro	Trp	Pro	Asn	Ser	Asp	Pro	Pro	Phe	Ser	Phe	Lys	Asn	Val	Ile
	195					200						205			
Ser	Leu	Thr	Glu	Asn	Val	Glu	Glu	Phe	Trp	Asn	Lys	Leu	Gln	Gly	Glu
	210					215					220				
Arg	Ile	Ser	Gly	Asn	Leu	Asp	Ala	Pro	Glu	Gly	Gly	Phe	Asp	Ala	Ile
225				230						235					240
Leu	Gln	Thr	Ala	Val	Cys	Thr	Arg	Asp	Ile	Gly	Trp	Arg	Ala	Asp	Ser
				245					250					255	
Thr	His	Leu	Leu	Val	Phe	Ser	Thr	Glu	Ser	Ala	Phe	His	Tyr	Glu	Ala
			260					265					270		
Asp	Gly	Ala	Asn	Val	Leu	Ala	Gly	Ile	Met	Asn	Arg	Asn	Asp	Glu	Lys
	275						280					285			
Cys	His	Leu	Asp	Ala	Ser	Gly	Ala	Tyr	Thr	Gln	Tyr	Lys	Thr	Gln	Asp
	290					295					300				
Tyr	Pro	Ser	Val	Pro	Thr	Leu	Val	Arg	Leu	Leu	Ala	Lys	His	Asn	Ile
305				310						315					320
Ile	Pro	Ile	Phe	Ala	Val	Thr	Asn	Tyr	Ser	Tyr	Ser	Tyr	Tyr	Glu	Lys
				325					330					335	
Leu	His	Lys	Tyr	Phe	Pro	Val	Ser	Ser	Leu	Gly	Val	Leu	Gln	Glu	Asp
			340					345					350		
Ser	Ser	Asn	Ile	Val	Glu	Leu	Leu	Glu	Glu	Ala	Phe	Tyr	Arg	Ile	Arg
		355					360					365			
Ser	Asn	Leu	Asp	Ile	Arg	Ala	Leu	Asp	Ser	Pro	Arg	Gly	Leu	Arg	Thr
	370					375					380				
Glu	Val	Thr	Ser	Asp	Thr	Leu	Gln	Lys	Thr	Glu	Thr	Gly	Ser	Phe	His
385					390					395					400
Ile	Lys	Arg	Gly	Glu	Val	Gly	Thr	Tyr	Asn	Val	His	Leu	Arg	Ala	Val
				405					410					415	
Glu	Asp	Ile	Asp	Gly	Thr	His	Val	Cys	Gln	Leu	Ala	Lys	Glu	Asp	Gln
			420					425					430		
Gly	Gly	Asn	Ile	His	Leu	Lys	Pro	Ser	Phe	Ser	Asp	Gly	Leu	Arg	Met
		435					440					445			
Asp	Ala	Ser	Val	Ile	Cys	Asp	Val	Cys	Pro	Cys	Glu	Leu	Gln	Lys	Glu
	450					455					460				
Val	Arg	Ser	Ala	Arg	Cys	His	Phe	Arg	Gly	Asp	Phe	Met	Cys	Gly	His
465				470						475					480
Cys	Val	Cys	Asn	Glu	Gly	Trp	Ser	Gly	Lys	Thr	Cys	Asn	Cys	Ser	Thr
			485						490					495	
Gly	Ser	Leu	Ser	Asp	Thr	Gln	Pro	Cys	Leu	Arg	Glu	Gly	Glu	Asp	Lys
			500					505					510		
Pro	Cys	Ser	Gly	His	Gly	Glu	Cys	Gln	Cys	Gly	Arg	Cys	Val	Cys	Tyr
		515					520					525			
Gly	Glu	Gly	Arg	Tyr	Glu	Gly	His	Phe	Cys	Glu	Tyr	Asp	Asn	Phe	Gln
	530					535					540				
Cys	Pro	Arg	Thr	Ser	Gly	Phe	Leu	Cys	Asn	Asp	Arg	Gly	Arg	Cys	Ser
545					550					555					560

17

Met	Gly	Glu	Cys	Val	Cys	Glu	Pro	Gly	Trp	Thr	Gly	Arg	Ser	Cys	Asp	565	570	575
Cys	Pro	Leu	Ser	Asn	Ala	Thr	Cys	Ile	Asp	Ser	Asn	Gly	Gly	Ile	Cys	580	585	590
Asn	Gly	Arg	Gly	Tyr	Cys	Glu	Cys	Gly	Arg	Cys	His	Cys	Asn	Gln	Gln	595	600	605
Ser	Leu	Tyr	Thr	Asp	Thr	Thr	Cys	Glu	Ile	Asn	Tyr	Ser	Ala	Ile	Leu	610	615	620
Gly	Leu	Cys	Glu	Asp	Leu	Arg	Ser	Cys	Val	Gln	Cys	Gln	Ala	Trp	Gly	625	630	635
Thr	Gly	Glu	Lys	Lys	Gly	Arg	Ala	Cys	Asp	Asp	Cys	Pro	Phe	Lys	Val	645	650	655
Lys	Met	Val	Asp	Glu	Leu	Lys	Lys	Glu	Glu	Val	Val	Glu	Tyr	Cys	Ser	660	665	670
Phe	Arg	Asp	Glu	Asp	Asp	Asp	Cys	Thr	Tyr	Ser	Tyr	Asn	Val	Glu	Gly	675	680	685
Asp	Gly	Ser	Pro	Gly	Pro	Asn	Ser	Thr	Val	Leu	Val	His	Lys	Lys	Lys	690	695	700
Asp	Cys	Leu	Pro	Ala	Pro	Ser	Trp	Trp	Leu	Ile	Pro	Leu	Leu	Ile	Phe	705	710	715
Leu	Leu	Leu	Leu	Leu	Ala	Leu	Leu	Leu	Leu	Leu	Cys	Trp	Lys	Tyr	Cys	725	730	735
Ala	Cys	Cys	Lys	Ala	Cys	Leu	Gly	Leu	Leu	Pro	Cys	Cys	Asn	Arg	Gly	740	745	750
His	Met	Val	Gly	Phe	Lys	Glu	Asp	His	Tyr	Met	Leu	Arg	Glu	Asn	Leu	755	760	765
Met	Ala	Ser	Asp	His	Leu	Asp	Thr	Pro	Met	Leu	Arg	Ser	Gly	Asn	Leu	770	775	780
Lys	Gly	Arg	Asp	Thr	Val	Arg	Trp	Lys	Ile	Thr	Asn	Asn	Val	Gln	Arg	785	790	795
Pro	Gly	Phe	Ala	Thr	His	Ala	Ala	Ser	Thr	Ser	Pro	Thr	Glu	Leu	Val	805	810	815
Pro	Tyr	Gly	Leu	Ser	Leu	Arg	Leu	Gly	Arg	Leu	Cys	Thr	Glu	Asn	Leu	820	825	830
Met	Lys	Pro	Gly	Thr	Arg	Glu	Cys	Asp	Gln	Leu	Arg	Gln	Glu	Val	Glu	835	840	845
Glu	Asn	Leu	Asn	Glu	Val	Tyr	Arg	Gln	Val	Ser	Gly	Ala	His	Lys	Leu	850	855	860
Gln	Gln	Thr	Lys	Phe	Arg	Gln	Gln	Pro	Asn	Ala	Gly	Lys	Lys	Gln	Asp	865	870	875
His	Thr	Ile	Val	Asp	Thr	Val	Leu	Leu	Ala	Pro	Arg	Ser	Ala	Lys	Gln	885	890	895
Met	Leu	Leu	Lys	Leu	Thr	Glu	Lys	Gln	Val	Glu	Gln	Gly	Ser	Phe	His	900	905	910
Glu	Leu	Lys	Val	Ala	Pro	Gly	Tyr	Tyr	Thr	Val	Thr	Ala	Glu	Gln	Asp	915	920	925
Ala	Arg	Gly	Met	Val	Glu	Phe	Gln	Glu	Gly	Val	Glu	Leu	Val	Asp	Val	930	935	940
Arg	Val	Pro	Leu	Phe	Ile	Arg	Pro	Glu	Asp	Asp	Asp	Glu	Lys	Gln	Leu	945	950	955
Leu	Val	Glu	Ala	Ile	Asp	Val	Pro	Val	Ser	Thr	Ala	Thr	Leu	Gly	Arg	965	970	975
Arg	Leu	Val	Asn	Ile	Thr	Ile	Ile	Lys	Glu	Gln	Ala	Ser	Gly	Val	Val	980	985	990
Ser	Phe	Glu	Gln	Pro	Glu	Tyr	Ser	Val	Ser	Arg	Gly	Asp	Gln	Val	Ala	995	1000	1005
Arg	Ile	Pro	Val	Ile	Arg	His	Ile	Leu	Asp	Asn	Gly	Lys	Ser	Gln	Val	1010	1015	1020
Ser	Tyr	Ser	Thr	Gln	Asp	Asn	Thr	Ala	His	Gly	His	Arg	Asp	Tyr	Val	1025	1030	1035
Pro	Val	Glu	Gly	Glu	Leu	Leu	Phe	His	Pro	Gly	Glu	Thr	Trp	Lys	Glu	1045	1050	1055

18

Leu Gln Val Lys Leu Leu Glu Leu Gln Glu Val Asp Ser Leu Leu Arg
 1060 1065 1070
 Gly Arg Gln Val Arg Arg Phe Gln Val Gln Leu Ser Asn Pro Lys Phe
 1075 1080 1085
 Gly Ala Arg Leu Gly Gln Pro Ser Thr Thr Thr Val Ile Leu Asp Glu
 1090 1095 1100
 Thr Asp Arg Ser Leu Ile Asn Gln Thr Leu Ser Ser Pro Pro Pro Pro
 1105 1110 1115 1120
 His Gly Asp Leu Gly Ala Pro Gln Asn Pro Asn Ala Lys Ala Ala Gly
 1125 1130 1135
 Ser Arg Lys Ile His Phe Asn Trp Leu Pro Pro Pro Gly Lys Pro Met
 1140 1145 1150
 Gly Tyr Arg Val Lys Tyr Trp Ile Gln Gly Asp Ser Glu Ser Glu Ala
 1155 1160 1165
 His Leu Leu Asp Ser Lys Val Pro Ser Val Glu Leu Thr Asn Leu Tyr
 1170 1175 1180
 Pro Tyr Cys Asp Tyr Glu Met Lys Val Cys Ala Tyr Gly Ala Lys Gly
 1185 1190 1195 1200
 Glu Gly Pro Tyr Ser Ser Leu Val Ser Cys Arg Thr His Gln Glu Val
 1205 1210 1215
 Pro Ser Glu Pro Gly Arg Leu Ala Phe Asn Val Val Ser Ser Thr Val
 1220 1225 1230
 Thr Gln Leu Ser Trp Ala Glu Pro Ala Glu Thr Asn Gly Glu Ile Thr
 1235 1240 1245
 Ala Tyr Glu Val Cys Tyr Gly Leu Val Asn Glu Asp Asn Arg Pro Ile
 1250 1255 1260
 Gly Pro Met Lys Lys Val Leu Val Asp Asn Pro Lys Asn Arg Met Leu
 1265 1270 1275 1280
 Leu Ile Glu Asn Leu Arg Asp Ser Gln Pro Tyr Arg Tyr Thr Val Lys
 1285 1290 1295
 Ala Arg Asn Gly Ala Gly Trp Gly Pro Glu Arg Glu Ala Ile Ile Asn
 1300 1305 1310
 Leu Ala Thr Gln Pro Lys Arg Pro Met Ser Ile Pro Ile Ile Pro Asp
 1315 1320 1325
 Ile Pro Ile Val Asp Ala Gln Gly Gly Glu Asp Tyr Glu Asn Phe Leu
 1330 1335 1340
 Met Tyr Ser Asp Asp Val Leu Arg Ser Pro Ala Ser Ser Gln Arg Pro
 1345 1350 1355 1360
 Ser Val Ser Asp Asp Thr Glu His Leu Val Asn Gly Arg Met Asp Phe
 1365 1370 1375
 Ala Tyr Pro Gly Ser Ala Asn Ser Leu His Arg Met Thr Ala Ala Asn
 1380 1385 1390
 Val Ala Tyr Gly Thr His Leu Ser Pro His Leu Ser His Arg Val Leu
 1395 1400 1405
 Ser Thr Ser Ser Thr Leu Thr Arg Asp Tyr His Ser Leu Thr Arg Thr
 1410 1415 1420
 Glu His Ser His Ser Gly Thr Leu Pro Arg Asp Tyr Ser Thr Leu Thr
 1425 1430 1435 1440
 Ser Leu Ser Ser Gln Ala Ser Leu Leu Ser Gly Lys Met Gly Gly Ala
 1445 1450 1455
 Gly Phe Arg Cys Pro Gly Leu Leu Gly Pro
 1460 1465

<210> 9

<211> 2205

<212> DNA

<213> Artificial Sequence

<220>

 <223> Description of Artificial Sequence; Note =
 synthetic construct

<400> 9

atggcagggc	cctgttgacg	cccatgggtg	aagctgctgc	tgctggcacg	aatgctgagt	60
gccagcctcc	ctggagacct	ggccaaccgc	tgcaagaagg	ctcaggtgaa	gagctgtacc	120
gagtgcatcc	gggtggacaa	gagctgtgcc	tactgcacag	acgagctgtt	caaggagagg	180
cgctgcaaca	cccaggcgga	cgttctggct	gcaggctgca	ggggagagag	catcctggtc	240
atggagagca	gccttgaaat	cacagagAAC	acccagatcg	tcaccagcct	gcaccgcagc	300
caggtatctc	cccaaggcct	gcaagtccgg	ctgcggcggg	gtgaggagcg	cacgtttgtg	360
ttccaggtct	ttgagccctt	ggagagcccc	gtggatctgt	atatcctcat	ggacttctcc	420
aactccatgt	ctgacgatct	ggacaacctc	aagcagatgg	ggcagaacct	ggccaagatc	480
ctgcgccagc	tcaccagcga	ctacaccatt	ggatttggaa	agtttgtgga	caaagtcagc	540
gtcccacaga	cagacatgag	gcccagagaaa	ctgaaggagc	cctggcccaa	cagtgatccc	600
ccgttctcct	tcaagaacgt	tatcagctta	acggagaatg	tggaagaatt	ctggaacaaa	660
ctgcaaggag	aacgcattct	aggcaacctg	gacgctcctg	aagggggcct	tgatgccatc	720
ctgcagacag	ctgtgtgcac	aaggggacatt	ggctggaggg	ctgacagcac	ccacctgctg	780
gtgttctcca	ccgagtctgc	cttccactac	gaggctgatg	gtgccaacgt	tctggccggc	840
atcatgaacc	gcaatgatga	gaaatgccac	ctggacgcct	cgggcgccta	cacccaatac	900
aagacacagg	actacccatc	agtgcccacg	ctgggttcgcc	tgcttgccaa	gcataacatc	960
atccccatct	ttgctgtcac	caactactct	tacagctact	atgagaagct	ccataagtat	1020
ttccccgtct	cctctctggg	cgctctgcag	gaggattcat	ccaacatcgt	ggagctgctg	1080
gaggaggcct	tctatcgaat	tcgctccaac	ctggacatcc	gggctctgga	cagccccaga	1140
ggcctgagaa	cagaggtcac	ctccgatact	ctccagaaga	cggagactgg	gtcctttcac	1200
atcaagcggg	gggaagtggg	cacatacaat	gtgcatctcc	gggcagtgga	ggacatagat	1260
gggacacatg	tgtgccagct	ggctaaagaa	gaccaagggg	gcaacatcca	cctgaaaccc	1320
tccttctctg	atggcctccg	gatggacgcg	agtgtgatct	gtgacgtgtg	cccctgtgag	1380
ctgcaaaagg	aagttcgatc	agctcgctgt	cacttcagag	gagacttcat	gtgtggacac	1440
tgtgtgtgca	atgagggctg	gagtggcaaa	acctgcaact	gctccaccgg	ctctctgagt	1500
gacacacagc	cctgcctgcg	tgaggggtgag	gacaaaccgt	gctcgggcca	cggcgagtgc	1560
cagtgcggac	gctgtgtgtg	ctatgggtgaa	ggccgctacg	agggtcactt	ctgcgagtat	1620
gacaacttcc	agtgtccccg	gacctctgga	ttcctgtgca	atgaccgggg	acgctgttct	1680
atgggagagt	gtgtgtgtga	gcctgggttg	acaggccgca	gctgcgactg	ttccctcagc	1740
aatgccacct	gcacgatag	caacgggggg	atctgcaacg	gccgaggcta	ctgtgagtgt	1800
ggccgttgtc	actgcaacca	gcagtcgctc	tacacggaca	ccacctgtga	gatcaactac	1860
tctgcgatac	tgggtctctg	tgaggatctc	cgctcctgcg	tacagtgcc	ggcctggggc	1920
accggggaga	agaaagggcg	cgcgtgtgac	gattgcccct	ttaaagtcaa	gatggtagac	1980
gagcttaaga	aagaagaggt	ggtggagtac	tgctccttcc	gggatgagga	tgacgactgc	2040
acttacagct	acaacgtgga	gggcgacggc	agccctgggc	ccaacagcac	agtcctggtc	2100
cacaaaaaga	aagactgcct	cccggctcct	tcctgggtgg	tcatccccct	gctcatcttc	2160
ctcctgttgc	tcctggcggt	gcttctgctg	ctctgctgga	aatga		2205

<210> 10

<211> 734

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence; Note =
synthetic construct

<400> 10

Met	Ala	Gly	Pro	Cys	Cys	Ser	Pro	Trp	Val	Lys	Leu	Leu	Leu	Leu	Ala
1				5					10					15	
Arg	Met	Leu	Ser	Ala	Ser	Leu	Pro	Gly	Asp	Leu	Ala	Asn	Arg	Cys	Lys
		20						25					30		
Lys	Ala	Gln	Val	Lys	Ser	Cys	Thr	Glu	Cys	Ile	Arg	Val	Asp	Lys	Ser
		35					40					45			
Cys	Ala	Tyr	Cys	Thr	Asp	Glu	Leu	Phe	Lys	Glu	Arg	Arg	Cys	Asn	Thr
	50					55					60				
Gln	Ala	Asp	Val	Leu	Ala	Gly	Cys	Arg	Gly	Glu	Ser	Ile	Leu	Val	
65				70				75					80		
Met	Glu	Ser	Ser	Leu	Glu	Ile	Thr	Glu	Asn	Thr	Gln	Ile	Val	Thr	Ser
				85				90					95		

20

Leu	His	Arg	Ser	Gln	Val	Ser	Pro	Gln	Gly	Leu	Gln	Val	Arg	Leu	Arg
			100					105					110		
Arg	Gly	Glu	Glu	Arg	Thr	Phe	Val	Phe	Gln	Val	Phe	Glu	Pro	Leu	Glu
		115					120					125			
Ser	Pro	Val	Asp	Leu	Tyr	Ile	Leu	Met	Asp	Phe	Ser	Asn	Ser	Met	Ser
	130					135					140				
Asp	Asp	Leu	Asp	Asn	Leu	Lys	Gln	Met	Gly	Gln	Asn	Leu	Ala	Lys	Ile
145					150					155					160
Leu	Arg	Gln	Leu	Thr	Ser	Asp	Tyr	Thr	Ile	Gly	Phe	Gly	Lys	Phe	Val
				165					170						175
Asp	Lys	Val	Ser	Val	Pro	Gln	Thr	Asp	Met	Arg	Pro	Glu	Lys	Leu	Lys
			180					185					190		
Glu	Pro	Trp	Pro	Asn	Ser	Asp	Pro	Pro	Phe	Ser	Phe	Lys	Asn	Val	Ile
		195					200					205			
Ser	Leu	Thr	Glu	Asn	Val	Glu	Glu	Phe	Trp	Asn	Lys	Leu	Gln	Gly	Glu
	210					215					220				
Arg	Ile	Ser	Gly	Asn	Leu	Asp	Ala	Pro	Glu	Gly	Gly	Phe	Asp	Ala	Ile
225					230					235					240
Leu	Gln	Thr	Ala	Val	Cys	Thr	Arg	Asp	Ile	Gly	Trp	Arg	Ala	Asp	Ser
				245					250					255	
Thr	His	Leu	Leu	Val	Phe	Ser	Thr	Glu	Ser	Ala	Phe	His	Tyr	Glu	Ala
			260					265					270		
Asp	Gly	Ala	Asn	Val	Leu	Ala	Gly	Ile	Met	Asn	Arg	Asn	Asp	Glu	Lys
		275					280					285			
Cys	His	Leu	Asp	Ala	Ser	Gly	Ala	Tyr	Thr	Gln	Tyr	Lys	Thr	Gln	Asp
	290					295					300				
Tyr	Pro	Ser	Val	Pro	Thr	Leu	Val	Arg	Leu	Leu	Ala	Lys	His	Asn	Ile
305					310					315					320
Ile	Pro	Ile	Phe	Ala	Val	Thr	Asn	Tyr	Ser	Tyr	Ser	Tyr	Tyr	Glu	Lys
			325					330						335	
Leu	His	Lys	Tyr	Phe	Pro	Val	Ser	Ser	Leu	Gly	Val	Leu	Gln	Glu	Asp
			340					345					350		
Ser	Ser	Asn	Ile	Val	Glu	Leu	Leu	Glu	Glu	Ala	Phe	Tyr	Arg	Ile	Arg
		355					360					365			
Ser	Asn	Leu	Asp	Ile	Arg	Ala	Leu	Asp	Ser	Pro	Arg	Gly	Leu	Arg	Thr
	370					375					380				
Glu	Val	Thr	Ser	Asp	Thr	Leu	Gln	Lys	Thr	Glu	Thr	Gly	Ser	Phe	His
385					390					395					400
Ile	Lys	Arg	Gly	Glu	Val	Gly	Thr	Tyr	Asn	Val	His	Leu	Arg	Ala	Val
				405					410					415	
Glu	Asp	Ile	Asp	Gly	Thr	His	Val	Cys	Gln	Leu	Ala	Lys	Glu	Asp	Gln
			420					425					430		
Gly	Gly	Asn	Ile	His	Leu	Lys	Pro	Ser	Phe	Ser	Asp	Gly	Leu	Arg	Met
		435					440					445			
Asp	Ala	Ser	Val	Ile	Cys	Asp	Val	Cys	Pro	Cys	Glu	Leu	Gln	Lys	Glu
	450					455					460				
Val	Arg	Ser	Ala	Arg	Cys	His	Phe	Arg	Gly	Asp	Phe	Met	Cys	Gly	His
465					470					475					480
Cys	Val	Cys	Asn	Glu	Gly	Trp	Ser	Gly	Lys	Thr	Cys	Asn	Cys	Ser	Thr
			485					490						495	
Gly	Ser	Leu	Ser	Asp	Thr	Gln	Pro	Cys	Leu	Arg	Glu	Gly	Glu	Asp	Lys
		500						505					510		
Pro	Cys	Ser	Gly	His	Gly	Glu	Cys	Gln	Cys	Gly	Arg	Cys	Val	Cys	Tyr
		515					520					525			
Gly	Glu	Gly	Arg	Tyr	Glu	Gly	His	Phe	Cys	Glu	Tyr	Asp	Asn	Phe	Gln
	530					535					540				
Cys	Pro	Arg	Thr	Ser	Gly	Phe	Leu	Cys	Asn	Asp	Arg	Gly	Arg	Cys	Ser
545					550					555					560
Met	Gly	Glu	Cys	Val	Cys	Glu	Pro	Gly	Trp	Thr	Gly	Arg	Ser	Cys	Asp
			565					570						575	
Cys	Pro	Leu	Ser	Asn	Ala	Thr	Cys	Ile	Asp	Ser	Asn	Gly	Gly	Ile	Cys
			580					585					590		

