(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 3 095 797 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
23.11.2016 Bulletin 2016/47

(21) Application number: **16164567.6**

(22) Date of filing: **22.02.2013**

(51) Int Cl.:
C07K 16/28 *(2006.01)* ***A61K 47/48*** *(2006.01)*
C07K 16/30 *(2006.01)* ***C07K 14/47*** *(2006.01)*
A61P 35/00 *(2006.01)*

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR
Designated Extension States:
BA ME

(30) Priority: **24.02.2012 US 201261603173 P**
29.10.2012 US 201261719803 P

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
13707525.5 / 2 817 338

(71) Applicant: **Stemcentrx, Inc.**
South San Francisco, CA 94080 (US)

(72) Inventors:
- **STULL, Robert, A.**
  Alameda, CA 94501 (US)
- **SAUNDERS, Laura**
  San Francisco, CA 94107 (US)
- **DYLLA, Scott, J.**
  Mountain View, CA 94043 (US)
- **FOORD, Orit**
  Foster City, CA 94404 (US)
- **LIU, David**
  San Francisco, CA 94112 (US)
- **TORGOV, Michael**
  Los Angeles, CA 90045-2227 (US)
- **SHAO, Hui**
  Foster City, CA 94404 (US)

(74) Representative: **Evenson, Jane Harriet**
Mathys & Squire LLP
The Shard
32 London Bridge Street
London SE1 9SG (GB)

Remarks:
•This application was filed on 08-04-2016 as a divisional application to the application mentioned under INID code 62.
•Claims filed after the date of filing of the application/after the date of receipt of the divisional application (Rule 68(4) EPC).

(54) ANTI DLL3 ANTIBODIES AND METHODS OF USE THEREOF

(57) Novel modulators, including antibodies and derivatives thereof, and methods of using such modulators to treat proliferative disorders are provided.

Biochemical Characteristics of Selected DLL3 Modulators

Clone	Bin	Domain	Affinity (nM)	% Live Cells (*in vitro*)	Cyno XR	Mouse & Rat XR
SC16.4	F	EGF4	0.5[F]	49	N.D.	Yes
SC16.8	A	EGF5	0.5[F]	82	N.D.	Yes
SC16.10	E	EGF2	4.0[F]	18	N.D.	No
SC16.13	B	EGF2	2.0[B]	31	No[Y]	No
SC16.15	G	N-terminal	0.5[B]	24	Yes[B]	Yes
SC16.25	C	N-terminal	0.2[B]	28	Yes[B]	No
SC16.34	D	DSL	0.2[B]	12	Yes[B]	Yes
SC16.39	I	EGF6	1.0[F]	98	N.D.	Yes
SC16.46	A	EGF1	0.5[F]	19	No[Y]	Yes
SC16.51	H	N-terminal	2.0[F]	56	Yes[B]	Yes
SC16.56	D	DSL	1.0[B]	16	Yes[B]	Yes
SC16.65	B	EGF2	0.9[B]	13	No[B]	No
SC16.67	D	EGF3	0.5[F]	37	Yes[Y]	No

[B] Biacore; [F] ForteBio; [Y] Yeast Display

FIG. 12

EP 3 095 797 A1

Description

CROSS REFERENCED APPLICATIONS

[0001] This application claims priority from U. S. Provisional Application No. 61/603,173 filed on February 24, 2012, and U.S. Provisional Application No. 61/719,803 filed on October 29, 2012 each of which is incorporated herein by reference in its entirety.

SEQUENCE LISTING

[0002] The instant application contains a sequence listing which has been submitted in ASCH format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on February 19,2013, is named 11200.0013-00304_SL.txt and is 381,637 bytes in size.

FIELD OF THE INVENTION

[0003] This application generally relates to novel compounds, compositions and methods of their use in diagnosing, preventing, treating or ameliorating proliferative disorders and any expansion, recurrence, relapse or metastasis thereof. In a broad aspect, the present invention relates to the use of delta-like ligand 3 (DLL3) modulators, including anti-DLL3 antibodies and fusion constructs, for the treatment, diagnosis or prophylaxis of neoplastic disorders. Selected embodiments of the present invention provide for the use of such DLL3 modulators, including antibody drug conjugates, for the immunotherapeutic treatment of malignancies preferably comprising a reduction in tumor initiating cell frequency.

BACKGROUND OF THE INVENTION

[0004] Stem and progenitor cell differentiation and cell proliferation are normal ongoing processes that act in concert to support tissue growth during organogenesis and cell replacement and repair of most tissues during the lifetime of all living organisms. In the normal course of events cellular differentiation and proliferation is controlled by numerous factors and signals that are generally balanced to maintain cell fate decisions and tissue architecture. Thus, to a large extent it is this controlled microenvironment that regulates cell division and tissue maturation where signals are properly generated based on the needs of the organism. In this regard cell proliferation and differentiation normally occurs only as necessary for the replacement of damaged or dying cells or for growth. Unfortunately, disruption of cell proliferation and/or differentiation can result from a myriad of factors including, for example, the under- or overabundance of various signaling chemicals, the presence of altered microenvironments, genetic mutations or some combination thereof. When normal cellular proliferation and/or differentiation is disturbed or somehow disrupted it can lead to various diseases or disorders including proliferative disorders such as cancer.

[0005] Conventional treatments for cancer include chemotherapy, radiotherapy, surgery, immunotherapy (e.g., biological response modifiers, vaccines or targeted therapeutics) or combinations thereof. Unfortunately, certain cancers are non-responsive or minimally responsive to such treatments. For example, in some patients tumors exhibit gene mutations that render them non-responsive despite the general effectiveness of selected therapies. Moreover, depending on the type of cancer and what form it takes some available treatments, such as surgery, may not be viable alternatives. Limitations inherent in current standard of care therapeutics are particularly evident when attempting to treat patients who have undergone previous treatments and have subsequently relapsed. In such cases the failed therapeutic regimens and resulting patient deterioration may contribute to refractory tumors which often manifest themselves as a relatively aggressive disease that ultimately proves to be incurable. Although there have been great improvements in the diagnosis and treatment of cancer over the years, overall survival rates for many solid tumors have remained largely unchanged due to the failure of existing therapies to prevent relapse, tumor recurrence and metastases. Thus, it remains a challenge to develop more targeted and potent therapies for proliferative disorders.

SUMMARY OF THE INVENTION

[0006] These and other objectives are provided for by the present invention which, in a broad sense, is directed to methods, compounds, compositions and articles of manufacture that may be used in the treatment of DLL3 associated disorders (e.g., proliferative disorders or neoplastic disorders). To that end, the present invention provides novel Delta-like ligand 3 (or DLL3) modulators that effectively target tumor cells and/or cancer stem cells and may be used to treat patients suffering from a wide variety of malignancies. As will be discussed in more detail herein, there are at least two naturally occurring DLL3 isoforms or variants and the disclosed modulators may comprise or associate selectively with one isoform or the other or with both. Moreover, in certain embodiments the disclosed DLL3 modulators may further

react with one or more DLL family members (e.g., DLL1 or DLL4) or, in other embodiments, may be generated and selected for so as to exclusively associate or react with one or more DLL3 isoforms. In any event the modulators may comprise any compound that recognizes, competes, agonizes, antagonizes, interacts, binds or associates with a DLL3 genotypic or phenotypic determinant (or fragment thereof) and modulates, adjusts, alters. regulates, changes or modifies the impact of the DLL3 protein on one or more physiological pathways and/or eliminates DLL3 associated cells. Thus, in a broad sense the present invention is generally directed to isolated DLL3 modulators and uses thereof. In preferred embodiments the invention is more particularly directed to isolated DLL3 modulators comprising antibodies (i.e., antibodies that immunopreferentially bind, react with or associate with at least one isoform of DLL3) that, in particularly preferred embodiments, are associated or conjugated to one or more cytotoxic agents. Moreover, as discussed extensively below, such modulators may be used to provide pharmaceutical compositions useful for the prophylaxis, diagnosis or treatment of proliferative disorders including cancer.

[0007] In selected embodiments of the invention, DLL3 modulators may comprise a DLL3 polypeptide or fragments thereof, either in an isolated form or fused or associated with other moieties (e.g., Fc-DLL3, PEG-DLL3 or DLL3 associated with a targeting moiety). In other selected embodiments DLL3 modulators may comprise DLL3 antagonists which, for the purposes of the instant application, shall be held to mean any construct or compound that recognizes, competes, interacts, binds or associates with DLL3 and neutralizes, eliminates, reduces, sensitizes, reprograms, inhibits or controls the growth of neoplastic cells including tumor initiating cells. In preferred embodiments the DLL3 modulators of the instant invention comprise anti-DLL3 antibodies, or fragments or derivatives thereof, that have unexpectedly been found to silence, neutralize, reduce, decrease, deplete, moderate, diminish, reprogram, eliminate, or otherwise inhibit the ability of tumor initiating cells to propagate, maintain, expand, proliferate or otherwise facilitate the survival, recurrence, regeneration and/or metastasis of neoplastic cells. In particularly preferred embodiments the antibodies or immunoreactive fragments may be associated with, or conjugated to, one or more anti-cancer agents (e.g., a cytotoxic agent).

[0008] With regard to such modulators it will be appreciated that compatible antibodies may take on any one of a number of forms including, for example, polyclonal and monoclonal antibodies, chimeric, CDR grafted, humanized and human antibodies and immunoreactive fragments and/or variants of each of the foregoing. Preferred embodiments will comprise antibodies that are relatively non-immunogenic such as humanized or fully human constructs. Of course, in view of the instant disclosure those skilled in the art could readily identify one or more complementarity determining regions (CDRs) associated with heavy and light chain variable regions of DLL3 antibody modulators and use those CDRs to engineer or fabricate chimeric, humanized or CDR grafted antibodies without undue experimentation. Accordingly, in certain preferred embodiments the DLL3 modulator comprises an antibody that incorporates one or more complementarity determining regions (CDRs) as defined in FIG. 11A and 11B and derived from the light (FIG. 11A) or heavy (FIG. 11B) contiguous chain murine variable regions (SEQ ID NOS: 20-203) set forth therein. Such CDR grafted variable regions are also shown in FIG. 11 comprising SEQ ID NOS: 204-213. In preferred embodiments such antibodies will comprise monoclonal antibodies and, in even more preferred embodiments, will comprise chimeric, CDR grafted or humanized antibodies.

[0009] Exemplary nucleic acid sequences encoding each of the amino acid sequences set forth in FIGS. 11A and 11B are appended hereto in the sequence listing and comprise SEQ ID NOS: 220 to 413. In this respect it will be appreciated that the invention further comprises nucleic acid molecules (and associated constructs, vectors and host cells) encoding disclosed antibody variable region amino acid sequences including those set forth in the attached sequence listing. More particularly in selected embodiments compatible DLL3 modulators may comprise an antibody having a light chain variable region and a heavy chain variable region wherein said light chain variable region comprises an amino acid sequence having at least 60% identity to an amino acid sequence selected from the group consisting of amino acid sequences as set forth in SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74, SEQ ID NO: 76, SEQ ID NO: 78 SEQ ID NO: 80, SEQ ID NO: 82, SEQ ID NO: 84, SEQ ID NO: 86, SEQ ID NO: 88, SEQ ID NO: 90, SEQ ID NO: 92, SEQ ID NO: 94, SEQ ID NO: 96, SEQ ID NO: 98, SEQ ID NO: 100, SEQ ID NO: 102, SEQ ID NO: 104, SEQ ID NO: 106, SEQ ID NO: 108, SEQ ID NO: 110, SEQ ID NO: 112, SEQ ID NO: 114, SEQ ID NO: 116, SEQ ID NO: 118, SEQ ID NO: 120, SEQ ID NO: 122, SEQ ID NO: 124, SEQ ID NO: 126, SEQ ID NO: 128, SEQ ID NO: 130, SEQ ID NO: 132, SEQ ID NO: 134, SEQ ID NO: 136, SEQ ID NO: 138, SEQ ID NO: 140, SEQ ID NO: 142, SEQ ID NO: 144, SEQ ID NO: 146, SEQ ID NO: 148, SEQ ID NO: 150, SEQ ID NO: 152, SEQ ID NO: 154, SEQ ID NO: 156, SEQ ID NO: 158, SEQ ID NO: 160, SEQ ID NO: 162 SEQ ID NO: 164, SEQ ID NO: 166, SEQ ID NO: 168, SEQ ID NO: 170, SEQ ID NO: 172, SEQ ID NO: 174, SEQ ID NO: 176, SEQ ID NO: 178, SEQ ID NO: 180, SEQ ID NO: 182, SEQ ID NO: 184, SEQ ID NO: 186, SEQ ID NO: 188, SEQ ID NO: 190, SEQ ID NO: 192, SEQ ID NO: 194, SEQ ID NO: 196, SEQ ID NO: 198, SEQ ID NO: 200 and SEQ ID NO: 202 and wherein said heavy chain variable region comprises an amino acid sequence having at least 60% identity to an amino acid sequence selected from the group consisting of amino acid sequences as set forth in SEQ ID NO: 21, SEQ ID NO: 23, SEQ ID NO: 25,

SEQ ID NO: 27, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51 , SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 71, SEQ ID NO: 73, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 79, SEQ ID NO: 81, SEQ ID NO: 83, SEQ ID NO: 85, SEQ ID NO: 87, SEQ ID NO: 89, SEQ ID NO: 91, SEQ ID NO: 93, SEQ ID NO: 95, SEQ ID NO: 97, SEQ ID NO: 99, SEQ ID NO: 101, SEQ ID NO: 103, SEQ ID NO: 105, SEQ ID NO: 107, SEQ ID NO: 109, SEQ ID NO: 111, SEQ ID NO: 113, SEQ ID NO: 115, SEQ ID NO: 117, SEQ ID NO: 119, SEQ ID NO: 121, SEQ ID NO: 123, SEQ ID NO: 125, SEQ ID NO: 127, SEQ ID NO: 129, SEQ ID NO: 131, SEQ ID NO: 133, SEQ ID NO: 135, SEQ ID NO: 137, SEQ ID NO: 139, SEQ ID NO: 141, SEQ ID NO: 143, SEQ ID NO: 145, SEQ ID NO: 147, SEQ ID NO: 149, SEQ ID NO: 151, SEQ ID NO: 153, SEQ ID NO: 155, SEQ ID NO: 157, SEQ ID NO: 159, SEQ ID NO: 161, SEQ ID NO: 163, SEQ ID NO: 165, SEQ ID NO: 167, SEQ ID NO: 169, SEQ ID NO: 171, SEQ ID NO: 173, SEQ ID NO: 175, SEQ ID NO: 177, SEQ ID NO: 179, SEQ ID NO: 181, SEQ ID NO: 183, SEQ ID NO: 185, SEQ ID NO: 187, SEQ ID NO: 189, SEQ ID NO: 191, SEQ ID NO: 193, SEQ ID NO: 195, SEQ ID NO: 197, SEQ ID NO: 199, SEQ ID NO: 201 and SEQ ID NO: 203. In other preferred embodiments the selected modulators will comprise heavy and light chain variable regions that comprise 65, 70, 75 or 80% identity to the aforementioned murine sequences. In still other embodiments the modulators will comprise heavy and light chain variable regions that comprise 85, 90 or even 95% identity to the disclosed murine sequences.

[0010] In other preferred embodiments the selected modulators will comprise one or more CDRs obtained from any of the foregoing light and heavy chain variable region amino acid sequences. Accordingly, selected embodiments of the invention include a DLL3 modulator comprising one or more CDRs from any one of SEQ ID NOS; 20 to 203. In still other embodiments the modulators of the instant invention will comprise any antibody or immunoreactive fragment thereof that competes for binding with any of the foregoing modulators.

[0011] Another aspect of the invention comprises modulators obtained or derived from SC16.3, SC16.4, SC16.5, SC16.7, SC16.8, SC16.10, SC16.11, SC16.13, SC16.15, SC16.18, SC16.19, SC16.20, SC16.21, SC16.22, SC16.23, SC16.25, SC16.26, SC16.29, SC16.30, SC16.31, SC16.34, SC16.35, SC16.36, SC16.38, SC16.39, SC16.41, SC16.42, SC16.45, SC16.47, SC16.49, SC16.50, SC16.52, SC16.55, SC16.56, SC16.57, SC16.58, SC16.61, SC16.62, SC16.63, SC16.65, SC16.67, SC16.68, SC16.72, SC16.73, SC16.78, SC16.79, SC16.80, SC16.81, SC16.84, SC16.88, SC16.101, SC16.103, SC16.104, SC16.105, SC16.106, SC16.107, SC16.108, SC16.109, SC16.110, SC16.111, SC16.113, SC16.114, SC16.115, SC16.116, SC16.117, SC16.118, SC16.120, SC16.121, SC16.122, SC16.123, SC16.124, SC16.125, SC16.126, SC16.129, SC16.130, SC16.131, SC16.132, SC16.133, SC16.134, SC16.135, SC16.136, SC16.137, SC16.138, SC16.139, SC16.140, SC16.141, SC16.142, SC16.143. SC16.144, SC16.147, SC16.148, SC16.149 and SC16.150. In other embodiments the invention will comprise a DLL3 modulator having one or more CDRs from any of the aforementioned modulators.

[0012] In yet other compatible embodiments the instant invention will comprise the CDR grafted or humanized DLL3 modulators hSC16.13, hSC16.15, hSC16.25, hSC16.34 and hSC16.56. Still other embodiments are directed to a DLL3 modulator comprising a humanized antibody wherein said humanized antibody comprises a light chain variable region and a heavy chain variable region wherein said light chain variable region comprises an amino acid sequence having at least 60% identity to an amino acid sequence selected from the group consisting of amino acid sequences as set forth in SEQ ID NO: 204, SEQ ID NO: 206, SEQ ID NO: 208, SEQ ID NO: 210 and SEQ ID NO: 212 and wherein said heavy chain variable region comprises an amino acid sequence having at least 60% identity to an amino acid sequence selected from the group consisting of amino acid sequences as set forth in SEQ ID NO: 205, SEQ ID NO: 207, SEQ ID NO: 209, SEQ ID NO: 211 and SEQ ID NO: 213. Moreover, as described immediately above nucleic acid sequences encoding the humanized heavy and light chain variable regions are set forth in the attached sequence listing as SEQ ID NOS: 404 - 413.

[0013] Besides the aforementioned aspects, other preferred embodiments of the instant invention will comprise DLL3 modulators associated or conjugated to one or more drugs to provide modulator conjugates that may be particularly effective in treating proliferative disorders (alone or in combination with other pharmaceutically active agents). More generally, once the modulators of the invention have been fabricated and selected they may be linked with, fused to, conjugated to (e.g., covalently or non-covalently) or otherwise associated with pharmaceutically active or diagnostic moieties or biocompatible modifiers. As used herein the term "conjugate" or "modulator conjugate" or "antibody conjugate" will be used broadly and held to mean any biologically active or detectable molecule or drug associated with the disclosed modulators regardless of the method of association. In this respect it will be understood that such conjugates may, in addition to the disclosed modulators, comprise peptides, polypeptides, proteins, prodrugs which are metabolized to an active agent *in vivo,* polymers, nucleic acid molecules, small molecules, binding agents, mimetic agents, synthetic drugs, inorganic molecules, organic molecules and radioisotopes. Moreover, as indicated above the selected conjugate may be covalently or non-covalently associated with, or linked to, the modulator and exhibit various stoichiometric molar ratios depending, at least in part, on the method used to effect the conjugation.

[0014] Particularly preferred aspects of the instant invention will comprise antibody modulator conjugates or antibody-

drug conjugates that may be used for the diagnosis and/or treatment of proliferative disorders. Such conjugates may be represented by the formula M-[L-D]n where M stands for a disposed modulator or target binding moiety, L is an optional linker or linker unit, D is a compatible drug or prodrug and n is an integer from about 1 to about 20. It will be appreciated that, unless otherwise dictated by context, the terms "antibody-drug conjugate" or "ADC" or the formula M-[L-D]n shall be held to encompass conjugates comprising both therapeutic and diagnostic moieties. In such embodiments antibody-drug conjugate compounds will typically comprise anti-DLL3 as the modulator unit (M), a therapeutic or diagnostic moiety (D), and optionally a linker (L) that joins the drug and the antigen binding agent. In a preferred embodiment, the antibody is a DLL3 mAb comprising at least one CDR from the heavy and light chain variable regions as described above.

[0015] As previously indicated one aspect of the invention may comprise the unexpected therapeutic association of DLL3 polypeptides with cancer stem cells. Thus, in certain other embodiments the invention will comprise a DLL3 modulator that reduces the frequency of tumor initiating cells upon administration to a subject. Preferably the reduction in frequency will be determined using *in vitro* or *in vivo* limiting dilution analysis. In particularly preferred embodiments such analysis may be conducted using *in vivo* limiting dilution analysis comprising transplant of live human tumor cells into immunocompromised mice (e.g., see Example 17 below). Alternatively, the limiting dilution analysis may be conducted using *in vitro* limiting dilution analysis comprising limiting dilution deposition of live human tumor cells into *in vitro* colony supporting conditions. In either case, the analysis, calculation or quantification of the reduction in frequency will preferably comprise the use of Poisson distribution statistics to provide an accurate accounting. It will be appreciated that, while such quantification methods are preferred, other, less labor intensive methodologies such as flow cytometry or immunohistochemistry may also be used to provide the desired values and, accordingly, are expressly contemplated as being within the scope of the instant invention. In such cases the reduction in frequency may be determined using flow cytometric analysis or immunohistochemical detection of tumor cell surface markers known to enrich for tumor initiating cells,

[0016] As such, another preferred embodiment of the instant invention comprises a method of treating a DLL3 associated disorder comprising administering a therapeutically effective amount of a DLL3 modulator to a subject in need thereof whereby the frequency of tumor initiating cells is reduced. Preferably the DLL3 associated disorder comprises a neoplastic disorder. Again, the reduction in the tumor initiating cell frequency will preferably be determined using *in vitro* or *in vivo* limiting dilution analysis.

[0017] In this regard it will be appreciated that the present invention is based, at least in part, upon the discovery that DLL3 immunogens are therapeutically associated with tumor perpetuating cells (i.e., cancer stem cells) that are involved in the etiology of various proliferative disorders including neoplasia. More specifically, the instant application unexpectedly demonstrates that the administration of various exemplary DLL3 modulators can mediate, reduce, deplete, inhibit or eliminate tumorigenic signaling by tumor initiating cells (i.e., reduce the frequency of tumor initiating cells). This reduced signaling, whether by depletion, neutralization, reduction, elimination, reprogramming or silencing of the tumor initiating cells or by modifying tumor cell morphology (e.g., induced differentiation, niche disruption), in turn allows for the more effective treatment of DLL3 associated disorders by inhibiting tumongenesis, tumor maintenance, expansion and/or metastasis and recurrence.

[0018] Besides the aforementioned association with cancer stem cells, there is evidence that DLL3 isoforms may be implicated in the growth, recurrence or metastatic potential of tumors comprising or exhibiting neuroendocrine features or determinants (geriotypic or phenotypic). For the purposes of the instant invention such tumors will comprise neuroendocrine tumors and pseudo neuroendocrine tumors. Intervention in the proliferation of such tumorigenic cells using the novel DLL3 mediators described herein, may thereby ameliorate or treat a disorder by more than one mechanism (e.g., tumor initiating cell reduction and disruption of oncogenic pathway signaling) to provide additive or synergistic effects. Still other preferred embodiments may take advantage of the cellular internalization of cell surface DLL3 protein to deliver a modulators mediated anti-cancer agent. In this regard it will be appreciated that the present invention is not limited by any particular mechanism of action but rather encompasses the broad use of the disclosed modulators to treat DLL3 associated disorders (including various neoplasia).

[0019] Thus, in other embodiments the present invention will comprise the use of the disclosed modulators to treat tumors comprising neuroendocrine features in a subject in need thereof. Of course the same modulators may be used for the prophylaxis, prognosis, diagnosis, theragnosis, inhibition or maintenance therapy of these same tumors.

[0020] Other facets of the instant invention exploit the ability of the disclosed modulators to potentially disrupt oncogenic pathways (e.g., Notch) while simultaneously silencing tumor initiating cells. Such mufti-active DLL3 modulators (e.g., DLL3 antagonists) may prove to be particularly effective when used in combination with standard of care anti-cancer agents or debulking agents. Accordingly preferred embodiments of the instant invention comprise using the disclosed modulators as anti-metastatic agents for maintenance therapy following initial treatments. In addition, two or more DLL3 antagonists (e.g. antibodies that specifically bind to two discrete epitopes on DLL3) may be used in combination in accordance with the present teachings. Moreover, as discussed in some detail below, the DLL3 modulators of the present invention may be used in a conjugated or unconjugated state and, optionally, as a sensitizing agent in combination with

a variety of chemical or biological anti-cancer agents,

[0021] Accordingly another preferred embodiment of the instant invention comprises a method of sensitizing a tumor in a subject for treatment with an anti-cancer agent comprising the step of administering a DLL3 modulator to said subject. Other embodiments comprise a method of reducing metastasis or tumor recurrence following treatment comprising administering a DLL3 modulator to a subject in need thereof. In a particularly preferred aspect of the invention the DLL3 modulator will specifically result in a reduction of tumor initiating cell frequency is as determined using *in vitro* or *in vivo* limiting dilution analysis.

[0022] More generally preferred embodiments of the invention comprise a method of treating a DLL3 associated disorder in a subject in need thereof comprising the step of administering a DLL3 modulator to the subject. In particularly preferred embodiments the DLL3 modulator will be associated (e.g., conjugated) with an anti-cancer agent, In yet other embodiments the DLL3 modulator will internalize following association or binding with DLL3 on or near the surface of the cell. Moreover the beneficial aspects of the instant invention, including any disruption of signaling pathways and collateral benefits, may be achieved whether the subject tumor tissue exhibits elevated levels of DLL3 or reduced or depressed levels of DLL3 as compared with normal adjacent tissue. Particularly preferred embodiments will comprise the treatment of disorders exhibiting elevated levels of DLL3 on tumorigenic cells as compared to normal tissue or non-tumorigenic cells.

[0023] In yet another aspect the present invention will comprise a method of treating a subject suffering from neoplastic disorder comprising the step of administering a therapeutically effective amount of at least one internalizing DLL3 modulator. Preferred embodiments will comprise the administration of internalizing antibody modulators wherein the modulators, are conjugated or associated with a cytotoxic agent.

[0024] Other embodiments are directed to a method of treating a subject suffering from a DLL3 associated disorder comprising the step of administering a therapeutically effective amount of at least one depleting DLL3 modulators.

[0025] In yet another embodiment the present invention provides methods of maintenance therapy wherein the disclosed effectors or modulators are administered over a period of time following an initial procedure (e.g., chemotherapeutic, radiation or surgery) designed to remove at least a portion of the tumor mass. Such therapeutic maintenance regimens may be administered over a period of weeks, a period of months or even a period of years wherein the DLL3 modulators may act prophylactically to inhibit metastasis and/or tumor recurrence. In yet other embodiments the disclosed modulators may be administrated in concert with known debulking regimens to prevent or retard metastasis, tumor maintenance or recurrence.

[0026] As previously alluded to the DLL3 modulators of the instant invention may be fabricated and/or selected to react with both of DLL3 or a single isoform of the protein or, conversely, may comprise a pan-DLL modulator that reacts or associates with at least one additional DLL family member in addition to DLL3. More specifically, preferred modulators such as antibodies may be generated and selected so that they react with domains (or epitopes therein) that are exhibited by DLL3 only or with domains that are at least somewhat conserved across multiple or all DLL family members.

[0027] In yet other preferred embodiments the modulators will associate or bind to a specific epitope, portion, motif or domain of DLL3. As will be discussed in some detail below, both DLL3 isoforms incorporate an identical extracellular region (see FIG. IF) comprising at least an N-terminal domain, a DSL (Delta/Serrate/lag-2) domain and six EGF-like domains (i.e., EGF1 - EGF6). Accordingly, in certain embodiments the mediators will bind or associate with the N-terminal domain of DLL3 (i.e. amino acids 27-175 in the mature protein) while in other selected embodiments the modulators will associate with the DSL domain (i.e. amino acids 176-215) or epitope therein. Other aspects of the instant invention comprise modulators that associate or bind to a specific epitope located in a particular EGF-like domain of DLL3. In this regard the particular modulator may associate or bind to an epitope located in EGF1 (amino acids 216-249), EGF2 (amino acids 274-310), EGF3 (amino acids 312-351), EGF4 (amino acids 353-389), EGF5 (amino acids 391-427) or EGF6 (amino acids 429-465). Of course it will be appreciated that each of the aforementioned domains may comprise more than one epitope and/or more than one bin. In particularly preferred embodiments the invention will comprise a modulator that binds, reacts or associates with the DSL domain or an epitope therein, In other preferred embodiments the invention will comprise modulators that bind, react or associate with a particular EGF-like domain or an epitope therein. In yet other preferred embodiments the modulators will bind, react or associate with the N-terminal domain or an epitope therein.

[0028] With regard to modulator or antibody "bins" it will be appreciated that the DLL3 antigen may be analyzed or mapped through competitive antibody binding using art-recognized techniques to define specific bins located on or along the protein. While discussed in more detail herein and shown in Examples 9 and 10 below, two antibodies (one of which may be termed a "reference antibody," "bin delineating antibody" or "delineating antibody") may be considered to be in the same bin if they compete with each other for binding to the target antigen. In such cases the subject antibody epitopes may be identical, substantially identical or close enough (either in a linear sense where they are separated by a few amino acids or conformationally) so that both antibodies are sterically or electrostatically inhibited or precluded from binding to the antigen. Such defined bins may be generally associated with certain DLL3 domains (e.g. the reference antibody will bind with an epitope contained in a specific domain) though the correlation is not always precise (e.g., there

may be more than one bin in a domain or the bin may be defined conformationally and comprise more than one domain). It will be appreciated that those skilled in the art can readily determine the relationship between the DLL3 domains and empirically determined bins.

[0029] With regard to the present invention competitive binding analysis using art-recognized techniques (e.g., ELISA, surface plasmon resonance or bio-layer interferometry) defined at least nine distinct bins, each of which was found to contain a number of antibody modulators. For the purposes of the instant disclosure the nine bins were termed bin A to bin I. Thus, in selected embodiments the present invention will comprise a modulator residing in a bin selected from the group consisting of bin A, bin B, bin C, bin D, bin E, bin F, bin G, bin H and bin I. In other embodiments the present invention comprise a modulator residing in a bin defined by a reference antibody selected from the group consisting of SC16.3, SC16.4, SC16.5, SC16.7, SC16.8, SC16.10, SC16.11, SC16.13, SC16.15, SC16.18, SC16.19, SC16.20, SC16.21, 8C16.22, SC16.23, SC16-25, SC16.26, 8C16,29, SC16.30, SC16.31, SC16.34, SC16.35, SC16.36, SC16.38, SC16.39, SC16.41, SC16.42, SC16.45, SC16.47, SC16.49, SC16.50, SC16.52, SC16.55, SC16.56, SC16.57, SC16.58, SC16.61 SC16.62, SC16.63, SC16.65, SC16.67, SC16.68, SC16.72, SC16.73, SC16.78, SC16.79. SC16.80, SC16.81, SC16.84, SC16.88, SC16.101, SC16.103, SC16.104, SC16.105, SC16.106, 8C16.107, SC16.108, 8C16.109, SC16.110, SC16.111 SC16.113, SC16.114, SC16-115, SC16.116, SC16.117, SC16.118, SC16,120, SC16.121, SC16.122, SC16.123, SC16.124, SC16.125, SC16.126, SC16.129, SC16.130, SC16.131, SC16.132, SC16.133, SC16.134, SC16.135, SC16.136, 5C16.137, SC16.138, SC16.139, 5C16.140, SC16.141, SC16.142, SC16.143, SC16.144, SC16.147, SC16.148, SC16.149 and SC16.150, In still other embodiments the invention will comprise modulators from bin A, modulators from bin B, modulator from bin C, modulators from bin D, modulators from bin E, modulators from bin F, modulators from bin G, modulators from bin H or modulators from bin L Yet other preferred embodiments will comprise a reference antibody modulator and any antibody that competes with the reference antibody.

[0030] The term "compete" or "competing antibody" when used in the context of the disclosed modulators means binding competition between antibodies as determined by an assay in which a reference antibody or immunologically functional fragment substantially prevents or inhibits (e.g., greater than 40%, 45%, 50%, 55%, 60%, 65%, 70%. 75%, 80%, 85% or 90%.) specific binding of a test antibody to a common antigen. Compatible methods for determining such competition comprise art known techniques such as, for example, bio-layer interferometry, surface plasmon resonance, flow cytometry, competitive ELISA, etc.

[0031] Besides the aforementioned modulators, in selected embodiments the invention comprises a pan-DLL modulator that associates with DLL3 and at least one other DLL family member. In other selected embodiments the invention comprises a DLL3 modulators that immunospecifically associates with one or more isoform of DLL3 but does not associated with any other DLL family member. In yet other embodiments the present invention comprises a method of treating a subject in need thereof comprising administering a therapeutically effective amount of a pan-DLL mediator. Still other embodiments comprise a method of treating a subject in need thereof comprising administering a therapeutically effective amount of a DLL3 modulator that immunospecifically associates with one or more isoforms of DLL3 but does not immunospecifically associate with any other DLL family member.

[0032] Beyond the therapeutic uses discussed above it will also be appreciated that the modulators of the instant invention may be used to detect, diagnose or classify DLL3 related disorders and, in particular, proliferative disorders, They may also be used in the prognosis and/or theragnosis of such disorders. In some embodiments the modulator may be administered to the subject and detected or monitored *in vivo.* Those of skill in the art will appreciate that such modulators may be labeled or associated with effectors, markers or reporters as disclosed below and detected using any one of a number of standard techniques (e.g., MRI, CAT scan, PET scan, etc.).

[0033] Thus, in some embodiments the invention will comprise a method of diagnosing, detecting or monitoring a DLL3 associated disorder *in vivo* in a subject in need thereof comprising the step of administering a DLL3 modulator.

[0034] In other instances the modulators may be used in an *in vitro* diagnostic setting using art-recognized procedures (e.g., immunohistochemistry or IHC), As such, a preferred embodiment comprises a method of diagnosing a hyperproliferative disorder in a subject in need thereof comprising the steps of:

a. obtaining a tissue sample from said subject;
b. contacting the tissue sample with at least one DLL3 modulator; and
c. detecting or quantifying the DLL3 modulator associated with the sample.

[0035] Such methods may be easily discerned in conjunction with the instant application and may be readily performed using generally available commercial technology such as automatic plate readers, dedicated reporter systems, etc. In selected embodiments the DLL3 mediator will be associated with tumor perpetuating cells (i.e., cancer stem cells) present in the sample, In other preferred embodiments the detecting or quantifying step will comprise a reduction of tumor initiating cell frequency which may be monitored as described herein.

[0036] In a similar vein the present invention also provides kits or devices and associated methods that are useful in the diagnosis and monitoring of DLL3 associated disorders such as cancer. To this end the present invention preferably

provides an article of manufacture useful for detecting, diagnosing or treating DLL3 associated disorders comprising a receptacle containing a DLL3 modulator and instructional materials for using said DLL3 modulator to treat, monitor or diagnose the DLL3 associated disorder. In selected embodiments the devices and associated methods will comprise the step of contacting at least one circulating tumor cell.

[0037] Other preferred embodiments of the invention also exploit the properties of the disclosed modulators as an instrument useful for identifying, characterizing, isolating, sectioning or enriching populations or subpopulation of tumor initiating cells through methods such as immunohistochemistry, flow cytometric analysis including fluorescence activated cell sorting (FACS) or laser mediated sectioning.

[0038] As such, another preferred embodiment of the instant invention is directed to a method of identifying, isolating, sectioning or enriching a population of tumor initiating cells comprising the step of contacting said tumor initiating cells with a DLL3 modulator.

[0039] The foregoing is a summary and thus contains, by necessity, simplifications, generalizations, and omissions of detail; consequently, those skilled in the art will appreciate that the summary is illustrative only and is not intended to be in any way limiting. Other aspects, features, and advantages of the methods, compositions and/or devices and/or other subject matter described herein will become apparent in the teachings set forth herein. The summary is provided to introduce a selection of concepts in a simplified form that are further described below in the Detailed Description. This summary is not intended to identify key features or essential features of the claimed subject matter, nor is it intended to be used as an aid in determining the scope of the claimed subject matter.

BRIEF DESCRIPTION OF THE FIGURES

[0040]

FIGS. 1A - 1F are various representations of DLL3 including nucleic acid or amino acid sequences wherein full length mRNAs containing the ORFs (underlined) encoding DLL3 isoforms are depicted in FIGS. 1A and 1B (SEQ ID NOS: 1 and 2), FIGS. 1C and ID provide the translation of the ORFs denoted in FIGS, 1A and 1B (SEQ ID NOS: 3 and 4), respectively, with underlined residues indicating the predicted transmembrane spanning domain for each protein isoform, FIG. 1E depicts the alignment of the two protein isoforms to illustrate the sequence differences in the cytoplasmic termini of each isoform, again with the underlined residues indicating the predicted transmembrane spanning domain and FIG. 1F provides a schematic representation of the extracellular region of DLL3 protein illustrating the positions of the various domains;

FIGS. 2A and 2B are tabular representations of the percent identity at the protein level between DLL3 and other Delta-like family members in the human genome (FIG. 2A), or the closest human isoform of DLL3 and rhesus monkey, mouse and rat DLL3 proteins (FIG. 2B);

FIG. 3 schematically illustrates genetic interactions between several "master" genes relevant to cell fate choices leading to either neuroendocrine or non-neuroendocrine phenotypes (arrows indicating promotion of gene expression and barred arrows indicating inhibition of gene expression), in which the expression of the transcription factor ASCL1 both initiates a gene cascade (open arrow) leading to a neuroendocrine phenotype while simultaneously activating DLL3, which in turn suppresses NOTCH and its effector HES1 both of which are normally responsible for the suppression of ASCL1 and the activation of gene cascades leading to a non-neuroendocrine phenotype;

FIGS. 4A and 4B are tabular (FIG. 4A) and graphical (FIG, 4B) depictions of gene expression levels of DLL3 and, in FIG. 4A, other Notch pathway genes or genes associated with a neuroendocrine phenotype as measured using whole transcriptome (SOLiD) sequencing of RNA derived from tumor cell subpopulations or normal tissues;

FIG. 5 is a graphical depiction of the relative expression levels of DLL3 mRNA transcript variants 1 and 2 as determined by whole transcriptome (SOLiD) sequencing in selected non-traditional xenograft (NTX) tumors derived from lung cancers;

FIGS. 6A - 6D show gene expression data and clustering of tumors exhibiting neuroendocrine features wherein FIG. 6A depicts unsupervised clustering of microarray profiles for 46 tumor lines and 2 normal tissues comprising selected tumors and normal control tissues, FIGS. 6B and 6C are tabular representations of normalized intensity values corresponding to relative expression levels of selected genes related to neuroendocrine phenotypes (FIG. 6B) or the Notch signaling pathway (FIG. 6C) wherein unshaded cells and relatively low numbers indicate little to no expression and darker cells and relatively higher numbers indicate higher expression levels and FIG, 6D is a graphical representation showing relative expression levels of HES6 mRNA in various tumors and normal tissues as measured using qRT-PCR;

FIG. 7 is a graphical representation showing relative expression levels of DLL3 transcripts as measured by qRT-PCR in a variety of RNA samples isolated from normal tissues, primary, unpassaged patient tumor specimens (denoted with "p0"), or bulk NTX tumors derived from lung, kidney and ovarian neoplasia wherein specific NTX lung tumors are grouped by small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) (denoted with p1,

p2, p3 or p4 to reflect the number of passages through mice), wherein the tumor type is denoted using the abbreviations set forth above;

FIGS. 8A --- 8C are graphical representations showing the relative (FIG. 8A) or absolute (FIG. 8B) gene expression levels of human DLL3 as measured by qRT-PCR in whole tumor specimens (grey dot) or matched normal adjacent tissue (NAT; white dot) from patients with one of eighteen different solid tumor types while FIG. 8C shows the relative protein expression of human DLL3 as measured using an electrochemiluminescent sandwich ELISA assay;

FIG. 9 provides graphical representations of flow cytometry-based determination of surface protein expression of various Notch receptors and ligands (e.g., DLL1, DLL4) in individual human tumor cell populations derived from kidney, ovarian and small cell lung NTX tumors, displayed as histogram plots (black line) referenced to fluorescence minus one (FMO) isotype-control stained population (solid gray) with indicated mean fluorescence intensities (MFI);

FIGS. 10A - 10D provide, respectively, the cDNA sequence (FIG. 10A; SEQ ID NO: 5) and the amino acid sequence (FIG. 10B; SEQ ID NO: 6) encoding mature murine DLL3 protein cloned into a lentiviral expression vector and the cDNA sequence (FIG. 10C; SEQ ID NO:7) and the amino acid sequence (FIG. 10D; SEQ ID NO: 8) encoding mature cynomolgus DLL3 protein cloned into a lentiviral expression vector where the vectors are used to generate cells overexpressing murine and cynomolgus DLL3;

FIGS. 11A and 11B provide, in a tabular form, contiguous amino acid sequences (SEQ ID NOS: 20-213) of light and heavy chain variable regions of a number of murine and humanized exemplary DLL3 modulators isolated, cloned and engineered as described in the Examples herein;

FIG. 12 sets forth biochemical and immunological properties of exemplary DLL3 modulators as well as their ability to kill KDY66 NTX cell *in vitro* as represented in a tabular format;

FIGS. 13A - 13C illustrate binding characteristics of selected modulators wherein FIGS. 13A and 13B show comparative binding characteristics of a selected murine modulator and its humanized counterpart using surface plasmon resonance while FIG. 13C provides certain properties of humanized constructs in a tabular form;

FIGS. 14A and 14B depict, in schematic and graphical form respectively, the results of domain level mapping analysis of exemplary DLL3 modulators isolated, cloned and engineered as described in the Examples herein (FIG. 14A) and a correlation between the binding domain of selected modulators and the ability to kill DLL3 expressing KDY66 NTX cells *in vitro* (FIG. 14B);

FIGS. 15A - 15C are flow cytometry histograms showing DLL3 expression using the exemplary anti-DLL3 modulator SC16,56 on naive 293 cells (FIG. 15A), 293 cells engineered to over-express human DLL3 proteins (h293-hDLL3; FIG. 15B) or 293 cells engineered to over-express murine DLL3 protein (h293-mDLL3; FIG. 15C);

FIGS. 16A - 16F comprise flow cytometry histograms (FIGS. 16A-16C) and immunohistochemistry results in a tabular form (FIGS. 16D-16F) illustrating, respectively, relatively high surface expression of DLL3 using the exemplary anti-DLL3 modulator SC16.56 on live human cells from ovary (OV26; FIG. 16A), kidney (KDY66; FIG. 16B) and a lung large cell neuroendocrine carcinoma (LU37; FIG. 16C) NTX tumors and the expression of DLL3 protein in various NTX tumors (FIG. 16D) and primary small cell carcinoma (FIG. 16F) tumor cells while demonstrating that normal tissue lack DLL3 expression (FIG. 16E);

FIGS. 17A - 17C illustrate the ability of the disclosed modulators to effectively direct cytotoxic payloads to cells expressing DLL3 wherein FIG. 17A documents the ability of exemplary modulators to kill KDY66 NTX tumors or 293 cells overexpressing hDLL3, and FIG. 17B and 17C demonstrate the ability of disclosed modulators to deliver cytotoxic payloads to OV26 (FIG. 17B) and LU37 (FIG. 17C) where the downward sloping curve is indicative of cell killing through internalized cytotoxin;

FIGS. 18A - 18E illustrate various properties of the disclosed modulators wherein FIGS. 18A and 18C demonstrate by flow cytometry that DLL3 NSHP KDY66 and naïve KDY66 have expression of DLL3 while expression of DLL3 was efficiently knocked down in DLL3HP2 KDY66 cells, FIG. 18B shows that growth of DLL3HP2 tumor cells lags behind naïve KDY66 cells and FIGS. 18D and 18E demonstrate that conjugated embodiments of the instant invention immunospecifically target and kill KDY66 expressing DLL3 tumor cells but not KDY66 with DLL3 knocked down;

FIGS. 19A - 19C show the ability of selected conjugated embodiments of the present invention to kill and/or suppress growth of exemplary lung tumorigenic cells *in vivo*;

FIG. 20A - 20F depict the ability of conjugated modulators of the instant invention to substantially eradicate tumors and prevent tumor recurrence *in vivo* - achieving durable remissions in immunodeficient mice engrafted with exemplary ovarian (FIG. 20A), lung (FIGS. 20B - 20D) and kidney tumors (FIGS. 20E and 20F); and

FIGS. 21A - 21F demonstrate that conjugated modulators of the instant invention reduce the frequency of cancer stem cells as determined by a limiting dilution assay (LDA) for two exemplary small cell lung tumors, LU95 (FIGS. 21A - 21C) and LU64 (FIGS. 21D - 21F) where FIGS. 21A and 21D show the effect of the conjugates on tumor growth, FIGS. 21B and 21E show the results of the LDA and FIGS. 21C and 21F graphically present the reduction in cancer stem cell frequency brought about by treatment with the selected anti-DLL3 antibody conjugate.

DETAILED DESCRIPTION OF THE INVENTION

1. Introduction

[0041] White the present invention may be embodied in many different forms, disclosed herein are specific illustrative embodiments thereof that exemplify the principles of the invention. It should be emphasized that the present invention is not limited to the specific embodiments illustrated. Moreover, any section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. Finally, for the purposes of the instant disclosure all identifying sequence Accession numbers may be found in the NCBI Reference Sequence (RefSeq) database and/or the NCBI GenBank® archival sequence database unless otherwise noted.

[0042] As discussed above it has surprisingly been found that DLL3 genotypic and/or phenotypic determinants are associated with various proliferative disorders, including neoplasia exhibiting neuroendocrine features, and that DLL3 and variants or isoforms thereof provide useful tumor markers which may be exploited in the treatment of related diseases. Moreover, as shown in the instant application it has unexpectedly been found that DLL3 markers or determinants such as cell surface DLL3 protein are therapeutically associated with cancer stem cells (also known as tumor perpetuating cells) and may be effectively exploited to eliminate or silence the same. The ability to selectively reduce or eliminate cancer stem cells (e.g., through the use of conjugated DLL3 modulators) is particularly surprising in that such cells are known to generally be resistant to many conventional treatments. That is, the effectiveness of traditional, as well as more recent targeted treatment methods, is often limited by the existence and/or emergence of resistant cancer stem cells that are capable of perpetuating tumor growth even in face of these diverse treatment methods. Further, determinants associated with cancer stem cells often make poor therapeutic targets due to low or inconsistent expression, failure to remain associated with the tumorigenic cell or failure to present at the cell surface. In sharp contrast to the teachings of the prior art, the instantly disclosed compounds and methods effectively overcome this inherent resistance and to specifically eliminate, deplete, silence or promote the differentiation of such cancer stem cells thereby negating their ability to sustain or re-induce the underlying tumor growth. Moreover, as expression of DLL3 protein has largely been associated with intracellular locations such as the Golgi, it was uncertain that phenotypic determinants could be successfully exploited as a therapeutic target as taught herein.

[0043] Thus, it is particularly remarkable that DLL3 modulators such as those disclosed herein may advantageously be used in the prognosis, diagnosis, theragnosis, treatment and/or prevention of selected proliferative (e.g., neoplastic) disorders in subjects in need thereof. It will be appreciated that, while preferred embodiments of the invention will be discussed extensively below, particularly in terms of particular domains, regions or epitopes or in the context of cancer stem cells or tumors comprising neuroendocrine features and their interactions with the disclosed modulators, those skilled in the art will appreciate that the scope of the instant invention is not limited by such exemplary embodiments. Rather, the most expansive embodiments of the present invention and the appended claims are broadly and expressly directed to DLL3 modulators (including conjugated modulators) and their use in the prognosis, diagnosis, theragnosis, treatment and/or prevention of a variety of DLL3 associated or mediated disorders, including neoplastic or cell proliferative disorders, regardless of any particular mechanism of action or specifically targeted tumor, cellular or molecular component.

[0044] To that end, and as demonstrated in the instant application, it has unexpectedly been found that the disclosed DLL3 modulators can effectively be used to target and eliminate or otherwise incapacitate proliferative or tumorigenic cells and treat DLL3 associated disorders (e.g., neoplasia). As used herein a "DLL3 associated disorder" shall be held to mean any disorder or disease (including proliferative disorders) that is marked, diagnosed, detected or identified by a phenotypic or genotypic aberration of DLL3 genetic components or expression ("DLL3 determinant") during the course or etiology of the disease or disorder. In this regard a DLL3 phenotypic aberration or determinant may, for example, comprise elevated or depressed levels of DLL3 protein expression, abnormal DLL3 protein expression on certain definable cell populations or abnormal DLL3 protein expression at an inappropriate phase or stage of a cell lifecycle. Of course, it will be appreciated that similar expression patterns of genotypic determinants (e.g., mRNA transcription levels) of DLL3 may also be used to classify, detect or treat DLL3 disorders.

[0045] As used herein the term "determinant" or "DLL3 determinant" shall mean any detectable trait, property, marker or factor that is identifiably associated with, or specifically found in or on a particular cell, cell population or tissue including those identified in or on a tissue, cell or cell population affected by a DLL3 associated disease or disorder. In selected preferred embodiments the DLL3 modulators may associate, bind or react directly with the DLL3 determinant (e.g., cell surface DLL3 protein or DLL3 mRNA) and thereby ameliorate the disorder. More generally determinants may be morphological, functional or biochemical in nature and may be genotypic or phenotypic. In other preferred embodiments the determinant is a cell surface antigen or genetic component that is differentially or preferentially expressed (or is not) by specific cell types (e.g., cancer stem cells) or by cells under certain conditions (e.g., during specific points of the cell cycle or cells in a particular niche). In still other preferred embodiments the determinant may comprise a gene or genetic entity that is differently regulated (up or down) in a specific cell or discrete cell population, a gene that is differentially

modified with regard to its physical structure and chemical composition or a protein or collection of proteins physically associated with a gene that show differential chemical modifications. Determinants contemplated herein are specifically held to be positive or negative and may denote a cell, cell subpopulation or tissue (e.g., tumors) by its presence (positive) or absence (negative).

[0046] In a similar vein "DLL3 modulators" of the invention broadly comprise any compound that recognizes, reacts, competes, antagonizes, interacts, binds, agonizes, or associates with a DLL3 variant or isoform (or specific domains, regions or epitopes thereof) or its genetic component. By these interactions, the DLL3 modulators may advantageously eliminate, reduce or moderate the frequency, activity, recurrence, metastasis or mobility of tumorigenic cells (e.g., tumor perpetuating cells or cancer stem cells). Exemplary modulators disclosed herein comprise nucteotides, oligonucleotides, polynudeotides, peptides or polypeptides. In certain preferred embodiments the selected modulators will comprise antibodies to a DLL3 protein isoform or immunoreactive fragments or derivatives thereof. Such antibodies may be antagonistic or agonistic in nature and may optionally be conjugated or associated with a therapeutic or diagnostic agent. Moreover, such antibodies or antibody fragments may comprise depleting, neutralizing or internalizing antibodies. In other embodiments, modulators within the instant invention will constitute a DLL3 construct comprising a DLL3 isoform or a reactive fragment thereof. It will be appreciated that such constructs may comprise fusion proteins and can include reactive domains from other polypeptides such as immunoglobulins or biological response modifiers. In still other aspects, the DLL3 modulator will comprise a nucleic acid moiety (e.g. miRNA, siRNA, shRNA, antisense constructs, etc.) that exerts the desired effects at a genomic level. Still other modulators compatible with the instant teachings will be discussed in detail below.

[0047] More generally DLL3 modulators of the present invention broadly comprise any compound that recognizes, reacts, competes, antagonizes, interacts, binds, agonizes, or associates with a DLL3 determinant (genotypic or phenotypic) including cell surface DLL3 protein. Whichever form of modulator is ultimately selected it will preferably be in an isolated and purified state prior to introduction into a subject. In this regard the term "isolated DLL3 modulator" or "isolated DLL3 antibody" shall be construed in a broad sense and in accordance with standard pharmaceutical practice to mean any preparation or composition comprising the modulator in a state substantially free of unwanted contaminants (biological or otherwise). Moreover these preparations may be purified and formulated as desired using various art-recognized techniques. Of course, it will be appreciated that such "isolated" preparations may be intentionally formulated or combined with inert or active ingredients as desired to improve the commercial, manufacturing or therapeutic aspects of the finished product and provide pharmaceutical compositions. In a broader sense the same general considerations may be applied to an "isolated" DLL3 isoform or variant or an "isolated" nucleic acid encoding the same.

[0048] Further, it has surprisingly been found that modulators interacting, associating or binding to particular DLL3 domains, motifs or epitopes are especially effective in eliminating tumorigenic cells and/or silencing or attenuating cancer stem cell influences on tumor growth or propagation. That is, while modulators that react or associate with domains that are proximal to the cell surface (e.g., one of the EGF-like domains) are effective in depleting or neutralizing tumorigenic cells it has unexpectedly been discovered that modulators associating or binding to domains, motifs or regions that are relatively more distal to the cell surface are also effective in eliminating, neutralizing, depleting or silencing tumorigenic cells. In particular, and as shown in the appended Examples, it has been discovered that modulators that react, associate or bind to the DSL or N-terminal regions of the DLL3 protein are surprisingly effective at eliminating or neutralizing tumorigenic cells including those exhibiting neuroendocrine features and/or cancer stem cells, This is especially true of conjugated modulators such as, for example, anti-DLL3 antibody drug conjugates comprising a cytotoxic agent. As such, it will be appreciated that certain preferred embodiments of the instant invention are directed to compounds, compositions and methods that comprise DLL3 modulators which associate, bind or react with a relatively distal portion of DLL3 including the DSL domain and the N-terminal region.

[0049] While the present invention expressly contemplates the use of any DLL3 modulator in the treatment of any DLL3 disorder, including any type of neoplasia, in particularly preferred embodiments the disclosed modulators may be used to prevent, treat or diagnose tumors comprising neuroendocrine features (genotypic or phenotypic) including neuroendocrine tumors. True or "canonical neuroendocrine tumors" (NETs) arise from the dispersed endocrine system and are typically highly aggressive. Neuroendocrine tumors occur in the kidney, genitourinary tract (bladder, prostate, ovary, cervix, and endometrium), gastrointestinal tract (stomach, colon), thyroid (medullary thyroid cancer), and lung (small cell lung carcinoma and large cell neuroendocrine carcinoma). Moreover, the disclosed modulators may advantageously be used to treat, prevent or diagnose pseudo neuroendocrine tumors (pNETs) that genotypically or phenotypically mimic, comprise, resemble or exhibit common traits with canonical neuroendocrine tumors. "Pseudo neuroendocrine tumors" are tumors that arise from cells of the diffuse neuroendocrine system or from cells in which a neuroendocrine differentiation cascade has been aberrantly reactivated during the oncogenic process. Such pNETs commonly share certain genotypic, phenotypic or biochemical characteristics with traditionally defined neuroendocrine tumors, including the ability to produce subsets of biologically active amines, neurotransmitters, and peptide hormones. Accordingly, for the purposes of the instant invention the phrases "tumors comprising neuroendocrine features" or "tumors exhibiting neuroendocrine features" shall be held to comprise both neuroendocrine tumors and pseudo neuroendocrine

tumors unless otherwise dictated by context.

[0050] Besides the association with tumors generally discussed above, there are also indications of phenotypic or genotypic association between selected tumor initiating cells (TIC) and DLL3 determinants. In this regard selected TICs (e.g., cancer stem cells) may express elevated levels of DLL3 protein when compared to normal tissue and non-tumorigenic cells (NTG), which together typically comprise much of a solid tumor. Thus, DLL3 determinants may comprise a tumor associated marker (or antigen or immunogen) and the disclosed modulators may provide effective agents for the detection and suppression of TIC and associated neoplasia due to altered levels of the proteins on cell surfaces or in the tumor microenvironment. Accordingly, DLL3 modulators, including immunoreactive antagonists and antibodies that associate, bind or react with the proteins, may effectively reduce the frequency of tumor initiating cells and could be useful in eliminating, depleting, incapacitating, reducing, promoting the differentiation of, or otherwise precluding or limiting the ability of these tumor-initiating cells to lie dormant and/or continue to fuel tumor growth, metastasis or recurrence in a patient. In this regard those skilled in the art will appreciate that the present invention further provides DLL3 modulators and their use in reducing the frequency of tumor initiating cells.

II. DLL3 Physiology

[0051] The Notch signaling pathway, first identified in *C. elegans* and *Drosophila* and subsequently shown to be evolutionarily conserved from invertebrates to vertebrates, participates in a series of fundamental biological processes including normal embryonic development, adult tissue homeostasis, and stem cell maintenance (D'Souza et al., 2010; Liu et al., 2010). Notch signaling is critical for a variety of cell types during specification, patterning and morphogenesis. Frequently, this occurs through the mechanism of lateral inhibition, in which cells expressing Notch ligand(s) adopt a default cell fate, yet suppress this fate in adjacent cells via stimulation of Notch signaling (Sternberg, 1988, Cabrera 1990). This binary cell fate choice mediated by Notch signaling is found to play a role in numerous tissues, including the developing nervous system (de la Pompa et al., 1997), the hematopoietic and immune systems (Bigas and Espinosoa, 2012; Hoyne et al, 2011; Nagase et al., 2011), the gut (Fre et al., 2005; Fre et al., 2009), the endocrine pancreas (Apelqvist et al., 1999; Jensen et al., 2000), the pituitary (Raetzman et al., 2004), and the diffuse neuroendocrine system (Ito et al., 2000; Schonhoff et al, 2004). A generalized mechanism for implementing this binary switch appears conserved despite the wide range of developmental systems in which Notch plays a role-- in cells where the default cell fate choice is determined by transcriptional regulators known as basic helix-loop-helix (bHLH) proteins, Notch signaling leads to activation of a class of Notch responsive genes, which in turn suppress the activity of the bHLH proteins (Ball, 2004), These binary decisions take place in the wider context of developmental and signaling cues that permit Notch signaling to effect proliferation or inhibit it, and to trigger self-renewal or inhibit it.

[0052] In *Drosophila*, Notch signaling is mediated primarily by one Notch receptor gene and two ligand genes, known as Serrate and Delta (Wharton et al, 1985; Rebay et al., 1991). In humans, there are four known Notch receptors and five DSL (Delta-Serrate LAG2) ligands -- two homologs of Serrate, known as Jagged1 and Jagged 2, and three homologs of Delta, termed delta-like ligands or DLL1, DLL3 and DLL4. In general, Notch receptors on the surface of the signal-receiving cell are activated by interactions with ligands expressed on the surface of an opposing, signal-sending cell (termed a trans-interaction). These trans-interactions lead to a sequence of protease mediated cleavages of the Notch receptor. In consequence, the Notch receptor intracellular domain is free to translocate from the membrane to the nucleus, where it partners with the CSL family of transcription factors (RBPJ in humans) and converts them from transcriptional repressors into activators of Notch responsive genes.

[0053] Of the human Notch ligands, DLL3 is different in that it seems incapable of activating the Notch receptor via trans-interactions (Ladi et al., 2005). Notch ligands may also interact with Notch receptors in cis (on the same cell) leading to inhibition of the Notch signal, although the exact mechanisms of cis-inhibition remain unclear and may vary depending upon the ligand (for instance, see Klein et al., 1997; Ladi et al., 2005; Glittenberg et al., 2006). Two hypothesized modes of inhibition include modulating Notch signaling at the cell surface by preventing trans-interactions, or by reducing the amount of Notch receptor on the surface of the cell by perturbing the processing of the receptor or by physically causing retention of the receptor in the endoplasmic reticulum or Golgi (Sakamoto et al., 2002; Dunwoodie, 2009). It is clear, however, that stochastic differences in expression of Notch receptors and ligands on neighboring cells can be amplified through both transcriptional and non-transcriptional processes, and subtle balances of cis- and trans-interactions can result in a fine tuning of the Notch mediated delineation of divergent cell fates in neighboring tissues (Sprinzak et al., 2010).

[0054] DLL3 (also known as Delta-like 3 or SCDO1) is a member of the Delta-like family of Notch DSL ligands. Representative DLL3 protein orthologs include, but are not limited to, human (Accession Nos. NP_058637 and NP_982353), chimpanzee (Accession No. XP_003316395), mouse (Accession No. NP_031892), and rat (Accession No. NP_446118). In humans, the DLL3 gene consists of 8 exons spanning 9.5 kBp located on chromosome 19q13. Alternate splicing within the last exon gives rise to two processed transcripts, one of 2389 bases (Accession No. NM_016941; FIG. 1A, SEQ ID NO: 1) and one of 2052 bases (Accession No. NM_203486; FIG. 1B, SEQ ID NO: 2).

The former transcript encodes a 618 amino acid protein (Accession No, NP_058637; FIG. 1C, SEQ ID NO: 3), whereas the latter encodes a 587 amino acid protein (Accession No. NP_982353; FIG. ID, SEQ ID NO: 4). These two protein isoforms of DLL3 share overall 100% identity across their extracellular domains and their transmembrane domains, differing only in that the longer isoform contains an extended cytoplasmic tail containing 32 additional residues at the carboxy terminus of the protein (FIG. 1E). The biological relevance of the isoforms is unclear, although both isoforms can be detected in tumor cells (FIG. 5). Percent identities for each of the members of the delta-like family of proteins in humans are shown in FIG. 2A, as well as cross species identities in FIG. 2B.

[0055] In general, DSL ligands are composed of a series of structural domains: a unique N-terminal domain, followed by a conserved DSL domain, multiple tandem epidermal growth factor (EGF)-like repeats, a transmembrane domain, and a cytoplasmic domain not highly conserved across ligands but one which contains multiple lysine residues that are potential sites for ubiquitination by unique E3 ubiquitin ligases. The DSL domain is a degenerate EGF-domain that is necessary but not sufficient for interactions with Notch receptors (Shimizu et ai., 1999). Additionally, the first two EGF-like repeats of most DSL ligands contain a smaller protein sequence motif known as a DOS domain that co-operatively interacts with the DSL domain when activating Notch signaling.

[0056] FIG. 1F provides a schematic diagram of the extracellular region of the DLL3 protein, illustrating the general juxtaposition of the six EGF-like domains, the single DSL domain and the N-terminal domain. Generally, the EGF domains are recognized as occurring at about amino acid residues 216-249 (domain 1), 274-310 (domain 2), 312-351 (domain 3), 353-389 (domain 4), 391-427 (domain 5) and 429-465 (domain 6), with the DSL domain at about amino acid residues 176-215 and the N-terminal domain at about amino acid residues 27-175 of hDLL3 (SEQ ID NOS: 3 and 4). As discussed in more detail herein and shown in Example 10 below, each of the EGF-like domains, the DSL domain and the N-terminal domain comprise part of the DLL3 protein as defined by a distinct amino acid sequence. Note that, for the purposes of the instant disclosure the respective EGF-like domains may be termed EGF1 to EGF6 with EGF1 being closest to the N-terminal portion of the protein. In regard to the structural composition of the protein one significant aspect of the instant invention is that the disclosed DLL3 mediators may be generated, fabricated, engineered or selected so as to react with a selected domain, motif or epitope. In certain cases such site specific modulators may provide enhanced reactivity and/or efficacy depending on their primary mode of action.

[0057] Note that, as used herein the terms "mature protein" or "mature polypeptide" as used herein refers to the form(s) of the protein produced by expression in a mammalian cell. It is generally hypothesized that once export of a growing protein chain across the rough endoplasmic reticulum has been initiated, proteins secreted by mammalian cells have a signal peptide (SP) sequence which is cleaved from the complete polypeptide to produce a "mature" form of the protein. In both isoforms of DLL3 the mature protein comprises a signals peptide of 26 amino acids that may be clipped prior to cell surface expression. Thus, in mature proteins the N-terminal domain will extend from position 27 in the protein until the beginning of the DSL domain. Of course, if the protein is not processed in this manner the N-terminal domain would be held to extend to position one of SEQ ID NOS: 3 & 4.

[0058] Of the various Delta-like ligands, DLL3 is the most divergent from the others in the family, since it contains a degenerate DSL domain, no DOS motifs, and an intracellular domain which lacks lysine residues. The degenerate DSL and lack of DOS motifs are consistent with the inability of DLL3 to trigger Notch signaling in trans (between cells), suggesting that DLL3, unlike DLLI or DLL4, acts only as an inhibitor of Notch signaling (Ladi et al., 2005). Studies have shown that DLL3 may be resident primarily in the cis-Golgi (Geffers et al., 2007), which would be consistent with a hypothesized ability to retain Notch receptor intracellulary, or to interfere with processing of Notch receptors, preventing export to the cell surface and instead retargeting it to the lysosome (Chapman et al., 2011). Some DLL3 protein may appear at the cell surface, however, when the protein is artificially overexpressed in model systems (Ladi et al., 2005), but it is not obvious that this would be the case in normal biological contexts nor in tumors in which the DLL3 mRNA transcript is elevated; somewhat surprisingly, the protein levels detected in tumor types disclosed herein indicate significant DLL3 protein is escaping to the cell surface of various tumors.

[0059] Detects in the DLL3 gene have been linked to spondylocostal dysostosis in humans, a severe congenital birth defect resulting in abnormal vertebrae formation and rib abnormalities (Dunwoodie, 2009). This is linked to alterations in Notch signaling, known to play a crucial role in determining the polarity and patterning of somites, the embryonic precursors to the vertebrae that require a finely regulated oscillating interplay between Notch, Wnt, and FGF signaling pathways for proper development (Kageyama et al., 2007; Goldbeter and Pourquie, 2008). Although DLL1 and DLL3 are typically expressed in similar locations within the developing mouse embryo, experiments with transgenic mice have demonstrated that DLL3 does not compensate for DLL1 (Geffers et al., 2007). DLL! knock-out mice are embryonic lethal, but DLL3 mutant mice do survive yet show a phenotype similar to that found in humans with spondylocostal dysostosis (Kusumi et al., 1998; Shinkai et al., 2004), These results data are consistent with a subtle interplay of Notch trans- and cis-interactions crucial for normal development.

[0060] Further, as discussed above Notch signaling plays a role in the development and maintenance of neuroendocrine cells and tumors exhibiting neuroendocrine features. In this regard Notch signaling is involved in a wide range of cell fate decisions in normal endocrine organs and in the diffuse neuroendocrine system. For instance, in the pancreas,

Notch signaling is required to suppress the development of a default endocrine phenotype mediated by the bHLH transcription factor NGN3 (Habener et al, 2005). Similar Notch mediated suppression of endocrine cell fates occurs in enteroendocrine cells (Schonhoff et al., 2004), thyroid parafollicular cells (Cook et al., 2010), in specifying the relative ratios of neuroendocrine cell types in the pituitary (Dutta et al., 2011), and is likely involved in decisions of cells within the lungs to adopt a neuroendocrine or non-neuroendocrine pheneotype (Chen et al., 1997; Ito et al., 2000; Sriuranpong et al., 2002). Hence it is clear that in many tissues, suppression of Notch signaling is linked to neuroendocrine phenotypes.

[0061] Inappropriate reactivation of developmental signaling pathways or disregulatíon of normal signaling pathways are commonly observed in tumors, and in the case of Notch signaling, have been associated with numerous tumor types (Koch and Radtke, 2010; Harris et al., 2012). The Notch pathway has been studied as an oncogene in lymphomas, colorectal, pancreatic, and some types of non-small cell lung cancer (see Zarenczan and Chen, 2010 and references therein). In contrast, Notch is reported to act as a tumor suppressor in tumors with neuroendocrine features (see Zarenczan and Chen, 2010 supra). Tumors with neuroendocrine features arise infrequently in a wide range of primary sites, and while their exhaustive classification remains problematic (Yao et al., 2008; Klimstra et a!., 2010; Klöppel, 2011), they may be classified into four major types: low grade benign carcinoids, low-grade well-differentiated neuroendocrine tumors with malignant behavior, tumors with mixed neuroendocrine and epithelial features, and high-grade poorly differentiated neuroendocrine carcinomas. Of these classifications, the poorly differentiated neuroendocrine carcinomas, which include small cell lung cancer (SCLC) and subsets of non-small cell lung cancer (NSCLC), are cancer types with dismal prognoses. It has been postulated that SCLC is bronchogenic in origin, arising in part from pulmonary neuroendocrine cells (Galluzzo and Bocchetta, 2011). Whatever the specific cellular source of origin for each of these tumors possessing a neuroendocrine phenotype, it may be expected that suppression of Notch signaling, either by direct lesions in the Notch pathway genes themselves, or by activation of other genes that suppress Notch signaling, may lead to the acquisition of the neuroendocrine phenotype of these tumors. By extension, the genes that lead to the perturbation of the Notch pathway may afford therapeutic targets for the treatment of tumors with neuroendocrine phenotypes, particularly for indications that currently have poor clinical outcomes.

[0062] ASCL1 is one such gene that appears to interact with Notch signaling pathway via DLL3. It is clear that many neuroendocrine tumors show a poorly differentiated (i.e. partially complete) endocrine phenotype; for instance, marked elevation or expression of various endocrine proteins and polypeptides (e.g. chromogranin A, CHGA; calcitonin, CALCA; propiomelanocorin, POMC; somatostatin, SST), proteins associated with secretory vesicles (e.g., synaptophysin, SYP), and genes involved in the biochemical pathways responsible for the synthesis of bioactive amines (e.g., dopa decarboxylase, DDC). Perhaps not surprisingly, these tumors frequently over-express ASCL1 (also known as mASH1 in mice, or bASH1 in humans), a transcription factor known to play a role in orchestrating gene cascades leading to neural and neuroendocrine phenotypes. Although the specific molecular details of the cascade remain illdefined, it is increasingly clear that for certain cell types, particularly thyroid parafollicular cells (Kameda et al., 2007), chromaffin cells of the adrenal medulla (Huber et al., 2002) and cells found in the diffuse neuroendocrine system of the lung (Chen et al., 1997; Ito et al., 2000; Sriuranpong et al., 2002), ASCL1 is part of a finely tuned developmental regulatory loop in which cell fate choices are mediated by the balance of ASCL1-mediated and Notch-mediated gene expression cascades (FIG. 3). For instance, ASCL1 was found in to be expressed in normal mouse pulmonary neuroendocrine cells, while the Notch signaling effector HES1, was expressed in pulmonary non-neuroendocrine cells (Ito et al., 2000). That these two cascades are in a fine balance with potential cross-regulation is increasingly appreciated. The Notch effector HES1 has been shown to downregulate ASCL1 expression (Chen et al, 1997; Sriuranpong et al., 2002). These results clearly demonstrate that Notch signaling can suppress neuroendocrine differentiation. However, demonstration that ASCL1 binding to the DLL3 promoter activates DLL3 expression (Henke et al., 2009) and the observation that DLL3 attenuates Notch signaling (Ladi et al., 2005) closes the genetic circuit for cell fate choices between neuroendocrine and non-neuroendocrine phenotypes.

[0063] Given that Notch signaling appears to have evolved to amplify subtle differences between neighboring cells to permit sharply bounded tissue domains with divergent differentiation paths (e.g., "lateral inhibition," as described above), these data together suggest that a finely tuned developmental regulatory loop (FIG. 3) has become reactivated and disregulated in cancers with neuroendocrine phenotypes. While it is not obvious that DLL3 would provide a suitable cell surface target for the development of antibody therapeutics given its normal residence within interior membranous compartments of the cell (Geffers et al., 2007) and its presumed interactions with Notch therein, it is possible that the resultant elevation of DLL3 expression in neuroendocrine tumors may offer a unique therapeutic target for tumors with the neuroendocrine phenotype (e.g., NETs and pNETs). It is commonly observed that vast overexpression of proteins in laboratory systems may cause mislocalization of the overexpressed protein within the cell. Therefore it is a reasonable hypothesis, yet not obvious without experimental verification, that overexpression of DLL3 in tumors may lead to some cell surface expression of the protein, and thereby present a target for the development of antibody therapeutics.

III. Cancer Stem Cells

[0064] As alluded to above it has surprisingly been discovered that aberrant DLL3 expression (genotypic and/or phenotypic) is associated with various tumorigenic cell subpopulations. In this respect the present invention provides DLL3 modulators that may be particularly useful for targeting such cells, and especially tumor perpetuating cells, thereby facilitating the treatment, management or prevention of neoplastic disorders. Thus, in preferred embodiments modulators of DLL3 determinants (phenotypic or genotypic) may be advantageously be used to reduce tumor initiating cell frequency in accordance with the present teachings and thereby facilitate the treatment or management of proliferative disorders.

[0065] For the purposes of the instant application the term "tumor initiating cell" (TIC) encompasses both "tumor perpetuating cells" (TPC; i.e., cancer stem cells or CSC) and highly proliferative "tumor progenitor cells" (termed TProg), which together generally comprise a unique subpopulation (i.e. 0.1-40%) of a bulk tumor or mass. For the purposes of the instant disclosure the terms "tumor perpetuating cells" and "cancer stem cells" or "neoplastic stem cells" are equivalent and may be used interchangeably herein. TPC differ from TProg in that TPC can completely recapitulate the composition of tumor cells existing within a tumor and have unlimited self-renewal capacity as demonstrated by serial transplantation (two or more passages through mice) of low numbers of isolated cells, whereas TProg will not display unlimited self-renewal capacity.

[0066] Those skilled in the art will appreciate that fluorescence-activated cell sorting (FACS) using appropriate cell surface markers is a reliable method to isolate highly enriched cancer stem cell subpopulations (e.g., > 99.5% purity) due, at least in part, to its ability to discriminate between single cells and clumps of cells (i.e. doublets, etc.). Using such techniques it has been shown that when cell numbers of highly purified TProg cells are transplanted into immunocompromised mice they can fuel tumor growth in a primary transplant. However, unlike purified TPC subpopulations the TProg generated tumors do not completely reflect the parental tumor in phenotypic cell heterogeneity and are demonstrably inefficient at reinitiating serial tumorigenesis in subsequent transplants. In contrast, TPC subpopulations completely reconstitute the cellular heterogeneity of parental tumors and can efficiently initiate tumors when serially isolated and transplanted. Thus, those skilled in the art will recognize that a definitive difference between TPC and TProg, though both may be tumor generating in primary transplants, is the unique ability of TPC to perpetually fuel heterogeneous tumor growth upon serial transplantation at low cell numbers. Other common approaches to characterize TPC involve morphology and examination of cell surface markers, transcriptional profile, and drug response although marker expression may change with culture conditions and with cell line passage *in vitro.*

[0067] Accordingly, for the purposes of the instant invention tumor perpetuating cells, like normal stem cells that support cellular hierarchies in normal tissue, are preferably defined by their ability to self-renew indefinitely while maintaining the capacity for multilineage differentiation. Tumor perpetuating cells are thus capable of generating both tumorigenic progeny (i.e., tumor initiating cells: TPC and TProg) and non-tumorigenic (NTG) progeny. As used herein a "non-tumorigenic cell" (NTG) refers to a tumor cell thai arises from tumor initiating cells, but does not itself have the capacity to self-renew or generate the heterogeneous lineages of tumor cells that comprise a tumor. Experimentally, NTG cells are incapable of reproducibly forming tumors in mice, even when transplanted in excess cell numbers.

[0068] As indicated, TProg are also categorized as tumor initiating cells (or TIC) due to their limited ability to generate tumors in mice. TProg are progeny of TPC and are typically capable of a finite number of non-self-renewing cell divisions. Moreover, TProg cells may further be divided into early tumor progenitor cells (ETP) and late tumor progenitor cells (LTP), each of which may be distinguished by phenotype cell surface markers) and different capacities to recapitulate tumor cell architecture. In spite of such technical differences, both ETP and LTP differ functionally from TPC in that they are generally less capable of serially reconstituting tumors when transplanted at low cell numbers and typically do not reflect the heterogeneity of the parental tumor. Notwithstanding the foregoing distinctions, it has also been shown that various TProg populations can, on rare occasion, gain self-renewal capabilities normally attributed to stem cells and themselves become TPC (or CDC) In any event both types of tumor-initiating cells are likely represented in the typical tumor mass of a single patient and are subject to treatment with the modulators as disclosed herein. That is, the disclosed compositions are generally effective in reducing the frequency or altering the chemosensitivity of such DLL3 positive tumor initiating cells regardless of the particular embodiment or mix represented in a tumor.

[0069] In the context of the instant invention, TPC are more tumorigenic, relatively more quiescent and often more chemoresistant than the TProg (both ETP and LTP), NTG cells and the tumor-infiltrating non-TPC derived cells (e.g., fibroblasts/stroma, endothelial & hematopotetic cells) that comprise the bulk of a tumor. Given that conventional therapies and regimens have, in large part, been designed to both debulk tumors and attack rapidly proliferating cells, TPC are likely to be more resistant to conventional therapies and regimens than the faster proliferating TProg and other bulk tumor cell populations. Further, TPC often express other characteristics that make them relatively chemoresistant to conventional therapies, such as increased expression of multi-drug resistance transporters, enhanced DNA repair mechanisms and anti-apoptotic proteins. These properties, each of which contribute to drug tolerance by TPC, constitute a key reason for the failure of standard oncology treatment regimens to ensure long-term benefit for most patients with advanced stage neoplasia; i.e. the failure to adequately target and eradicate those cells that fuel continued tumor growth

and recurrence (i.e. TPC or CSC).

[0070] Unlike many prior art treatments, the novel compositions of the present invention preferably reduce the frequency of tumor initiating cells upon administration to a subject regardless of the form or specific target (e.g., genetic material, DLL3antibody or ligand fusion construct) of the selected modulator. As noted above, the reduction in tumor initiating cell frequency may occur as a result of a) elimination, depletion, sensitization, silencing or inhibition of tumor initiating cells; b) controlling the growth, expansion or recurrence of tumor initiating cells; c) interrupting the initiation, propagation, maintenance, or proliferation of tumor initiating cells; or d) by otherwise hindering the survival, regeneration and/or metastasis of the tumorigenic cells. In some embodiments, the reduction in the frequency of tumor initiating cells occurs as a result of a change in one or more physiological pathways, The change in the pathway, whether by reduction or elimination of the tumor initiating cells or by modifying their potential (e.g., induced differentiation, niche disruption) or otherwise interfering with their ability to influence the tumor environment or other cells, in turn allows for the more effective treatment of DLL3 associated disorders by inhibiting tumorigenesis, tumor maintenance and/or metastasis and recurrence.

[0071] Among art-recognized methods that can be used to assess such a reduction in the frequency of tumor initiating cells is limiting dilution analysis either *in vitro* or *in vivo,* preferably followed by enumeration using Poisson distribution statistics or assessing the frequency of predefined definitive events such as the ability to generate tumors *in vivo* or not. While such limiting dilution analysis comprise preferred methods of calculating reduction of tumor initiating cell frequency other, less demanding methods, may also be used to effectively determine the desired values, albeit slightly Jess accurately, and are entirely compatible with the teachings herein. Thus, as will be appreciated by those skilled in the art, it is also possible to determine reduction of frequency values through well-known flow cytometric or immunohistochemical means. As to all the aforementioned methods see, for example, Dylla et al. 2008, PMID: 18560594 & Hoey et al. 2009, PMID: 19664991; each of which is incorporated herein by reference in its entirety and, in particular, for the disclosed methods.

[0072] With respect to limiting dilution analysis, *in vitro* enumeration of tumor initiating cell frequency may be accomplished by depositing either fractionated or unfractionated human tumor cells (e.g. from treated and untreated tumors, respectively) into *in vitro* growth conditions that foster colony formation. In this manner, colony forming cells might be enumerated by simple counting and characterization of colonies, or by analysis consisting of, for example, the deposition of human tumor cells into plates in serial dilutions and scoring each well as either positive or negative for colony formation at least 10 days after plating. *In vivo* limiting dilution experiments or analyses, which are generally more accurate in their ability to determine tumor initiating cell frequency encompass the transplantation of human tumor cells, from either untreated control or treated populations, for example, into immunocompromised mice in serial dilutions and subsequently scoring each mouse as either positive or negative for tumor formation at least 60 days after transplant. The derivation of cell frequency values by limiting dilution analysis *in vitro* or *in vivo* is preferably done by applying Poisson distribution statistics to the known frequency of positive and negative events, thereby providing a frequency for events fulfilling the definition of a positive event; in this case, colony or tumor formation, respectively.

[0073] As to other methods compatible with the instant invention that may be used to calculate tumor initiating cell frequency, the most common comprise quantifiable flow cytometric techniques and immunohistochemical staining procedures. Though not as precise as the limiting dilution analysis techniques described immediately above, these procedures are much less labor intensive and provide reasonable values in a relatively short time frame. Thus, it will be appreciated that a skilled artisan may use flow cytometric cell surface marker profile determination employing one or more antibodies or reagents that bind art-recognized cell surface proteins known to enrich for tumor initiating cells (e.g., potentially compatible markers as are set forth in PCT application 2012/031280 which is incorporated herein in its entirety) and thereby measure TIC levels from various samples. In still another compatible method one skilled in the art might enumerate TIC frequency *in situ* (e.g., in a tissue section) by immunohistochemistry using one or more antibodies or reagents that are able to bind cell surface proteins thought to demarcate these cells.

[0074] Those skilled in the art will recognize that numerous markers (or their absence) have been associated with various populations of cancer stem cells and used to isolate or characterize tumor cell subpopulations. In this respect exemplary cancer stem cell markers comprise OCT4, Nanog, STAT3, EPCAM, CD24, CD34, NB84, TrkA, GD2, CD133, CD20, CD56, CD29, B7H3, CD46, transferrin receptor, JAM3, carboxypeptidase M, ADAM9, oncostatin M, Lgr5, Lgr6, CD324, CD325, nestin, Sox1, Bmi-1, eed, easyh1, easyh2, mf2, yy1, smarcA3, smarckA5, smarcD3, smarcE1, milt3, FZD1, FZD2, FZD3, FZD4, FZD6, FZD7, FZD8, FZD9, FZD10, WNT2, WNT2B, WNT3, WNT5A, WNT10B, WNT16, AXIN1, BCL9, MYC, (TCF4) SLC7A8, ILIRAP, TEM8, TMPRSS4, MUC16, GPRC5B, SLC6A14, SLC4A11, PPAP2C, CAV1, CAV2, PTPN3, EPHA1, EPHA2, SLC1A1, CX3CL1, ADORA2A, MPZL1, FLJ10052, C4.4A, EDG3, RARRES1, TMEPAI, PTS, CEACAM6, NID2, STEAP, ABCA3, CRIM1, IL1R1, OPN3, DAF, MUC1, MCP, CPD, NMA, ADAM9, GJA1, SLC19A2, ABCA1, PCDH7, ADCY9, SLC39A1, NPC1, ENPP1, N33, GPNMB, LY6E, CELSR1, LRP3, C20orf52, TMEPA1, FLVCR, PCDHA10, GPR54, TGFBR3, SEMA4B, PCDHB2, ABCG2, CD166, AFP, BMP-4, β-catenin, CD2, CD3, CD9, CD14, CD31, CD38, CD44, CD45, CD74, CD90, CXCR4, decorin, EGFR, CD105, CD64, CD16, CD16a, CD16b, GLI1, GLI2, CD49b, and CD49f. See, for example, Schulenburg et al., 2010, PMID: 20185329, U.S.P.N.

7,632,678 and U.S.P.Ns. 2007/0292414, 2008/0175870, 2010/0275280, 2010/0162416 and 2011/0020221 each of which is incorporated herein by reference. It will further be appreciated that each of the aforementioned markers may also be used as a secondary target antigen in the context of the bispecific or multispecific antibodies of the instant invention.

[0075] Similarly, non-limiting examples of cell surface phenotypes associated with cancer stem cells of certain tumor types include $CD44^{hi}CD24^{low}$, $ALDH^{+}$, $CD133^{+}$, $CD123^{+}$, $CD34^{+}CD38^{-}$, $CD44^{+}CD24^{-}$, $CD46^{hi}CD324^{+}CD66c^{-}$, $CD133^{+}CD34^{+}CD10^{-}CD19^{-}$, $CD138^{-}CD34^{-}CD19^{+}$, $CD133^{+}RC2^{-}$, $CD44^{+}\alpha_2\,\beta_1{}^{hi}CD133^{+}$, $CD44^{+}CD24^{+}ESA^{+}$, $CD271^{+}$, $ABCB5^{+}$ as well as other cancer stem cell surface phenotypes that are known in the art. See, for example, Schulenburg et al., 2010, supra, Visvader et al., 2008, PMID: 18784658 and U.S.P.N. 2008/0138313, each of which is incorporated herein in its entirety by reference. Those skilled in the art will appreciate that marker phenotypes such as those exemplified immediately above may be used in conjunction with standard flow cytometrie analysis and cell sorting techniques to characterize, isolate, purify or enrich TIC and/or TPC cells or cell populations for further analysis. Of interest with regard to the instant invention CD46, CD324 and, optionally, CD66c are either highly or heterogeneously expressed on the surface of many human colorectal ("CR"), breast ("BR"), non-small cell lung (NSCLC), small cell lung (SCLC), pancreatic ("PA"), melanoma ("Mel"), ovarian ("OV"), and head and neck cancer ("HN") tumor cells, regardless of whether the tumor specimens being analyzed were primary patient tumor specimens or patient-derived NTX tumors.

[0076] Using any of the above-referenced methods and selected markers as known in the art (and shown in Example 17 below) it is then possible to quantify the reduction in frequency of TIC (or the TPC therein) provided by the disclosed DLL3 modulators (including those conjugated to cytotoxic agents) in accordance with the teachings herein. In some instances, the compounds of the instant invention may reduce the frequency of TIC or TPC (by a variety of mechanisms noted above, including elimination, induced differentiation, niche disruption, silencing, etc.) by 10%, 15%, 20%, 25%, 30% or even by 35%. In other embodiments, the reduction in frequency of TIC or TPC may be on the order of 40%, 45%, 50%, 55%, 60% or 65%. In certain embodiments, the disclosed compounds my reduce the frequency of TIC or TPC by 70%, 75%, 80%, 85%, 90% or even 99%. Of course it will be appreciated that any reduction of the frequency of the TIC or TPC likely results in a corresponding reduction in the tumorigenicity, persistence, recurrence and aggressiveness of the neoplasia.

IV. DLL3 Modulators

[0077] In any event, the present invention is directed to the use of DLL3 modulators, including DLL3 antagonists, for the diagnosis, theragnosis, treatment and/or prophylaxis of various disorders including any one of a number of DLL3 associated malignancies. The disclosed modulators may be used alone or in conjunction with a wide variety of anti-cancer compounds such as chemotherapeutic or immunotherapeutic agents (e.g., therapeutic antibodies) or biological response modifiers. In other selected embodiments, two or more discrete DLL3 modulators may be used in combination to provide enhanced anti-neoplastic effects or may be used to fabricate multispecific constructs.

[0078] In certain embodiments, the DLL3 modulators of the present invention will comprise nucleotides, oligonucleotides, polynucleotides, peptides or polypeptides. More particularly, exemplary modulators of the invention may comprise antibodies and antigen-binding fragments or derivatives thereof, proteins, peptides, glycoproteins, glycopeptides, glycolipids, polysaccharides, oligosaccharides, nucleic acids, antisense constructs, siRNA, miRNA, bioorganic molecules, peptidomimetics, pharmacological agents and their metabolites, transcriptional and translation control sequences, and the like. In certain embodiments the modulators will comprise soluble DLL3 (sDLL3) or a form, variant, derivative or fragment thereof including, for example, DLL3 fusion constructs (e.g., DLL3-Fc, DLL3-targeting moiety, etc.) or DLL3-conjugates (e.g., DLL3-PEG, DLL3-cytotoxic agent, DLL3-brm, etc.). In other preferred embodiments the DLL3 modulators comprise antibodies or immunoreactive fragments or derivatives thereof. In particularly preferred embodiments the modulators of the instant invention will comprise neutralizing, depleting or internalizing antibodies or derivatives or fragments thereof. Moreover, as with the aforementioned fusion constructs, such antibody modulators may be conjugated, linked or otherwise associated with selected cytotoxic agents, polymers, biological response modifiers (BRMs) or the like to provide directed immunotherapies with various (and optionally multiple) mechanisms of action. As alluded to above such antibodies may be pan-DLL antibodies and associate with two or more DLL family members or, in the alternative, comprise antigen binding molecules that selectively react with one or both isoforms of DLL3. In yet other preferred embodiments the modulators may operate on the genetic level and may comprise compounds as antisense constructs, siRNA, miRNA and the like that interact or associate with the genotypic component of a DLL3 determinant.

[0079] It will further be appreciated that the disclosed DLL3 modulators may deplete, silence, neutralize, eliminate or inhibit growth, propagation or survival of tumor cells, inducting TPC, and/or associated neoplasia through a variety of mechanisms, including agonizing or antagonizing selected pathways or eliminating specific cells depending, for example, on the form of DLL3 modulator, any associated payload or dosing and method of delivery. Thus, while preferred embodiments disclosed herein are directed to the depletion, inhibition or silencing of specific tumor cell subpopulations such as tumor perpetuating cells or to modulators that interact with a specific epitope or domain, it must be emphasized that such embodiments are merely illustrative and not limiting in any sense. Rather, as set forth in the appended claims,

the present invention is broadly directed to DLL3 modulators and their use in the treatment, management or prophylaxis of various DLL3 associated disorders irrespective of any particular mechanism, binding region or target tumor cell population.

[0080] Regardless of the form of the modulator selected it will be appreciated that the chosen compound may be antagonistic in nature. As used herein an "antagonist" refers to a molecule capable of neutralizing, blocking, inhibiting, abrogating, reducing or interfering with the activities of a particular or specified target (e.g., DLL3), including the binding of receptors to ligands or the interactions of enzymes with substrates. In this respect it will be appreciated that DLL3 antagonists of the instant invention may comprise any ligand, polypeptide, peptide, fusion protein, antibody or immunologically active fragment or derivative thereof that recognizes, reacts, binds, combines, competes, associates or otherwise interacts with the DLL3 protein or fragment thereof and eliminates, silences, reduces, inhibits, hinders, restrains or controls the growth of tumor initiating cells or other neoplastic cells including bulk tumor or NTG cells. Compatible antagonists may further include small molecule inhibitors, aptamers, antisense constructs, siRNA, miRNA and the like, receptor or ligand molecules and derivatives thereof which recognize or associate with a DLL3 genotypic or phenotypic determinant thereby altering expression patterns or sequestering its binding or interaction with a substrate, receptor or ligand.

[0081] As used herein and applied to two or more molecules or compounds, the terms "recognizes" or "associates" shall be held to mean the reaction, binding, specific binding, combination, interaction, connection, linkage, uniting, coalescence, merger or joining, covalently or non-covalently, of the molecules whereby one molecule exerts an effect on the other molecule.

[0082] Moreover, as demonstrated in the examples herein (e.g., see FIG. 2B), some modiators of human DLL3 may, in certain cases, cross-react with DLL3 from a species other than human (e.g., murine). In other cases exemplary modulators may be specific for one or more isoforms of human DLL3 and will not exhibit cross-reactivity with DLL3 orthologs from other species. Of course, in conjunction with the teachings herein such embodiments may comprise pan-DLL antibodies that associate with two or more DLL family members from a single species or antibodies that exclusively associate with DLL3.

[0083] In any event, and as will be discussed in more detail below, those skilled in the art will appreciate that the disclosed modulators may be used in a conjugated or unconjugated form. That is, the modulator may be associated with or conjugated to (e.g. covalently or non-covalently) pharmaceutically active compounds, biological response modifiers, anti-cancer agents, cytotoxic or cytostatic agents, diagnostic moieties or biocompatible modifiers. In this respect it will be understood that such conjugates may comprise peptides, polypeptides, proteins, fusion proteins, nucleic acid molecules, small molecules, mimetic agents, synthetic drugs, inorganic molecules, organic molecules and radioisotopes. Moreover, as indicated herein the selected conjugate may be covalently or non-covalently linked to the DLL3 modulator in various molar ratios depending, at least in part, on the method used to effect the conjugation.

V. Modulator Fabrication and Supply

A. Antibody Modulators

1. Overview

[0084] As previously alluded to particularly preferred embodiments of the instant invention comprise DLL3 modulators in the form of antibodies that preferentially associate with one or more domains of an isoform of DLL3 protein and, optionally, other DLL family members. Those of ordinary skill in the art will appreciate the well developed knowledge base on antibodies such as set forth, for example, in Abbas et a/., Cellular and Molecular Immunology, 6th ed., W.B. Saunders Company (2010) or Murphey et al., Janeway's Immunobiology, 8th ed., Garland Science (2011), each of which is incorporated herein by reference in its entirety.

[0085] The term "antibody" is intended to cover polyclonal antibodies, multiclonal antibodies, monoclonal antibodies, chimeric antibodies, humanized and primatized antibodies, human antibodies, recombinantly produced antibodies, intrabodies, multispecific antibodies, bispecific antibodies, monovalent antibodies, multivalent antibodies, anti-idiotypic antibodies, synthetic antibodies, including muteins and variants thereof; antibody fragments such as Fab fragments, F(ab') fragments, single-chain FvFcs, single-chain Fvs; and derivatives thereof including Fc fusions and other modifictaions, and any other immunologically active molecule so long as they exhibit the desired biological activity (i.e., antigen association or binding). Moreover, the term further comprises all classes of antibodies (i.e. IgA, IgD, IgE, IgG, and IgM) and all isotypes (i.e., IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2), as well as variations thereof unless otherwise dictated by context. Heavy-chain constant domains that correspond to the different classes of antibodies are denoted by the corresponding lower case Greek letter α, δ, ε, γ, and μ, respectively. Light chains of the antibodies from any vertebrate species can be assigned to one of two clearly distinct types, called kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains.

[0086] While all such antibodies are within the scope of the present invention, preferred embodiments comprising the IgG class of immunoglobulin will be discussed in some detail herein solely for the purposes of illustration. It will be understood that such disclosure is, however, merely demonstrative of exemplary compositions and methods of practicing the present invention and not in any way limiting of the scope of the invention or the claims appended hereto.

[0087] As is well known, the variable domains of both the light (V_L) and heavy (V_H) chain portions determine antigen recognition and specificity and the constant domains of the light chain (C_L) and the heavy chain (C_H1, C_H2 or C_H3) confer and regulate important biological properties such as secretion, transplacental mobility, circulation half-life, complement binding, and the like.

[0088] The "variable" region includes hypervariable sites that manifest themselves in three segments commonly termed complementarity determining regions (CDRs), in both the light-chain and the heavy-chain variable domains. The more highly conserved portions of variable domains flanking the CDRs are termed framework regions (FRs). For example, in naturally occurring monomeric immunoglobulin G (IgG) antibodies, the six CDRs present on each arm of the "Y" are short, non-contiguous sequences of amino acids that are specifically positioned to form the antigen binding site as the antibody assumes its three dimensional configuration in an aqueous environment. Thus, each naturally occurring IgG antibody comprises two identical binding sites proximal to the ammo-terminus of each arm of the Y.

[0089] It will be appreciated that the position of CDRs can be readily identified by one of ordinary skill in the art using standard techniques. Also familiar to those in the art is the numbering system described in Kabat et al. (1991, NIH Publication 91-3242, National Technical Information Service, Springfield, Va.). In this regard Kabat et al. defined a numbering system for variable domain sequences that is applicable to any antibody. One of ordinary skill in the art can unambiguously assign this system of "Kabat numbering" to any variable domain sequence, without reliance on any experimental data beyond the sequence itself. Unless otherwise specified, references to the numbering of specific amino acid residue positions in an antibody are according to the Kabat numbering system.

[0090] Thus, according to Kabat, in the V_H, residues 31-35 comprise CDR1, residues 50-65 make up CDR2, and 95-102 comprise CDR3, while in the V_L, residues 24-34 are CDR1, 50-56 comprise CDR2, and 89-97 make up CDR3. For context, in a V_H, FR1 corresponds to the domain of the variable region encompassing amino acids 1-30; FR2 corresponds to the domain of the variable region encompassing amino acids 36-49; FR3 corresponds to the domain of the variable region encompassing amino acids 66-94, and FR4 corresponds to the domain of the variable region from amino acids 103 to the end of the variable region. The FRs for the light chain are similarly separated by each of the light chain variable region CDRs.

[0091] Note that CDRs vary considerably from antibody to antibody (and by definition will not exhibit homology with the Kabat consensus sequences). In addition, the identity of certain individual residues at any given Kabat site number may vary from antibody chain to antibody chain due to interspecies or allelic divergence. Alternative numbering is set forth in Chothia et al., J. Mol. Biol. 196:901-917 (1987) and MacCallum et al., J. Mol. Biol. 262:732-745 (1996), although as in Kabat, the FR boundaries are separated by the respective CDR termini as described above. See also Chothia et al., Nature 342, pp. 877-883 (1989) and S. Dubel, ed., Handbook of Therapeutic Antibodies, 3rd ed., WILEY-VCH Verlag GmbH and Co. (2007), where the definitions include overlapping or subsets of amino acid residues when compared against each other. Each of the aforementioned references is incorporated herein by reference in its entirety and the amino acid residues which comprise binding regions or CDRs as defined by each of the above cited references and are set forth for comparison below.

CDR Definitions

	Kabat[1]	Chothia[2]	MacCallum[3]
V_H CDR1	31-35	26-32	30-35
V_H CDR2	50-65	50-58	47-58
V_H CDR3	95-102	95-102	93-101
V_L CDR1	24-34	23-34	30-36
V_L CDR2	50-56	50-56	46-55
V_L CDR3	89-97	89-97	89-96

[1]Residue numbering follows the nomenclature of Kabat et al., supra
[2]Residue numbering follows the nomenclature ofChothia et al., supra
[3]Residue numbering follows the nomenclature of MacCallum et al., supra

[0092] In the context of the instant invention it will be appreciated that any of the disclosed light and heavy chain CDRs derived from the murine variable region amino acid sequences set forth in FIG. 11A or FIG. 11B may be combined or

rearranged to provide optimized anti-DLL3 (e.g. humanized or chimeric anti-hDLL3) antibodies in accordance with the instant teachings. That is, one or more of the CDRs derived from the contiguous light chain variable region amino acid sequences set forth in FIG. 11A (SEQ ID NOS: 20 - 202, even numbers) or the contiguous heavy chain variable region amino acid sequences set forth in FIG. 11B (SEQ ID NOS: 21 - 203, odd numbers) may be incorporated in a DLL3 modulator and, in particularly preferred embodiments, in a CDR grafted or humanized antibody that immunospecifically associates with one or more DLL3 isoforms. Examples of light (SEQ ID NOS: 204 - 212, even numbers) and heavy (SEQ ID NOS: 205 - 213, odd numbers) chain variable region amino acid sequences of such humanized modulators are also set forth in FIGS. 11A and 11B. Taken together these novel amino acid sequences depict ninety-two murine and five humanized exemplary modulators in accordance with the instant invention. Moreover, corresponding nucleic acid sequences of each of the ninety-two exemplary murine modulators and five humanized modulators set forth in FIGS, 11A and 11B are included in the sequence listing appended to the instant application (SEQ ID NOS: 220 - 413).

[0093] In FIGS. 11A and 11B the annotated CDRs are defined using Chothia numbering. However, as discussed herein and demonstrated in Example 8 below, one skilled in the art could readily define, identify, derive and/or enumerate the CDRs as defined by Kabat et al., Chothia et al. or MacCallum et al. for each respective heavy and light chain sequence set forth in FIG. 11A or FIG. 11B, Accordingly, each of the subject CDRs and antibodies comprising CDRs defined by all such nomenclature are expressly included within the scope of the instant invention. More broadly, the terms "variable region CDR amino acid residue" or more simply "CDR" includes amino acids in a CDR as identified using any sequence or structure based method as set forth above.

2. Antibody Modulator Generation

a. Polyclonal antibodies

[0094] The production of polyclonal antibodies in various host animals, including rabbits, mice, rats, etc. is well known in the art. In some embodiments, polyclonal anti-DLL3 antibody-containing serum is obtained by bleeding or sacrificing the animal. The serum may be used for research purposes in the form obtained from the animal or, in the alternative, the anti-DLL3 antibodies may be partially or fully purified to provide immunoglobulin fractions or homogeneous antibody preparations.

[0095] Briefly the selected animal is immunized with a DLL3 immunogen (e.g., soluble DLL3 or sDLL3) which may, for example, comprise selected isoforms, domains and/or peptides, or live cells or cell preparations expressing DLL3 or immunoreactive fragments thereof. Art known adjuvants that may be used to increase the immunological response, depending on the inoculated species include, but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants may protect the antigen from rapid dispersal by sequestering it in a local deposit, or they may contain substances that stimulate the host to secrete factors that are chemotactic for macrophages and other components of the immune system. Preferably the immunization schedule will involve two or more administrations of the selected immunogen spread out over a predetermined period of time.

[0096] The amino acid sequence of a DLL3 protein as shown in FIGS. IC or ID can be analyzed to select specific regions of the DLL3 protein for generating antibodies. For example, hydrophobicity and hydrophilicity analyses of a DLL3 amino acid sequence are used to identify hydrophilic regions in the DLL3 structure. Regions of a DLL3 protein that show immunogenic structure, as well as other regions and domains, can readily be identified using various other methods known in the art, such as Chou-Fasman, Garnier-Robson, Kyte-Doolittle, Eisenberg, Karplus-Schultz or Jameson-Wolf analysis. Average Flexibility profiles can be generated using the method of Bhaskaran R., Ponnuswamy P. K., 1988, Int. J. Pept. Protein Res. 32:242-255. Beta-turn profiles can be generated using the method of Deleage, G., Roux B., 1987, Protein Engineering 1:289-294. Thus, each DLL3 region, domain or motif identified by any of these programs or methods is within the scope of the present invention and may be isolated or engineered to provide immunogens giving rise to modulators comprising desired properties. Preferred methods for the generation of DLL3 antibodies are further illustrated by way of the Examples provided herein. Methods for preparing a protein or polypeptide for use as an immunogen are well known in the art Also well known in the art are methods for preparing immunogenic conjugates of a protein with a carrier, such as BSA, KLH or other carrier protein. In some circumstances, direct conjugation using, for example, carbodiimide reagents are used; in other instances linking reagents are effective. Administration of a DLL3 immunogen is often conducted by injection over a suitable time period and with use of a suitable adjuvant, as is understood in the art. During the immunization schedule, titers of antibodies can be taken as described in the Examples below to determine adequacy of antibody formation.

b. Monoclonal antibodies

[0097] In addition, the invention contemplates use of monoclonal antibodies. As known in the art, the term "monoclonal antibody" (or mAb) refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible mutations (e.g., naturally occurring mutations), that may be present in minor amounts. In certain embodiments, such a monoclonal antibody includes an antibody comprising a polypeptide sequence that binds or associates with an antigen wherein the antigen-binding polypeptide sequence was obtained by a process that includes the selection of a single target binding polypeptide sequence from a plurality of polypeptide sequences.

[0098] More generally, and as exemplified in Example 6 herein, monoclonal antibodies can be prepared using a wide variety of techniques known in the art including hybridoma, recombinant techniques, phage display technologies, transgenic animals (e.g., a enoMouse®) or some combination thereof. For example, monoclonal antibodies can be produced using hybridoma and art-recognized biochemical and genetic engineering techniques such as described in more detail in An, Zhigiang (ed.) Therapeutic Monoc/onal Antibodies: Frorn Bench to Clinic, John Wiley and Sons, 1st ed. 2009; Shire et. al. (eds.) Current Trends in Monoclonal Antibody Development and Manufacturing, Springer Science + Business Media LLC, 1st ed. 2010; Harlow et al., Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press, 2nd ed. 1988; Hammerling, et al., in: Monoclonal Antibodies and T-Cell Hybridomas 563-681 (Elsevier, N,Y., 1981) each of which is incorporated herein in its entirety by reference. It should be understood that a selected binding sequence can be further altered, for example, to improve affinity for the target, to humanize the target binding sequence, to improve its production in cell culture, to reduce its immunogenictiy in vivo, to create a multispecific antibody, etc., and that an antibody comprising the altered target binding sequence is also an antibody of this invention.

c. Chimeric antibodies

[0099] In another embodiment, the antibody of the invention may comprise chimeric antibodies derived from covalently joined protein segments from at least two different species or types of antibodies. As known in the art, the term "chimeric" antibodies is directed to constructs in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. P.N. 4,816,567; Morrison et al., Proc. Natl. Acad. Sci. USA, 81:6851-6855 (1984)).

[0100] In one embodiment, a chimeric antibody in accordance with the teachings herein may comprise murine V_H and V_L amino acid sequences and constant regions derived from human sources. in other compatible embodiments a chimeric antibody of the present invention may comprise a humanized antibody as described below. In another embodiment, the so-called "CDR-grafted" antibody, the antibody comprises one or more CDRs from a particular species or belonging to a particular antibody class or subclass, while the remainder of the antibody chain(s) is/are identical with or homologous to a corresponding sequence in antibodies derived from another species or belonging to another antibody class or subclass. For use in humans, selected rodent CDRs may be grafted into a human antibody, replacing one or more of the naturally occurring variable regions or CDRs of the human antibody. These constructs generally have the advantages of providing full strength modulator functions (e.g., CDC (complement dependent cytotoxicity), ADCC (antibody-dependent cell-mediated cylotoxicity), etc.) while reducing unwanted immune responses to the antibody by the subject.

d. Humanized antibodies

[0101] Similar to the CDR-grafted antibody is a "humanized" antibody. As used herein, "humanized" forms of non-human (e.g., murine) antibodies are chimeric antibodies that contain a minimal sequence derived from one or more non-human immunoglobulins. In one embodiment, a humanized antibody is a human immunoglobulin (recipient or acceptor antibody) in which residues from a CDR of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat, rabbit, or nonhuman primate having the desired specificity, affinity, and/or capacity. In certain preferred embodiments, residues in one or more FRs in the variable domain of the human immunoglobulin are replaced by corresponding non-human residues from the donor antibody to help maintain the appropriate three-dimensional configuration of the grafted CDR(s) and thereby improve affinity. Furthermore, humanized antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody to, for example, further refine antibody performance.

[0102] CDR grafting and humanized antibodies are described, for example, in U.S.P.Ns. 6,180,370 and 5,693,762, The humanized antibody optionally may also comprise at least a portion of an immunoglobulin Fc, typically that of a human immunoglobulin. For further details, see, e.g., Jones et al., Nature 321:522-525 (1986); and I.I.S.P.Ns. 6,982,321

and 7,087,409. Still another method is termed ''humaneering" which is described, for example, in U.S.P.N. 2005/0008625. Additionally, a non-human antibody may also be modified by specific deletion of human T-cell epitopes or "deimmunization" by the methods disclosed in WO 98/52976 and WO 00/34317. Each of the aforementioned references are incorporated herein in their entirety.

[0103] Humanized antibodies may also be bioengineered using common molecular biology techniques, such as isolating, manipulating, and expressing nucleic acid sequences that encode all or part of immunoglobulin variable regions from at least one of a heavy or light chain. In addition to the sources of such nucleic acid noted above, human germline sequences are available as disclosed, for example, in Tomlinson, I. A. et al. (1992) J. Mol, Biol.227:776-798; Cook, G. P. et al. (1995) Immunol. Today 16: 237-242; Chothia, D. et al. (1992) J. Mol. Biol. 227:799-817; and Tomlinson et al. (1995) EMBO J 14:4628-4638. The V.BASE directory (VBASE2 - Retter et al., Nucleic Acid Res. 33; 671-674, 2005) provides a comprehensive directory of human immunoglobulin variable region sequences (compiled by Tomlinson, **I**. A. *et al.* MRC Centre for Protein Engineering, Cambridge, UK). Consensus human FRs can also be used, e.g., as described in U.S.P.N. 6,300,064.

[0104] In selected embodiments, and as detailed in Example 8 below, at least 60%, 65%, 70%, 75%, or 80% of the humanized or CDR grafted antibody heavy or light chain variable region amino acid residues will correspond to those of the recipient human FR and CDR sequences. In other embodiments at least 85% or 90% of the humanized antibody variable region residues will correspond to those of the recipient FR and CDR sequences. In a further preferred embodiment, greater than 95% of the humanized antibody variable region residues will correspond to those of the recipient FR and CDR sequences.

e. Human antibodies

[0105] In another embodiment, the antibodies may comprise fully human antibodies. The term "human antibody" refers to an antibody which possesses an amino acid sequence that corresponds to that of an antibody produced by a human and/or has been made using any of the techniques for making human antibodies.

[0106] Human antibodies can be produced using various techniques known in the art. One technique is phage display in which a library of (preferably human) antibodies is synthesized on phages, the library is screened with the antigen of interest or an antibody-binding portion thereof, and the phage that binds the antigen is isolated, from which one may obtain the immmoreactive fragments. Methods for preparing and screening such libraries are well known in the art and kits for generating phage display libraries are commercially available (e.g., the Pharmacia Recombinant Phage Antibody System, catalog no. 27-9400-01; and the Stratagene SurfZAP™ phage display kit, catalog no. 240612). There also are other methods and reagents that can be used in generating and screening antibody display libraries (see, e.g., U.S.P.N. 5,223,409; PCT Publication Nos. WO 92/18619, WO 91/17271, WO 92/20791, WO 92/15679, WO 93/01288, WO 92/01047, WO 92/09690; and Barbas et al., Proc. Natl. Acad. Sci. USA 88:7978-7982 (1991)).

[0107] In one embodiment, recombinant human antibodies may be isolated by screening a recombinant combinatorial antibody library prepared as above. In one embodiment, the library is a scFv phage display library, generated using human V_L and V_H cDNAs prepared from mRNA isolated from B-cells.

[0108] The antibodies produced by naive libraries (either natural or synthetic) can be of moderate affinity (K_a of about 10^6 to 10^7 M^{-1}), but affinity maturation can also be mimicked *in vitro* by constructing and respecting from secondary libraries as described in the art. For example, mutation can be introduced at random in vitro by using error-prone polymerase (reported in Leung et al., Technique, 1: 11-15 (1989)). Additionally, affinity maturation can be performed by randomly mutating one or more CDRs, e.g. using PCR with primers carrying random sequence spanning the CDR of interest, in selected individual Fv clones and screening for higher-affinity clones. WO 9607754 described a method for inducing mutagenesis in a CDR of an immunoglobulin light chain to create a library of light chain genes. Another effective approach is to recombine the V_H or V_L domains selected by phage display with repertoires of naturally occurring V domain variants obtained from unimmunized donors and to screen for higher affinity in several rounds of chain reshuffling as described in Marks et a/., Biotechnol., 10: 779-783 (1992). This technique allows the production of antibodies and antibody fragments with a dissociation constant K_D (k_{off}/k_{on}) of about 10^{-9} M or less.

[0109] In other embodiments, similar procedures may be employed using libraries comprising eukaryotic cells (e.g., yeast) that express binding pairs on their surface. See, for example, U.S.P.N. 7,700,302 and U.S.S.N. 12/404,059. In one embodiment, the human antibody is selected from a phage library, where that phase library expresses human antibodies (Vaughan et al. Nature Biotechnology 14:309-314 (1996): Sheets et al. Proc. Natl. Acad. Sci. USA 95:6157-6162 (1998). In other embodiments, human binding pairs may be isolated from combinatorial antibody libraries generated in eukaryotic cells such as yeast See e.g., U.S.P.N. 7,700,302. Such techniques advantageously allow for the screening of large numbers of candidate modulators and provide for relatively easy manipulation of candidate sequences (e.g., by affinity maturation or recombinant shuffling).

[0110] Human antibodies can also be made by introducing human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated and human immu-

noglobulin genes have been introduced. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S.P.Ns. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, and U.S.P.Ns. 6,075,181 and 6,150,584 regarding XenoMouse® technology; and Lonberg and Huszar, Intern. Rev. Immunol. 13:65-93 (1995). Alternatively, the human antibody may be prepared via immortalization of human B lymphocytes producing an antibody directed against a target antigen (such B lymphocytes may be recovered from an individual suffering from a neoplastic disorder or may have been immunized *in vitro). See.* e.g., Cole et al., Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, p. 77 (1985); Boerner et al., J Immunol, 147 (1):86-95 (1991): and U.S.P.N. 5,750,373.

3. Further Processing

[0111] No matter how obtained, modulator-producing cells (e.g., hybridomas, yeast colonies, etc.) may be selected, cloned and further screened for desirable characteristics including, for example, robust growth, high antibody production and, as discussed in more detail below, desirable antibody characteristics. Hybridomas can be expanded *in vivo* in syngeneic animals, in animals that lack an immune system, e.g., nude mice, or in cell culture *in vitro.* Methods of selecting, cloning and expanding hybridomas and/or colonies, each of which produces a discrete antibody species, are well known to those of ordinary skill in the art.

B. Recombinant Modulator Production

1. Overview

[0112] Once the source is perfected DNA encoding the desired DLL3 modulators may be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding antibody heavy and light chains). Isolated and subcloned hybridoma cells (or phage or yeast derived colonies) may serve as a preferred source of such DNA if the modulator is an antibody. If desired, the nucleic acid can further be manipulated as described herein to create agents including fusion proteins, or chimeric, humanized or fully human antibodies. More particularly, isolated DNA (which may be modified) can be used to clone constant and variable region sequences for the manufacture antibodies.

[0113] Accordingly, in exemplary embodiments antibodies may be produced recombinantly, using conventional procedures (such as those set forth in Al-Rubeal; An, and Shire et. al. all supra, and Sambrook J. & Russell D. Molecular Cloning: A Laboratory Manual, 3rd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (2000); Ausubel et al., Short Protocols in Molecular Biology: A Compendium of Methods from Current Protocols in Molecular Biology, Wiley, John & Sons, Inc. (2002)) in which the isolated and subcloned hybridoma cells (or phage or yeast derived colonies) serve as a preferred source of nucleic acid molecules.

[0114] The term "nucleic acid molecule", as used herein, is intended to include DNA molecules and RNA molecules and artificial variants thereof (e.g., peptide nucleic acids), whether single-stranded or double-stranded. The nucleic acids may encode one or both chains of an antibody of the invention, or a fragment or derivative thereof. The nucleic acid molecules of the invention also include polynucleotides sufficient for use as hybridization probes, PCR primers or sequencing primers for identifying, analyzing, mutating or amplifying a polynucleotide encoding a polypeptide; anti-sense nucleic acids for inhibiting expression of a polynucleotide, and as well as complementary sequences. The nucleic acids can be any length. They can be, for example, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, 400, 450, 500, 750, 1,000, 1,500, 3,000, 5,000 or more nucleotides in length, and/or can comprise one or more additional sequences, for example, regulatory sequences, and/or be part of a larger nucleic acid, for example, a vector. It will be appreciated that such nucleic acid sequences can further be manipulated to create modulators including chimeric, humanized or fully human antibodies. More particularly, isolated nucleic acid molecules (which may be modified) can be used to clone constant and variable region sequences for the manufacture antibodies as described in U.S.P.N. 7,709,611.

[0115] The term "isolated nucleic acid" means a that the nucleic acid was (i) amplified in vitro, for example by polymerase chain reaction (PCR), (ii) recombinantly produced by cloning, (iii) purified, for example by cleavage and gel-electrophoretic fractionation, or (iv) synthesized, for example by chemical synthesis. An isolated nucleic acid is a nucleic acid that is available for manipulation by recombinant DNA techniques.

[0116] Whether the source of the nucleic acid encoding the desired immunoreactive portion of the antibody is obtained or derived from phage display technology, yeast libraries, hybridoma-based technology or synthetically, it is to be understood that the present invention encompasses the nucleic acid molecules and sequences encoding the antibodies or antigen-binding fragments or derivatives thereof. Further, the instant invention is directed to vectors and host cells comprising such nucleic acid molecules.

2. Hybridization and Sequence Identity

[0117] As indicated, the invention further provides nucleic acids that hybridize to other nucleic acids under particular hybridization conditions. More specifically the invention encompasses nucleic acids molecules that hybridize under moderate or high stringency hybridization conditions (e.g., as defined below), to the nucleic acid molecules of the invention. Methods for hybridizing nucleic acids are well-known in the art. As is well known, a moderately stringent hybridization conditions comprise a prewashing solution containing 5x sodium chloride/sodium citrate (SSC), 0.5% SDS, 1.0 mM EDTA (pH 8.0), hybridization buffer of about 50% formamide, 6xSSC, and a hybridization temperature of 55°C (or other similar hybridization solutions, such as one containing about 50% formamide, with a hybridization temperature of 42"C), and washing conditions of 60°C, in 0.5xSSC, 0.1% SDS. By way of comparison hybridization under highly stringent hybridization conditions comprise washing with 6xSSC at 45°C, followed by one or more washes in 0.1xSSC, 0.2% SDS at 68°C. Furthermore, one of skill in the art can manipulate the hybridization and/or washing conditions to increase or decrease the stringency of hybridization such that nucleic acids comprising nucleotide sequences that are at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or 99% identical to each other typically remain hybridized to each other.

[0118] The invention also includes nucleic acid molecules that are "substantially identical" to the described nucleic acid molecules. In one embodiment, the term substantially identical with regard to a nucleic acid sequence means may be construed as a sequence of nucleic acid molecules exhibiting at least about 65%, 70%, 75%, 80%, 85%, or 90% sequence identity. In other embodiments, the nucleic acid molecule exhibit 95% or 98% sequence identity to the reference nucleic acid sequence.

[0119] The basic parameters affecting the choice of hybridization conditions and guidance for devising suitable conditions are set forth by, for example, Sambrook, Fritsch, and Maniatis (1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., chapters 9 and 11; and Current Protocols in Molecular Biology, 1995, Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4), and can be readily determined by those having ordinary skill in the art based on, for example, the length and/or base composition of the nucleic acid.

[0120] Sequence similarity for polypeptides, which is also referred to as sequence identity, is typically measured using sequence analysis software. Protein analysis software matches similar sequences using measures of similarity assigned to various substitutions, deletions and other modifications, including conservative amino acid substitutions. For instance, the sequence analysis tool GCG (Accelrys Software Inc.) contains programs such as "GAP" and "BEST-FIT" which can be used with default parameters to determine sequence homology or sequence identity between closely related polypeptides, such as homologous polypeptide from different species of organisms or between a wild type protein and a mutein thereof. (See, e.g., GCG Version 6.1 or Durbin et. Al., Biological Sequence Analysis: Probabilistic models of proteins and nucleic acids., Cambridge Press (1998)).

[0121] Polypeptide sequences can also be compared using FASTA using default or recommended parameters, a program in GCG Version 6.1. FASTA (e.g., FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson (2000) supra). Another preferred algorithm when comparing a sequence of the invention to a database containing a large number of sequences from different organisms is the computer program BLAST, especially blastp or tblastn, using default parameters. See, e.g., Altschul et al. (1990) J. Mol. Biol. 215:403 410 and Altschul et al. (1997) Nucleic Acids Res. 25:3389 402, each of which is herein incorporated by reference.

[0122] In this regard the invention also includes nucleic acid molecules that encode polypeptides that are "substantially identical" with respect to an antibody variable region polypeptide sequence (e.g., either the donor light or heavy chain variable region or the acceptor light or heavy chain variable region). As applied to such polypeptides, the term "substantial identity" or "substantially identical" means that two peptide sequences, when optimally aligned, such as by the programs GAP or BEST-FIT using default gap weights, share at least 60% or 65% sequence identity, preferably at least 70%, 75%, 80%, 85%, or 90% sequence identity, even more preferably at least 93%, 95%, 98% or 99% sequence identity. Preferably, residue positions which are not identical differ by conservative amino acid substitutions. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent sequence identity or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution.

3. Expression

[0123] The varied processes of recombinant expression, i.e., the production of RNA or of RNA and protein/peptide, are well known as set forth, for example, in Berger and Kimmel, Guide to Molecular Cloning Techniques, Methods in Enzymology volume 152 Academic Press, Inc., San Diego, Calif.; Sambrook et al., Molecular Cloning-A Laboratory

Manual (3rd Ed.), Vol. 1-3, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., (2000); and Current Protocols in Molecular Biology, F. M. Ausubel et al., eds., Current Protocols, a joint venture between Greene Publishing Associates, Inc. and John Wiley & Sons, Inc., (supplemented through 2006).

[0124] Certain terms of interest include "expression control sequence" which comprises promoters, ribosome binding sites, enhancers and other control elements which regulate transcription of a gene or translation of mRNA. As is well known, a "promoter" or "promoter region" relates to a nucleic acid sequence which generally is located upstream (5') to the nucleic acid sequence being expressed and controls expression of the sequence by providing a recognition and binding site for RNA-polymerase.

[0125] Exemplary promoters which are compatible according to the invention include promoters for SP6, T3 and T7 polymerase, human U6 RNA promoter, CMV promoter, and artificial hybrid promoters thereof (e.g. CMV) where a part or parts are fused to a part or parts of promoters of genes of other cellular proteins such as e.g. human GAPDH (glyceraldehyde-3-phosphate dehydrogenase), and including or not including (an) additional intron(s).

[0126] In certain embodiments, the nucleic acid molecule may be present in a vector, where appropriate with a promoter, which controls expression of the nucleic acid. The well known term "vector" comprises any intermediary vehicle for a nucleic acid which enables said nucleic acid, for example, to be introduced into prokaryotic and/or eukuryotic cells and, where appropriate, to be integrated into a genome. Methods of transforming mammalian cells are well known in the art. See, for example, U.S.P.Ns. 4,399,216, 4,912,040, 4,740,461, and 4.959,455. The vectors may include a nucleotide sequence encoding an antibody of the invention (e.g., a whole antibody, a heavy or light chain of an antibody, a V_H or V_L of an antibody, or a portion thereof, or a heavy- or light-chain CDR, a single chain Fv, or fragments or variants thereof), operably linked to a promoter (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S.P.N. 5,122,464).

[0127] A variety of host-expression vector systems are commercially available, and many are compatible with the teachings herein and may be used to express the modulators of the invention. Such systems include, but are not limited to, microorganisms such as bacteria (e.g., E. coli, B. subtilis, streptomyces) transformed with Recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing modulator coding sequences; yeast (e.g., Saccharomyces, Pichia) transfected with recombinant yeast expression vectors containing modulator coding sequences; insect cell systems infeded with recombinant virus expression vectors (e.g., baculovirus) containing modulator coding sequences; plant cell systems (e.g., Nicotiana, Arabidopsis, duckweed, corn, wheat, potato, etc.) infected with recombinant viral expression vectors (e.g., cauliflower mosaic virus; tobacco mosaic virus) or transfected with recombinant plasmid expression vectors (e.g., Ti plasmid) containing modulator coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3 cells, etc.) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter).

[0128] As used herein, the term "host cell" covers any kind of cellular system which can be engineered to generate the polypeptides and antigen-binding molecules of the present invention. In one embodiment, the host cell is engineered to allow the production of an antigen binding molecule with modified In a preferred embodiment, the antigen binding molecule, or variant antigen binding molecule, is an antibody, antibody fragment, or fusion protein. In certain embodiments, the host cells have been further manipulated to express increased levels of one or more polypeptides having N-acetylglucosaminyltransferase III (GnTI11) activity. Compatible host cells include cultured cells, e.g., mammalian cultured cells, such as CHO cells, BHK cells, NSO cells, SP2/0 cells, YO myeloma cells, P3X63 mouse myeloma cells, PER cells, PER.C6 cells or hybridoma cells, yeast cells, insect cells, and plant cells, to name only a few, but also cells comprised within a transgenic animal, transgenic plant or cultured plant or animal tissue.

[0129] For long-term, high-yield production of Recombinant proteins stable expression is preferred. Accordingly, cell lines that stably express the selected modulator may be engineered using standard art-recognized techniques. Rather than using expression vectors that contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Any of the selection systems well known in the art may be used, including the glutamine synthetase gene expression system (the GS system) which provides an efficient approach for enhancing expression under certain conditions. The GS system is discussed in whole or part in connection with EP patents 0 216 846, 0 256 055, 0 323 997 and 0 338 841 and U.S.P.N.s 5,591,639 and 5,879,936 each of which is incorporated herein by reference. Another preferred expression system, the Freedom™ CHO-S Kit is commercially provided by Life Technologies (Catalog Number A13696-01) also allows for the development of stable cell lines that may be used for modulator production.

[0130] Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express a molecule of the invention in situ. The host cell may be co-transfected with two expression vectors of the invention, for example, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide.

[0131] Thus, in certain embodiments, the present invention provides recombinant host cells allowing for the expression of antibodies or portions thereof. Antibodies produced by expression in such recombinant host cells are referred to herein as recombinant antibodies. The present invention also provides progeny cells of such host cells, and antibodies produced by the same.

C. Chemical Synthesis

[0132] In addition, the modulators may be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and Molecular Principles, W.H. Freeman & Co., N.Y., and Hunkapiller, M., et al., 1984, Nature 310:105-111). Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs (such as D-isomers of the common amino acids, 2,4-diaminobutyric acid, a-amino isobutyric acid, 4-aminobutyric acid, and the like) can be introduced as a substitution or addition into a polypeptide sequence.

D. Transgenic Systems

[0133] In other embodiments modulators may be produce transgenically through the generation of a mammal or plant that is transgenic for Recombinant molecules such as the immunoglobulin heavy and light chain sequences and that produces the desired compounds in a recoverable form. This includes, for example, the production of protein modulators (e.g., antibodies) in, and recovery from, the milk of goats, cows, or other mammals. See, e.g., U.S.P.Ns. 5,827,690, 5,756,687, 5,750,172, and 5,741,957. In some embodiments, non-human transgenic animals that comprise human immunoglobulin loci are immunized to produce antibodies.

[0134] Other transgenic techniques are set forth in Hogan et al., Manipulating the Mouse Embryo: A Laboratory Manual 2nd ed., Cold Spring Harbor Press (1999); Jackson et al., Mouse Genetics and Transgenics: A Practical Approach, Oxford University Press (2000); and Pinkert, Transgenic Animal Technology: A Laboratory Handbook, Academic Press (1999) and U.S. P.N. 6,417,429. In some embodiments, the non-human animals are mice, rats, sheep, pigs, goats, cattle or horses, and the desired product is produced in blood, milk, urine, saliva, tears, mucus and other bodily fluids from which it is readily obtainable using art-recognized purification techniques.

[0135] Other compatible production systems include methods for making antibodies in plants such as described, for example, in U.S.P.Ns. 6,046,037 and 5,959,177 which are incorporated herein with respect to such techniques.

E. Isolation/Purification

[0136] Once a modulator of the invention has been produced by recombinant expression or any other of the disclosed techniques, it may be purified by any method known in the art for purification of immunoglobulins or proteins. In this respect the modulator may be "isolated" which means that it has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would interfere with diagnostic or therapeutic uses for the polypeptide and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. Isolated modulators include a modulators *in situ* within recombinant cells because at least one component of the polypeptide's natural environment will not be present.

[0137] if the desired molecule is produced intracellularly, as a first step, the particulate debris, either host cells or lysed fragments, may be removed, for example, by centrifugation or ultrafiltration. Where the modulator is secreted into the medium, supernatants from such expression systems are generally first concentrated using a commercially available protein concentration filter, for example, an Amicon or Pellicon ultrafiltration unit (Millipore Corp.). Once the insoluble contaminants are removed the modulator preparation may be further purified using standard techniques such as, for example, hydroxylapatite chromatography, gel electrophoresis, dialysis, and affinity chromatography, with affinity chromatography of particular interest. In this regard protein A can be used to purify antibodies that are based on human IgG1, IgG2 or IgG4 heavy chains (Lindmark, et al., J Immunol Meth 62:1 (1983)) while protein G is recommended for all mouse isotypes and for human IgG3 (Guss, et al., EMBO J 5:1567 (1986)). Other techniques for protein purification such as fractionation on an ionexchange column, ethanol precipitation, reverse phase HPLC, chromatography on silica, chromatography on heparin, sepharose chromatography on an anion or cation exchange resin (such as a polyaspartic acid column), chromatofocusing, SDS-PAGE and ammonium sulfate precipitation are also available depending on the antibody to be recovered. In particularly preferred embodiments the modulators of the instant invention will be purified, at least in part, using Protein A or Protein G affinity chromatography.