21

Asn	Gly	Arg	Gly	Tyr	Cys	Glu	Cys	Gly	Arg	Cys	His	Cys	Asn	Gln	Gln
		595					600					605			
Ser	Leu	Tyr	Thr	Asp	Thr	Thr	Cys	Glu	Ile	Asn	Tyr	Ser	Ala	Ile	Leu
	610					615					620				
Gly	Leu	Cys	Glu	Asp	Leu	Arg	Ser	Cys	Val	Gln	Cys	Gln	Ala	Trp	Gly
625					630					635					640
Thr	Gly	Glu	Lys	Lys	Gly	Arg	Ala	Cys	Asp	Asp	Cys	Pro	Phe	Lys	Val
				645					650					655	
Lys	Met	Val	Asp	Glu	Leu	Lys	Lys	Glu	Glu	Val	Val	Glu	Tyr	Cys	Ser
			660					665					670		
Phe	Arg	Asp	Glu	Asp	Asp	Asp	Cys	Thr	Tyr	Ser	Tyr	Asn	Val	Glu	Gly
		675					680					685			
Asp	Gly	Ser	Pro	Gly	Pro	Asn	Ser	Thr	Val	Leu	Val	His	Lys	Lys	Lys
	690					695					700				
Asp	Cys	Leu	Pro	Ala	Pro	Ser	Trp	Trp	Leu	Ile	Pro	Leu	Leu	Ile	Phe
705					710					715					720
Leu	Leu	Leu	Leu	Leu	Ala	Leu	Leu	Leu	Leu	Leu	Cys	Trp	Lys		
				725					730						

<210> 11

<211> 3579

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence; Note =
synthetic construct

<400> 11

atgcctgcgc	tctggctcag	ctgctgcctc	ggtgtcgcgc	tcctgctgcc	cgccagccag	60
gccacctcca	ggagggaagt	ctgtgattgc	aatgggaagt	ccaggcaatg	tgtctttgat	120
caggagctcc	atcgacaagc	aggcagcggg	ttccgttgcc	tcaactgcaa	tgacaataca	180
gcgggggttc	actgcgagcg	gtcgagggag	gggttttacc	agcatcagag	caagagccgc	240
tgcctaccct	gcaactgcca	ctcaaagggt	tccctcagtg	ctggatgtga	caactctgga	300
caatgcaggt	gtaagccagg	tgtgacagga	caaagatgtg	accagtgtca	gccaggcttc	360
catatgctca	ccgatgctgg	atgcacccga	gaccaggggc	aactagattc	caagtgtgac	420
tgtgacccag	ctggcatctc	tggaccctgt	gattctggcc	gatgtgtctg	caaaccagcc	480
gtcactggag	agcgtgtga	taggtgccga	ccacgtgact	atcatctgga	ccgggcaaac	540
cctgagggct	gtacccagtg	tttctgctat	gggcattcag	ccagctgcca	cgctctgcc	600
gacttcagtg	tccacaaaat	cacttcaact	ttcagtcagg	atgtggatgg	ttggaaggcg	660
gttcagagaa	acggggcacc	tgcaaaactc	cactggtcac	agcgccatcg	ggacgtgttt	720
agttctgccc	gaagatcaga	ccccgtctat	ttcgtggccc	ctgccaaaat	cctcggtaac	780
cagcaagtga	gttacgggca	gagcctgtct	tttgactacc	gcgtggacag	aggaggtaga	840
cagccgtctg	cctacgatgt	gatcctggaa	ggtgctggtc	tacagatcag	agctcctctg	900
atggctccag	gcaagacact	tccttgtggg	atcacaaaga	cttacacatt	cagactgaat	960
gaacatccaa	gcagtcactg	gagtcctccg	ctgagttatt	tcgaatatcg	aaggttactg	1020
cggaacctca	cagccctcct	gatgatccga	gctacgtacg	gagaatatag	tacagggtag	1080
attgataacg	tgaccctggg	ttcagcccgc	cctgtccttg	gagccccagc	cccttggggt	1140
gaacgttgtg	tatgcctgct	ggggtacaag	ggacaattct	gccaggaatg	tgcttctggg	1200
tacaaaagag	attcggcaag	attgggcgct	tttggcgcct	gtgttccctg	taactgccaa	1260
ggggaggggg	cctgtgatec	agacacggga	gattgctact	cgggggacga	gaatcctgac	1320
attgagtgtg	ctgactgtcc	catcggtttc	tacaatgacc	cacatgaccc	ccgcagctgc	1380
aagccatgtc	cctgtcacaa	tgggttcagc	tgttcagtg	tgcttgagac	agaggagggt	1440
gtgtgttaaca	actgtccccc	tgggggtcaca	ggtgcccgct	gtgagctctg	tgctgatggc	1500
ttctttgggg	atcccttttg	ggaacatggc	ccagtgaggc	cttgtcaacg	ctgccaatgc	1560
aacaacaacg	tggaccccaa	tgcctctggg	aactgtgacc	agttgacagg	cagatgcttg	1620
aaatgtatct	acaacacggc	cggtgtctac	tgtgaccagt	gcaaagcagg	ttacttttga	1680
gacctattgg	ctcccaaccc	agcagacaag	tgtcgagctt	gcaactgcag	ccccatgggt	1740
gcggagcctg	gagagtgtcg	aggtgatggc	agctgtgttt	gcaagccagg	ctttggcgcc	1800
ttcaactgtg	atcacgcagc	cctaaccagt	tgtcctgctt	gctacaatca	agtgaagatt	1860
cagatggacc	agtttaccca	gcagctccag	agcctggagg	ccctgggtttc	aaaggctcag	1920
ggtgggtgggtg	gtgggtgggtac	agtcccagtg	cagctggaag	gcaggatcga	gcaggctgag	1980

```

caggcccttc aggacattct gggagaagct cagatttcag aaggggcaat gagagccgtt 2040
gctgtccggc tggccaaggc aaggagccaa gagaacgact acaagacccg cctggatgac 2100
ctcaagatga ctgcagaaag gatccggggc ctgggcagtc agcatcagaa cagagttcag 2160
gatacgagca gactcatctc tcagatgcgc ctgagtctgg caggaagcga agctctcttg 2220
gaaaacacta atatccattc ttctgagcac tacgtggggc cgaatgattt taaaagtctg 2280
gctcaggagg ctacaagaaa ggcagacagc cacgctgagt cagctaacgc aatgaagcaa 2340
ctagcaaggg aaactgagga ctactccaaa caagcacttt cattggcccg caagctcttg 2400
agtggaggag gcggaagtgg ctcttggggc agctccgtgg tacaagggtc tatgggaaaa 2460
ttagagaaaa ccaagtcctc gagccagcag ctgtcattgg agggcaccca agccgacatt 2520
gaagctgata ggtcgtatca gcacagtctc cgcctcctgg attctgcctc tcagcttcag 2580
ggagtcagtg atctgtcctt tcagggtgaa gcaaagagga tcagacaaaa ggctgattct 2640
ctctcaaacc tggtgaccag acaaacggat gcattcacgc gtgtgcgaaa caatctgggg 2700
aactgggaaa aagaaacacg gcagctttta cagactggaa aggataggag acagacttca 2760
gatcagctgc tttcccgtgc caaccttgct aaaaacagag cccaagaagc gctaagtatg 2820
ggcaatgcca ctttttatga agttgagaac atcctgaaga acctccgaga gtttgatctg 2880
caggttgaag acagaaaagc agaggctgaa gaggccatga agagactctc ctctattagc 2940
cagaaggttg cggatgccag tgacaagacc cagcaagcag aaacggccct ggggagcgcc 3000
actgccgaca cccaacgggc aaagaacgca gctagggagg ccctggagat cagcagcgag 3060
atagagctgg agataggagg tctgaacttg gaagctaata tgacagcaga tggggccttg 3120
gccatggaga aagggactgc cactctgaag agcgagatga gagagatgat tgagctggcc 3180
agaaaggagc tggagtttga cacggataag gacacggtgc agctgggtgat tactgaagcc 3240
cagcaagctg atgccagagc cacgagtgcc ggagttacca tccaagacac rctcaacaca 3300
ttggacggca tcctacacct catagaccag cctggcagtg tggatgaaga agggatgatg 3360
ctattagaac aagggtcttt ccaagccaag acccagatca acagtcgact tcggcccttg 3420
atgtctgacc tggaggagag ggtgcgtcgg cagaggaacc acctccatct gctggagact 3480
agcatagatg gaattcttgc tgatgtgaag aacctggaga acattcgaga caacctgccc 3540
ccaggctgct acaataccca agctcttgag caacagtga 3579

```

<210> 12

<211> 1192

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence; Note =
synthetic construct

<400> 12

```

Met Pro Ala Leu Trp Leu Ser Cys Cys Leu Gly Val Ala Leu Leu Leu
 1          5          10          15
Pro Ala Ser Gln Ala Thr Ser Arg Arg Glu Val Cys Asp Cys Asn Gly
 20          25          30
Lys Ser Arg Gln Cys Val Phe Asp Gln Glu Leu His Arg Gln Ala Gly
 35          40          45
Ser Gly Phe Arg Cys Leu Asn Cys Asn Asp Asn Thr Ala Gly Val His
 50          55          60
Cys Glu Arg Ser Arg Glu Gly Phe Tyr Gln His Gln Ser Lys Ser Arg
 65          70          75          80
Cys Leu Pro Cys Asn Cys His Ser Lys Gly Ser Leu Ser Ala Gly Cys
 85          90          95
Asp Asn Ser Gly Gln Cys Arg Cys Lys Pro Gly Val Thr Gly Gln Arg
100          105          110
Cys Asp Gln Cys Gln Pro Gly Phe His Met Leu Thr Asp Ala Gly Cys
115          120          125
Thr Arg Asp Gln Gly Gln Leu Asp Ser Lys Cys Asp Cys Asp Pro Ala
130          135          140
Gly Ile Ser Gly Pro Cys Asp Ser Gly Arg Cys Val Cys Lys Pro Ala
145          150          155          160
Val Thr Gly Glu Arg Cys Asp Arg Cys Arg Pro Arg Asp Tyr His Leu
165          170          175
Asp Arg Ala Asn Pro Glu Gly Cys Thr Gln Cys Phe Cys Tyr Gly His
180          185          190

```

Ser	Ala	Ser	Cys	His	Ala	Ser	Ala	Asp	Phe	Ser	Val	His	Lys	Ile	Thr
	195						200					205			
Ser	Thr	Phe	Ser	Gln	Asp	Val	Asp	Gly	Trp	Lys	Ala	Val	Gln	Arg	Asn
	210						215				220				
Gly	Ala	Pro	Ala	Lys	Leu	His	Trp	Ser	Gln	Arg	His	Arg	Asp	Val	Phe
225					230					235					240
Ser	Ser	Ala	Arg	Arg	Ser	Asp	Pro	Val	Tyr	Phe	Val	Ala	Pro	Ala	Lys
				245					250					255	
Phe	Leu	Gly	Asn	Gln	Gln	Val	Ser	Tyr	Gly	Gln	Ser	Leu	Ser	Phe	Asp
			260					265					270		
Tyr	Arg	Val	Asp	Arg	Gly	Gly	Arg	Gln	Pro	Ser	Ala	Tyr	Asp	Val	Ile
		275					280					285			
Leu	Glu	Gly	Ala	Gly	Leu	Gln	Ile	Arg	Ala	Pro	Leu	Met	Ala	Pro	Gly
	290					295					300				
Lys	Thr	Leu	Pro	Cys	Gly	Ile	Thr	Lys	Thr	Tyr	Thr	Phe	Arg	Leu	Asn
305					310					315					320
Glu	His	Pro	Ser	Ser	His	Trp	Ser	Pro	Gln	Leu	Ser	Tyr	Phe	Glu	Tyr
				325					330					335	
Arg	Arg	Leu	Leu	Arg	Asn	Leu	Thr	Ala	Leu	Leu	Met	Ile	Arg	Ala	Thr
			340					345					350		
Tyr	Gly	Glu	Tyr	Ser	Thr	Gly	Tyr	Ile	Asp	Asn	Val	Thr	Leu	Val	Ser
		355					360					365			
Ala	Arg	Pro	Val	Leu	Gly	Ala	Pro	Ala	Pro	Trp	Val	Glu	Arg	Cys	Val
	370					375					380				
Cys	Leu	Leu	Gly	Tyr	Lys	Gly	Gln	Phe	Cys	Gln	Glu	Cys	Ala	Ser	Gly
385					390					395					400
Tyr	Lys	Arg	Asp	Ser	Ala	Arg	Leu	Gly	Ala	Phe	Gly	Ala	Cys	Val	Pro
				405					410					415	
Cys	Asn	Cys	Gln	Gly	Glu	Gly	Ala	Cys	Asp	Pro	Asp	Thr	Gly	Asp	Cys
			420					425					430		
Tyr	Ser	Gly	Asp	Glu	Asn	Pro	Asp	Ile	Glu	Cys	Ala	Asp	Cys	Pro	Ile
		435					440					445			
Gly	Phe	Tyr	Asn	Asp	Pro	His	Asp	Pro	Arg	Ser	Cys	Lys	Pro	Cys	Pro
	450					455					460				
Cys	His	Asn	Gly	Phe	Ser	Cys	Ser	Val	Met	Pro	Glu	Thr	Glu	Glu	Val
465					470					475					480
Val	Cys	Asn	Asn	Cys	Pro	Pro	Gly	Val	Thr	Gly	Ala	Arg	Cys	Glu	Leu
				485					490					495	
Cys	Ala	Asp	Gly	Phe	Phe	Gly	Asp	Pro	Phe	Gly	Glu	His	Gly	Pro	Val
			500					505					510		
Arg	Pro	Cys	Gln	Arg	Cys	Gln	Cys	Asn	Asn	Asn	Val	Asp	Pro	Asn	Ala
		515					520					525			
Ser	Gly	Asn	Cys	Asp	Gln	Leu	Thr	Gly	Arg	Cys	Leu	Lys	Cys	Ile	Tyr
	530					535					540				
Asn	Thr	Ala	Gly	Val	Tyr	Cys	Asp	Gln	Cys	Lys	Ala	Gly	Tyr	Phe	Gly
545					550					555					560
Asp	Pro	Leu	Ala	Pro	Asn	Pro	Ala	Asp	Lys	Cys	Arg	Ala	Cys	Asn	Cys
				565					570					575	
Ser	Pro	Met	Gly	Ala	Glu	Pro	Gly	Glu	Cys	Arg	Gly	Asp	Gly	Ser	Cys
			580					585					590		
Val	Cys	Lys	Pro	Gly	Phe	Gly	Ala	Phe	Asn	Cys	Asp	His	Ala	Ala	Leu
		595					600					605			
Thr	Ser	Cys	Pro	Ala	Cys	Tyr	Asn	Gln	Val	Lys	Ile	Gln	Met	Asp	Gln
						615					620				
Phe	Thr	Gln	Gln	Leu	Gln	Ser	Leu	Glu	Ala	Leu	Val	Ser	Lys	Ala	Gln
625					630					635					640
Gly	Gly	Gly	Gly	Gly	Gly	Thr	Val	Pro	Val	Gln	Leu	Glu	Gly	Arg	Ile
				645					650					655	
Glu	Gln	Ala	Glu	Gln	Ala	Leu	Gln	Asp	Ile	Leu	Gly	Glu	Ala	Gln	Ile
		660						665					670		
Ser	Glu	Gly	Ala	Met	Arg	Ala	Val	Ala	Val	Arg	Leu	Ala	Lys	Ala	Arg
		675					680					685			

Ser	Gln	Glu	Asn	Asp	Tyr	Lys	Thr	Arg	Leu	Asp	Asp	Leu	Lys	Met	Thr
690						695					700				
Ala	Glu	Arg	Ile	Arg	Ala	Leu	Gly	Ser	Gln	His	Gln	Asn	Arg	Val	Gln
705					710					715					720
Asp	Thr	Ser	Arg	Leu	Ile	Ser	Gln	Met	Arg	Leu	Ser	Leu	Ala	Gly	Ser
				725					730					735	
Glu	Ala	Leu	Leu	Glu	Asn	Thr	Asn	Ile	His	Ser	Ser	Glu	His	Tyr	Val
			740				745						750		
Gly	Pro	Asn	Asp	Phe	Lys	Ser	Leu	Ala	Gln	Glu	Ala	Thr	Arg	Lys	Ala
		755					760					765			
Asp	Ser	His	Ala	Glu	Ser	Ala	Asn	Ala	Met	Lys	Gln	Leu	Ala	Arg	Glu
	770					775					780				
Thr	Glu	Asp	Tyr	Ser	Lys	Gln	Ala	Leu	Ser	Leu	Ala	Arg	Lys	Leu	Leu
785					790					795					800
Ser	Gly	Gly	Gly	Gly	Ser	Gly	Ser	Trp	Asp	Ser	Ser	Val	Val	Gln	Gly
			805						810					815	
Leu	Met	Gly	Lys	Leu	Glu	Lys	Thr	Lys	Ser	Leu	Ser	Gln	Gln	Leu	Ser
			820					825					830		
Leu	Glu	Gly	Thr	Gln	Ala	Asp	Ile	Glu	Ala	Asp	Arg	Ser	Tyr	Gln	His
		835					840				845				
Ser	Leu	Arg	Leu	Leu	Asp	Ser	Ala	Ser	Gln	Leu	Gln	Gly	Val	Ser	Asp
	850					855					860				
Leu	Ser	Phe	Gln	Val	Glu	Ala	Lys	Arg	Ile	Arg	Gln	Lys	Ala	Asp	Ser
865					870					875					880
Leu	Ser	Asn	Leu	Val	Thr	Arg	Gln	Thr	Asp	Ala	Phe	Thr	Arg	Val	Arg
			885						890					895	
Asn	Asn	Leu	Gly	Asn	Trp	Glu	Lys	Glu	Thr	Arg	Gln	Leu	Leu	Gln	Thr
		900						905						910	
Gly	Lys	Asp	Arg	Arg	Gln	Thr	Ser	Asp	Gln	Leu	Leu	Ser	Arg	Ala	Asn
		915				920						925			
Leu	Ala	Lys	Asn	Arg	Ala	Gln	Glu	Ala	Leu	Ser	Met	Gly	Asn	Ala	Thr
	930				935						940				
Phe	Tyr	Glu	Val	Glu	Asn	Ile	Leu	Lys	Asn	Leu	Arg	Glu	Phe	Asp	Leu
945					950					955					960
Gln	Val	Glu	Asp	Arg	Lys	Ala	Glu	Ala	Glu	Glu	Ala	Met	Lys	Arg	Leu
			965						970					975	
Ser	Ser	Ile	Ser	Gln	Lys	Val	Ala	Asp	Ala	Ser	Asp	Lys	Thr	Gln	Gln
		980						985					990		
Ala	Glu	Thr	Ala	Leu	Gly	Ser	Ala	Thr	Ala	Asp	Thr	Gln	Arg	Ala	Lys
		995					1000					1005			
Asn	Ala	Ala	Arg	Glu	Ala	Leu	Glu	Ile	Ser	Ser	Glu	Ile	Glu	Leu	Glu
	1010					1015					1020				
Ile	Gly	Ser	Leu	Asn	Leu	Glu	Ala	Asn	Val	Thr	Ala	Asp	Gly	Ala	Leu
1025					1030					1035					1040
Ala	Met	Glu	Lys	Gly	Thr	Ala	Thr	Leu	Lys	Ser	Glu	Met	Arg	Glu	Met
			1045						1050					1055	
Ile	Glu	Leu	Ala	Arg	Lys	Glu	Leu	Glu	Phe	Asp	Thr	Asp	Lys	Asp	Thr
		1060						1065					1070		
Val	Gln	Leu	Val	Ile	Thr	Glu	Ala	Gln	Gln	Ala	Asp	Ala	Arg	Ala	Thr
	1075						1080				1085				
Ser	Ala	Gly	Val	Thr	Ile	Gln	Asp	Thr	Leu	Asn	Thr	Leu	Asp	Gly	Ile
	1090					1095					1100				
Leu	His	Leu	Ile	Asp	Gln	Pro	Gly	Ser	Val	Asp	Glu	Glu	Gly	Met	Met
1105					1110					1115					1120
Leu	Leu	Glu	Gln	Gly	Leu	Phe	Gln	Ala	Lys	Thr	Gln	Ile	Asn	Ser	Arg
			1125						1130					1135	
Leu	Arg	Pro	Leu	Met	Ser	Asp	Leu	Glu	Glu	Arg	Val	Arg	Arg	Gln	Arg
		1140						1145					1150		
Asn	His	Leu	His	Leu	Leu	Glu	Thr	Ser	Ile	Asp	Gly	Ile	Leu	Ala	Asp
	1155					1160					1165				
Val	Lys	Asn	Leu	Glu	Asn	Ile	Arg	Asp	Asn	Leu	Pro	Pro	Gly	Cys	Tyr
1170						1175					1180				

Asn Thr Gln Ala Leu Glu Gln Gln
1185 1190

<210> 13
<211> 3582
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence; Note =
synthetic construct

<400> 13
atgcctgcgc tctggctggg ctgctgcctc tgcttctcgc tctctctgcc cgcagcccg 60
gccacctcca ggaggggaagt ctgtgattgc aatgggaagt ccaggcagtg tatctttgat 120
cgggaaacttc acagacaaac tggtaatgga ttccgctgcc tcaactgcaa tgacaacact 180
gatggcattc actgcgagaa gtgcaagaat ggcttttacc ggcacagaga aagggaccgc 240
tgtttgccct gcaattgtaa ctccaaagg tctcttagtg ctogatgtga caactctgga 300
cgggtgcagct gtaaaccagg tgtgacagga gccagatgcg accgatgtct gccaggcttc 360
cacatgctca cggatgcggg gtgcacccaa gaccagagac tgctagactc caagtgtgac 420
tgtgacccag ctggcatcgc agggccctgt gacgcgggcc gctgtgtctg caagccagct 480
gttactggag aacgctgtga taggtgtcga tcaggttact ataactctgga tggggggaac 540
cctgagggct gtacccagtg tttctgctat gggcattcag ccagctgccg cagctctgca 600
gaatacagtg tccataagat cacctctacc ttctcatcaag atgttgatgg ctggaaggct 660
gtccaacgaa atgggtctcc tgcaaagctc caatgggtcac agcgccatca agatgtgttt 720
agctcagccc aacgactaga cctgtctat tttgtggctc ctgccaaatt tcttgggaa 780
caacaggtga gctatgggca aagcctgtcc tttgactacc gtgtggacag aggaggcaga 840
caccatctg cccatgatgt gattctggaa ggtgctggtc tacggatcac agctcccttg 900
atgccacttg gcaagacact gccttgtggg ctaccaaga cttacacatt caggttaaat 960
gagcatccaa gcaataattg gagccccag ctgagttact ttgagtatcg aaggttactg 1020
cggaatctca cagccctccg catccgagct acatatggag aatacagtac tgggtacatt 1080
gacaatgtga ccttgatttc agcccgccct gtctctggag cccagcacc ctgggttgaa 1140
cagtgtatat gtctgtttgg gtacaagggg caattctgcc aggattgtgc ttctggctac 1200
aagagagatt cagcgagact ggggcctttt ggcacctgta ttccttgtaa ctgtcaaggg 1260
ggaggggctt gtgatccaga cacaggagat tgttattcag gggatgagaa tcttgacatt 1320
gagtgtgctg actgcccatt tggtttctac aacgatccgc acgacccccg cagctgcaag 1380
ccatgtccct gtcataacgg gttcagctgc tcagtgatgc cggagacgga ggaggtgggtg 1440
tgcaataact gccctcccgg ggtcacccgt gcccgctgtg agctctgtgc tgatggctac 1500
tttggggacc cctttgggtg acatggccca gtgaggcctt gtcagccctg tcaatgcaac 1560
aacaatgtgg accccagtgct ctctgggaat tgtgaccggc tgacaggcag gtgtttgaag 1620
tgtatccaca acacagccgg catctactgc gaccagtgc aagcaggcta cttcggggac 1680
ccattggctc ccaaccagc agacaagtgt cgagcttgca actgtaacct catgggctca 1740
gagcctgtag gatgtcgaag tgatggcacc tgtgttttgca agccaggatt tgggtggccc 1800
aactgtgagc atggagcatt cagctgtcca gcttgctata atcaagtga gattcagatg 1860
gatcagttta tgcagcagct tcagagaatg gaggccctga tttcaaagge tcagggtgggt 1920
gatggagtag tacctgatac agagctggaa ggcaggatgc agcaggctga gcaggccctt 1980
caggacattc tgagagatgc ccagatttca gaagggtgcta gcagatccct tggctctccag 2040
ttggccaagg tgaggagcca agagaacagc taccagagcc gcctggatga cctcaagatg 2100
actgtggaag gagttcgggc tctgggaagt cagtaccaga accgagttcg ggatactcac 2160
aggctcatca ctacagatgca gctgagcctg gcagaaagtg aagcttccct gggaaacact 2220
aacattcctg cctcagacca ctacgtgggg ccaaattggct ttaaaagtct ggctcaggag 2280
gccacaagat tagcagaaag ccacgttgag tcagccagta acatggagca actgacaagg 2340
gaaactgagg actattccaa acaagccctc tcaactggtgc gcaaggccct gcatgaagga 2400
gtcgggaagc gaagcggtag cccggacggg gctgtggtgc aagggcttgt ggaaaaattg 2460
gagaaaacca agtccctggc ccagcagttg acaaggaggg ccactcaagc ggaaattgaa 2520
gcagataggt cttatcagca cagtctccgc ctctggatt cagtgtctcg gcttcaggga 2580
gtcagtgatc agtcccttca ggtggaagaa gcaaagagga tcaaacaaaa agcggattca 2640
ctctcaacgc tggtaaccag gcatatggat gagttcaagc gtacacaaaa gaatctggga 2700
aactggaaag aagaagcaca gcagctctta cagaatggaa aaagtgggag agagaaatca 2760
gatcagctgc tttcccgctg caatcttgct aaaagcagag cacaagaagc actgagtatg 2820
ggcaatgcc a ttttttatga agttgagagc atccttaaaa acctcagaga gtttgacctg 2880
cagggtggaca acagaaaagc agaagctgaa gaagccatga agagactctc ctacatcagc 2940

26

```

cagaagggttt cagatgccag tgacaagacc cagcaagcag aaagagccct ggggagcgct 3000
gctgctgatg cacagagggc aaagaatggg gccggggagg ccctggaaat ctccagtggag 3060
attgaacagg agattggggag tctgaacttg gaagccaatg tgacagcaga tggagccttg 3120
gccatggaaa agggactggc ctctctgaag agtgagatga gggagtgga aggagagctg 3180
gaaaggaagg agctggagtt tgacacgaat atggatgcag tacagatggg gattacagaa 3240
gcccagaagg ttgataccag agccaagaac gctgggggta caatccaaga cacactcaac 3300
acattagacg gcctcctgca tctgatggac cagcctctca gtgtagatga agaggggctg 3360
gtcttactgg agcagaagct ttcccagacc aagaccacga tcaacagcca actgcggccc 3420
atgatgtcag agctggaaga gagggcacgt cagcagaggg gccacctcca tttgctggag 3480
acaagcatag atgggattct ggctgatgtg aagaacttgg agaacattag ggacaacctg 3540
ccccaggct gctacaatac ccaggctctt gagcaacagt ga 3582

```

<210> 14

<211> 1193

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence; Note =
synthetic construct

<400> 14

```

Met Pro Ala Leu Trp Leu Gly Cys Cys Leu Cys Phe Ser Leu Leu Leu
 1      5      10      15
Pro Ala Ala Arg Ala Thr Ser Arg Arg Glu Val Cys Asp Cys Asn Gly
      20      25      30
Lys Ser Arg Gln Cys Ile Phe Asp Arg Glu Leu His Arg Gln Thr Gly
      35      40      45
Asn Gly Phe Arg Cys Leu Asn Cys Asn Asp Asn Thr Asp Gly Ile His
 50      55      60
Cys Glu Lys Cys Lys Asn Gly Phe Tyr Arg His Arg Glu Arg Asp Arg
 65      70      75      80
Cys Leu Pro Cys Asn Cys Asn Ser Lys Gly Ser Leu Ser Ala Arg Cys
      85      90      95
Asp Asn Ser Gly Arg Cys Ser Cys Lys Pro Gly Val Thr Gly Ala Arg
      100      105      110
Cys Asp Arg Cys Leu Pro Gly Phe His Met Leu Thr Asp Ala Gly Cys
      115      120      125
Thr Gln Asp Gln Arg Leu Leu Asp Ser Lys Cys Asp Cys Asp Pro Ala
      130      135      140
Gly Ile Ala Gly Pro Cys Asp Ala Gly Arg Cys Val Cys Lys Pro Ala
      145      150      155      160
Val Thr Gly Glu Arg Cys Asp Arg Cys Arg Ser Gly Tyr Tyr Asn Leu
      165      170      175
Asp Gly Gly Asn Pro Glu Gly Cys Thr Gln Cys Phe Cys Tyr Gly His
      180      185      190
Ser Ala Ser Cys Arg Ser Ser Ala Glu Tyr Ser Val His Lys Ile Thr
      195      200      205
Ser Thr Phe His Gln Asp Val Asp Gly Trp Lys Ala Val Gln Arg Asn
      210      215      220
Gly Ser Pro Ala Lys Leu Gln Trp Ser Gln Arg His Gln Asp Val Phe
      225      230      235      240
Ser Ser Ala Gln Arg Leu Asp Pro Val Tyr Phe Val Ala Pro Ala Lys
      245      250      255
Phe Leu Gly Asn Gln Gln Val Ser Tyr Gly Gln Ser Leu Ser Phe Asp
      260      265      270
Tyr Arg Val Asp Arg Gly Gly Arg His Pro Ser Ala His Asp Val Ile
      275      280      285
Leu Glu Gly Ala Gly Leu Arg Ile Thr Ala Pro Leu Met Pro Leu Gly
      290      295      300
Lys Thr Leu Pro Cys Gly Leu Thr Lys Thr Tyr Thr Phe Arg Leu Asn
      305      310      315      320

```

27

Glu	His	Pro	Ser	Asn	Asn	Trp	Ser	Pro	Gln	Leu	Ser	Tyr	Phe	Glu	Tyr
				325					330					335	
Arg	Arg	Leu	Leu	Arg	Asn	Leu	Thr	Ala	Leu	Arg	Ile	Arg	Ala	Thr	Tyr
			340					345					350		
Gly	Glu	Tyr	Ser	Thr	Gly	Tyr	Ile	Asp	Asn	Val	Thr	Leu	Ile	Ser	Ala
		355					360					365			
Arg	Pro	Val	Ser	Gly	Ala	Pro	Ala	Pro	Trp	Val	Glu	Gln	Cys	Ile	Cys
	370					375					380				
Pro	Val	Gly	Tyr	Lys	Gly	Gln	Phe	Cys	Gln	Asp	Cys	Ala	Ser	Gly	Tyr
385					390					395					400
Lys	Arg	Asp	Ser	Ala	Arg	Leu	Gly	Pro	Phe	Gly	Thr	Cys	Ile	Pro	Cys
				405					410					415	
Asn	Cys	Gln	Gly	Gly	Gly	Ala	Cys	Asp	Pro	Asp	Thr	Gly	Asp	Cys	Tyr
			420					425					430		
Ser	Gly	Asp	Glu	Asn	Pro	Asp	Ile	Glu	Cys	Ala	Asp	Cys	Pro	Ile	Gly
		435					440					445			
Phe	Tyr	Asn	Asp	Pro	His	Asp	Pro	Arg	Ser	Cys	Lys	Pro	Cys	Pro	Cys
	450					455					460				
His	Asn	Gly	Phe	Ser	Cys	Ser	Val	Met	Pro	Glu	Thr	Glu	Glu	Val	Val
465					470					475					480
Cys	Asn	Asn	Cys	Pro	Pro	Gly	Val	Thr	Gly	Ala	Arg	Cys	Glu	Leu	Cys
				485					490					495	
Ala	Asp	Gly	Tyr	Phe	Gly	Asp	Pro	Phe	Gly	Glu	His	Gly	Pro	Val	Arg
			500					505					510		
Pro	Cys	Gln	Pro	Cys	Gln	Cys	Asn	Asn	Asn	Val	Asp	Pro	Ser	Ala	Ser
		515					520					525			
Gly	Asn	Cys	Asp	Arg	Leu	Thr	Gly	Arg	Cys	Leu	Lys	Cys	Ile	His	Asn
	530					535					540				
Thr	Ala	Gly	Ile	Tyr	Cys	Asp	Gln	Cys	Lys	Ala	Gly	Tyr	Phe	Gly	Asp
545					550					555					560
Pro	Leu	Ala	Pro	Asn	Pro	Ala	Asp	Lys	Cys	Arg	Ala	Cys	Asn	Cys	Asn
				565				570					575		
Pro	Met	Gly	Ser	Glu	Pro	Val	Gly	Cys	Arg	Ser	Asp	Gly	Thr	Cys	Val
			580					585					590		
Cys	Lys	Pro	Gly	Phe	Gly	Gly	Pro	Asn	Cys	Glu	His	Gly	Ala	Phe	Ser
		595					600					605			
Cys	Pro	Ala	Cys	Tyr	Asn	Gln	Val	Lys	Ile	Gln	Met	Asp	Gln	Phe	Met
	610					615					620				
Gln	Gln	Leu	Gln	Arg	Met	Glu	Ala	Leu	Ile	Ser	Lys	Ala	Gln	Gly	Gly
625					630					635					640
Asp	Gly	Val	Val	Pro	Asp	Thr	Glu	Leu	Glu	Gly	Arg	Met	Gln	Gln	Ala
				645				650					655		
Glu	Gln	Ala	Leu	Gln	Asp	Ile	Leu	Arg	Asp	Ala	Gln	Ile	Ser	Glu	Gly
			660					665					670		
Ala	Ser	Arg	Ser	Leu	Gly	Leu	Gln	Leu	Ala	Lys	Val	Arg	Ser	Gln	Glu
		675					680					685			
Asn	Ser	Tyr	Gln	Ser	Arg	Leu	Asp	Asp	Leu	Lys	Met	Thr	Val	Glu	Arg
	690					695					700				
Val	Arg	Ala	Leu	Gly	Ser	Gln	Tyr	Gln	Asn	Arg	Val	Arg	Asp	Thr	His
705					710					715					720
Arg	Leu	Ile	Thr	Gln	Met	Gln	Leu	Ser	Leu	Ala	Glu	Ser	Glu	Ala	Ser
				725					730					735	
Leu	Gly	Asn	Thr	Asn	Ile	Pro	Ala	Ser	Asp	His	Tyr	Val	Gly	Pro	Asn
			740					745					750		
Gly	Phe	Lys	Ser	Leu	Ala	Gln	Glu	Ala	Thr	Arg	Leu	Ala	Glu	Ser	His
		755					760					765			
Val	Glu	Ser	Ala	Ser	Asn	Met	Glu	Gln	Leu	Thr	Arg	Glu	Thr	Glu	Asp
	770					775					780				
Tyr	Ser	Lys	Gln	Ala	Leu	Ser	Leu	Val	Arg	Lys	Ala	Leu	His	Glu	Gly
785					790					795					800
Val	Gly	Ser	Gly	Ser	Gly	Ser	Pro	Asp	Gly	Ala	Val	Val	Gln	Gly	Leu
				805					810					815	

28

Val Glu Lys Leu Glu Lys Thr Lys Ser Leu Ala Gln Gln Leu Thr Arg
 820 825 830
 Glu Ala Thr Gln Ala Glu Ile Glu Ala Asp Arg Ser Tyr Gln His Ser
 835 840 845
 Leu Arg Leu Leu Asp Ser Val Ser Arg Leu Gln Gly Val Ser Asp Gln
 850 855 860
 Ser Phe Gln Val Glu Glu Ala Lys Arg Ile Lys Gln Lys Ala Asp Ser
 865 870 875 880
 Leu Ser Thr Leu Val Thr Arg His Met Asp Glu Phe Lys Arg Thr Gln
 885 890 895
 Lys Asn Leu Gly Asn Trp Lys Glu Glu Ala Gln Gln Leu Leu Gln Asn
 900 905 910
 Gly Lys Ser Gly Arg Glu Lys Ser Asp Gln Leu Leu Ser Arg Ala Asn
 915 920 925
 Leu Ala Lys Ser Arg Ala Gln Glu Ala Leu Ser Met Gly Asn Ala Thr
 930 935 940
 Phe Tyr Glu Val Glu Ser Ile Leu Lys Asn Leu Arg Glu Phe Asp Leu
 945 950 955 960
 Gln Val Asp Asn Arg Lys Ala Glu Ala Glu Glu Ala Met Lys Arg Leu
 965 970 975
 Ser Tyr Ile Ser Gln Lys Val Ser Asp Ala Ser Asp Lys Thr Gln Gln
 980 985 990
 Ala Glu Arg Ala Leu Gly Ser Ala Ala Ala Asp Ala Gln Arg Ala Lys
 995 1000 1005
 Asn Gly Ala Gly Glu Ala Leu Glu Ile Ser Ser Glu Ile Glu Gln Glu
 1010 1015 1020
 Ile Gly Ser Leu Asn Leu Glu Ala Asn Val Thr Ala Asp Gly Ala Leu
 1025 1030 1035 1040
 Ala Met Glu Lys Gly Leu Ala Ser Leu Lys Ser Glu Met Arg Glu Val
 1045 1050 1055
 Glu Gly Glu Leu Glu Arg Lys Glu Leu Glu Phe Asp Thr Asn Met Asp
 1060 1065 1070
 Ala Val Gln Met Val Ile Thr Glu Ala Gln Lys Val Asp Thr Arg Ala
 1075 1080 1085
 Lys Asn Ala Gly Val Thr Ile Gln Asp Thr Leu Asn Thr Leu Asp Gly
 1090 1095 1100
 Leu Leu His Leu Met Asp Gln Pro Leu Ser Val Asp Glu Glu Gly Leu
 1105 1110 1115 1120
 Val Leu Leu Glu Gln Lys Leu Ser Arg Ala Lys Thr Gln Ile Asn Ser
 1125 1130 1135
 Gln Leu Arg Pro Met Met Ser Glu Leu Glu Glu Arg Ala Arg Gln Gln
 1140 1145 1150
 Arg Gly His Leu His Leu Leu Glu Thr Ser Ile Asp Gly Ile Leu Ala
 1155 1160 1165
 Asp Val Lys Asn Leu Glu Asn Ile Arg Asp Asn Leu Pro Pro Gly Cys
 1170 1175 1180
 Tyr Asn Thr Gln Ala Leu Glu Gln Gln
 1185 1190

<210> 15

<211> 1111

<212> PRT

<213> Artificial Sequence

<220>

 <223> Description of Artificial Sequence; Note =
 synthetic construct

<400> 15

 Met Pro Ala Leu Trp Leu Gly Cys Cys Leu Cys Phe Ser Leu Leu Leu
 1 5 10 15

29

Pro	Ala	Ala	Arg	Ala	Thr	Ser	Arg	Arg	Glu	Val	Cys	Asp	Cys	Asn	Gly
			20					25					30		
Lys	Ser	Arg	Gln	Cys	Ile	Phe	Asp	Arg	Glu	Leu	His	Arg	Gln	Thr	Gly
		35					40					45			
Asn	Gly	Phe	Arg	Cys	Leu	Asn	Cys	Asn	Asp	Asn	Thr	Asp	Gly	Ile	His
	50					55					60				
Cys	Glu	Lys	Cys	Lys	Asn	Gly	Phe	Tyr	Arg	His	Arg	Glu	Arg	Asp	Arg
65					70					75					80
Cys	Leu	Pro	Cys	Asn	Cys	Asn	Ser	Lys	Gly	Ser	Leu	Ser	Ala	Arg	Cys
				85					90					95	
Asp	Asn	Ser	Gly	Arg	Cys	Ser	Cys	Lys	Pro	Gly	Val	Thr	Gly	Ala	Arg
			100					105					110		
Cys	Asp	Arg	Cys	Leu	Pro	Gly	Phe	His	Met	Leu	Thr	Asp	Ala	Gly	Cys
		115					120					125			
Thr	Gln	Asp	Gln	Arg	Leu	Leu	Asp	Ser	Lys	Cys	Asp	Cys	Asp	Pro	Ala
	130					135					140				
Gly	Ile	Ala	Gly	Pro	Cys	Asp	Ala	Gly	Arg	Cys	Val	Cys	Lys	Pro	Ala
145					150					155					160
Val	Thr	Gly	Glu	Arg	Cys	Asp	Arg	Cys	Arg	Ser	Gly	Tyr	Tyr	Asn	Leu
				165					170					175	
Asp	Gly	Gly	Asn	Pro	Glu	Gly	Cys	Thr	Gln	Cys	Phe	Cys	Tyr	Gly	His
			180					185					190		
Ser	Ala	Ser	Cys	Arg	Ser	Ser	Ala	Glu	Tyr	Ser	Val	His	Lys	Ile	Thr
		195					200					205			
Ser	Thr	Phe	His	Gln	Asp	Val	Asp	Gly	Trp	Lys	Ala	Val	Gln	Arg	Asn
	210					215					220				
Gly	Ser	Pro	Ala	Lys	Leu	Gln	Trp	Ser	Gln	Arg	His	Gln	Asp	Val	Phe
225					230					235					240
Ser	Ser	Ala	Gln	Arg	Leu	Asp	Pro	Val	Tyr	Phe	Val	Ala	Pro	Ala	Lys
				245					250					255	
Phe	Leu	Gly	Asn	Gln	Gln	Val	Ser	Tyr	Gly	Gln	Ser	Leu	Ser	Phe	Asp
			260					265					270		
Tyr	Arg	Val	Asp	Arg	Gly	Gly	Arg	His	Pro	Ser	Ala	His	Asp	Val	Ile
		275					280					285			
Leu	Glu	Gly	Ala	Gly	Leu	Arg	Ile	Thr	Ala	Pro	Leu	Met	Pro	Leu	Gly
	290					295					300				
Lys	Thr	Leu	Pro	Cys	Gly	Leu	Thr	Lys	Thr	Tyr	Thr	Phe	Arg	Leu	Asn
305					310					315					320
Glu	His	Pro	Ser	Asn	Asn	Trp	Ser	Pro	Gln	Leu	Ser	Tyr	Phe	Glu	Tyr
				325					330					335	
Arg	Arg	Leu	Leu	Arg	Asn	Leu	Thr	Ala	Leu	Arg	Ile	Arg	Ala	Thr	Tyr
			340					345					350		
Gly	Glu	Tyr	Ser	Thr	Gly	Tyr	Ile	Asp	Asn	Val	Thr	Leu	Ile	Ser	Ala
		355					360					365			
Arg	Pro	Val	Ser	Gly	Ala	Pro	Ala	Pro	Trp	Val	Glu	Gln	Cys	Ile	Cys
	370					375					380				
Pro	Val	Gly	Tyr	Lys	Gly	Gln	Phe	Cys	Gln	Asp	Cys	Ala	Ser	Gly	Tyr
385					390					395					400
Lys	Arg	Asp	Ser	Ala	Arg	Leu	Gly	Pro	Phe	Gly	Thr	Cys	Ile	Pro	Cys
				405					410					415	
Asn	Cys	Gln	Gly	Gly	Gly	Ala	Cys	Asp	Pro	Asp	Thr	Gly	Asp	Cys	Tyr
			420					425					430		
Ser	Gly	Asp	Glu	Asn	Pro	Asp	Ile	Glu	Cys	Ala	Asp	Cys	Pro	Ile	Gly
		435					440					445			
Phe	Tyr	Asn	Asp	Pro	His	Asp	Pro	Arg	Ser	Cys	Lys	Pro	Cys	Pro	Cys
	450					455					460				
His	Asn	Gly	Phe	Ser	Cys	Ser	Val	Met	Pro	Glu	Thr	Glu	Glu	Val	Val
465					470					475					480
Cys	Asn	Asn	Cys	Pro	Pro	Gly	Val	Thr	Gly	Ala	Arg	Cys	Glu	Leu	Cys
				485					490					495	
Ala	Asp	Gly	Tyr	Phe	Gly	Asp	Pro	Phe	Gly	Glu	His	Gly	Pro	Val	Arg
			500					505					510		