VI. DLL3 Modulator Fragments and Derivatives

[0138] Whatever generation and production methodology is selected, modulators of the instant invention will react, bind, combine, complex, connect, attach, join, interact or otherwise associate with a target determinant (e.g., antigen)

and thereby provide the desired results. Where the modulator comprises an antibody or fragment, construct or derivative thereof such associations may be through one or more "binding sites" or "binding components" expressed on the antibody, where a binding site comprises a region of a polypeptide that is responsible for selectively binding to a target molecule or antigen of interest. Binding domains comprise at least one binding site (e.g., an intact IgG antibody will have two binding domains and two binding sites). Exemplary binding domains include an antibody variable domain, a receptor-binding domain of a ligand, a ligand-binding domain of a receptor or an enzymatic domain.

A. Antibodies

[0139] As noted above, the term "antibody" is intended to cover, at least, polyclonal antibodies, multiclonal antibodies, chimeric antibodies, CDR grafted antibodies, humanized and primatized antibodies, human antibodies, recombinantly produced antibodies, intrabodies, multispecific antibodies, bispecific antibodies, monovalent antibodies, multivalent antibodies, anti-idiotypic antibodies, as well as synthetic antibodies.

B. Fragments

[0140] Regardless of which form of the modulator (e.g. chimeric, humanized, etc.) is selected to practice the invention it will be appreciated that immunoreactive fragments of the same may be used in accordance with the teachings herein. An "antibody fragment" comprises at least a portion of an intact antibody. As used herein, the term "fragment" of an antibody molecule includes antigen-binding fragments of antibodies, and the term "antigen-binding fragment" refers to a polypeptide fragment of an immunoglobulin or antibody that immunospecifically binds or reacts with a selected antigen or immunogenic determinants thereof or competes with the intact antibody from which the fragments were derived for specific antigen binding.

[0141] Exemplary fragments include: V_L, V_H, scFv, F(ab')2 fragment, Fab fragmcnt, Fd fragment, Fv fragment, single domain antibody fragments, diabodies, linear antibodies, single-chain antibody molecules and multispecific antibodies formed from antibody fragments. In addition, an active fragment comprises a portion of the antibody that retains its ability to interact with the antigen/substrates or receptors and modify them in a manner similar to that of an intact antibody (though maybe with somewhat less efficiency).

[0142] In other embodiments, an antibody fragment is one that comprises the Fc region and that retains at least one of the biological functions normally associated with the Fc region when present in an intact antibody, such as FcRn binding, antibody half-life modulation, ADCC function and complement binding. In one embodiment, an antibody fragment is a monovalent antibody that has an *in vivo* half-life substantially similar to an intact antibody. For example, such an antibody fragment may comprise an antigen binding arm linked to an Fc sequence capable of conferring *in vivo* stability to the fragment.

[0143] As would be well recognized by those skilled in the art, fragments can be obtained via chemical or enzymatic treatment (such as papain or pepsin) of an intact or complete antibody or antibody chain or by recombinant means. See, e.g., Fundamental Immunology, W. E. Paul, ed., Raven Press, N.Y. (1999), for a more detailed description of antibody fragments.

C. Derivatives

[0144] The invention further includes immunoreactive modulator derivatives and antigen binding molecules comprising one or more modifications.

1. Multivalent Antibodies

[0145] In one embodiment, the modulators of the invention may be monovalent or multivalent (e.g., bivalent, trivalent, etc.). As used herein, the term "valency" refers to the number of potential target binding sites associated with an antibody. Each target binding site specifically binds one target molecule or specific position or locus on a target molecule. When an antibody is monovalent, each binding site of the molecule will specifically bind to a single antigen position or epitope. When an antibody comprises more than one target binding site (multivalent), each target binding site may specifically bind the same or different molecules (e.g., may bind to different ligands or different antigens, or different epitopes or positions on the same antigen). See, for example, U.S.P.N. 2009/0130105. In each case at least one of the binding sites will comprise an epitope, motif or domain associated with a DLL3 isoform.

[0146] In one embodiment, the modulators are bispecific antibodies in which the two chains have different specificities, as described in Millstein et al., 1983, Nature, 305:537-539. Other embodiments include antibodies with additional specificities such as trispecific antibodies. Other more sophisticated compatible multispecific constructs and methods of their fabrication are set forth in U.S.P.N. 2009/0155255, as well as WO 94/04690; Suresh et al., 1986, Methods in

Enzymology, 121:210; and WO96/27011.

[0147] As alluded to above, multivalent antibodies may immunospecifically bind to different epitopes of the desired target molecule or may immunospecifically bind to both the target molecules as well as a heterologous epitope, such as a heterologous polypeptide or solid support material. While preferred embodiments of the anti-DLL3 antibodies only bind two antigens (i.e. bispecific antibodies), antibodies with additional specificities such as trispecific antibodies are also encompassed by the instant invention. Bispecific antibodies also include cross-linked or "heteroconjugate" antibodies. For example, one of the antibodies in the heteroconjugate can be coupled to avidin, the other to biotin. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells (U.S.P.N. 4,676,980), and for treatment of HIV infection (WO 91/00360, WO 92/200373, and EP 03089). Heteroconjugate antibodies may be made using any convenient cross-linking methods. Suitable cross-linking agents are well known in the art, and are disclosed in U.S. P.N. 4,676,980, along with a number of cross-linking techniques.

[0148] In yet other embodiments, antibody variable domains with the desired binding specificities (antibody-antigen combining sites) are fused to immunoglobulin constant domain sequences, such as an immunoglobulin heavy chain constant domain comprising at least part of the hinge, C_H2, and/or C_H3 regions, using methods well known to those of ordinary skill in the art.

2. Fc Region Modifications

[0149] In addition to the various modifications, substitutions, additions or deletions to the variable or binding region of the disclosed modulators (e.g., Fc-DLL3 or anti-DLL3 antibodies) set forth above, those skilled in the art will appreciate that selected embodiments of the present invention may also comprise substitutions or modifications of the constant region (i.e. the Fc region). More particularly, it is contemplated that the DLL3 modulators of the invention may contain *inter alia* one or more additional amino acid residue substitutions, mutations and/or modifications which result in a compound with preferred characteristics including, but not limited to: altered pharmacokinetics, increased serum half life, increase binding affinity, reduced immunogenicity, increased production, altered Fc ligand binding to an Fc receptor (FcR), enhanced or reduced "ADCC" (antibody-dependent cell mediated cytotoxicity) or "CDC" (complement-dependent cytotoxicity) activity, altered glycosylation and/or disulfide bonds and modified binding specificity. In this regard it will be appreciated that these Fc variants may advantageously be used to enhance the effective anti-neoplastic properties of the disclosed modulators.

[0150] To this end certain embodiments of the invention may comprise substitutions or modifications of the Fc region, for example the addition of one or more amino acid residue, substitutions, mutations and/or modifications to produce a compound with enhanced or preferred Fc effector functions. For example, changes in amino acid residues involved in the interaction between the Fc domain and an Fc receptor (e.g., FcγRI, FcγRIIA and B, FcγRIII and FcRn) may lead to increased cytotoxicity and/or altered pharmacokinetics, such as increased serum half-life (see, for example, Ravetch and Kinet, Annu. Rev. Immunol 9:457-92 (1991); Capel et a/., Immunomethods 4:25-34 (1994): and de Haas et al., J. Lab. Clin. Med. 126:330-41 (1995) each of which is incorporated herein by reference).

[0151] In selected embodiments, antibodies with increased *in vivo* half-lives can be generated by modifying (e.g., substituting, deleting or adding) amino acid residues identified as involved in the interaction between the Fc domain and the FcRn receptor (see, e.g., International Publication Nos. WO 97/34631; WO 04/029207; U.S.P.N. 6,737,056 and U.S.P.N. 2003/0190311. With regard to such embodiments, Fc variants may provide half-lives in a mammal, preferably a human, of greater than 5 days, greater than 10 days, greater than 15 days, preferably greater than 20 days, greater than 25 days, greater than 30 days, greater than 35 days, greater than 40 days, greater than 45 days, greater than 2 months, greater than 3 months, greater than 4 months, or greater than 5 months. The increased half-life results in a higher serum titer which thus reduces the frequency of the administration of the antibodies and/or reduces the concentration of the antibodies to be administered. Binding to human FcRn in vivo and serum half life of human FcRn high affinity binding polypeptides can be assayed, e.g., in transgenic mice or transfected human cell lines expressing human FcRn, or in primates to which the polypeptides with a variant Fc region are administered. WO 2000/42072 describes antibody variants with improved or diminished binding to FcRns. See also, e.g., Shields et al. J. Biol. Chem. 9(2):6591-6604 (2001).

[0152] In other embodiments, Fc alterations may lead to enhanced or reduced ADCC or CDC activity. As in known in the art, CDC refers to the lysing of a target cell in the presence of complement, and ADCC refers to a form of cytotoxicity) in which secreted Ig bound onto FcRs present on certain cytotoxic cells (e.g., Natural Killer cells, neutrophils, and macrophages) enables these cytotoxic effector cells to bind specifically to an antigen-bearing target cell and subsequently kill the target cell with cytotoxins. In the context of the instant invention antibody variants are provided with "altered" FcR binding affinity, which is either enhanced or diminished binding as compared to a parent or unmodified antibody or to an antibody comprising a native sequence FcR. Such variants which display decreased binding may possess little or no appreciable binding, e.g., 0-20% binding to the FcR compared to a native sequence, e.g. as determined by techniques well known in the art. In other embodiments the variant will exhibit enhanced binding as compared to the native immu-

noglobulin Fc domain. It will be appreciated that these types of Fc variants may advantageously be used to enhance the effective anti-neoplastic properties of the disclosed antibodies. In yet other embodiments, such alterations lead to increased binding affinity, reduced immunogenicity, increased production, altered glycosylation and/or disulfide bonds (e.g., for conjugation sites), modified binding specificity, increased phagocytosis; and/or down regulation of cell surface receptors (e.g. B cell receptor; BCR), etc.

3. Altered Glycosylation

[0153] Still other embodiments comprise one or more engineered glycoforms, i.e., a DLL3 modulator comprising an altered glycosylation pattern or altered carbohydrate composition that is covalently attached to the protein (e.g., in the Fc domain). See, for example, Shields, R. L. et al. (2002) J. Biol. Chem. 277:26733-26740. Engineered glycoforms may be useful for a variety of purposes, including but not limited to enhancing or reducing effector function, increasing the affinity of the modulator for a target or facilitating production of the modulator. In certain embodiments where reduced effector function is desired, the molecule may be engineered to express an aglycosylated form. Substitutions that may result in elimination of one or more variable region framework glycosylation sites to thereby eliminate glycosylation at that site are well known (see e.g. U.S. P.Ns. 5,714,350 and 6,350,861). Conversely, enhanced effector functions or improved binding may be imparted to the Fc containing molecule by engineering in one or more additional glycosylation sites.

[0154] Other embodiments include an Fc variant that has an altered glycosylation composition, such as a hypofucosylated antibody having reduced amounts of fucosyl residues or an antibody having increased bisecting GlcNAc structures. Such altered glycosylation patterns have been demonstrated to increase the ADCC ability of antibodies. Engineered glycoforms may be generated by any method known to one skilled in the art, for example by using engineered or variant expression strains, by co-expression with one or more enzymes (for example N-acetylglucosaminyltransferase III (GnTI11)), by expressing a molecule comprising an Fc region in various organisms or cell lines from various organisms or by modifying carbohydrate(s) after the molecule comprising Fc region has been expressed (see, for example, WO 2012/117002).

4. Additional Processing

[0155] The modulators may be differentially modified during or after production, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, $NaBH_4$, acetylation, formylation, oxidation, reduction, metabolic synthesis in the presence of tunicamycin, etc.

[0156] Various post-translational modifications also encompassed by the invention include, for example, N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends, attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of prokaryotic host cell expression. Moreover, the modulators may also be modified with a detectable label, such as an enzymatic, fluorescent, radioisotopic or affinity label to allow for detection and isolation of the modulator.

VII. Modulator Characteristics

[0157] No matter how obtained or which of the aforementioned forms the modulator takes, various embodiments of the disclosed modulators may exhibit certain characteristics. In selected embodiments, antibody-producing cells (e.g., hybridomas or yeast colonies) may be selected, cloned and further screened for favorable properties including, for example, robust growth, high modulator production and, as discussed in more detail below, desirable modulator characteristics. In other cases characteristics of the modulator may be imparted or influenced by selecting a particular antigen (e.g., a specific DLL3 isoform) or immunoreactive fragment of the target antigen for inoculation of the animal. In still other embodiments the selected modulators may be engineered as described above to enhance or refine immunochemical characteristics such as affinity or pharmacokinetics.

A. Neutralizing Modulators

[0158] In certain embodiments, the modulators will comprise "neutralizing" antibodies or derivatives or fragments thereof. That is, the present invention may comprise antibody molecules that bind specific domains, motifs or epitopes and are capable of blocking, reducing or inhibiting the biological activity of DLL3. More generally the term "neutralizing

antibody" refers to an antibody that binds to or interacts with a target molecule or ligand and prevents binding or association of the target molecule to a binding partner such as a receptor or substrate, thereby interrupting a biological response that otherwise would result from the interaction of the molecules.

[0159] It will be appreciated that competitive binding assays known in the art may be used to assess the binding and specificity of an antibody or immunologically functional fragment or derivative thereof. With regard to the instant invention an antibody or fragment will be held to inhibit or reduce binding of DLL3 to a binding partner or substrate when an excess of antibody reduces the quantity of binding partner bound to DLL3 by at least about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 97%, 99% or more as measured, for example, by Notch receptor activity or in an *in vitro* competitive binding assay. In the case of antibodies to DLL3 for example, a neutralizing antibody or antagonist will preferably alter Notch receptor activity by at least about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 97%, 99% or more. It will be appreciated that this modified activity may be measured directly using art-recognized techniques or may be measured by the impact the altered activity has downstream (e.g., oncogenesis, cell survival or activation or suppression of Notch responsive genes). Preferably, the ability of an antibody to neutralize DLL3 activity is assessed by inhibition of DLL3 binding to a Notch receptor or by assessing its ability to relieve DLL3 mediated repression of Notch signaling.

B. Internalizing Modulators

[0160] There is evidence that a substantial portion of expressed DLL3 protein remains associated with the tumorigenic cell surface, thereby allowing for localization and internalization of the disclosed modulators. In preferred embodiments such modulators may be associated with, or conjugated to, anti-cancer agents such as cytotoxic moieties that kill the cell upon internalization. In particularly preferred embodiments the modulator will comprise an internalizing antibody drug conjugate.

[0161] As used herein, a modulator that "internalizes" is one that is taken up (along with any payload) by the cell upon binding to an associated antigen or receptor. As will be appreciated, the internalizing modulator may, in preferred embodiments, comprise an antibody including antibody fragments and derivatives thereof, as well as antibody conjugates. Internalization may occur *in vitro* or *in vivo.* For therapeutic applications, internalization will preferably occur *in vivo* in a subject in need thereof. The number of antibody molecules internalized may be sufficient or adequate to kill an antigen-expressing cell, especially an antigen-expressing cancer stem cell. Depending on the potency of the antibody or antibody conjugate, in some instances, the uptake of a single antibody molecule into the cell sufficient to kill the target cell to which the antibody binds. For example, certain toxins are so highly potent that the internalization of a few molecules of the toxin conjugated to the antibody is sufficient to kill the tumor cell. Whether an antibody internalizes upon binding to a mammalian cell can be determined by various assays including those described in the Examples below (e.g., Examples 12 and 15-17). Methods of detecting whether an antibody internalizes into a cell are also described in U.S.P.N. 7,619,068 which is incorporated herein by reference in its entirety.

C. Depleting Modulators

[0162] In other embodiments the antibodies will comprise depleting antibodies or derivatives or fragments thereof. The term "depleting" antibody refers to an antibody that preferably binds to or associates with an antigen on or near the cell surface and induces, promotes or causes the death or elimination of the cell (e.g., by CDC, ADCC or introduction of a cytotoxic agent). In some embodiments, the selected depleting antibodies will be associated or conjugated to a cytotoxic agent.

[0163] Preferably a depleting antibody will be able to remove, incapacitate, eliminate or kill at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 97%, or 99% of DLL3 tumorigenic cells in a defined cell population. In some embodiments the cell population may comprise enriched, sectioned, purified or isolated tumor perpetuating cells. In other embodiments the cell population may comprise whole tumor samples or heterogeneous tumor extracts that comprise tumor perpetuating cells. Those skilled in the art will appreciate that standard biochemical techniques as described in the Examples below (e.g., Examples 13 and 14) may be used to monitor and quantify the depletion of tumorigenic cells or tumor perpetuating cells in accordance with the teachings herein.

D. Binning and Epitope Binding

[0164] It will further be appreciated the disclosed anti-DLL3 antibody modulators will associate with, or bind to, discrete epitopes or immunogenic determinants presented by the selected target or fragment thereof. In certain embodiments, epitope or immunogenic determinants include chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl groups, or sulfonyl groups, and, in certain embodiments, may have specific three-dimensional structural characteristics, and/or specific charge characteristics. Thus, as used herein the term "epitope" includes any protein determinant capable of specific binding to an immunoglobulin or T-cell receptor or otherwise interacting with

a molecule. In certain embodiments, an antibody is said to specifically bind (or immunospecifically bind or react) an antigen when it preferentially recognizes its target antigen in a complex mixture of proteins and/or macromolecules. In preferred embodiments, an antibody is said to specifically bind an antigen when the equilibrium dissociation constant (K_D) is less than or equal to 10^{-6}M or less than or equal to 10^{-7}M, more preferably when the equilibrium dissociation constant is less than or equal to 10^{-8}M, and even more preferably when the dissociation constant is less than or equal to 10^{-9}M

[0165] More directly the term "epitope" is used in its common biochemical sense and refers to that portion of the target antigen capable of being recognized and specifically bound by a particular antibody modulator. When the antigen is a polypeptide such as DLL3, epitopes may generally be formed from both contiguous amino acids and noncontiguous amino acids juxtaposed by tertiary folding of a protein ("conformational epitopes"). In such conformational epitopes the points of interaction occur across amino acid residues on the protein that are linearly separated from one another. Epitopes formed from contiguous amino acids (sometimes referred to as "linear" or "continuous" epitopes) are typically retained upon protein denaturing, whereas epitopes formed by tertiary folding are typically lost upon protein denaturing. In any event an antibody epitope typically includes at least 3, and more usually, at least 5 or 8-10 amino acids in a unique spatial conformation.

[0166] In this respect it will be appreciated that, in certain embodiments, an epitopes may be associated with, or reside in, one or more regions, domains or motifs of the DLL3 protein (e.g., amino acids 1-618 of isoform I). As discussed in more detail herein the extracellular region of the DLL3 protein comprises a series of generally recognized domains including six EGF-like domains and a DSL domain. For the purposes of the instant disclosure the term "domain'" will be used in accordance with its generally accepted meaning and will be held to refer to an identifiable or definable conserved structural entity within a protein that exhibits a distinctive secondary structure content, In many cases, homologous domains with common functions will usually show sequence similarities and be found in a number of disparate proteins (e.g., EGF-like domains are reportedly found in at least 471 different proteins). Similarly, the art-recognized term "motif" will be used in accordance with its common meaning and shall generally refer to a short, conserved region of a protein that is typically ten to twenty contiguous amino acid residues. As discussed throughout, selected embodiments comprise modulators that associate with or bind to an epitope within specific regions, domains or motifs of DLL3.

[0167] In any event once a desired epitope on an antigen is determined, it is possible to generate antibodies to that epitope, e.g., by immunizing with a peptide comprising the epitopes using techniques described in the present invention. Alternatively, during the discovery process, the generation and characterization of antibodies may elucidate information about desirable epitope located in specific domains or motifs. From this information, it is then possible to competitively screen antibodies for binding to the same epitope. An approach to achieve this is to conduct competition studies to find antibodies that competitively bind with one another, i.e. the antibodies compete for binding to the antigen. A high throughput process for binning antibodies based upon their cross-competition is described in WO 03/48731. Other methods of binning or domain level or epitope mapping comprising modulator competition or antigen fragment expression on yeast is set forth in Examples 9 and 10 below.

[0168] As used herein, the term "binning" refers to methods used to group or classify antibodies based on their antigen binding characteristics and competition. While the techniques are useful for defining and categorizing modulators of the instant invention, the bins do not always directly correlate with epitopes and such initial determinations of epitope binding may be further refined and confirmed by other art-recognized methodology as described herein. However, as discussed and shown in the Examples below, empirical assignment of antibody modulators to individual bins provides information that may be indicative of the therapeutic potential of the disclosed modulators.

[0169] More specifically, one can determine whether a selected reference antibody (or fragment thereof) binds to the same epitope or cross competes for binding with a second test antibody (i.e., is in the same bin) by using methods known in the art and set forth in the Examples herein. In one embodiment, a reference antibody modulator is associated with DLL3 antigen under saturating conditions and then the ability of a secondary or test antibody modulator to bind to DLL3 is determined using standard immunochemical techniques. If the test antibody is able to substantially bind to DLL3 at the same time as the reference anti-DLL3 antibody, then the secondary or test antibody binds to a different epitope than the primary or reference antibody. However, if the test antibody is not able to substantially bind to DLL3 at the same time, then the test antibody binds to the same epitope, an overlapping epitope, or an epitope that is in close proximity (at least sterically) to the epitope bound by the primary antibody. That is, the test antibody competes for antigen binding and is in the same bin as the reference antibody.

[0170] The term "compete" or "competing antibody" when used in the context of the disclosed modulators means competition between antibodies as determined by an assay in which a test antibody or immunologically functional fragment under test prevents or inhibits specific binding of a reference antibody to a common antigen. Typically, such an assay involves the use of purified antigen (e.g., DLL3 or a domain or fragment thereof) bound to a solid surface or cells bearing either of these, an unlabeled test immunoglobulin and a labeled reference immunoglobulin. Competitive inhibition is measured by determining the amount of label bound to the solid surface or cells in the presence of the test immunoglobulin. Usually the test immunoglobulin is present in excess and/or allowed to bind first. Antibodies identified

by competition assay (competing antibodies) include antibodies binding to the same epitope as the reference antibody and antibodies binding to an adjacent epitope sufficiently proximal to the epitope bound by the reference antibody for steric hindrance to occur. Additional details regarding methods for determining competitive binding are provided in the Examples herein. Usually, when a competing antibody is present in excess, it will inhibit specific binding of a reference antibody to a common antigen by at least 30%, 40%, 45%, 50%, 55%, 60%, 65%, 70% or 75%. In some instance, binding is inhibited by at least 80%, 85%, 90%, 95%, or 97% or more.

[0171] Conversely, when the reference antibody is bound it will preferably inhibit binding of a subsequently added test antibody (i.e., a DLL3 modulator) by at least 30%, 40%, 45%), 50%, 55%, 60%, 65%, 70% or 75%. In some instance, binding of the test antibody is inhibited by at least 80%, 85%, 90%, 95%, or 97% or more.

[0172] With regard to the instant invention, and as set forth in the Examples 9 and 10 below, it has been determined (via surface plasmon resonance or bio-layer interferometry) that the extracellular domain of DLL3 defines at least nine bins by competitive binding termed "bin A" to "bin I'' herein. Given the resolution provided by modulator binning techniques, it is believed that these nine bins comprise the majority of the bins that are present in the extracellular region of the DLL3 protein.

[0173] In this respect, and as known in the art and detailed in the Examples below, the desired binning or competitive binding data can be obtained using solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA or ELISA), sandwich competition assay, a Biacore™ 2000 system (i.e., surface plasmon resonance - GE Healthcare), a ForteBio® Analyzer (i.e., bio-layer interferometry - ForteBio, Inc.) or flow cytometric methodology. The term "surface plasmon resonance," as used herein, refers to an optical phenomenon that allows for the analysis of real-time specific interactions by detection of alterations in protein concentrations within a biosensor matrix. The term "bio-layer interferometry" refers to an optical analytical technique that analyzes the interference pattern of white light reflected from two surfaces: a layer of immobilized protein on a biosensor tip, and an internal reference layer. Any change in the number of molecules bound to the biosensor tip causes a shift in the interference pattern that can be measured in real-time. In particularly preferred embodiments the analysis (whether surface plasmon resonance, bio-layer interferometry or flow cytometry) is performed using a Biacore or ForteBio instrument or a flow cytometer (e.g., FACSAria II) as demonstrated in the Examples below.

[0174] In order to further characterize the epitopes that the disclosed DLL3 antibody modulators associate with or bind to, domain-level epitope mapping was performed using a modification of the protocol described by Cochran et al. (J Immunol Methods. 287 (1-2):147-158 (2004) which is incorporated herein by reference). Briefly, individual domains of DLL3 comprising specific amino acid sequences were expressed on the surface of yeast and binding by each DLL3 antibody was determined through flow cytometry. The results are discussed below in Example 10 and shown in FIGS. 14A and 14B.

[0175] Other compatible epitope mapping techniques include alanine scanning mutants, peptide blots (Reineke (2004) Methods Mol Biol 248:443-63) (herein specifically incorporated by reference in its entirety), or peptide cleavage analysis. In addition, methods such as epitope excision, epitope extraction and chemical modification of antigens can be employed (Tomer (2000) Protein Science 9: 487-496) (herein specifically incorporated by reference in its entirety). In other embodiments Modification-Assisted Profiling (MAP), also known as Antigen Structure-based Antibody Profiling (ASAP) provides a method that categorizes large numbers of monoclonal antibodies (mAbs) directed against the same antigen according to the similarities of the binding profile of each antibody to chemically or enzymatically modified antigen surfaces (U.S.P.N, 2004/0101920, herein specifically incorporated by reference in its entirety). Each category may reflect a unique epitope either distinctly different from or partially overlapping with epitope represented by another category. This technology allows rapid filtering of genetically identical antibodies, such that characterization can be focused on genetically distinct antibodies. It will be appreciated that MAP may be used to sort the hDLL3 antibody modulators of the invention into groups of antibodies binding different epitopes

[0176] Agents useful for altering the structure of the immobilized antigen include enzymes such as proteolytic enzymes (e.g., trypsin, endoproteinase Glu-C, endoproteinase Asp-N, chymotrypsin, etc.). Agents useful for altering the structure of the immobilized antigen may also be chemical agents, such as, succinimidyl esters and their derivatives, primary amine-containing compounds, hydrazines and carbohydrazines, free amino acids, etc.

[0177] The antigen protein may be immobilized on either biosensor chip surfaces or polystyrene beads. The latter can be processed with, for example, an assay such as multiplex LUMINEX™ detection assay (Luminex Corp.). Because of the capacity of LUMINEX to handle multiplex analysis with up to 100 different types of beads, LUMINEX provides almost unlimited antigen surfaces with various modifications, resulting in improved resolution in antibody epitope profiling over a biosensor assay.

E. Modulator Binding Characteristics

[0178] Besides epitope specificity the disclosed antibodies may be characterized using physical characteristics such as, for example, binding affinities. In this regard the present invention further encompasses the use of antibodies that

have a high binding affinity for one or more DLL3 isoforms or, in the case of pan-antibodies, more than one member of the DLL family.

[0179] The term "K_D", as used herein, is intended to refer to the dissociation constant of a particular antibody-antigen interaction. An antibody of the invention is said to immunospecifically bind its target antigen when the dissociation constant K_D (k_{off}/k_{on}) is $\leq 10^{-7}$M. The antibody specifically binds antigen with high affinity when the K_D is $\leq 5x10^{-9}$M, and with very high affinity when the K_D is $\leq 5x10^{-10}$M. In one embodiment of the invention, the antibody has a K_D of $\leq 10^{-9}$M and an off-rate of about $1x10^{-4}$/sec. In one embodiment of the invention, the off-rate is $< 1x10^{-5}$/sec. In other embodiments of the invention, the antibodies will bind to DLL3 with a K_D of between about 10^{-7}M and 10^{-10}M, and in yet another embodiment it will bind with a $K_D \leq 2x10^{-10}$M. Still other selected embodiments of the present invention comprise antibodies that have a disassociation constant or K_D (k_{off}/k_{on}) of less than 10^{-2}M, less than $5x10^{-2}$M, less than 10^{-3}M, less than $5x10^{-3}$M, less than 10^{-4}M, less than $5x10^{-4}$M, less than 10^{-5}M, less than $5x10^{-5}$M, less than 10^{-6}M, less than $5x10^{-6}$M, Jess than 10^{-7}M, less than $5x10^{-7}$M, less than 10^{-8}M, less than $5x10^{-8}$M, less than 10^{-9}M, less than $5x10^{-9}$M, less than 10^{-10}M, less than $5x10^{-10}$M, less than 10^{-11}M, less than $5x10^{-11}$M, less than 10^{-12}M, less than $5x10^{-12}$M, less than 10^{-13}M, less than $5x10^{-13}$M, less than 10^{-14}M, less than $5x10^{-14}$M, less than 10^{-15}M or less than $5x10^{-15}$M.

[0180] In specific embodiments, an antibody of the invention that immunospecifically binds to DLL3 has an association rate constant or k_{on} (or k_a) rate (DLL3 (Ab) + antigen (Ag) $^{k_{on}}\leftarrow$ Ab-Ag) of at least $10^5M^{-1}s^{-1}$, at least $2x10^5M^{-1}s^{-1}$, at least $5x10^5M^{-1}s^{-1}$, at least $10^6M^{-1}s^{-1}$, at least $5x10^6M^{-1}s^{-1}$, at least $10^7M^{-1}s^{-1}$, at least $5x10^7M^{-1}s^{-1}$, or at least $10^8M^{-1}s^{-1}$.

[0181] In another embodiment, an antibody of the invention that **immunospecifically** binds to DLL3 has a disassociation rate constant or k_{off} (or k_{dj} rate (DLL3 (Ab) + antigen (Ag) $^{k_{off}}\leftarrow$ Ab-Ag) of less than $10^{-1}s^{-1}$, less than $5x10^{-1}s^{-1}$, less than $10^{-2}s^{-1}$, less than $5x10^{-2}s^{-1}$, less than $10^{-3}s^{-1}$, less than $5x10^{-3}s^{-1}$, less than $10^{-4}s^{-1}$, less than $5x10^{-4}s^{-1}$, less than $10^{-5}s^{-1}$, less than $5x10^{-5}s^{-1}$, less than $10^{-6}s^{-1}$, less than $5x10^{-6}s^{-1}$ less than $10^{-7}s^{-1}$, less than $5x10^{-7}s^{-1}$, less than $10^{-8}s^{-1}$, less than $5x10^{-8}s^{-1}$, less than $10^{-9}s^{-1}$, less than $5x10^{-9}s^{-1}$ or less than $10^{-10}s^{-1}$.

[0182] In other selected embodiments of the present invention anti-DLL3 antibodies will have an affinity constant or K_a (k_{on}/k_{off}) of at least 10^2M^{-1}, at least $5x10^2M^{-1}$, at least 10^3M^{-1}, at least $5x10^3M^{-1}$, at least 10^4M^{-1}, at least $5x10^4M^{-1}$, at least 10^5M^{-1}, at least $5x10^5M^{-1}$, at least 10^6M^{-1}, at least $5x10^6M^{-1}$, at least 10^7M^{-1}, at least $5x10^7M^{-1}$, at least 10^8M^{-1}, at least $5x10^8M^{-1}$, at least 10^9M^{-1}, at least $3x10^9M^{-1}$, at least $10^{10}M^{-1}$, at least $5x10^{10}M^{-1}$, at least $10^{11}M^{-1}$, at least $5x10^{11}M^{-1}$, at least $10^{12}M^{-1}$, at least $5x10^{12}M^{-1}$, at least $10^{13}M^{-1}$, at least $5x10^{13}M^{-1}$, at least $10^{14}M^{-1}$, at least $5x10^{14}M^{-1}$, at least $10^{15}M^{-1}$ or at least $5x10^{15}M^{-1}$.

[0183] Besides the aforementioned modulator characteristics antibodies of the instant invention may further be characterized using additional physical characteristics including, for example, thermal stability (i.e, melting temperature; Tm), and isoelectric points. (See, e.g., Bjellqvist et al., 1993, Electrophoresis 14:1023; Vermeer et al., 2000, Biophys. J. 78:394-404; Vermeer et al., 2000, Biophys. J. 79:2150-2154 each of which is incorporated herein by reference).

VIII. Conjugated Modulators

A. Overview

[0184] Once the modulators of the invention have been generated and/or fabricated and selected according to the teachings herein they may be linked with, fused to, conjugated to (e.g., covalently or non-covalently) or otherwise associated with pharmaceutically active or diagnostic moieties or biocompatible modifiers. As used herein the term "conjugate" or "modulator conjugate" or "antibody conjugate" will be used broadly and held to mean any biologically active or detectable molecule or drug associated with the disclosed modulators regardless of the method of association. In this respect it will be understood that such conjugates may, in addition to the disclosed modulators, comprise peptides, polypeptides, proteins, prodrugs which are metabolized to an active agent in vivo, polymers, nucleic acid molecules, small molecules, binding agents, mimetic agents, synthetic drugs, inorganic molecules, organic molecules and radioisotopes. Moreover, as indicated above the selected conjugate may be covalently or non-covalently associated with, or linked to, the modulator and exhibit various stoichiometric molar ratios depending, at least in part, on the method used to effect the conjugation.

[0185] Particularly preferred aspects of the instant invention will comprise antibody modulator conjugates or antibody-drug conjugates that may be used for the diagnosis and/or treatment of proliferative disorders. It will be appreciated that, unless otherwise dictated by context, the term "antibody-drug conjugate" or "ADC" or the formula M-[L-D]n shall be held to encompass conjugates comprising both therapeutic and diagnostic moieties. In such embodiments antibody-drug conjugate compounds will comprise a DLL3 modulator (typically an anti-DLL3 antibody) as the modulator or cellular binding unit (abbreviated as CBA, M, or Ab herein), a therapeutic (e.g., anti-cancer agent) or diagnostic moiety (D), and optionally a linker (L) that joins the drug and the antigen binding agent. For the purposes of the instant disclosure "n" shall be held to mean an integer from 1 to 20. In a preferred embodiment, the modulator is a DLL3 mAb comprising at least one CDR from the heavy and light chain variable regions as described above,

[0186] Those skilled in the art will appreciate that a number of different reactions are available for the attachment or

association of therapeutic or diagnostic moieties and/or linkers to binding agents. In selected embodiments this may be accomplished by reaction of the amino acid residues of the binding agent, e.g., antibody molecule, including the amine groups of lysine, the free carboxylic acid groups of glutamic and aspartic acid, the sulfhydryl groups of cysteine and the various moieties of the aromatic amino acids. One of the most commonly used non-specific methods of covalent attachment is the carbodiimide reaction to link a carboxy (or amino) group of a compound to amino (or carboxy) groups of the antibody. Additionally, bifunctional agents such as dialdehydes or imidoesters have been used to link the amino group of a compound to amino groups of an antibody molecule. Also available for attachment of drugs to binding agents is the Schiff base reaction. This method involves the periodate oxidation of a drug that contains glycol or hydroxy groups, thus forming an aldehyde which is then reacted with the binding agent. Attachment occurs via formation of a Schiff base with amino groups of the binding agent. and azlactones can also be used as coupling agents for covalently attaching drugs to binding agents.

[0187] in other embodiments the disclosed modulators of the invention may be conjugated or associated with proteins, polypeptides or peptides that impart selected characteristics (e.g., biotoxins, biomarkers, purification tags, etc.). In certain preferred embodiments the present invention encompasses the use of modulators or fragments thereof recombinantly fused or chemically conjugated (including both covalent and non-covalent conjugations) to a heterologous protein or peptide wherein the protein or peptide comprises at least 10, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90 or at least 100 amino acids. The construct does not necessarily need to be directly linked, but may occur through amino acid linker sequences. For example, antibodies may be used to target heterologous polypeptides to particular cell types expressing DLL3, either *in vitro* or *in vivo,* by fusing or conjugating the modulators of the present invention to antibodies specific for particular cell surface receptors to provide bispecific constructs. Moreover, modulators fused or conjugated to heterologous polypeptides may also be used in *in vitro* immunoassays and may be particularly compatible with purification methodology (e.g., his-tags) as is known in the art. See e.g., International publication No. WO 93/21232; European Patent No. EP 439,095; Naramura et al., 1994, Immunol. Lett. 39:91-99; U.S. Pat. No. 5,474,981; Gillies et al., 1992, PNAS 89:1428-1432; and Fell et al., 1991, J. Immunol. 146:2446-2452.

B. Linkers

[0188] Besides the aforementioned peptide linkers or spacers, it will be appreciated that several other varieties or types of linker may be used to associate the diseased modulators with pharmaceutically active or diagnostic moieties or biocompatible modifiers. In some embodiments, the linker is cleavable under intracellular conditions, such that cleavage of the linker releases the drug unit from the antibody in the intracellular environment. In yet other embodiments, the linker unit is not cleavable and the drug is released, for example, by antibody degradation.

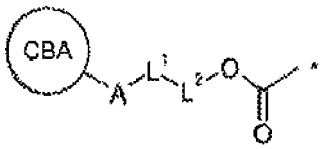
[0189] The linkers of the ADC are preferably stable extracellularly, prevent aggregation of ADC molecules and keep the ADC freely soluble in aqueous media and in a monomeric state. Before transport or delivery into a cell, the antibody-drug conjugate (ADC) is preferably stable and remains intact, i.e. the antibody remains linked to the drug moiety. The linkers are stable outside the target cell and may be cleaved at some efficacious rate inside the cell. An effective linker will: (i) maintain the specific binding properties of the antibody; (ii) allow intracellular delivery of the conjugate or drug moiety; (iii) remain stable and intact, i.e. not cleaved, until the conjugate has been delivered or transported to its targeted site; and (iv) maintain a cytotoxic, cell-killing effect or a cytostatic effect of the PBD drug moiety. Stability of the ADC may be measured by standard analytical techniques such as mass spectroscopy, HPLC, and the separation/analysis technique LC/MS. Covalent attachment of the antibody and the drug moiety requires the linker to have two reactive functional groups, i.e. bivalency in a reactive sense. Bivalent linker reagents which are useful to attach two or more functional or biologically active moieties, such as peptides, nucleic acids, drugs, toxins, antibodies, happens, and reporter groups are known, and methods have been described their resulting conjugates (Hermanson, G.T. (1996) Bioconjugate Techniques; Academic Press: New York, p 234-242).

[0190] To this end certain embodiments of the invention comprise the use a linker that is cleavable by a cleaving agent that is present in the intracellular environment (e.g., within a lysosome or endosome or caveolae). The linker can be, for example, a **peptidyl** linker that is cleaved by an intracellular peptidase or protease enzyme, including, but not limited to, a lysosomal or endosomal protease. In some embodiments, the peptidyl linker is at least two amino acids long or at least three amino acids long. Cleaving agents can include cathepsins B and D and plasmin, each of which is known to hydrolyze dipeptide drug derivatives resulting in the release of active drug inside target cells. Exemplary peptidyl linkers that are cleavable by the thiol-dependent protease Cathepsin-B are peptides comprising Phe-Leu since Cathepsin-B has been found to be highly expressed in cancerous tissue. Other examples of such linkers are described, for example, in U.S.P.N. 6,214,345 and U.S.P.N. 2012/0078028 each of which incorporated herein by reference in its entirety. In a specific preferred embodiment, the peptidyl linker cleavable by an intracellular protease is a Val-Cit linker, an Ala-Val linker or a Phe-Lys linker such as is described in U.S.P.N. 6,214,345. One advantage of using intracellular proteolytic release of the therapeutic agent is that the agent is typically attenuated when conjugated and the serum stabilities of the conjugates are typically high.

[0191] In other embodiments, the cleavable linker is pH-sensitive, i.e., sensitive to hydrolysis at certain pH values. Typically, the pH-sensitive linker hydrolyzable under acidic conditions. For example, an acid-labile linker that is hydrolyzable in the lysosome (e.g., a hydrazone, oxime, semicarbazone, thiosemicarbazone, cis-aconitic amide, orthoester, acetal, ketal, or the like) can be used (See, e.g., U.S.P.N. 5,122,368; 5,824,805; 5,622,929). Such linkers are relatively stable under neutral pH conditions, such as those in the blood, but are unstable at below pH 5.5 or 5.0, the approximate pH of the lysosome.

[0192] In yet other embodiments, the linker is cleavable under reducing conditions (e.g., a disulfide linker). A variety of disulfide linkers are known in the art, including, for example, those that can be formed using SATA (N-succinimidyl-S-acetylthioacetate), SPDP (N-succinimidyl-3-(2-pyridyldithio)propionate), SPDB (N-succinimidyl-3-(2-pyridyldithio) butyrate) and SMPT (N-succinimidyl-oxycarbonyl-alpha-methyl-alpha-(2-pyridyl-dithio)toluene). In yet other specific embodiments, the linker is a malonate linker (Johnson et al., 1995, Anticancer Res. 15:1387-93), a maleimidobenzoyl linker (Lau et al., 1995, Bioorg-Med-Chem. 3(10):1299-1304), or a 3'-N-amide analog (Lau et al., 1995, Bioorg-Med-Chem, 3(10):1305-12). In yet other embodiments, the linker unit is not cleavable and the drug is released by antibody degradation. (See U.S. Publication No. 2005/0238649 incorporated by reference herein in its entirety and for all purposes).

[0193] More particularly, in preferred embodiments (set forth in U.S.P.N. 2011/0256157 which is incorporated herein by reference in its entirety) compatible linkers will comprise:



where the asterisk indicates the point of attachment to the cytotoxic agent, CBA is a cell binding agent/modulator, L^1 is a linker, A is a connecting group connecting L^1 to the cell binding agent, L^2 is a covalent bond or together with -OC(=O)- forms a self-immolative linker, and L^1 or L^2 is a cleavable linker.

[0194] L^1 is preferably the cleavable linker, and may be referred to as a trigger for activation of the linker for cleavage.

[0195] The nature of L^1 and L^2, where present, can vary widely. These groups are chosen on the basis of their cleavage characteristics, which may be dictated by the conditions at the site to which the conjugate is delivered. Those linkers that are cleaved by the action of enzymes are preferred, although linkers that are cleavable by changes in pH (e.g. acid or base labile), temperature or upon irradiation (e.g. photolabile) may also be used. Linkers that are cleavable under reducing or oxidising conditions may also find use in the present invention.

[0196] L^1 may comprise a contiguous sequence of amino acids. The amino acid sequence may be the target substrate for enzymatic cleavage, thereby allowing release of R^{10} from the N10 position.

[0197] In one embodiment, L^1 is cleavable by the action of an enzyme. In one embodiment, the enzyme is an esterase or a peptidase.

[0198] In one embodiment, L^2 is present and together with -C(=O)O- forms a self-immolative linker. In one embodiment, L^2 is a substrate for enzymatic activity, thereby allowing release of R^{10} from the N10 position.

[0199] In one embodiment, where L^1 is cleavable by the action of an enzyme and L^2 is present, the enzyme cleaves the bond between L^1 and L^2.

[0200] L^1 and L^2, where present, may be connected by a bond selected from:

-C(=O)NH-, -C(=O)O-, -NHC(=O)-, -OC(=O)-, -OC(=O)O-, -NHC(=O)O-, -OC(=O)NH-, and -NHC(=O)NH-.

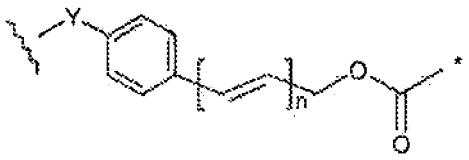
[0201] An amino group of L^1 that connects to L^2 may be the N-terminus of an amino acid or may be derived from an amino group of an amino acid side chain, for example a lysine amino acid side chain.

[0202] A carboxyl group of L^1 that connects to L_2 may be the C-terminus of an amino acid or may be derived from a carboxyl group of an amino acid side chain, for example a glutamic acid amino acid side chain.

[0203] A hydroxyl group of L^1 that connects to L^2 may be derived from a hydroxyl group of an amino acid side chain, for example a serine amino acid side chain.

[0204] The term "amino acid side chain" includes those groups found in: (i) naturally occurring amino acids such as alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine; (ii) minor amino acids such as ornithine and citrulline; (iii) unnatural amino acids, beta-amino acids, synthetic analogs and derivatives of naturally occurring amino acids; and (iv) all enantiomers, diastereomers, isomericaily enriched, isotopically labelled (e.g. ^2H, ^3H, ^{14}C, ^{15}N), protected forms, and racemic mixtures thereof.

[0205] In one embodiment, -C(=O)O- and L_2 together form the group:



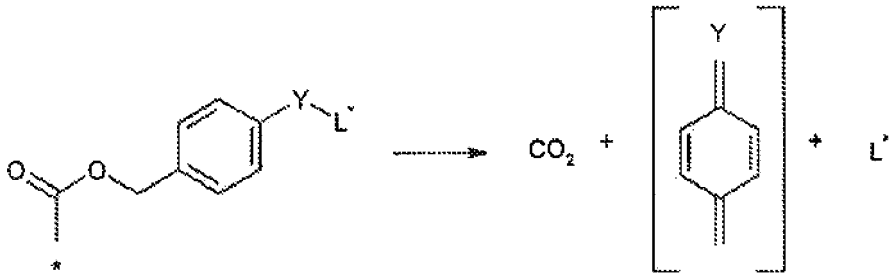
where the asterisk indicates the point of attachment to the drug or cytotoxic agent position, the wavy line indicates the point of attachment to the linker L^1, Y is -N(H)-, -O-, -C(=O)N(H)- or -C(=O)O-, and n is 0 to 3. The phenylene ring is optionally substituted with one, two or three substituents as described herein. In one embodiment, the phenylene group is optionally substituted with halo, NO_2, R or OR.

[0206] In one embodiment, Y is NH.

[0207] In one embodiment, n is 0 or 1. Preferably, n is 0.

[0208] Where Y is NH and n is 0, the self-immolative linker may be referred to as a p-aminobenzylcarbonyl linker (PABC).

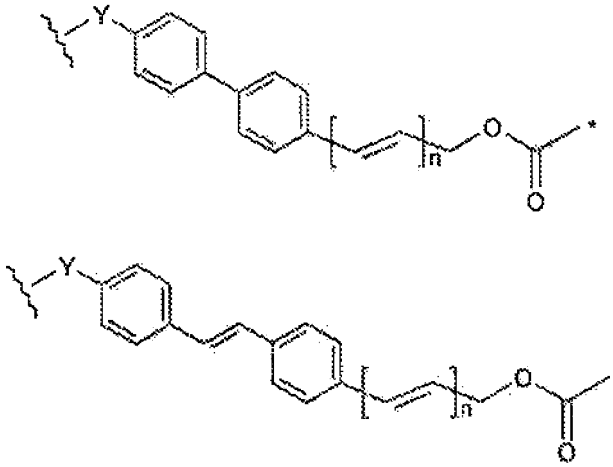
[0209] The self-immolative linker will allow for release of the protected compound when a remote site is activated, proceeding along the lines shown below (for n=0):



where L^* is the activated form of the remaining portion of the linker. These groups have the advantage of separating the site of activation from the compound being protected. As described above, the phenylene group may be optionally substituted.

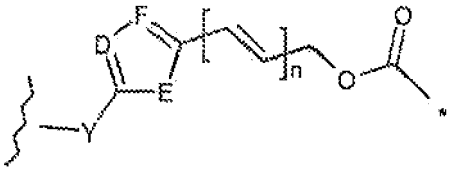
In one embodiment described herein, the group L^* is a linker L^1 as described herein, which may include a dipeptide group.

[0210] In another embodiment, -C(=O)O- and L^2 together form a group selected from:



where the asterisk, the wavy line, Y, and n are as defined above. Each phenylene ring is optionally substituted with one, two or three substituents as described herein. In one embodiment, the phenviene ring having the Y substituent is optionally substituted and the phenylene ring not having the Y substituent is unsubstituted. In one embodiment, the phenylene ring having the Y substituent is unsubstituted and the phenylene ring not having the Y substituent is optionally substituted.

[0211] In another embodiment, -C(=O)O- and L^2 together form a group selected from:



where the asterisk, the wavy line, Y, and n arc as defined above, E is O, S or NR, D is N, CH, or CR, and F is N, CH, or CR.

[0212] In one embodiment, D is N.

[0213] In one embodiment, D is CH.

[0214] In one embodiment, E is O or S.

[0215] In one embodiment, F is CH.

[0216] In a preferred embodiment, the linker is a cathepsin labile linker.

[0217] In one embodiment, L^1 comprises a dipeptide. The dipeptide may be represented as -NH-X_1-X_2-CO-, where -NH- and -CO- represent the N- and C-terminals of the amino acid groups X_1 and X_2 respectively. The amino acids in the dipeptide may be any combination of natural amino acids. Where the linker is a cathepsin labile linker, the dipeptide may be the site of action for cathepsin-mediated cleavage.

[0218] Additionally, for those amino acids groups having carboxyl or amino side chain functionality, for example Glu and Lys respectively, CO and NH may represent that side chain functionality.

[0219] In one embodiment, the group -X_1-X_2- in dipeptide, -NH-X_1-X_2-CO-, is selected from:

-Phe-Lys-, -Val-Ala-, -Val-Lys-, -Ala-Lys-, -Val-Cit-, -Phe-Cit-, -Leu-Cit-, -Phe- Arg- and -Trp-Cit- where Cit is citrulline.

[0220] Preferably, the group -X_1-X_2- in dipeptide, -NH-X_1-X2-CO-, is selected from:

-Phe-Lys-, -Val-Ala-, -Val-Lys-, -Ala-Lys-, and -Val-Cit-.

[0221] Most preferably, the group -X_1-X_2- in dipeptide, -NH-X_1-X_2-CO-, is -Phe-Lys- or -Val-Ala-.

[0222] Other dipeptide combinations may be used, including those described by Dubowchik et al., Bioconjugate Chemistry, 2002, 13,855-869, which is incorporated herein by reference,

[0223] In one embodiment, the amino acid side chain is derivatised, where appropriate. For example, an amino group or carboxy group of an amino acid side chain may be derivatised.

[0224] In one embodiment, an amino group NH2 of a side chain amino acid, such as lysine, is a derivatised form selected from the group consisting of NHR and NRR'.

[0225] In one embodiment, a carboxy group COOH of a side chain amino acid, such as aspartic acid, is a derivatised form selected from the group consisting of COOR, $CONH_2$, CONHR and CONRR'.

[0226] In one embodiment, the amino acid side chain is chemically protected, where appropriate. The side chain protecting group may be a group as discussed below in relation to the group R^L. Protected amino acid sequences are cleavable by enzymes. For example, it has been established that a dipeptide sequence comprising a Boc side chain-protected Lys residue is cleavable by cathepsin.

[0227] Protecting groups for the side chains of amino acids are well known in the art and are described in the Novabiochem Catalog. Additional protecting group strategies are set out in Protective Groups in Organic Synthesis, Greene and Wuts.

[0228] Possible side chain protecting groups are shown below for those amino acids having reactive side chain functionality:

Arg: Z, Mtr, Tos;
Asn: Trt, Xan;
Asp: Bzl, t-Bu;
Cys: Acm, Bzl, Bzl-OMe, Bzl-Me, Trt;
Glu: Bzl, t-Bu;
Gln: Trt, Xan;
His: Boc, Dnp, Tos. Trt;
Lys: Boc, Z-Cl, Fmoc, Z, Alloc;
Ser: Bzl, TBDMS, TBDPS;
Thr: Bz;
Trp: Boc;
Tyr: Bzl, Z, Z-Br.

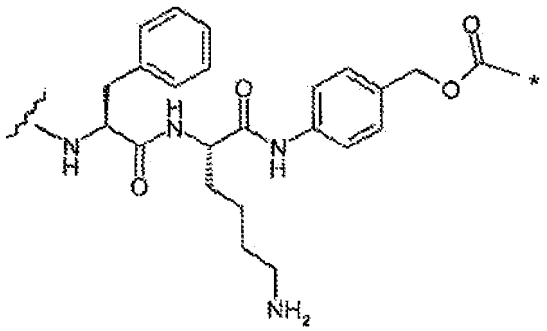
[0229] In one embodiment, the side chain protection is selected to be orthogonal to a group provided as, or as part of, a capping group, where present. Thus, the removal of the side chain protecting group does not remove the capping group, or any protecting group functionality that is part of the capping group.

[0230] In other embodiments of the invention, the amino acids selected are those having no reactive side chain functionality. For example, the amino acids may be selected from: Ala, Gly, Ile, Leu, Met, Phe, Pro, and Val.

[0231] In one embodiment, the dipeptide is used in combination with a self-immolative linker. The self-immolative linker may be connected to $-X_2-$.

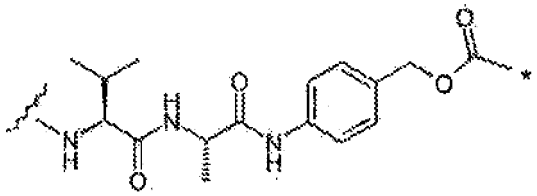
[0232] Where a self-immolative linker is present, $-X_2-$ is connected directly to the self-immolative iinker. Preferably the group $-X_2-CO-$ is connected to Y, where Y is NH, thereby forming the group $-X_2-CO-NH-$. $-NH-X_1-$ is connected directly to A. A may comprise the functionality -CO- thereby to form an amide link with $-X_1-$.

[0233] In one embodiment, L^1 and L^2 together with -OC(=O)- comprise the group $NH-X_1-X_2-CO-PABC-$. The PABC group is connected directly to the cytotoxic agent. Preferably, the self-immolative linker and the dipeptide together form the group -NH-Phe-Lys-CO-NH-PABC-, which is illustrated below:



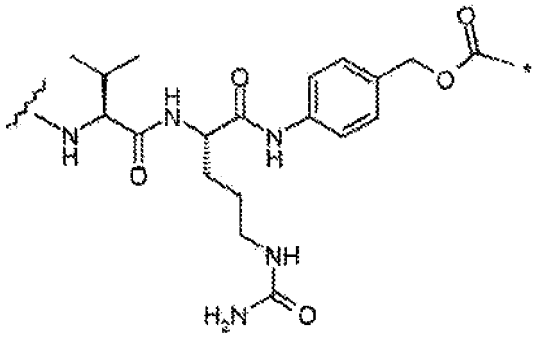
where the asterisk indicates the point of attachment to the selected cytotoxic moiety, and the wavy line indicates the point of attachment to the remaining portion of the linker L^1 or the point of attachment to A. Preferably, the wavy line indicates the point of attachment to A. The side chain of the Lys amino acid may be protected, for example, with Boc, Fmoc, or Alloc, as described above.

[0234] Alternatively, the self-immolative linker and the dipeptide together form the group -NH-Val-Ala-CO-NH-PABC-, which is illustrated below:



where the asterisk and the wavy line are as defined above.

[0235] Alternatively, the self-immolative linker and the dipeptide together form the group -NH-Val-Cit-CO-NH-PABC-, which is illustrated below:



where the asterisk and the wavy line are as defined above.

[0236] In some embodiments of the present invention, it may be preferred that if the drug moiety contains an unprotected imine bond, e.g. if moiety B is present, then the linker does not contain a free amino (H_2N-) group. Thus if the linker has the structure -A-L^1-L^2- then this would preferably not contain a free amino group. This preference is particularly relevant when the linker contains a dipeptide, for example as L^1; in this embodiment, it would be preferred that one of the two amino acids is not selected from lysine.

[0237] Without wishing to be bound by theory, the combination of an unprotected imine bond in the drug moiety and a free amino group in the linker can cause dimerisation of the drug-linker moiety which may interfere with the conjugation of such a drug-linker moiety to an antibody. The cross-reaction of these groups may be accelerated in the case the free amino group is present as an ammonium ion (H_3N^+-), such as when a strong acid (e.g. TFA) has been used to deprotect the free amino group.

[0238] In one embodiment, A is a covalent bond. Thus, L^1 and the cell binding agent are directly connected. For example, where L^1 comprises a contiguous amino acid sequence, the N-terminus of the sequence may connect directly to the cell binding agent.

[0239] Thus, where A is a covalent bond, the connection between the cell binding agent and **L^1** may be selected from:

-C(=O)NH-, -C(=O)O-, -NHC(=O)-, -OC(=O)-, -OC(=O)O-, -NHC(=O)O-, -OC(=O)NH-, -NHC(=O)NH-, -C(=O)NHC(=O)-, -S-, -S-S-, -CH_2C(=O)-, and =N-NH-,

[0240] An amino group of L^1 that connects to the DLL3 modulator may be the N-terminus of an amino acid or may be derived from an amino group of an amino acid side chain, for example a lysine amino acid side chain.

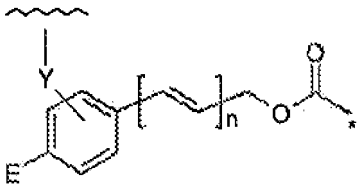
[0241] A carboxyl group of L^1 that connects to the modulator may be the C-terminus of an amino acid or may be derived from a carboxyl group of an amino acid side chain, for example a glutamic acid amino acid side chain.

[0242] A hydroxyl group of L^1 that connects to the cell binding agent may be derived from a hydroxyl group of an amino acid side chain, for example a serine amino acid side chain.

[0243] A thiol group of L^1 that connects to a modulator agent may be derived from a thiol group of an amino acid side chain, for example a serine amino acid side chain.

[0244] The comments above in relation to the amino, carboxyl, hydroxyl and thiol groups of L^1 also apply to the cell binding agent.

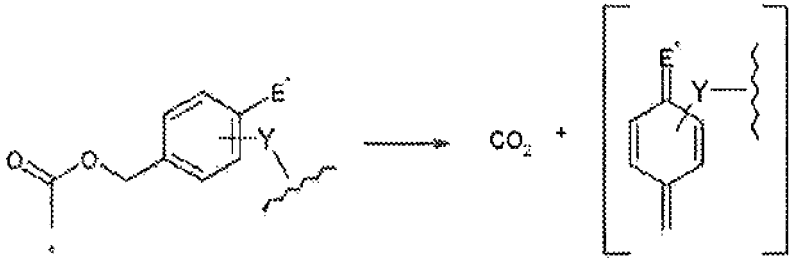
[0245] In one embodiment, together with -OC(=O)- represents:



where the asterisk indicates the point of attachment to the N10 position, the wavy line indicates the point of attachment to L^1, n is 0 to 3, Y is a covalent bond or a functional group, and E is an activatable group, for example by enzymatic action or light, thereby to generate a self-immolative unit. The phenylene ring is optionally further substituted with one, two or three substituents as described herein. In one embodiment, the phenylene group is optionally further substituted with halo, NO_2, R or OR. Preferably n is 0 or 1, most preferably 0.

[0246] E is selected such that the group is susceptible to activation, e.g. by light or by the action of an enzyme. E may be -NO_2 or glucoronic acid. The former may be susceptible to the action of a nitroreductase, the latter to the action of a β-glucoronidase.

[0247] In this embodiment, the self-immolative linker will allow for release of the protected compound when E is activated, proceeding along the lines shown below (for n=0):



where the asterisk indicates the point of attachment to the N10 position, E^* is the activated form of E, and Y is as described above. These groups have the advantage of separating the site of activation from the compound being protected. As described above, the phenylene group may be optionally further substituted.

[0248] The group Y may be a covalent bond to L^1.

[0249] The group Y may be a functional group selected from:

-C(=O)-, -NH-, -O-, -C(=O)NH-, -C(=O)O-, -NHC(=O)-, -OC(=O)-, -OC(=O)O,-NHC(=O)O-, -OC(=O)NH-, -NHC(=O)NH-, -NHC(=O)NH, and -S-.

[0250] Where L^1 is a dipeptide, it is preferred that Y is -NH- or -C(=O)-, thereby to form an amide bond between L^1 and Y. In this embodiment, the dipeptide sequence need not be a substrate for an enzymatic activity.

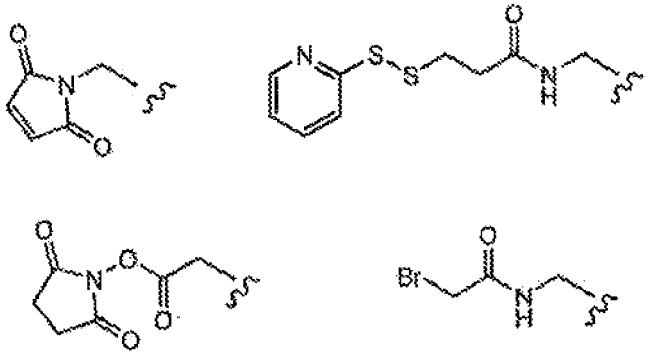
[0251] In another embodiment, A is a spacer group. Thus, L^1 and the cell binding agent are indirectly connected.

[0252] L^1 and A may be connected by a bond selected from:

-C(=O)NH-, -C(=O)O-, -NHC(=O)-, -OC(=O)-, -OC(=O)O-, -NHC(O)O-, -OC(=O)NH-, and -NHC(=O)NH-.

[0253] Preferably, the linker contains an electrophilic functional group for reaction with a nucleophilic, functional group on the modulator. Nucleophilic groups on antibodies include, but are not limited to: (i) N-terminal amine groups, (ii) side chain amine groups, e.g. lysine, (iii) side chain thiol groups, e.g. cysteine, and (iv) sugar hydroxyl or amino groups where the antibody is glycosylated. Amine, thiol, and hydroxyl groups are nucleophilic and capable of reacting to form covalent bonds with electrophilic groups on linker moieties and linker reagents including:

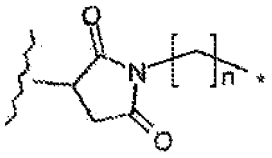
(i) maleimide groups (ii) activated disulfides, (iii) active esters such as NHS (N-hydroxysuccinimide) esters, HOBt (N-hydroxybenzotriazole) esters, haloformates, and acid halides; (iv) alkyl and benzyl halides such as haloacetamides; and (v) aldehydes, ketones, carboxyl, and, some of which are exemplified as follows:



[0254] Certain antibodies have reducible interchain disulfides, i.e. cysteine bridges. Antibodies may be made reactive for conjugation with linker reagents by treatment with a reducing agent such as DTT (dithiothreitol). Each cysteine bridge will thus form, theoretically, two reactive thiol nucleophiles. Additional nucleophilic groups can be introduced into antibodies through the reaction of lysines with 2-iminothiolane (Traut's reagent) resulting in conversion of an amine into a thioL Reactive thiol groups may be introduced into the antibody (or fragment thereof) by introducing one, two, three, four, or more cysteine residues (e.g., preparing mutant antibodies comprising one or more non-native cysteine amino acid residues). US 7521541 teachers engineering antibodies by introduction of reactive cysteine amino acids.

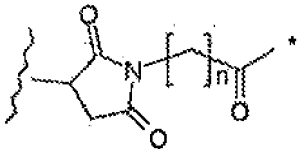
[0255] In some embodiments, a linker has a reactive nucleophilic group which is reactive with an electrophilic group present on an antibody. Useful electrophilic groups on an antibody include, but are not limited to, aldehyde and ketone carbonyl groups. The heteroatom of a nucleophilic group of a Linker can react with an electrophilic group on an antibody and form a covalent bond to an antibody unit. Useful nucleophilic groups on a linker include, but are not limited to, hydrazide, oxime, amino, hydroxyl, hydrazine, thiosemicarbazone, hydrazine carboxylate, and arylhydrazide. The electrophilic group on an antibody provides a convenient site for attachment to a Linker.

[0256] In one embodiment, the group A is:



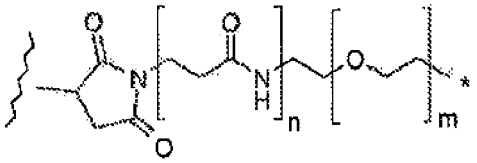
where the asterisk indicates the point of attachment to L^1, the wavy line indicates the point of attachment to the cell binding agent, and n is 0 to 6. In one embodiment, n is 5,

[0257] In one embodiment, the group A is:



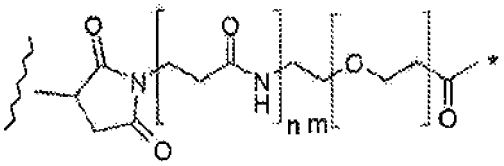
where the asterisk indicates the point of attachment to L^1, the wavy line indicates the point of attachment to the cell binding agent, and n is 0 to 6. in one embodiment, n is 5.