30

Pro	Cys	Gln	Pro	Cys	Gln	Cys	Asn	Asn	Asn	Val	Asp	Pro	Ser	Ala	Ser	
		515					520					525				
Gly	Asn	Cys	Asp	Arg	Leu	Thr	Gly	Arg	Cys	Leu	Lys	Cys	Ile	His	Asn	
	530					535					540					
Thr	Ala	Gly	Ile	Tyr	Cys	Asp	Gln	Cys	Lys	Ala	Gly	Tyr	Phe	Gly	Asp	
545					550					555					560	
Pro	Leu	Ala	Pro	Asn	Pro	Ala	Asp	Lys	Cys	Arg	Ala	Cys	Asn	Cys	Asn	
				565					570					575		
Pro	Met	Gly	Ser	Glu	Pro	Val	Gly	Cys	Arg	Ser	Asp	Gly	Thr	Cys	Val	
			580					585					590			
Cys	Lys	Pro	Gly	Phe	Gly	Gly	Pro	Asn	Cys	Glu	His	Gly	Ala	Phe	Ser	
		595					600					605				
Cys	Pro	Ala	Cys	Tyr	Asn	Gln	Val	Lys	Ile	Gln	Met	Asp	Gln	Phe	Met	
	610					615					620					
Gln	Gln	Leu	Gln	Arg	Met	Glu	Ala	Leu	Ile	Ser	Lys	Ala	Gln	Gly	Gly	
625					630					635					640	
Asp	Gly	Val	Val	Pro	Asp	Thr	Glu	Leu	Glu	Gly	Arg	Met	Gln	Gln	Ala	
				645						650					655	
Glu	Gln	Ala	Leu	Gln	Asp	Ile	Leu	Arg	Asp	Ala	Gln	Ile	Ser	Glu	Gly	
			660					665					670			
Ala	Ser	Arg	Ser	Leu	Gly	Leu	Gln	Leu	Ala	Lys	Val	Arg	Ser	Gln	Glu	
		675					680					685				
Asn	Ser	Tyr	Gln	Ser	Arg	Leu	Asp	Asp	Leu	Lys	Met	Thr	Val	Glu	Arg	
	690					695					700					
Val	Arg	Ala	Leu	Gly	Ser	Gln	Tyr	Gln	Asn	Arg	Val	Arg	Asp	Thr	His	
705				710					715						720	
Arg	Leu	Ile	Thr	Gln	Met	Gln	Leu	Ser	Leu	Ala	Glu	Ser	Glu	Ala	Ser	
				725					730						735	
Leu	Gly	Asn	Thr	Asn	Ile	Pro	Ala	Ser	Asp	His	Tyr	Val	Gly	Pro	Asn	
			740					745					750			
Gly	Phe	Lys	Ser	Leu	Ala	Gln	Glu	Ala	Thr	Arg	Leu	Ala	Glu	Ser	His	
		755					760					765				
Val	Glu	Ser	Ala	Ser	Asn	Met	Glu	Gln	Leu	Thr	Arg	Glu	Thr	Glu	Asp	
	770					775					780					
Tyr	Ser	Lys	Gln	Ala	Leu	Ser	Leu	Val	Arg	Lys	Ala	Leu	His	Glu	Gly	
785					790				795						800	
Val	Gly	Ser	Gly	Ser	Gly	Ser	Pro	Asp	Gly	Ala	Val	Val	Gln	Gly	Leu	
				805					810					815		
Val	Glu	Lys	Leu	Glu	Lys	Thr	Lys	Ser	Leu	Ala	Gln	Gln	Leu	Thr	Arg	
			820					825					830			
Glu	Ala	Thr	Gln	Ala	Glu	Ile	Glu	Ala	Asp	Arg	Ser	Tyr	Gln	His	Ser	
		835					840					845				
Leu	Arg	Leu	Leu	Asp	Ser	Val	Ser	Arg	Leu	Gln	Gly	Val	Ser	Asp	Gln	
	850					855					860					
Ser	Phe	Gln	Val	Glu	Glu	Ala	Lys	Arg	Ile	Lys	Gln	Lys	Ala	Asp	Ser	
865					870					875					880	
Leu	Ser	Thr	Leu	Val	Thr	Arg	His	Met	Asp	Glu	Phe	Lys	Arg	Thr	Gln	
				885					890					895		
Lys	Asn	Leu	Gly	Asn	Trp	Lys	Glu	Glu	Ala	Gln	Gln	Leu	Leu	Gln	Asn	
			900					905					910			
Gly	Lys	Ser	Gly	Arg	Glu	Lys	Ser	Asp	Gln	Leu	Leu	Ser	Arg	Ala	Asn	
		915					920						925			
Leu	Ala	Lys	Ser	Arg	Ala	Gln	Glu	Ala	Leu	Ser	Met	Gly	Asn	Ala	Thr	
	930					935					940					
Phe	Tyr	Glu	Val	Glu	Ser	Ile	Leu	Lys	Asn	Leu	Arg	Glu	Phe	Asp	Leu	
945					950					955					960	
Gln	Val	Asp	Asn	Arg	Lys	Ala	Glu	Ala	Glu	Glu	Ala	Met	Lys	Arg	Leu	
				965					970						975	
Ser	Tyr	Ile	Ser	Gln	Lys	Val	Ser	Asp	Ala	Ser	Asp	Lys	Thr	Gln	Gln	
			980					985					990			
Ala	Glu	Arg	Ala	Leu	Gly	Ser	Ala	Ala	Ala	Asp	Ala	Gln	Arg	Ala	Lys	
		995					1000						1005			

31

Asn Gly Ala Gly Glu Ala Leu Glu Ile Ser Ser Glu Ile Glu Gln Glu
 1010 1015 1020
 Ile Gly Ser Leu Asn Leu Glu Ala Asn Val Thr Ala Asp Gly Ala Leu
 1025 1030 1035 1040
 Ala Met Glu Lys Gly Leu Ala Ser Leu Lys Ser Glu Met Arg Glu Val
 1045 1050 1055
 Glu Gly Glu Leu Glu Arg Lys Glu Leu Glu Phe Asp Thr Asn Met Asp
 1060 1065 1070
 Ala Val Gln Met Val Ile Thr Glu Ala Gln Lys Val Asp Thr Arg Ala
 1075 1080 1085
 Lys Asn Ala Gly Val Thr Ile Gln Asp Thr Leu Asn Thr Leu Asp Gly
 1090 1095 1100
 Leu Leu His Leu Met Gly Met
 1105 1110

<210> 16
 <211> 5622
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence; Note =
 synthetic construct

<400> 16
 atggcagcgc cacgccccag cccatggggc aggetgctcc tggcagcctt gatcagcgtc 60
 agcctctctg ggaccttgaa ccgctgcaag aaggccccag tgaagagctg cacggagtgt 120
 gtccgtgtgg ataaggactg cgcctactgc acagacgaga tggttcaggga ccggcgctgc 180
 aacacccagg cggagctgct ggccgcgggc tgccagcggg agagcatcgt ggtcatggag 240
 agcagcttcc aaatcacaga ggagaccacag attgacacca ccctgcggcg cagccagatg 300
 tcccccaag gcctgcgggt ccgtctgogg ccgggtgagg agcggcattt tgagctggag 360
 gtgtttgagc cactggagag ccccgctggac ctgtacatcc tcatggactt ctccaactcc 420
 atgtccgatg atctggacaa cctcaagaag atggggcaga acctggctcg ggtcctgagc 480
 cagctcacca gcgactacac tattggattt ggcaagtbtg tggacaaagt cagcgtcccc 540
 cagacggaca tgaggcctga gaagctgaag gagccttggc ccaacagtga ccccccttc 600
 tccttcaaga acgtcatcag cctgacagaa gatgtggatg agttccggaa taaactgcag 660
 ggagagcgga tctcaggcaa cctggatgct cctgagggcg gcttcgatgc catcctgcag 720
 acagctgtgt gcacgaggga cattggctgg cgcccggaca gcacccacct gctggctctc 780
 tccaccgagt cagccttcca ctatgaggct gatggcgcca acgtgctggc tggcatcatg 840
 agccgcaacg atgaacggtg ccacctggac accacgggca cctacacca gtacaggaca 900
 caggactacc cgtcgggtgcc caccctgggt cgctgctcg ccaagcacia catcatcccc 960
 atctttgctg tcaccaacta ctcttatagc tactacgaga agcttcacac ctatttccct 1020
 gtctcctcac tgggggtgct gcaggaggac tcgtccaaca tcgtggagct gctggaggag 1080
 gccttcaatc ggatccgctc caacctggac atccggggcc tagacagccc ccgaggcctt 1140
 cggacagagg tcacctcaa gatgttccag aagacgagga ctgggtcctt tcacatccgg 1200
 cggggggaag tgggtatata ccagggtgac ctgcggggcc ttgagcacgt ggatgggacg 1260
 cacgtgtgcc agctgccgga ggaccagaag ggcaacatcc atctgaaacc ttcttctctc 1320
 gacggcctca agatggacgc gggcatcatc tgtgatgtgt gcacctgcga gctgcaaaaa 1380
 gaggtgcggt cagctcgctg cagcttcaac ggagacttcg tgtgcggaca gtgtgtgtgc 1440
 agcgagggtt ggagtggcca gacctgcaac tgctccaccg gctctctgag tgacattcag 1500
 ccctgcctgc gggagggcga ggacaagccg tgctccggcc gtggggagtg ccagtgcggg 1560
 cactgtgtgt gctacggcga aggccgctac gagggtcagt tctgcgagta tgacaacttc 1620
 cagtgtcccc gcacttccgg gttcctctgc aatgaccgag gacgtgctc catgggccag 1680
 tgtgtgtgtg agcctggttg gacaggccca agctgtgact gtcccctcag caatgccacc 1740
 tgcacgcaca gcaatggggg catctgtaat ggacgtggcc actgtgagtg tggccgctgc 1800
 cactgccacc agcagtcgct ctacacggac accatctgcg agatcaacta ctcggcgtcc 1860
 acccgggcct ctgcgaggac ctacgctcct gcgtgcagtg ccaggcgtgg ggcaccggcg 1920
 agaagaaggg gcgcacgtgt gaggaatgca acttcaaggc caagatgggtg gacgagctta 1980
 agagaggcga ggaggtggtg gtgcgctgct ccttccggga cgaggatgac gactgcacct 2040
 acagctacac catggaaggc gacggcgccc ctggggccaa cagcactgtc ctggtgcaca 2100
 agaagaaggg actgccctcc gggctccttc tgggtggtca tccccctgct cctcctctc 2160
 ctgccgctcc tggccctgct actgctgcta tgctggaagt actgtgcctg ctgcaaggcc 2220

tgccctggcac	ttctcccgtg	ctgcaaccga	ggtcacatgg	tgggctttaa	ggaagaccac	2280
tacatgctgc	gggagaacct	gatggcctct	gaccacttgg	acacgcccac	gctgcgcagc	2340
gggaacctca	agggccgtga	cgtgggtccg	tggaggtca	ccaacaacat	gcagcggcct	2400
ggcttttgcca	ctcatgccgc	cagcatcaac	cccacagagc	tgggtgcccta	cgggctgtcc	2460
ttgcgcctgg	cccgcctttg	caccgagaac	ctgctgaagc	ctgacactcg	ggagtgcgcc	2520
cagctgcgcc	aggaggtgga	ggagaacctg	aacgaggtct	acaggcagat	ctccggtgta	2580
cacaagctcc	agcagaccaa	gttccggcag	cagcccaatg	ccgggaaaaa	gcaagaccac	2640
accattgtgg	acacagtgc	gatggcgccc	cgctcggcca	agccggccct	gctgaagctt	2700
acagagaagc	aggtggaaca	gagggccttc	cacgacctca	aggtggcccc	cggctactac	2760
accctcactg	cagaccagga	cgcccggggc	atgggtggagt	tccaggaggg	cgtggagctg	2820
gtggacgtac	gggtgcccc	ctttatccgg	cctgaggatg	acgacgagaa	gcagctgctg	2880
gtggaggcca	tcgacgtgcc	cgcaggcact	gccaccctcg	gccgcgcct	ggtaaacatc	2940
accatcatca	aggagcaagc	cagagacgtg	gtgtcctttg	agcagcctga	gttctcggtc	3000
agccgcgggg	accaggtggc	ccgcatccct	gtcatccggc	gtgtcctgga	cggcgggag	3060
tcccaggtct	cctaccgcac	acaggatggc	accgcgcagg	gcaaccggga	ctacatcccc	3120
gtggaggggtg	agctgctgtt	ccagcctggg	gaggcctgga	aagagctgca	ggtgaagctc	3180
ctggagctgc	aagaagttga	ctccctcctg	cggggccggc	aggtccgccc	tttccacgtc	3240
cagctcagca	accctaagtt	tggggcccac	ctggggccagc	cccactccac	caccatcatc	3300
atcagggacc	cagatgaact	ggaccggagc	ttcacgagtc	agatgttgtc	atcacagcca	3360
ccccctcacg	gcgacctggg	cgcgccgcag	aaccccaatg	ctaaggccgc	tgggtccagg	3420
aagatccatt	tcaactggct	gcccccttct	ggcaagccaa	tgggggtacag	ggtaaagtac	3480
tggattcagg	gtgactccga	atccgaagcc	cacctgctcg	acagcaaggt	gccctcagtg	3540
gagctcacca	acctgtaccc	gtattgcgac	tatgagatga	aggtgtgcgc	ctacggggct	3600
cagggcgagg	gaccctacag	ctccctgggtg	tcctgccgca	cccaccagga	agtgccagc	3660
gagccagggc	gtctggcctt	caatgtcgtc	tcctccacgg	tgaccagct	gagctgggct	3720
gagccggctg	agaccaacgg	tgagatcaca	gcctacgagg	tctgctatgg	cctgggtcaac	3780
gatgacaacc	gacctattgg	gcccattgaag	aaagtgtctg	ttgacaaccc	taagaaccgg	3840
atgctgctta	ttgagaacct	tcgggagtc	cagccctacc	gctacacgg	gaaggcgcgc	3900
aacggggccg	gctggggggc	tgagcgggag	gccatcatca	acctggccac	ccagcccaag	3960
aggcccatgt	ccatccccat	catccctgac	atccctatcg	tggacgcccc	gagcggggag	4020
gactacgaca	gcttccttat	gtacagcgat	gacgtttctac	gctctccatc	gggcagccag	4080
aggccacagc	tctccgatga	cactggctgc	ggctggaagt	tcgagccct	gctgggggag	4140
gagctggacc	tgcggcgcg	cacgtggcgg	ctgcccccg	agctcatccc	gcgcctgtcg	4200
gccagcagcg	ggcgctcctc	cgacgcgcag	gcgccccacg	ggcccccgga	cgacggcggc	4260
gcgggcgggg	agggcggcag	cctgccccgc	agtgcgacac	ccgggcccc	cggagagcac	4320
ctgggtgaatg	gccggatgga	ctttgccttc	ccgggcagca	ccaactccct	gcacaggatg	4380
accacgacca	gtgctgctgc	ctatggcacc	cacctgagcc	cacacgtgcc	ccaccgcgtg	4440
ctaagcacat	cctccaccct	cacacgggac	tacaactcac	tgaccgcctc	agaacactca	4500
cactcgacca	cactgccgag	ggactactcc	acctcacct	ccgtctcctc	ccacggcctc	4560
cctcccatct	gggaacacgg	gaggagcagg	cttccgctgt	cctgggcccc	ggggtcccgg	4620
agtcgggctc	agatgaaagg	gttccccct	tccagggg	cacgagactc	tataatcctg	4680
gctgggaggc	cagcagcgcc	ctcctggggc	ccagactctc	gcctgactgc	tgggtgtgcc	4740
gacacgcca	cccgctgggt	gttctctgcc	ctggggccca	catctctcag	agtgagctgg	4800
caggagcgcg	ggtgcgagcg	gccgctgcag	ggctacagtg	tggagtacca	gctgctgaac	4860
ggcgggtgagc	tgcctcggct	caacatcccc	aacctgccc	agacctcgg	ggtggtggaa	4920
gacctcctgc	ccaaccactc	ctacgtgttc	cgcgtgcggg	cccagagcca	ggaaggctgg	4980
ggccgagagc	gtgagggtgt	catcaccatt	gaatcccagg	tgcacccgca	gagccactg	5040
tgtcccctgc	caggctccgc	cttcaactttg	agcactccca	gtgccccagg	cccgtggtg	5100
ttcaactgcc	tgagcccaga	ctcgtctgcag	ctgagctggg	agcggccacg	gaggcccaat	5160
ggggatatcg	tcggctacct	ggtgacctgt	gagatggccc	aaggaggagg	tccagccacc	5220
gcattccggg	tggatggaga	cagccccgag	agccggctga	ccgtgccggg	cctcagcgag	5280
aacgtgccct	acaagttcaa	ggtgcaggcc	aggaccactg	agggcttcgg	gccagagcgc	5340
gagggcatca	tcacataga	gtcccaggat	ggaggtccct	tcccgcagct	gggcagccgt	5400
gccgggctct	tccagcacc	gctgcaaagc	gagtacagca	gcctctccac	caccacacc	5460
agcgccaccg	agcccttcct	agtgggtccg	acctggggg	cccagcacct	ggaggcaggc	5520
ggctccctca	cccgcatgt	gaccagggag	tttgtgagcc	ggacactgac	caccagcgga	5580
acctttagca	cccacatgga	ccaacagttc	ttccaaactt	ga		5622

<210> 17

<211> 1873

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence; Note =
synthetic construct

<400> 17

Met 1	Ala	Gly	Pro	Arg 5	Pro	Ser	Pro	Trp	Ala 10	Arg	Leu	Leu	Leu	Ala 15	Ala
Leu	Ile	Ser	Val 20	Ser	Leu	Ser	Gly	Thr 25	Leu	Asn	Arg	Cys	Lys 30	Lys	Ala
Pro	Ile	Lys 35	Ser	Cys	Thr	Glu	Cys 40	Val	Arg	Val	Asp	Lys 45	Asp	Cys	Ala
Tyr	Cys 50	Thr	Asp	Glu	Met	Phe 55	Arg	Asp	Arg	Arg	Cys 60	Asn	Thr	Gln	Ala
Glu 65	Leu	Leu	Ala	Ala	Gly 70	Cys	Gln	Arg	Glu	Ser 75	Ile	Val	Val	Met	Glu 80
Ser	Ser	Phe	Gln	Ile 85	Thr	Glu	Glu	Thr	Gln 90	Ile	Asp	Thr	Thr	Leu 95	Arg
Arg	Ser	Gln	Met 100	Ser	Pro	Gln	Gly	Leu 105	Arg	Val	Arg	Leu	Arg 110	Pro	Gly
Glu	Glu	Arg 115	His	Phe	Glu	Leu	Glu	Val 120	Phe	Glu	Pro	Leu	Glu 125	Ser	Pro
Val	Asp 130	Leu	Tyr	Ile	Leu	Met 135	Asp	Phe	Ser	Asn	Ser 140	Met	Ser	Asp	Asp
Leu 145	Asp	Asn	Leu	Lys	Lys 150	Met	Gly	Gln	Asn	Leu 155	Ala	Arg	Val	Leu	Ser 160
Gln	Leu	Thr	Ser	Asp 165	Tyr	Thr	Ile	Gly	Phe 170	Gly	Lys	Phe	Val	Asp 175	Lys
Val	Ser	Val	Pro 180	Gln	Thr	Asp	Met	Arg 185	Pro	Glu	Lys	Leu	Lys 190	Glu	Pro
Trp	Pro	Asn 195	Ser	Asp	Pro	Pro	Phe 200	Ser	Phe	Lys	Asn 205	Val	Ile	Ser	Leu
Thr	Glu 210	Asp	Val	Asp	Glu	Phe 215	Arg	Asn	Lys	Leu	Gln 220	Gly	Glu	Arg	Ile
Ser 225	Gly	Asn	Leu	Asp	Ala 230	Pro	Glu	Gly	Gly	Phe 235	Asp	Ala	Ile	Leu	Gln 240
Thr	Ala	Val	Cys 245	Thr	Arg	Asp	Ile	Gly	Trp 250	Arg	Pro	Asp	Ser	Thr 255	His
Leu	Leu	Val	Phe 260	Ser	Thr	Glu	Ser	Ala 265	Phe	His	Tyr	Glu	Ala 270	Asp	Gly
Ala	Asn	Val 275	Leu	Ala	Gly	Ile	Met 280	Ser	Arg	Asn	Asp 285	Glu	Arg	Cys	His
Leu	Asp 290	Thr	Thr	Gly	Thr	Tyr 295	Thr	Gln	Tyr	Arg	Thr 300	Gln	Asp	Tyr	Pro
Ser 305	Val	Pro	Thr	Leu	Val 310	Arg	Leu	Leu	Ala	Lys 315	His	Asn	Ile	Ile	Pro 320
Ile	Phe	Ala	Val	Thr 325	Asn	Tyr	Ser	Tyr	Ser 330	Tyr	Tyr	Glu	Lys	Leu	His 335
Thr	Tyr	Phe	Pro 340	Val	Ser	Ser	Leu	Gly 345	Val	Leu	Gln	Glu	Asp 350	Ser	Ser
Asn	Ile 355	Val	Glu	Leu	Leu	Glu	Glu	Ala 360	Phe	Asn	Arg	Ile	Arg 365	Ser	Asn
Leu	Asp 370	Ile	Arg	Ala	Leu	Asp 375	Ser	Pro	Arg	Gly	Leu 380	Arg	Thr	Glu	Val
Thr 385	Ser	Lys	Met	Phe 390	Gln	Lys	Thr	Arg	Thr	Gly 395	Ser	Phe	His	Ile	Arg 400
Arg	Gly	Glu	Val	Gly 405	Ile	Tyr	Gln	Val	Gln 410	Leu	Arg	Ala	Leu	Glu 415	His
Val	Asp	Gly	Thr 420	His	Val	Cys	Gln	Leu 425	Pro	Glu	Asp	Gln	Lys 430	Gly	Asn