[0258] In one embodiment the group A is:



where the asterisk indicates the point of attachment to L^1, the wavy line indicates the point of attachment to the cell binding agent, n is 0 or 1, and m is 0 to 30. In a preferred embodiment, n is 1 and m is 0 to 10, 1 to 8, preferably 4 to 8, and most preferably 4 or 8. In another embodiment, m is 10 to 30, and preferably 20 to 30. Alternatively, m is 0 to 50. In this embodiment, m is preferably 10-40 and n is 1.

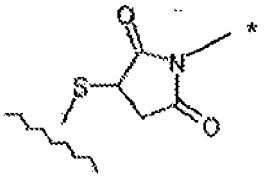
[0259] In one embodiment, the group A is:



where the asterisk indicates the point of attachment to L^1, the wavy line indicates the point of attachment to the cell binding agent, n is 0 or 1, and m is 0 to 30. In a preferred embodiment, n is 1, and m is 0 to 10, 1 to 8, preferably 4 to 8, and most preferably 4 or 8. In another embodiment, m is 10 to 30, and preferably 20 to 30. Alternatively, m is 0 to 50. In this embodiment, m is preferably 10-40 and is 1.

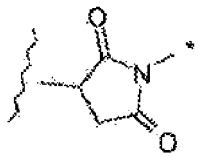
[0260] In one embodiment, the connection between the cell binding agent and A is through a thiol residue of the cell binding agent and a maleimide group of A.

[0261] In one embodiment, the connection between the cell binding agent and A is:



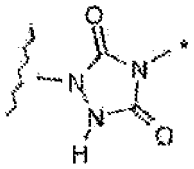
where the asterisk indicates the point of attachment to the remaining portion of A and the wavy line indicates the point of attachment to the remaining portion of the cell binding agent. In this embodiment, the S atom is typically derived from the modulator.

[0262] In each of the embodiments above, an alternative functionality may be used in place of the maleimide-derived group shown bellow:



where the wavy line indicates the point of attachment to the cell binding agent as before, and the asterisk indicates the bond to the remaining portion of the A group.

[0263] In one embodiment, the maleimide-derived group is replaced with the group:

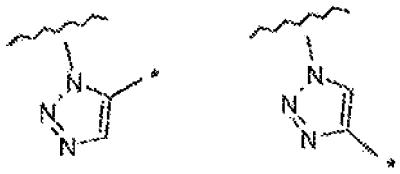


where the wavy line indicates point of attachment to the cell binding agent, and the asterisk indicates the bond to the remaining portion of the A group.

[0264] In one embodiment, the maleimide-derived group is replaced with a group, which optionally together with the cell binding agent, is selected from:

- C(=O)NH-, -C(=O)O-, -NHC(=O)-, -OC(=O)-, -OC(=O)O-, -NHC(=O)O-, -OC(=O)NH-, -NHC(=O)NH-, -NHC(=O)NH, -C(=O)NHC(=O)-, -S-, -S-S-, $-CH_2C(=O)-$, $-C(=O)CH_2-$, =N-NH- and -NH-N=.

[0265] In one embodiment, the maleimide-derived group is replaced with a group, which optionally together with the cell binding agent, is selected from:



where the wavy line indicates either the point of attachment to the cell binding agent or the bond to the remaining portion of the A group, and the asterisk indicates the other of the point of attachment to the cell binding agent or the bond to the remaining portion of the A group.

[0266] Other groups suitable for connecting L^1 to the selected modulator are described in WO 2005/082023.

[0267] In another preferred embodiment the modulators of the instant invention may be associated with biocompatible polymers comprising drug linker units. In this respect one such type of compatible polymer comprises Fleximer® polymers (Mersana Therapeutics). Such polymers are reportedly biodegradable, well tolerated and have been clinically validated. Moreover, such polymers are compatible with a number of customizable linker technologies and chemistries allowing for control of pharmacokinetics, localization of drug release and improved biodistribution.

[0268] The selected modulators can also be directly conjugated radioisotopes or may comprise macrocyclic chelators useful for conjugating radiometal ions (as described herein). In certain embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N",N"-tetraacetic acid (DOTA) which can be attached to the antibody via a linker molecule. Such linker molecules are commonly known in the art and described in Denardo et al., 1998, Clin Cancer Res. 4:2483; Peterson et al., 1999, Bioconjug. Chem. 10:553; and Zimmerman et al., 1999, Nucl. Med. Biol. 26:943.

[0269] More generally, techniques for conjugating therapeutic moieties or cytotoxic agents to modulators are well known. As discussed above moieties can be conjugated to modulators by any art-recognized method, including, but not limited to aldehyde/Schiff linkage, sulphydryl linkage, acid-labile linkage, cis-aconityl linkage, hydrazone linkage, enzymatically degradable linkage (see generally Garnett, 2002, Adv Drug Deliv Rev 53:171). Also see, e.g., Amon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer

Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1995); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., 1982, Immunol. Rev. 62:119. In preferred embodiments a DLL3 modulator that is conjugated to a therapeutic moiety or cytotoxic agent may be internalized by a cell upon binding to a DLL3 molecule associated with the cell surface thereby delivering the therapeutic payload.

C. Biocompatible Modifiers

[0270] In selected embodiments the modulators of the invention may be conjugated or otherwise associated with biocompatible modifiers that may be used to adjust, alter, improve or moderate modulator characteristics as desired. For example, antibodies or fusion constructs with increased *in vivo* half-lives can be generated by attaching relatively high molecular weight polymer molecules such as commercially available polyethylene glycol (PEG) or similar biocompatible polymers. Those skilled in the art will appreciate that PEG may be obtained in many different molecular weight and molecular configurations that can be selected to impart specific properties to the antibody (e.g. the half-life may be tailored). PEG can be attached to modulators or antibody fragments or derivatives with or without a multifunctional linker either through site-specific conjugation of the PEG to the N- or C-terminus of said antibodies or antibody fragments or via epsilon-amino groups present on lysine residues. Linear or branched polymer derivatization that results in minimal loss of biological activity may be used. The degree of conjugation can be closely monitored by SDS-PAGE and mass spectrometry to ensure optimal conjugation of PEG molecules to antibody molecules. Unreacted PEG can be separated from antibody-PEG conjugates by, e.g., size exclusion or ion-exchange chromatography. In a similar manner, the disclosed modulators can be conjugated to albumin in order to make the antibody or antibody fragment more stable in vivo or have a longer half life in vivo. The techniques are well known in the art, see e.g., International Publication Nos. WO 93/15199, WO 93/15200, and WO 01/77137; and European Patent No. 0 413, 622. Other biocompatible conjugates are evident to those of ordinary skill and may readily be identified in accordance with the teachings herein.

D. Diagnostic or Detection Agents

[0271] In other preferred embodiments, modulators of the present invention, or fragments or derivatives thereof, are conjugated to a diagnostic or detectable agent, marker or reporter which may be, for example, a biological molecule (e.g., a peptide or nucleotide), a small molecule, fluorophore, or radioisotope. Labeled modulators can be useful for monitoring the development or progression of a hyperproliferative disorder or as part of a clinical testing procedure to determine the efficacy of a particular therapy including the disclosed modulators (i.e. theragnostics) or to determine a future course of treatment. Such markers or reporters may also be useful in purifying the selected modulator, modulator analytics (e.g., epitope binding or antibody binning), separating or isolating TIC or in preclinical procedures or toxicology studies.

[0272] Such diagnosis analysis and/or detection can be accomplished by coupling the modulator to detectable substances including, but not limited to, various enzymes comprising for example horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; prosthetic groups, such as but not limited to streptavidinlbiotin and avidin/biotin; fluorescent materials, such as but not limited to, umbelliferone, fluorescein, fluorescein isothiocynate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chlorine or phycoerythrin; luminescent materials, such as but not limited to, luminol; bioluminescent materials, such as but not limited to, luciferase, luciferin, and aequorin; radioactive materials, such as but not limited to iodine (^{131}I, ^{125}I, ^{123}I, ^{121}I,), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{115}In, ^{113}In, ^{112}In, ^{111}In,), and technetium (^{99}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{156}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175Y}b, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re ^{188}Re, ^{142}Pr, ^{105}Rh, ^{97}Ru, ^{68}Ge, ^{57}Co, ^{65}Zn, ^{85}Sr, ^{32}P, ^{153}Gd, ^{169}Yb, ^{51}Cr, ^{75}Mn, ^{75}Se, ^{113}Sn, and ^{117}Tin; positron emitting metals using various positron emission tomographies, noradioactive paramagnetic metal ions, and molecules that are radiolabeled or conjugated to specific radioisotopes. In such embodiments appropriate detection methodology is well known in the art and readily available from numerous commercial sources.

[0273] As indicated above, in other embodiments the modulators or fragments thereof can be fused or conjugated to marker sequences or compounds, such as a peptide or fluorophore to facilitate purification or diagnostic or analytic procedures such as immunohistochemistry, bio-layer interferometry, surface plasmon resonance, flow cytometry, competitive ELISA, FACs, etc. In preferred embodiments, the marker comprises a his-tag such as that provided by the pQE vector (Qiagen), among others, many of which are commercially available, Other peptide tags useful for purification include, but are not limited to, the hemagglutinin "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., 1984, Cell 37:767) and the "flag" tag (U.S.P.N. 4,703,004).

E, Therapeutic Moieties

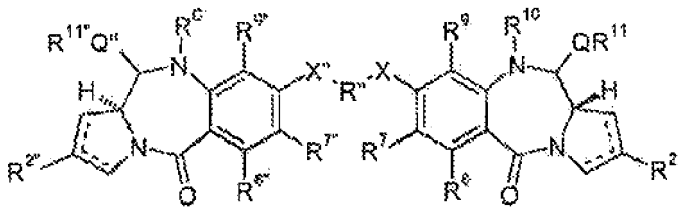
[0274] As previously alluded to the modulators or fragments or derivatives thereof may also be conjugated, linked or fused to or otherwise associated with a" therapeutic moiety" or "drug" such as an anti-proliferative or anti-cancer agent including, but not limited to, cytotoxic agents, cytostatic agents, anti-angiogenic agents, debulking agents, chemotherapeutic agents, radiotherapy and radiotherapeutic agents, targeted anti-cancer agents, BRMs, therapeutic antibodies, cancer vaccines, cytokines, hormone therapies, radiation therapy and anti-metastatic agents and immunotherapeutic agents.

[0275] Preferred exemplary anti-cancer agents include cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubiein, daunorubicin, dihydroxy anthracin, maytansinoids such as DM-1 and DM-4 (Immunogen, Inc.), dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, puromycin, epirubicin, and cyclophosphamide and analogs or homologs thereof. Additional compatible cytotoxins comprise dolastatins and auristatins, including monomethyl auristatin E (MMAE) and monomethyl auristatin F (MMAF) (Seattle Genetics, Inc.), amanitins such as alpha-amanitin, beta-amanitin, gamma-amanitin or epsilon-amanitin (Heidelberg Pharma AG), DNA minor groove binding agents such as duocarmycin derivatives (Syntarga, B.V.) and modified pyrrolobenzodiaxepine dimers (Spirogen, Ltd.), splicing inhibitors such as meayamycin analogs or derivatives (e.g., FR901464 as set forth in U.S.P.N. 7,825,267), tubular binding agents such as epothilone analogs and paclitaxel and DNA damaging agents such as calicheamicins and esperamicins. Furthermore, in certain embodiments the DLL3 modulators of the instant invention may be associated with anti-CD3 binding molecules to recruit cytotoxic T-cells and have them target the tumor initiating cells (BiTE technology; see e.g., Fuhrmann, S. et. al. Annual Meeting ofAACR Abstract No. 5625 (2010) which is incorporated herein by reference).

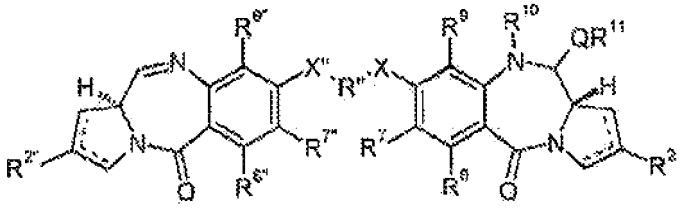
[0276] Still additional compatible anti-cancer agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa, chlorambucil, melphalan, carmustine (BCNU) and lomustine (CCNU), busulfan, dibromomannitol, streptozotocin, and cisdichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, and anthramycin (AMC)), and antimitotic agents (e.g., vincristine and vinblastine). A more extensive list of therapeutic moieties can be found in PCT publication WO 03/075957 and U.S.P.N. 2009/0155255 each of which is incorporated herein by reference.

[0277] As indicated above selected embodiments of the instant invention are directed to conjugated DLL3 modulators such as anti-DLL3 antibody drug conjugates that comprise pyrrolobenzodiazepine (PBD) as a cytotoxic agent. It will be appreciated that PBDs are alkylating agents that exert antitumor activity by covalently binding to DNA in the minor groove and inhibiting nucleic acid synthesis. In this respect PBDs have been shown to have potent antitumor properties while exhibiting minimal bone marrow depression. PBDs compatible with the present invention may be linked to the DLL3 modulator using any one of several types of linker (e.g., a peptidyl linker comprising a maleimido moiety with a free sulfhydryl) and, in certain embodiments are dimeric in form (i.e., PBD dimers). Compatible PBDs (and optional linkers) that may be conjugated to the disclosed modulators are described, for example, in U.S.P.N.s 6,362,331, 7,049,311, 7,189,710, 7,429,658, 7,407,951, 7,741,319, 7,557,099, 8,034,808, 8,163,736 U.S.P.N. 2011/0256157 and PCT filings WO2011/130613, WO2011/128650 and WO2011/130616 each of which is incorporated herein by reference. Accordingly, in particularly preferred embodiments the modulator will comprise an anti DLL3 antibody conjugated or associated with one or more PBD dimers (i.e., a DLL3-PBD ADC).

[0278] In particularly preferred embodiments compatible PBDs that may be conjugated to the disclosed modulators are described, in U.S.P.N. 2011/0256157. In this disclosure, PBD dimers, i.e. those comprising two PBD moieties may be preferred. Thus, preferred conjugates of the present invention are those having the formulae (AB) or (AC):



AB



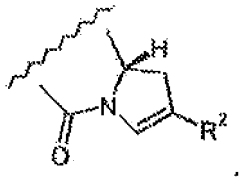
AC

wherein:

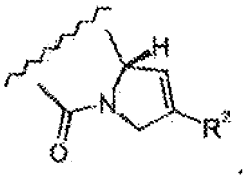
the dotted lines indicate the optional presence of a double bond between C1 and C2 or C2 and C3;
R^2 is independently selected from H, OH, =O, $=CH_2$, CN, R, OR, $=CH\text{-}R^D$, $=C(R^D)_2$, $O\text{-}SO_2\text{-}R$, CO_2R and COR, and optionally further selected from halo or dihalo;
where R^D is independently selected from R, CO_2R, COR, CHO, CO_2H, and halo;
R^6 and R^9 are independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', NO_2, Me_3Sn and halo;
R^7 is independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', NO_2, Me_3Sn and halo;
R^{10} is a linker connected to a modulator or fragment or derivative thereof, as described above;
Q is independently selected from O, S and NH;
R^{11} is either H, or R or, where Q is O, SO_3M, where M is a metal cation;
R and R' are each independently selected from optionally substituted $C_{1\text{-}12}$ alkyl, $C_{3\text{-}20}$ heterocyclyl and $C_{5\text{-}20}$ aryl groups, and optionally in relation to the group NRR', R and R' together with the nitrogen atom to which they are attached form an optionally substituted 4-, 5-, 6- or 7-membered heterocyclic ring; and
wherein $R^{2"}$, $R^{6"}$, $R^{7"}$, $R^{9"}$, X", Q" and $R^{11"}$ and are as defined according to R^2, R^6, R^7, R^9, X, Q and R^{11} respectively, and R^C is a capping group.

Double Bond

[0279] In one embodiment, there is no double bond present between C1 and C2, and C2 and C3.
[0280] In one embodiment, the dotted lines indicate the optional presence of a double bond between C2 and C3, as shown below:



[0281] In one embodiment, a double bond is present between C2 and C3 when R^2 is $C_{5\text{-}20}$ aryl or $C_{1\text{-}12}$ alkyl.
[0282] In one embodiment, the dotted lines indicate the optional presence of a double bond between C1 and C2, as shown below:



[0283] In one embodiment, a double bond is present between C1 and C2 when R^2 is $C_{5\text{-}20}$ aryl or $C_{1\text{-}12}$ alkyl.

R^2

[0284] In one embodiment, R^2 is independently selected from H, OH, =O, $=CH_2$, CN, R, OR, $=CH\text{-}R^D$, $-C(R^D)_2$, $O\text{-}SO_2\text{-}R$, CO_2R and COR, and optionally further selected from halo or dihalo.
[0285] In one embodiment, R^2 is independently selected from H, OH, =O, $=CH_2$, CN, R, OR, $=CH\text{-}R^D$, $=C(R^D)_2$, O-

SO_2-R, CO_2R and COR.

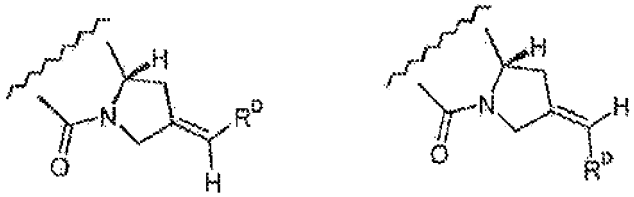
[0286] In one embodiment, R^2 is independently selected from H, =O, $=CH_2$, R, =CH-R^D, and $=C(R^D)_2$.

[0287] In one embodiment, R^2 is independently H.

[0288] In one embodiment, R^2 is independently =O.

[0289] In one embodiment, R^2 is independently $=CH_2$.

[0290] In one embodiment, R^2 is independently =CH-R^D. Within the PBD compound, the group =CH-R^D may have either configuration shown below:



(I) (II)

[0291] In one embodiment, the configuration is configuration (I).

[0292] In one embodiment, R^2 is independently $=C(R^D)_2$.

[0293] In one embodiment, R^2 is independently $=CF_2$.

[0294] In one embodiment, R^2 is independently R.

[0295] In one embodiment, R^2 is independently optionally substituted C_{5-20} aryl.

[0296] In one embodiment, R^2 is independently optionally substituted C_{1-12} alkyl.

[0297] In one embodiment, R^2 is independently optionally substituted C_{5-20} aryl.

[0298] In one embodiment, R^2 is independently optionally substituted C_{5-7} aryl.

[0299] In one embodiment, R2 is independently optionally substituted C_{8-10} aryl.

[0300] In one embodiment, R^2 is independently optionally substituted phenyl.

[0301] In one embodiment, R^2 is independently optionally substituted napthyl.

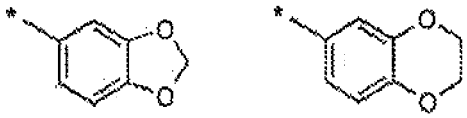
[0302] In one embodiment, R^2 is independently optionally substituted pyridyl.

[0303] In one embodiment, R^2 is independently optionally substituted quinolinyl or isoquinolinyl.

[0304] In one embodiment, R^2 bears one to three substituent groups, with 1 and 2 being more preferred, and singly substituted groups being most preferred. The substituents may be any position.

[0305] Where R^2 is a C_{5-7} aryl group, a single substituent is preferably on a ring atom that is not adjacent the bond to the remainder of the compound, i.e. it is preferably β or γ to the bond to the remainder of the compound. Therefore, where the C_{5-7} aryl group is phenyl, the substituent is preferably in the meta- or para- positions, and more preferably is in the para- position.

[0306] In one embodiment, R^2 is selected from:



where the asterisk indicates the point of attachment.

[0307] Where R^2 is a C_{8-10} aryl group, for example quinolinyl or isoquinolinyl, it may bear any number of substituents at any position of the quinoline or isoquinoline rings. In some embodiments, it bears one, two or three substituents, and these may be on either the proximal and distal rings or both (if more than one substituent).

[0308] In one embodiment, where R^2 is optionally substituted, the substituents are selected from those substituents given in the substituent section below.

[0309] Where R is optionally substituted, the substituents are preferably selected from:

Halo, Hydroxyl, Ether, Formyl, Acyl, Carboxy, Ester, Acyloxy, Amino, Amido, Acylamido, Aminocarbonyloxy, Ureido, Nitro, Cyano and Thioether.

[0310] In one embodiment, where R or R^2 is optionally substituted, the substituents are selected from the group consisting of R, OR, SR, NRR', NO_2, halo, CO_2R, COR, $CONH_2$, CONHR, and CONRR'.

[0311] Where R^2 is C_{1-12} alkyl, the optional substituent may additionally include C_{1-20} heterocyclyl and C_{5-20} aryl groups.

[0312] Where R^2 is C_{3-20} heterocyclyl, the optional substituent may additionally include C_{1-12} alkyl and C_{5-20} aryl groups.

[0313] Where R^3 is C_{5-20} aryl groups, the optional substituent may additionally include C_{3-20} heterocyclyl and C_{1-12} alkyl groups.

[0314] It is understood that the term "alkyl" encompasses the sub-classes alkenyl and alkynyl as well as cycloalkyl. Thus, where R^2 is optionally substituted C_{1-12} alkyl, it is understood that the alkyl group optionally contains one or more carbon-carbon double or triple bonds, which may form part of a conjugated system. In one embodiment, the optionally substituted C_{1-12} alkyl group contains at least one carbon-carbon double or triple bond, and this bond is conjugated with a double bond present between C1 and C2, or C2 and C3. In one embodiment, the C_{1-12} alkyl group is a group selected from saturated C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl and C_{3-12} cycloalkyl.

[0315] If a substituent on R^2 is halo, it is preferably F or Cl, more preferably Cl.

[0316] If a substituent on R^2 is ether, it may in some embodiments be an alkoxy group, for example, a C_{1-7} alkoxy group (e.g. methoxy, ethoxy) or it may in some embodiments be a C_{5-7} aryloxy group (e.g phenoxy, pyridyloxy, furanyloxy).

[0317] If a substituent on R^2 is C_{1-7} alkyl, it may preferably be a C_{1-4} alkyl group (e.g. methyl, ethyl, propyl, butyl).

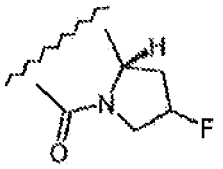
[0318] If a substituent on R^2 is C_{3-7} heterocyclyl, it may in some embodiments be C_6 nitrogen contacting heterocyclyl group, e.g. morpholino, thiomorpholino, piperidinyl, piperazinyl. These groups may be bound to the rest of the PBD moiety via the nitrogen atom. These groups may be further substituted, for example, by C_{1-4} alkyl groups.

[0319] If a substituent on R^2 is bis-oxy-C_{1-3} alkylene, this is preferably bis-oxy-methylene or bis-oxy-ethylene.

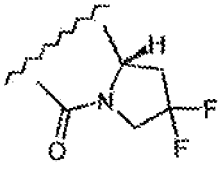
[0320] Particularly preferred substituents for R^2 include methoxy, ethoxy, fluoro, chloro, cyano, bis-oxy-methylene, methyl-piperazinyl, morpholino and methyl-thienyl.

[0321] Particularly preferred substituted R^2 groups include, but are not limited to, 4-methoxy-phenyl, 3-methoxyphenyl, 4-ethoxy-phenyl, 3-ethoxy-phenyl 4-fluoro-phenyl, 4-chloro-phenyl, 3,4-bisoxymethylene-phenyl, 4-methylthienyl, 4-cyanophenyl, 4-phenoxyphenyl, quinolin-3-yl and quinolin-6-yl, isoquinolin-3-yl and isoquinolin-6-yl, 2-thienyl, 2-furanyl, methoxynaphthyl, and naphthyl.

[0322] In one embodiment, R^2 is halo or dihalo. In one embodiment, R^2 is -F or -F_2, which substituents are illustrated below as (III) and (IV) respectively:



(III)



(IV)

R^D

[0323] In one embodiment, R^D is independently selected from R, CO_2R, COR, CHO, CO_2H, and halo.

[0324] In one embodiment, R^D is independently R.

[0325] In one embodiment, H^D is independently halo.

R^6

[0326] In one embodiment, R^6 is independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', NO_2, Me_3Sn- and Halo.

[0327] In one embodiment, R^6 is independently selected from H, OH, OR, SH, NH_2, NO_2 and Halo.

[0328] In one embodiment, R^6 is independently selected from H and Halo.

[0329] In one embodiment, R^6 is independently H.

[0330] In one embodiment, R^6 and R^7 together form a group -O-$(CH_2)_p$-O-, where p is 1 or 2.

R^7

[0331] R^7 is independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', NO_2, Me_3Sn and halo.

[0332] In one embodiment, R^7 is independently OR.

[0333] In one embodiment, R^7 is independently OR^{7A}, where R^{7A} is independently optionally substituted C_{1-6} alkyl.

[0334] In one embodiment, R^{7A} is independently optionally substituted saturated C_{1-6} alkyl. In one embodiment, R^{7A} is independently optionally substituted C_{2-4} alkenyl.

[0335] In one embodiment, R^{7A} is independently Me.

[0336] In one embodiment, R^{7A} is independently CH_2Ph.

[0337] In one embodiment, R^{7A} is independently allyl.

[0338] In one embodiment, the compound is a dimer where the R^7 groups of each monomer form together a dimer bridge having the formula X-R"-X linking the monomers.

R^8.

[0339] In one embodiment, the compound is a dimer where the R^8 groups of each monomer form together a dimer bridge having the formula X-R"-X linking the monomers.

[0340] In one embodiment, R^8 is independently OR^{8A}, where R^{8A} is independently optionally substituted C_{1-4} alkyl.

[0341] In one embodiment, R^{8A} is independently optionally substituted saturated C_{1-8} alkyl or optionally substituted C_{2-4} alkenyl.

[0342] In one embodiment, R^{8A} is independently Me.

[0343] In one embodiment, R^{8A} is independently CH_2Ph.

[0344] In one embodiment, R^{8A} is independently allyl.

[0345] In one embodiment, R^8 and R^7 together form a group $-O-(CH_2)_p-O-$, where p is 1 or 2.

[0346] In one embodiment, R^8 and R^9 together form a group $-O-(CH_2)_p-O-$, where p is 1 or 2.

R^9

[0347] In one embodiment, R^9 is independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', NO_2, Me_1Sn- and Halo.

[0348] In one embodiment, R^9 is independently H.

[0349] In one embodiment, R^9 is independently R or OR.

R and R'

[0350] In one embodiment, R is independently selected from optionally substituted C_{1-12} alkyl, C_{1-2} heterocyclyl and C_{5-20} aryl groups. These groups are each defined in the substituents section below.

[0351] In one embodiment, R is independently optionally substituted C_{1-12} alkyl.

[0352] In one embodiment, R is independently optionally substituted C_{3-20} heterocyclyl.

[0353] In one embodiment, R is independently optionally substituted C_{5-20} aryl.

[0354] In one embodiment, R is independently optionally substituted C_{1-12} alkyl.

[0355] Described above in relation to R^2 are various embodiments relating to preferred alkyl and aryl groups and the identity and number of optional substituents. The preferences set out for R^2 as it applies to R are applicable, where appropriate, to all other groups R, for examples where R^6, R^7, R^8 or R^9 is R.

[0356] The preferences for R apply also to R'.

[0357] In some embodiments of the invention there is provided a compound having a substituent group -NRR'. In one embodiment, R and R' together with the nitrogen atom to which they are attached form an optionally substituted 4-, 5-, 6- or 7-membered heterocyclic ring. The ring may contain a further heteroatom, for example N, O or S.

[0358] In one embodiment, the heterocyclic ring is itself substituted with a group R. Where a further N heteroatom is present, the substituent may be on the N heteroatom.

R"

[0359] R" is a C_{3-12} alkylene group, which chain may be interrupted by one or more heteroatoms, e.g. O, S, N(H), NMe and/or aromatic rings, e.g. benzene or pyridine, which rings are optionally substituted.

[0360] In one embodiment, R" is a C_{3-12} alkylene group, which chain may be interrupted by one of more heteroatoms and/or aromatic rings, e.g. benzene or pyridine.

[0361] In one embodiment, the alkylene group is optionally interrupted by one or more heteroatoms selected from O, S, and NMe and/or aromatic rings, which rings are optionally substituted.

[0362] In one embodiment, the aromatic ring is a C_{5-20} arylene group, where arylene pertains to a divalent moiety obtained by removing two hydrogen atoms from two aromatic ring atoms of an aromatic compound, which moiety has from 5 to 20 ring atoms,

[0363] In one embodiment, R" is a C_{3-12} alkylene group, which chain may be interrupted by one or more heteroatoms, e.g. O, S, N(H), NMe and/or aromatic rings, e.g. benzene or pyridine, which rings are optionally substituted by NH_2.

[0364] In one embodiment, R" is a C_{3-12} alkylene group.

[0365] In one embodiment, R" is selected from a C_3, C_5, C_7, C_9 and a C_{11} alkylene group.

[0366] in one embodiment, R" is selected from a C_3, C_5 and a C_7 alkylene group.

[0367] In one embodiment, R" is selected from a C_3 and a C_5 alkylene group.

[0368] In one embodiment, R" is a C_3 alkylene group.

[0369] In one embodiment, R" is a C_5 alkylene group.

[0370] The alkylene groups listed above may be optionally interrupted by one or more heteroatoms and/or aromatic rings, e.g. benzene or pyridine, which rings are optionally substituted.

[0371] The alkylene groups listed above may be optionally interrupted by one or more heteroatoms and/or aromatic rings, e.g. benzene or pyridine.

[0372] The alkylene groups listed above may be unsubstituted linear aliphatic alkylene groups.

X

[0373] In one embodiment, X is selected from O, S, or N(H).

[0374] Preferably, X is O.

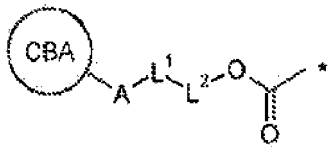
R^{10}

[0375] Preferably compatible linkers such as those described above attach a DLL3 modulator (CBA/Ab/M), to a PBD drug moiety D through covalent bond(s) at the R^{10} position (i.e., N10). The linker is a bifunctional or multifunctional moiety which can be used to link one or more drug moiety (D) and a modulator (preferably an antibody) to form antibody-drug conjugates (ADC). The linker (L) may be stable outside a cell, i.e. extracellular, or it may be cleavable by enzymatic activity, hydrolysis, or other metabolic conditions. Antibody-drug conjugates (ADC) can be conveniently prepared using a linker having reactive functionality for binding to the drug moiety and to the antibody. A cysteine thiol, or an amino, e.g. N-terminus or amino acid side chain such as lysine, of the antibody (Ab) can form a bond with a functional group of a linker or spacer reagent, PBD drug moiety (D) or drug-linker reagent (D-L).

[0376] Many functional groups on the linker attached to the N10 position of the PBD moiety may be useful to react with the cell binding agent. For example, ester, thioester, amide, thioamide, carbamate, thiocarbamate, urea, thiourea, ether, thioether, or disulfide linkages may be formed from reaction of the linker-PBD drug intermediates and the cell binding agent.

[0377] In another embodiment, the linker may be substituted with groups that modulate aggregation, solubility or reactivity. For example, a suffonate substituent may increase water solubility of the reagent and facilitate the coupling reaction of the linker reagent with the antibody or the drug moiety, or facilitate the coupling reaction of Ab-L with D, or D-L with Ab, depending on the synthetic route employed to prepare the ADC.

[0378] In one preferred embodiment, R^{10} is a group:



where the asterisk indicates the point of attachment to the N10 position, CBA is a cell binding agent/modulator, L^1 is a linker, A is a connecting group connecting L^1 to the cell binding agent, L^2 is a covalent bond or together with -OC(=O)- forms a self-immolative linker, and L^1 or L^2 is a cleavable linker.

[0379] L^1 is preferably the cleavable linker, and may be referred to as a trigger for activation of the linker for cleavage.

[0380] As discussed in the linker section above the nature of L^1 and L^2, where present, can vary widely. These groups are chosen on the basis of their cleavage characteristics, which may be dictated by the conditions at the site to which the conjugate is delivered. Those linkers that are cleaved by the action of enzymes are preferred, although linkers that are cleavable by changes in pH (e.g. acid or base labile), temperature or upon irradiation (e.g. photolabile) may also be used. Linkers that are cleavable under reducing or oxidizing conditions may also find use in the present invention.

[0381] L^1 may comprise a contiguous sequence of amino acids. The amino acid sequence may be the target substrate for enzymatic cleavage, thereby allowing release of R^{10} from the N10 position.

[0382] In one embodiment, L^1 is cleavable by the action of an enzyme. In one embodiment, the enzyme is an esterase or a peptidase.

[0383] In one embodiment, L^2 is present and together with -C(=O)O- forms a self-immolative linker. In one embodiment, L^2 is a substrate for enzymatic activity, thereby allowing release of R^{10} from the N10 position.

[0384] In one embodiment, where L^1 is cleavable by the action of an enzyme and L^2 is present, the enzyme cleaves the bond between L^1 and L^2.

[0385] With regard to attaching the chosen linker to a selected PBD the group R^C is removable from the N10 position of certain PBD moieties to leave an N10-C11 imine bond, a carbinolamine, a substituted carbinolamine, where QR^{11} is OSO_3M, a bisulfite adduct, a thiocarbinolamine, a substituted thiocarbinolamine, or a substituted carbinalamine.

[0386] In one embodiment, R^C, may be a protecting group that is removable to leave an N10-C11 imine bond, a carbinolamine, a substituted cabinolamine, or, where QR^{11} is OSO_3M, a bisulfite adduct. In one embodiment, R^C is a protecting group that is removable to leave an N10-C11 imine bond.

[0387] The group R^C is intended to be removable under the same conditions as those required for the removal of the group R^{10}, for example to yield an N10-C11 imine bond, a carbinolamine and so on. The capping group acts as a protecting group for the intended functionality at the N10 position. The capping group is intended not to be reactive towards a cell binding agent. For example, R^C is not the same as R^L.

[0388] Compounds having a capping group may be used as intermediates in the synthesis of dimers having an imine monomer. Alternatively, compounds having a capping group may be used as conjugates, where the capping group is removed at the target location to yield an imine, a carbinolamine, a substituted cabinolamine and so on. Thus, in this embodiment, the capping group may be referred to as a therapeutically removable nitrogen protecting group, as defined in WO 00/12507.

[0389] In one embodiment, the group R^C is removable under the conditions that cleave the linker R^L of the group R^{10}. Thus, in one embodiment, the capping group is cleavable by the action of an enzyme.

[0390] In an alternative embodiment, the capping group is removable prior to the connection of the linker R^L to the modulator. In this embodiment, the capping group is removable under conditions that do not cleave the linker R^L.

[0391] Where a compound includes a functional group G^1 to form a connection to the cell binding agent, the capping group is removable prior to the addition or unmasking of G^1.

[0392] The capping group may be used as part of a protecting group strategy to ensure that only one of the monomer units in a dimer is connected to a cell binding agent.

[0393] The capping group may be used as a mask for a N10-C11 imine bond. The capping group may be removed at such time as the imine functionality is required in the compound. The capping group is also a mask for a carbinolamine, a substituted cabinolamine, and a bisulfite adduct, as described above.

[0394] In one embodiment, R^C is a carbamate protecting group.

[0395] In one embodiment, the carbamate protecting group is selected from:

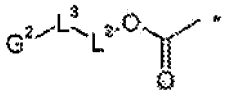
Alloc, Fmoc, Boc, Troc, Teoc, Psec, Cbz and PNZ.

[0396] Optionally, the carbamate protecting group is further selected from Moc.

[0397] In one embodiment, R^C is a linker group R^L lacking the functional group for connection to the cell binding agent.

[0398] This application is particularly concerned with those R^C groups which are carbamates.

[0399] In one embodiment, R^C is a group:



where the asterisk indicates the point of attachment to the N10 position, G^2 is a a terminating group, L^3 is a covalent bond or a cleavable linker L^1, L^2 is a covalent bond or together with OC(=O) terms a self-immolative linker.
Where L^3 and L^2 are both covalent bonds, G^2 and OC(=O) together form a carbamate protecting group as defined above.

[0400] L^1 is as defined above in relation to R^{10}.

[0401] L^2 is as defined above in relation to R^{10}.

[0402] Various terminating groups are described below, including those based on well known protecting groups.

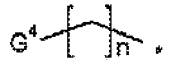
[0403] In one embodiment L^3 is a cleavable linker L^1, and L^2, together with OC(=O), forms a self-immolative linker. In this embodiment, G^2 is Ac (acetyl) or Moc, or a carbamate protecting group selected from: Alloc, Fmoc, Boc, Troc, Teoc, Psec, Cbz and PNZ. Optionally, the carbamate protecting group is further selected from Moc.

[0404] In another embodiment, G^2 is an acyl group -C(=O)G^3, where G^3 is selected from alkyl (including cycloalkyl, alkenyl and alkynyl), heteroalkyl, heterocyclyl and aryl (including heteroaryl and carboaryl). These groups may be optionally substituted. The acyl group together with an amino group or L^3 or L^2, where appropriate, may form an amide bond. The acyl group together with a hydroxy group of L^3 or L^2, where appropriate, may form an ester bond.

[0405] In one embodiment, G^3 is heteroalkyl. The heteroalkyl group may comprise polyethylene glycol. The heteroalkyl group may have a heteroatom, such as O or N, adjacent to the acyl group, thereby forming a carbamate or carbonate group, where appropriate, with a heteroatom present in the group L^3 or L^2, where appropriate.

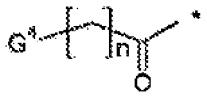
[0406] In one embodiment, G^3 is selected from NH_2, NHR and NRR'. Preferably, G^3 is NRR'.

[0407] In one embodiment G^2 is the group:



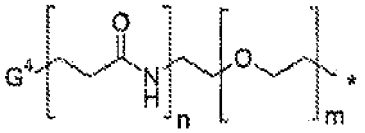
where the asterisk indicates the point of attachment to L^3, n is 0 to 6 and G^4 is selected from OH, OR, SH, SR, COOR, $CONH_2$, CONHR, $CONRR^8$, NH_2, NHR, NRR', NO_2, and halo. The groups OH, SH, NB_2 and NHR are protected. In one embodiment, n is 1 to 6, and preferably n is 5. In one embodiment, G^4 is OR, SR, COOR, $CONH_2$, CONHR, CONRR', and NRR'. In one embodiment, G^4 is OR, SR, and NRR'. Preferably G^4 is selected from OR and NRR', most preferably G^4 is OR. Most preferably G^4 is OMe.

[0408] In one embodiment, the group G^2 is:



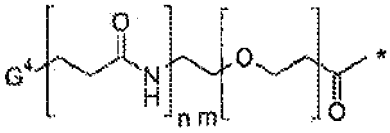
where the asterisk indicates the point of attachment to L^3, and n and G^4 are as defined above.

[0409] In one embodiment, the group G^2 is:



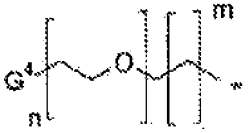
where the asterisk indicates the point of attachment to L^3, n is 0 or l, m is 0 to 50, and G^4 is selected from OH, OR, SH, SR, COOR, $CONH_2$, CONHR, CONRR', NH_2, NHR, NRR', NO_2, and halo. In a preferred embodiment, n is 1 and m is 0 to 10, 1 to 2, preferably 4 to 8, and most preferably 4 or 8. In another embodiment, n is 1 and m is 10 to 50, preferably 20 to 40. The groups OH, SH, NH_2 and NHR are protected. In one embodiment, G^4 is OR, SR, COOR, $CONH_2$, CONHR, CONRR', and NRR'. In one embodiment, G^4 is OR, SR, and NRR', Preferably G^4 is selected from OR and NRR', most preferably G^4 is OR. Preferably G^4 is OMe.

[0410] In one embodiment, the group G^2 is:



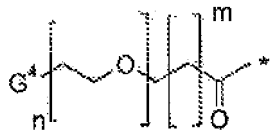
where the asterisk indicates the point of attachment to L^3, and n, m and G^4 are as defined above.

[0411] In one embodiment, the group G^2 is:



where n is 1-20, m is 0-6, and G^4 is selected from OH, OR, SH, SR, COOR, $CONH_2$, CONHR, CONRR', NH_2, NHR, NRR', NO_2, and halo. In one embodiment, n is 1-10. In another embodiment, n is 10 to 50, preferably 20 to 40. In one embodiment, n is 1. In one embodiment, m is 1. The groups OH, SH, NH_2 and NHR are protected. In one embodiment, G^4 is OR, SR, COOR, $CONH_2$, CONHR, CONRR', and NRR'. In one embodiment, G^4 is OR, SR, and NRR'. Preferably G^4 is selected from OR and NRR', most preferably G^4 is OR. Preferably G^4 is OMe.

[0412] In one embodiment, the group G^2 is:



where the asterisk indicates the point of attachment to L^3, and n, m and G^4 are as defined above.

[0413] In each of the embodiments above G^4 may be OH, SH, NH_2 and NHR. These groups are preferably protected.

[0414] In one embodiment, OH is protected with Bzl, TBDMS, or TBDPS.

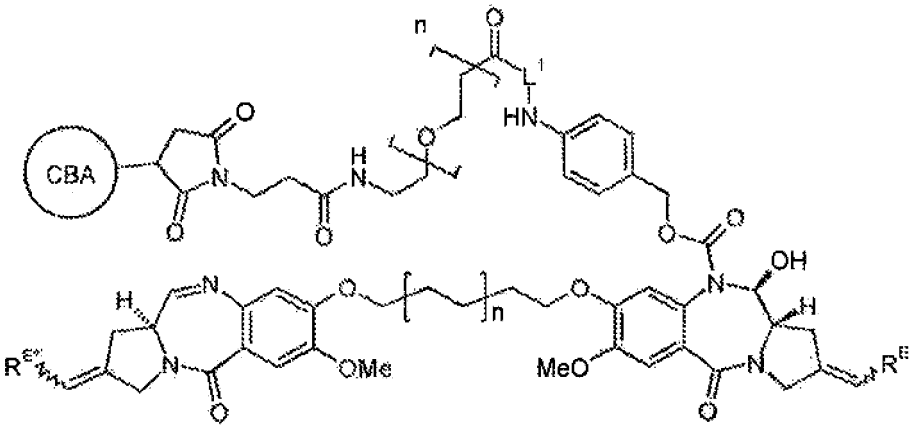
[0415] In one embodiment, SH is protected with Acm, Bzl, Bzl-OMe, Bzi-Me, or Trt.

[0416] In one embodiment, NH_2 or NHR are protected with Boc, Moc, Z-Cl, Fmoc, Z, or Alloc.

[0417] In one embodiment, the group G^2 is present in combination with a group L^3, which group is a dipeptide.

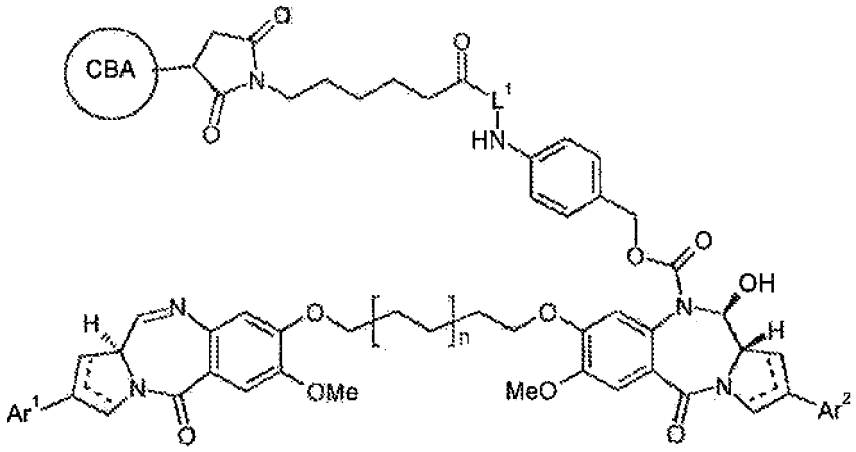
[0418] The capping group is not intended for connection to the modulator. Thus, the other monomer present in the dimer serves as the point of connection to the modulator via a linker. Accordingly, it is preferred that the functionality present in the capping group is not available for reaction with a modulator. Thus, reactive functional groups such as OH, SH, NH_2, COOH are preferably avoided. However, such functionality may be present in the capping group if protected, as described above.

[0419] Thus, in accordance with the teachings herein one embodiment of the invention comprises a conjugate comprising a compound:



wherein CBA is a cell binding agent/modulator, and n is 0 or 1. L^1 is as previously defined, and R^E and $R^{E''}$ are each independently selected from H or R^D.

[0420] In another embodiment, the conjugate comprises a compound:



wherein CBA is a cell binding agent/modulator, L^1 is as previously defined, Ar^1 and Ar^2 are each independently optionally substituted C_{5-20} aryl, and n is 0 or 1.

[0421] Those of skill in the art will appreciate that other symmetric and asymmetric PBD dimers and linkers are

compatible with the instant invention and could be selected without undue experimentation based on the teachings herein and the prior art.

[0422] Another aspect of the invention includes ADCs comprising radioisotopes. Exemplary radioisotopes that may be compatible with such embodiments include, but are not limited to, iodine (^{131}I, ^{125}I, ^{123}I, ^{121}I,), carbon (^{14}C), copper (^{62}Cu, ^{64}Cu, 67Cu), sulfur (^{35}S), tritium (^{3}H), indium (^{115}In, ^{113}In, ^{112}In, ^{111}In,), bismuth (^{212}Bi, ^{213}Bi), technetium (^{99}Tc), thallium (^{201}Ti), gallium (^{68}Ga), ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, ^{97}Ru, ^{68}Ge, ^{57}Co, ^{65}Zn, ^{85}Sr, ^{32}P, ^{153}Gd, ^{169}Yb, ^{51}Cr, ^{54}Mn, ^{75}Se, ^{113}Sn, ^{157}Sn, ^{225}Ac, ^{76}Br, and ^{211}At. Other radionuclides are also available as diagnostic and therapeutic agents, especially those in the energy range of 60 to 4,000 keV. Depending on the condition to be treated and the desired therapeutic profile, those skilled in the art may readily select the appropriate radioisotope for use with the disclosed modulators.

[0423] DLL3 modulators of the present invention may also be conjugated to a therapeutic moiety or drug that modifies a given biological response (e.g., biological response modifiers or BRMs). That is, therapeutic agents or moieties compatible with the instant invention are not to be construed as limited to classical chemical therapeutic agents. For example, in particularly preferred embodiments the drug moiety may be a protein or polypeptide or fragment thereof possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, Onconase (or another cytotoxic RNase), pseudomonas exotoxin, cholera toxin, or diphtheria toxin; a protein such as tumor necrosis factor, α-interferon, β-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF- a, TNF-β, AIM I (see, International Publication No. WO 97/33899), AIM II (see, International Publication No. WO 97/34911), Fas Ligand (Takahashi et al., 1994, J. Immunol., 6:1567), and VEGI (see, International Publication No. WO 99/23105), a thrombotic agent or an anti-angiogenic agent, e.g., angiostatin or endostatin; or, a biological response modifier such as, for example, a lymphokine (e.g., intefleukin-1 ("IL-1"), intedeukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), and granulocyte colony stimulating factor ("G-CSF")), or a growth factor (e.g., growth hormone ("GH")). As set forth above, methods for fusing or conjugating modulators to polypeptide moieties are known in the art. In addition to the previously disclosed subject references see, e.g., U.S.P.Ns. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851, and 5,112,946; EP 307,434; EP 367,166; PCT Publications WO 96/04388 and WO 91/06570; Ashkenazi et al., 1991, PNAS USA 88:10535; Zheng et al., 1995, J Immunol 154:5590; and Vil et al., 1992, PNAS USA 89:11337 each of which is incorporated herein by reference. Moreover, as set forth above the association of a modulator with such moieties does not necessarily need to be direct, but may occur through linker sequences. As previously alluded to, such linker molecules are commonly known in the art and described in Denardo et al., 1998, Clin Cancer Res 4:2483; Peterson et al., 1999, Bioconjug Chem 10:553; Zimmerman et al., 1999, Nucl Med Biol 26:943; Garnett, 2002, Adv Drug Deliv Rev 53:171 each of which is incorporated herein.

IX. Diagnostics and Screening

A. Diagnostics

[0424] In yet other embodiments, the invention provides *in vitro* or *in vivo* methods for detecting, diagnosing or monitoring proliferative disorders and methods of screening cells from a patient to identify tumorigenic cells including CSCs. Such methods include identifying an individual having cancer for treatment or monitoring progression of a cancer comprising contacting the patient or a sample obtained from a patient (i.e. either *in vivo* or *in vitro*) with a modulator as described herein and detecting presence or absence, or level of association, of the modulator to bound or free target molecules in the sample. In particularly preferred embodiments the modulator will comprise a detectable label or reporter molecule as described herein.

[0425] In some embodiments, the association of the modulator, such as an antibody, with particular cells in the sample likely denotes that the sample may contain CSCs, thereby indicating that the individual having cancer may be effectively treated with a modulator as described herein. The methods may further comprise a step of comparing the level of binding to a control. Conversely, when the modulator is a Fc-construct, the binding properties may be exploited and monitored (directly or indirectly, *in vivo* or *in vitro*) when in contact with the sample to provide the desired information.

[0426] Exemplary compatible assay methods include radioimmunoassays, enzyme immunoassays, competitive-binding assays, fluorescent immunoassay, immunoblot assays, Western Blot analysis, flow cytometry assays, and ELISA assays. Compatible *in vivo* theragnostics or diagnostics may comprise art-recognized imaging or monitoring techniques such as magnetic resonance imaging, computerized tomography (e.g. CAT scan), positron tomography (e.g., PET scan) radiography, ultrasound, etc., as would be known by those skilled in the art.

[0427] In another embodiment, the invention provides a method of analyzing cancer progression and/or pathogenesis *in vivo*. In another embodiment, analysis of cancer progression and/or pathogenesis *in vivo* comprises determining the extent of tumor progression. In another embodiment, analysis comprises the identification of the tumor. In another embodiment, analysis of tumor progression is performed on the primary tumor. In another embodiment, analysis is

performed over time depending on the type of cancer as known to one skilled in the art. In another embodiment, further analysis of secondary tumors originating from metastasizing cells of the primary tumor is analyzed *in-vivo*. In another embodiment, the size and shape of secondary tumors are analyzed. In some embodiments, further *ex vivo* analysis is performed.

[0428] In another embodiment, the invention provides a method of analyzing cancer progression and/or pathogenesis *in vivo* including determining cell metastasis or detecting and quantifying the level of circulating tumor cells. In yet another embodiment, analysis of cell metastasis comprises determination of progressive growth of cells at a site that is discontinuous from the primary tumor. In another embodiment, the site of cell metastasis analysis comprises the route of neoplastic spread. In some embodiment, cells can disperse via blood vasculature, lymphatics, within body cavities or combinations thereof. In another embodiment, cell metastasis analysis is performed in view of cell migration, dissemination, extravasation, proliferation or combinations thereof.

[0429] Accordingly, in a particularly preferred embodiment the modulators of the instant invention may be used to detect and quantity DLL3 levels in a patient sample (e.g., plasma or blood) which may, in turn, be used to detect, diagnose or monitor DLL3 associated disorders including proliferative disorders. In related embodiments the modulators of the instant invention may be used to detect, monitor and/or quantify circulating tumor cells either *in vivo* or *in vitro* (see, for example, WO 2012/0128801 which is incorporated herein by reference). In still other preferred embodiments the circulating tumor cells may comprise cancer stem cells.

[0430] In certain examples, the tumorigenic cells in a subject or a sample from a subject may be assessed or characterized using the disclosed modulators prior to therapy or regimen to establish a baseline. In other examples the sample is derived from a subject that was treated. In some examples the sample is taken from the subject at least about 1, 2, 4, 6, 7, 8, 10, 12, 14, 15, 16, 18, 20, 30, 60, 90 days, 6 months, 9 months, 12 months, or >12 months after the subject begins or terminates treatment. In certain examples, the tumorigenic cells are assessed or characterized after a certain number of doses (e.g., after 2, 5, 10, 20, 30 or more doses of a therapy). In other examples, the tumorigenic cells are characterized or assessed after 1 week, 2 weeks, 1 month, 2 months, 1 year, 2 years, 3 years, 4 years or more after receiving one or more therapies.

[0431] In another aspect, and as discussed in more detail below, the present invention provides kits for detecting, monitoring or diagnosing a hyperproliferative disorder, identifying individual having such a disorder for possible treatment or monitoring progression (or regression) of the disorder in a patient, wherein the kit comprises a modulator as described herein, and reagents for detecting the impact of the modulator on a sample.

[0432] Yet another aspect of the instant invention comprises the use of labeled DLL3 for immunohistochemistry (IHC). In this respect DLL3 IHC may be used as a diagnostic tool to aid in the diagnosis of various proliferative disorders and to monitor the potential response to treatments including DLL3 modulator therapy. Compatible diagnostic assays may be performed on tissues that have been chemically fixed (including but not limited to: formaldehyde, gluteraldehyde, osmium tetroxide, potassium dichromate, acetic acid, alcohols, zinc salts, mercuric chloride, chromium tetroxide and picric acid) and embedded (including but not limited to: glycol methacrylate, paraffin and resins) or preserved via freezing. As discussed in more detail below such assays could be used to guide treatment decisions and determine dosing regimens and timing.

B. Screening

[0433] In certain embodiments, the modulators can also be used to screen for or identity compounds or agents (e.g., drugs) that alter a function or activity of tumorigenic cells or progeny thereof by interacting with an antigen (e.g., genotypic or phenotypic components thereof). Such compounds and agents can be drug candidates that are screened for the treatment of a proliferative disorder, for example. In one embodiment, a system or method includes tumorigenic cells comprising DLL3 and a compound or agent (e.g., drug), wherein the cells and compound or agent are in contact with each other. In such embodiments the subject cells may have been identified, monitored and/or enriched using the disclosed modulators.

[0434] In yet another embodiment, a method includes contacting, directly or indirectly, tumorigenic cells or progeny thereof with a test agent or compound and determining if the test agent or compound modulates an activity or function of the antigen-associated tumorigenic cells. One example of direct interaction is physical interaction, while an indirect interaction includes the action of a composition upon an intermediary molecule that, in turn, acts upon the referenced entity (e.g., cell or cell culture). Exemplary activities or functions that can be modulated include changes in cell morphology or viability, expression of a marker, differentiation or dedifferentiation, cell respiration, mitochondrial activity, membrane integrity, maturation, proliferation, viability, apoptosis or cell death.

[0435] Methods of screening and identifying agents and compounds include those suitable for high throughput screening, which include arrays of cells (e.g., microarrays) positioned or placed, optionally at pre-determined locations or addresses. For example, cells can be positioned or placed (pre-seeded) on a culture dish, tube, flask, roller bottle or plate (e.g., a single multi-well plate or dish such as an 8, 16, 32, 64, 96, 384 and 1536 multi-well plate or dish). High-

throughput robotic or manual handling methods can probe chemical interactions and determine levels of expression of many genes in a short period of time. Techniques have been developed that utilize molecular signals (e.g., via fluorophores) and automated analyses that process information at a very rapid rate (see, e.g., Pinhasov et al., Comb. Chem. High Throughput Screen. 7:133 (2004)). For example, microarray technology has been extensively used to probe the interactions of thousands of genes at once, while providing information for specific genes (see, e.g., Mocellin and Rossi, Adv. Exp. Med. Biol, 593:19 (2007)).

[0436] Libraries that can be screened include, for example, small molecule libraries, phage display libraries, fully human antibody yeast display libraries (Adimab, LLC), siRNA libraries, and adenoviral transfection vectors.

X. Pharmaceutical Preparations and Therapeutic Uses

A. Formulations and Routes of Administration

[0437] Depending on the form of the modulator along with any optional conjugate, the mode of intended delivery, the disease being treated or monitored and numerous other variables, compositions of the invention may be formulated as desired using art-recognized techniques. In some embodiments, the therapeutic compositions of the invention may be administered neat or with a minimum of additional components while others may optionally be formulated to contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries that are well known in the art (see, e.g., Gennaro, Remington: The Science and Practice of with Facts and Comparisons: Drugfacts Plus, 20th ed. (2003); Ansel et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, 7th ed., Lippencott Williams and Wilkins (2004); Kibbe et al., Handbook of Pharmaceutical Excipients, 3rd ed,, Pharmaceutical Press (2000)). Various pharmaceutically acceptable carriers, which include vehicles, adjuvants, and diluents, are readily available from numerous commercial sources. Moreover, an assortment of pharmaceutically acceptable auxiliary substances, such as pH adjusting and buffering agents, tonicity adjusting agents, stabilizers, wetting agents and the like, are also available. Certain non-limiting exemplary carriers include saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof.

[0438] More particularly it will be appreciated that, in some embodiments, the therapeutic compositions of the invention may be administered neat or with a minimum of additional components. Conversely the DLL3 modulators of the present invention may optionally be formulated to contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries that are Well known in the art and are relatively inert substances that facilitate administration of the modulator or which aid processing of the active compounds into preparations that are pharmaceutically optimized for delivery to the site of action. For example, an excipient can give form or consistency or act as a diluent to improve the pharmacokinetics or stability of the modulator. Suitable excipients or additives include, but are not limited to, stabilizing agents, wetting and emulsifying agents, salts for varying osmolarity, encapsulating agents, buffers, and skin penetration enhancers. In certain preferred embodiments the pharmaceutical compositions may be provided in a lyophilized form and reconstituted in, for example, buffered saline prior to administration.

[0439] Disclosed modulators for systemic administration may be formulated for enteral, parenteral or topical administration. Indeed, all three types of formulation may be used simultaneously to achieve systemic administration of the active ingredient. Excipients as well as formulations for parenteral and nonparenteral drug delivery are set forth in Remington, The Science and Practice of Pharmacy 20th Ed. Mack Publishing (2000). Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts. In addition, suspensions of the active compounds as appropriate for oily injection suspensions may be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, hexylsubstituted poly(lactide), sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension and include, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers. Liposomes can also be used to encapsulate the agent for delivery into the cell.

[0440] Suitable formulations for enteral administration include hard or soft gelatin capsules, pills, tablets, including coated tablets, elixirs, suspensions, syrups or inhalations and controlled release forms thereof.

[0441] In general the compounds and compositions of the invention, comprising DLL3 modulators may be administered *in vivo,* to a subject in need thereof, by various routes, including, but not limited to, moral, intravenous, intra-arterial, subcutaneous, parenteral, intranasal, intramuscular, intracranial, intracardiac, inti-aventricular, intratracheal, buccal, rectal, intraperitoneal, intradermal, topical, transdermal, and intrathecal, or otherwise by implantation or inhalation. The subject compositions may be formulated into preparations in solid, semi-solid, liquid, or gaseous forms; including, but not limited to, tablets, capsules, powders, granules, ointments, solutions, suppositories, enemas, injections, inhalants, and aerosols. The appropriate formulation and route of administration may be selected according to the intended application and therapeutic regimen.

B, Dosages

[0442] Similarly, the particular dosage regimen, i.e., dose, timing and repetition, will depend on the particular individual and that individual's medical history, is well as empirical considerations such as pharmacokinetics (e.g., half-life, clearance rate, etc.). Frequency of administration may be determined and adjusted over the course of therapy, and is based on reducing the number of proliferative or tumorigenic cells, maintaining the reduction of such neoplastic cells, reducing the proliferation of neoplastic cells, or delaying the development of metastasis, In other embodiments the dosage administered may be adjusted or attenuated to manage potential side effects and/or toxicity. Alternatively, sustained continuous release formulations of a subject therapeutic composition may be appropriate.

[0443] In general, the modulators of the invention may be administered in various ranges. These include about 10 μg/kg body weight to about 100 mg/kg body weight per dose; about 50 μg/kg body weight to about 5 mg/kg body weight per dose; about 100 μg/kg body weight to about 10 mg/kg body weight per dose. Other ranges include about 100 μg/kg body weight to about 20 mg/kg body weight per dose and about 0.5 mg/kg body weight to about 20 mg/kg body weight per dose. In certain embodiments, the dosage is at least about 100 μg/kg body weight, at least about 250 μg/kg body weight, at least about 750 μg/kg body weight, at least about 3 mg/kg body weight, at least about 5 mg/kg body weight, at least about 10 bods weight.

[0444] In selected embodiments the modulators will be administered at approximately 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 μg/kg body weight per dose. Other embodiments will comprise the administration of modulators at 200, 300, 400, 500, 600, 700, 800 or 900 μg/kg body weight per dose. In other preferred embodiments the disclosed modulators will be administered at 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 mg/kg. In still other embodiments the modulators may be administered at 12, 14, 16, 18 or 20 mg/kg body weight per dose. In yet other embodiments the modulators may be administered at 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 90 or 100 mg/kg body weight. per dose. In accordance with the teachings herein it will be appreciated that the aforementioned dosages are applicable to both unconjugated modulators and modulators conjugated to a cytotoxic agent. One of skill in the art could readily determine appropriate dosages for various conjugated and unconjugated modulators based on preclinical animal studies, clinical observations and standard medical and biochemical techniques and measurements.

[0445] With regard to conjugated modulators particularly preferred embodiments will comprise dosages of between about 50 μg/kg to about 5 mg/kg body weight per dose. In this regard conjugated modulators may be administered at 50, 75 or 100 μg/kg or at 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 or 1 mg/kg body weight per dose. In other preferred embodiments the conjugated modulators of the instant invention may be administered at 1.25, 1.5, 175, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75 or 5 mg/kg body weight per dose. In particularly preferred embodiments such conjugated modulator dosages will be administered intravenously over a period of time. Moreover, such dosages may be administered multiple times over a defined course of treatment.

[0446] Other dosing regimens may be predicated on Body Surface Area (BSA) calculations as disclosed in U.S.P.N. 7,744,877. As is well known, the BSA is calculated using the patient's height and weight and provides a measure of a subject's size as represented by the surface area of his or her body. In certain embodiments, the modulators may be administered in dosages from 10 mg/m^2 to 800 mg/m^2, from 50 mg/m^2 to 500 mg/m^2 and at dosages of 100 mg/m^2, 150 mg/m^2, 200 mg/m^2, 250 mg/m^2, 300 mg/m^2, 350 mg/m^2, 400 mg/m^2 or 450 mg/m^2.

[0447] It will also be appreciated that art recognized and empirical techniques may be used to determine appropriate dosage for conjugated modulators (i.e., ADCs).

[0448] In any event, DLL3 modulators (both conjugated and unconjugated) are preferably administered as needed to subjects in need thereof. Determination of the frequency of administration may be made by persons skilled in the art, such as an attending physician based on considerations of the condition being treated, age of the subject being treated, severity of the condition being treated, general state of health of the subject being treated and the like. Generally, an effective dose of the DLL3 modulator is administered to a subject one or more times. More particularly, an effective dose of the modulator is administered to the subject once a month, more than once a month, or less than once a month. In certain embodiments, the effective dose of the DLL3 modulator may be administered multiple times, including for periods of at least a month, at least six months, at least a year, at least two years or a period of several years. In yet other embodiments, several days (2, 3, 4, 5, 6 or 7), several weeks (1, 2, 3, 4, 5, 6, 7 or 8) or several months (1, 2, 3, 4, 5, 6, 7 or 8) or even a year or several years may lapse between administration of the disclosed modulators.

[0449] In certain preferred embodiments the course of treatment involving conjugated modulators will comprise multiple doses of the selected drug product (i.e., an ADC) over a period of weeks or months. More specifically, conjugated modulators of the instant invention may administered once every day, every two days, every four days, every week, every ten days, every two weeks, every three weeks, every month, every six weeks, every two months, every ten weeks or every three months. In this regard it will be appreciated that the dosages may be altered or the interval may be adjusted based on patient response and clinical practices.