Ile	His	Leu	Lys	Pro	Ser	Phe	Ser	Asp	Gly	Leu	Lys	Met	Asp	Ala	Gly
		435					440					445			
Ile	Ile	Cys	Asp	Val	Cys	Thr	Cys	Glu	Leu	Gln	Lys	Glu	Val	Arg	Ser
	450					455					460				
Ala	Arg	Cys	Ser	Phe	Asn	Gly	Asp	Phe	Val	Cys	Gly	Gln	Cys	Val	Cys
465					470					475					480
Ser	Glu	Gly	Trp	Ser	Gly	Gln	Thr	Cys	Asn	Cys	Ser	Thr	Gly	Ser	Leu
				485					490					495	
Ser	Asp	Ile	Gln	Pro	Cys	Leu	Arg	Glu	Gly	Glu	Asp	Lys	Pro	Cys	Ser
			500					505					510		
Gly	Arg	Gly	Glu	Cys	Gln	Cys	Gly	His	Cys	Val	Cys	Tyr	Gly	Glu	Gly
		515					520					525			
Arg	Tyr	Glu	Gly	Gln	Phe	Cys	Glu	Tyr	Asp	Asn	Phe	Gln	Cys	Pro	Arg
	530					535					540				
Thr	Ser	Gly	Phe	Leu	Cys	Asn	Asp	Arg	Gly	Arg	Cys	Ser	Met	Gly	Gln
545					550					555					560
Cys	Val	Cys	Glu	Pro	Gly	Trp	Thr	Gly	Pro	Ser	Cys	Asp	Cys	Pro	Leu
				565					570						575
Ser	Asn	Ala	Thr	Cys	Ile	Asp	Ser	Asn	Gly	Gly	Ile	Cys	Asn	Gly	Arg
			580					585					590		
Gly	His	Cys	Glu	Cys	Gly	Arg	Cys	His	Cys	His	Gln	Gln	Ser	Leu	Tyr
		595					600					605			
Thr	Asp	Thr	Ile	Cys	Glu	Ile	Asn	Tyr	Ser	Ala	Ser	Thr	Arg	Ala	Ser
	610					615						620			
Ala	Arg	Thr	Tyr	Ala	Pro	Ala	Cys	Ser	Ala	Arg	Arg	Gly	Ala	Pro	Ala
625					630					635					640
Arg	Arg	Arg	Gly	Ala	Arg	Val	Arg	Asn	Ala	Thr	Ser	Arg	Ser	Arg	Trp
				645					650						655
Trp	Thr	Ser	Leu	Arg	Glu	Ala	Arg	Arg	Trp	Trp	Cys	Ala	Ala	Pro	Ser
			660					665					670		
Gly	Thr	Arg	Met	Thr	Thr	Ala	Pro	Thr	Ala	Thr	Pro	Trp	Lys	Val	Thr
		675					680					685			
Ala	Pro	Leu	Gly	Pro	Thr	Ala	Leu	Ser	Trp	Cys	Thr	Arg	Arg	Arg	Asp
	690					695					700				
Cys	Pro	Pro	Gly	Ser	Phe	Trp	Trp	Leu	Ile	Pro	Leu	Leu	Leu	Leu	Leu
705					710					715					720
Leu	Pro	Leu	Leu	Ala	Leu	Leu	Leu	Leu	Leu	Cys	Trp	Lys	Tyr	Cys	Ala
				725					730						735
Cys	Cys	Lys	Ala	Cys	Leu	Ala	Leu	Leu	Pro	Cys	Cys	Asn	Arg	Gly	His
			740					745					750		
Met	Val	Gly	Phe	Lys	Glu	Asp	His	Tyr	Met	Leu	Arg	Glu	Asn	Leu	Met
		755					760					765			
Ala	Ser	Asp	His	Leu	Asp	Thr	Pro	Met	Leu	Arg	Ser	Gly	Asn	Leu	Lys
	770					775						780			
Gly	Arg	Asp	Val	Val	Arg	Trp	Lys	Val	Thr	Asn	Asn	Met	Gln	Arg	Pro
785					790					795					800
Gly	Phe	Ala	Thr	His	Ala	Ala	Ser	Ile	Asn	Pro	Thr	Glu	Leu	Val	Pro
				805					810						815
Tyr	Gly	Leu	Ser	Leu	Arg	Leu	Ala	Arg	Leu	Cys	Thr	Glu	Asn	Leu	Leu
			820					825					830		
Lys	Pro	Asp	Thr	Arg	Glu	Cys	Ala	Gln	Leu	Arg	Gln	Glu	Val	Glu	Glu
		835					840					845			
Asn	Leu	Asn	Glu	Val	Tyr	Arg	Gln	Ile	Ser	Gly	Val	His	Lys	Leu	Gln
	850					855					860				
Gln	Thr	Lys	Phe	Arg	Gln	Gln	Pro	Asn	Ala	Gly	Lys	Lys	Gln	Asp	His
865					870					875					880
Thr	Ile	Val	Asp	Thr	Val	Leu	Met	Ala	Pro	Arg	Ser	Ala	Lys	Pro	Ala
				885					890						895
Leu	Leu	Lys	Leu	Thr	Glu	Lys	Gln	Val	Glu	Gln	Arg	Ala	Phe	His	Asp
			900					905					910		
Leu	Lys	Val	Ala	Pro	Gly	Tyr	Tyr	Thr	Leu	Thr	Ala	Asp	Gln	Asp	Ala
		915					920					925			

35

Arg	Gly	Met	Val	Glu	Phe	Gln	Glu	Gly	Val	Glu	Leu	Val	Asp	Val	Arg	930	935	940
Val	Pro	Leu	Phe	Ile	Arg	Pro	Glu	Asp	Asp	Asp	Glu	Lys	Gln	Leu	Leu	945	950	955
Val	Glu	Ala	Ile	Asp	Val	Pro	Ala	Gly	Thr	Ala	Thr	Leu	Gly	Arg	Arg	965	970	975
Leu	Val	Asn	Ile	Thr	Ile	Ile	Lys	Glu	Gln	Ala	Arg	Asp	Val	Val	Ser	980	985	990
Phe	Glu	Gln	Pro	Glu	Phe	Ser	Val	Ser	Arg	Gly	Asp	Gln	Val	Ala	Arg	995	1000	1005
Ile	Pro	Val	Ile	Arg	Arg	Val	Leu	Asp	Gly	Gly	Lys	Ser	Gln	Val	Ser	1010	1015	1020
Tyr	Arg	Thr	Gln	Asp	Gly	Thr	Ala	Gln	Gly	Asn	Arg	Asp	Tyr	Ile	Pro	1025	1030	1035
Val	Glu	Gly	Glu	Leu	Leu	Phe	Gln	Pro	Gly	Glu	Ala	Trp	Lys	Glu	Leu	1045	1050	1055
Gln	Val	Lys	Leu	Leu	Glu	Leu	Gln	Glu	Val	Asp	Ser	Leu	Leu	Arg	Gly	1060	1065	1070
Arg	Gln	Val	Arg	Arg	Phe	His	Val	Gln	Leu	Ser	Asn	Pro	Lys	Phe	Gly	1075	1080	1085
Ala	His	Leu	Gly	Gln	Pro	His	Ser	Thr	Thr	Ile	Ile	Ile	Arg	Asp	Pro	1090	1095	1100
Asp	Glu	Leu	Asp	Arg	Ser	Phe	Thr	Ser	Gln	Met	Leu	Ser	Ser	Gln	Pro	1105	1110	1115
Pro	Pro	His	Gly	Asp	Leu	Gly	Ala	Pro	Gln	Asn	Pro	Asn	Ala	Lys	Ala	1125	1130	1135
Ala	Gly	Ser	Arg	Lys	Ile	His	Phe	Asn	Trp	Leu	Pro	Pro	Ser	Gly	Lys	1140	1145	1150
Pro	Met	Gly	Tyr	Arg	Val	Lys	Tyr	Trp	Ile	Gln	Gly	Asp	Ser	Glu	Ser	1155	1160	1165
Glu	Ala	His	Leu	Leu	Asp	Ser	Lys	Val	Pro	Ser	Val	Glu	Leu	Thr	Asn	1170	1175	1180
Leu	Tyr	Pro	Tyr	Cys	Asp	Tyr	Glu	Met	Lys	Val	Cys	Ala	Tyr	Gly	Ala	1185	1190	1195
Gln	Gly	Glu	Gly	Pro	Tyr	Ser	Ser	Leu	Val	Ser	Cys	Arg	Thr	His	Gln	1205	1210	1215
Glu	Val	Pro	Ser	Glu	Pro	Gly	Arg	Leu	Ala	Phe	Asn	Val	Val	Ser	Ser	1220	1225	1230
Thr	Val	Thr	Gln	Leu	Ser	Trp	Ala	Glu	Pro	Ala	Glu	Thr	Asn	Gly	Glu	1235	1240	1245
Ile	Thr	Ala	Tyr	Glu	Val	Cys	Tyr	Gly	Leu	Val	Asn	Asp	Asp	Asn	Arg	1250	1255	1260
Pro	Ile	Gly	Pro	Met	Lys	Lys	Val	Leu	Val	Asp	Asn	Pro	Lys	Asn	Arg	1265	1270	1275
Met	Leu	Leu	Ile	Glu	Asn	Leu	Arg	Glu	Ser	Gln	Pro	Tyr	Arg	Tyr	Thr	1285	1290	1295
Val	Lys	Ala	Arg	Asn	Gly	Ala	Gly	Trp	Gly	Pro	Glu	Arg	Glu	Ala	Ile	1300	1305	1310
Ile	Asn	Leu	Ala	Thr	Gln	Pro	Lys	Arg	Pro	Met	Ser	Ile	Pro	Ile	Ile	1315	1320	1325
Pro	Asp	Ile	Pro	Ile	Val	Asp	Ala	Gln	Ser	Gly	Glu	Asp	Tyr	Asp	Ser	1330	1335	1340
Phe	Leu	Met	Tyr	Ser	Asp	Asp	Val	Leu	Arg	Ser	Pro	Ser	Gly	Ser	Gln	1345	1350	1355
Arg	Pro	Ser	Val	Ser	Asp	Asp	Thr	Gly	Cys	Gly	Trp	Lys	Phe	Glu	Pro	1365	1370	1375
Leu	Leu	Gly	Glu	Glu	Leu	Asp	Leu	Arg	Arg	Val	Thr	Trp	Arg	Leu	Pro	1380	1385	1390
Pro	Glu	Leu	Ile	Pro	Arg	Leu	Ser	Ala	Ser	Ser	Gly	Arg	Ser	Ser	Asp	1395	1400	1405
Ala	Glu	Ala	Pro	His	Gly	Pro	Pro	Asp	Asp	Gly	Gly	Ala	Gly	Gly	Lys	1410	1415	1420

36

Gly Gly Ser Leu Pro Arg Ser Ala Thr Pro Gly Pro Pro Gly Glu His
 1425 1430 1435 1440
 Leu Val Asn Gly Arg Met Asp Phe Ala Phe Pro Gly Ser Thr Asn Ser
 1445 1450 1455
 Leu His Arg Met Thr Thr Thr Ser Ala Ala Tyr Gly Thr His Leu
 1460 1465 1470
 Ser Pro His Val Pro His Arg Val Leu Ser Thr Ser Thr Leu Thr
 1475 1480 1485
 Arg Asp Tyr Asn Ser Leu Thr Arg Ser Glu His Ser His Ser Thr Thr
 1490 1495 1500
 Leu Pro Arg Asp Tyr Ser Thr Leu Thr Ser Val Ser Ser His Gly Leu
 1505 1510 1515 1520
 Pro Pro Ile Trp Glu His Gly Arg Ser Arg Leu Pro Leu Ser Trp Ala
 1525 1530 1535
 Leu Gly Ser Arg Ser Arg Ala Gln Met Lys Gly Phe Pro Pro Ser Arg
 1540 1545 1550
 Gly Pro Arg Asp Ser Ile Ile Leu Ala Gly Arg Pro Ala Ala Pro Ser
 1555 1560 1565
 Trp Gly Pro Asp Ser Arg Leu Thr Ala Gly Val Pro Asp Thr Pro Thr
 1570 1575 1580
 Arg Leu Val Phe Ser Ala Leu Gly Pro Thr Ser Leu Arg Val Ser Trp
 1585 1590 1595 1600
 Gln Glu Pro Arg Cys Glu Arg Pro Leu Gln Gly Tyr Ser Val Glu Tyr
 1605 1610 1615
 Gln Leu Leu Asn Gly Gly Glu Leu His Arg Leu Asn Ile Pro Asn Pro
 1620 1625 1630
 Ala Gln Thr Ser Val Val Val Glu Asp Leu Leu Pro Asn His Ser Tyr
 1635 1640 1645
 Val Phe Arg Val Arg Ala Gln Ser Gln Glu Gly Trp Gly Arg Glu Arg
 1650 1655 1660
 Glu Gly Val Ile Thr Ile Glu Ser Gln Val His Pro Gln Ser Pro Leu
 1665 1670 1675 1680
 Cys Pro Leu Pro Gly Ser Ala Phe Thr Leu Ser Thr Pro Ser Ala Pro
 1685 1690 1695
 Gly Pro Leu Val Phe Thr Ala Leu Ser Pro Asp Ser Leu Gln Leu Ser
 1700 1705 1710
 Trp Glu Arg Pro Arg Arg Pro Asn Gly Asp Ile Val Gly Tyr Leu Val
 1715 1720 1725
 Thr Cys Glu Met Ala Gln Gly Gly Gly Pro Ala Thr Ala Phe Arg Val
 1730 1735 1740
 Asp Gly Asp Ser Pro Glu Ser Arg Leu Thr Val Pro Gly Leu Ser Glu
 1745 1750 1755 1760
 Asn Val Pro Tyr Lys Phe Lys Val Gln Ala Arg Thr Thr Glu Gly Phe
 1765 1770 1775
 Gly Pro Glu Arg Glu Gly Ile Ile Thr Ile Glu Ser Gln Asp Gly Gly
 1780 1785 1790
 Pro Phe Pro Gln Leu Gly Ser Arg Ala Gly Leu Phe Gln His Pro Leu
 1795 1800 1805
 Gln Ser Glu Tyr Ser Ser Ile Ser Thr Thr His Thr Ser Ala Thr Glu
 1810 1815 1820
 Pro Phe Leu Val Gly Pro Thr Leu Gly Ala Gln His Leu Glu Ala Gly
 1825 1830 1835 1840
 Gly Ser Leu Thr Arg His Val Thr Gln Glu Phe Val Ser Arg Thr Leu
 1845 1850 1855
 Thr Thr Ser Gly Thr Leu Ser Thr His Met Asp Gln Gln Phe Phe Gln
 1860 1865 1870
 Thr

<210> 18

<211> 5622

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence; Note =
synthetic construct

<400> 18

atggcagggc	cacgccccag	cccatggggc	aggctgctcc	tggcagcctt	gatcagcgtc	60
agcctctctg	ggaccttgaa	ccgctgcaag	aaggcccca	taaagagctg	cacggagtgt	120
gtccgtgtgg	ataaggactg	cgcctactgc	acagacgaga	tgttcaggga	ccggcgctgc	180
aacacccagg	cggagctgct	ggccgcgggc	tgccagcggg	agagcatcgt	ggcatggag	240
agcagcttcc	aatcacaga	ggagaccag	attgacacca	ccctgcggcg	cagccagatg	300
tcccccaag	gcctgcgggt	ccgtctgcgg	cccggtgagg	agcggcattt	tgagctggag	360
gtgtttgagc	cactggagag	ccccgtggac	ctgtacatcc	tcatggactt	ctccaactcc	420
atgtccgatg	atctggacaa	cctcaagaag	atggggcaga	acctggctcg	ggcctgagc	480
cagctcacca	gcgactacac	tattggattt	ggcaagtgtg	tggacaaagt	cagcgtcccg	540
cagacggaca	tgaggcctga	gaagctgaag	gagccttggc	ccaacagtga	cccccccttc	600
tccttcaaga	acgtcatcag	cctgacagaa	gatgtggatg	agttccggaa	taaactgcag	660
ggagagcgga	tctcaggcaa	cctggatgct	cctgagggcg	gcttcgatgc	catcctgcag	720
acagctgtgt	gcacgagggg	cattggctgg	cgcccggaca	gcaccacct	gctgggtcttc	780
tccaccgagt	cagccttcca	ctatgaggct	gatggcgcca	acgtgctggc	tggcatcatg	840
agccgcaacg	atgaacggtg	ccacctggac	accacgggca	cctacacca	gtacaggaca	900
caggactacc	cgtcgggtgc	caccctgggtg	cgctgctcg	ccaagcaca	catcatcccc	960
atctttgctg	tcaccaacta	ctcctatagc	tactacgaga	agcttcacac	ctatttccct	1020
gtctcctcac	tgggggtgct	gcaggaggac	tcgtccaaca	tcgtggagct	gctggaggag	1080
gccttcaatc	ggatccgctc	caacctggac	atccgggccc	tagacagccc	ccgaggcctt	1140
cggacagagg	tcacctcaa	gatgttccag	aagacgagga	ctgggtcctt	tcacatccgg	1200
cggggggaag	tgggtatata	ccagggtgcag	ctgcgggccc	ttgagcacgt	ggatgggaag	1260
cacgtgtgcc	agctgccgga	ggaccagaag	ggcaacatcc	atctgaaacc	ttccttctcc	1320
gacggcctca	agatggacgc	gggcatcatc	tgtgatgtgt	gcacctgcga	gctgcaaaaa	1380
gaggtgcggt	cagctcgctg	cagcttcaac	ggagacttcg	tgtgcggaca	gtgtgtgtgc	1440
agcgagggct	ggagtggcca	gacctgcaac	tgtctccaccg	gctctctgag	tgacattcag	1500
ccctgcctgc	gggagggcga	ggacaagccg	tgtctccggcc	gtggggagtg	ccagtgcggg	1560
cactgtgtgt	gctacggcga	aggccgctac	gagggtcagt	tctgcgagta	tgacaacttc	1620
cagtgtcccc	gcacttccgg	gttccctctgc	aatgaccgag	gacgctgctc	catgggccag	1680
tgtgtgtgtg	agcctgggtg	gacaggccca	agctgtgact	gtcccctcag	caatgccacc	1740
tgcctcgaca	gcaatggggg	catctgtaat	ggacgtggcc	actgtgagtg	tggccgctgc	1800
cactgccacc	agcagtcgct	ctacacggac	accatctgcg	agatcaacta	ctcggcgtcc	1860
acccgggcct	ctgcgaggac	ctacgctcct	gcgtgcagtg	ccaggcgtgg	ggcaccggcg	1920
agaagaaggg	gcgcacgtgt	gaggaatgca	acttcaagggt	caagatgggtg	gacgagctta	1980
agagaggcga	ggaggtggtg	gtgcgctgct	ccttccggga	cgaggatgac	gactgcacct	2040
acagctacac	catggaagggt	gacggcgccc	ctgggcccga	cagcactgtc	ctggtgcaca	2100
agaagaaggg	actgccctcc	gggctccttc	tgggtggetca	tcccctgct	cctcctcctc	2160
ctgcccgtcc	tggccctgct	actgctgcta	tgtctggaagt	actgtgcctg	ctgcaaggcc	2220
tgcctggcac	ttctcccgtg	ctgcaaccga	ggtcacatgg	tgggctttaa	ggaagaccac	2280
tacatgctgc	gggagaacct	gatggcctct	gaccacttgg	acacgcccac	gctgcgcagc	2340
gggaacctca	agggccgtga	cgtgggtccgc	tgggaagggtca	ccaacaacat	gcagcggcct	2400
ggctttgccca	ctcatgccgc	cagcatcaac	cccacagagc	tgggtgcccta	cgggctgtcc	2460
ttgcgcctgg	cccgcctttg	caccgagaac	ctgctgaagc	ctgacactcg	ggagtgcgcc	2520
cagctgcgcc	aggaggtgga	ggagaacctg	aacgaggtct	acaggcagat	ctccggtgta	2580
cacaagctcc	agcagaccaa	gttccggcag	cagcccaatg	ccgggaaaaa	gcaagaccac	2640
accattgtgg	acacagtgtc	gatggcgccc	cgctcggcca	agccggccct	gctgaagctt	2700
acagagaagc	aggtggaaca	gagggccttc	cacgacctca	aggtggcccc	cggctactac	2760
accctcactg	cagaccagga	cgcgcggggc	atgggtggagt	tccaggaggg	cgtggagctg	2820
gtggacgtac	gggtgcccct	ctttatcccg	cctgaggatg	acgacgagaa	gcagctgctg	2880
gtggaggcca	tcgacgtgcc	cgcaggcact	gccaccctcg	gccgcgcct	ggtaaacatc	2940
accatcatca	aggagcaagc	cagagacgtg	gtgtcctttg	agcagcctga	gttctcggtc	3000
agccgcgggg	accaggtggc	cgcctccct	gtcatccggc	gtgtcctgga	cggcgggaag	3060
tcccaggtct	cctaccgcac	acaggatggc	accgcgcagg	gcaaccggga	ctacatcccc	3120
gtggaggggtg	agctgctgtt	ccagcctggg	gagggcctgga	aagagctgca	ggtgaagctc	3180
ctggagctgc	aagaagttga	ctccctcctg	cggggccggc	aggtccgccc	tttccacgtc	3240
cagctcagca	accctaagtt	tggggcccac	ctggggccagc	cccactccac	caccatcatc	3300

atcagggacc	cagatgaact	ggaccggagc	ttcacgagtc	agatgttgtc	atcacagcca	3360
ccccctcacg	gcgacctggg	cgccccgcag	aaccccaatg	ctaaggccgc	tgggtccagg	3420
aagatccatt	tcaactggct	gcccccttct	ggcaagccaa	tggggtacag	ggtaaagtac	3480
tggattcagg	gtgactccga	atccgaagcc	cacctgctcg	acagcaaggt	gccctcagtg	3540
gagctcacca	acctgtaccc	gtattgcgac	tatgagatga	aggtgtgcgc	ctacggggct	3600
cagggcgagg	gacctacag	ctccctgggtg	tcctgcccga	cccaccagga	agtgccagc	3660
gagccagggc	gtctggcctt	caatgtcgtc	tcctccacgg	tgaccagct	gagctgggt	3720
gagccggctg	agaccaacgg	tgagatcaca	gcctacgagg	tctgctatgg	cctgggtcaac	3780
gatgacaacc	gacctattgg	gcccattgaag	aaagtgtctg	ttgacaaccc	taagaaccgg	3840
atgctgctta	ttgagaacct	tcgggagtc	cagccctacc	gctacacgg	gaaggcgcg	3900
aacggggccg	gctggggg	tgagcgggag	gccatcatca	acctggccac	ccagcccaag	3960
aggcccatgt	ccatcccat	catccctgac	atccctatcg	tggacgcccc	gagcggggag	4020
gactacgaca	gcttccttat	gtacagcgat	gacgttctac	gctctccatc	gggcagccag	4080
aggccagcg	tctccgatga	caactggctgc	ggctggaagt	tcgagccct	gctgggggag	4140
gagctggacc	tgcggcgcg	cacgtggcgg	ctgcccccg	agctcatccc	gcgcctgtcg	4200
gccagcagcg	ggcgctcctc	cgacgccgag	gcgccccacg	ggcccccgga	cgacggcggc	4260
gcgggcgga	agggcggcag	cctgccccgc	agtgcgacac	ccgggcccc	cggagagcac	4320
ctggtgaatg	gccggatgga	ctttgccttc	ccgggcagca	ccaactccct	gcacaggatg	4380
accacgacca	gtgctgctgc	ctatggcacc	cacctgagcc	cacacgtgcc	ccaccgcgtg	4440
ctaagcacat	cctccaccct	cacacgggac	tacaactcac	tgaccgcgtc	agaacactca	4500
cactcgacca	cactgccgag	ggactactcc	accctcacct	ccgtctcctc	ccacggcctc	4560
cctcccatct	gggaacacgg	gaggagcagg	cttccgctgt	cctgggccc	ggggtcccgg	4620
agtcgggctc	agatgaaagg	gttccccct	tccaggggcc	cacgagactc	tataatcctg	4680
gctgggaggc	cagcagcgcc	ctcctggggc	ccagactctc	gcctgactgc	tgggtgtgcc	4740
gacacgcca	cccgctgggt	gttctctgcc	ctggggccca	catctctcag	agtgagctgg	4800
caggagccgc	ggtgcgagcg	gccgctgcag	ggctacagtg	tggagtacca	gctgctgaac	4860
ggcggtgagc	tgcctcggt	caacatcccc	aacctgccc	agacctcggt	ggtggtggaa	4920
gacctcctgc	ccaaccactc	ctacgtgttc	cgctgcggg	cccagagcca	ggaaggctgg	4980
ggccgagagc	gtgagggtgt	catcaccatt	gaatcccagg	tgcacccgca	gagccactg	5040
tgtcccctgc	caggctccgc	cttcactttg	agcactccca	gtgccccagg	cccgctgggtg	5100
ttcactgccc	tgagcccaga	ctcgctgcag	ctgagctggg	agcggccacg	gaggcccaat	5160
ggggatatcg	tcggctacct	ggtgacctgt	gagatggccc	aaggaggagg	tccagccacc	5220
gcattccggg	tggatggaga	cagccccgag	agccggctga	ccgtgccggg	cctcagcgag	5280
aacgtgccct	acaagttaa	ggtgcaggcc	aggaccactg	agggttcgg	gccagagcgc	5340
gagggcatca	tcacataga	gtcccaggat	ggaggtccct	tccgcagct	gggcagccgt	5400
gccgggctct	tccagcacc	gctgcaaagc	gagtacagca	gcctctccac	caccacacc	5460
agcgccaccg	agcccttcct	agtgggtccg	accctggggg	cccagcacct	ggaggcaggc	5520
ggctccctca	cccgcatgt	gaccagagg	tttgtgagcc	ggacactgac	caccagcgga	5580
acccttagca	cccacatgga	ccaacagttc	ttccaaactt	ga		5622