[0450] Dosages and regimens may also be determined empirically for the disclosed therapeutic compositions in individuals who have been given one or more administration(s). For example, individuals may be given incremental dosages

of a therapeutic composition produced as described herein. In selected embodiments the dosage may be gradually increased or reduced or attenuated based respectively on empirically determined or observed side effects or toxicity. To assess efficacy of the selected composition, a marker of the specific disease, disorder or condition can be followed as described previously. In embodiments where the individual has cancer, these include direct measurements of tumor size via palpation or visual observation, indirect measurement of tumor size by x-ray or other imaging techniques; an improvement as assessed by direct tumor biopsy and microscopic examination of the tumor sample; the measurement of an indirect tumor marker (e.g., PSA for prostate cancer) or an antigen identified according to the methods described herein, a decrease in pain or paralysis; improved speech, vision, breathing or other disability associated with the tumor; increased appetite; or an increase in quality of life as measured by accepted tests or prolongation of survival. It will be apparent to one of skill in the art that the dosage will vary depending on the individual, the type of neoplastic condition, the stage of neoplastic condition, whether the neoplastic condition has begun to inetastasize to other location in the individual, and the past and concurrent treatments being used.

C. Combination Therapies

[0451] Combination therapies may be particularly useful in decreasing or inhibiting unwanted neoplastic cell proliferation, decreasing the occurrence of cancer, decreasing or preventing the recurrence of cancer, or decreasing or preventing the spread or metastasis of cancer. In such cases the modulators of the instant invention may function as sensitizing or chemosensitizing agents by removing the CSCs that would otherwise prop up and perpetuate the tumor mass and thereby allow for more effective use of current standard of care debulking or anti-cancer agents. That is, the disclosed modulators may, in certain embodiments provide an enhanced effect (e.g., additive or synergistic in nature) that potentiates the mode of action of another administered therapeutic agent. In the context of the instant invention "combination therapy" shall be interpreted broadly and merely refers to the administration of a modulator and one or more anti-cancer agents that include, but are not limited to, cytotoxic agents, cytostatic agents, anti-angiogenic agents, debulking agents, chemotherapeutic agents, radiotherapy and radiotherapeutic agents, targeted anti-cancer agents (including both monoclonal antibodies and small molecule entities), BRMs, therapeutic antibodies, cancer vaccines, cytokines, hormone therapies, radiation therapy and anti-metastatic agents and immunotherapeutic agents, including both specific and non-specific approaches.

[0452] There is no requirement for the combined results to be additive of the effects observed when each treatment (e.g., antibody and anti-cancer agent) is conducted separately. Although at least additive effects are generally desirable, any increased anti-tumor effect above one of the single therapies is beneficial. Furthermore, the invention does not require the combined treatment to exhibit synergistic effects. However, those skilled in the art will appreciate that with certain selected combinations that comprise preferred embodiments, synergism may be observed.

[0453] In practicing combination therapy, the modulator and anti-cancer agent may be administered to the subject simultaneously, either in a single composition, or as two or more distinct compositions using the same or different administration routes. Alternatively, the modulator may precede, or follow, the anti-cancer agent treatment by, e.g., intervals ranging from minutes to weeks. The time period between each delivery is such that the anti-cancer agent and modulator are able to exert a combined effect on the tumor. In at least one embodiment, both the anti-cancer agent and the modulator are administered within about 5 minutes to about two weeks of each other. In yet other embodiments, several days (2, 3, 4, 5, 6 or 7), several weeks (1, 2, 3, 4, 5, 6, 7 or 8) or several months (1, 2, 3, 4, 5, 6, 7 or 8) may lapse between administration of the modulator and the anti-cancer agent.

[0454] The combination therapy may be administered once, twice or at least for a period of time until the condition is treated, palliated or cured. In some embodiments, the combination therapy is administered multiple times, for example, from three times daily to once every six months. The administering may be on a schedule such as three times daily, twice daily, once daily, once every two days, once every three days, once weekly, once every two weeks, once every month, once every two months, once every three months, once every six months or may be administered continuously via a minipump. The combination therapy may be administered via any route, as noted previously. The combination therapy may be administered at a site distant from the site of the tumor.

[0455] In one embodiment a modulator is administered in combination with one or more anti-cancer agents for a short treatment cycle to a subject in need thereof. The invention also contemplates discontinuous administration or daily doses divided into several partial administrations. The modulator and anti-cancer agent may be administered interchangeably, on alternate days or weeks; or a sequence of antibody treatments may be given, followed by one or more treatments of anti-cancer agent therapy. In any event, as will be understood by those of ordinary skill in the art, the appropriate doses of chemotherapeutic agents will be generally around those already employed in clinical therapies wherein the chemotherapeutics are administered alone or in combination with other chemotherapeutics.

[0456] In another preferred embodiment the DLL3 modulators of the instant invention may be used in maintenance therapy to reduce or eliminate the chance of tumor recurrence following the initial presentation of the disease. Preferably the disorder will have been treated and the initial tumor mass eliminated, reduced or otherwise ameliorated so the patient

is asymptomatic or in remission. At such time the subject may be administered pharmaceutical effective amounts of the disclosed modulators one or more times even though there is little or no indication of disease using standard diagnostic procedures. In some embodiments, the modulators will be administered on a regular schedule over a period of time, such as weekly, every two weeks, monthly, every six weeks, every two months, every three months every six months or annually. Given the teachings herein, one skilled in the art could readily determine favorable dosages and dosing regimens to reduce the potential of disease recurrence. Moreover such treatments could be continued for a period of weeks, months, years or even indefinitely depending on the patient response and clinical and diagnostic parameters.

[0457] In yet mother preferred embodiment the modulators of the present invention may be used to prophylactically or as an adjuvant therapy to prevent or reduce the possibility of tumor metastasis following a debulking procedure. As used in the instant disclosure a "debulking procedure" is defined broadly and shall mean any procedure, technique or method that eliminates, reduces, treats or ameliorates a tumor or tumor proliferation. Exemplary debulking procedures include, but are not limited to, surgery, radiation treatments (i.e., beam radiation), chemotherapy, immunotherapy or ablation. At appropriate times readily determined by one skilled in the art in view of the instant disclosure the disclosed modulators may be administered as suggested by clinical, diagnostic or theragnostic procedures to reduce tumor metastasis. The modulator may be administered one or more times at pharmaceutical effective dosages as determined using standard techniques. Preferably the dosing regimen will be accompanied by appropriate diagnostic or monitoring techniques that allow it to be modified.

[0458] Yet other embodiments of the invention comprise administering the disclosed modulators to subjects that are asymptomatic but at risk of developing a proliferative disorder. That is, the modulators of the instant invention may be used in a truly preventative sense and given to patients that have been examined or tested and have one or more noted risk factors (e.g., genomic. indications, family history, *in vivo* or *in vitro* test results, etc.) but have not developed neoplasia. In such cases those skilled in the art would be able to determine an effective dosing regimen through empirical observation or through accepted clinical practices.

D. Anti-Cancer Agents

[0459] The term "'anti-cancer agent" or "anti-proliferative agent" means any agent that can be used to treat a cell proliferative disorder such as cancer, and includes, but is not limited to, cytotoxic agents, cytostatic agents, anti-angiogenic agents, debulking agents, chemotherapeutic agents, radiotherapy and radiotherapeutic agents, targeted anti-cancer agents, BRMs, therapeutic antibodies, cancer vaccines, cytokines, hormone therapies, radiation therapy and anti-metastatic agents and immunotherapeutic agents. It will be appreciated that, in selected embodiments as discussed above, such anti-cancer agents may comprise conjugates and may be associated with modulators prior to administration. In certain embodiments the disclosed anti-cancer agent will be linked to a DLL3 modulator to provide an ADC as set forth herein.

[0460] As used herein the term "cytotoxic agent" means a substance that is toxic to the cells and decreases or inhibits the function of cells and/or causes destruction of cells. Typically, the substance is a naturally occurring molecule derived from a living organism. Examples of cytotoxic agents include, but are not limited to, small molecule toxins or enzymatically active toxins of bacteria (e.g., Diptheria toxin, Pseudomonas endotoxin and exotoxin, Staphylococcal enterotoxin A), fungal (e.g., α-sarcin, restrictocin), plants (e.g., abrin, ricin, modeccin, viscumin, pokeweed anti-viral protein, saporin, gelonin, momoridin, trichosanthin, barley toxin, Aleurites fordii proteins, dianthin proteins, Phytolacca mericana proteins (PAPI, PAPII, and PAP-S), Momordica charantia inhibitor, curcin, crotin, saponaria officinalis inhibitor, gelonin, mitegellin, restrictocin, phenomycin, neomycin, and the tricothecenes) or animals, (e.g., cytotoxic RNases, such as extracellular pancreatic RNases; DNase 1, including fragments and/or variants thereof).

[0461] For the purposes of the instant invention a "chemotherapeutic agent" comprises a chemical compound that non-specifically decreases or inhibits the growth, proliferation, and/or survival of cancer cells cytotoxic or cytostatic agents). Such chemical agents are often directed to intracellular processes necessary for cell growth or division, and are thus particularly effective against cancerous cells, which generally grow and divide rapidly. For example, vincristine depolymerizes microtubules, and thus inhibits cells from entering mitosis. In general, chemotherapeutic agents can include any chemical agent that inhibits, or is designed to inhibit, a cancerous cell or a cell likely to become cancerous or generate tumorigenic progeny (e.g., TIC). Such agents are often administered, and are often most effective, in combination, e.g., in regimens such as CHOP or FOLFIRI. Again, in selected embodiments such chemotherapeutic agents may be conjugated to the disclosed modulators.

[0462] Examples of anti-cancer agents that may be used in combination with (or conjugated to) the modulators of the present invention include, but are not limited to, alkylating agents, alkyl sulfonates, aziridines, ethylenimines and methylamelamines, acetogenins, a camptothecin, bryostatin, callystatin, CC-1065, cryptophycins, dolastatin, duocarmycin, eleutherobin, pancratistatin, a sarcodictyin, spongistatin, nitrogen mustards, antibiotics, enediyne antibiotics, dynemicin, bisphosphonates, esperamicin, chromoprotein enediyne antiobiotic chromophores, aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, carminomycin, carzinophilin, chromomycinis, dactinomycin,

daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, ADRIAMYCIN® doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, hibercidin, ubenimex, zinostatin, zorubicin; anti-metabolites, erlotinib, vemurafenib, crizotinib,sorafenib, ibrutinib, enzalutamide, folic acid analogues, purine analogs, androgens, anti-adrenals, folic acid replenisher such as frolinic acid, aceglatone, aldophosphamide glycoside, aminolevulinic acid, eniluracil, amsacrine, bestrabucil, bisantrene, edatraxate, defofamine, demecolcine, diaziquone elfornithine, elliptinium acetate, an epothilone, etoglucid, gallium nitrate, hydroxyurea, lentinan, lonidainine, maytansinoids, mitoguazone, mitoxantrone, mopidanmol, nitraerine, pentostatin, phenamet, pirarubicin, losoxantrone, podophyllinic acid, 2- ethylhydrazide, procarbazinc, PSK® polysaccharide complex (JHS Natural Products, Eugene, OR), razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, chloranbucil; GEMZAR® gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs, vinblastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; NAVELBINE® vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; irinotecan (Camptosar, CPT-II), topoisomerase inhibitor RFS 2000; difluorometlhylornithine; retinoids; capecitabine; combretastatin; leucovorin; oxaliplatin; inhibitors of PKC-alpha, Raf, H-Ras, EGFR and VEGF-A that reduce cell proliferation and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included in this definition are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators, aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, and anti-androgens; as well as troxacitabine (a 1,3- dioxolane nucleoside cytosine analog); antisense oligonucleotides, ribozymes such as a VEGF expression inhibitor and a HER2 expression inhibitor; vaccines, PROLEUKIN® rIL-2; LURTOTECAN® topoisomerase 1 inhibitor; ABARELIX® rmRH; Vinorelbine and Esperamicins and pharmaceutically acceptable salts, acids or derivatives of any of the above.

[0463] In other embodiments the modulators of the instant invention may be used in combination with any one of a number of antibodies (or immunotherapeutic agents) presently in clinical trials or commercially available. To this end the disclosed modulators may be used in combination with an antibody selected from the group consisting of abagovomab, adecatumumab, afutuzumab, alemtuzumab, altumomab, amatuximab, anatumomab, arcitumomab, bavituximab, bectumomab, bevacizumah, bivatuzumab, blinatumomab, brentuximab, cantuzumab, catumaxomab, cetuximab, citatuzumab, cixutumumab, clivatuzumab, conatumumab, daratumumab, drozitumab, duligotumab, dusigitumab, detumomab, dacetuzumab, dalotuzumab, ecromeximab, elotuzumab, ensituximab, ertumaxomab, etaracizumab, farletuzumab, ficlatuzumab, figitumumab, flanvotumab, futuximab, ganitumab, gemtuzumab, girentuximab, glembatumumab, ibritumomab, igovomab, imgatuzumab, indatuximab, inotuzumab, intetumumab, ipilimumab, iratumumab, labetuzumab, lexatumumab, lintuzumab, lorvotuzumab, lucatumumab, mapatumumab, matuzumab, milatuzumab, minretumomab, mitumomab, moxetumomab, narnatumab, naptumomab, necitumumab, nimotuzumab, nofetumomabn, ocaratuzumab, ofatumumab, olaratumab, onartuzumab, oportuzumab, oregovomab, panitumumab, parsatuzumab, patritumab, pemtumomab, pertuzumab, pintumomab, pritumumab, racotumomab, radretumab, rilotumumab, rituximab, robatumumab, satumomab, sibrotuzumab, siltuximab, simtuzumab, solitomab, tacatuzumab, taplitumomab, tenatumomab, teprotumumab, tigatuzumab, tositumomab, trastuzumab, tucotuzumab, ublituximab, veltuzumab, vorsetuzumab, votumumab, zalutumumab, CC49, 3F8 and combinations thereof.

[0464] Still other particularly preferred embodiments will comprise the use of antibodies approved for cancer therapy including, but not limited to, rituximab, trastuzumab, gemtuzumab ozogamcin, alemtuzumab, ibritumomab tiuxetan, tositumomab, bevacizumab, cetuximab, panitumumab, ofatumumab, ipilimumab and brentuximab vedotin. Those skilled in the art will be able to readily identify additional anti-cancer agents that are compatible with the teachings herein.

E. Radiotherapy

[0465] The present invention also provides for the combination of modulators with radiotherapy (i.e., any mechanism for inducing DNA damage locally within tumor cells such as gamma-irradiation, X-rays. UV-irradiation, microwaves, electronic emissions and the like). Combination therapy using the directed delivery of radioisotopes to tumor cells is also contemplated, and may be used in connection with a targeted anti-cancer agent or other targeting means. Typicaly, radiation therapy is administered in pulses over a period of time from about 1 to about 2 weeks. The radiation therapy may be administered to subjects having head and neck cancer for about 6 to 7 weeks. Optionally, the radiation therapy may be administered as a single dose or as multiple, sequential doses.

XI. Indications

[0466] It will be appreciated that the modulators of the instam invention may be used to diagnose, treat or inhibit the occurrence or recurrence of any DLL3 associated disorder. Accordingly, whether administered alone or in combination

with an anti-cancer agent or radiotherapy, the modulators of the invention are particularly useful for generally treating neoplastic conditions in patients or subjects which may include benign or malignant tumors (e.g., adrenal, liver, kidney, bladder, breast, gastric, ovarian, colorectal, prostate, pancreatic, lung, thyroid, hepatic, cervical, endometrial, esophageal and uterine carcinomas; sarcomas; glioblastomas; and various head and neck tumors); leukemias and lymphoid malignancies; other disorders such as neuronal, glial, astrocytal, hypothalamic and other glandular, macrophagal, epithelial, stromal and blastocoelic disorders; and inflammatory, angiogenic, immunologic disorders and disorders caused by pathogens. Particularly, key targets for treatment are neoplastic conditions comprising solid tumors, although hematologic malignancies are within the scope of the invention. Preferably the "subject" or "patient'" to be treated will be human although, as used herein, the terms are expressly held to comprise any mammalian species.

[0467] More specifically, neoplastic conditions subject to treatment in accordance with the instant invention may be selected from the group including, but not limited to, adrenal gland tumors, AIDS-associated cancers, alveolar soft part sarcoma, astrocytic tumors, bladder cancer (squamous cell carcinoma and transitional cell carcinoma), bone cancer (adamantinoma, aneurismal bone cysts, osteochondroma, osteosarcoma), brain and spinal cord cancers, metastatic brain tumors, breast cancer, carotid body tumors, cervical cancer, chondrosarcoma, chordoma, chromophobe renal cell carcinoma, clear cell carcinoma, colon cancer, colorectal cancer, cutaneous benign fibrous histiocytomas, desmoplastic small round cell tumors, ependymomas, Ewing's tumors, extraskeletal myxoid chondrosarcoma, fibrogenesis imperfecta ossium, fibrous dysplasia of the bone, gallbladder and bile duct cancers, gestational trophoblastic disease, germ cell tumors, head and neck cancers, islet cell tumors, Kaposi's Sarcoma, kidney cancer (nephroblastoma, papillary renal cell carcinoma), leukemias, lipoma/benign lipomatous tumors, liposarcoma/malignant lipomatous tumors, liver cancer (hepatoblastoma, hepatocellular carcinoma), lymphomas, lung cancers (small cell carcinoma, adenocarcinoma, squamous cell carcinoma, large cell carcinoma etc.), medulloblastoma, melanoma, meningiomas, multiple endocrine neoplasia, multiple myeloma, myelodysplastic syndrome, neuroblastoma, neuroendocrine tumors, ovarian cancer, pancreatic cancers, papillary thyroid carcinomas, parathyroid tumors, pediatric cancers, peripheral nerve sheath tumors, phaeochromocytoma, pituitary tumors, prostate cancer, posterious unveal melanoma, rare hematologic disorders, renal metastatic cancer, rhabdoid tumor, rhabdomysarcoma, sarcomas, skin cancer, soft-tissue sarcomas, squamous cell cancer, stomach cancer, synovial sarcoma, testicular cancer, thymic carcinoma, thymoma, thyroid metastatic cancer, and uterine cancers (carcinoma of the cervix, endometrial carcinoma, and leiomyoma).

[0468] In certain preferred embodiments the proliferative disorder will comprise a solid tumor including, but not limited to, adrenal, liver, kidney, bladder, breast, gastric, ovarian, cervical, uterine, esophageal, colorectal, prostate, pancreatic, lung (both small cell and non-small cell), thyroid, carcinomas, sarcomas, glioblastomas and various head and neck tumors. In other preferred embodiments, and as shown in the Examples below, the disclosed modulators are especially effective at treating small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) (e.g., squamous cell cell lung cancer or squamous cell small cell lung cancer). In one embodiment, the lung cancer is refractory, relapsed or resistant to a platinum based agent (e.g., carboplatin, cisplatin, oxaliplatin, topotecan) and/or a taxane (e.g., docetaxel; paclitaxel, or cabazitaxel). Further, in particularly preferred embodiments the disclosed modulators may be used in a conjugated form to treat small cell lung cancer.

[0469] With regard to small cell lung cancer particularly preferred embodiments will comprise the administration of conjugated modulators (ADCs). In selected embodiments the conjugated modulators will be administered to patients exhibiting limited stage disease. In other embodiments the disclosed modulators will be administered to patients exhibiting extensive stage disease. In other preferred embodiments the disclosed conjugated modulators will be administered to refractory patients (i.e., those who recur during or shortly after completing a course of initial therapy). Still other embodiments comprise the administration of the disclosed modulators to sensitive patients (i.e, those whose relapse is longer than 2-3 months after primary therapy. In each case it will be appreciated that compatible modulators may be in a conjugated or unconjugated state depending the selected dosing regimen and the clinical diagnosis.

[0470] As discussed above the disclosed modulators may further be used to prevent, treat or diagnose tumors with neuroendocrine features or phenotypes including neuroendocrine tumors. True or canonical neuroendocrine tumors (NETs) arising from the dispersed endocrine system are relatively rare, with an incidence of 2-5 per 100,000 people, but highly aggressive. Neuroendocrine tumors occur in the kidney, genitourinary tract (bladder, prostate, ovary, cervix, and endometrium), gastrointestinal tract (colon, stomach), thyroid (medullary thyroid cancer), and lung (small cell lung carcinoma and large cell neuroendocrine carcinoma). These tumors may secrete several hormones including serotonin and/or chromogranin A that can cause debilitating symptoms known as carcinoid syndrome. Such tumors can be denoted by positive immunohistochemical markers such as neuron-specific enolase (NSE, also known as gamma enolase, gene symbol = ENO2), CD56 (or NCAM1), chromogranin A (CHGA), and synaptophysin (SYP) or by genes known to exhibit elevated expression such as ASCL1. Unfortunately traditional chemotherapies have not been particularly effective in treating NETs and liver metastasis is a common outcome.

[0471] While the disclosed modulators may be advantageously used to treat neuroendocrine tumors they may also be used to treat, prevent or diagnose pseudo neuroendocrine tumors (pNETs) that genotypically or phenotypically mimic, resemble or exhibit common traits with canonical neuroendocrine tumors. Pseudo neuroendocrine tumors or tumors

with neuroendocrine features are tumors that arise from cells of the diffuse neuroendocrine system or from cells in which a neuroendocrine differentiation cascade has been aberrantly reactivated during the oncogenic process. Such pNETs commonly share certain phenotypic or biochemical characteristics with traditionally defined neuroendocrine tumors, including the ability to produce subsets of biologically active amines, neurotransmitters, and peptide hormones. Histologically, such tumors (NETs and pNETs) share a common appearance often showing densely connected small cells with minimal cytoplasm of bland cytopathology and round to oval stippled nuclei. For the purposes of the instant invention commonly expressed histological markers or genetic markers that may be used to define neuroendocrine and pseudo neuroendocrine tumors includes, but are not limited to, chromogranin A, CD56, synaptophysin, PGP9.5, ASCL1 and neuron-specific enolase (NSE).

[0472] Accordingly the modulators of the instant invention may beneficially be used to treat both pseudo neuroendocrine tumors and canonical neuroendocrine tumors. In this regard the modulators may be used as described herein to treat neuroendocrine tumors (both NET and pNET) arising in the kidney, genitourinary tract (bladder, prostate, ovary, cervix, and endometrium), gastrointestinal tract (colon, stomach), thyroid (medullary thyroid cancer), and lung (small cell lung carcinoma and large cell neuroendocrine carcinoma). Moreover, the modulators of the instant invention may be used to treat tumors expressing one or more markers selected from the group consisting of NSE, CD56, synaptophysin, chromogranin A, ASCL1 and PGP9.5 (UCHL1). That is, the present invention may be used to treat a subject suffering from a tumor that is NSE^+ or $CD56^+$ or $PGP9.5^+$ or $ASCL1^+$ or SYP^+ or $CHGA^+$ or some combination thereof.

[0473] With regard to hematologic malignancies it will be further be appreciated that the compounds and methods of the present invention may be particularly effective in treating a variety of B-cell lymphomas, including low grade/NHL follicular cell lymphoma (FCC), mantle cell lymphoma (MCL), diffuse large cell lymphoma (DLCL), small lymphocytic (SL) NHL, intermediate grade/follicular NHL, intermediate grade diffuse NHL, high grade immunoblastic NHL, high grade lymphoblastic NHL, high grade small non-cleaved cell NHL, bulky disease NHL, Waldenstrom's Macroglobulinemia, lymphoplasmacytoid lymphoma (LPL), mantle cell lymphoma (MCL), follicular lymphoma (FL), diffuse large cell lymphoma (DLCL), Burkitt's lymphoma (BL), AIDS-related lymphomas, monocytic B cell lymphoma, angioimmunoblastic lymphoadenopathy, small lymphocytic, follicular, diffuse large cell, diffuse small cleaved cell, large cell immunoblastic lymphoblastoma, small, non-cleaved, Burkitt's and non-Burkitt's, follicular, predominantly large cell; follicular, predominantly small cleaved cell; and follicular, mixed small cleaved and large cell lymphomas. See, Gaidono et al., "Lymphomas", IN CANCER: PRINCIPLES & PRACTICE OF ONCOLOGY, Vol. 2: 2131-2145 (DeVita et al., eds., 5.sup.th ed. 1997). It should be clear to those of skill in the art that these lymphomas will often have different names due to changing systems of classification, and that patients having lymphomas classified under different names may also benefit from the combined therapeutic regimens of the present invention.

[0474] The present invention also provides for a preventative or prophylactic treatment of subjects who present with benign or precancerous tumors. Beyond being a DLL3 associated disorder it is not believed that any particular type of tumor or proliferative disorder should be excluded from treatment using the present invention. However, the type of tumor cells may be relevant to the use of the invention in combination with secondary therapeutic agents, particularly chemotherapeutic agents and targeted anti-cancer agents.

XII. Articles of Manufacture

[0475] Pharmaceutical packs and kits comprising one or more containers, comprising one or more doses of a DLL3 modulator are also provided. In certain embodiments, a unit dosage is provided wherein the unit dosage contains a predetermined amount of a composition comprising, for example, an anti-DLL3 antibody, with or without one or more additional agents. For other embodiments, such a unit dosage is supplied in single-use prefilled syringe for injection, In still other embodiments, the composition contained in the unit dosage may comprise saline, sucrose, or the like; a buffer, such as phosphate, or the like; and/or be formulated within a stable and effective pH range. Alternatively, in certain embodiments, the composition may be provided as a lyophilized powder that may be reconstituted upon addition of an appropriate liquid, for example, sterile water. In certain preferred embodiments, the composition comprises one or more substances that inhibit protein aggregation, including, but not limited to, sucrose and arginine. Any label on, or associated with, the container(s) indicates that the enclosed composition is used for diagnosing or treating the disease condition of choice.

[0476] The present invention also provides kits for producing single-dose or multi-dose administration units of a DLL3 modulator and, optionally, one or more anti-cancer agents. The kit comprises a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, etc. The containers may be formed from a variety of materials such as glass or plastic and contain a pharmaceutically effective amount of the disclosed modulators in a conjugated or unconjugated form. In other preferred embodiments the container(s) comprise a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). Such kits will generally contain in a suitable container a pharmaceutically acceptable formulation of the DLL3 modulator and, optionally, one or more anti-cancer agents in the same or different containers.

The kits may also contain other pharmaceutically acceptable formulations, either for diagnosis or combined therapy. For example, in addition to the DLL3 modulator of the invention such kits may contain any one or more of a range of anti-cancer agents such as chemotherapeutic or radiotherapeutic drugs; anti-angiogenic agents; anti-metastatic agents; targeted anti-cancer agents; cytotoxic agents; and/or other anti-cancer agents. Such kits may also provide appropriate reagents to conjugate the DLL3 modulator with an anti-cancer agent or diagnostic agent (e.g., see U.S.P.N. 7,422,739 which is incorporated herein by reference in its entirety).

[0477] More specifically the kits may have a single container that contains the DLL3 modulator, with or without additional components, or they may have distinct containers for each desired agent. Where combined therapeutics are provided for conjugation, a single solution may be premixed, either in a molar equivalent combination, or with one component in excess of the other. Alternatively, the DLL3 modulator and any optional anti-cancer agent of the kit may be maintained separately within distinct containers prior to administration to a patient. The kits may also comprise a second/third container means for containing a sterile, pharmaceutically acceptable buffer or other diluent such as bacteriostatic water for injection (BWFI), phosphate-buffered saline (PBS), Ringer's solution and dextrose solution.

[0478] When the components of the kit are provided in one or more liquid solutions, the liquid solution is preferably an aqueous solution, with a sterile aqueous solution being particularly preferred. However, the components of the kit may be provided as dried powder(s). When reagents or components are provided as a dry powder, the powder can be reconstituted by the addition of a suitable solvent. It is envisioned that the solvent may also be provided in another container.

[0479] As indicated briefly above the kits may also contain a means by which to administer the antibody and any optional components to an animal or patient, e.g., one or more needles or syringes, or even an eye dropper, pipette, or other such like apparatus, from which the formulation may be injected or introduced into the animal or applied to a diseased area of the body. The kits of the present invention will also typically include a means for containing the vials, or such like, and other component in close confinement for commercial sale, such as, e.g., injection or blow-molded plastic containers into which the desired vials and other apparatus are placed and retained. Any label or package insert indicates that the DLL3 modulator composition is used for treating cancer, for example small cell lung cancer.

[0480] In other preferred embodiments the modulators of the instant invention may be used in conjunction with, or comprise, diagnostic or therapeutic devices useful in the diagnosis or treatment of proliferative disorders. For example, in on preferred embodiment the compounds and compositions of the instant invention may be combined with certain diagnostic devices or instruments that may be used to detect, monitor, quantify or profile cells or marker compounds involved in the etiology or manifestation of proliferative disorders. For selected embodiments the marker compounds may comprise NSE, CD56, synaptophysin, chromogranin A, and PGP9.5.

[0481] In particularly preferred embodiments the devices may be used to detect, monitor and/or quantify circulating tumor cells either *in vivo* or in *vitro* (see, for example, WO 2012/0128801 which is incorporated herein by reference). In still other preferred embodiments, and as discussed above, the circulating tumor cells may comprise cancer stem cells.

XIII. Research Reagents

[0482] Other preferred embodiments of the invention also exploit the properties of the disclosed modulator as an instrument useful for identifying, monitoring, isolating, sectioning or enriching populations or subpopulations of tumor initiating cells through methods such as flow cytometry, fluorescent activated cell sorting (FACS), magnetic activated cell sorting (MACS) or laser mediated sectioning. Those skilled in the art will appreciate that the modulators may be used in several compatible techniques for the characterization and manipulation of TIC including cancer stem cells (e.g., see U.S.S.Ns. 12/686,359, 12/669,136 and 12/757,649 each of which is incorporated herein by reference in its entirety).

XIV. Miscellaneous

[0483] Unless otherwise defined herein, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. More specifically, as used in this 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 protein" includes a plurality of proteins; reference to "a cell" includes mixtures of cells, and the like. In addition, ranges provided in the specification and appended claims include both end points and all points between the end points. Therefore, a range of 2.0 to 3.0 includes 2.0, 3.0, and all points between 2,0 and 3.0.

[0484] Generally, nomenclature used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein are those well known and commonly used in the art. The methods and techniques of the present invention are generally performed according to conventional methods well known in the art and as described in various general and more specific references

that are cited and discussed throughout the present specification unless otherwise indicated. See, e.g., Abbas et al., Cellular and Molecular Immunology, 6th ed., W.B. Saunders Company (2010); Sambrook J. & Russell D. Molecular Cloning: A Laboratory Manual, 3rd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (2000); Ausubel et al., Short Protocols in Molecular Biology: A Compendium of Methods from Current Protocols in Molecular Biology, Wiley, John & Sons, Inc. (2002); Harlow and Lane Using Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor. N.Y. (1998); and Coligan et al., Short Protocols in Protein Science, Wiley, John & Sons, Inc. (2003). Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The nomenclature used in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Moreover, any section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

XV. DLL3 References

[0485] All references or documents disclosed or cited within this specification, including those set forth immediately below are, without limitation, incorporated herein by reference in their entirety.

Apelqvist A et al. (1999). Notch signalling controls pancreatic cell differentiation. Nature. 400:877-81. PMID: 10476967.

Bigas A and Espinosa L (2012). Hematopoietic stem cells: to be or Notch to be. Blood. 2012 PMID: 22308291.

Cabrera CV (1990). Lateral inhibition and cell fate during neurogenesis in Drosophila: the interactions between scute, Notch and Delta. Development. 110:733-42. PMID: 1709404. Chapman G et al. (2011). Notch inhibition by the ligand DELTA-LIKE 3 defines the mechanism of abnormal vertebral segmentation in spondylocostal dysostosis. Hum Mol Genet. 20:905-16. PMID: 21147753.

Chen H et al. (1997). Conservation of the Drosophila lateral inhibition pathway in human lung cancer: a hairy-related protein (HES-1) directly represses achaete-scute homolog-1 expression. Proc Natl Acad Sci U S A. 94:5355-60. PMID: 9144241.

Cook M et al., (2010). Notch in the development of thyroid C-cells and the treatment of medullary thyroid cancer. Am J Transl Res. 2:119-25. PMID: 20182588.

de la Pompa JL et al (1997). Conservation of the Notch signaling pathway in mammalian neurogenesis. Development. 124:1139-48. PMID: 9102301.

D'Souza B et al. (2010), Canonical and non-canonical Notch ligands. Curr Top Dev Biol. 92:73-129. PMID: 20816393.

Dunwoodie SL (2009). The role of Notch in patterning the human vertebral column. Curr Opin Genet Dev. 19:329-37. PMID:19608404.

Dutta S et al., (2008). Notch signaling regulates endocrine cell specification in the zebrafish anterior pituitary. Dev Biol. 319:248-57. PubMed PMID: 18534570.

Fre S et al. (2005). Notch signals control the fate of immature progenitor cells in the intestine. Nature. 435:964-8. PMID: 15959516.

Fre S et al. (2009). Notch and Wnt signals cooperatively control cell proliferation and tumorigenesis in the intestine. Proc Natl Acad Sci U S A. 106:6309-14. PMID: 19251639.

Galluzzo P, and Bocchetta M (2011). Notch signaling in lung cancer. Expert Rev Anticancer Ther. 11:533-40. PMID:21504320.

Geffers I et al. (2007). Divergent functions and distinct localization of the Notch ligands DLL1 and DLL3 in vivo. J Cell Biol. 178:465-76. PMID: 17664336.

Glittenberg M, et al., (2006). Role of conserved intracellular motifs in Serrate signalling, cis-inhibition and endocytosis. EMBO J. 25:4697-706. PMID: 17006545.

Goldbeter A, and Pourquié O (2008). Modeling the segmentation clock as a network of coupled oscillations in the Notch, Wnt and FGF signaling pathways. J Theor Biol. 252:574-85.PMID: 18309339.

Habener JF et al. (2005). Minireview: transcriptional regulation in pancreatic development. Endocrinology.146:1025-34. PMID: 15604203.

Harris PJ et al. (2012). Targeting embryonic signaling pathways in cancer therapy. Expert Opin Ther Targets. PMID: 22239436.

Henke RM et al. (2009). AscII and Neurog2 form novel complexes and regulate Delta-like3 (DLL3) expression in the neural tube. Dev Biol. 328:529-40. PMID:19389376.

Hoyne GF, et al. (2011). A cell autonomous role for the Notch ligand Delta-like 3 in $\alpha\beta$ T-cell development. Immunol Cell Biol. 89:696-705. PMID: 21151194.

Huber K et al., (2002). Development of chromaffin cells depends on MASHI function. Development. 129:4729-38. PMID: 12361965.

Ito T et al. (2000). Basic helix-loop-helix transcription factors regulate the neuroendocrine differentiation of fetal mouse pulmonary epithelium. Development. 127:3913-21. PMID: 10952889.
Jensen J et al. (2000). Control of endodermal endocrine development by Hes-1. Nat Genet. 24:36-44. PMID: 10615124.
Kageyama R, et al. (2007). Oscillator mechanism of Notch pathway in the segmentation clock. Dev Dyn. 236:1403-9. PMID:17366573.
Kameda Y et al. (2007). Mashl regulates the development of C cells in mouse thyroid glands. Dev Dyn. 236:262-70. PMID: 17103415.
Klein T, et al. (1997). An intrinsic dominant negative activity of serrate that is modulated during wing development in Drosophila. Dev Biol. 189: 123-34. PMID: 9281342.
Klimstra DS, et al. (2010). The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas. 39:707-12. PMID: 20664470.
Klöppel G. (2011). Classification and pathology of gastroenteropancreatic neuroendocrine neoplasms. Endocr Relat Cancer. 18 Suppl 1:S1-16. PMID: 22005112.
Koch U and Radtke F (2010), Notch signaling in solid tumors. Curr Top Dev Biol. 92:411-55. PMID: 20816403.
Kusumi K et al, (1998). The mouse pudgy mutation disrupts Delta homologue DLL3 and initiation of early somite boundaries. Nat Genet. 19:274-8. PMID: 9662403.
Ladi E et al. (2005). The divergent DSL ligand DLL3 does not activate Notch signaling but cell autonomously attenuates signaling induced by other DSL ligands. J Cell Biol. 170:983-92. PMID: 16144902.
Liu J et al. (2010). Notch signaling in the regulation of stem cell self-renewal and differentiation. Curr Top Dev Biol. 92:367-409. PMID: 20816402.
Nagase H et al. (2011). γ-Secretase-regulated signaling pathways, such as notch signaling, mediate the differentiation of hematopoietic stem cells, development of the immune system, and peripheral immune responses. Curr Stem Cell Res Ther, 6:131-41. PMID: 211904540.
Raetzman LT et at, (2004). Developmental regulation of Notch signaling genes in the embryonic pituitary: Prop1 deficiency affects Notch2 expression. Dev Biol. 265:329-40. PMID: 14732396.
Rebay I, et al., (1991). Specific EGF repeats of Notch mediate interactions with Delta and Serrate: implications for Notch as a multifunctional receptor. Cell. 67:687-99. PMID: 1657403.
Sakamoto K et al, (2002). Intracellular cell-autonomous association of Notch and its ligands: a novel mechanism of Notch signal modification. Dev Biol. 241:313-26. PMID: 11784114,
Schonhoff SE et al. (2004), Minireview: Development and differentiation of gut endocrine cells. Endocrinology. 145:2639-44. PMID: 15044355,
Shimizu K et al. (1999). Mouse jagged1 physically interacts with notch2 and other notch receptors. Assessment by quantitative methods. J Biol Chem. 274:32961-9. PMID: 10551863.
Shinkai Y et al. (2004). New mutant mouse with skeletal deformities caused by mutation in delta like 3 (DLL3) gene. Exp Anim. 53:129-36. PMID: 15153675.
Schonhoff SE et al. (2004). Minireview: Development and differentiation of gut endocrine cells. Endocrinology. 145:2639-44, PMID: 15044355.
Sprinzak D etal. (2010). Cis-interactions between Notch and Delta generate mutually exclusive signalling states. Nature. 465:86-90. PMID: 20418862.
Sriuranpong V et al. (2002). Notch signaling induces rapid degradation of achaete-scute homolog 1. Mol Cell Biol. 22:3129-39, PMID; 11940670.
Sternberg PW (1988), Lateral inhibition during vulval induction in Caenorhabditis elegans. Nature. 335:551-4. PMID: 3419532.
Wharton KA, et al., (1985). Nucleotide sequence from the neurogenic locus notch implies a gene product that shares homology with proteins containing EGF-like repeats. Cell. 43:567-81. PMID: 3935325.
Yao JC et al. (2008). One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 26:3063-72. PMID: 18565894.
Zarebczan B, Chen H (2010). Signaling mechanisms in neuroendocrine tumors as targets for therapy. Endocrinol Metab Clin North Am. 39:801-10. PMID: 21095546.

XVI. Selected Embodiments of the Invention.

[0486] In addition to the disclosure and Examples herein, the present invention is directed to selected embodiments specifically set forth immediately below.

PUTATIVE CLAIMS:

[0487]

1. An isolated DLL3 modulator.
2. The isolated DLL3 modulator of claim 1, wherein the DLL3 modulator comprises a DLL3 antagonist.
3. The isolated DLL3 modulator of claim 1, wherein the DLL3 modulator comprises an antibody or immunoreactive fragment thereof.
4. The isolated DLL3 modulator of claim 3 wherein the antibody or immunoreactive fragment thereof comprises a monoclonal antibody.
5. The isolated DLL3 modulator of claim 4 wherein the monoclonal antibody is selected from the group consisting of chimeric antibodies, humanized antibodies and human antibodies.
6. The isolated DLL3 modulator of claim 4 wherein said monoclonal antibody comprises a neutralizing antibody.
7. The isolated DLL3 modulator of claim 4 wherein said monoclonal antibody comprises a depleting antibody.
8. The isolated DLL3 modulator of claim 4 wherein said monoclonal antibody comprises an internalizing antibody.
9. The isolated DLL3 modulator of claim 8 wherein said monoclonal antibody further comprises a cytotoxic agent.
10. The isolated DLL3 modulator of claim 4 wherein said monoclonal antibody comprises a light chain variable region having three complementarity determining regions and a heavy chain variable region having three complementarity determining regions wherein the heavy and light chain complementarity determining regions comprise at least one complementarity determining region set forth in FIG. 11A and FIG. 11B.
11. The isolated DLL3 modulator of claim 4 wherein said monoclonal antibody comprises a light chain variable region and a heavy chain variable region wherein said light chain variable region comprises an amino acid sequence having at least 60% identity to an amino acid sequence selected from the group consisting of amino acid sequences as set forth in SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74, SEQ ID NO: 76, SEQ ID NO: 78 SEQ ID NO: 80, SEQ ID NO: 82, SEQ ID NO: 84, SEQ ID NO: 86, SEQ ID NO: 88, SEQ ID NO: 90, SEQ ID NO: 92, SEQ ID NO: 94, SEQ ID NO: 96, SEQ ID NO: 98, SEQ ID NO: 100, SEQ ID NO: 102, SEQ ID NO: 104, SEQ ID NO: 106, SEQ ID NO: 108, SEQ ID NO: 110, SEQ ID NO: 112, SEQ ID NO: 114, SEQ ID NO: 116, SEQ ID NO: 118, SEQ ID NO: 120, SEQ ID NO: 122, SEQ ID NO: 124, SEQ ID NO: 126, SEQ ID NO: 128, SEQ ID NO: 130, SEQ ID NO: 132, SEQ ID NO: 134, SEQ ID NO: 136, SEQ ID NO: 138, SEQ ID NO: 140, SEQ ID NO: 142, SEQ ID NO: 144, SEQ ID NO: 146, SEQ ID NO: 148, SEQ ID NO: 150, SEQ ID NO: 152, SEQ ID NO: 154, SEQ ID NO: 56, SEQ ID NO: 158, SEQ ID NO: 160, SEQ ID NO: 162 SEQ ID NO: 164, SEQ ID NO: 166, SEQ ID NO: 168, SEQ ID NO: 170, SEQ ID NO: 172, SEQ ID NO: 174, SEQ ID NO: 176, SEQ ID NO: 178, SEQ ID NO: 180, SEQ ID NO: 182, SEQ ID NO: 184, SEQ ID NO: 186, SEQ ID NO: 188, SEQ ID NO: 190, SEQ ID NO: 192, SEQ ID NO: 194, SEQ ID NO: 196, SEQ ID NO: 198, SEQ ID NO: 200 and SEQ ID NO: 202 and wherein said heavy chain variable region comprises an amino acid sequence having at least 60% identity to an amino acid sequence selected from the group consisting of amino acid sequences as set forth in SEQ ID NO: 21, SEQ ID NO: 23, SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 71, SEQ ID NO: 73, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 79, SEQ ID NO: 81, SEQ ID NO: 83, SEQ ID NO: 85, SEQ ID NO: 87, SEQ ID NO: 89, SEQ ID NO: 91, SEQ ID NO: 93, SEQ ID NO: 95, SEQ ID NO: 97, SEQ ID NO: 99, SEQ ID NO: 101, SEQ ID NO: 103, SEQ ID NO: 105, SEQ ID NO: 107, SEQ ID NO: 109, SEQ ID NO: 111, SEQ ID NO: 113, SEQ ID NO, 115, SEQ ID NO: 117, SEQ ID NO: 119, SEQ ID NO: 121, SEQ ID NO: 123, SEQ ID NO: 125, SEQ ID NO: 127, SEQ ID NO: 129, SEQ ID NO: 131, SEQ ID NO: 133, SEQ ID NO: 135, SEQ ID NO: 137, SEQ ID NO: 139, SEQ ID NO: 141, SEQ ID NO: 143, SEQ ID NO: 145, SEQ ID NO: 147, SEQ ID NO: 149, SEQ ID NO: 151, SEQ ID NO: 153, SEQ ID NO: 155, SEQ ID NO: 157, SEQ ID NO: 159, SEQ ID NO: 161, SEQ ID NO: 163, SEQ ID NO: 165, SEQ ID NO: 167, SEQ ID NO: 169, SEQ ID NO: 171, SEQ ID NO: 173, SEQ ID NO: 175, SEQ ID NO: 177, SEQ ID NO: 179, SEQ ID NO: 181, SEQ ID NO: 183, SEQ ID NO: 185, SEQ ID NO: 187, SEQ ID NO: 189, SEQ ID NO: 191, SEQ ID NO: 193, SEQ ID NO: 195, SEQ ID NO: 197, SEQ ID NO: 199, SEQ ID NO: 201 and SEQ ID NO: 203.
12. An isolated DLL3 modulator comprising a CDR from any one of the heavy or light chain variable regions set forth in of claim 11.
13. An isolated DLL3 modulator comprising a competing antibody wherein said competing antibody inhibits the binding of an isolated DLL3 modulator of claim 10 or 11 to DLL3 by at least about 40%.

14. A nucleic acid encoding an amino acid heavy chain variable region or an amino acid light chain variable region of claim 11.

15. A vector comprising the nucleic acid of claim 14.

16. The isolated DLL3 modulator of claim 1 comprising an amino acid sequence as set forth in SEQ ID NO: 3 or a fragment thereof.

17. The isolated DLL3 modulator of claim 16 wherein the DLL3 modulator further comprises at least a portion of an immunoglobulin constant region.

18. The isolated DLL3 modulator of claim 1 wherein said modulator reduces the frequency of tumor initiating cells upon administration to a subject in need thereof.

19. The isolated DLL3 modulator of claim 18 wherein the reduction in frequency is determined using flow cytometric analysis of tumor cell surface markers known to enrich for tumor initiating cells.

20. The isolated DLL3 modulator of claim 18 wherein the reduction in frequency is determined using immunohistochemical detection of tumor cell surface markers known to enrich for tumor initiating cells.

21. The isolated DLL3 modulator of claim 18 wherein said tumor initiating cells comprise tumor perpetuating cells.

22. The isolated DLL3 modulator of claim 1 further comprising a cytotoxic agent.

23. A pharmaceutical composition comprising the isolated DLL3 modulator of claim 1.

24. The pharmaceutical composition of claim 23 wherein said isolated DLL3 modulator comprises a monoclonal antibody.

25. The pharmaceutical composition of claim 24 wherein said monoclonal antibody comprises a humanized antibody.

26. The pharmaceutical composition of claim 25 wherein said humanized antibody comprises a cytotoxic agent.

27. The pharmaceutical composition of claim 26 wherein said cytotoxic agent comprises a pyrrolobenzodiazepine.

28. A method of treating a DLL3 associated disorder comprising administering a therapeutically effective amount of a DLL3 modulator to a subject in need thereof.

29. The method of claim 28 wherein said DLL3 modulator comprises a DLL3 antagonist.

30. The method of claim 28 wherein said DLL3 modulator comprises an antibody or immunoreactive fragment thereof.

31. The method of claim 30 wherein the antibody or immunoreactive fragment thereof comprises a monoclonal antibody.

32. The method of claim 31 wherein the monoclonal antibody is selected from the group consisting of chimeric antibodies, humanized antibodies and human antibodies.

33. The method of claim 32 wherein said monoclonal antibody comprises a light chain variable region and a heavy chain variable region wherein said light chain variable region comprises an amino acid sequence having at least 60% identity to an amino acid sequence selected from the group consisting of amino acid sequences as set forth in SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74, SEQ ID NO: 76, SEQ ID NO: 78 SEQ ID NO: 80, SEQ ID NO: 82, SEQ ID NO: 84, SEQ ID NO: 86, SEQ ID NO: 88, SEQ ID NO: 90, SEQ ID NO: 92, SEQ ID NO: 94, SEQ ID NO: 96, SEQ ID NO: 98, SEQ ID NO: 100, SEQ ID NO: 102, SEQ ID NO: 104, SEQ ID NO: 106, SEQ ID NO: 108, SEQ ID NO: 110, SEQ ID NO: 112, SEQ ID NO: 114, SEQ ID NO: 116, SEQ ID NO: 118, SEQ ID NO: 120, SEQ ID NO: 122, SEQ ID NO: 124, SEQ ID NO: 126, SEQ ID NO: 128, SEQ ID NO: 130, SEQ ID NO: 132, SEQ ID NO: 134, SEQ ID NO: 136, SEQ ID NO: 138, SEQ ID NO: 140, SEQ ID NO: 142, SEQ ID NO: 144, SEQ ID NO: 146, SEQ ID NO: 148, SEQ ID NO: 150, SEQ ID NO: 152, SEQ ID NO: 154, SEQ ID NO: 156, SEQ ID NO: 158, SEQ ID NO: 160, SEQ ID NO: 162 SEQ ID NO: 164, SEQ ID NO: 166, SEQ ID NO: 168, SEQ ID NO: 170, SEQ ID NO: 172, SEQ ID NO: 174, SEQ ID NO: 176, SEQ ID NO: 178, SEQ ID NO: 180, SEQ ID NO: 182, SEQ ID NO: 184, SEQ ID NO: 186, SEQ ID NO: 188, SEQ ID NO: 190, SEQ ID NO: 192, SEQ ID NO: 194, SEQ ID NO: 196, SEQ ID NO: 198, SEQ ID NO: 200 and SEQ ID NO: 202 and wherein said heavy chain variable region comprises an amino acid sequence having at least 60% identity to an amino acid sequence selected from the group consisting of amino acid sequences as set forth in SEQ ID NO: 21, SEQ ID NO: 23, SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 71, SEQ ID NO: 73, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 79, SEQ ID NO: 81, SEQ ID NO: 83, SEQ ID NO: 85, SEQ ID NO: 87, SEQ ID NO: 89, SEQ ID NO: 91, SEQ ID NO: 93, SEQ ID NO: 95, SEQ ID NO: 97, SEQ ID NO: 99, SEQ ID NO: 101, SEQ ID NO: 103, SEQ ID NO: 105, SEQ ID NO: 107, SEQ ID NO: 109, SEQ ID NO: 111, SEQ ID NO: 113, SEQ ID NO: 115, SEQ ID NO: 117, SEQ ID NO: 119, SEQ ID NO: 121, SEQ ID NO: 123, SEQ ID NO: 125, SEQ ID NO: 127, SEQ ID NO: 129, SEQ ID NO: 131, SEQ ID NO: 133, SEQ ID NO: 135, SEQ ID NO: 137, SEQ ID NO: 139, SEQ ID NO: 141, SEQ ID NO: 143, SEQ ID NO: 145, SEQ ID NO: 147, SEQ ID NO: 149, SEQ

ID NO: 151, SEQ ID NO: 153, SEQ ID NO: 155, SEQ ID NO: 157, SEQ ID NO: 159, SEQ ID NO: 161, SEQ ID NO: 163, SEQ ID NO: 165, SEQ ID NO: 167, SEQ ID NO: 169, SEQ ID NO: 171, SEQ ID NO: 173, SEQ ID NO: 175, SEQ ID NO: 177, SEQ ID NO: 179, SEQ ID NO: 181, SEQ ID NO: 183, SEQ ID NO: 185, SEQ ID NO: 187, SEQ ID NO: 189, SEQ ID NO: 191, SEQ ID NO: 193, SEQ ID NO: 195, SEQ ID NO: 197, SEQ ID NO: 199, SEQ ID NO: 201 and SEQ ID NO: 203.

34. The method of claim 33 wherein said monoclonal antibody is a humanized antibody.

35. The method of claim 31 wherein said monoclonal antibody comprises a neutralizing antibody.

36. The method of claim 31 wherein said monoclonal antibody comprises an internalizing antibody.

37. The method of claim 36 wherein said internalizing antibody comprises a cytotoxic agent.

38. The method of claim 37 wherein said cytotoxic agent comprises a pyrrolobenzodiazepine.

39. The method of claim 38 wherein said DLL3 associated disorder comprises a neoplastic disorder.

40. The method of claim 39 wherein said neoplastic disorder comprises a tumor exhibiting neuroendocrine features.

41. The method of claim 40 wherein said tumor exhibiting neuroendocrine features comprises a neuroendocrine tumor.

42. The method of claim 39 wherein said neoplastic disorder comprises a hematologic malignancy.

43. The method of claim 42 wherein said hematologic malignancy comprises leukemia or lymphoma.

44. The method of claim 39 wherein the subject suffering said neoplastic disorder exhibits tumors comprising tumor initiating cells.

45. The method of claim 44 further comprising the step of reducing the frequency of tumor initiating cells in said subject.

46. The method of claim 45 wherein the reduction in frequency is determined using flow cytometric analysis of tumor cell surface markers known to enrich for tumor initiating cells or immunohistochemical detection of tumor cell surface markers known to enrich for tumor initiating cells.

47. The method of claim 45 wherein the reduction in frequency is determined using *in vitro* or *in vivo* limiting dilution analysis.

48. The method of claim 47 wherein the reduction in frequency is determined using *in vivo* limiting dilution analysis comprising transplant of live human tumor cells into immunocompromised mice.

49. The method of claim 48 wherein the reduction of frequency determined using *in vivo* limiting dilution analysis comprises quantification of tumor initiating cell frequency using Poisson distribution statistics.

50. The method of claim 47 wherein the reduction of frequency is determined using *in vitro* limiting dilution analysis comprising limiting dilution deposition of live human tumor cells into *in vitro* colony supporting conditions.

51. The method of claim 50 wherein the reduction of frequency determined using *in vitro* limiting dilution analysis comprises quantification of tumor initiating cell frequency using Poisson distribution statistics.

52. The method of claim 28 further comprising the step of administering an anti-cancer agent.

53. The method of claim 28 wherein said DLL3 modulator comprises one or more CDRs from any one ofSEQ ID NOS: 20 to 203.

54. The method of claim 28 wherein said DLL3 modulator comprises a pan-DLL modulator.

55. A method of reducing the frequency of tumor initiating cells in a subject in need thereof comprising the step of administering a DLL3 modulator to said subject.

56. The method of claim 55 wherein the tumor initiating cells comprise tumor perpetuating cells.

57. The method of claim 56 wherein said tumor perpetuating cells are $CD324^+$ or $CD46^+$ cells.

58. The method of claim 55 wherein said DLL3 modulator comprises an antibody.

59. The method of claim 58 wherein said antibody comprises a monoclonal antibody.

60. The method of claim 59 wherein said monoclonal antibody further comprises a cytotoxic agent.

61. The method of claim 55 wherein the subject is suffering from a neoplastic disorder selected from the group consisting of adrenal cancer, bladder cancer, cervical cancer, endometrial cancer, kidney cancer, liver cancer, lung cancer, ovarian cancer, colorectal cancer, pancreatic cancer, prostate cancer and breast cancer.

62. The method of claim 55 wherein the frequency of tumor initiating cells is reduced by at least 10%.

63. The method of claim 55 wherein the reduction in frequency is determined using flow cytometric analysis of tumor cell surface markers known to enrich for tumor initiating cells or immunohistochemical detection of tumor cell surface markers known to enrich for tumor initiating cells.

64. A method of treating a subject suffering from a hematologic malignancy comprising the step of administering a DLL3 modulator to said subject.

65. The method of claim 64 wherein said DLL3 modulator comprises a monoclonal antibody.

66. A method of sensitizing a tumor in a subject for treatment with an anti-cancer agent comprising the step of administering a DLL3 modulator to said subject.

67. The method of claim 66 wherein said DLL3 modulator comprises an antibody.

68. The method of claim 66 wherein said tumor is a solid tumor.

69. The method of claim 66 wherein said anti-cancer agent comprises a chemotherapeutic agent.

70. The method of claim 66 wherein said anti-cancer agent comprises an immunotherapeutic agent.
71. A method of diagnosing a proliferative disorder in a subject in need thereof comprising the steps of:

a. obtaining a tissue sample from said subject;
b. contacting the tissue sample with at least one DLL3 modulator; and
c. detecting or quantifying the DLL3 modulator associated with the sample.

72. The method of claim 71 wherein the DLL3 modulator comprises a monoclonal antibody.
73. The method of claim 72 wherein the antibody is operably associated with reporter.
74. An article of manufacture useful for diagnosing or treating DLL3 associated disorders comprising a receptacle comprising a DLL3 modulator and instructional materials for using said DLL3 modulator to treat or diagnose the DLL3 associated disorder.
75. The article of manufacture of claim 74 wherein said DLL3 modulator is a monoclonal antibody.
76. The article of manufacture of claim 74 wherein the receptacle comprises a readable plate.
77. A method of treating a subject suffering from neoplastic disorder comprising the step of administering a therapeutically effective amount of at least one internalizing DLL3 modulator.
78. The method of claim 77 wherein said DLL3 modulator comprises an antibody.
79. The method of claim 78 wherein said antibody comprises a monoclonal antibody.
80. The method of claim 79 wherein the monoclonal antibody further comprises a cytotoxic agent.
81. The method of claim 80 further comprising the step of administering an anti-cancer agent.
82. A method of treating a subject suffering from neoplastic disorder comprising the step of administering a therapeutically effective amount of at least one neutralizing DLL3 modulator.
83. The method of claim 82 wherein said DLL3 modulator comprises an antibody.
84. The method of claim 83 wherein said antibody comprises a monoclonal antibody.
85. The method of claim 84 wherein said monoclonal antibody comprises a humanized antibody.
86. The method of claim 85 wherein said humanized antibody further comprises a cytotoxic agent.
87. The method of claim 82 wherein the neoplastic disorder comprises a tumor exhibiting neuroendocrine features.
88. A method of identifying, isolating, sectioning or enriching a population of tumor initiating cells comprising the step of contacting said tumor initiating cells with a DLL3 modulator.
89. The method of claim 88 wherein said DLL3 modulator comprises an antibody.
90. A DLL3 modulator comprising a humanized antibody wherein said humanized antibody comprises a light chain variable region and a heavy chain variable region wherein said light chain variable region comprises an amino acid sequence having at least 60% identity to an amino acid sequence selected from the group consisting of amino acid sequences as set forth in SEQ ID NO: 204, SEQ ID NO: 206, SEQ ID NO: 208, SEQ ID NO: 210 and SEQ ID NO: 212 and wherein said heavy chain variable region comprises an amino acid sequence having at least 60% identity to an amino acid sequence selected from the group consisting of amino acid sequences as set forth in SEQ ID NO: 205, SEQ ID NO: 207, SEQ ID NO: 209, SEQ ID NO: 211 and SEQ ID NO: 213.
91. A method inhibiting or preventing metastasis in a subject in need thereof comprising the step of administering a pharmaceutically effective amount of a DLL3 3 modulator.
92. The method of claim 91 wherein the subject undergoes a debulking procedure before or after the administration of the DLL3 modulator.
93. The method of claim 92 wherein said debulking procedure comprises the administration of at least one anti-cancer agent.
94. A method of performing maintenance therapy on a subject in need thereof comprising the step of administering a pharmaceutically effective amount of a DLL3 modulator.
95. The method of claim 94 wherein said subject was treated for a neoplastic disorder prior to the administration of the DLL3 modulator.
96. A method of depleting tumor initiating cells in a subject suffering from a proliferative disorder comprising the step of administering a DLL3 modulator.
97. A method of diagnosing, detecting or monitoring a DLL3 associated disorder *in vivo* in a subject in need thereof comprising the step of administering a DLL3 modulator.
98. A method of diagnosing, detecting or monitoring a DLL3 associated disorder in a subject in need thereof comprising the step contacting circulating tumor cells with a DLL3 modulator.
99. The method of claim 98 wherein said contacting step occurs *in vivo.*
100. The method of claim 98 wherein said contacting step occurs *in vitro.*
101. A method of treating a tumor exhibiting neuroendocrine features in a patient in need thereof comprising the step of administering a therapeutically effective amount of a DLL3 modulator.
102. The method of claim 101 wherein said tumor exhibiting neuroendocrine features is a neuroendocrine tumor.

103. A DLL3 modulator derived from an antibody selected from the group consisting of SC16.3, SC16.4, SC16.5, SC16.7, SC16.8, SC16.10, SC16.11, SC16.13, SC16.15, SC16.18, SC16.19, SC16.20, SC16.21, SC16.22, SC16.23, SC16.25, SC16.26, SC16.29, SC16.30, SC16.31, SC16.34, SC16.35, SC16.36, SC16.38, SC16.39, SC16.41, SC16.42, SC16.45, SC16.47, SC16.49, SC16.50, SC16.52, SC16.55, SC16.56, SC16.57, SC16.58, SC16.61, SC16.62, SC16.63, SC16.65, SC16.67, SC16.68, SC16.72, SC16.73, SC16.78, SC16.79, SC16.80, SC16.81, SC16.84, SC16.88, SC16.101, SC16.103, SC16.104, SC16.105, SC16.106, SC16.107, SC16.108, SC16.109, SC16.110, SC16.111, SC16.113. SC16.1141, SC16.115, SC16.116, SC16.117, SC16.118, SC16.120, SC16.121, C16.122, SC16.123, SC16.124, SC16.125, SC16.126, SC16,129, SC16.130, SC16.131, SC16.132, SC16.133, SC16.134, SC16.135, SC16.136, SC16.137, SC16.138, SC16.139, SC16.140, SC16.141, SC16.142, SC16,143, SC16.144, SC136.147, SC16,148, SC16.149 and SC16.150.

104. An isolated DLL3 modulator that binds to an epitope associated with the EGF1 domain of DLL3.

105. The DLL3 modulator of claim 104 wherein said DLL3 modulator comprises an antibody or immunoreactive fragment thereof.

106. The DLL3 modulator of claim 105 wherein said antibody or immunoreactive fragment thereof comprises a monoclonal antibody.

107. The DLL3 modulator of claim 106 wherein said DLL3 modulator comprises an ADC.

108. The DLL3 modulator of claim 107 wherein said ADC comprises a pyrrolobenzodiazepine.

109. The DLL3 modulator of claim 108 further comprising a linker.

110. An isolated DLL3 modulator that binds to an epitope associated with the EGF2 domain of DLL3.

111. The DLL3 modulator of claim 110 wherein said DLL3 modulator comprises an antibody or immunoreactive fragment thereof.

112. The DLL3 modulator of claim 111 wherein said antibody or immunoreactive fragment thereof comprises a monoclonal antibody.

113. The DLL3 modulator of claim 112 wherein said DLL3 modulator comprises an ADC.

114. The DLL3 modulator of claim 113 wherein said ADC comprises a pyrrolobenzodiazepine.

115. The DLL3 modulator of claim 114 further comprising a linker.

116. An isolated DLL3 modulator that binds to an epitope associated with the EGF3 domain of DLL3.

117. The DLL3 modulator of claim 116 wherein said DLL3 modulator comprises an antibody or immunoreactive fragment thereof.

118. The DLL3 modulator of claim 117 wherein said antibody or immunoreactive fragment thereof comprises a monoclonal antibody.

119. The DLL3 modulator of claim 118 wherein said DLL3 modulator comprises an ADC.

120. The DLL3 modulator of claim 119 wherein said ADC comprises a pyrrolobenzodiazepine.

121. The DLL3 modulator of claim 120 further comprising a linker.

122. An isolated DLL3 modulator that binds to an epitope associated with the EGF4 domain of DLL3.

123. The DLL3 modulator of claim 122 wherein said DLL3 modulator comprises an antibody or immunoreactive fragment thereof.

124. The DLL3 modulator of claim 123 wherein said antibody or immunoreactive fragment thereof comprises a monoclonal antibody.

125. The DLL3 modulator of claim 124 wherein said DLL3 modulator comprises an ADC.

126. The DLL3 modulator of claim 125 wherein said ADC comprises a pyrrolobenzodiazepine.

127. The DLL3 modulator of claim 126 further comprising a linker.

128. An isolated DLL3 modulator that binds to an epitope associated with the EGF5 domain of DLL3.

129. The DLL3 modulator of claim 128 wherein said DLL3 modulator comprises an antibody or immunoreactive fragment thereof.

130. The DLL3 modulator of claim 129 wherein said antibody or immunoreactive fragment thereof comprises a monoclonal antibody.

131. The DLL3 modulator of claim 130 wherein said DLL3 modulator comprises an ADC.

132. The DLL3 modulator of claim 131 wherein said ADC comprises a pyrrolobenzodiazepine.

133. The DLL3 modulator of claim 132 further comprising a linker.

134. An isolated DLL3 modulator that binds to an epitope associated with the EGF6 domain of DLL3.

135. The DLL3 modulator of claim 134 wherein said DLL3 modulator comprises an antibody or immunoreactive fragment thereof.

136. The DLL3 modulator of claim 135 wherein said antibody or immunoreactive fragment thereof comprises a monoclonal antibody.