<210> 19

<211> 5622

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence; Note =
synthetic construct

<400> 19

atggcagggc	cacggcccag	cccatggggc	aggctgctcc	tggcagcctt	gatcagcgtc	60
agcctctctg	ggaccttgaa	ccgctgcaag	aaggcccaaa	taaagagctg	cacggagtgt	120
gtccgtgtgg	ataaggactg	cgcctactgc	acagacgaga	tgttcaggga	ccggcgctgc	180
aacacccagg	cggagctgct	ggccgcgggc	tgccagcggg	agagcatcgt	ggtcatggag	240
agcagcttcc	aaatcacaga	ggagacccag	attgacacca	ccctgcggcg	cagccagatg	300
tccccccaag	gcctgcgggt	ccgtctgcgg	cccggtgagg	agcggcattt	tgagctggag	360
gtgtttgagc	cactggagag	ccccgtggac	ctgtacatcc	tcatggactt	ctccaaactcc	420
atgtccgatg	atctggacaa	cctcaagaag	atggggcaga	acctggctcg	ggtcctgagc	480
cagctcacca	gcgactacac	tattggattt	ggcaagtgtg	tggacaaagt	cagcgtccc	540
cagacggaca	tgaggcctga	gaagctgaag	gagccttggc	ccaacagtga	cccccccttc	600

tccttcaaga	acgtcatcag	cctgacagaa	gatgtggatg	agttccggaa	taaactgcag	660
ggagagcgga	tctcaggcaa	cctggatgct	cctgagggcg	gcttcgatgc	catcctgcag	720
acagctgtgt	gcacgagggg	cattggctgg	cgccccgaca	gcacccacct	gctgggtcttc	780
tccaccgagt	cagccttcca	ctatgaggct	gatggcgcca	acgtgctggc	tggcatcatg	840
agccgcaacg	atgaacggtg	ccacctggac	accacgggca	cctacaccca	gtacaggaca	900
caggactacc	cgtcggtgcc	cacctggtg	cgcttgctcg	ccaagcacia	catcatcccc	960
atctttgctg	tcaccaacta	ctcctatagc	tactacgaga	agcttcacac	ctatttccct	1020
gtctcctcac	tgggggtgct	gcaggaggac	tcgtccaaca	tcgtggagct	gctggaggag	1080
gccttcaatc	ggatccgctc	caacctggac	atccggggcc	tagacagccc	ccgaggcctt	1140
cggacagagg	tcacctccaa	gatgttccag	aagacgagga	ctgggtcctt	tcacatccgg	1200
cggggggaag	tgggtatata	ccagggtgcag	ctgcggggcc	ttgagcacgt	ggatgggacg	1260
cacgtgtgcc	agctgccgga	ggaccagaag	ggcaacatcc	atctgaaacc	ttccttctcc	1320
gacggcctca	agatggacgc	gggcatcatc	tgtgatgtgt	gcacctgcga	gctgcaaaaa	1380
gaggtgcggt	cagctcgctg	cagcttcaac	ggagacttcg	tgtgcggaca	gtgtgtgtgc	1440
agcgagggct	ggagtggcca	gacctgcaac	tgctccaccg	gctctctgag	tgacattcag	1500
ccctgcctgc	gggagggcga	ggacaagccg	tgctccggcc	gtggggagtg	ccagtgcggg	1560
cactgtgtgt	gctacggcga	aggccgctac	gagggtcagt	tctgcgagta	tgacaacttc	1620
cagtgtcccc	gcacttccgg	gttccctctgc	aatgaccgag	gacgctgctc	catgggccag	1680
tgtgtgtgtg	agcctggttg	gacaggccca	agctgtgact	gtccccctcag	caatgccacc	1740
tgcatacgaca	gcaatggggg	catctgtaat	ggacgtggcc	actgtgagtg	tggccgctgc	1800
cactgccacc	agcagtcgct	ctacacggac	accatctgcg	agatcaacta	ctcggcgctc	1860
acccgggcct	ctgcgaggac	ctacgctcct	gcgtgcagtg	ccaggcgctg	ggcaccggcg	1920
agaagaaggg	gcgcacgtgt	gaggaatgca	acttcaaggt	caagatgggt	gacgagctta	1980
agagaggcga	ggaggtggtg	gtgcgctgct	ccttccggga	cgaggatgac	gactgcacct	2040
acagctacac	catggaaggt	gacggcgccc	ctggggcccaa	cagcactgtc	ctggtgcaca	2100
agaagaaggg	actgcccctc	gggctccttc	tggtgggtca	tccccctgct	cctcctcctc	2160
ctgccgctcc	tggccctgct	actgctgcta	tgctggaagt	actgtgcctg	ctgcaaggcc	2220
tgcctggcac	ttctcccgtg	ctgcaaccga	ggtcacatgg	tgggctttaa	ggaagaccac	2280
tacatgctgc	gggagaacct	gatggcctct	gaccacttgg	acacgcccac	gctgcgcgac	2340
gggaacctca	agggccgtga	cgtggtccgc	tggaagggtca	ccaacaacat	gcagcggcct	2400
ggctttgcca	ctcatgccgc	cagcatcaac	cccacagagc	tggtgcccta	cgggctgtcc	2460
ttgcgccctg	cccgcctttg	caccgagaac	ctgctgaagc	ctgacactcg	ggagtgcgcc	2520
cagctgcgcc	aggaggtgga	ggagaacctg	aacgaggtct	acaggcagat	ctccggtgta	2580
cacaagctcc	agcagaccaa	gttccggcag	cagcccaatg	ccgggaaaaa	gcaagaccac	2640
accattgtgg	acacagtgct	gatggcgccc	cgctcggcca	agccggccct	gctgaagctt	2700
acagagaagc	aggtggaaca	gagggccttc	cacgacctca	aggtggcccc	cggctactac	2760
accctcactg	cagaccagga	cgccccgggg	atggtggagt	tccaggaggg	cgtggagctg	2820
gtggacgtac	gggtgcccct	cttttatccg	cctgaggatg	acgacgagaa	gcagctgctg	2880
gtggaggcca	tcgacgtgcc	cgcaggcact	gccaccctcg	gccgcgcctc	ggtaaacatc	2940
accatcatca	aggagcaagc	cagagacgtg	gtgtcccttg	agcagcctga	gttctcggtc	3000
agccgcgggg	accaggtggc	ccgcatacct	gtcatccggc	gtgtcctgga	cggcgggaag	3060
tcccaggtct	cctaccgcac	acaggatggc	accgcgcagg	gcaaccggga	ctacatcccc	3120
gtggaggggt	agctgctggt	ccagcctggg	gagggcctgga	aagagctgca	ggtgaagctc	3180
ctggagctgc	aagaagttga	ctccctcctg	cggggccggc	aggtccgccc	tttccacgtc	3240
cagctcagca	accctaagtt	tggggcccac	ctggggccagc	cccactccac	caccatcatc	3300
atcagggacc	cagatgaact	ggaccggagc	ttcacgagtc	agatgttggt	atcacagcca	3360
ccccctcacg	gcgacctggg	cgccccgcag	aaccccaatg	ctaaggccgc	tgggtccagg	3420
aagatccatt	tcaactggct	gcccccttct	ggcaagccaa	tgggggtacag	ggtaaagtac	3480
tggattcagg	gtgactccga	atccgaagcc	cacctgctcg	acagcaaggt	gccctcagtg	3540
gagctcacca	acctgtaccc	gtattgcgac	tatgagatga	aggtgtgcgc	ctacggggct	3600
cagggcgagg	gaccttacag	ctccctgggt	tcctgccgca	cccaccagga	agtgcccgac	3660
gagccagggc	gtctggcctt	caatgtcgtc	tcctccacgg	tgaccagct	gagctgggct	3720
gagccggctg	agaccaacgg	tgagatcaca	gcctacgagg	tctgctatgg	cctgggtcaac	3780
gatgacaacc	gacctattgg	gcccatagaag	aaagtgtctg	ttgacaaccc	taagaaccgg	3840
atgctgctta	ttgagaacct	tcgggagtcc	cagccctacc	gctacacggt	gaaggcgcg	3900
aacggggccg	gctggggggc	tgagcgggag	gccatcatca	acctggccac	ccagcccaag	3960
aggcccatgt	ccatccccat	catccctgac	atccctatcg	tggacgcccc	gagcggggag	4020
gactacgaca	gcttccctat	gtacagcgat	gacgttctac	gctctccatc	gggcagccag	4080
aggcccgagc	tctccgatga	cactggctgc	ggctggaagt	tcgagccctc	gctgggggag	4140
gagctggacc	tgcggcgcg	cacgtggcgg	ctgccccccg	agctcatccc	gcgcctgtcg	4200
gccagcagcg	ggcgctcctc	cgacgcccag	gcgccccacg	ggcccccgga	cgacggcggc	4260
gcgggcccga	agggcgggcag	cctgccccgc	agtgcgacac	ccgggcccccc	cggagagcac	4320

ctggtgaatg	gccggatgga	ctttgccttc	ccgggcagca	ccaactccct	gcacaggatg	4380
accacgacca	gtgctgctgc	ctatggcacc	cacctgagcc	cacacgtgcc	ccaccgcgtg	4440
ctaagcacat	cctccaccct	cacacgggac	tacaactcac	tgacccgctc	agaacactca	4500
cactcgacca	cactgccgag	ggactactcc	accctcacct	ccgtctcctc	ccacggcctc	4560
cctcccatct	gggaacacgg	gaggagcagg	cttccgctgt	cctgggccct	ggggtcccg	4620
agtccgggctc	agatgaaagg	gttccccctt	tccagggggc	cacgagactc	tataatcctg	4680
gctgggaggg	cagcagcgcc	ctcctggggc	ccagactctc	gcctgactgc	tggtgtgccc	4740
gacacgcca	ccgcctggt	gttctctgcc	ctggggccca	catctctcag	agtgagctgg	4800
caggagccgc	ggtgcgagcg	gccgctgcag	ggctacagtg	tggagtacca	gctgctgaac	4860
ggcggtgagc	tgcctcggt	caacatcccc	aacctgccc	agacctcgg	ggtggtggaa	4920
gacctcctgc	ccaaccactc	ctacgtgttc	cgctgcggg	cccagagcca	ggaaggctgg	4980
ggccgagagc	gtgaggggtg	catcaccatt	gaatcccagg	tgcacccgca	gagcccactg	5040
tgtcccctgc	caggctccgc	cttcaactttg	agcactccca	gtgccccagg	cccgtggtg	5100
ttcaactgccc	tgagcccaga	ctcgtctgcag	ctgagctggg	agcggccacg	gaggcccaat	5160
ggggatatcg	tgggtacct	ggtgacctgt	gagatggccc	aaggaggagg	tccagccacc	5220
gcattccggg	tggatggaga	cagccccgag	agccggctga	ccgtgccggg	cctcagcgag	5280
aacgtgccct	acaagttaa	ggtgcaggcc	aggaccactg	agggcttcgg	gccagagcgc	5340
gagggcatca	tcacataga	gtcccaggat	ggaggtccct	tcccgcagct	gggcagccgt	5400
gccgggctct	tccagcacc	gctgcaaagc	gagtacagca	gcctctccac	caccacacc	5460
agcggccaccg	agcccttct	agtgggtccg	accctggggg	cccagcacct	ggaggcaggc	5520
ggctccctca	ccggcatgt	gaccagagg	tttgtgagcc	ggacactgac	caccagcgga	5580
acccttagca	cccacatgga	ccaacagttc	ttccaaactt	ga		5622

What is claimed is:

1. A method of reducing the proliferation of a cancer cell which comprises inhibiting ligand binding to an integrin receptor on the cancer cell, wherein the integrin receptor comprises an integrin.
2. The method of claim 1, wherein the integrin receptor comprises integrin B4.
3. The method of claim 1, wherein the integrin receptor comprises integrin A6.
4. The method of claim 1, wherein the ligand that binds to the integrin receptor is laminin5.
5. The method of claim 1, wherein the integrin receptor is A6B4.
6. The method of claim 1, wherein the ligand comprises laminin5.
7. The method of claim 1, wherein the ligand comprises the gamma-2 subunit of laminin5.
8. The method of claim 1, wherein inhibiting ligand binding to an integrin receptor comprises contacting a A6 integrin with a composition that inhibits ligand binding.
9. The method of claim 1, wherein inhibiting ligand binding to an integrin receptor comprises contacting a B4 integrin with a composition that inhibits ligand binding.
10. The method of claim 1, wherein inhibiting ligand binding to an integrin receptor comprises contacting a laminin5 with a composition that inhibits ligand binding.
11. The method of claim 1, wherein inhibiting ligand binding to an integrin receptor comprises contacting a gamma-2 subunit with a composition that inhibits ligand binding.
12. A method of reducing the proliferation of a cancer cell which comprises reducing integrin-integrin interaction, integrin receptor clustering interaction, or integrin-non-integrin protein interaction.
13. The method of claim 12, wherein reducing integrin-integrin interaction, integrin receptor clustering interaction, or integrin-non-integrin protein interaction comprises contacting a A6 integrin with a composition that inhibits an interaction between the B4 integrin and another integrin or protein molecule.
14. The method of claim 12, wherein reducing integrin-integrin interaction, integrin receptor clustering interaction, or integrin-non-integrin protein interaction comprises contacting a B4 integrin with a composition that inhibits the interaction between the B4 integrin and another integrin or protein molecule..
15. The method of claim 12, wherein reducing integrin-integrin interaction, integrin receptor clustering interaction, or integrin-non-integrin protein interaction comprises contacting a

laminin5 with a composition that inhibits ligand binding.

16. The method of claim 12, wherein reducing integrin-integrin interaction, integrin receptor clustering interaction, or integrin-non-integrin protein interaction comprises contacting a gamma2 subunit with a composition that inhibits ligand binding.

17. The method of claim 12, wherein the non-integrin protein comprises a growth factor receptor.

18. The method of claim 12, wherein the non-integrin protein comprises a hemidesmosome junction.

19. The method of claim 12, wherein the non-integrin protein comprises a SH2 domain.

20. The method of claim 19, wherein the non-integrin protein comprises a Shc protein.

21. The method of claim 12, wherein the non-integrin protein comprises a IRS-1 protein.

22. The method of claim 12, wherein the non-integrin protein comprises a IRS-2 protein.

23. A method of reducing the proliferation of a cancer cell which comprises reducing the production of an integrin by the cancer cell.

24. The method of claim 23, wherein the production of an integrin is reduced by inhibiting signaling leading to induction of expression of an integrin.

25. The method of claim 23, wherein reducing the production of an integrin comprises inhibiting alpha6 production.

26. The method of claim 25, wherein inhibiting alpha6 production further comprises using antisense molecules to alpha6 mRNA.

27. The method of claim 23, wherein reducing the production of an integrin comprises inhibiting beta4 production.

28. The method of claim 27, wherein inhibiting beta4 production further comprises using antisense molecules to beta4 mRNA.

29. A method of reducing the proliferation of a cancer cell which comprises reducing the production of an integrin receptor ligand by the cancer cell.

30. The method of claim 29, wherein reducing the production of an integrin receptor ligand comprises inhibiting gamma2 production.

31. The method of claim 29, wherein reducing the production of an integrin receptor ligand comprises inhibiting laminin production.

32. The method of claim 29, wherein reducing the production of an integrin receptor

ligand comprises inhibiting laminin5 production.

33. A method of reducing the proliferation of a cancer cell which comprises interfering with an integrin signaling pathway.

34. The method of claim 33, wherein interfering with an integrin signaling pathway comprises contacting an A6 integrin in the cell with a composition that inhibits ligand binding.

35. The method of claim 33, wherein interfering with an integrin signaling pathway comprises contacting a B4 integrin with a composition that inhibits ligand binding.

36. The method of claim 33, wherein interfering with an integrin signaling pathway comprises contacting a laminin5 with a composition that inhibits ligand binding.

37. The method of claim 33, wherein interfering with an integrin signaling pathway comprises contacting a gamma2 subunit with a composition that inhibits ligand binding.

38. The method of claim 33, wherein interfering with an integrin signaling pathway comprises contacting the cancer cell with a molecule that interferes with at least one of talin, paxillin, vinculin, a CAS family protein, CRX, NCK, FAK, ILK, Src, Fyn, Shc, Grb-2, Guanine nucleotide exchange factors, SOS, DOCK 180, Vav, Syk, P-1-3 kinase, AKT, Bad, Bid, Caspase 9, Cdc42, PAK, Rac, Rho, Rho kinase, Ras, Caveolin, Tetraspan, Receptor-type protein tyrosine phosphatase, SHP-2, Alpha-actinin, Filamin, Cytohesin, Beta3-endonexin, ICAP-1, RACK-1, CIB, actin, receptor tyrosine kinase, IRS-1 or IRS-2.

39. The method of claim 33, wherein interfering with an integrin signaling pathway comprises contacting the cancer cell with an agent that interferes with post-translational modification of integrins.

40. The method of claim 39, wherein the post translational modification is glycosylation or phosphorylation.

41. The method of claims 1, 12, 23, 29, 33, wherein the integrin comprises an A6 integrin.

42. The method of claims 1, 12, 23, 29, 33, wherein the integrin comprises a B4 integrin.

43. The method of claims 1, 12, 23, 29, 33, further comprising reducing a laminin5-integrin interaction.

44. The method of claims 1, 12, 23, 29, 33, further comprising reducing a laminin5 gamma2 integrin interaction.

45. The method of claims 1, 12, 23, 29, 33, wherein reducing the proliferation of the cancer cells is selective.

46. The method of claims 1, 12, 23, 29, 33, wherein the cancer cell is not an MDA-MB-

435 cell.

47. The method of claims 1, 12, 23, 29, 33, wherein the cancer cell is not an HMT-3522 cell.

48. The method of claims 1, 12, 23, 29, 33, wherein the cancer cell is not an RKO colon carcinoma line.

49. The method of claims 1, 12, 23, 29, 33, wherein the cancer cell does not express exogenous B4 integrin.

50. The method of claims 1, 12, 23, 29, 33, further comprising contacting the cancer cells with a small molecule, peptide, peptide mimetic, or oligonucleotide or synthetic analog thereof.

51. The method of claim 50, wherein the cancer cells are contacted with dominant-negative beta 4 integrin.

52. The method of claim 50, wherein the cancer cell is contacted with an antisense molecule.

53. The method of claim 52, wherein the antisense molecule is linked to a leader sequence which enables translocation across a cell membrane.

54. The method of claim 53, wherein the leader sequence binds to a cell surface protein which facilitates internalization.

55. The method of claim 54, wherein the leader sequence is TAT or antennapedia, or fragment thereof.

56. The method of claim 52, wherein the antisense molecule is an alpha6 RNA antisense molecule.

57. The method of claim 47, wherein the small molecule peptide, peptide mimetic, or oligonucleotide or synthetic analog thereof is linked to a carrier.

58. The method of claim 57, wherein the carrier is at least one of a lipidic carrier, charged carrier, retroviral carrier, TAT or fragment thereof, antennapedia or fragment thereof, or polyethylene glycol.

59. The method of any one of claims 1, 12, 23, 29, 33, further comprising contacting the cancer cell with another agent which modulates cell signaling, a chemotherapeutic drug, or treated with radiation or angiogenesis inhibitor.

60. The method of any of claims 1, 12, 23, 29, 33, wherein reducing the proliferation of cancer cell is *in vitro*.

61. The method of any of claims 1, 12, 23, 29, 33, wherein reducing the proliferation

of the cancer cell is *in vivo*.

62. The method of any of claims 1, 12, 23, 29, 33, wherein the cancer cell is selected from the group consisting of melanoma, adenoma, lymphoma, myeloma, carcinoma, plasmocytoma, sarcoma, glioma, thyoma, leukemia, skin cancer, retinal cancer, breast cancer, prostate cancer, colon cancer, esophageal cancer, stomach cancer, pancreas cancer, brain tumors, lung cancer, ovarian cancer, cervical cancer, hepatic cancer, gastrointestinal cancer, and head and neck cancer cells.

63. The method of claims 1, 12, 23, 29, 33, wherein the cancer cell is killed.

64. The method of claims 1, 12, 23, 29, 33, wherein the cancer cell expresses a mutated Ras.

65. The method of claims 1, 12, 23, 29, 33, wherein the cancer cell expresses a mutated Ras and a mutated p53.

66. The method of claims 1, 12, 23, 29, 33, wherein the cancer cell expresses a mutated Ras and activates the AKT/PKB protein.

67. The method of claims 1, 12, 23, 29, 33, wherein the cancer cell expresses a mutated Ras, a mutated p53, and activates the AKT/PKB protein.