137. The DLL3 modulator of claim 136 wherein said DLL3 modulator comprises an ADC.

138. The DLL3 modulator of claim 137 wherein said ADC comprises a pyrrolobenzodiazepine.

139. The DLL3 modulator of claim 138 further comprising a linker.

140. An isolated DLL3 modulator that binds to an epitope associated with the DSL domain of DLL3.
141. The DLL3 modulator of claim 140 wherein said DLL3 modulator comprises an antibody or immunoreactive fragment thereof.
142. The DLL3 modulator of claim 141 wherein said antibody or immunoreactive fragment thereof comprises a monoclonal antibody.
143. The DLL3 modulator of claim 142 wherein said DLL3 modulator comprises an ADC.
144. The DLL3 modulator of claim 143 wherein said ADC comprises a pyrrolobenzodiazepine.
145. The DLL3 modulator of claim 144 further comprising a linker.
146. An isolated DLL3 modulator that binds to an epitope associated with the N-terminal domain of DLL3.
147. The DLL3 modulator of claim 146 wherein said DLL3 modulator comprises an antibody or immunoreactive fragment thereof.
148. The DLL3 modulator of claim 147 wherein said antibody or immunoreactive fragment thereof comprises a monoclonal antibody.
149. The DLL3 modulator of claim 148 wherein said DLL3 modulator comprises an ADC.
150. The DLL3 modulator of claim 149 wherein said ADC comprises a pyrrolobenzodiazepine.
151. The DLL3 modulator of claim 150 further comprising a linker.
152. An isolated DLL3 modulator residing in a bin selected from the group consisting of bin A, bin B, bin C, bin D, bin E, bin F, bin G, bin H and bin I.
153. An isolated DLL3 modulator residing in a bin defined by a reference antibody selected from the group consisting of SC16.3, SC16.4, SC16.5, SC16.7, SC16.8, SC16.10, SC16.11, SC16.13, SC16.15, SC16.18, SC16.19, SC16.20, SC16.21, SC16.22, SC16.23, SC16.25, SC16.26, SC16.29, SC16.30, SC16.31, SC16.34, SC16.35, SC16.36, SC16.38, SC16.39, SC16.41, SC16.42, SC16.45, SC16.47, SC16.49, SC16.50, SC16.52, SC16.55, SC16.56, SC16.57, SC16.58, SC16.61, SC16.62, SC16.63, SC16.65, SC16.67, SC16.68, SC16.72, SC16.73, SC16.78, SC16.79, SC16.80, SC16.81, SC16.84, SC16.88, SC16.101, SC16.103, SC16.104, SC16.105, SC16.106, SC16.107, SC16.108, SC16.109, SC16.110, SC16.111, SC16.113, SC16.114, SC16.115, SC16.116, SC16.117, SC16.118, SC16.120, SC16.121, SC16.122, SC16.123, SC16.124, SC16.125, SC16.126, SC16,129, SC16.130, SC16.131, SC16.132, SC16.133, SC16.134, SC16.135, SC16.136, SC16-137, SC16.138, SC16.139, SC16,140, SC16.141, SC16.142, SC16.143, SC16.144, SC16.147, SC16.148, SC16.149 and SC16.150.
154. An antibody drug conjugate of the formula:

M-[L-D]n

or a pharmaceutically acceptable salt thereof wherein

a) M comprises a DLL3 modulator;
b) L comprises an optional linker;
c) D is a anti-proliferative agent; and
d) n is an integer from about 1 to about 20.

155. The antibody drug conjugate of claim 154 wherein said DLL3 modulator comprises an antibody or immunoreactive fragment thereof.
156. The antibody drug conjugate of claim 155 wherein said antibody comprises a monoclonal antibody.
157. The antibody drug conjugate of claim 156 wherein said antibody is derived from an antibody selected from the group consisting of SC16.3, SC16.4, SC16.5, SC16.7, SC16.8, SC16.10, SC16.11, SC16.13, SC16.15, SC16.18, SC16.19, SC16.20, SC16.21, SC16.22, SC16.23, SC16.25, SC16.26, SC16.29, SC16.30, SC16.31, SC16.34, SC16.35, SC16.36, SC16.38, SC16.39, SC16.41, SC16.42, SC16.45, SC16.47, SC16.49, SC16.50, SC16.52, SC16.55, SC16.56, SC16.57, SC16.58, SC16.61, SC16.62, SC16.63, SC16.65, SC16.67, SC16.68, SC16.72, SC16.73, SC16.78, SC16.79, SC16.80, SC16.81, SC16.84, SC16.88, SC16.101, SC16.103, SC16.104, SC16.105, SC16.106, SC16.107, SC16.108, SC16.109, SC16.110, SC16.111, SC16.113, SC16.114, SC16.115, SC16.116, SC16.117, SC16.118, SC16.120, SC16.121, SC16.122, SC16.123, SC16.124, SC16.125, SC16.126, SC16.129, SC16.130, SC16.131, SC16.132, SC16.133, SC16.134, SC16.135, SC16.136, SC16.137, SC16.138, SC16.139, SC16.140, SC16.141, SC16.142, SC16.143, SC16.144, SC16.147, SC16.148, SC16.149 and SC16.150,
158. The antibody drug conjugate of claim 157 wherein said antibody is humanized.
159. The antibody drug conjugate of claim 154 wherein the linker comprises a cleavable linker.
160. The antibody drug conjugate of claim 59 wherein said cleavable linker comprises a peptidyl linker.
161. The antibody drug conjugate of claim 154 wherein said anti-proliferative agent comprises a cytotoxic agent.
162. The antibody drug conjugate of claim 161 wherein said cytotoxic agent comprises a pyrrolobenzodiazepine.
163. The antibody drug conjugate of claim 162 wherein said pyrrolobenzodiazepine comprises a pyrrolobenzodi-

azepine dimer,

164. A DLL3 modulator comprising a CDR from any one ofSEQ ID NOS: 20-203.

165. The DLL3 modulator of claim 164 wherein said modulator comprises a plurality of CDRs from any one ofSEQ ID NOS: 20-203.

166. A DLL3 antibody modulator that competes for binding to a DLL3 protein with a reference antibody selected from the group consisting of SC16.3, SC16.4, SC16.5, SC16.7, SC16.8, SC16.10, SC16.11, SC16.13, SC16.15, SC16.18, SC16.19, SC16.20, SC16.21, SC16.22, SC16.23, SC16.25, SC16.26, SC16.29, SC16.30, SC16.31, SC16.34, SC16.35, SC16.36, SC16.38, SC16.39, SC16.41, SC16.42, SC16.45, SC16.47, SC16.49, SC16.50, SC16.52, SC16.55, SC16.56, SC16.57, SC16.58, SC16.61, SC16.62, SC16.63, SC16.65, SC16.67, SC16.68, SC16.72, SC16.73, SC16.78, SC16.79, SC16.80, SC16.81, SC16.84, SC16.88, SC16.101, SC16.103, SC16.104, SC16.105, SC16.106, SC16.107, SC16.108, SC16.109, SC16.110, SC16.111, SC16.113, SC16.114, SC16.115, SC16.116, SC16.117, SC16.118, SC16.120, SC16.121, SC16.122, SC16.123, SC16.124, SC16.125, SC16.126, SC16.129, SC16.130, SC16.131, SC16.132, SC16.133, SC16.134, SC16.135, SC16.136, SC16.137, SC16.138, SC16.139, SC16.140, SC16.141, SC16.142, SC16.143, SC16.144, SC16.147, SC16.148, SC16.149 and SC16.150 wherein binding of the DLL3 antibody modulator to the DLL3 protein is inhibited by at least 30%.

167. A DLL3 modulator that binds to a DLL3 protein epitope comprising amino acids Q93, P94, G95, A96 and P97 (SEQ ID NO: 9).

168. A DLL3 modulator that binds to a DLL3 protein epitope comprising amino acids G203, R205 and P206 (SEQ ID NO: 10).

EXAMPLES

[0488] The present invention, thus generally described above, will be understood more readily by reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the instant invention. The examples are not intended to represent that the experiments below are all or the only experiments performed. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1

Analysis of Marker Expression in Selected Tumors with Neuroendocrine Features

[0489] Neuroendocrine tumors (NETs) arising from the dispersed endocrine system are rare, with an incidence of 2-5 per 100,000 people, but highly aggressive. Neuroendocrine tumors occur in the adrenal gland, kidney, genitourinary tract (bladder, prostate, ovary, cervix, and endometrium), pancreas, gastrointestinal tract (stomach and colon), thyroid (medullary thyroid cancer), and lung (small cell lung carcinoma, large cell neuroendocrine carcinoma, and carcinoid). These tumors may secrete several hormones including serotonin and/or chromogranin A that can cause debilitating symptoms known as carcinoid syndrome. These tumors can be denoted by positive immunohistochemical markers such as neuron-specific enolase (NSE, also known as gamma enolase, gene symbol = ENO2), CD56/NCAM1, and synaptophysin. Traditional chemotherapies have not been successful in treating NETs, and mortality due to metastatic spread is a common outcome. Unfortunately, in most cases surgery is the only potential curative treatment, provided it takes place following early detection and prior to tumor metastasis. In this context work was undertaken to identify novel therapeutic targets associated with tumors comprising neuroendocrine features.

[0490] To identify and characterize such tumors as they exist in cancer patients a large non-traditional xenograft (NTX) tumor bank was developed and maintained using art-recognized techniques. The NTX tumor bank, comprising a substantial number of discrete tumor cell lines, was propagated in immunocompromised mice through multiple passages of heterogeneous tumor cells originally obtained from numerous cancer patients afflicted by a variety of solid tumor malignancies. (Note that in some of the Examples and FIGS. herein the passage number of the tested sample is indicated by p0-p# appended to the sample designation where p0 is indicative of an unpassaged sample obtained directly from a patient tumor and p# is indicative of the number of times the tumor has been passaged through a mouse prior to testing.) The continued availability of a large number of discrete early passage NTX tumor cell lines having well defined lineages greatly facilitate the identification and characterization of cells purified from the cell lines. In such work the use of minimally passaged cell lines simplifies *in vivo* experimentation and provides readily verifiable results. Moreover, early passage NTX tumors respond to therapeutic agents such as irinotecan (i.e. Camptosar®) and Cisplatin/Etoposide regimens, which provides clinically relevant insights into underlying mechanisms driving tumor growth, resistance to current therapies and tumor recurrence.

[0491] As the NTX tumor cell lines were established, their phenotype was characterized in various ways to examine global gene expression. To identify which NTX lines in the bank might be NETs, gene expression profiles were generated

by whole transcriptome sequencing and/or microarray analysis. Specifically, the data was examined to identify tumors expressing high levels of specific genes known to be elevated in NETs or used as histochemical markers of neuroendocrine differentiation (e.g., ASCL1, NCAM1, CHGA) as well as tumors with changes in NOTCH pathway genes indicative of suppression of NOTCH signaling (e.g., reduced levels of NOTCH receptors, and changes to ligands and effector molecules).

[0492] More particularly, upon establishing various NTX tumor cell lines as is commonly done for human tumors in severely immune compromised mice, the tumors were resected after reaching 800 - 2,000 mm^3 and the cells were dissociated and dispersed into suspension using art-recognized enzymatic digestion techniques (see, for example, U.S.P.N. 2007/0292414 which is incorporated herein). The dissociated cell preparations from these NTX lines were then depleted of murine cells, and human tumor cell subpopulation were then further isolated by fluorescence activated cell sorting and lysed in RLTplus RNA lysis buffer (Qiagen). These lysates were then stored at -80°C until used. Upon thawing, total RNA was extracted using a RNeasy isolation kit (Qiagen) following the vendor's instructions and quantified on a Nanodrop spectrophotometer (Thermo Scientific) and a Bioanalyzer 2100 (Agilent Technologies) again using the manufacturer's protocols and recommended instrument settings. The resulting total RNA preparations were suitable for genetic sequencing and gene expression analysis.

[0493] Whole transcriptome sequencing using an Applied Biosystems (ABI) SOLiD (Sequencing by Oligo Ligation/Detection) 4,5 or SOLiD 5500xl next generation sequencing system (Life Technologies) was performed on RNA samples from NTX lines. cDNA was generated from total RNA samples using either a modified whole transcriptome (WT) protocol from ABI designed for low input total RNA or Ovation RNA-Seq System V2™ (NuGEN Technologies Inc.). The modified low input WT protocol uses 1.0 ng of total RNA to amplify mRNA at the 3' end which leads to a heavy 3' bias of mapped gene expression, while NuGen's system allows for a more consistent amplification throughout the transcript, and includes amplification of both mRNA and non-polyadenylated transcript cDNA using random hexamers. The cDNA library was fragmented, and barcodes adapters were added to allow pooling of fragment libraries from different samples.

[0494] ABI's SOLiD 4.5 and SOLiD 5500xl next generation sequencing platforms enables parallel sequencing of transcriptomes from multiple NTX lines and sorted populations. A cDNA library is constructed from each RNA sample, which is fragmented and barcoded. Barcodes on each fragment library allow multiple samples to be pooled at equal concentrations and run together while ensuring sample specificity. The samples are taken through emulsion PCR using ABI's SOLiD™ EZ Bead™ robotics system, which ensures sample consistency. Paired-end sequencing generates a 50 base read in the 5' to 3' direction and a 25 base read in the 3' to 5' direction for each clonally amplified fragment on a single bead that exists in the pool. In the case of the 5500xl platform, for every set of 8 samples pooled in the method mentioned above, beads are evenly deposited into 6 single channel lanes on a single chip. This will, on average, generate more than 50 million 50 base reads and 50 million 25 base reads for each of the 8 samples and generates a very accurate representation of mRNA transcript level in the tumor cells. Data generated by the SOLiD platform mapped to 34,609 genes as annotated by RefSeq version 47 using NCBI version hg19.2 of the published human genome and provided verifiable measurements of RNA levels in most samples.

[0495] The SOLiD platform is able to capture not only expression, but SNPs, known and unknown alternative splicing events, small non-coding RNAs, and potentially new exon discoveries based solely on read coverage (reads mapped uniquely to previously un-annotated genomic locations). Thus, use of this next generation sequencing platform paired with proprietary data analysis and visualization software thus allowed for discovery of differential transcript expression as well as differences and/or preferences for specific splice variants of expressed mRNA transcripts. Sequencing data from the SOLiD platform is nominally represented as a transcript expression value using the metrics RPM (reads per million) and RPKM (read per kilobase per million), enabling basic differential expression analysis as is standard practice.

[0496] Whole transcriptome sequencing of four small cell lung cancer (SCLC) tumors (LU73, LU64, LU86 and LU95), one ovarian tumor (OV26) and a large cell neuroendocrine carcinoma (LCNEC; LU37) resulted in the determination of gene expression patterns commonly found in NETs (FIG. 4A). More specifically, these tumors had high expression of several NET markers (ASCL1, NCAMI CHGA) as well as reduced levels of Notch receptors and effector molecules (e.g., HES1, HEY1) and elevated markers of Notch suppression (e.g., DLL3 and HES6). In contrast, 4 normal lung samples, 3 lung adenocarcinoma tumors (LU137, LU146 and LU153), and 3 squamous cell lung carcinomas (LU49, LU70 and LU76) all have expression of various Notch receptors and effector molecules, and do not show elevated expression of Notch suppressors such as HES6 and DLL3.

[0497] After identifying which NTX in the tumor bank are NETs, each was analyzed using whole transoriptome sequencing data to find potential therapeutic targets upregulated in NETs when compared to non-NETs (including LU_SCC, LU_Ad, and normal lung). High expression of DLL3 was found in NET NTX tumors including SCLC, LCNEC, and OV26, compared to low to non-existent expression in normal lung, normal ovary, other OV NTX, LU_Ad and LU_SCC NTX lines (FIG 4B). High expression of DLL3 in NETs relative to a variety of normal tissue types was of great interest, as DLL3 is a known suppressor of Notch signaling. Given this, and in view of the generated data, DLL3 was selected for further analysis as a potential immunotherapeutic target.

[0498] With the discovery that DLL3 may prove to be a viable target for modulation and treatment of certain proliferative

disorders, work was undertaken to determine the expression pattern and levels of DLL3 variants. As discussed above, there are two known splice variants of DLL3 encoding proteins which differ only in that isoform 1 has an extended intracellular C-terminus (FIG. IE). More specifically isoform 2 is a 587 amino acid protein (FIG. 1D; SEQ ID NO: 4) encoded by mRNA variant 2 (FIG. 1B: SEQ ID NO: 2), which contains exons 8a and 8c while isoform 1 is a 618 amino acid protein (FIG. 1C; SEQ ID NO: 3) encoded by mRNA variant 1 (FIG. 1A; SEQ ID NO: 1), which contains exon 8b. A schematic diagram illustrating the identical extracellular domain (ECD) of isoform 1 and isoform 2 in presented in FIG. 1F.

[0499] Again, using the whole transcriptome data obtained as described above, selected NET tumors were examined to determine the expression patterns of the aforementioned exons which, by extension, provides the expression ratio of the two isoforms. As shown in FIG. 5 it was found that while the particular expression ratio between the two isoforms may vary somewhat, isoform 1 expression was predominant in each tumor. In this respect it is important to note that, as described above, the cumulative DLL3 expression (both isoforms) in each of the tested tumors was elevated with regard to normal tissues. Accordingly, while isoform ratios may be indicative of certain tumor types and relevant to genotype modulator selection it is not as critical with regard to phenotypic modulator strategies. That is, because the ECD region of both DLL3 isoforms are identical, it is expected that a phenotypic modulator of the instant invention directed to the ECD region (e.g., an anti-DLL3 antibody) would react with either isoform. Thus it is the absolute expression levels of the DLL3 ECD (regardless of isoform) that is dispositive as to the effectiveness of such strategies.

Example 2

Microarray and RT-PCR Analysis of Gene Expression in Selected NTX Tumors with Neuroendocrine Features

[0500] In an effort to identify additional NETs in the aforementioned NTX bank beyond those for which SOLiD whole transcriptome data existed, a larger set of NTX lines was examined using microarray analysis. Specifically, 2-6μg of total RNA samples derived from whole tumors in 46 NTX lines or from 2 normal tissues were analyzed using a OneArray® microarray platform (Phalanx Biotech Group), which contains 29,187 probes designed against 19,380 genes in the human genome. More specifically, RNA samples were obtained (as described in Example 1) from forty-six patient derived whole NTX tumors comprising colorectal (CR), melanoma (SK), kidney (KD), lung (LU), ovarian (OV), endometrial (EM), breast (BR), liver (LIV), or pancreatic (PA) cancers. Normal colorectal (NormCR) and normal pancreas (NormPA) tissues were used as controls. Still more specifically, lung tumors were further subclassified as small cell lung cancers (SCLC), squamous cell cancers (SCC), or large cell neuroendocrine carcinoma (LCNEC). RNA samples were run in triplicate using the manufacturer's protocols and the resulting data was analyzed using standard industry practices for normalizing and transforming the measured intensity values obtained for the subject gene in each sample. An unbiased Pearson Spearman hierarchical clustering algorithm in the R/BioConductor suite of packages called hclust.2 was used to create a standard microarray dendrogram for these 48 samples. As known in the art R/BioConductor is an open-source, statistical programming language widely used in academia, finance and the pharmaceutical industry for data analysis. Generally the tumors were arranged and clustered based on gene expression patterns, expression intensity, etc.

[0501] As shown in FIG. 6A, the dendrogram derived from the 48 samples and across all 19380 genes, clustered NTX lines together based upon their tumor type or tissue of origin. Several tumors typically associated with neuroendocrine phenotypes clustered together on the branch denoted by (1); these included skin cancers, numerous lung cancers and other NETs. Interestingly, a sub-branch, denoted by (2), showed that two large cell lung cancers with neuroendocrine features (LU50.LCNEC and LU37.LCNEC) and a small cell lung cancer (LU102.SCLC) clustered with an ovarian (OV26) and a kidney (KD66) tumor (cluster C) suggesting these later tumors also possessed neuroendocrine phenotypes. Moreover, FIG. 6A shows cluster D which consists of 3 additional SCLC tumors, and to its right is a small cluster containing an additional SCLC NTX (LU100) and a neuroendocrine endometrial tumor (BM6), all expected to possess some neuroendocrine features as is generally understood from the literature and pathology experience in the clinic. The fact that cluster G, comprised of squamous cell carcinomas of the lung, can be found on a completely different branch of the dendrogram of FIG. 6A indicates that the clustering is not driven exclusively by the organ of origin for the tumor.

[0502] Closer inspection of a collection of gene markers associated with NETs (FIG. 6B) shows that they are strongly expressed in tumors comprising clusters C and D, white they are minimally expressed in tumors in Cluster G (squamous cell carcinoma of the lung), suggesting clusters C and D represent NETs or tumors with a neuroendocrine phenotype. More specifically, cluster C NETs highly express ASCL1, CALCA, CHGA, SST and NKX2-1, while cluster D NETs highly express CHGA, ENO2, and NCAM1, and it is the expression of these neuroendocrine phenotype genes that is in part responsible for the clustering of these tumors. An interesting feature is the strong expression of KIT in cluster D, a gene occasionally reported to be associated with neuroendocrine tumors, but clearly linked to oncogenesis in other contexts. This is in contrast to the SCC tumors in cluster G which lack strong expression any of these genes (FIG. 6B).

[0503] With regard to Notch signaling, tumors in cluster C show a phenotype consistent with a reduction in Notch signaling: a lack of expression of any Notch receptors, a relative lack of JAG1 and HES1 expression, and strong levels of ASCL1 expression (FIG. 6C). Interestingly, cluster D shows high expression of HES6, a transcription factor that can

support ASCL1 activity by antagonizing HES1 activity through heterodimer formation. Most importantly, these microarray data show high levels of DLL3 transcription in tumors in clusters C and D (relative to cluster G), suggesting that in these tumor types, DLL3 provides an attractive therapeutic target for treatment of NETs,

[0504] In view of the aforementioned results, mRNA expression of HES6 was examined from various NTX lines and normal tissues using an Applied Biosystems 7900HT Machine (Life Technologies) to perform Taqman real-time quantitative RT-PCR (qRT-PCR) in accordance with the manufacturer's protocols. RNA was isolated as described above and checked to ensure quality was suitable for gene expression analysis. RNA from normal tissues was purchased (Agilent Technologies and Life Technologies). 200 ng of RNA was used for cDNA synthesis using the cDNA archive kit (Life Technologies). cDNA was used for qRT-PCR analysis on Taqman Low Density Arrays (TLDA; Life Technologies) which contained the HES6 Taqman assay to measure mRNA levels of HES6.

[0505] HES6 mRNA levels are shown for each NTX line or normal tissue sample (single dot on graph) after normalization to endogenous controls. Normalized values are plotted relative to the average expression in the normal tissues of toxicity concern (NormTox). This technique allowed for the rapid identification and characterization of a variety of tumors having neuroendocrine features from the NTX tumor bank through measurement of HES6 and other relevant markers. FIG. 6D illustrates general overexpression of HES6 in the sampled tumors with neuroendocrine features (e.g., LU-SCLC, LU-LCNEC) compared to normal tissues, breast, colon, liver and other selected tumors. Significantly these microarray and qPCR data show that at least some endometrial, kidney and ovarian tumors may exhibit neuroendocrine tumor features (FIGS. 6A and 6D).

Example 3

RT- PCR Analysis of DLL3 in Tumors with Neuroendocrine Features

[0506] To confirm the generated SOLID and microarray data and extend the analysis to additional NTX samples, DLL3 mRNA expression was analyzed by qRT-PCR using RNA samples from various NTX lines, primary biopsies and normal tissues. The analysis was again performed using an Applied Biosystems 7900HT Machine (Life Technologies) substantially as described immediately above but optimized for DLL3 detection. DLL3 expression is shown relative to the average expression in normal tissues and normalized to expression of the endogenous control gene ALAS1. As seen in FIG. 7, qRT-PCR interrogation of gene expression showed that DLL3 mRNA is elevated more than 10,000,000-fold in NET populations versus normal tissues. In this Example the sampled tumors include additional SCLC NTX lines beyond those tested previously as well as a number of RNA samples derived from primary biopsies (p0). Taken together these data demonstrate that DLL3 gene expression is dramatically upregulated in tumors exhibiting neuroendocrine features and, given that the same pattern is seen in primary biopsy samples, that the observed upregulation is not an artifact of growing human tumors in mice.

[0507] In addition, three subtypes ofNSCLC as defined by clinical pathology are also represented in FIG. 7. LU25 is a spindle cell lung carcinoma, LU50 is a large cell neuroendocrine carcinoma (LCNEC), and LU85 is a squamous cell carcinoma (SCC). The highest DLL3 expression was seen in the LCNEC tumor LU50, though elevated levels were also noted in the SCC and spindle cell tumors. KDY66 and OV26, a kidney and ovarian tumor, respectively, clustered on the microarray with SCLC and LCNEC tumors (FIG. 6A), suggesting they comprise tumors exhibiting neuroendocrine features (i.e., NETs or pNETs). Such a conclusion is corroborated by the high mRNA levels of DLL3 seen in both tumor samples (FIG. 7). While all of the tumors display a striking upregulation of DLL3 mRNA relative to normal tissues (FIG. 7), comparison of tumors found both on FIGS. 6A and 7 shows that subtle differences in measured DLL3 mRNA expression in FIG. 7 correspond to differential clustering in FIG. 6A; e.g., cluster C contains KD66, LU50, OV26 and LU102, which are at the high end of DLL3 expression as shown on FIG 7, whereas LU85 and LU100, each of which cluster away from clusters C and D in FIG. 6A, are among the lower end of DLL3 expression for the tumor samples measured. Small cell lung cancer tumors in cluster D in FIG. 6A (e.g., LU86, LU64, and LU95) show intermediate levels of DLL3 mRNA expression and may very well be susceptible to treatment with the modulators of the instant invention.

Example 4

Expression of DLL3 mRNA and Protein in Various Tumor Specimens

[0508] To extend the analysis of DLL3 expression to a wider array of tumor specimens, Taqman qRT-PCR was performed substantially as described in the previous Examples on a TissueScan™ qPCR (Origene Technologies) 384-well array. This array enables comparison of gene expression across 18 different solid tumor types, with multiple patient derived samples for each tumor type and from normal adjacent tissue.

[0509] In this regard, FIGS. 8A and 8B show the relative and absolute gene expression levels, respectively, of DLL3 in whole tumor specimens (grey dots) or normal adjacent tissue (NAT; white dots) from patients with one of eighteen

different solid tumor types. Data is normalized in FIG. 8A against mean gene expression in NAT for each tumor type analyzed. Specimens in which DLL3 was not detected were assigned a Ct value of 50, which represents the last cycle of amplification in the experimental protocol. Each dot represents a single tissue specimen, with the geometric mean value represented as a black line. Using this Origene TissueScan Array, overexpression of DLL3 was seen in a subset of adrenal breast, cervical, endometrial, lung, ovarian, pancreatic, thyroid and bladder cancer, many of which may represent NETs or tumors with poorly differentiated neuroendocrine phenotypes. A subset of lung tumors showed the greatest overexpression of DLL3. The highest expression was seen in 2 LCNEC tumors on the array. As shown by the absolute gene expression in FIG. 8B, normal testis is the only normal tissue with high expression of DLL3. This suggests that DLL3 expression in NETs and other tumorigenic cells might play a role in tumorigenesis and/or tumor progression in a wide variety of tumors.

[0510] Given the elevated DLL3 transcript levels associated with various tumors, work was undertaken to demonstrate a corresponding increase in the expression of DLL3 protein in NETs relative to other tumors. To this end a DLL3 sandwich ELISA was developed using the MSD Discovery Platform (Meso Scale Discovery, LLC) to detect and quantify DLL3 expression in selected NTX tumor samples. Briefly, NTX tumor samples were lysed and total protein concentration, as well as DLL3 protein concentration, were measured in the lysates using an electrochemiluminescence detection based sandwich ELISA format. More specifically, DLL3 concentrations from the samples were interpolated from electrochemoiluminescent values using a standard curve generated from purified recombinant protein and are expressed in FIG. 8C as nanograms of DLL3 per milligram of total protein.

[0511] More specifically NTX tumors were excised from mice and flash frozen on dry ice/ethanol. Protein Extraction Buffer (Biochain Institute, Inc.) was added to the thawed tumor pieces and tumors were pulverized using a Tissue Lyser system (Qiagen). Lysates were cleared by centrifugation (20,000g, 20 minutes, 4°C) and protein was quantified using bicinchoninic acid (BCA). Protein lysates were stored at -80C until assayed.

[0512] MSD standard plates (Meso Scale Discovery, LLC) were coated overnight at 4°C with 30μl of SC16.34 antibody (obtained as set forth in Example 7 below) at 2μg/ml in PBS. Plates were washed in PBST and blocked in 150ul MSD 3% Blocker A solution for 1 hour. Plates were again washed in PBST. 25μl of the SC16.4 antibody (obtained as set forth in Example 7 below) conjugated to the MSD sulfo-tag and was added to the washed plates at 0.5μg/ml in MSD 1% Blocker A. 25μl of 10x diluted lysate in MSD 1% Blocker A or serially diluted recombinant DLL3 standard in MSD 1% Blocker A containing 10% Protein Extraction Buffer was also added to the wells and incubated for 2 hours. Plates were washed in PBST. MSD Read Buffer T with surfactant was diluted to 1X in water and 150μl was added to each well. Plates were read on a MSD Sector Imager 2400 using an integrated software analysis program to derive DLL3 concentrations in NTX samples via interpolation. Values were then divided by total protein concentration to yield nanograms of DLL3 per milligram of total lysate protein. The resulting concentrations are set forth in FIG. 8C wherein each spot represents concentrations derived from a single NTX tumor line. While each spot is derived from a single NTX line, in most cases multiple biological samples were tested from the same NTX line and values were averaged to provide the data point.

[0513] In any event FIG. 8C shows that the highest expression of DLL3 was found in SCLC, LCNEC, as well as other neuroendocrine tumors including selected kidney samples and a single ovarian tumor. FIG. 8C also demonstrates that certain melanoma NTX lines exhibited elevated DLL3 protein expression which is particularly interesting in that these NTX lines also clustered near NET NTX lines in the microarray analysis conducted in Example 4 (FIG. 6A).

[0514] These data, combined with the transcription data for DLL3 expression set forth above strongly reinforces the proposition that DLL3 determinants provide attractive targets for therapeutic intervention.

Example 5

Expression of NOTCH Receptors and Delta-like Ligands on the Cell Surface of Selected NTX Tumor Lines

[0515] To further extend the observations from Examples 1 and 2 above, cells isolated from several NTX tumors found in Clusters C and D (KDY66, OV26, LU64; FIG 6A) as well as a SCLC tumor determined to have high expression of DLL3 by SOLiD sequencing or qRT-PCR (LU73, FIGS. 4 and 7) were analyzed using flow cytometry for determination of the levels of protein expression for various Notch receptors and other DLL family members. Generally flow cytometry-based protein expression data was generated using a FACSCanto II (BD Biosciences) as per the manufacturer's instructions. Data in FIG. 9 shows individual tumor cells displayed as histogram plots, wherein the background staining of isotype control antibodies is shown in the gray, filled histograms and expression of the protein of interest, as determined using commercially available antibodies is displayed by the bold, black line.

[0516] As can be seen graphically in FIG. 9, little to no expression of any of the Notch receptors (e.g., NOTCH1-4) was observed in any of these tumors, as determined relative to fluorescence minus one (FMO) isotype-control stained cells. This is indicated graphically by the histograms, as well as numerically in the reported mean fluorescence intensities (MFI) for each measurement. Similarly, the two lung cancer derived NTX cells showed no expression of either DLL1 or

DLL4. Slight expression of DLL4 alone (OV26) or DLL1 and DLL4 (KDY66) could be observed for two of the tumors. In general, these observations confirm the results obtained and presented in Examples 1 and 2 above, that these tumor types show little to no expression of Notch signaling pathway components, consistent with loss of Notch signaling in NETs or poorly differentiated tumors with neuroendocrine phenotypes.

Example 6

Generation of anti-DLL3 Modulators

[0517] DLL3 modulators in the form of murine antibodies were produced in accordance with the teachings herein through inoculation with recombinant human DLL3-Fc or with human DLL3-His (each comprising the mature ECD of DLL3 set forth in FIG. 1C; SEQ ID NO: 3) in two separate immunization campaigns. In this regard three strains of mice (Balb/c, CD-1 and FVB) were inoculated with human recombinant DLL3 to provide hybridomas secreting high affinity, murine monoclonal antibody modulators.

[0518] The hDLL3-Fc fusion construct was obtained from Adipogen International (Catalog No. AG-40A-0113) where it had been purified from the supernatant of DLL3-Fc overexpressing HEK 293 cells as described in the manufacturer's product data sheet. Recombinant hDLL3-His protein was purified from the supernatants of CHOK1 cells engineered to overexpress hDLL3-His. 10 μg of hDLL3-Fc or hDLL3-His immunogen was emulsified with an equal volume of TITER-MAX® Gold (CytRx Corporation) or alum adjuvant and used for the immunization of each mouse. The resulting emulsions were then injected into three female mice (1 each: Balb/c, CD-1 and FVB) via the footpad route.

[0519] Solid-phase ELISA assays were used to screen mouse sera for mouse IgG antibodies specific for human DLL3. A positive signal above background was indicative of antibodies specific for DLL3. Briefly, 96 well plates (VWR International, Cat. #610744) were coated with recombinant DLL3-His at 0.5μg/ml in ELISA coating buffer overnight. After washing with PBS containing 0.02% (v/v) Tween 20, the wells were blocked with 3% (w/v) BSA in PBS, 200 μL/well for 1 hour at room temperature (RT). Mouse serum was titrated (1:100, 1:200, 1:400, and 1:800) and added to the DLL3 coated plates at 50 μL/well and incubated at RT for 1 hour. The plates are washed and then incubated with 50 μL/well HRP-labeled goat anti-mouse IgG diluted 1:10,000 in 3% BSA-PBS or 2% FCS in PBS for 1 hour at RT. Again the plates were washed and 40 μL/well of a TMB substrate solution (Thermo Scientific 34028) was added for 15 minutes at RT. After developing, an equal volume of 2N H_2SO_4 was added to stop substrate development and the plates were analyzed by spectrophotometer at OD 450.

[0520] Sera-positive immunized mice were sacrificed and draining lymph nodes (popliteal and inguinal, and medial iliac if enlarged) were dissected out and used as a source for antibody producing cells. A single cell suspension of B cells (228.9x10^6 cells) was fused with non-secreting P3x63Ag8.653 myeloma cells (ATCC #CRL-1580) at a ratio of 1:1 by electrofusion. Electrofusion was performed using the BTX Hybrimmune™ System, (BTX Harvard Apparatus) as per the manufacturer's directions. After the fusion procedure the cells were resuspended in hybridoma selection medium supplemented with Azaserine (Sigma #A9666), high glucose DMEM medium with sodium pyruvate (Cellgro cat#15-017-CM) containing 15% Fetal Clone I serum (Hyclone), 10% BM Condimed (Roche Applied Sciences), 4 mM L-glutamine, 100 IU Penicillin-Streptomycin and 50 μM 2-mercaptoethanol and then plated in three T225 flasks in 90 mL selection medium per flask. The flasks were then placed in a humidified 37°C incubator containing 5% CO_2, and 95% air for 6-7 days.

[0521] After six to seven days of growth the library consisting of the cells grown in bulk in the T225s was plated at 1 cell per well in Falcon 96 well U-bottom plates using the Aria I cell sorter. The selected hybridomas were then grown in 200 μL of culture medium containing 15% Fetal Clone I serum (Hyclone), 10% BM-Condimed (Roche Applied Sciences), 1 mM sodium pyruvate, 4 mM L-glutamine, 100 IU Penicillin-Streptamycin, 50 μM 2-mercaptoethanol, and 100 μM hypoxanthine. Any remaining unused hybridoma library cells were frozen for future library testing. After ten to eleven days of growth supernatants from each well of the plated cells were assayed for antibodies reactive for DLL3 by ELISA and FACS assays.

[0522] For screening by ELISA 96 well plates were coated with denatured human DLL3 or cell lysates of 293 cells overexpressing human DLL3 (obtained as discussed below), in sodium carbonate buffer overnight at 4°C. The plates were washed and blocked with 3% BSA in PBS/Tween for one hour at 37°C and used immediately or kept at 4°C. Undiluted hybridoma supernatants were incubated on the plates for one hour at RT. The plates were washed and probed with HRP labeled goat anti-mouse IgG diluted 1:10,000 in 3% BSA-PBS for one hour at RT. The plates were then incubated with substrate solution as described above and read at OD 450. Wells containing immunoglobulin that preferentially bound human DLL3, as determined by a signal above background, were transferred and expanded.

[0523] Growth positive hybridoma wells secreting murine immunoglobulin were also screened for human DLL3 specificity and cynomolgus, rat and murine DLL3 cross reactivity using a flow cytometry based assay with 293 cells engineered to over-express either human DLL3 (h293-hDLL3), cynomolgus DLL3 (h293-cDLL3), rat (h293-rDLL3) or murine DLL3 (h293-mDLL3) proteins. h293-hDLL3 cells were made by transduction of 293T cells using a lentivirus made from a commercial bicistronic lentiviral vector (Open Biosystems) that expressed both hDLL3 and a GFP marker. h293-mDLL3

cells were made by transduction of 293T cells using a bicistronic lentiviral vector expressing both mDLL3 and a RFP marker, constructed as follows. A DNA fragment (FIG. 10A; SEQ ID NO: 5) encoding the mature murine DLL3 protein (FIG. 10B; SEQ ID NO: 6) was obtained by PCR amplification from a commercial murine DLL3 construct (Origene) and subcloned downstream of an IgG K signal peptide sequence previously engineered upstream of the multiple cloning site of pCDH-EF1-MCS-IRES-RFP (System Biosciences) using standard molecular cloning techniques. Similarly, h293-rDLL3 cells were made by transduction of 293T cells using a bicistronic lentiviral vector expressing both rat DLL3 and a GFP marker, constructed by cloning a synthetic DNA fragment (GeneWiz) comprising a codon-optimized sequence encoding the mature rat DLL3 protein (accession NP_446118.1, residues 25 - 589) downstream of an IgK signal peptide sequence previously engineered upstream of the multiple cloning site of pCDH-EF1-MCS-IRES-GFP (System Biosciences) using standard molecular cloning techniques. Finally, cynomolgus (e.g., *Macaca fascicularis*) DLL3 (cDLL3) sequence was deduced using the human DLL3 sequence to BLAST against the publically available *Macaca fascicularis* whole-genome shotgun contigs, and assembling the exon sequences of the Cynomolgus gene assuming maintenance of exonic structure in the gene across species. PCR amplification and direct sequencing of the individual exons 2 -7 from Cynomolgus genomic DNA (Zyagen) was used to confirm that the deduced sequence was correct across the ECD region of the protein. The cDLL3 DNA sequence (FIG. 10C; SEQ ID NO: 7), encoding the cDLL3 protein (FIG. 10D; SEQ ID NO: 8), was manufactured synthetically (GeneWiz) and subcloned downstream of an IgG K signal peptide sequence previously engineered upstream of the multiple cloning site of pCDH-EF1-MCS-IRES-GFP (System Biosciences) using standard molecular cloning techniques. Transduction of 293T cells with this vector yielded the h293-cDLL3 cells.

[0524] For the flow cytometry assays, $50x10^4$ h293 cells transduced respectively with human, cynomolgus, rat or murine DLL3 were incubated for 30 minutes with 25-100 μL hybridoma supernatant. Cells were washed with PBS, 2% FCS, twice and then incubated with 50 μL of a goat-anti-mouse IgG Fc fragment specific secondary conjugated to DyLight 649 diluted 1:200 in PBS/2%FCS. After 15 minutes of incubation, cells were washed twice with PBS/2%FCS and re-suspended in PBS/2%FCS with DAPI and analyzed by flow cytometry using a FACSCanto II as per the manufacturer's instructions. Wells containing immunoglobulin that preferentially bound the $DLL3^+$ GFP^+ cells were transferred and expanded. The resulting hDLL3 specific clonal hybridomas were cryopreserved in CS-10 freezing medium (Biolife Solutions) and stored in liquid nitrogen. Antibodies that bound h293-hDLL3, h293-cDLL3, h293-rDLL3 and/or h293-mDLL3 cells were noted as cross-reactive (see FIG. 12). Based on this assay all the selected modulators that were cross reactive with the murine antigen were also cross reactive with the rat antigen.

[0525] ELISA and flow cytometry analysis confirmed that purified antibody from most or all of these hybridomas bound DLL3 in a concentration-dependent manner. One fusion of each immunization campaign was performed and seeded in 64 plates (6144 wells at approximately 60 - 70% cloning efficiency). The hDLL3-Fc immunization campaign and screening yielded approximately 90 murine antibodies specific for human DLL3, several of which were cross reactive with murine DLL3. The hDLL3-His immunization campaign yielded 50 additional murine antibodies specific for human DLL3, a number of which cross reacted with murine DLL3.

Example 7

Sequencing of Murine DLL3 Modulators

[0526] Based on the foregoing, a number of exemplary distinct monoclonal antibodies that bind immobilized human DLL3 or h293-hDLL3 cells with apparently high affinity were selected for sequencing and further analysis. As shown in a tabular fashion in FIGS. 11A and 11B, sequence analysis of the light chain variable regions (FIG. 11A) and heavy chain variable regions (FIG. 11B) from selected monoclonal antibodies generated in Example 6 confirmed that many had novel complementarity determining regions and often displayed novel VDJ arrangements. Note that the complementarity determining regions set forth in FIGS. 11A and 11B are defined as per Chothia et al., supra.

[0527] As a first step in sequencing exemplary modulators, the selected hybridoma cells were lysed in Trizol® reagent (Trizol Plus RNA Purification System, Life Technologies) to prepare the RNA. In this regard between 10^4 and 10^5 cells were resuspended in 1 mL Trizol and shaken vigorously after addition of 200 μL of chloroform. Samples were then centrifuged at 4°C for 10 minutes and the aqueous phase was transferred to a fresh microfuge tube where an equal volume of isopropanol was added. The tubes were again shaken vigorously and allowed to incubate at RT for 10 minutes before being centrifuged at 4°C for 10 minutes. The resulting RNA pellets were washed once with 1 mL of 70% ethanol and dried briefly at RT before being resuspended in 40 μL of DEPC-treated water. The quality of the RNA preparations was determined by fractionating 3 μL in a 1% agarose gel before being stored at - 80°C until used.

[0528] The variable region of the 1g heavy chain of each hybridoma was amplified using a 5' primer mix comprising thirty-two mouse specific leader sequence primers, designed to target the complete mouse V_H repertoire, in combination with a 3' mouse Cγ primer specific for all mouse Ig isotypes. A 400 bp PCR fragment of tie V_H was sequenced from both ends using the same PCR primers. Similarly a mix of thirty-two 5' Vκ leader sequence primers designed to amplify each of the Vκ mouse families combined with a single reverse primer specific to the mouse kappa constant region were used

to amplify and sequence the kappa light chain. The V_H and V_L transcripts were amplified from 100 ng total RNA using reverse transcriptase polymerase chain reaction (RT-PCR).

[0529] A total of eight RT-PCR reactions were run for each hybridoma: four for the Vκ light chain and four for the V gamma heavy chain (γl). The One Step RT-PCR kit was used for amplification (Qiagen). This kit provides a blend of Sensiscript and Omniscript Reverse Transcriptases, HotStarTaq DNA Polymerase, dNTP mix, buffer and Q-Solution, a novel additive that enables efficient amplification of "difficult" (e.g., GC-rich) templates. Reaction mixtures were prepared that included 3 μL of RNA, 0.5 of 100 μM of either heavy chain or kappa light chain primers (custom synthesized by IDT), 5 μL of 5x RT-PCR buffer, 1 μL dNTPs, 1 μL of enzyme mix containing reverse transcriptase and DNA polymerase, and 0.4 μL of ribonuclease inhibitor RNasin (1 unit). The reaction mixture contains all of the reagents required for both reverse transcription and PCR. The thermal cycler program was set for an RT step 50°C for 30 minutes, 95°C for 15 minutes, followed by 30 cycles of PCR (95°C for 30 seconds, 48°C for 30 seconds, 72°C for one minute). There was then a final incubation at 72°C for 10 minutes.

[0530] To prepare the PCR products for direct DNA sequencing, they were purified using the QIAquick™ PCR Purification Kit (Qiagen) according to the manufacturer's protocol. The DNA was eluted from the spin column using 50 μL of sterile water and then sequenced directly from both strands. The extracted PCR products were directly sequenced using specific V region primers. Nucleotide sequences were analyzed using IMGT to identify germiline V, D and J gene members with the highest sequence homology. The derived sequences were compared to known germline DNA sequences of the Ig V- and J-regions using V-BASE2 (Retter et al., supra) and by alignment of V_H and V_L genes to the mouse germline database to provide the annotated sequences set forth in FIGS. 11A and 11B.

[0531] More specifically, FIG. 11A depicts the contiguous amino acid sequences of ninety-two novel murine light chain variable regions from anti-DLL3 antibodies (SEQ ID NOS: 20 - 202, even numbers) and five humanized light chain variable regions (SEQ ID NOS: 204 - 212, even numbers) derived from representative murine light chains. Similarly, FIG. 11B depicts the contiguous amino acid sequences of ninety-two novel murine heavy chain variable regions (SEQ ID NOS: 21 - 203, odd numbers) from the same anti-DLL3 antibodies and five humanized heavy chain variable regions (SEQ ID NOS: 205 - 213, odd numbers) from the same murine antibodies providing the humanized light chains. Thus, taken together FIGS. 11A and 11B provide the annotated sequences of ninety-two operable murine anti-DLL3 antibodies (termed SC16.3, SC16.4, SC16.5, SC16.7, SC16.8, SC16.10, SC16.11, SC16.13, SC16.15, SC16.18, SC16.19, SC16.20, SC16.21, SC16.22, SC16.23, SC16.25, SC16.26, SC16.29, SC16.30, SC16.31, SC16.34, SC16.35, SC16.36, SC16.38, SC16.41, SC16.42, SC16.45, SC16.47, SC16.49, SC16.50, SC16.52, SC16.55, SC16.56, SC16.57, SC16.58, SC16.61, SC16.62, SC16.63, SC16.65, SC16.67, SC16.68, SC16.72, SC16.73, SC16.78, SC16.79, SC16.80, SC16.81, SC16.84, SC16.88, SC16.101, SC16.103, SC16.104, SC16.105, SC16.106, SC16.107, SC16.108, SC16.109, SC16.110, SC16.111, SC16.113, SC16.114, SC16,115, SC16.116, SC16.117, SC16.118, SC16.120, SC16.121, SC16.122, SC16.123, SC16.124, SC16.125, SC16.126, SC16.129, SC16.130, SC16.131, SC16.132, SC16.133, SC16.134, SC16.135, SC16.136, SC16.137, SC16.138, SC16.139, SC16.140, SC16.141, SC16.142, SC16.143, SC16.144, SC16.147, SC16.148, SC16.149 and SC16.150) and five humanized antibodies (termed hSC16.13, hSC16.15, hSC16.25, hSC16.34 and hSC16.56). Note that these same designations may refer to the clone that produces the subject antibody and, as such, the use of any particular designation should be interpreted in the context of the surrounding disclosure.

[0532] For the purposes of the instant application the SEQ ID NOS of each particular antibody are sequential. Thus mAb SC16.3 comprises SEQ ID NOS: 20 and 21 for the light and heavy chain variable regions respectively. In this regard SC16.4 comprises SEQ ID NOS: 22 and 23, SC16.5 comprises SEQ ID NOS: 24 and 25, and so on. Moreover, corresponding nucleic acid sequences for each antibody amino acid sequence in FIGS. 11A and 11B are appended to the instant application in the sequence listing filed herewith. In the subject sequence listing the included nucleic acid sequences comprise SEQ ID NOS that are two hundred greater than the corresponding amino acid sequence (light or heavy chain). Thus, nucleic acid sequences encoding the light and heavy chain variable region amino acid sequences of mAb SC16.3 (i.e., SEQ ID NOS: 20 and 21) comprise SEQ ID NOS: 220 and 221 in the sequence listing. In this regard nucleic acid sequences encoding all of the disclosed light and heavy chain variable region amino acid sequences, including those encoding the humanized constructs, are numbered similarly and comprise SEQ ID NOS: 220 - 413.

Example 8

Humanization of DLL3 Modulators

[0533] As alluded to above, five of the murine antibodies from Example 7 were humanized using complementarity determining region (CDR) grafting. Human frameworks for heavy and light chains were selected based on sequence and structure similarity with respect to functional human germline genes. In this regard structural similarity was evaluated by comparing the mouse canonical CDR structure to human candidates with the same canonical structures as described in Chothia et al. (supra).

[0534] More particularly murine antibodies SC16.13, SC16.15, SC16.25, SC16.34 and SC16.56 were humanized using a computer-aided CDR-grafting method (Abysis Database, UCL Business Plc.) and standard molecular engineering techniques to provide hSC16.13, hSC16.15, hSC16.25, hSC16.34 and hSC16.56 modulators. The human framework regions of the variable regions were selected based on their highest sequence homology to the subject mouse framework sequence and its canonical structure. For the purposes of the humanization analysis the assignment of amino acids to each of the CDR domains is in accordance with Kabat et al. numbering (supra).

[0535] Molecular engineering procedures were conducted using art-recognized techniques. To that end total mRNA was extracted from the hybridomas and amplified as set forth in Example 7 immediately above.

[0536] From the nucleotide sequence in formation, data regarding V, D and J gene segments of the heavy and light chains of subject murine antibodies were obtained. Based on the sequence data new primer sets specific to the leader sequence of the Ig V_H and V_K light chain of the antibodies were designed for cloning of the recombinant monoclonal antibody. Subsequently the V-(D)-J sequences were aligned with mouse Ig germ line sequences. The resulting genetic arrangements for each of the five humanized constructs are shown in Table 1 immediately below.

TABLE 1

mAb	human VH	human DH	human JH	FW changes	human VK	human JK	FW changes
hSC16.13	IGHV2-5	IGHD1-1	JH6	None	IGKV-O2	JK1	None
hSC16.15	VH1-46	IGHD2-2	JH4	None	IGKV-L4	JK4	87F
hSC16.25	IGHV2-5	IGHD3-16	JH6	None	IGVK-A10	JK2	None
hSG16.34	IGHV1-3	IGHD3-22	JH4	None	IGVK-A20	JK1	87F
hSC16.56	IGHV1-18	IGHD2-21	JH4	None	IGKV-L2	JK2	None

[0537] The sequences depicted in TABLE 1 correspond to the annotated heavy and light chain sequences set forth in FIGS. 11A and 11B for the subject clones. More specifically, the entries in Table 1 above correspond to the contiguous variable region sequences set forth SEQ ID NOS: 204 and 205 (hSC16.13), SEQ ID NOS: 206 and 207 (hSC16.15), SEQ ID NOS: 208 and 209 (hSC16.25), SEQ ID NOS: 210 and 211 (hSC16.34) and SEQ ID NOS: 212 and 213 (hSC16.56). Furthermore. TABLE 1 shows that very few framework changes were necessary to maintain the favorable properties of the binding modulators. In this respect there were no framework changes or back mutations made in the heavy chain variable regions and only two framework modifications were undertaken in the light chain variable regions (i.e., 87F in hSC16.15 and hSC16.34).

[0538] Following humanization of all selected antibodies by CDR grafting, the resulting light and heavy chain variable region amino acid sequences were analyzed to determine their homology with regard to the murine donor and human acceptor light and heavy chain variable regions. The results, shown in Table 2 immediately below, reveal that the humanized constructs consistency exhibited a higher homology with respect to the human acceptor sequences than with the murine donor sequences. More particularly, the murine heavy and light chain variable regions show a similar overall percentage homology to a closest match of human germline genes (83%-93%) compared with the homology of the humanized antibodies and the donor hybridoma protein sequences (74%-83%).

TABLE 2

mAb	Homology to Human (CDR acceptor)	Homology to Murine Parent (CDR donor)
hSC16.13 HC	93%	81%
hSC16.13 LC	87%	77%
hSC16.15 HC	85%	83%
hSC16.15 LC	85%	83%
hSC16.25 HC	91%	83%
hSC16.2.5 LC	85%	79%
hSC16.34 HC	87%	79%
hSC16.34 LC	85%	81%
hSC16.56 HC	87%	74%
hSC16.56 LC	87%	76%

[0539] Upon testing, and as will be discussed in more detail below, each of the humanized constructs exhibited favorable binding characteristics roughly comparable to those shown by the murine parent antibodies.

[0540] Whether humanized or murine, once the nucleic acid sequences of the variable regions are determined the antibodies of the instant invention may be expressed and isolated using art-recognized techniques. To that end synthetic DNA fragments of the chosen heavy chain (humanised or murine) variable region were cloned into a human IgG1 expression vector. Similarly the variable region light chain DNA fragment (again humanized or murine) was cloned into a human light chain expression vector. The selected antibody was then expressed by co-transfection of the derived heavy and the light chain nucleic acid constructs into CHO cells.

[0541] More particularly, one compatible method of antibody production comprised directional cloning of murine or humanized variable region genes (amplified using PCR) into selected human immunoglobulin expression vectors. All primers used in Ig gene-specific PCRs included restriction sites which allowed direct cloning into expression vectors containing human IgG1 heavy chain and light chain constant regions. In brief, PCR products were purified with Qiaquick PCR purification kit (Qiagen) followed by digestion with AgeI and XhoI (for the heavy chain) and XmaI and DraIII (for the light chain), respectively. Digested PCR products were purified prior to ligation into expression vectors. Ligation reactions were performed in a total volume of 10 μL with 200U T4-DNA Ligase (New England Biolabs), 7.5 μL of digested and purified gene-specific PCR product and 25ng linearized vector DNA. Competent E. coli DH10B bacteria (Life Technologies) were transformed via heat shock at 42°C with 3 μL ligation product and plated onto ampicillin plates (100 μg/mL). The AgeI-EcoRI fragment of the V_H region was than inserted into the same sites of pEE6.4HuIgG1 expression vector while the synthetic XmaI-DraIII VK insert was cloned into the XmaI-DraIII sites of the respective pEE12.4Hu-Kappa expression vector.

[0542] Cells producing the selected antibody were generated by transfection of HEK 293 cells with the appropriate plasmids using 293fectin. In this respect plasmid DNA was purified with QIAprep Spin columns (Qiagen). Human embryonic kidney (HEK) 293T (ATCC No CRL-11268) cells were cultured in 150mm plates (Falcon, Becton Dickinson) under standard conditions in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% heat inactivated FCS, 100 μg/mL streptomycin, 100 U/mL penicillin G (all from Life Technologies).

[0543] For transient transfections cells were grown to 80% confluency. Equal amounts of IgH and corresponding IgL chain vector DNA (12.5 μg of each) was added to 1.5 mL Opti-MEM mixed with 50 μL HEK 293 transfection reagent in 1.5 mL opti-MEM. The mix was incubated for 30 min at room temperature and distributed evenly to the culture plate. Supernatants were harvested three days after transfection, replaced by 20 mL of fresh DMEM supplemented with 10% FBS and harvested again at day 6 after transfection. Culture supernatants were cleared of cell debris by centrifugation at 800×g for 10 min and stored at 4°C. Recombinant chimeric and humanized antibodies were purified with Protein G beads (GE Healthcare) and stored under appropriate conditions.

Example 9

Characteristics of DLL3 Modulators

[0544] Various methods were used to analyze the binding and immunochemical characteristics of selected DLL3 modulators generated as set forth above. Specifically, a number of the antibody modulators were characterized as to affinity, kinetics, binning, binding location and cross reactivity with regard to human, cynomolgus, rat and mouse antigen recognition (i.e., using the cells and constructs from Example 6) by art-recognized methods including flow cytometry. Affinities and kinetic constants k_{on} and k_{off} of the selected modulators were measured using bio-layer interferometry analysis on a ForteBio RED (ForteBio, Inc.) or surface plasmon resonance using a Biacore 2000 each according to the manufacturers instructions.

[0545] The characterization results are set forth in tabular form in FIG. 12 where it may be seen that the selected modulators generally exhibited relatively high affinities in the nanomolar range and, in many cases, were cross-reactive. FIG. 12 further lists the empirically determined modulator bin as well as the DLL3 domain bound by the subject modulator as determined using yeast mediated antigen fragment expression such as described in more detail in Example 10 immediately below. Additionally, FIG. 12 further includes the ability of the modulators to mediate cytotoxic induced cell killing of an NTX kidney tumor line (% Live Cells) determined as set forth in Example 12 below. Taken together, these data demonstrate the varied binding properties of the disclosed modulators as well as their potential for use in a pharmaceutical setting.

[0546] As to antibody binning, a ForteBio RED was used per manufacturer's instructions to identify competing antibodies that bound to the same or different bins. Briefly, a reference antibody (Ab1) was captured onto an anti-mouse capture chip, a high concentration of non-binding antibody was then used to block the chip and a baseline was collected. Monomeric, recombinant human DLL3-Flag (Adipogen International) was then captured by the specific antibody (Ab1) and the tip was dipped into a well with either the same antibody (Ab1) as a control or into a well with a different test antibody (Ab2). If additional binding was observed with a new antibody, then Ab1 and Ab2 were determined to be in a

different bin. If no further binding occurred, as determined by comparing binding levels with the control Ab1, then Ab2 was determined to be in the same bin. As known in the art this process can be expanded to screen large libraries of unique antibodies using a full row of antibodies representing unique bins in a 96-well plate. In the instant case this binning process showed the screened antibodies bound to at least nine different bins (designated as Bins A though I in FIG. 12) on the DLL3 protein. Based on the apparent size of the DLL3 antigen (where the ECD is approximately 56kD) and the resolution of the binning methodology employed, it is believed that the nine identified bins represent the majority of the bins present on the DLL3 extracellular antigen.

[0547] In addition to evaluating the exemplary modulators as set forth above, flow cytometry was performed in order to confirm that selected SC16 antibody modulators can immunospecifically associate with human DLL3 and to determine whether the same modulators cross-react with cynomolgus, rat and/or murine DLL3. More particularly the exemplary murine modulators were analyzed by flow cytometry using a FACSCanto II and 293 cells overexpressing murine, rat, cynomolgus or human DLL3 (i.e., h293-hDLL3, h293-cDLL3, h293-rDLL3 and h293-mDLL3 expressing GFP) substantially as described in Example 6 above. In some cases, exemplary murine modulators were analyzed by flow cytometry using a FACSCanto **II** and yeast cells displaying cynomologus DLL3 using the methods described by Cochran et al, (J Immunol Methods. 287 (1-2): 147-158 (2004).

[0548] Based on flow cytometry all of the selected antibody modulators were found to bind to human DLL3 overexpressed on 293 cells (data not shown) while a number of the tested antibodies were found to cross-react with cynomolgus and/or murine DLL3 (all antibodies reacting with mouse also reacted with rat). In this regard, and as listed in FIG. 12, it was found that eight out of the thirteen modulators that immunospecifically react with human DLL3 also react with murine (or rat) DLL3. Specifically mAbs SC16.4, SC16.8, SC16.15, SC16.34. SC16.39, SC16.46, SC16.51 and SC16.56 were found to cross-react with murine DLL3 to a greater or lesser extent while mAbs SC16.7, SC16.10, SC16.13, SC16.25 and SC16.65 did not appreciably associate with murine DLL3. Such results are not unexpected given that murine DLL3 is approximately 83% homologous with isoform 2 of human DLL3 (see FIG. 2B). It will be appreciated that this cross-reactivity may be advantageously exploited in the context of the instant invention through the use of animal models in drug discovery and development

[0549] Besides the aforementioned assays, humanized constructs hSC16.13, hSC16.15, bSC16.25, hSC16.34 and hSC16.56 from Example 8 were analyzed to determine if the CDR grafting process had appreciably altered their binding characteristics. In this respect the humanized constructs (CDR grafted) were compared with "traditional" chimeric antibodies comprising the murine parent (or donor) heavy and light chain variable domains and a human constant region substantially equivalent to that used in the humanized constructs. With these constructs surface plasmon resonance (SPR) was conducted using a Biacore 2000 (GE Healthcare) to identify any subtle changes in rate constants brought about by the humanization process.

[0550] Exemplary results for one of the tested modulators (SC16.15) and a tabular summary of the results for each of the humanized and chimeric constructs are shown in FIGS. 13A - 13C. Based on a concentration series of 25 and 12.5 nM of human DLL3 antigen (generating the curves from top to bottom in the FIGS. 13A and 13B for SC16.15) and using a 1:1 Langmuir binding model, the K_D of the SC16.15 antibody binding to human DLL3 antigen was estimated to be 0.2 nM. Similar experiments were then run with the other humanized constructs and chimeric constructs (data not shown) to provide the affinity values set forth in FIG. 13C. Such results indicated that the humanization process had not materially impacted the affinity of the modulators.

Example 10

Domain and Epitope Mapping of DLL3 Modulators

[0551] In order to characterize and position the epitopes that the disclosed DLL3 antibody modulators associate with or bind to, domain-level epitope mapping was performed using a modification of the protocol described by Cochran et al., 2004 (supra). Briefly, individual domains of DLL3 comprising specific amino acid sequences were expressed on the surface of yeast, and binding by each DLL3 antibody was determined through flow cytometry.

[0552] More specifically, yeast display plasmid constructs were created for the expression of the following constructs: DLL3 extracellular domain (amino acids 27-466); DLL1-DLL3 chimera, which consists of the N-terminal region and DSL domain of DLL1 (amino acids 22-225) fused to EGF-like domains through 6 of DLL3 (amino acids 220-466); DLL3-DLL1 chimera, which consists of the N-terminal region and DSL domain of DLL3 (amino acids 27-214) fused to EGF-like domains 1 through 8 of DLL1 (amino acids 222-518); EGF-like domain #1 (amino acids 215-249); EGF-like domain #2 (amino acids 274-310); EGF-like domains #1 and #2 (amino acids 215-310); EGF-like domain #3 (amino acids 312-351); EGF-like domain #4 (amino acids 353-389); EGF-like domain #5 (amino acids 391-427); and EGF-like domain #6 (amino acids 429-469). (For domain information see generally UniProtKB/Swiss-Prot database entry Q9NYJ7 which is incorporated herein by reference. Note that the amino acid numbering is by reference to an unprocessed DLL3 protein with a leader sequence such as set forth in SEQ ID NO. 3.) For analysis of the N-terminal region or the EGF domains as a

whole, chimeras with the family member DLL1 (DLL1-DLL3 and DLL3-DLL1) were used as opposed to fragments to minimize potential problems with protein folding. Domain-mapped antibodies had previously been shown not to cross react with DLL1 indicating that any binding to these constructs was occurring through association with the DLL3 portion of the construct. These plasmids were transformed into yeast, which were then grown and induced as described in Cochran et al.

[0553] To test for binding to a particular construct, 200,000 induced yeast cells expressing the desired construct were washed twice in PBS + 1 mg/mL BSA (PBSA), and incubated in 50 μL of PBSA with biotinylated anti-HA clone 3F10 (Roche Diagnostics) at 0.1 μg/mL and either 50nM purified antibody or 1:2 dilution of unpurified supernatant from hybridomas cultured for 7 days. Cells were incubated for 90 minutes on ice, followed by 2 washes in PBSA. Cells were then incubated in 50 μL PBSA with the appropriate secondary antibodies: for murine antibodies, Alexa 488 conjugated streptavidin, and Alexa 647 conjugated goat anti mouse (both Life Technologies) were added at 1 μg/mL each, and for humanized or chimeric antibodies, Alexa 647 conjugated streptavidin (Life Technologies) and R-phycoerythrin conjugated goat anti human (Jackson Immunoresearch) were added at 1 μg/mL each. After a twenty minute incubation on ice, cells were washed twice with PBSA and analyzed on a FACS Canto II. Antibodies that bound to DLL3-DLL1 chimera were designated as binding to the N-terminal region + DSL. Antibodies that bound specifically to an epitope present on a particular EGF-like domain were designated as binding to its respective domain (FIG. 14A).

[0554] In order to classify an epitope as conformational (e.g., discontinuous) or linear, yeast displaying the DLL3 extracellular domain was heat treated for 30 minutes at 80°C, then washed twice in ice-cold PBSA. Yeast displaying denatured antigen (denatured yeast) were then subjected to the same staining protocol and flow cytometry analysis as described above. Antibodies that bound to both the denatured and native yeast were classified as binding to a linear epitope, whereas antibodies that bound native yeast but not denatured yeast were classified as conformationally specific.

[0555] A schematic summary of the domain-level epitope mapping data of the antibodies tested is presented in FIG. 14A, with antibodies binding a linear epitope underlined and, where determined, the corresponding bin noted in parenthesis. A review of FIG. 14A shows that the majority of modulators tended to map to epitopes found either in the N-terminal/DSL region of DLL3 or to the second EGF-like domain. As previously alluded to, FIG. 12 presents similar data regarding bin determination and domain mapping for a number of selected modulators in a tabular form.

[0556] To document the ability of the disclosed modulators to effectively eliminate tumorigenic cells despite binding to different DLL3 regions, killing data was correlated with domain binding. More particularly, FIG. 14B shows modulator mediated *in vitro* killing of the KDY66 PDX line (derived as set forth in Example 12 below) plotted against the binding domain of the selected modulator. These data show that domain specific modulator killing is somewhat variable as measured using this *in vitro* killing assay. However, for modulators that are effective, an interesting trend appears where maximum killing in each domain increases as the epitope moves towards the N-terminus in the primary sequence. In particular, maximum killing efficiency improves from EGF6 to LGF2, and plateaus across the N-terminal domain, EGF1, and EGF2. Additionally, out of the antibodies tested in this assay, the highest percentage of efficacious antibodies bind at the N-terminal domain. This suggests that modulators that associate or bind with the DSL domain or N-terminal region of DLL3 may prove to be particularly effective as drugs or as targeting moieties for cytotoxic agents.

[0557] Fine epitope mapping was further performed on selected antibodies using one of two methods. The first method employed the Ph.D.-12 phage display peptide library kit (New England Biolabs E8110S) which was used in accordance with the manufacturer's instructions. Briefly, the antibody for epitope mapping was coated overnight at 50 μg/mL in 3mL 0.1M sodium bicarbonate solution, pH 8, onto a Nunc MaxiSorp tube (Nunc). The tube was blocked with 3% BSA solution in bicarbonate solution. Then, 10^{11} input phage in PBS + 0.1% Tween-20 was allowed to bind, followed by ten consecutive washes at 0.1% Tween-20 to wash away non-binding phage. Remaining phage were eluted with 1mL 0.2 M glycine for 10 minutes at room temperature with gentle agitation, followed by neutralization with 150 μL, 1M Tris-HCl pH 9. Eluted phage were amplified and panned again with 10^{11} input phage, using 0.5% Tween-20 during the wash steps to increase selection stringency. DNA from 24 plaques of the eluted phage from the second round was isolated using the Qiaprep M13 Spin kit (Qiagen) and sequenced. Binding of clonal phage was confirmed using an ELISA assay, where the mapped antibody or a control antibody is coated onto an ELISA plate, blocked, and exposed to each phage clone. Phage binding was detected using horseradish peroxidase conjugated anti-M13 antibody (GE Healthcare), and the 1-Step Turbo TMB ELISA solution (Pierce). Phage peptide sequences from specifically binding phage were aligned using Vector NT1 (Life Technologies) against the antigen ECD peptide sequence to determine the epitope of binding.

[0558] Alternatively, a yeast display method (Chao et al., Nat Protoc. 1(2): 755-768, 2007) was used to epitope map select antibodies. Briefly, libraries of DLL3 ECD mutants were generated with error prone PCR using nucleotide analogues 8-oxo-2'deoxyguanosine-5'-triphosphate and 2'-deoxy-p-nucleoside-5'triphosphate (both from TriLink Bio) for a target mutagenesis rate of one amino acid mutation per clone. These were transformed into a yeast display format. Using the technique described above for domain-level mapping, the library was stained for HA and antibody binding at 50nM. Using a FACS Aria (BD), clones that exhibited a loss of binding compared to wild type DLL3 ECD were sorted. These clones were re-grown, and subjected to another round of FACS sorting for loss of binding to the target antibody. Using the Zymoprep Yeast Plasmid Miniprep kit (Zymo Research), individual ECD clones were isolated and sequenced. Where

necessary, mutations were reformatted as single-mutant ECD clones using the Quikchange site directed mutagenesis kit (Agilent).

[0559] Individual ECD clones were next screened to determine whether loss of binding was due to a mutation in the epitope, or a mutation that caused misfolding. Mutations that involved cysteine, proline, and stop codons were automatically discarded due to the high likelihood of a misfolding mutation. Remaining ECD clones were then screened for binding to a non-competing, conformationally specific antibody. ECD clones that lost binding to non-competing, conformationally specific antibodies were concluded to contain misfolding mutations, whereas ECD clones that retained equivalent binding as wild type DLL3 ECD were concluded to be properly folded. Mutations in the ECD clones in the latter group were concluded to be in the epitope. The results are listed in TABLE 3 immediately below.

TABLE 3

Antibody Clone	Epitope	SEQ ID NO:
SC16.23	Q93, P94, G95, A96, P97	9
SC16.34	G203, R205, P206	10
SC16.56	G203, R205, P206	10

[0560] More particularly, a summary of selected antibodies with their derived epitopes comprising amino acid residues that are involved in antibody binding are listed in TABLE 3. In this respect antibodies SC16.34 and SC16.56 apparently interact with common amino acid residues which is consistent with the binning information and domain mapping results shown in FIG. 14A. Moreover, SC16.23 was found to interact with a distinct contiguous epitope and was found not to bin with SC16.34 or SC16.56. Note that for the purposes of the appended sequence listing SEQ ID NO: 10 will comprise a placeholder amino acid at position 204.

Example 11

Flow Cytometry Based Detection of DLL3 on the Surface of Cells and Immunohistochemical Staining of DLL3 in Tumors

[0561] To confirm the immunospecific nature of the disclosed modulators, exemplary SC16 antibody modulators were tested using flow cytometry to determine their ability to selectively recognize engineered 293 cell lines expressing DLL3 protein on their surface. In this regard cells expressing DLL3 were produced as set forth substantially in Example 6, exposed to selected modulators and examined by flow cytometry as described herein. Isotype-stained and fluorescence minus one (FMO) controls were employed to confirm staining specificity. As demonstrated by the representative data shown in FIG. 15 for the SC16.56 modulator, some of the SC16 antibodies (e.g., SC16.56) gave strong staining of 293-hDLL3 cells (FIG. 15B) and 293-mDLL3 cells (FIG. 15C), but not of non-DLL3 expressing parental 293 cells (FIG. 15A). These data demonstrate, via flow cytometry, that the disclosed modulators immunospecifically recognize human DLL3, and in the instance of SC16.56, murine DLL3 as well.

[0562] To confirm these findings and demonstrate that DLL3 expression could be detected on human tumor cells, DLL3 protein expression on the surface of selected NTX tumors was assessed by flow cytometry using several exemplary SC16 antibodies. In this regard data for one of these antibodies, SC16.56, and three particular tumors, OV26, KDY66, and LU37, are set forth in FIG. 16. More specifically, NTX tumors were harvested, dissociated, and co-stained with commercially available anti-mouse CD45, anti-mouse H-2Kd, anti-human EpCAM and the above-described anti-human/mouse DLL3 (SC16.56) antibodies. Similar to the 293-staining experiments described above, isotype-stained and fluorescence minus one (FMO) controls were employed to confirm lack of non-specific staining. As seen in FIG. 16, anti-DLL3 staining was higher in a fraction of the human NTX tumor cells, as indicated by the fluorescent profile shift to the right, and by changes in the mean fluorescence intensity (MFI) values, for the ovarian OV26 NTX (FIG. 16A), kidney KDY66 NTX (FIG. 16B), and lung LU37 NTX (FIG. 16C) tumor cell lines. SCLC NTX tumors were also stained in an identical manner and similarly demonstrated positive expression of DLL3 (data not shown). These data suggest that DLL3 protein is expressed on the surface of various NTX tumors and therefore amenable to modulation using anti-DLL3 antibody type modulators.

[0563] To further corroborate the presence of DLL3 protein and localize it in the tumor architecture, immunohistochemistry (IHC) was performed on human patient tumor-derived NTX tumors, normal human tissues and primary SCLC tumors. More specifically IHC was performed on formalin fixed paraffin embedded (FFPE) tissue sections, using an indirect detection method, including a murine monoclonal primary antibody against DLL3 (SCJ6.65), mouse specific biotin conjugated secondary antibodies, avidin/biotin complex coupled with horse-radish peroxidase, tyramide signal

amplification and DAB detection (Nakene PK 1968; 16:557-60). When staining human patient tumor derived NTX tumors, a mouse IgG blocking step was used to reduce background due to non-specific binding. SC16.65 was first validated and confirmed to be appropriate for IHC by showing specific staining in 293 cells overexpressing DLL3, but not non-DLL3 expressing parental 293 cells, and that staining was diminished in cells treated with DLL3-targeted hairpins designed and validated to knockdown expression of DLL3 RNA and protein (see Example 14 below, data not shown). IHC on a panel of xenograft NTX tumors showed that DLL3 is localized both on the membrane and in the cytoplasm of many of SCLC NTX and NET tumors that previously tested positive for DLL3 mRNA (FIG. 16D). Staining intensity was scored from no staining (-) to high expression (+++) with the percent of positive cells also noted. Staining of normal human tissues showed no detectable expression of DLL3 (FIG. 16E). Significantly, staining of primary SCLC tumor samples confirmed that 36/43 tumors were positive for DLL3 (FIG. 16F). Chromagranin A (CHGA) staining was also performed to confirm that tumors were indeed SCLC tumors. Most tumors that lacked DLL3 also lacked CHGA staining, indicating these sections might not contain tumor tissue or that the tissue was compromised during processing. Two tumors that tested positive for DLL3 but were negative for CHGA, were both later stage (IIIa) SCLC tumors. This data suggests that DLL3 provides an effective therapeutic target as it is not generally expressed in normal human tissues, but is present in the majority of SCLC tumors.

Example 12

DLL3 Modulators Facilitate Delivery of Cytotoxie Agents

[0564] To determine whether DLL3 antibody modulators of the instant invention are able to mediate the delivery of a cytotoxic agent to live cells, an *in vitro* cell killing assay was performed using randomly selected DLL3 antibody modulators.

[0565] Specifically 2,500 cells/well of human KDY66, a NET NTX expressing endogenous DLL3, were dissociated into a single cell suspension and plated on BD Primaria™ plates (BD Biosciences) in growth factor supplemented serum free media as is known in the art, one day before the addition of antibodies and toxin. Various concentrations of purified DLL3 modulators, such as those described in Examples 6 and 7, and a fixed concentration of 4nM anti-Mouse IgG Fab fragment covalently linked to saporin toxin (Advanced Targeting Systems, #IT-48) were added to the cultures for seven days. For killing on 293-hDLL3, 500cells/well were plated in a single cell suspension and plated on BD tissue culture plates in DMEM with 10% FBS one day before addition of antibodies and toxin. Two concentrations of various DLL3 modulators and a fixed concentration of 2nM anti-Mouse IgG Fab fragment covalently linked to saporin were added to the cultures for three days. The ability of the saporin complexes to internalize and kill cells was determined by enumerating viable cell numbers using Cell Titer Glo® (Promega) as per manufacturer's instructions. Raw luminescence counts using cultures containing cells with the saporin Fab fragment were set as 100% reference values and all other counts calculated accordingly (referred to as "Normalized RLU"). Using this assay it was demonstrated that a subset of DLL3 antibodies tested at 500 and 50 pM killed KDY66 cells, as well as a subset of antibodies tested at 250 and 25pM on 293-hDLL3 overexpressing cells (FIG. 17A). Isotype controls did not affect cell counts as shown by the IgG2a, IgG2b, and MOPC bars at the left of the graph (FIG. 17A).

[0566] A subset of DLL3 modulators showing efficient killing in the first assay described above were tested in dilution to determine EC50 values for activity. Two such representative antibodies, SC16.34 and SC16.15, are shown in FIG. 17B, in which it was determined that SC16-15 showed efficient killing of OV26, an ovarian NET NTX tumor, with a subpicomolar EC50 (e.g., 0.14 pM) relative to the killing profile shown by SC16.34 (e.g., 5.7 pM). As saporin kills cells only upon uptake into the cytoplasm where it inactivates ribosomes, this assay also demonstrates that internalization may occur upon binding of the DLL3-specific antibody to the cell surface, without the need for additional crosslinking or dimerization.

[0567] Lastly, LU37 was treated with humanized SC16.15 conjugated to ADC1 or with a humanized IgG1 control ADC1 (conjugated as per Example 13 immediately below). Specifically, 2,500 LU37 NTX cells were plated in each well on BD PrimariaTM plates (BD Biosciences) in growth factor supplemented serum free media as is known in the art one day before the addition of the conjugated antibodies. Various concentrations of hulgG1-ADC1 or hSC16.15-ADC were added to the cultures for seven days, and the ability of the cytotoxic agents to kill was determined by enumerating cell numbers (as detailed above). Using this assay it was demonstrated that hSC16.15-ADC1 efficiently killed LU37. In contrast to >1,000ng/ml of control ADC needed to kill 50% of LU37, <10ng/ml of hSC16.15-ADC1 killed 50% of LU37 (FIG. 17C).

Example 13

Preparation of DLL3 Antibody-Drug Conjugates

[0568] Based on the foregoing results with saporin and to further demonstrate the versatility of the instant invention,

anti-DLL3 antibody drug conjugates (DLL3-ADCs) were prepared using covalently linked cytotoxic agents. More specifically, DLL3-ADCs were prepared comprising a linker as described herein, or in the references immediately below, and selected pyrrolobenzodiazepine (PBD) dimers that were covalently attached to the disclosed modulators (see, e.g., U.S.P.Ns. 2011/0256157 and 2012/0078028 and U.S.P.N 6,214,345 each of which is incorporated herein by reference in its entirety)

[0569] PBD drug-linker combinations were synthesized and purified using art-recognized techniques in view of the cited references. While various PBD dimers and linkers were employed to fabricate the selected drug-linker combinations, each linker unit comprised a terminal maleimido moiety with a free sulthydryl. Using these linkers, conjugations were prepared via partial reduction of the mAb with tris (2-carboxyethyl)-phosphine (TCEP) followed by reaction of reduced Cys residues with the maleimido-linker payload.

[0570] More particularly, the selected DLL3 antibody modulator was reduced with 1.3 mol TCEP per mol mAb for 2 hr at 37°C in 25 mM Tris HCl pH 7.5 and 5 mM EDTA buffer. The reaction was allowed to cool to 15°C and the linker payload in DMSO was added at a ratio of 2.7 mol/mol mAb followed by an additional amount of DMSO to a final concentration of 6% (v/v). The reaction was allowed to proceed for 1 hour, The transacted drug-linker was capped by addition of an excess of N-acetyl cysteine. The DLL3-ADC (or SC 16-ADC) was then purified by ion exchange column using an AKTA Explorer FPLC system (G.E. Healthcare) to remove aggregated high molecular weight antibody, co-solvent and small molecules. The eluted ADC was then buffer-exchanged by tangential flow filtration (TFF) into formulation buffer followed by concentration adjustment and addition of a detergent. The final ADC was analyzed for protein concentration (by measuring UV), aggregation (SEC), drug to antibody ratio (DAR) by reverse phase (RP) HPLC, presence of unconjugated antibody by hydrophobic interaction chromatography (HIC) HPLC, non-proteinaceous materials by RP HPLC and *in vitro* cytotoxicity using a DLL3 expressing cell line.

[0571] Using the aforementioned procedure, or substantially similar methodology, a number of ADCs (i.e., M-[L-D]n) comprising various DLL3 modulators and PBD dimers were generated and tested in a variety of *in vivo* and *in vitro* models. For the purposes of these Examples and the instant disclosures, such ADCs may generally be termed DLL3-ADCs or SC16-ADCs. Discrete ADCs will be named according to the antibody (e.g., SC16.13) and the specific linker-cytotoxic agent designation ADC1, ADC2, etc. Thus, exemplary modulators compatible with the instant invention may comprise SC16.13-ADC1 or SC16.67-ADC2 where ADC1 and ADC2 represent individual PBD dimer cytotoxic agents (and optionally a linker).

Example 14

Specificity of Anti-DLL3 Antibody-Drug Conjugate Mediated Toxicity

[0572] To demonstrate that toxicity from anti-DLL3 antibody-drug conjugates is specific to cells expressing endogenous DLL3, experiments were conducted to show that tumor cells known to have endogenous DLL3 expression are no longer killed by SC16-ADC *in vitro* when DLL3 expression is suppressed by knocking down expression of DLL3 mRNA and protein using a short-hairpin RNA (shRNA).

[0573] KDY66 is a patient-derived xenograft from a papillary renal cell carcinoma that exhibits neuroendocrine features and expresses DLL3 mRNA and protein (e.g., see FIG. 7 and FIG. 16B). Expression of DLL3 was reduced in KDY66 cells by transduction with GIPZ Lentiviral Human DLL3-targeted shRNA (Thermo Fisher Scientific Inc.) containing an anti-DLL3 shRNA. More specifically the lentiviral vector was generated through transfection of 293T cells with a bicistronic lentiviral plasmid expressing anti-DLL3 shRNA (DLL3HP2) or control non-silencing shRNA (DLL3NSHP) in the presence of viral packaging plasmids. Resulting lentiviral particles contained in the supernatant were concentrated and harvested by ultracentrifugation. These particles were then used to transduce the KDY66 cell cultures and introduce the shRNA (i.e., DLL3HP2 or NSHP) wherein the anti-DLL3 shRNA binds endogenous DLL3 mRNA and targets it for destruction thereby preventing translation into DLL3 protein. Both vector constructs contained an independent GFP expression module for verification of successful transduction and selection of transduced cells,

[0574] Following transduction, expression of DLL3 was evaluated by flow cytometry. Briefly, a sample of disassociated, single cell suspension of DLL3HP2-transduced cells were labeled with a DLL3 modulator (SC16.34) conjugated to Alexa Fluor 647 (Life Technologies) and analyzed on a FACS Canto II flow cytometer under standard conditions. To demonstrate a reduction of DLL3 protein expression on the surface of the DLL3HP2 transduced cells, fluorescence intensity was compared with a similarly prepared sample of KDY66 DLL3NSHP cells stained with a non-reactive control antibody (647-IgG1) and KDY66 DLL3NSHP cells stained with 647-DLL3. DLL3NSHP.KDY66 cells were found to exhibit DLL3 protein expression substantially equivalent to naïve KDY66 cells (data not shown). As seen in FIG. 18A, DLL3 protein surface expression was reduced in cells transduced with DLL3HP2 compared with naïve cells stained with the same AlexaFluor-647 labeled antibody.

[0575] In order to examine the consequences of DLL3 expression on the growth of tumors DLL3HP2 transduced cells (DLL3) and naïve KDY66 cells ($DLL3^+$) were transplanted into immunodeficient mice. From the sample prepared as

described above, live human GFP$^+$ cells were sorted to collect cells that contain the anti-DLL3 shRNA. Five-mouse cohorts were injected (140 cells/mouse) with either DLL3HP2 or naïve KDY66 cells and tumor growth was monitored weekly. From each cohort, two of five recipients grew tumors. Tumor formation in the two DLL3HP2.KDY66 recipients lagged roughly 22 days behind tumor formation in the two naïve KDY66 recipients (FIG. 18B). This observed delay in growth suggests that DLL3 expression may be connected to increased or accelerated tumor formation since knockdown of DLL3 impacted tumor growth.

[0576] As they reached the appropriate volume for randomization (~ 160 mm^3), the DLL3HP2 KDY66 tumors and naïve KDY66 tumors were harvested from recipient mice and dispersed into suspensions of single cells. Continued reduction of DLL3 expression (i.e., that DLL3 expression was not induced during *in vivo* growth) in DLL3HP2 cells was confirmed on suspensions of single tumor cells by flow cytometry as described above. In this respect FIG. 18C shows that DLL3HP2 transduced cells grown *in vitro* show reduced expression of DLL3 protein when compared to naïve cells grown in similar conditions.

[0577] Using standard biochemical techniques naïve KDY66 cells or DLL3HP2 KDY66 cells were plated into 96 well plates and grown in serum-free media. A dilution series of either humanized hSC16.56-ADC1 (SC16-ADC1) or humanized anti-hapten IgG-ADC1 (as a control) antibody-drug conjugates produced as set forth above were added to cells in triplicate. After 7 days of exposure to antibody-drug conjugate, the quantity of live cells was measured with a luminescence-based detection of ATP in the cell lysates of each well (Cell Titer Glo, Promega) substantially as set forth in Example 12.

[0578] While 50% of naïve KDY66 cells were killed by a relatively low dose of 13.27 pM SC16-ADC, no dose of SC16-ADC1 was able to kill even 20% of DLL3HP2.KDY66 cells (FIGS. 18D and 18E). Of note, loss of endogenous DLL3 protein expression resulted in a complete loss of *in vitro* killing by SC16-ADC1. This demonstrates that hSC16-ADC1 cytotoxicity is specifically targeted to DLL3-expressing cells with little, if any, non-specific toxicity,

Example 15

Conjugated DLL3 Modulators Suppress Tumor Growth

[0579] Based on the aforementioned results work was undertaken to demonstrate that conjugated DLL3 modulators of the instant invention shrink and suppress growth of DLL3 expressing human tumors *in vivo*, In this regard a number of selected murine antibody modulators were covalently associated with a PBD cytotoxic agent and the resulting ADCs were tested to demonstrate their ability to suppress human NTX tumor growth in immunodeficient mice.

[0580] To this end patient-derived NTX tumors were grown subcutaneousty in the Hanks of female NOD/SCID recipient mice using art-recognized techniques. Tumor volumes and mouse weights were monitored twice weekly. When tumor volumes reached J 50-250 mm^3, mice were randomly assigned to treatment groups and injected with indicated doses of SC16-ADC2 or an anti-hapten control IgG1-ADC2 (each produced substantially as described in Example 13 above using the PBD dimer ADC2) via intraperitoneal injection. Mice were given three equal injections, spaced evenly across seven days. Following treatment, tumor volumes and mouse weights were monitored until tumors exceeded 800 mm^3 or mice became sick. For all tests, treated mice exhibited no adverse health effects beyond those typically seen in immunodeficient tumor-bearing NOD/SCID mice.

[0581] FIG. 19 shows the impact of the disclosed ADCs on tumor growth in mice bearing different lung tumors exhibiting neuroendocrine features (two small cell lung cancer and one large cell lung cancer with neuroendocrine features), In this respect treatment of LU37, a large cell neuroendocrine lung carcinoma, with three exemplary modulators (SC16.13, SC16.46 and SC16.67) conjugated to ADC2 resulted in tumor growth suppression lasting as long as 20 days in the case of SC16.13-ADC2 and SC16.67-ADC2 (FIG. 19A); conversely, though SC16.46 moderately reduced tumor growth it exhibited less activity than the other tested modulators. Similarly, treatment of LU73, a small cell lung carcinoma, with four exemplary modulators (SC16.4, SC16.13, SC16.15 and SC16.46) produced durable remissions lasting, in some cases, beyond 120 days post-treatment (FIG. 19B). However, as with the antibodies tested against LU37, the antibodies tested against LU73 varied somewhat in the duration of tumor repression. Finally. treatment of LU86, another small cell lung carcinoma, with two conjugated modulators (SC16.46-ADC2 and SC16.67-ADC2) produced tumor shrinkage with a time to progression of 40 days in one case (SC16.67-ADC2; FIG. 19C). Note that in FIG. 19C two of the curves substantially overlap (mIgG1-ADC2 and SC16.46-ADC2) and are difficult to distinguish.

[0582] The surprising ability of a variety of conjugated modulators to dramatically retard or suppress tumor growth *in vivo* for extended periods further validates the use of the DLL3 as a therapeutic target for the treatment of proliferative disorders.

Example 16

Humanized DLL3-ADC Modulators Suppress Tumor Growth

[0583] Given the impressive results provided by DLL3-ADC2, additional experiments were performed to demonstrate the efficacy of exemplary humanized ADC modulators in treating various types of tumors (including ovarian, lung and kidney cancer) *in vivo.* Specifically, selected humanized anti-DLL3 antibodies (hSC16.13, hSC16.15, hSC16.34 and hSC16.56 produced as set forth in Example 8 above) were conjugated (via a linker unit) to two discrete PBD cytotoxic agents (ADC1 and ADC2) as described above and, with controls, administered to NTX tumor implanted immunodeficient mice as set forth in the previous Example. In each study, tumor volumes and mouse weights of the control animals were monitored until tumors exceeded 800 mm^3 or mice became sick. The results of these experiments are presented in FIGS. 20A to 20F.

[0584] A review of FIGS. 20A - 20F show that tumor volume reduction and durable remission was achieved in various tumor types, some exhibiting neuroendocrine features, following treatment with 1 mg/kg hSC16-ADC. For example, treatment regimens, where administration is delineated by the vertical lines in the subject FIGS., produced complete and durable eliminations of tumor mass in ovarian carcinoma with neuroendocrine features (OV26, hSC16.15-ADC2, FIG. 20A), a papillary renal cell carcinoma with neuroendocrine features (KDY66, hSC16.34-ADC1, FIG. 20E) and three small cell lung carcinomas (LU86, hSC16.13-ADC1, FIG. 20B), (LU64, hSC16.13-ADC1, FIG. 20C; LU64, hSC16.13-ADC2 + hSC16.13-ADC1, FIG. 20D), Absence of tumor recurrence was observed for more than 100 days in all these cases, and in some cases beyond 225 days post-treatment where mice were followed for an extended period of time. Additionally, treatment with the disclosed modulators produced tumor volume reduction and growth suppression in a clear cell renal cell carcinoma that exhibits high levels of DLL3 using a lower dose of 0.5 mg/kg (KDY27, hSC16.56-ADC1, FIG. 20F).

[0585] Finally, it should be noted that certain recurrent tumors remained sensitive to hSC16-ADC toxicity. Eighty days after initial treatment with SC16.13-ADC2, recurrence was observed in LU64 (FIG. 20D). Treatment of recurrent tumors with hSC16.13-ADC1 resulted in elimination of observable tumor mass that persisted more than 100 days after the second treatment.

[0586] Again these results demonstrate the surprising versatility and applicability of the modulators of the instant invention in treating a variety of proliferative disorders.

Example 17

Reduction of Cancer Stem Cell Frequency by DLL3 Antibody-Drug Conjugates

[0587] As shown in the previous Examples the disclosed modulators are extremely effective in suppressing tumor growth, particularly in ADC form. Moreover, as demonstrated above, DLL3 expression is associated with cancer stem cells that are generally known to be both drug resistant and fuel tumor recurrence and metastasis. Accordingly, to demonstrate that treatment with DLL3-ADCs reduces the recurrence potential of NTX lines, *in vivo* limiting dilution assays (LDA) were performed to determine the frequency of tumor-initiating cells (TIC) in small cell lung cancer tumors following treatment with hSC16.13-ADC1 (labeled SC16-ADC in FIG 21). Patient-derived small cell lung cancer xenograft tumors (LU95 and LU64) were grown subcutaneously in immunodeficient host mice. When tumor volumes averaged 150 mm^3 - 250 mm^3, the mice were randomly segregated into two groups of seven mice. Via intraperitoneal injection, mice were injected on days 0, 4 and 7 (FIGS. 21A and 21D, dashed vertical lines), with either human IgG1-ADC1 (1 mg/kg; n=7 mice) as a negative control or hSC16.13-ADC1 (1 mg/kg; n=7 mice). On day 8, two representative mice from each group were euthanized and their tumors were harvested and dispersed to single-cell suspensions. As shown in FIGS. 21A and 21D while tumors treated with hIgG1-ADC1 (IgG1-ADC) continued to grow in the five remaining mice, volumes of tumors treated with hSC16.13-ADC1 (SC16-ADC) were reduced to zero or nearly zero in the five remaining mice.

[0588] Using standard flow cytometry techniques and a labeled anti-DLL3 antibody, the two harvested tumors from each of the two treatment groups were confirmed to have similarly positive DLL3 expression. The tumors cells from each respective treatment group were then pooled and live human cells were isolated by FACS using a FACSAria III (Becton Dickenson) in accordance with the manufacturer's instructions and art-recognized techniques. Briefly, the cells were labeled with FITC conjugated anti-murine H2Kd and anti-murine CD45 antibodies (both BioLegend, Inc.) and then resuspended in 1 μg/ml DAPI The resulting suspension was then sorted under standard conditions with $DAPI^-$, $mH2Kd^-$ and $mCD45^-$ human cells being collected and the murine cells being discarded.

[0589] Cohorts of five recipient mice were then transplanted with either 2000, 500, 120 or 30 sorted live human cells from tumors treated with hSC16.13-ADC1. For comparison, cohorts of five recipient mice were transplanted with either 1000, 250, 60 or 15 sorted live human cells from tumors treated with the control IgG1-ADC1. Tumors in recipient mice were measured weekly, and individual mice were euthanized before tumors reached 1500mm^3. After the onset of tumor

growth, the study was ended after four consecutive weeks without a new tumor appearing in any additional mouse. At that time, recipient mice were scored as positive or negative for tumor growth, with positive growth having volumes exceeding $100mm^3$.

[0590] Across all injected cells doses, recipients of LU95 cells treated with hSC16.13-ADC1 produced only one tumor, compared to twelve in recipients of LU95 cells treated with IgG1-ADC1 (FIG. 21B). Similarly, recipients of LU64 cells treated with SC16.13-ADC1 produced three tumors, compared to 13 tumors in recipients of LU64 cells treated with IgG1-ADC1 (FIG. 21E).

[0591] Using Poisson distribution statistics (L-Calc software, Stemcell Technologies), injected cell doses of recipients with and without tumors at 18 weeks post-transplant were used to calculate the frequencies of tumor-initiating cells in each population. The number of TIC per 10,000 live human cells in LU95 was reduced more than 100-fold, from 78.1 in tumors treated with IgC1-ADC to 0.769 in tumors treated with hSC16.13-ADC1 (FIG. 21C, from 1:128 cells in the control treated to 1:12,998 in the modulator treated). In LU64, the number of TIC was reduced 16.6-fold, from 47.4 TIC to 2.86 TIC per 10,000 live human cells in tumors treated with IgG1-ADC1 or hSC16.13-ADC1, respectively (FIG. 21F, from 1:211 cells in the control treated to 1:3,500 cells in the modulator treated). This substantial reduction in TIC (e.g., cancer stem cell) frequency demonstrates that, in addition to reducing tumor volumes as previously demonstrated, the modulators of the instant invention are significantly and specifically reducing cancer stem cell populations and, by extension, the recurrence, metastatic and re-growth potential of the tumors. This reduction in recurrence and re-growth potential are strongly evidenced by the significant tumor-free survival observed in the forgoing Examples.

[0592] The complete disclosure of all patents, patent applications, and publications, and electronically available material (including, for example, nucleotide sequence submissions in, e.g., GenBank and RefSeq, and amino acid sequence submissions in, e.g., SwissProt, PIR, PRF, PBD, and translations from annotated coding regions in GenBank and RefSeq cited herein are incorporated by reference. The foregoing detailed description and examples have been given for clarity of understanding only. No unnecessary limitations are to be understood therefrom. The invention is not limited to the exact details shown and described, for variations obvious to one skilled in the art will be included within the invention defined by the claims.

[0593] Preferred embodiments of the present invention are described below and referred to as embodiments E1 to E20.

E1. An isolated DLL3 modulator.

E2. The isolated DLL3 modulator of E 1, wherein the DLL3 modulator comprises an antibody or immunoreactive fragment thereof.

E3. The isolated DLL3 modulator of E 2 wherein the antibody or immunoreactive fragment thereof comprises a monoclonal antibody.

E4. The isolated DLL3 modulator of E 3 wherein the monoclonal antibody is selected from the group consisting of chimeric antibodies, humanized antibodies and human antibodies.

E5. The isolated DLL3 modulator of E3 or E4 wherein said monoclonal antibody or immunoreactive fragment thereof binds to a DLL3 protein N-terminal domain or DSL domain.

E6. The isolated DLL3 antibody modulator of any of E2 to E5 wherein said antibody or immunoreactive fragment thereof comprises a light chain variable region having three complementarity determining regions and a heavy chain variable region having three complementarity determining regions wherein the heavy and light chain complementarity determining regions comprise at least one complementarity determining region set forth in FIG. 11A or FIG. 11B.

E7. The isolated DLL3 antibody modulator of any of E2 to E5 that competes for binding to a DLL3 protein with a reference antibody selected from the group consisting of SC16.3, SC16.4, SC16.5, SC16.7, SC16.8, SC16.10, SC16.11, SC16.13, SC16.15, SC16.18, SC16.19, SC16.20, SC16.21, SC16.22, SC16.23, SC16,25, SC16.26, SC16.29, SC16.30, SC16.31, SC16.34, SC16.35, SC16.36, SC16.38, SC16.39, SC16.41, SC16.42, SC16.45, SC16.47, SC16.49, SC16.50, SC16.52, SC16.55, SC16.56, SC16.57, SC16.58, SC16.61, SC16.62, SC16.63, SC16.65, SC16.67, SC16.68, SC16.72, SC16.73, SC16,78, SC16.79, SC16.80, SC16.81, SC16.84, SC16.88, SC16.101, SC16.103, SC16.104, SC16.105, SC16.106, SC16.107, SC16.108, SC16.109, SC16.110, SC16.111, SC16.113, SC16.114, SC16.115, SC16.116, SC16.117, SC16.118, SC16,120, SC16.121, SC16.122, SC16.123, SC16.124, SC16.125, SC16.126, SC16.129, SC16.130, SC16.131, SC16.132, SC16.133, SC16.134, SC16.135, SC16.136, SC16.137, SC16.138, SC16.139, SC16.140, SC16.141 SC16.142, SC16.143, SC16.144, SC16.147, SC16.148, SC16.149 and SC16.150 wherein binding of the DLL3 antibody modulator to the DLL3 protein is inhibited by at least 30%,

E8. The isolated DLL3 modulator of any of E2 to E7 wherein said antibody comprises an internalizing antibody.

E9. The isolated DLL3 modulator of any of E2 to E8 wherein said antibody further comprises a cytotoxic agent.

E10. A nucleic acid encoding an amino acid heavy chain variable region or an amino acid light chain variable region of an antibody or immunoreactive fragment thereof of E1- E8.

E11. A host cell comprising the nucleic acid of E 10.

E12. An antibody drug conjugate of the formula:

M-[L-D]n or a pharmaceutically acceptable salt thereof wherein

a) M comprises a DLL3 modulator;
b) L comprises an optional linker;
c) D is a anti-proliferative agent; and
d) n is an integer from about 1 to about 20.

E13. The antibody drug conjugate of E12 wherein said DLL3 modulator comprises an antibody or immunoreactive fragment thereof and said antibody or immunoreactive fragment thereof comprises a light chain variable region having three complementarity determining regions and a heavy chain variable region having three complementarity determining regions wherein the heavy and light chain complementarity determining regions comprise at least one complementarity determining region set forth in FIG. 11A or FIG. 11B.
E14. The antibody drug conjugate of E12 or E13 wherein said DLL3 modulator comprises an internalizing antibody.
E15. The isolated DLL3 modulator of any of E1- E9 or the antibody drug conjugate of E12 or E14 for use in a medicine.
E16. The isolated DLL3 modulator of any of E1- E9 or the antibody drug conjugate of E12 or E14 for the treatment of cancer in a patient wherein the cancer is selected from the group consisting of adrenal cancer, bladder cancer, cervical cancer, endometrial cancer, kidney cancer, liver cancer, lung cancer, ovarian cancer, colorectal cancer, pancreatic cancer, prostate cancer and breast cancer.
E17. Use of a DLL3 modulator for the manufacture of a medicament for treating small cell lung cancer in a subject in need thereof.
E18. The medicament of E 17 wherein said DLL3 modulator comprises a monoclonal antibody.
E19. The medicament of any of E17 or E18 wherein said DLL3 modulator binds to a DLL3 protein N-terminal domain or DSL domain.
E20. The medicament of any of E17 to E19 wherein said DLL3 modulator comprises a cytotoxic agent.

SEQUENCE LISTING

<110> STEM CENTRX, INC.

<120> NOVEL MODULATORS AND METHODS OF USE

<130> 11200.0013-00304

<140>
<141>

<150> 61/719,803
<151> 2012-10-29

<150> 61/603,173
<151> 2012-02-24

<160> 413

<170> PatentIn version 3.5

<210> 1
<211> 2387
<212> DNA
<213> Homo sapiens

<400> 1
agatataagg cttggaagcc agcagctgcg actcccgaga ccccccccacc agaaggccat 60

ggtctcccca cggatgtccg ggctcctctc ccagactgtg atcctagcgc tcattttcct 120

cccccagaca cggcccgctg gcgtcttcga gctgcagatc cactctttcg ggccgggtcc 180

aggccctggg gccccgcggt ccccctgcag cgcccggctc ccctgccgcc tcttcttcag 240

agtctgcctg aagcctgggc tctcagagga ggccgccgag tccccgtgcg ccctgggcgc 300

ggcgctgagt gcgcgcggac cggtctacac cgagcagccc ggagcgcccg cgcctgatct 360

cccactgccc gacggcctct tgcaggtgcc cttccgggac gcctggcctg gcaccttctc 420

tttcatcatc gaaacctgga gagaggagtt aggagaccag attggagggc ccgcctggag 480

cctgctggcg cgcgtggctg gcaggcggcg cttggcagcc ggaggcccgt gggcccggga 540

cattcagcgc gcaggcgcct gggagctgcg cttctcgtac cgcgcgcgct gcgagccgcc 600

tgccgtcggg accgcgtgca cgcgcctctg ccgtccgcgc agcgcccccct cgcggtgcgg 660

tccgggactg cgcccctgcg caccgctcga ggacgaatgt gaggcgccgc tggtgtgccg 720

agcaggctgc agccctgagc atggcttctg tgaacagccc ggtgaatgcc gatgcctaga 780

gggctggact ggacccctct gcacggtccc tgtctccacc agcagctgcc tcagccccag 840

gggcccgtcc tctgctacca ccggatgcct tgtccctggg cctgggccct gtgacgggaa 900

cccgtgtgcc aatggaggca gctgtagtga gacacccagg tcctttgaat gcacctgccc 960

gcgtgggttc tacgggctgc ggtgtgaggt gagcggggtg acatgtgcag atggaccctg 1020

cttcaacggc ggcttgtgtg tcgggggtgc agaccctgac tctgcctaca tctgccactg 1080

cccacccggt ttccaaggct ccaactgtga gaagagggtg gaccggtgca gcctgcagcc 1140

atgccgcaat ggcggactct gcctggacct gggccacgcc ctgcgctgcc gctgccgcgc 1200

cggcttcgcg ggtcctcgct gcgagcacga cctggacgac tgcgcgggcc gcgcctgcgc 1260

taacggcggc acgtgtgtgg agggcggcgg cgcgcaccgc tgctcctgcg cgctgggctt 1320

cggcggccgc gactgccgcg agcgcgcgga cccgtgcgcc gcgcgcccct gtgctcacgg 1380

cggccgctgc tacgcccact tctccggcct cgtctgcgct tgcgctcccg gctacatggg 1440

agcgcggtgt gagttcccag tgcaccccga cggcgcaagc gccttgcccg cggccccgcc 1500

gggcctcagg cccggggacc ctcagcgcta ccttttgcct ccggctctgg gactgctcgt 1560

ggccgcgggc gtggccggcg ctgcgctctt gctggtccac gtgcgccgcc gtggccactc 1620

ccaggatgct gggtctcgct tgctggctgg gaccccggag ccgtcagtcc acgcactccc 1680

ggatgcactc aacaacctaa ggacgcagga gggttccggg gatggtccga gctcgtccgt 1740

agattggaat cgccctgaag atgtagaccc tcaagggatt tatgtcatat ctgctccttc 1800

catctacgct cgggaggtag cgacgccccc tttcccccccg ctacacactg ggcgcgctgg 1860

gcagaggcag cacctgcttt ttccctaccc ttcctcgatt ctgtccgtga aatgaattgg 1920

gtagagtctc tggaaggttt taagcccatt ttcagttcta acttactttc atcctatttt 1980

gcatccctct tatcgttttg agctacctgc catcttctct ttgaaaaacc tatgggcttg 2040

aggaggtcac gatgccgact ccgccagagc ttttccactg attgtactca gcggggaggc 2100

aggggaggca gaggggcagc ctctctaatg cttcctactc attttgtttc taggcctgac 2160

gcgtctcctc catccgcacc tggagtcaga gcgtggattt ttgtatttgc tcggtggtgc 2220

ccagtctctg ccccagaggc tttggagttc aatcttgaag gggtgtctgg gggaacttta 2280

ctgttgcaag ttgtaaataa tggttattta tatcctattt tttctcaccc catctctcta 2340

gaaacaccta taaaggctat tattgtgatc agttttgact aacaaaa 2387

<210> 2
<211> 2052
<212> DNA
<213> Homo sapiens

<400> 2
agatataagg cttggaagcc agcagctgcg actcccgaga ccccccccacc agaaggccat 60

ggtctcccca cggatgtccg ggctcctctc ccagactgtg atcctagcgc tcattttcct 120

cccccagaca cggcccgctg gcgtcttcga gctgcagatc cactctttcg ggccgggtcc 180

aggccctggg gccccgcggt ccccctgcag cgcccggctc ccctgccgcc tcttcttcag 240

agtctgcctg aagcctgggc tctcagagga ggccgccgag tccccgtgcg ccctgggcgc 300

ggcgctgagt gcgcgcggac cggtctacac cgagcagccc ggagcgcccg cgcctgatct 360

cccactgccc gacggcctct tgcaggtgcc cttccgggac gcctggcctg gcaccttctc 420

tttcatcatc gaaacctgga gagaggagtt aggagaccag attggagggc ccgcctggag 480

cctgctggcg cgcgtggctg gcaggcggcg cttggcagcc ggaggcccgt gggcccggga 540

cattcagcgc gcaggcgcct gggagctgcg cttctcgtac cgcgcgcgct gcgagccgcc 600

tgccgtcggg accgcgtgca cgcgcctctg ccgtccgcgc agcgcccccc cgcggtgcgg 660

tccgggactg cgcccctgcg caccgctcga ggacgaatgt gaggcgccgc tggtgtgccg 720

agcaggctgc agccctgagc atggcttctg tgaacagccc ggtgaatgcc gatgcctaga 780

gggctggact ggacccctct gcacggtccc tgtctccacc agcagctgcc tcagccccag 840

gggcccgtcc tctgctacca ccggatgcct tgtccctggg cctgggccct gtgacgggaa 900

cccgtgtgcc aatggaggca gctgtagtga gacacccagg tcctttgaat gcacctgccc 960

gcgtgggttc tacgggctgc ggtgtgaggt gagcggggtg acatgtgcag atggaccctg 1020

cttcaacggc ggcttgtgtg tcgggggtgc agaccctgac tctgcctaca tctgccactg 1080

cccacccggt ttccaaggct ccaactgtga gaagagggtg gaccggtgca gcctgcagcc 1140

atgccgcaat ggcggactct gcctggacct gggccacgcc ctgcgctgcc gctgccgcgc 1200

cggcttcgcg ggtcctcgct gcgagcacga cctggacgac tgcgcgggcc gcgcctgcgc 1260

taacggcggc acgtgtgtgg agggcggcgg cgcgcaccgc tgctcctgcg cgctgggctt 1320

cggcggccgc gactgccgcg agcgcgcgga cccgtgcgcc gcgcgccccc gtgctcacgg 1380

cggccgctgc tacgcccact tctccggcct cgtctgcgct tgcgctcccg gctacatggg 1440

agcgcggtgt gagttcccag tgcaccccga cggcgcaagc gccttgcccg cggccccgcc 1500

gggcctcagg cccggggacc ctcagcgcta ccttttgcct ccggctctgg gactgctcgt 1560

ggccgcgggc gtggccggcg ctgcgctctt gctggtccac gtgcgccgcc gtggccactc 1620

ccaggatgct gggtctcgct tgctggctgg gaccccggag ccgtcagtcc acgcactccc 1680

ggatgcactc aacaacctaa ggacgcagga gggttccggg gatggtccga gctcgtccgt 1740

agattggaat cgccctgaag atgtagaccc tcaagggatt tatgtcatat ctgctccttc 1800

catctacgct cgggaggcct gacgcgtctc ctccatccgc acctggagtc agagcgtgga 1860

tttttgtatt tgctcggtgg tgcccagtct ctgccccaga ggctttggag ttcaatcttg 1920

aaggggtgtc tgggggaact ttactgttgc aagttgtaaa taatggttat ttatatccta 1980

ttttttctca ccccatctct ctagaaacac ctataaaggc tattattgtg atcagttttg 2040

actaacaaaa aa 2052

<210> 3
<211> 618
<212> PRT
<213> Homo sapiens

<400> 3

```
Met Val Ser Pro Arg Met Ser Gly Leu Leu Ser Gln Thr Val Ile Leu
1               5                  10                  15

Ala Leu Ile Phe Leu Pro Gln Thr Arg Pro Ala Gly Val Phe Glu Leu
            20                  25                  30

Gln Ile His Ser Phe Gly Pro Gly Pro Gly Pro Gly Ala Pro Arg Ser
        35                  40                  45

Pro Cys Ser Ala Arg Leu Pro Cys Arg Leu Phe Phe Arg Val Cys Leu
    50                  55                  60

Lys Pro Gly Leu Ser Glu Glu Ala Ala Glu Ser Pro Cys Ala Leu Gly
65                  70                  75                  80

Ala Ala Leu Ser Ala Arg Gly Pro Val Tyr Thr Glu Gln Pro Gly Ala
                85                  90                  95

Pro Ala Pro Asp Leu Pro Leu Pro Asp Gly Leu Leu Gln Val Pro Phe
            100                 105                 110

Arg Asp Ala Trp Pro Gly Thr Phe Ser Phe Ile Ile Glu Thr Trp Arg
        115                 120                 125

Glu Glu Leu Gly Asp Gln Ile Gly Gly Pro Ala Trp Ser Leu Leu Ala
    130                 135                 140

Arg Val Ala Gly Arg Arg Arg Leu Ala Ala Gly Gly Pro Trp Ala Arg
145                 150                 155                 160

Asp Ile Gln Arg Ala Gly Ala Trp Glu Leu Arg Phe Ser Tyr Arg Ala
                165                 170                 175

Arg Cys Glu Pro Pro Ala Val Gly Thr Ala Cys Thr Arg Leu Cys Arg
            180                 185                 190

Pro Arg Ser Ala Pro Ser Arg Cys Gly Pro Gly Leu Arg Pro Cys Ala
        195                 200                 205

Pro Leu Glu Asp Glu Cys Glu Ala Pro Leu Val Cys Arg Ala Gly Cys
    210                 215                 220

Ser Pro Glu His Gly Phe Cys Glu Gln Pro Gly Glu Cys Arg Cys Leu
225                 230                 235                 240

Glu Gly Trp Thr Gly Pro Leu Cys Thr Val Pro Val Ser Thr Ser Ser
```

245 250 255

Cys Leu Ser Pro Arg Gly Pro Ser Ser Ala Thr Thr Gly Cys Leu Val
260 265 270

Pro Gly Pro Gly Pro Cys Asp Gly Asn Pro Cys Ala Asn Gly Gly Ser
275 280 285

Cys Ser Glu Thr Pro Arg Ser Phe Glu Cys Thr Cys Pro Arg Gly Phe
290 295 300

Tyr Gly Leu Arg Cys Glu Val Ser Gly Val Thr Cys Ala Asp Gly Pro
305 310 315 320

Cys Phe Asn Gly Gly Leu Cys Val Gly Gly Ala Asp Pro Asp Ser Ala
325 330 335

Tyr Ile Cys His Cys Pro Pro Gly Phe Gln Gly Ser Asn Cys Glu Lys
340 345 350

Arg Val Asp Arg Cys Ser Leu Gln Pro Cys Arg Asn Gly Gly Leu Cys
355 360 365

Leu Asp Leu Gly His Ala Leu Arg Cys Arg Cys Arg Ala Gly Phe Ala
370 375 380

Gly Pro Arg Cys Glu His Asp Leu Asp Asp Cys Ala Gly Arg Ala Cys
385 390 395 400

Ala Asn Gly Gly Thr Cys Val Glu Gly Gly Gly Ala His Arg Cys Ser
405 410 415

Cys Ala Leu Gly Phe Gly Gly Arg Asp Cys Arg Glu Arg Ala Asp Pro
420 425 430

Cys Ala Ala Arg Pro Cys Ala His Gly Gly Arg Cys Tyr Ala His Phe
435 440 445

Ser Gly Leu Val Cys Ala Cys Ala Pro Gly Tyr Met Gly Ala Arg Cys
450 455 460

Glu Phe Pro Val His Pro Asp Gly Ala Ser Ala Leu Pro Ala Ala Pro
465 470 475 480

Pro Gly Leu Arg Pro Gly Asp Pro Gln Arg Tyr Leu Leu Pro Pro Ala
485 490 495

Leu Gly Leu Leu Val Ala Ala Gly Val Ala Gly Ala Ala Leu Leu Leu
500 505 510

Val His Val Arg Arg Arg Gly His Ser Gln Asp Ala Gly Ser Arg Leu
515 520 525

Leu Ala Gly Thr Pro Glu Pro Ser Val His Ala Leu Pro Asp Ala Leu
530 535 540

Asn Asn Leu Arg Thr Gln Glu Gly Ser Gly Asp Gly Pro Ser Ser Ser
545 550 555 560

Val Asp Trp Asn Arg Pro Glu Asp Val Asp Pro Gln Gly Ile Tyr Val
565 570 575

Ile Ser Ala Pro Ser Ile Tyr Ala Arg Glu Val Ala Thr Pro Leu Phe
580 585 590

Pro Pro Leu His Thr Gly Arg Ala Gly Gln Arg Gln His Leu Leu Phe
595 600 605

Pro Tyr Pro Ser Ser Ile Leu Ser Val Lys
610 615

<210> 4
<211> 587
<212> PRT
<213> Homo sapiens

<400> 4
Met Val Ser Pro Arg Met Ser Gly Leu Leu Ser Gln Thr Val Ile Leu
1 5 10 15

Ala Leu Ile Phe Leu Pro Gln Thr Arg Pro Ala Gly Val Phe Glu Leu
20 25 30

Gln Ile His Ser Phe Gly Pro Gly Pro Gly Pro Gly Ala Pro Arg Ser
35 40 45

Pro Cys Ser Ala Arg Leu Pro Cys Arg Leu Phe Phe Arg Val Cys Leu
50 55 60

Lys Pro Gly Leu Ser Glu Glu Ala Ala Glu Ser Pro Cys Ala Leu Gly
65 70 75 80

Ala Ala Leu Ser Ala Arg Gly Pro Val Tyr Thr Glu Gln Pro Gly Ala
85 90 95

Pro Ala Pro Asp Leu Pro Leu Pro Asp Gly Leu Leu Gln Val Pro Phe

```
                100                 105                 110

Arg Asp Ala Trp Pro Gly Thr Phe Ser Phe Ile Ile Glu Thr Trp Arg
        115                 120                 125

Glu Glu Leu Gly Asp Gln Ile Gly Gly Pro Ala Trp Ser Leu Leu Ala
    130                 135                 140

Arg Val Ala Gly Arg Arg Arg Leu Ala Ala Gly Gly Pro Trp Ala Arg
145                 150                 155                 160

Asp Ile Gln Arg Ala Gly Ala Trp Glu Leu Arg Phe Ser Tyr Arg Ala
                165                 170                 175

Arg Cys Glu Pro Pro Ala Val Gly Thr Ala Cys Thr Arg Leu Cys Arg
            180                 185                 190

Pro Arg Ser Ala Pro Ser Arg Cys Gly Pro Gly Leu Arg Pro Cys Ala
        195                 200                 205

Pro Leu Glu Asp Glu Cys Glu Ala Pro Leu Val Cys Arg Ala Gly Cys
    210                 215                 220

Ser Pro Glu His Gly Phe Cys Glu Gln Pro Gly Glu Cys Arg Cys Leu
225                 230                 235                 240

Glu Gly Trp Thr Gly Pro Leu Cys Thr Val Pro Val Ser Thr Ser Ser
                245                 250                 255

Cys Leu Ser Pro Arg Gly Pro Ser Ser Ala Thr Thr Gly Cys Leu Val
            260                 265                 270

Pro Gly Pro Gly Pro Cys Asp Gly Asn Pro Cys Ala Asn Gly Gly Ser
        275                 280                 285

Cys Ser Glu Thr Pro Arg Ser Phe Glu Cys Thr Cys Pro Arg Gly Phe
    290                 295                 300

Tyr Gly Leu Arg Cys Glu Val Ser Gly Val Thr Cys Ala Asp Gly Pro
305                 310                 315                 320

Cys Phe Asn Gly Gly Leu Cys Val Gly Gly Ala Asp Pro Asp Ser Ala
                325                 330                 335

Tyr Ile Cys His Cys Pro Pro Gly Phe Gln Gly Ser Asn Cys Glu Lys
            340                 345                 350
```

Arg Val Asp Arg Cys Ser Leu Gln Pro Cys Arg Asn Gly Gly Leu Cys
355 360 365

Leu Asp Leu Gly His Ala Leu Arg Cys Arg Cys Arg Ala Gly Phe Ala
370 375 380

Gly Pro Arg Cys Glu His Asp Leu Asp Asp Cys Ala Gly Arg Ala Cys
385 390 395 400

Ala Asn Gly Gly Thr Cys Val Glu Gly Gly Gly Ala His Arg Cys Ser
405 410 415

Cys Ala Leu Gly Phe Gly Gly Arg Asp Cys Arg Glu Arg Ala Asp Pro
420 425 430

Cys Ala Ala Arg Pro Cys Ala His Gly Gly Arg Cys Tyr Ala His Phe
435 440 445

Ser Gly Leu Val Cys Ala Cys Ala Pro Gly Tyr Met Gly Ala Arg Cys
450 455 460

Glu Phe Pro Val His Pro Asp Gly Ala Ser Ala Leu Pro Ala Ala Pro
465 470 475 480

Pro Gly Leu Arg Pro Gly Asp Pro Gln Arg Tyr Leu Leu Pro Pro Ala
485 490 495

Leu Gly Leu Leu Val Ala Ala Gly Val Ala Gly Ala Ala Leu Leu Leu
500 505 510

Val His Val Arg Arg Arg Gly His Ser Gln Asp Ala Gly Ser Arg Leu
515 520 525

Leu Ala Gly Thr Pro Glu Pro Ser Val His Ala Leu Pro Asp Ala Leu
530 535 540

Asn Asn Leu Arg Thr Gln Glu Gly Ser Gly Asp Gly Pro Ser Ser Ser
545 550 555 560

Val Asp Trp Asn Arg Pro Glu Asp Val Asp Pro Gln Gly Ile Tyr Val
565 570 575

Ile Ser Ala Pro Ser Ile Tyr Ala Arg Glu Ala
580 585

<210> 5
<211> 1686
<212> DNA

<213> Mus sp.

<400> 5

gctggtgtct tcgagctaca aattcattct ttcgggccag gcccaggcct cgggacccca 60

cgctcccccc gcaacgcccg aggcccttgc cgcctcttct tcagggtctg cctgaagccc 120

ggagtctccc aggaggccac cgagtccctg tgcgccctgg gcgcagcact gagcacgagc 180

gtcccggtct atacggagca ccccggagag tcagcggctg ccctgccgct gcctgatggc 240

ctcgtacgtg tgcccttccg cgatgcttgg ccgggcacct tctccctcgt cattgaaacc 300

tggagagagc agctgggaga gcatgctgga gggcccgcct ggaacctgct agcacgtgtg 360

gtcggccgta gacgcctggc ggctgggggc ccgtgggccc gcgatgtgca gcgcacaggc 420

acatgggagt tgcacttctc ctaccgcgcg cggtgcgagc cgcccgccgt cggggccgcc 480

tgcgcgcgcc tgtgccgctc acgcagtgcc ccctcgcggt gtggcccggg actgcgaccc 540

tgcacgccat tcccagacga gtgcgaagcc ccgtctgtgt gtcgaccagg ctgcagcccc 600

gagcacggct actgtgaaga gcctgatgaa tgccgttgcc tggagggctg gactggaccc 660

ctctgcacgg tccctgtctc caccagtagc tgcctgaact ccagggttcc tggtcctgcc 720

agcactggat gccttttacc tgggcctgga ccttgtgatg ggaacccatg tgccaatggg 780

ggcagctgta gtgaaacctc tggctccttt gaatgtgcct gtccccgggg attctacggg 840

cttcgatgtg aggtgagcgg ggtcacgtgc gcagatggac cctgcttcaa tggcggcttg 900

tgtgttggcg gtgaagatcc tgactctgcc tatgtctgtc attgcccacc tggtttccaa 960

ggctctaact gtgagaagag ggtggaccgc tgtagcctgc agccatgtca gaatggcggc 1020

ctctgcctgg acctgggcca cgcgttgcgc tgccgctgtc gcgcgggatt cgccgggccg 1080

cgctgcgagc acgacctgga cgactgcgcc ggccgcgcct gtgccaacgg cggcacgtgc 1140

gtggagggcg gcggctcgcg ccgctgctcc tgtgcgctgg gcttcggcgg gcgcgactgc 1200

cgagaacgcg ccgacccctg cgcctcccgc ccctgcgcgc atggaggccg ttgctacgcc 1260

cacttctctg gcctggtctg cgcctgcgcg cccggctaca tgggcgtgag atgcgagttc 1320

gctgtgcgcc cggacggcgc ggacgcggtg cccgccgccc cgcggggcct gaggcaggcg 1380

gatccacagc gctttcttct gcctcccgcc ttggggctgc tggtggccgc cggtttggct 1440

ggcgccgcac tcttggtcat ccacgttcgc cgccgaggtc ctggccagga taccgggact 1500

cgcctgcttt ctgggacccg ggagccttcg gtccacacgc tcccggatgc actcaacaac 1560

ctgaggttac aagacggtgc tggggatggc cccagttcgt cggctgactg gaatcatcct 1620

gaagatggag actctagatc catttatgtc ataccagccc cttccattta tgcacgagag 1680

gcctga 1686

<210> 6

<211> 561
<212> PRT
<213> Mus sp.