68. The method of claims 1, 12, 23, 29, 33, wherein the cancer cell expresses a mutated APC.

69. The method of claims 1, 12, 23, 29, 33, wherein the cancer cell expresses a mutated Ras and mutated APC.

70. A method of isolating molecules that bind with a target molecule selected from the group consisting, B4 integrin, alpha6 integrin, and the gamma2 subunit of laminin5 comprising 1) contacting a library of molecules with the target molecule and 2) collecting molecules that bind the target molecule producing an enriched population of molecules.

71. The method of claim 70, further comprising the step of repeating steps 1 and 2 with the enriched population of molecules.

72. The method of claim 70, wherein the library comprises a small molecule, peptide, peptide mimetic, or oligonucleotide.

73. A method of assessing a subject's risk of developing cancer comprising determining the amount of A6 present in a target cell obtained from the subject, wherein a determination of increased levels of A6 correlates with an increased risk of cancer.

74. The method of claim 73, further comprising comparing the amount A6 present to the

amount in a control cell.

75. The method of claim 73, wherein determining the amount of A6 present in the target cell comprises assaying the amount of A6 mRNA in the cell.

76. The method of claim 75, wherein the assaying the amount of mRNA in the cell comprises hybridizing a A6 probe to a sample of the subject's mRNA.

77. The method claim 75, wherein the assaying the amount of mRNA in the cell comprises hybridizing a A6 primer to a sample of the subject's mRNA.

78. The method claim 77, wherein the assaying the amount of mRNA further comprises performing an nucleic acid amplification reaction involving the primer.

79. The method of claim 78, wherein the nucleic acid amplification reaction comprises reverse transcription, producing a cDNA.

80. The method of claim 79, wherein the nucleic acid amplification reaction further comprises performing a polymerase chain reaction on the cDNA.

81. The method of claim 73, wherein determining the amount of A6 present in the target cell comprises assaying the amount of A6 protein in the cell.

82. A method of assessing a subject's risk of acquiring cancer comprising determining the amount of B4 present in a target cell obtained from the subject, wherein a determination of increased levels of B4 correlates with an increased risk of cancer.

83. The method of claim 82, further comprising comparing the amount B4 present to the amount in a control cell.

84. A method of assessing a subject's risk of acquiring cancer comprising determining the amount of laminin5 present in a target cell obtained from the subject, wherein a determination of increased levels of laminin5 correlates with an increased risk of cancer.

85. The method of claim 84, further comprising comparing the amount laminin5 present to the amount in a control cell.

86. A method of assessing a subject's risk of acquiring cancer comprising determining the amount of gamma2 subunit present in a target cell obtained from the subject, wherein a determination of increased levels of gamma2 subunit correlates with an increased risk of cancer.

87. The method of claim 86, further comprising comparing the amount gamma2 subunit present to the amount in a control cell.

88. A method of reducing the proliferation of a cancer cell in a patient which comprises administering to the patient a composition which inhibits ligand binding to an integrin receptor on

the cancer cell, wherein the integrin receptor comprises an integrin.

89. A method of reducing the proliferation of a cancer cell in a patient which comprises administering to the patient a composition which reduces integrin-integrin interaction, integrin receptor clustering interaction, or integrin-non-integrin protein interaction.

90. A method of reducing the proliferation of a cancer cell in a patient which comprises administering to the patient a composition which reduces the production of an integrin or laminin by the cancer cell.

91. A method of reducing the proliferation of a cancer cell in a patient which comprises administering to the patient a composition which interferes with an integrin signaling pathway.

92. The methods of claims 88-91, wherein the reduction in cancer cell proliferation is selective.

93. The method of any of claims 88-91, wherein the administering is local or systemic.

94. The method of any of claims 88-91, wherein the patient is additionally administered an agent which modulates cell signaling, a chemotherapeutic drug, or treated with radiation or angiogenesis inhibitor.

95. The method of claim 94, wherein the additional agent is administered serially or in combination.

96. The method of claim 93, wherein the local administering is direct application to cancer cells.

97. The method of claim 96, wherein the direct application to cancer cells is performed during surgery.

98. The method of claim 97, wherein the direct application to cancer cells is performed topically to cancerous tissue.

99. The method of claim 94, wherein the systemic administration is by subcutaneous, intraperitoneal, intra-arterial, intravenous, or bolus administration, or by application through a catheter or similar apparatus.

100. The method of claim 94, wherein the systemic administration comprises a long-term release formulation.

101. The method of claim 94, wherein the systemic administration is by oral administration.

102. The method of claim 101 wherein the oral administration comprises administering a pill, capsule, tablet, liquid or suspension.

103. A method of reducing the proliferation of a cancer cell in a patient which comprises administering to a patient a vector comprising coding sequence for a protein or peptide which inhibits ligand binding to integrin receptors on cancer cells wherein the coding sequence is under the control of a promoter which functions in mammalian cells.

104. A method of reducing the proliferation of a cancer cell in a patient which comprises administering to a patient a vector comprising coding sequence for a protein or peptide which prevents integrin receptor subunits from interacting with one another, prevents integrin receptor clustering interaction, or prevents integrin receptor subunits from interacting with other proteins on cancer cells wherein the coding sequence is under the control of a promoter which functions in mammalian cells.

105. A method of reducing the proliferation of a cancer cell in a patient which comprises administering to a patient a vector comprising coding sequence for a protein or peptide which prevents integrin receptor subunits from interacting with one another, prevents integrin receptor clustering interaction, or prevents integrin receptor subunits from interacting with other proteins in cancer cells wherein the coding sequence is under the control of a promoter which functions in mammalian cells.

106. A method of reducing the proliferation of a cancer cell in a patient which comprises administering to a patient a vector comprising coding sequence for a protein or peptide which interferes with integrin subunit or laminin production wherein the coding sequence is under the control of a promoter which functions in mammalian cells.

107. A method of reducing the proliferation of a cancer cell in a patient which comprises administering to a patient a vector comprising coding sequence for a protein or peptide which interferes with an integrin signaling pathway of cells wherein the coding sequence is under the control of a promoter which functions in mammalian cells.

108. The methods of claims 103-107, wherein the reduction in cancer cell proliferation is selective.

109. The method of claims 103-107 wherein the vector is administered directly to a cancer cell.

110. The method of claims 103-107, wherein the vector is administered directly to a normal cell.

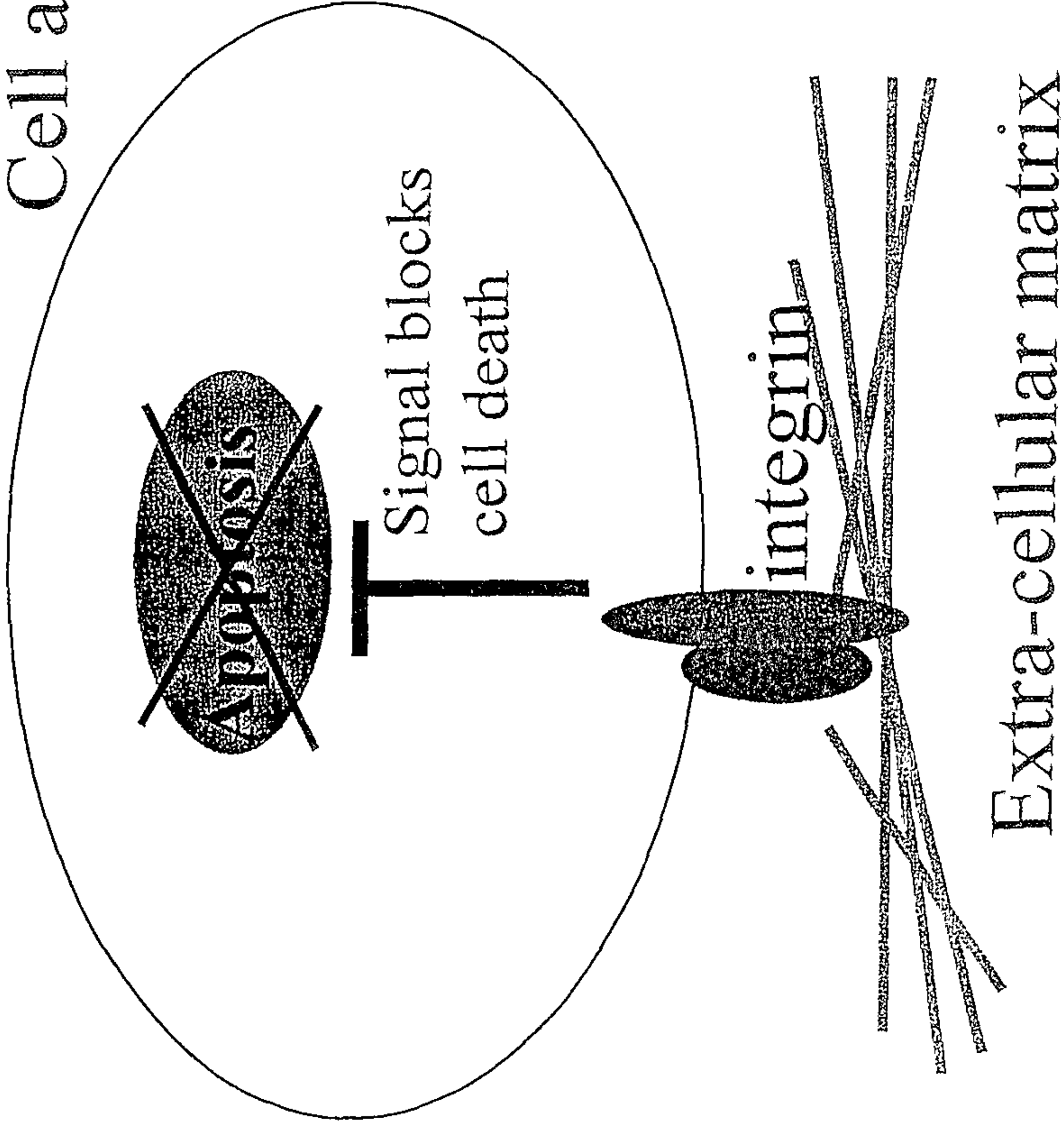
111. The method of claims 103-107, wherein the vector is packaged in a viral vector or liposome.

112. The method of claim 88 wherein the vector is a retroviral vector.

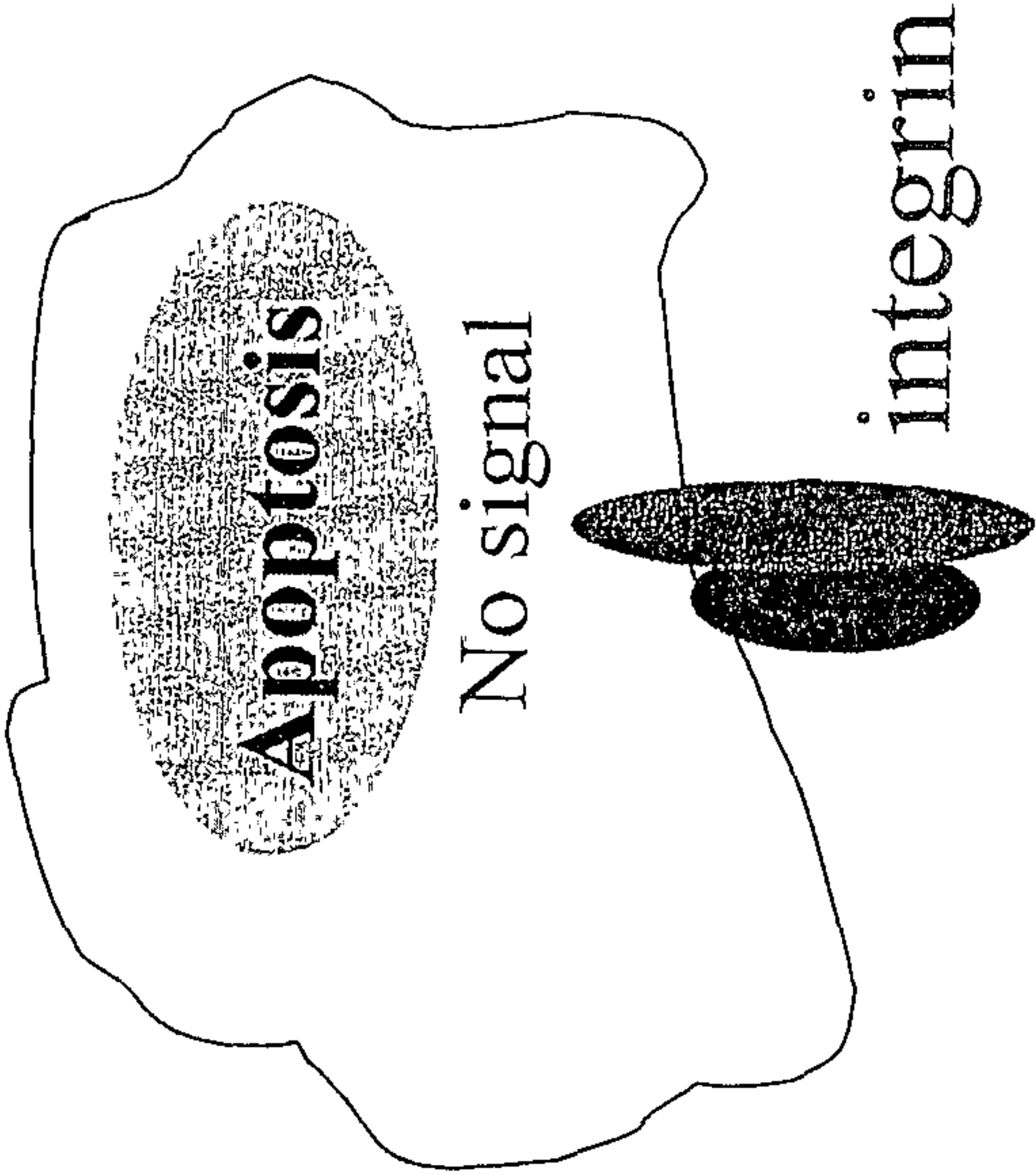
113. The method of any one of claims 103-107, wherein the vector is administered systemically.
114. The method of claim 109, wherein the direct administration is by topical application.
115. The method of claim 111, wherein the direct administration is by topical application.
116. The method of claim 114, wherein the direct administration is performed during surgery.
117. The method of claim 115, wherein the direct administration is performed during surgery.
118. The method of any of claims 103-107, wherein the patient is an animal.
119. The method of claim 118 wherein the animal is a mammal.
120. The method of claim 119, wherein the mammal is human.
121. The method of claims 103-107, wherein the cancer cells are selected from the group consisting of melanoma, adenoma, lymphoma, myeloma, carcinoma, plasmocytoma, sarcoma, glioma, thoma, leukemia, skin cancer, retinal cancer, breast cancer, prostate cancer, colon cancer, esophageal cancer, stomach cancer, pancreas cancer, brain tumors, lung cancer, ovarian cancer, cervical cancer, hepatic cancer, gastrointestinal cancer, and head and neck cancer cells.
122. The method of any of claims 103-107 wherein the patient is additionally administered at least one of another agent which modulates cell signaling, a chemotherapeutic drug, an angiogenesis inhibitor or treated with radiation.
123. The method of claim 120 wherein the other agent which modifies cell signaling, chemotherapeutic drug, angiogenesis inhibitor or radiation treatment is administered serially or in combination.

Normal cells require integrin-matrix interactions for survival

Cell alive



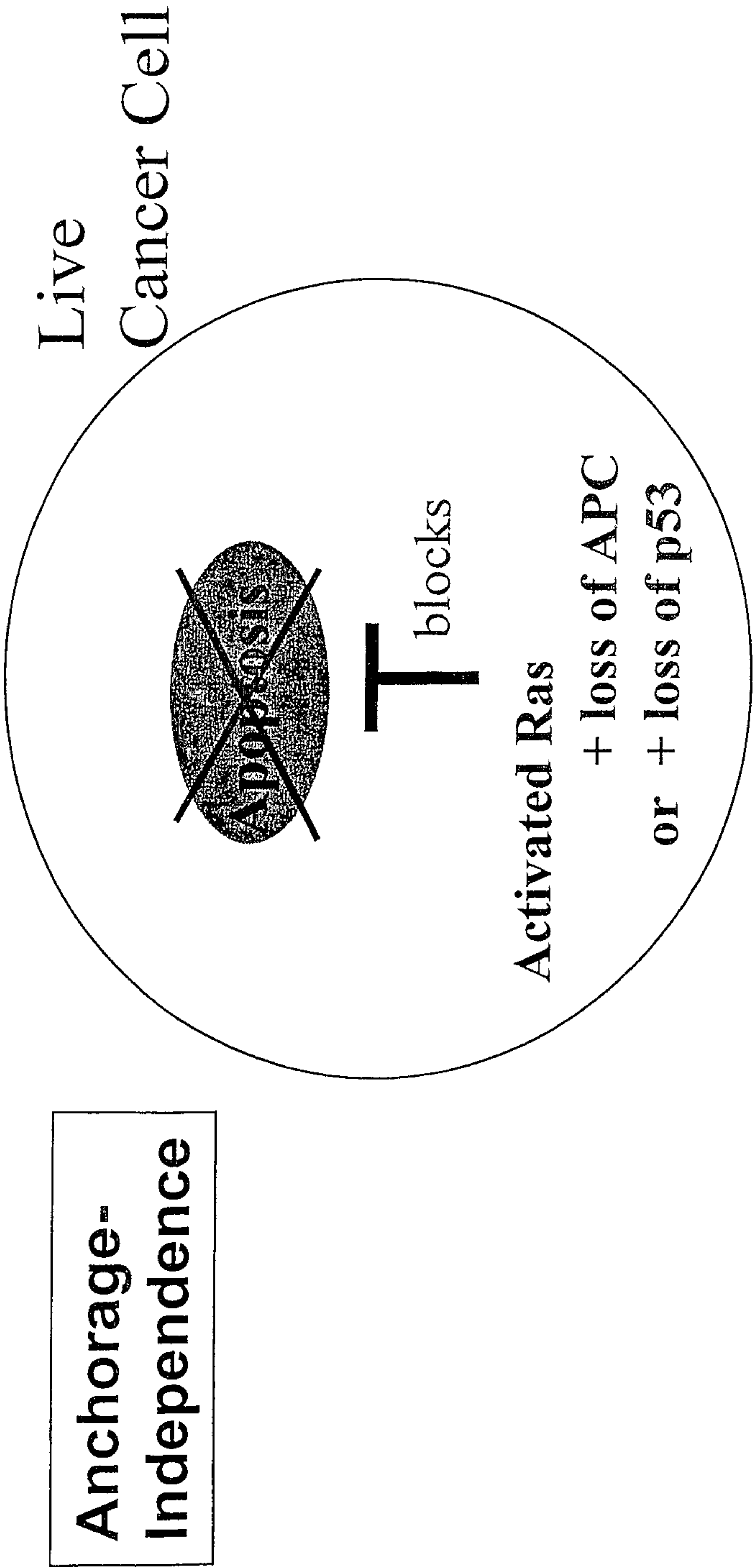
Cell dead



Lost contact with
Extra-cellular matrix

1/8
FIG. 1A

**Cells transformed by co-operating oncogenic mutations
survive without contact to extra-cellular matrix**



**Anchorage-
Independence**

No contact with
Extra-cellular matrix

Panel 2

FIG. 1B

Oncogenes co-operate to induce cancer cell survival via engagement of autocrine integrin signaling

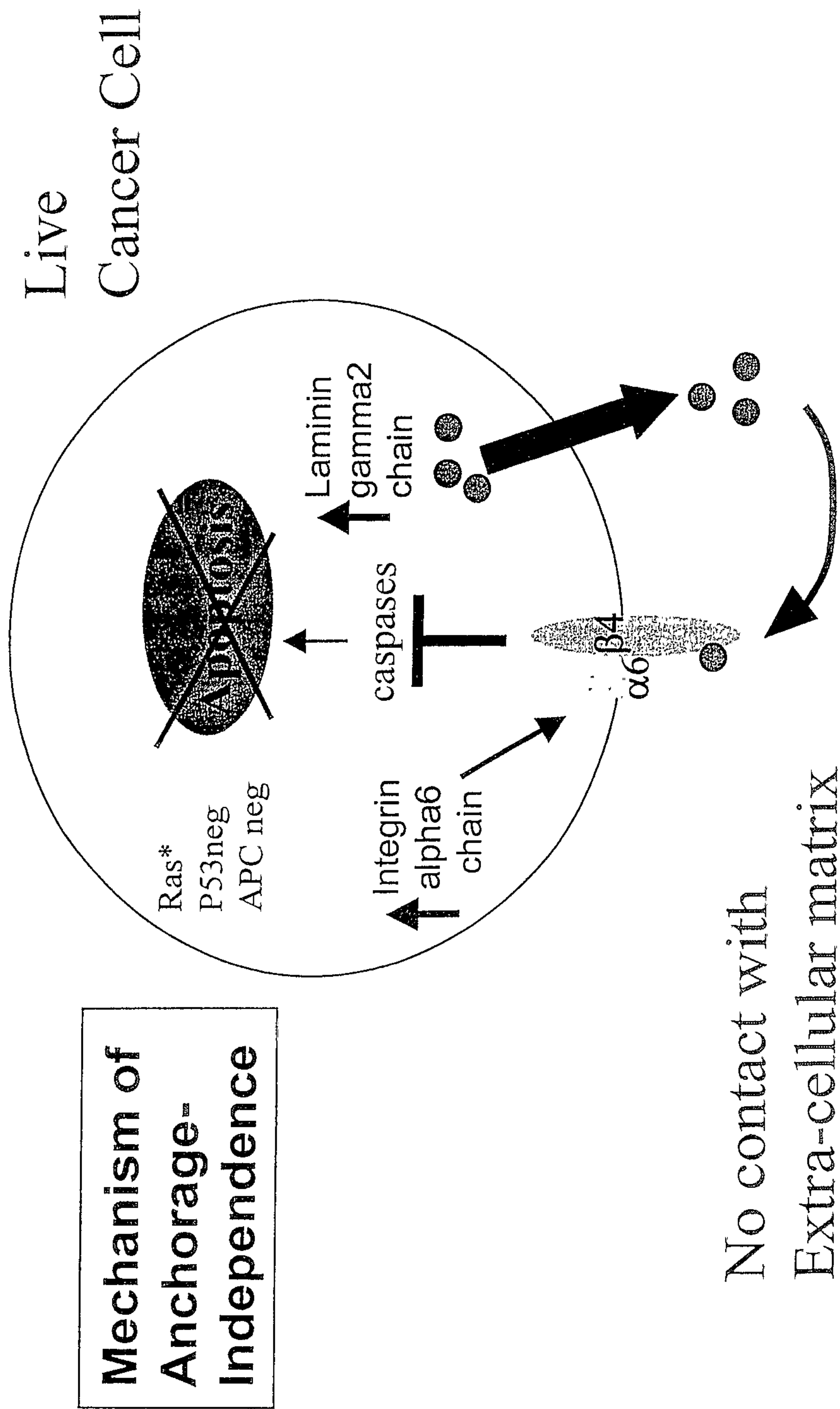


FIG. 1C

Panel 3

Inhibition of oncogene-induced autocrine integrin signaling loop causes cancer cell death

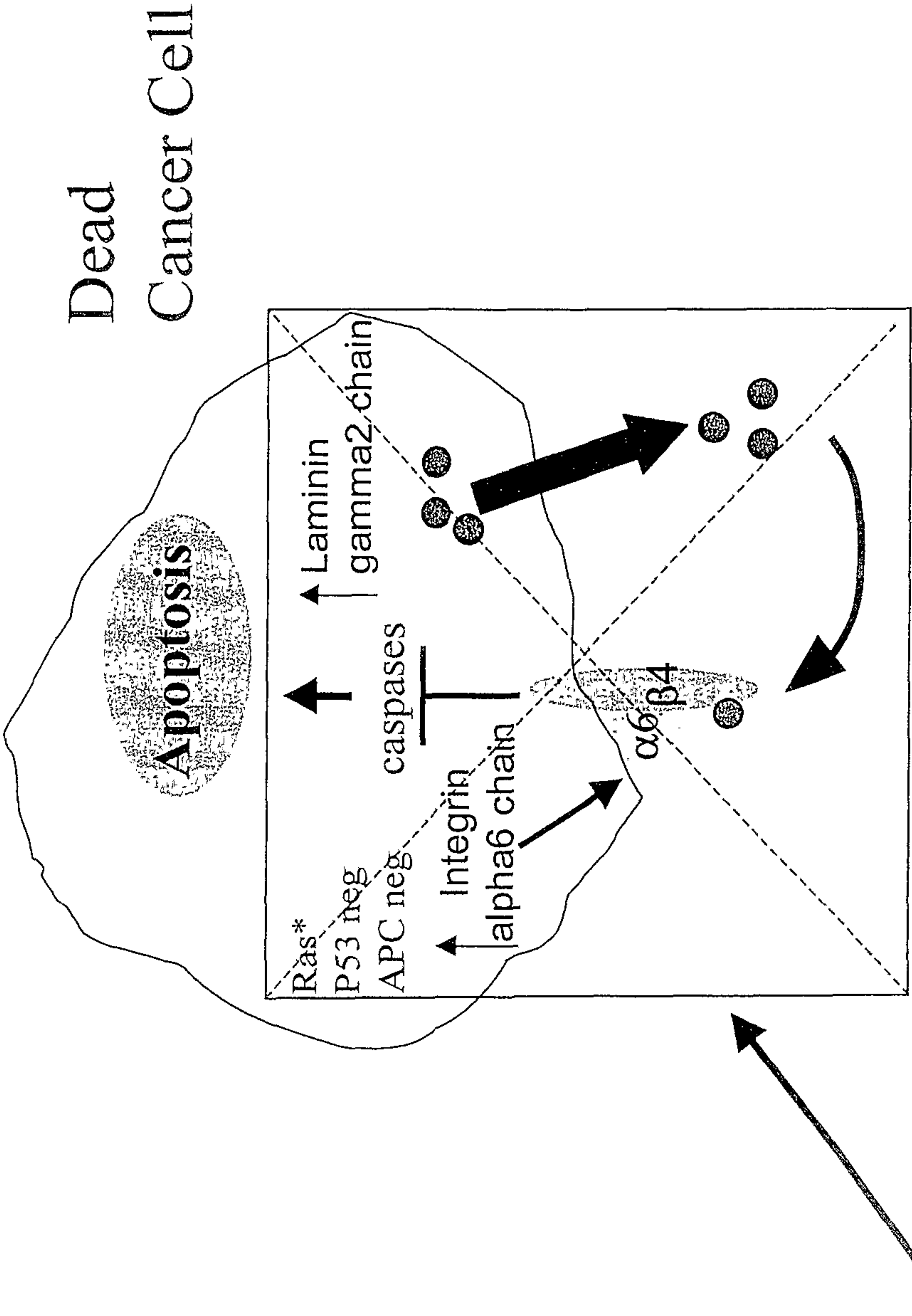


FIG. 1D

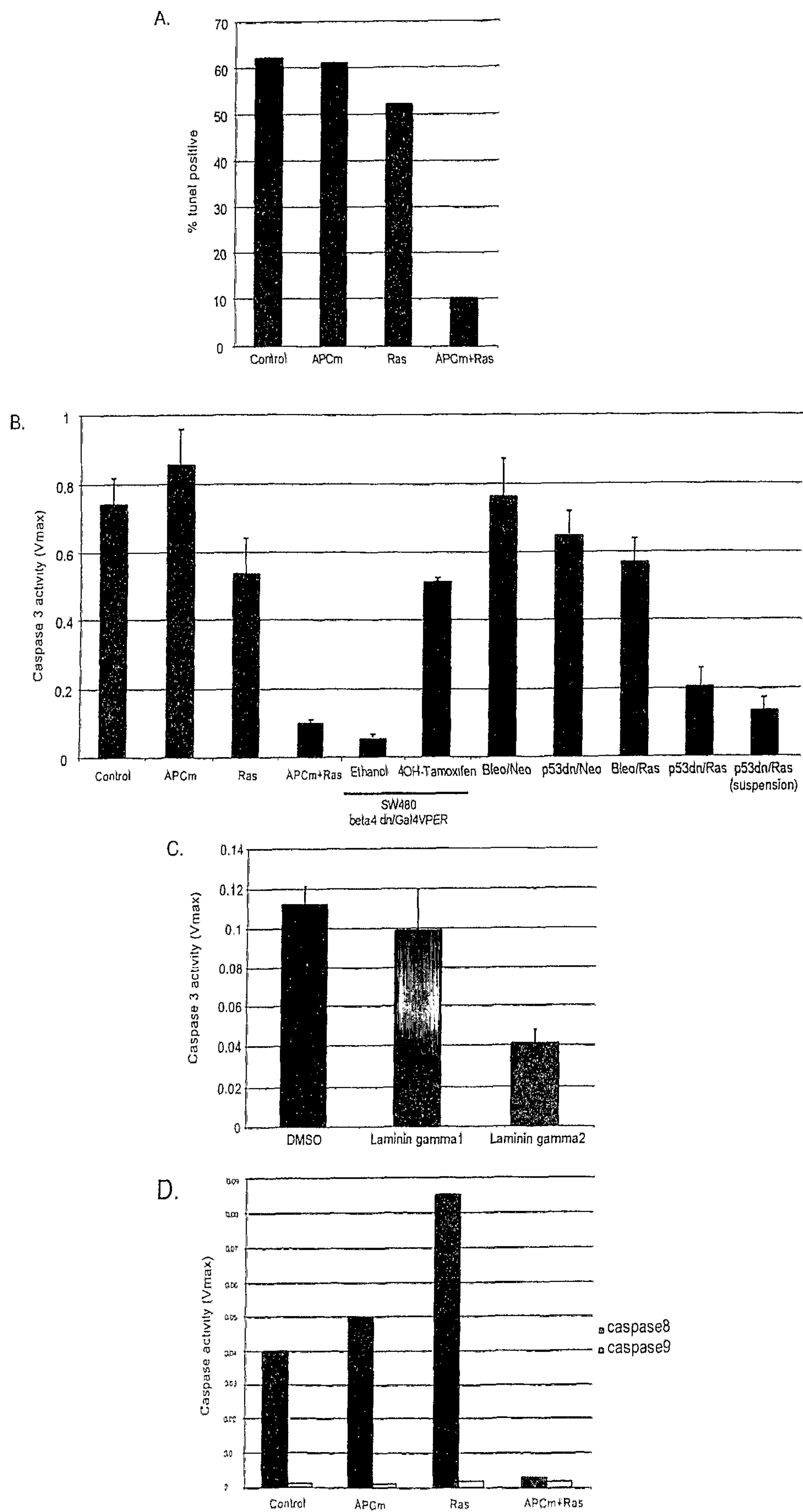
5/8
FIG. 2

FIG. 3

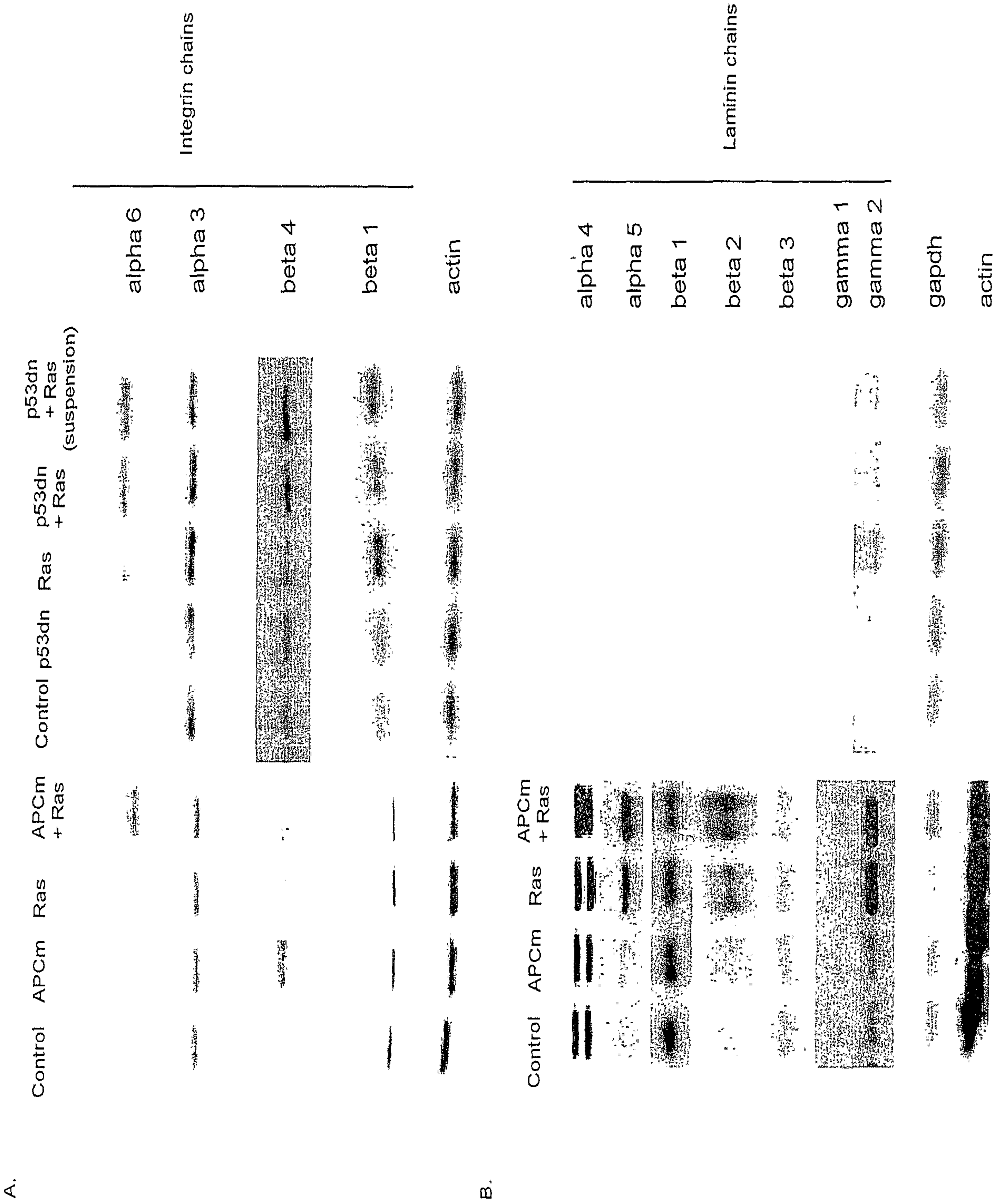


FIG. 4

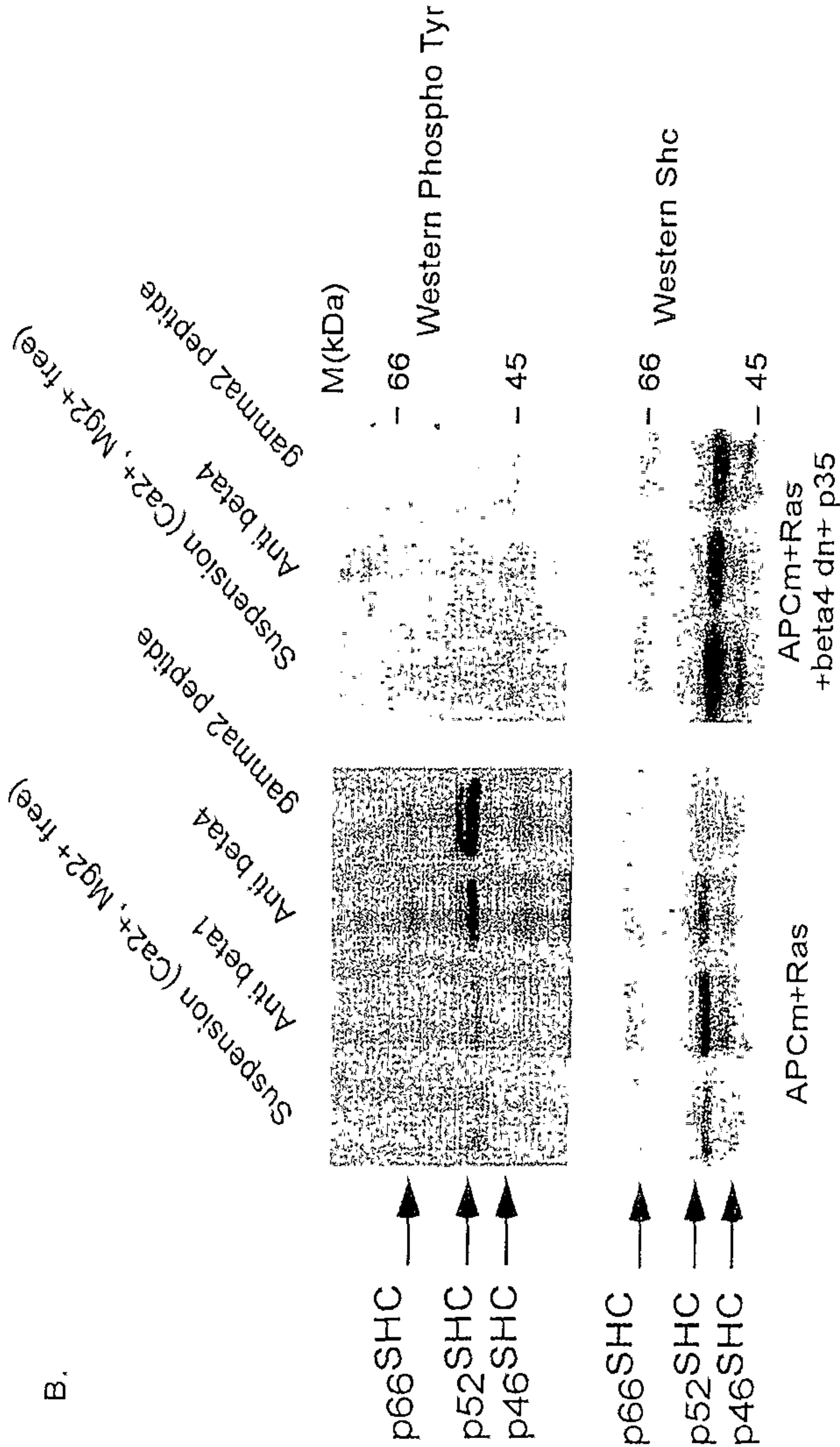
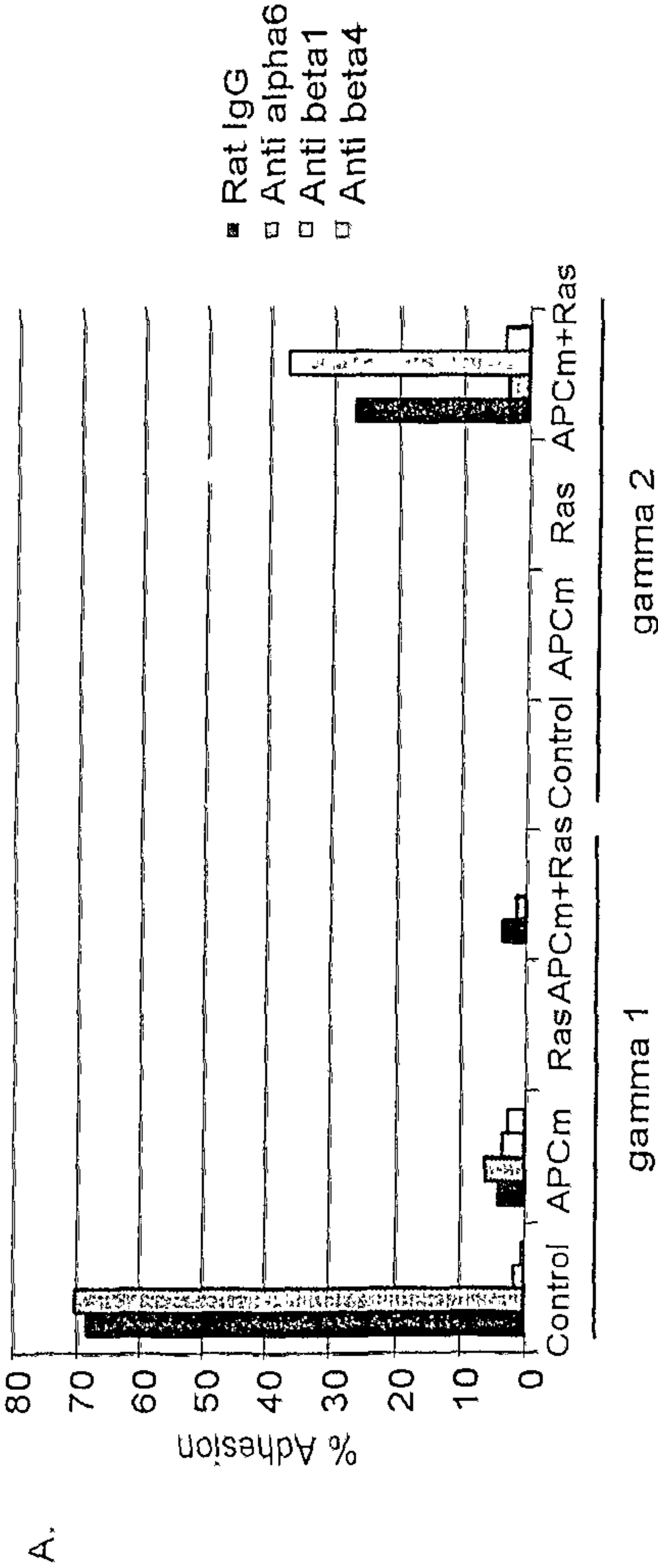
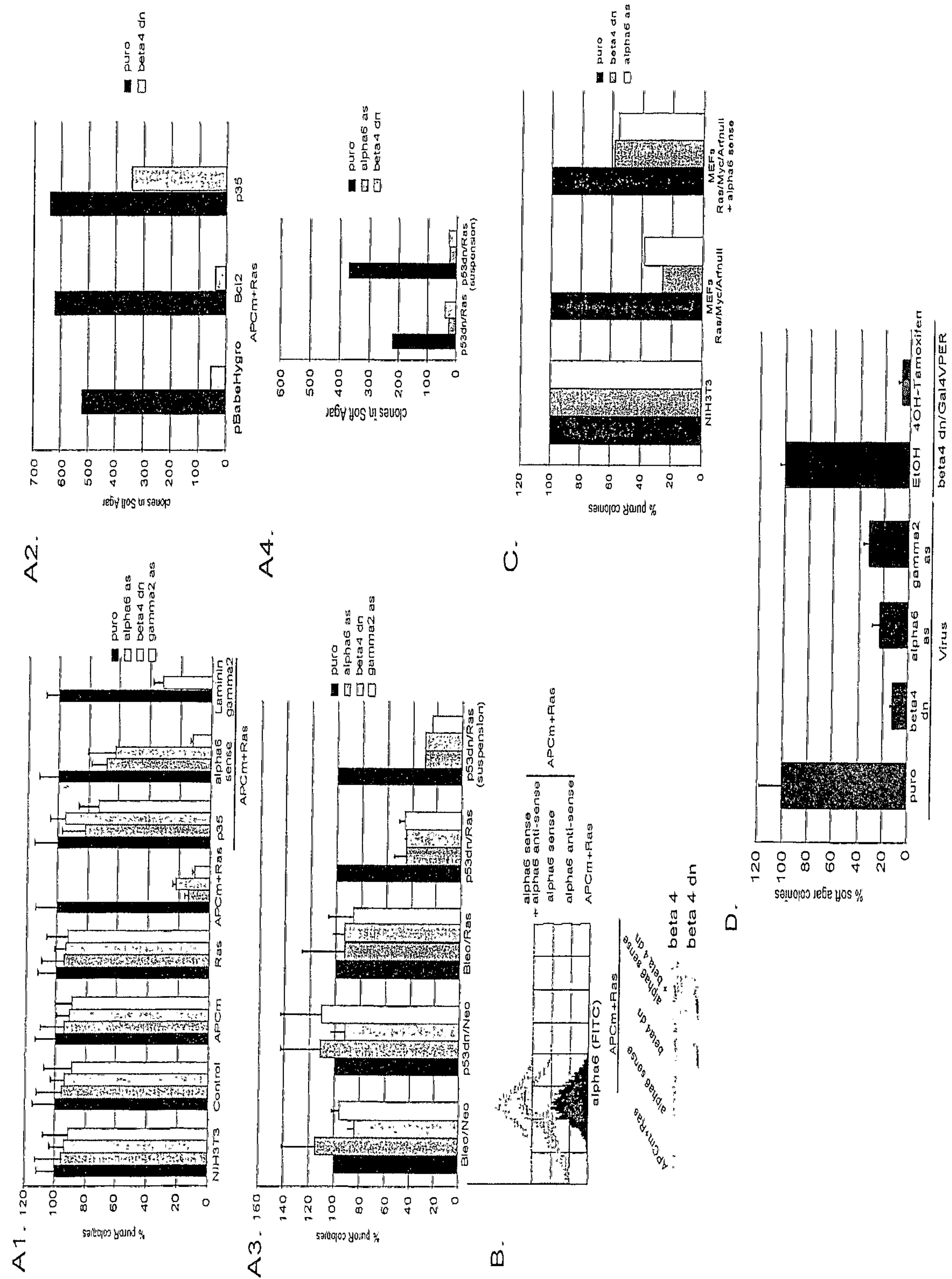


FIG. 5



Normal cells require integrin-matrix interactions for survival