<400> 6

```
Ala Gly Val Phe Glu Leu Gln Ile His Ser Phe Gly Pro Gly Pro Gly
1               5                  10                  15

Leu Gly Thr Pro Arg Ser Pro Cys Asn Ala Arg Gly Pro Cys Arg Leu
            20                  25                  30

Phe Phe Arg Val Cys Leu Lys Pro Gly Val Ser Gln Glu Ala Thr Glu
        35                  40                  45

Ser Leu Cys Ala Leu Gly Ala Ala Leu Ser Thr Ser Val Pro Val Tyr
    50                  55                  60

Thr Glu His Pro Gly Glu Ser Ala Ala Ala Leu Pro Leu Pro Asp Gly
65                  70                  75                  80

Leu Val Arg Val Pro Phe Arg Asp Ala Trp Pro Gly Thr Phe Ser Leu
                85                  90                  95

Val Ile Glu Thr Trp Arg Glu Gln Leu Gly Glu His Ala Gly Gly Pro
            100                 105                 110

Ala Trp Asn Leu Leu Ala Arg Val Val Gly Arg Arg Arg Leu Ala Ala
        115                 120                 125

Gly Gly Pro Trp Ala Arg Asp Val Gln Arg Thr Gly Thr Trp Glu Leu
    130                 135                 140

His Phe Ser Tyr Arg Ala Arg Cys Glu Pro Pro Ala Val Gly Ala Ala
145                 150                 155                 160

Cys Ala Arg Leu Cys Arg Ser Arg Ser Ala Pro Ser Arg Cys Gly Pro
                165                 170                 175

Gly Leu Arg Pro Cys Thr Pro Phe Pro Asp Glu Cys Glu Ala Pro Ser
            180                 185                 190

Val Cys Arg Pro Gly Cys Ser Pro Glu His Gly Tyr Cys Glu Glu Pro
        195                 200                 205

Asp Glu Cys Arg Cys Leu Glu Gly Trp Thr Gly Pro Leu Cys Thr Val
    210                 215                 220

Pro Val Ser Thr Ser Ser Cys Leu Asn Ser Arg Val Pro Gly Pro Ala
225                 230                 235                 240
```

```
Ser Thr Gly Cys Leu Leu Pro Gly Pro Gly Pro Cys Asp Gly Asn Pro
                245                 250                 255

Cys Ala Asn Gly Gly Ser Cys Ser Glu Thr Ser Gly Ser Phe Glu Cys
            260                 265                 270

Ala Cys Pro Arg Gly Phe Tyr Gly Leu Arg Cys Glu Val Ser Gly Val
        275                 280                 285

Thr Cys Ala Asp Gly Pro Cys Phe Asn Gly Gly Leu Cys Val Gly Gly
    290                 295                 300

Glu Asp Pro Asp Ser Ala Tyr Val Cys His Cys Pro Pro Gly Phe Gln
305                 310                 315                 320

Gly Ser Asn Cys Glu Lys Arg Val Asp Arg Cys Ser Leu Gln Pro Cys
                325                 330                 335

Gln Asn Gly Gly Leu Cys Leu Asp Leu Gly His Ala Leu Arg Cys Arg
            340                 345                 350

Cys Arg Ala Gly Phe Ala Gly Pro Arg Cys Glu His Asp Leu Asp Asp
        355                 360                 365

Cys Ala Gly Arg Ala Cys Ala Asn Gly Gly Thr Cys Val Glu Gly Gly
    370                 375                 380

Gly Ser Arg Arg Cys Ser Cys Ala Leu Gly Phe Gly Gly Arg Asp Cys
385                 390                 395                 400

Arg Glu Arg Ala Asp Pro Cys Ala Ser Arg Pro Cys Ala His Gly Gly
                405                 410                 415

Arg Cys Tyr Ala His Phe Ser Gly Leu Val Cys Ala Cys Ala Pro Gly
            420                 425                 430

Tyr Met Gly Val Arg Cys Glu Phe Ala Val Arg Pro Asp Gly Ala Asp
        435                 440                 445

Ala Val Pro Ala Ala Pro Arg Gly Leu Arg Gln Ala Asp Pro Gln Arg
    450                 455                 460

Phe Leu Leu Pro Pro Ala Leu Gly Leu Leu Val Ala Ala Gly Leu Ala
465                 470                 475                 480

Gly Ala Ala Leu Leu Val Ile His Val Arg Arg Arg Gly Pro Gly Gln
```

485 490 495

Asp Thr Gly Thr Arg Leu Leu Ser Gly Thr Arg Glu Pro Ser Val His
500 505 510

Thr Leu Pro Asp Ala Leu Asn Asn Leu Arg Leu Gln Asp Gly Ala Gly
515 520 525

Asp Gly Pro Ser Ser Ser Ala Asp Trp Asn His Pro Glu Asp Gly Asp
530 535 540

Ser Arg Ser Ile Tyr Val Ile Pro Ala Pro Ser Ile Tyr Ala Arg Glu
545 550 555 560

Ala

<210> 7
<211> 1794
<212> DNA
<213> Macaca fascicularis

<400> 7
ccccaagcca ggcccgctgg cgtgttcgaa ctgcagatcc atagcttcgg ccctggccct 60

ggacccggag cccctagaag cccttgttcc gctagaggcc cctgcagact gttcttcaga 120

gtctgcctga agcctggcct gagcgaggag gctgctgaga gcccttgtgc tctgggagct 180

gccctcagcg ctaggggccc tgtctacacc gagcaacctg aggctcccgc tcccgatctg 240

cctctcccta acggcctgct gcaggtgccc ttcagggatg cttggcccgg aaccttcagc 300

ctcatcatcg agacctggag ggaggaactc ggagaccaga ttggaggacc cgcctggtcc 360

ctgctcgcta gagtgacaag aagaagaagg ctggctgctg gcggaccttg ggctagagat 420

atccagagag ctggcgcctg ggagctcagg ttcagctaca gggccagatg tgagctccct 480

gccgtgggca ccgcttgtac caggctgtgt aggcccagat ccgccccttc cagatgtggc 540

cccggactca gaccttgcgc tcctctcgag gacgagtgtg aagctcctcc cgtctgtagg 600

gccggatgca gcctcgagca cggcttctgt gagcagcctg gcgaatgtag gtgcctcgaa 660

ggctggaccg gccctctctg tatggtgcct gtctccacct cctcctgtct cggactgagg 720

ggcccttcct ccgctacaac cggatgtctg gtccctggac ctggaccttg cgacggaaac 780

ccttgtgcca acggaggctc ctgtagcgag acccccggaa gctttgaatg tacctgcccc 840

aggggctttt acggcctcag atgcgaggtc agcggagtca catgcgccga cggaccctgc 900

tttaatggag gactctgcgt gggaggagcc gaccctgata gcgcttacat ctgtcactgt 960

ccccccggct ttcagggctc caactgcgag aagagggtcg acaggtgctc cctgcaaccc 1020

tgtagaaatg gcggcctctg cctggatctg ggacatgctc tcaggtgcag atgtagagct 1080

ggattcgccg gacccaggtg cgagcatgat ctcgacgatt gtgctggcag ggcctgcgct 1140

aatggaggaa catgtgtgga aggaggcgga gcccacagat gcagctgcgc tctcggcttc 1200

ggcggaagag actgcagaga gagggctgac ccttgtgccg ccaggccttg tgctcatggc 1260

ggaaggtgct acgcccattt ctccggactc gtgtgcgcct gcgcccctgg atatatgggc 1320

gctaggtgcg agtttcccgt ccaccctgat ggagtcagcg ctctccctgc cgctcctcct 1380

ggactgagac ctggagatcc tcagagatac ctgctccctc ctgccctcgg actcctggtc 1440

gctgctggag tcgctggagc cgctctcctc ctgggacacg tcaggagaag aggccacgcc 1500

caggatgctg gaagcagact gctggccgga acacccgagc cttccgtcca tgccctgcct 1560

gacgccctca acaacctgag gacccaggag ggccctggag atgtgcctag cagctccgtc 1620

gactggaaca gacctgagga tgtggactcc aggggcatct acgtgatcag cgccccctcc 1680

atctatgcca gggaggtcgc catgccccctc tttcctcctc tgcatacagg cagagccggc 1740

cagagacaga acctgctctt cccctacccc agcagcatcc tgtccgtgaa gtga 1794

<210> 8
<211> 597
<212> PRT
<213> Macaca fascicularis

<400> 8

Pro Gln Ala Arg Pro Ala Gly Val Phe Glu Leu Gln Ile His Ser Phe
1 5 10 15

Gly Pro Gly Pro Gly Pro Gly Ala Pro Arg Ser Pro Cys Ser Ala Arg
20 25 30

Gly Pro Cys Arg Leu Phe Phe Arg Val Cys Leu Lys Pro Gly Leu Ser
35 40 45

Glu Glu Ala Ala Glu Ser Pro Cys Ala Leu Gly Ala Ala Leu Ser Ala
50 55 60

Arg Gly Pro Val Tyr Thr Glu Gln Pro Glu Ala Pro Ala Pro Asp Leu
65 70 75 80

Pro Leu Pro Asn Gly Leu Leu Gln Val Pro Phe Arg Asp Ala Trp Pro
85 90 95

Gly Thr Phe Ser Leu Ile Ile Glu Thr Trp Arg Glu Glu Leu Gly Asp
100 105 110

Gln Ile Gly Gly Pro Ala Trp Ser Leu Leu Ala Arg Val Thr Arg Arg
115 120 125

```
Arg Arg Leu Ala Ala Gly Gly Pro Trp Ala Arg Asp Ile Gln Arg Ala
    130                 135                 140

Gly Ala Trp Glu Leu Arg Phe Ser Tyr Arg Ala Arg Cys Glu Leu Pro
145                 150                 155                 160

Ala Val Gly Thr Ala Cys Thr Arg Leu Cys Arg Pro Arg Ser Ala Pro
                165                 170                 175

Ser Arg Cys Gly Pro Gly Leu Arg Pro Cys Ala Pro Leu Glu Asp Glu
            180                 185                 190

Cys Glu Ala Pro Pro Val Cys Arg Ala Gly Cys Ser Leu Glu His Gly
        195                 200                 205

Phe Cys Glu Gln Pro Gly Glu Cys Arg Cys Leu Glu Gly Trp Thr Gly
    210                 215                 220

Pro Leu Cys Met Val Pro Val Ser Thr Ser Ser Cys Leu Gly Leu Arg
225                 230                 235                 240

Gly Pro Ser Ser Ala Thr Thr Gly Cys Leu Val Pro Gly Pro Gly Pro
                245                 250                 255

Cys Asp Gly Asn Pro Cys Ala Asn Gly Gly Ser Cys Ser Glu Thr Pro
            260                 265                 270

Gly Ser Phe Glu Cys Thr Cys Pro Arg Gly Phe Tyr Gly Leu Arg Cys
        275                 280                 285

Glu Val Ser Gly Val Thr Cys Ala Asp Gly Pro Cys Phe Asn Gly Gly
    290                 295                 300

Leu Cys Val Gly Gly Ala Asp Pro Asp Ser Ala Tyr Ile Cys His Cys
305                 310                 315                 320

Pro Pro Gly Phe Gln Gly Ser Asn Cys Glu Lys Arg Val Asp Arg Cys
                325                 330                 335

Ser Leu Gln Pro Cys Arg Asn Gly Gly Leu Cys Leu Asp Leu Gly His
            340                 345                 350

Ala Leu Arg Cys Arg Cys Arg Ala Gly Phe Ala Gly Pro Arg Cys Glu
        355                 360                 365

His Asp Leu Asp Asp Cys Ala Gly Arg Ala Cys Ala Asn Gly Gly Thr
```

370 375 380

Cys Val Glu Gly Gly Gly Ala His Arg Cys Ser Cys Ala Leu Gly Phe
385 390 395 400

Gly Gly Arg Asp Cys Arg Glu Arg Ala Asp Pro Cys Ala Ala Arg Pro
405 410 415

Cys Ala His Gly Gly Arg Cys Tyr Ala His Phe Ser Gly Leu Val Cys
420 425 430

Ala Cys Ala Pro Gly Tyr Met Gly Ala Arg Cys Glu Phe Pro Val His
435 440 445

Pro Asp Gly Val Ser Ala Leu Pro Ala Ala Pro Pro Gly Leu Arg Pro
450 455 460

Gly Asp Pro Gln Arg Tyr Leu Leu Pro Pro Ala Leu Gly Leu Leu Val
465 470 475 480

Ala Ala Gly Val Ala Gly Ala Ala Leu Leu Leu Gly His Val Arg Arg
485 490 495

Arg Gly His Ala Gln Asp Ala Gly Ser Arg Leu Leu Ala Gly Thr Pro
500 505 510

Glu Pro Ser Val His Ala Leu Pro Asp Ala Leu Asn Asn Leu Arg Thr
515 520 525

Gln Glu Gly Pro Gly Asp Val Pro Ser Ser Ser Val Asp Trp Asn Arg
530 535 540

Pro Glu Asp Val Asp Ser Arg Gly Ile Tyr Val Ile Ser Ala Pro Ser
545 550 555 560

Ile Tyr Ala Arg Glu Val Ala Met Pro Leu Phe Pro Pro Leu His Thr
565 570 575

Gly Arg Ala Gly Gln Arg Gln Asn Leu Leu Phe Pro Tyr Pro Ser Ser
580 585 590

Ile Leu Ser Val Lys
595

<210> 9
<211> 5
<212> PRT
<213> Homo sapiens

<400> 9
Gln Pro Gly Ala Pro
1 5

<210> 10
<211> 4
<212> PRT
<213> Homo sapiens

<220>
<221> MOD_RES
<222> (2)..(2)
<223> Any amino acid

<400> 10
Gly Xaa Arg Pro
1

<210> 11

<400> 11
000

<210> 12

<400> 12
000

<210> 13

<400> 13
000

<210> 14

<400> 14
000

<210> 15

<400> 15
000

<210> 16

<400> 16
000

<210> 17

<400> 17
000

<210> 18

<400> 18
000

<210> 19

<400> 19
000

<210> 20
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 20
Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Val Ser Leu Gly
1 5 10 15

Glu Arg Val Thr Met Thr Cys Thr Ala Ser Ser Ser Val Ser Ser Ser
20 25 30

Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Leu Trp
35 40 45

Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Ser Tyr Phe Phe Thr Ile Ser Ser Met Glu
65 70 75 80

Ala Glu Asp Ala Ala Thr Tyr Tyr Cys His Gln Tyr His Arg Ser Pro
85 90 95

Phe Thr Phe Gly Ala Gly Thr Lys Leu Lys Ile Arg
100 105

<210> 21
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 21
Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln

1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
35 40 45

Trp Leu Ala His Ile Trp Trp Asp Asp Val Lys Arg Tyr Asn Pro Ala
50 55 60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Ser Ser Gln Val
65 70 75 80

Phe Leu Lys Ile Ala Ser Val Asp Thr Ala Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Arg Ile Ala Asp Tyr Gly Gly Asp Tyr Tyr Ala Met Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 22
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 22
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
35 40 45

Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Leu
65 70 75 80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asp Met Leu Pro Trp

85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 23
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 23
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Ser Met His Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Glu Thr Gly Glu Pro Gly Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys
85 90 95

Ala Arg Tyr Asp Gly Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
100 105 110

Val Thr Val Ser Ser
115

<210> 24
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 24
Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
20 25 30

His Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr
35 40 45

Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Thr Arg Asn Pro Leu Thr
85 90 95

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 25
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 25
Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Glu Gly Leu Glu
35 40 45

Trp Leu Ala Asp Ile Trp Trp Asp Asp Asn Lys Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Ser Asn Gln Val
65 70 75 80

Phe Leu Lys Ile Thr Ser Val Asp Thr Ala Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Arg Arg Val Asn Tyr Val Tyr Asp Pro Tyr Tyr Ala Met Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 26
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 26
Asn Ile Met Met Thr Gln Ser Pro Ser Ser Leu Ala Val Ser Ala Gly
1 5 10 15

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Thr Val Gln Val Glu Asp Leu Ala Val Tyr Tyr Cys His Gln
85 90 95

Tyr Leu Ser Ser Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 27
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 27
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
20 25 30

Lys Met His Trp Val Lys Gln Ser His Val Lys Ser Leu Glu Trp Ile
35 40 45

Gly Arg Ile Asn Pro Tyr Asn Gly Ala Thr Ser Tyr Asn Gln Asn Phe
50 55 60

Lys Asp Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Asp Leu His Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
85 90 95

Ala Arg Gly Asp Tyr Arg Tyr Asp Trp Phe Ala Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ala
115

<210> 28
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 28
Glu Ile Gln Met Thr Gln Ser Pro Ser Ser Met Ser Ala Ser Leu Gly
1 5 10 15

Asp Arg Ile Thr Ile Thr Cys Gln Ala Thr Gln Asp Ile Val Lys Asn
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Pro Pro Ser Phe Leu Ile
35 40 45

Tyr Tyr Ala Ile Glu Leu Ala Glu Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Ser Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Ser
65 70 75 80

Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln Phe Tyr Glu Phe Pro Phe
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 29
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 29
Gln Ala Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Thr
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn Tyr
20 25 30

Leu Ile Glu Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Val Ile Asn Pro Gly Thr Gly Gly Thr Asn Tyr Asn Glu Asn Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Asp Asp Ser Ala Val Tyr Phe Cys
85 90 95

Ala Arg Ser Pro Tyr Asp Tyr His Glu Gly Ala Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 30
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 30
Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Thr Met Thr Cys Thr Ala Ser Ser Ser Val Ser Ser Ser
20 25 30

Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Leu Trp
35 40 45

Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Thr Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu
65 70 75 80

Ala Glu Asp Ala Ala Thr Tyr Tyr Cys His Gln Tyr His Arg Ser Pro
85 90 95

Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 31
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 31
Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Ser Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
35 40 45

Trp Leu Ala His Ile Trp Trp Asp Asp Val Lys Arg Tyr Asn Pro Val
50 55 60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Ser Ser Gln Val
65 70 75 80

Phe Leu Lys Ile Ala Ser Val Asp Thr Ala Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Arg Leu Val Asp Asp Leu Tyr Tyr Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Leu Thr Val Ser Ser
115 120

<210> 32
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 32
Asp Val Glu Met Thr Gln Thr Pro Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Ser Asp Ser
20 25 30

Asp Gly Lys Thr Tyr Leu Asn Trp Met Phe Gln Arg Pro Gly Arg Ser
35 40 45

Pro Lys Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
50 55 60

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Trp Gln Gly
85 90 95

Lys His Phe Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 33
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 33
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Ser Met His Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Glu Thr Val Glu Pro Thr Tyr Ala Asp Asp Phe

50 55 60

Met Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Phe
65 70 75 80

Leu Gln Ile Asn Asn Leu Glu Asn Glu Asp Thr Ala Thr Tyr Phe Cys
85 90 95

Ala Arg Phe Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
100 105 110

Val Thr Val Ser Ser
115

<210> 34
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 34
Gln Ile Val Leu Thr Gln Ser Pro Ala Leu Val Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Arg Ser Ser Pro Lys Pro Trp Ile Tyr
35 40 45

Leu Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Arg Ser Asn Pro Phe Thr
85 90 95

Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 35
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 35
Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
35 40 45

Trp Leu Ala His Ile Trp Trp Asp Asp Val Lys Arg Tyr Asn Pro Ala
50 55 60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Ser Ser Gln Val
65 70 75 80

Phe Leu Lys Ile Ala Ser Val Asp Thr Ala Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Arg Ile Val Ser Phe Asp Asn Asp Val Val Ser Ala Met Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 36
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 36
Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ala Ala Ser Val Gly
1 5 10 15

Glu Thr Val Ala Ile Thr Cys Arg Ala Ser Glu Asn Ile Tyr Tyr Asn
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Ile
35 40 45

Tyr Thr Ala Asn Ser Leu Glu Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Asn Ser Met Gln Pro
65 70 75 80

Glu Asp Ser Ala Thr Tyr Phe Cys Lys Gln Ala Tyr Asp Val Pro Pro
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 37
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 37
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
20 25 30

Trp Ile His Trp Ile Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Thr Thr Val Tyr Thr Glu Phe Asn Gln Asn Phe
50 55 60

Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Thr Thr Ala Ser
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Ser Asn Phe Phe Asp Tyr Trp Gly Gln Gly Thr Thr
100 105 110

Leu Thr Val Ser Ser
115

<210> 38
<211> 108
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 38
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asn Ile Ile Asn Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
35 40 45

Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Glu Arg Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> 39
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 39
Glu Val Lys Leu Glu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Glu
1 5 10 15

Ser Met Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala
20 25 30

Trp Met Asp Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val
35 40 45

Ala Glu Ile Arg Asn Lys Ala Asn Asn His Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Lys Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Arg
65 70 75 80

Val Tyr Leu Gln Met Asn Asn Leu Arg Ala Ala Asp Thr Gly Ile Tyr
85 90 95

Tyr Cys Thr Ala Tyr Ser Asn Phe Ala Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Thr
115

<210> 40
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 40
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Gly Lys Val Thr Phe Thr Cys Lys Ala Ser Gln Asp Ile His Lys Tyr
20 25 30

Val Ala Trp Tyr Gln His Lys Pro Gly Lys Gly Pro Arg Leu Leu Ile
35 40 45

His Tyr Thr Ser Thr Leu Gln Pro Gly Ile Ser Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Arg Asp Tyr Ser Phe Ser Ile Ser Asn Leu Glu Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Leu Gln Tyr Asn Asn Leu Tyr Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> 41
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 41

Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Ser
20 25 30

Leu Leu His Trp Val Lys Gln Arg Pro Glu Lys Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Asp Pro Glu Asp Gly Glu Thr Lys Tyr Ala Pro Asn Phe
50 55 60

Gln Asp Lys Ala Thr Ile Thr Thr Asp Ser Ser Ser Asn Thr Ala Tyr
65 70 75 80

Leu Gln Leu Ile Ser Leu Thr Ser Val Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Tyr Gly Asn Tyr Val Arg His Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Thr Leu Thr Val Ser Ser
115

<210> 42
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 42
Glu Ile Gln Met Thr Gln Ser Pro Ser Ser Met Ser Ala Ser Leu Gly
1 5 10 15

Asp Arg Ile Thr Ile Thr Cys Gln Ala Thr Gln Asp Ile Val Lys Asn
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Pro Pro Ser Phe Leu Ile
35 40 45

Tyr Tyr Ala Thr Glu Leu Ala Glu Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Ser Asp Tyr Ser Leu Thr Ile Arg Asn Leu Glu Ser
65 70 75 80

Glu Asp Phe Ala Asp His Tyr Cys Leu Gln Phe Tyr Glu Phe Pro Phe
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 43
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 43
Gln Val Gln Leu Gln Gln Ser Gly Thr Glu Leu Val Arg Pro Gly Thr
1 5 10 15

Ser Val Arg Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Gly Asn His
20 25 30

Leu Ile Glu Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Val Ile Asn Pro Gly Thr Gly Gly Thr His Tyr Asn Glu Lys Phe
50 55 60

Lys Asp Lys Ala Arg Leu Thr Ala Asp Lys Ser Ser Asn Thr Ala Tyr
65 70 75 80

Met His Leu Asn Ser Leu Thr Ser Asp Asp Ser Ala Val Tyr Phe Cys
85 90 95

Ala Arg Ser Pro Tyr Asp Tyr His Glu Gly Ala Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 44
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 44
Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ala Met Ser Val Gly

1 5 10 15

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Glu Pro Gly Gln
35 40 45

Ser Pro Lys Leu Leu Val Ser Phe Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Gly Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln
85 90 95

His Tyr Ser Ile Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> 45
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 45
Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Ser
20 25 30

Trp Met Asn Trp Val Lys Gln Arg Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Arg Ile Tyr Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys

85 90 95

Ala Met Gly Ile Tyr Asn Tyr Asp Gly Ser Arg Tyr Tyr Ser Met Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 46
<211> 105
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 46
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Lys Asn Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Pro Leu Ile
35 40 45

Tyr Tyr Thr Ser Arg Val His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
65 70 75 80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Tyr Thr Leu Pro Phe
85 90 95

Thr Phe Gly Ser Gly Thr Lys Leu Glu
100 105

<210> 47
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 47
Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr Tyr
20 25 30

Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asp Pro Ser Asp Ser Tyr Thr Tyr Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Asp Tyr Gly Asn Pro Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Ser Ser Val Thr Val Ser Ser
115 120

<210> 48
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 48
Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Leu Thr Cys Ser Ala Ser Ser Ser Val Ser Ser Arg
20 25 30

Tyr Leu Tyr Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Leu Trp
35 40 45

Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Ile Ile Ser Ser Met Glu
65 70 75 80

Ala Glu Asp Ala Ala Ser Tyr Phe Cys His Gln Trp Ser Asn Tyr Pro
85 90 95

Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 49
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 49
Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

Asn Thr Gly Ile Gly Trp Ile Arg Gln Pro Ser Gly Thr Gly Leu Glu
35 40 45

Trp Leu Ala His Ile Trp Trp Asn Asp Asp Lys Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Glu Thr Ser Asn Asn Gln Val
65 70 75 80

Phe Leu Lys Ile Thr Asn Val Asp Thr Ala Asp Thr Ala Ser Tyr Phe
85 90 95

Cys Val Gln Ile Gly Arg Asp Tyr Ser Asn Tyr Ala Trp Tyr Phe Asp
100 105 110

Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 50
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 50
Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1 5 10 15

```
Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
            20                  25                  30

His Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr
        35                  40                  45

Asp Ser Ser Lys Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
    50                  55                  60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Ala Glu
65                  70                  75                  80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr
                85                  90                  95

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
            100                 105
```

<210> 51
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 51

```
Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
            20                  25                  30

Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Glu Gly Leu Glu
        35                  40                  45

Trp Leu Thr Asp Ile Trp Trp Asp Asp Asn Lys Tyr Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Ser Asn Gln Val
65                  70                  75                  80

Phe Leu Asn Ile Thr Ser Val Asp Thr Ala Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

Cys Ala Arg Arg Val Asn Tyr Tyr Tyr Asp Pro Tyr Tyr Ala Met Asp
            100                 105                 110
```

Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 52
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 52
Asp Val Glu Met Thr Gln Thr Pro Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Ser Asp Ser
20 25 30

Asp Gly Lys Thr Tyr Leu Asn Trp Met Phe Gln Arg Pro Gly Arg Ser
35 40 45

Pro Lys Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
50 55 60

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Trp Gln Gly
85 90 95

Lys His Phe Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 53
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 53
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Asp Tyr
20 25 30

Ser Met His Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Glu Thr Val Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Met Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Phe
65 70 75 80

Leu Gln Ile Asn Asn Leu Glu Asn Glu Asp Thr Ala Thr Tyr Phe Cys
85 90 95

Ala Arg Phe Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
100 105 110

<210> 54
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 54
Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
20 25 30

His Trp Phe Gln Gln Lys Pro Gly Thr Ser Pro Lys Leu Trp Ile Tyr
35 40 45

Thr Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Val Ser Arg Met Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Leu Tyr Pro Tyr Thr
85 90 95

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 55
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 55
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Gln
20 25 30

Tyr Ile Asn Trp Val Lys Gln Arg Thr Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Tyr Pro Gly Arg Gly Asn Thr Tyr Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
85 90 95

Ala Arg Glu Asp Gly Gly Tyr Asp Asp Ala Trp Phe Ala Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ala
115 120

<210> 56
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 56
Gln Ile Val Leu Thr Gln Ser Pro Thr Ile Met Ser Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Thr Met Thr Cys Thr Ala Ser Ser Ser Val Thr Ser Ser
20 25 30

Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Leu Trp
35 40 45

Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser

50 55 60

Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu
65 70 75 80

Ala Glu Asp Ala Ala Thr Tyr Tyr Cys His Gln Phe His Arg Ser Pro
85 90 95

Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 57
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 57
Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
35 40 45

Trp Leu Ala His Ile Trp Trp Asp Asp Val Lys Arg Tyr Lys Pro Ala
50 55 60

Leu Lys Ser Arg Leu Thr Val Ser Lys Asp Thr Ser Ser Asn Gln Val
65 70 75 80

Phe Leu Lys Ile Ala Thr Val Asp Ala Ala Asp Thr Gly Thr Tyr Tyr
85 90 95

Cys Ala Arg Ile Val Asp Gly His Pro Pro Phe Ala Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ala
115 120

<210> 58
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 58
Asp Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Asn Ile Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Lys Ser Thr Lys Ser Leu Leu Asn Ser
20 25 30

Asp Gly Phe Thr Tyr Leu Asp Trp Tyr Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Gln Phe Leu Ile Tyr Leu Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Ser
85 90 95

Asn Tyr Leu Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Arg
100 105 110

<210> 59
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 59
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Ser Arg Phe
20 25 30

Tyr Met His Trp Val Lys Gln Ser Pro Glu Asn Ser Leu Glu Trp Gly
35 40 45

Glu Ile Asn Pro Ser Thr Gly Gly Thr Ile Ser Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Lys Ser Leu Thr Ser Glu Glu Ser Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Gly Tyr Gly Ser Asn Trp Tyr Phe Asp Val Trp Gly Ala Gly
100 105 110

Thr Thr Val Thr Val Ser Thr
115

<210> 60
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 60
Ser Ile Val Met Thr Gln Thr Pro Lys Phe Leu Leu Val Ser Ala Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn Asp
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Tyr Ala Ser Asn Arg Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Tyr Gly Thr Asp Phe Thr Phe Thr Ile Ser Thr Val Gln Ala
65 70 75 80

Glu Asp Leu Ala Val Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 61
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 61
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Arg Pro Gly Glu
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Asp Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys
85 90 95

Ala Arg Ile Gly Gly Asn Ser Pro Ser Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Ser Leu Thr Val Ser Ser
115

<210> 62
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 62
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
35 40 45

Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
65 70 75 80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 63
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 63
Ser Asp Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser
1 5 10 15

Gln Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Tyr Ser Ile Thr Ser
20 25 30

Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu
35 40 45

Trp Met Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Ser Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Phe Leu Gln Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Arg Phe Tyr Tyr Gly Ser Ser Tyr Ala Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 64
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 64

```
Glu Thr Thr Val Thr Gln Ser Pro Ala Ser Leu Ser Val Thr Thr Gly
1               5                   10                  15

Glu Lys Val Thr Ile Arg Cys Ile Thr Thr Pro Asp Ile Asp Asp Asp
            20                  25                  30

Met Asn Trp Tyr Gln Gln Lys Pro Gly Glu Pro Pro Asn Leu Leu Ile
        35                  40                  45

Ser Glu Gly Asn Ser Leu Arg Pro Gly Val Pro Ser Arg Phe Ser Ser
    50                  55                  60

Ser Gly Tyr Gly Thr Asn Phe Val Phe Thr Ile Glu Asn Thr Leu Ser
65                  70                  75                  80

Glu Asp Val Ala Asp Tyr Tyr Cys Leu Gln Ser Asp Asn Met Pro Phe
                85                  90                  95

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

<210> 65
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 65

```
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr Tyr
            20                  25                  30

Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Tyr Ile Asn Pro Ser Ser Gly Tyr Thr Glu Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ser Val Tyr Tyr Cys
                85                  90                  95
```

Ala Arg Lys Gly Ser Asn Arg Gly Phe Ala Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser
115

<210> 66
<211> 104
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 66
Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Ile Asn Tyr Met
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Thr Ser Pro Lys Arg Trp Ile Tyr
35 40 45

Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys His Gln Arg Ser Thr Trp Thr Phe Gly
85 90 95

Gly Gly Thr Lys Leu Glu Ile Lys
100

<210> 67
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 67
Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Thr Val Ser Gly Phe Asn Ile Lys Asp Thr

20 25 30

Tyr Ile His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile
35 40 45

Gly Arg Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Asp Pro Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65 70 75 80

Leu Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Pro Thr Gly Tyr Phe Glu Tyr Trp Gly Gln Gly Thr Thr Leu
100 105 110

Thr Val Ser Ser
115

<210> 68
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 68
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Val Ile Asn Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
35 40 45

Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Arg Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Glu Arg Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg

100 105

<210> 69
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 69
Glu Val Lys Leu Glu Glu Ser Gly Gly Gly Leu Val Gln Phe Gly Gly
1 5 10 15

Ser Met Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala
20 25 30

Trp Met Asp Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val
35 40 45

Ala Glu Ile Arg Asn Lys Ala Asn Asn His Ala Thr Tyr Tyr Pro Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Arg
65 70 75 80

Val Tyr Leu Gln Met Asn Asn Leu Arg Ala Glu Asp Thr Gly Ile Tyr
85 90 95

Tyr Cys Thr Gly Tyr Ser Ser Phe Ala Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ala
115

<210> 70
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 70
Asp Val Leu Met Thr Gln Ser Pro Leu Ser Leu Ser Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Asn Ile Val His Ser
20 25 30

Asp Arg Tyr Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Lys Leu Leu Ile Tyr Gly Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Met Gly Val Tyr Tyr Cys Phe Gln Gly
85 90 95

Thr His Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 71
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 71
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr Ala
20 25 30

Gly Met Gln Trp Val Gln Lys Met Pro Gly Lys Gly Phe Lys Trp Ile
35 40 45

Gly Trp Ile Asn Thr His Ser Gly Glu Pro Lys Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Ser Asn Leu Lys Asp Glu Asp Thr Ala Thr Phe Phe Cys
85 90 95

Ala Pro Leu Trp Ser Asp Ser Ser Phe Ala Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ala
115

<210> 72
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 72

Glu	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Met	Ser	Ala	Ser	Leu	Gly
1					5				10						15
Asp	Arg	Ile	Thr	Ile	Thr	Cys	Gln	Ala	Thr	Gln	Asp	Ile	Val	Lys	Asn
			20					25					30		
Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Pro	Pro	Ser	Phe	Leu	Ile
		35					40					45			
Tyr	Tyr	Ala	Thr	Glu	Leu	Ala	Glu	Gly	Val	Pro	Ala	Arg	Phe	Ser	Gly
	50					55					60				
Ser	Gly	Ser	Gly	Ser	Asp	Tyr	Ser	Leu	Thr	Ile	Ser	Asn	Leu	Glu	Ser
65					70					75					80
Glu	Asp	Phe	Ala	Asp	Tyr	His	Cys	Leu	Gln	Phe	Tyr	Glu	Phe	Pro	Phe
				85					90					95	
Thr	Phe	Gly	Ala	Gly	Thr	Lys	Leu	Glu	Leu	Lys					
			100					105							

<210> 73
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 73

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

Gly Val Ile Asn Pro Gly Ser Gly Gly Thr His Tyr Asn Glu Lys Phe
50 55 60

Lys Asp Lys Ala Val Leu Thr Ala Asp Lys Ser Ser Thr Thr Ala His
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Asp Asp Ser Ala Val Tyr Phe Cys
85 90 95

Ala Arg Ser Pro Tyr Asp Tyr Asn Asp Gly Ala Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 74
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 74
Asp Val Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Asn Ile Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Lys Ser Thr Lys Ser Leu Leu Asn Ser
20 25 30

Asp Gly Phe Thr Tyr Leu Asp Trp Tyr Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Gln Phe Leu Ile Tyr Leu Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Ser
85 90 95

Asn Tyr Leu Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Arg
100 105 110

<210> 75
<211> 119
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 75
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Ser Arg Phe
20 25 30

Tyr Met His Trp Val Lys Gln Ser Pro Glu Asn Ser Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asn Pro Ser Thr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Lys Ser Leu Thr Ser Glu Glu Ser Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Gly Tyr Gly Ser Asn Cys Tyr Phe Asp Val Trp Gly Ala Gly
100 105 110

Thr Thr Val Thr Val Ser Thr
115

<210> 76
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 76
Asp Ile Lys Met Thr Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Ser Tyr
20 25 30

Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
35 40 45

Tyr Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Thr Ser Leu Glu Tyr
65 70 75 80

Glu Asp Met Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Glu Phe Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 77
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 77
Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Thr
1 5 10 15

Leu Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Asp Ile Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Tyr Pro Gly Asp Gly Asn Thr Lys Tyr Ser Glu Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Thr Ser Leu Thr Ser Glu Asn Ser Ala Val Tyr Phe Cys
85 90 95

Ala Arg Asp Tyr Asp Tyr Pro Phe Ala Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ala
115

<210> 78
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 78
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
35 40 45

Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
65 70 75 80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Arg Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 79
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 79
Glu Val Gln Leu Val Glu Cys Gly Gly Cys Leu Val Lys Pro Gly Gly
1 5 10 15

Tyr Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ser Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

Ala Glu Ile Ser Ile Gly Gly Ser Tyr Thr Tyr Tyr Pro Asp Thr Val
50 55 60

Thr Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr

65 70 75 80

Leu Glu Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Asp Tyr Asp Val Arg Ala Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 80
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 80
Asp Ile Gln Met Ile Gln Ser Pro Ser Ser Met Phe Ala Ser Leu Gly
1 5 10 15

Asp Arg Val Ser Leu Ser Cys Arg Ala Ser Gln Gly Ile Arg Gly Thr
20 25 30

Leu Asp Trp Tyr Gln Gln Lys Pro Asn Gly Thr Ile Lys Leu Leu Ile
35 40 45

Tyr Ser Thr Ser Asn Leu Asn Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Ser Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
65 70 75 80

Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln Arg Asn Ala Tyr Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 81
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 81
Gln Val Gln Leu Lys Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15

Ser Leu Ser Ile Thr Cys Ala Val Ser Gly Phe Ser Leu Thr Ser Phe
20 25 30

Ala Ile His Trp Phe Arg Lys Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Val Ile Trp Thr Gly Gly Thr Thr Asn Tyr Asn Ser Ala Leu Met
50 55 60

Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Lys Ser Gln Val Phe Leu
65 70 75 80

Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Asp Asp Tyr Asp Asn Asn Tyr Ala Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Ser Val Thr Val Ser Ser
115

<210> 82
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 82
Asp Ile Lys Met Thr Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Ser Tyr
20 25 30

Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
35 40 45

Tyr Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Tyr
65 70 75 80

Glu Asp Met Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Glu Phe Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> 83
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 83
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Lys Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Val Ser Ala Phe Thr Phe Thr Thr Tyr
20 25 30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Arg Asn Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
50 55 60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Gln Ser Met
65 70 75 80

Leu Tyr Leu Gln Met Asn Asn Leu Lys Ile Glu Asp Thr Ala Met Tyr
85 90 95

Tyr Cys Val Phe Tyr Tyr Asp Tyr Val Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ala
115

<210> 84
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 84
Ser Ile Val Met Thr Gln Thr Pro Lys Phe Leu Leu Val Ser Ala Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn Asp
20 25 30

Val Val Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Tyr Ala Ser Asn Arg Tyr Thr Gly Val Pro Asp Arg Phe Ala Gly
50 55 60

Ser Gly Tyr Gly Thr Asp Phe Ser Phe Thr Ile Ser Thr Val Gln Ala
65 70 75 80

Glu Asp Leu Ala Val Tyr Phe Cys Gln Gln Asp Tyr Thr Ser Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Arg
100 105

<210> 85
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 85
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
35 40 45

Ala Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Ser
65 70 75 80

Leu Gln Ile Ile Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys
85 90 95

Ala Arg Ile Gly Asp Ser Ser Pro Ser Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Thr Leu Thr Val Ser Ser
115

<210> 86
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 86
Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Ile Ser Val Gly
1 5 10 15

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Phe
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Ile Phe Thr Ile Ser Ser Val Gln Ala
65 70 75 80

Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Gly Thr Pro Phe
85 90 95

Thr Phe Gly Ser Gly Thr Lys Leu Lys Ile Arg
100 105

<210> 87
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 87
Glu Val Lys Leu Val Glu Ser Gly Gly Asp Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Ala Phe Ser Ser Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Ser Gly Gly Ser Tyr Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Arg Asp Thr Leu Tyr
65 70 75 80

Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Arg Gln Ala Ile Gly Thr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Thr Leu Thr Val Ser Ser
115

<210> 88
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 88
Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ser Ser Val Gly
1 5 10 15

Glu Thr Val Thr Ile Thr Cys Arg Ala Ser Glu Asn Ile Tyr Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val
35 40 45

Tyr Asn Ala Lys Thr Leu Ala Glu Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Gln Phe Ser Leu Lys Ile Asn Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Gly Thr Tyr Tyr Cys Gln His His Tyr Asp Ser Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Arg
100 105

<210> 89
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 89
Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Arg Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
35 40 45

Ala Tyr Ile Ser Ser Gly Ser Ser Asn Ile Tyr Tyr Ala Asp Thr Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Pro Lys Asn Thr Leu Phe
65 70 75 80

Leu Gln Met Thr Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Gly Tyr Tyr Gly Asn Tyr Asp Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 90
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 90
Asp Ile Val Met Thr Gln Ser Thr Ser Ser Leu Ala Met Ser Val Gly
1 5 10 15

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser

20 25 30

Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Glu Pro Gly Gln
35 40 45

Ser Pro Lys Leu Leu Val Ser Phe Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Gly Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln
85 90 95

His Tyr Ser Ile Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> 91
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 91
Glu Val Leu Leu Gln Arg Ser Gly Pro Asp Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Thr Ile Pro Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Asn Met Asp Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Asn Ile Asn Thr Tyr Asn Gly Gly Thr Ile Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Pro Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Leu Arg Tyr Gly Gly His Tyr Phe Asp Tyr Trp Gly Gln

100 105 110

Gly Thr Ala Leu Thr Val Ser Ser
115 120

<210> 92
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 92
Asp Ile Lys Met Thr Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Ser Phe
20 25 30

Leu Ser Trp Phe Gln Arg Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
35 40 45

Tyr Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Gln Glu Phe Ser Leu Thr Ile Ser Ser Leu Glu Tyr
65 70 75 80

Glu Asp Leu Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Glu Phe Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> 93
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 93
Glu Val Met Leu Val Glu Ser Gly Gly Asp Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

Ala Tyr Ile Ser Gly Gly Gly Asp His Ile Tyr Tyr Pro Asp Ser Val
50 55 60

Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asp Thr Leu Tyr
65 70 75 80

Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Leu Tyr Asp Cys
85 90 95

Ala Arg Val Arg Asp Trp Tyr Phe Asp Val Trp Gly Ala Gly Thr Thr
100 105 110

Val Thr Val Ser Ser
115

<210> 94
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 94
Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
20 25 30

Tyr Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr
35 40 45

Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Tyr Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 95
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 95
Gln Val Gln Leu Gln Gln Ser Gly Thr Glu Leu Leu Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Thr Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Met Glu Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Ser Gly Thr Thr Gln Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Lys Ala Thr Phe Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65 70 75 80

Met His Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Thr Asn Ser Leu Trp Gly Gln Gly Thr Leu Val Thr Val
100 105 110

Ser Ala

<210> 96
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 96
Gln Ile Val Leu Thr Gln Ser Pro Ala Leu Met Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Met Thr Cys Ser Val Thr Ser Ser Val Ser Tyr Met
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Arg Ser Ser Pro Lys Pro Trp Ile Tyr
35 40 45

Leu Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Val Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Arg Asn Asn Pro Phe Thr
85 90 95

Phe Gly Ser Gly Thr Lys Val Glu Ile Lys
100 105

<210> 97
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 97
Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
35 40 45

Trp Leu Ala Leu Ile Trp Trp Asp Asp Val Lys Arg Tyr Asn Pro Ala
50 55 60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Ala Ser Ser Ser Gln Val
65 70 75 80

Phe Leu Lys Ile Ala Ser Val Asp Thr Ala Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Arg Ile Ala Ser Tyr Asp Tyr Asp Val Val Tyr Ala Met Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Ser Val Ser Val Ser Ser
115 120

<210> 98
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 98

Gln	Ala	Val	Val	Thr	Gln	Glu	Ser	Ala	Leu	Thr	Thr	Ser	Pro	Gly	Glu
1				5				10						15	
Thr	Val	Thr	Leu	Thr	Cys	Arg	Ser	Ser	Thr	Gly	Ala	Val	Thr	Thr	Ser
			20					25					30		
Asn	Tyr	Ala	Asn	Trp	Ile	Gln	Glu	Lys	Pro	Asp	His	Leu	Phe	Thr	Gly
		35					40					45			
Leu	Ile	Gly	Gly	Thr	Asn	Asn	Arg	Ala	Pro	Gly	Val	Pro	Ala	Arg	Phe
	50					55					60				
Ser	Gly	Ser	Leu	Ile	Gly	Asp	Lys	Ala	Ala	Leu	Thr	Ile	Thr	Gly	Ala
65					70					75					80
Gln	Thr	Glu	Asp	Glu	Ala	Ile	Tyr	Phe	Cys	Gly	Leu	Trp	Tyr	Ser	Asn
				85					90					95	
His	Leu	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu			
			100					105							

<210> 99
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 99

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

Ala Arg Ile Arg Asn Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
50 55 60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Gln Ser Met
65 70 75 80

Leu Tyr Leu Gln Met Asn Asn Leu Lys Ile Glu Asp Thr Ala Met Tyr
85 90 95

Tyr Cys Val Phe Tyr Tyr Asp Tyr Val Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ala
115

<210> 100
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 100
Glu Thr Thr Val Thr Gln Ser Pro Ala Phe Leu Ser Val Ala Thr Gly
1 5 10 15

Glu Lys Val Thr Ile Arg Cys Ile Thr Ser Thr Asp Ile Asp Asp Asp
20 25 30

Met Asn Trp Tyr Gln Gln Lys Pro Gly Glu Pro Pro Asn Val Leu Ile
35 40 45

Ser Glu Gly Asn Thr Leu Arg Pro Gly Val Pro Ser Arg Phe Ser Ser
50 55 60

Ser Gly Tyr Gly Thr Asp Phe Val Phe Thr Ile Glu Asn Thr Leu Ser
65 70 75 80

Glu Asp Val Ala Asp Tyr Tyr Cys Leu Gln Ser Asp Asn Met Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 101
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 101
Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Asn Met His Trp Val Lys Gln Thr Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Phe Pro Gly Asn Gly Gly Thr Ser Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Thr Ser Leu Thr Ser Gly Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Gly Tyr Gly Ser Gly Leu Tyr Ala Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 102
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 102
Glu Asn Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Leu Gly
1 5 10 15

Glu Lys Val Thr Met Ser Cys Arg Ala Ser Ser Ser Val Asn Tyr Met
20 25 30

Ser Trp Tyr Gln Gln Lys Ser Asp Ala Ser Pro Lys Leu Trp Ile Tyr
35 40 45

Tyr Thr Ser Asn Leu Ala Pro Gly Val Pro Ala Arg Phe Ser Gly Ser

50 55 60

Gly Ser Gly Asn Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Gly Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Phe Thr Ser Ser Pro Tyr Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> 103
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 103
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Leu Arg Ser Arg Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
100 105 110

Val Thr Val Ser Ser
115

<210> 104
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 104
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Ser Leu Thr Cys Arg Ala Ser Gln Asp Ile Gly Tyr Ser
20 25 30

Leu Asn Trp Leu Gln Gln Glu Pro Asp Gly Thr Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Thr Ser Ser Leu Asp Ser Gly Val Pro Lys Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
65 70 75 80

Glu Asp Phe Val Asp Tyr Tyr Cys Leu Gln Tyr Ala Ser Ser Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 105
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 105
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Met Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Asn Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Leu Arg Gln Arg Pro Gly His Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Ser Asp Asn Ser Asn Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Lys Ala Thr Phe Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Glu Ser Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Gly Leu Arg Arg Asp Gly Ser Tyr Tyr Tyr Val Met Glu His
100 105 110

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 106
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 106
Asp Ile Lys Met Thr Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Ser Tyr
20 25 30

Leu Ser Trp Phe Gln Gln Lys Pro Gly Arg Ser Pro Lys Thr Leu Ile
35 40 45

Tyr Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Asp Tyr
65 70 75 80

Glu Asp Met Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Glu Phe Pro Phe
85 90 95

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 107
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 107
Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Gly Arg Tyr
20 25 30

Val Met Ser Trp Val Arg Gln Thr Pro Glu Lys Lys Leu Glu Trp Val
35 40 45

Ala Ser Ile Thr Ser Gly Gly Thr Thr Tyr Tyr Pro Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Ile Leu Tyr Leu
65 70 75 80

Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Val Tyr Tyr His Tyr Asp Asp Ile Phe Ala Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ala
115

<210> 108
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 108
Asp Ile Val Met Ser Gln Ser Pro Ser Ser Leu Ala Val Ser Ala Gly
1 5 10 15

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Arg Thr Arg Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Lys Gln
85 90 95

Ser Tyr Asn Leu Tyr Thr Phe Gly Gly Gly Thr Lys Leu Lys Ile Lys
100 105 110

Arg

<210> 109
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 109
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr Glu Tyr
20 25 30

Thr Met His Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Gly Ile Asn Pro Asn Asn Gly Gly Thr Ser Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Pro Ala Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ala
115

<210> 110
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 110

Glu Thr Thr Val Thr Gln Ser Pro Ala Ser Leu Ser Met Ala Ile Gly
1 5 10 15

Glu Lys Val Thr Ile Arg Cys Ile Thr Ser Thr Asp Ile Asp Asp Asp
20 25 30

Met Ile Trp Tyr Gln Gln Lys Pro Gly Glu Pro Pro Lys Leu Leu Ile
35 40 45

Ser Glu Gly Asn Thr Leu Arg Pro Gly Val Pro Ser Arg Phe Ser Ser
50 55 60

Ser Gly Tyr Gly Thr Asp Phe Val Phe Thr Ile Glu Asn Met Leu Ser
65 70 75 80

Glu Asp Val Ala Asp Tyr Tyr Cys Leu Lys Arg Asp Asp Leu Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Gln Val Glu Ile Lys Arg
100 105

<210> 111
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 111

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Lys Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
20 25 30

Ser Met Asn Trp Val Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile
35 40 45

Gly Leu Ile Asn Pro Tyr Ser Gly Gly Thr Ile Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ser Asp Tyr Pro Leu Val Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ala
115

<210> 112
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 112
Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Thr Leu Thr Cys Thr Ala Ser Ser Ser Val Ser Ser Ser
20 25 30

Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Leu Trp
35 40 45

Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Thr Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Arg Ile Ser Ser Met Glu
65 70 75 80

Ala Glu Asp Ala Ala Thr Tyr Tyr Cys His Gln Tyr Asn Arg Ser Pro
85 90 95

Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 113
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 113
Gln Val Gln Leu Lys Glu Ser Gly Pro Val Leu Val Ala Pro Ser Gln

1 5 10 15

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Tyr
20 25 30

Gly Val His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Ser Ala Leu Met
50 55 60

Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Lys Ser Gln Val Phe Leu
65 70 75 80

Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Lys Gln Gly Asn Phe Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
100 105 110

Val Thr Val Ser Ser
115

<210> 114
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 114
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Gly Lys Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Lys Lys Tyr
20 25 30

Ile Ala Trp Tyr Gln His Lys Pro Gly Lys Gly Pro Arg Leu Leu Ile
35 40 45

His Tyr Thr Ser Thr Leu Glu Pro Gly Ile Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Arg Asp Tyr Ser Phe Ser Ile Ser Asn Leu Glu Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Leu Gln Tyr Asp Ile Leu Trp Thr

85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 115
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 115
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
20 25 30

Thr Met Asn Trp Val Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile
35 40 45

Gly Leu Ile Asn Pro Tyr Asn Gly Gly Thr Thr Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Leu Gly Tyr Tyr Gly Asn Tyr Arg Arg Tyr Phe Asp Val Trp Gly
100 105 110

Ala Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 116
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 116
Glu Asn Val Leu Thr Gln Ser Pro Ala Ile Met Ala Ala Ser Leu Gly
1 5 10 15

```
Gln Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Ser Ser
            20                  25                  30

Tyr Leu His Trp Tyr Gln Gln Lys Ser Gly Ala Ser Pro Lys Pro Leu
        35                  40                  45

Ile His Arg Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser
    50                  55                  60

Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Val Glu
65                  70                  75                  80

Ala Glu Asp Asp Ala Thr Tyr Tyr Cys Arg Gln Trp Ser Gly Tyr Pro
                85                  90                  95

Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

<210> 117
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 117

```
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
1               5                   10                  15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Cys Thr Ser Tyr
            20                  25                  30

Trp Met Gln Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Ala Ile Tyr Pro Gly Asp Gly Asp Thr Arg Tyr Thr Gln Lys Phe
    50                  55                  60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80

Met Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Arg Arg Thr Glu Ala Trp Phe Ala Tyr Trp Gly Gln Gly
            100                 105                 110
```

Thr Leu Val Thr Val Ser Ala
115

<210> 118
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 118
Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Thr Met Thr Cys Thr Ala Ser Ser Ser Val Ser Ser Ser
20 25 30

Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Leu Trp
35 40 45

Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser
50 55 60

Gly Ser Glu Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Asn Met Glu
65 70 75 80

Ala Glu Asp Ala Ala Thr Tyr Tyr Cys His Gln Tyr His Arg Ser Pro
85 90 95

Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 119
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 119
Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
35 40 45

Trp Leu Ala His Ile Trp Trp Asp Asp Val Lys Arg Tyr Asn Pro Ala
50 55 60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Ala Ser Ser Ser Gln Val
65 70 75 80

Phe Leu Lys Ile Ala Ser Val Asp Thr Ala Glu Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala His Ile Leu Asp Arg Ala Tyr Tyr Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Leu Thr Val Thr Ser
115 120

<210> 120
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 120
Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Lys Ser Val Ser Thr Ser
20 25 30

Gly Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65 70 75 80

Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln His Ser Arg
85 90 95

Glu Leu Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

<210> 121
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 121
Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

Gly Met Ile Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu Trp
35 40 45

Leu Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Gln Leu Thr Ile Ser Lys Asp Ser Ser Arg Asn Gln Val Phe
65 70 75 80

Leu Lys Ile Thr Ser Val Asp Thr Ala Asp Thr Ala Thr Tyr Tyr Cys
85 90 95

Ala Arg Arg Gly Thr Ala Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Thr Leu Thr Val Ser Ser
115

<210> 122
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 122
Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Ile
20 25 30

```
His Trp Tyr Arg Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
        35                  40                  45

Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
    50                  55                  60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65                  70                  75                  80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Pro Thr
                85                  90                  95

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
            100                 105
```

<210> 123
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 123

```
Gln Val Gln Leu Lys Glu Ser Gly Pro Asp Leu Val Gln Pro Ser Gln
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Phe Tyr
            20                  25                  30

Gly Val His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Gly Thr Met Gly Trp Asp Asp Lys Lys Tyr Tyr Asn Ser Ala Leu Lys
    50                  55                  60

Ser Arg Leu Ser Ile Ser Arg Asp Thr Ser Lys Asn Gln Val Phe Leu
65                  70                  75                  80

Lys Leu Ser Ser Leu Gln Thr Glu Asp Thr Ala Met Tyr Tyr Cys Thr
                85                  90                  95

Arg Gly Gly Thr Gly Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr
            100                 105                 110

Val Ser Ser
        115
```

<210> 124
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 124
Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Ile Thr Lys Ala Ser Gln Asp Val Gly Thr Ala Val
20 25 30

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr
35 40 45

Trp Ala Ser Ile Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly Ser
50 55 60

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser Glu
65 70 75 80

Asp Leu Ala Asp Tyr Phe Cys Gln Gln Tyr Ser Ser Tyr Pro Leu Thr
85 90 95

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 125
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 125
Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Val Ile Asn Pro Ser Asn Gly Arg Thr Asn Tyr Asn Glu Lys Phe

50 55 60

Lys Ser Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Arg Glu Leu Gly Thr Leu Tyr Ala Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 126
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 126
Asp Ile Lys Met Thr Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Ser Tyr
20 25 30

Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
35 40 45

Tyr Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Tyr
65 70 75 80

Glu Asp Met Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Glu Phe Pro Phe
85 90 95

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 127
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 127
Gln Val Gln Leu Lys Gln Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15

Ser Leu Phe Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Tyr
20 25 30

Glu Ile Asn Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Val Ile Trp Thr Gly Gly Ser Thr Asn Tyr Asn Ser Ala Leu Ile
50 55 60

Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Lys Ser Leu Val Phe Leu
65 70 75 80

Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Val
85 90 95

Arg Gly Val Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr
100 105 110

Val Ser Ser
115

<210> 128
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 128
Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Val Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Val Gln Ala
65 70 75 80

Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Ser Ser Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> 129
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 129
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Thr Thr Ala Tyr
65 70 75 80

Met Ala Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Val Ala Tyr Tyr Ser Asn Trp Gly Phe Ala Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ala
115

<210> 130
<211> 108
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 130
Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Glu Thr Val Thr Ile Thr Cys Arg Ala Ser Glu Asn Ile Tyr Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val
35 40 45

Tyr Asn Ala Lys Thr Leu Ala Glu Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Gln Phe Ser Leu Lys Ile Asn Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His His Tyr Gly Thr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> 131
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 131
Gln Val Gln Leu Glu Glu Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ser Tyr Trp Met Gln
20 25 30

Trp Ile Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Ala Ile
35 40 45

Tyr Pro Gly Asn Gly Asp Thr Arg Tyr Thr Gln Lys Phe Lys Gly Lys
50 55 60

Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu
65 70 75 80

Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Ser
85 90 95

Pro Ala Tyr Tyr Arg Tyr Gly Glu Gly Tyr Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Leu Thr Val Ser Ser
115 120

<210> 132
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 132
Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Arg Leu Leu Ile Tyr
35 40 45

Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Phe Ser Leu Thr Ile Ser Arg Met Glu Ala Glu
65 70 75 80

Asp Thr Ala Thr Tyr Tyr Cys Gln Glu Trp Ser Gly Asn Pro Leu Thr
85 90 95

Phe Gly Asp Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 133
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 133

```
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1               5                   10                  15

Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
            20                  25                  30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
        35                  40                  45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Ala Tyr Ala Asp Asp Phe
    50                  55                  60

Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Ala Ala Tyr
65                  70                  75                  80

Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Phe Phe Cys
                85                  90                  95

Ala Asn Met Arg Pro Thr Arg Gly Phe Ala Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Gly Thr Val Ser Ala
        115
```

<210> 134
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 134

```
Asn Ile Val Met Thr Gln Thr Pro Lys Phe Leu Leu Val Ser Ala Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn Asp
            20                  25                  30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Tyr Ala Ser Asn Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
    50                  55                  60

Ser Gly Tyr Gly Thr Asp Phe Thr Phe Thr Ile Ser Thr Val Gln Ala
65                  70                  75                  80
```

Glu Asp Leu Ala Val Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Pro Pro
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 135
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 135
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Arg Thr Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
20 25 30

Tyr Met His Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Ser Cys Tyr Asn Gly Ala Thr Thr Tyr Asn Gln Asn Phe
50 55 60

Lys Gly Lys Ala Thr Phe Ile Val Asp Thr Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Phe Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Asp Gly Gly His Ala Met Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Ser Val Thr Val Ser Ser
115

<210> 136
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 136
Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ala Ala Ser Val Gly

1 5 10 15

Glu Thr Val Thr Ile Thr Cys Arg Ala Ser Glu Asn Ile Tyr Tyr Ser
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Ile
35 40 45

Tyr Asn Ala Asn Ser Leu Glu Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Gln Tyr Ser Met Lys Ile Asn Ser Met Gln Pro
65 70 75 80

Glu Asp Thr Ala Thr Tyr Phe Cys Lys Gln Thr Tyr Asp Val Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 137
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 137
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Glu Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
20 25 30

Asn Met Asn Trp Val Lys Gln Ser Asn Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Asn Ile Asp Pro Tyr Tyr Gly Gly Ser Ser Tyr Lys Gln Lys Phe
50 55 60

Glu Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Lys Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Ser Asn Phe Phe Asp Tyr Trp Gly Gln Gly Thr Thr

100 105 110

Leu Thr Val Ser Ser
115

<210> 138
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 138
Asp Val Val Met Thr Gln Thr Pro Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Asp Gly Thr Thr Tyr Leu Asn Trp Leu Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Lys Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
50 55 60

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Trp Gln Gly
85 90 95

Thr His Phe Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

<210> 139
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 139
Asp Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Thr Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Ser Gly Gly Ser Tyr Pro Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Thr Arg Asp Val Tyr Asp Gly Tyr Ser Tyr Trp Gly Gln Gly Thr Thr
100 105 110

Leu Thr Val Ser Ser
115

<210> 140
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 140
Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Met
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
35 40 45

Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Tyr Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> 141
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 141
Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Thr
20 25 30

Tyr Ile His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile
35 40 45

Gly Arg Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Asp Pro Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Pro Asp Thr Ser Ser Asn Thr Ala Tyr
65 70 75 80

Leu Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Trp Arg Asn Tyr Gly Ser Ser Phe Trp Tyr Phe Asp Val
100 105 110

Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 142
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 142
Asp Val Val Met Thr Gln Thr Pro Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Asp Gly Thr Thr Tyr Leu Asn Trp Leu Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Lys Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
50 55 60

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Trp Gln Gly
85 90 95

Thr His Phe Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

<210> 143
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 143
Asp Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Thr Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Ser Gly Gly Ser Tyr Pro Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Thr Arg Asp Val Tyr Asp Gly Tyr Ser Tyr Trp Gly Gln Gly Thr Thr
100 105 110

Leu Thr Val Ser Ser
115

<210> 144
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 144
Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Thr Val Thr Ala Gly
1 5 10 15

Glu Lys Val Thr Met Ser Cys Thr Ser Ser Gln Ser Leu Leu Thr Ser
20 25 30

Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Asn
85 90 95

Asp Tyr Ser Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

<210> 145
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 145
Gln Val Gln Leu Lys Gln Ser Gly Pro Gly Arg Val Gln Pro Ser Gln
1 5 10 15

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Asn
20 25 30

Gly Val Val His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp
35 40 45

Leu Gly Val Leu Trp Ser Gly Gly Ser Thr Asp Tyr Asn Ala Ala Phe
50 55 60

Ile Ser Arg Leu Ser Ile Ser Lys Asp Asn Tyr Lys Ser Gln Val Phe
65 70 75 80

Phe Lys Met Asn Ser Leu Gln Ala Asn Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Arg Asn Asn Asn Arg Tyr Gly Ala Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Ser Val Thr Val Ser Ser
115

<210> 146
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 146
Asp Ile Gln Met Asn Gln Ser Pro Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Thr Ile Thr Ile Thr Cys His Val Ser Gln Asn Ile Asn Val Trp
20 25 30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Asn Ile Pro Lys Leu Leu Ile
35 40 45

Gln Lys Ala Ser Asn Leu His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Gly Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Gly Gln Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 147
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 147
Gln Val Gln Leu Lys Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15

Ser Leu Ser Ile Pro Cys Thr Val Ser Gly Phe Ser Leu Thr Asn Tyr
20 25 30

Gly Val His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Ser Ala Leu Met
50 55 60

Ser Arg Leu Ser Ile Ser Glu Asp Asn Ser Lys Ser Gln Val Phe Leu
65 70 75 80

Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Asn Leu Gly Pro Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
100 105 110

Val Thr Val Ser Ser
115

<210> 148
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 148
Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
20 25 30

Gly Asp Ser Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala

50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65 70 75 80

Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Ser Asn
85 90 95

Glu Asp Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105 110

<210> 149
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 149
Glu Val Gln Leu Gln Gln Ser Gly Pro Asp Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
20 25 30

Tyr Met His Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Arg Val Asn Pro Asn Asn Gly Gly Thr Ser Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Ile Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Ser Tyr Asp Tyr Ala Glu Gly Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ala
115

<210> 150
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 150
Asp Ile Val Met Ser Gln Ser Pro Ser Ser Leu Ala Val Ser Val Gly
1 5 10 15

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
20 25 30

Ser Thr Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Val Lys Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Ser Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
100 105 110

Lys Arg

<210> 151
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 151
Glu Ile Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Ser Tyr
20 25 30

Asn Met Tyr Trp Val Met Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Tyr Val Asp Pro Tyr Asn Gly Gly Thr Ser Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met His Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Asn Tyr Arg Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Thr
100 105 110

Leu Thr Val Ser Ser
115

<210> 152
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 152
Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
20 25 30

His Trp Phe Gln Gln Lys Pro Gly Thr Ser Pro Lys Leu Trp Ile Tyr
35 40 45

Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Met Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Ser Tyr Pro Pro Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> 153
<211> 124
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 153
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Lys Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr
20 25 30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Arg Ile Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
50 55 60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Gln Asn Met
65 70 75 80

Leu Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Val Arg Gln Gly Tyr Ser Tyr Asp Trp Gly Pro Trp Phe Ala
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala
115 120

<210> 154
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 154
Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Val Leu Ile
35 40 45

Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
65 70 75 80

Glu Asp Leu Ala Glu Phe Phe Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 155
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 155
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Tyr Met Phe Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Asp Gly Gly Ser Tyr Thr Tyr Phe Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Gln Asn Asn Leu Tyr
65 70 75 80

Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Ala Gly Thr Leu Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Ser Val Thr Val Ser Ser
115

<210> 156
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 156

Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Thr Met Thr Cys Thr Ala Ser Ser Ser Val Ser Ser Ser
20 25 30

Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Leu Trp
35 40 45

Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu
65 70 75 80

Thr Glu Asp Ala Ala Thr Tyr Tyr Cys His Gln Tyr His Arg Ser Pro
85 90 95

Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 157
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 157

Gln Val Ala Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
35 40 45

Trp Leu Ala His Ile Trp Trp Asp Asp Val Lys Arg Tyr Asn Pro Ala
50 55 60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Ser Ser Gln Val
65 70 75 80

Phe Leu Lys Ile Ala Ser Val Asp Thr Ala Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Arg Met Glu Asp Tyr Gly Ser Ser Ser Tyr Phe Asp Phe Trp
100 105 110

Gly His Gly Thr Thr Leu Thr Val Ser Ser
115 120

<210> 158
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 158
Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Gln Ser Ala Ser Leu Gly
1 5 10 15

Glu Ser Val Thr Ile Thr Cys Leu Ala Ser Gln Thr Ile Gly Thr Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro Gln Leu Leu Ile
35 40 45

Ser Ala Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Lys Phe Ser Phe Lys Ile Ser Ser Leu Gln Ala
65 70 75 80

Glu Asp Phe Val Ser Tyr Tyr Cys Gln Gln Leu Tyr Ser Thr Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 159
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 159
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala

1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Ala Leu Tyr Tyr Gly Asn Tyr Leu Gly Tyr Phe Asp Val
100 105 110

Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 160
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 160
Asp Ile Gln Met Asn Gln Ser Pro Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Thr Ile Thr Ile Thr Cys His Ala Ser Gln Asn Ile Asn Val Trp
20 25 30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Asn Ile Pro Lys Leu Leu Ile
35 40 45

Tyr Lys Ala Ser Ile Leu His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Gly Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Ser Cys Gln Gln Gly Gln Ser Tyr Pro Tyr

85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 161
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 161
Ser Asp Val Gln Leu Gln Glu Ser Gly Pro Asp Leu Val Lys Pro Ser
1 5 10 15

Gln Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Tyr Ser Ile Thr Ser
20 25 30

Gly Tyr Ser Trp His Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu
35 40 45

Trp Met Gly Tyr Ile His Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Phe Leu Gln Phe Lys Ser Val Thr Thr Glu Asp Ser Ala Thr Tyr Tyr
85 90 95

Cys Ala Leu Glu Gly Asn Tyr Asp Gly Phe Ala Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser
115

<210> 162
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 162
Asp Ile Gln Met Asn Gln Ser Pro Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Thr Ile Thr Ile Thr Cys His Ala Ser Gln Asn Ile Asn Val Trp
20 25 30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Asn Ile Pro Lys Leu Leu Ile
35 40 45

Tyr Lys Ala Ser Asn Leu His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Gly Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Gly Gln Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 163
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 163
Gln Val Gln Met Lys Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Ser Ser Leu Thr Asn Tyr
20 25 30

Gly Val His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Ser Ala Leu Met
50 55 60

Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Lys Ser Gln Val Phe Leu
65 70 75 80

Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Asp Trp Glu Gly Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ala
115

<210> 164
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 164
Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Gln Ser Ala Ser Leu Gly
1 5 10 15

Glu Ser Val Thr Ile Thr Cys Leu Ala Ser Gln Thr Ile Gly Thr Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro Gln Leu Leu Ile
35 40 45

Tyr Ala Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Lys Phe Ser Phe Lys Ile Ser Ser Leu Gln Ala
65 70 75 80

Glu Asp Phe Val Ser Tyr Tyr Cys Gln Gln Leu Tyr Ser Thr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> 165
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 165
Gln Val Gln Leu Lys Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15

Ser Leu Ser Ile Thr Cys Thr Val Ser Ser Gly Phe Ser Leu Thr Asp
20 25 30

Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45

Leu Gly Val Ile Trp Gly Gly Gly Ser Thr Tyr Tyr Asn Ser Ala Leu
50 55 60

Lys Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Lys Ser Gln Val Phe
65 70 75 80

Leu Glu Leu Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Lys His Tyr Gly His Tyr Ala Ala Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ala
115

<210> 166
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 166
Asp Ile Gln Leu Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Glu Thr Val Thr Ile Thr Cys Arg Ala Ser Gly Ser Ile His Asn Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val
35 40 45

Tyr Asn Ala Lys Thr Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Asn Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Gly Tyr Tyr Tyr Cys Gln His Phe Trp Thr Thr Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 167
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 167
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Glu Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Val Tyr Asp Gly Tyr Ser Tyr Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Leu Thr Val Ser Ser
115 120

<210> 168
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 168
Asp Ile Gln Met Asn Gln Ser Pro Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Thr Ile Thr Ile Thr Cys His Val Ser Gln Asn Ile Asn Val Trp
20 25 30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Asn Ile Pro Lys Leu Leu Ile
35 40 45

Gln Lys Ala Ser Asn Leu His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Gly Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Gly Gln Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 169
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 169
Gln Val Gln Leu Lys Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Asn Tyr
20 25 30

Gly Val Val His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45

Leu Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Ser Ala Leu
50 55 60

Met Ser Arg Leu Ser Ile Ser Glu Asp Asn Ser Lys Ser Gln Val Phe
65 70 75 80

Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Asn Leu Gly Pro Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Ser Val Thr Val Ser Ser
115

<210> 170
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 170
Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Gln Ser Ala Ser Leu Gly
1 5 10 15

Glu Ser Val Thr Ile Thr Cys Leu Ala Ser Gln Thr Ile Gly Thr Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro Gln Leu Leu Ile
35 40 45

Tyr Ala Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Lys Phe Ser Phe Lys Ile Ser Ser Leu Gln Ala
65 70 75 80

Glu Asp Phe Val Ser Tyr Tyr Cys Gln Gln Leu Tyr Ser Thr Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 171
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 171
Gln Val Gln Leu Lys Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Asp Tyr
20 25 30

Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Val Val Trp Gly Gly Gly Ser Thr Tyr Tyr Asn Ser Ala Leu Lys

50 55 60

Ser Arg Leu Ser Ile Thr Lys Asp Asn Ser Lys Ser Gln Val Phe Leu
65 70 75 80

Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Lys Gln Arg Gly Gln Tyr Gly Ala Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ala
115

<210> 172
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 172
Ser Ile Val Met Thr Gln Thr Pro Lys Phe Leu Leu Val Ser Ala Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn Asp
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Cys Ala Ser Asn Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Tyr Gly Thr Asp Phe Thr Phe Thr Ile Ser Thr Val Gln Ala
65 70 75 80

Glu Asp Leu Ala Val Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 173
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 173
Gln Val Gln Leu Lys Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Asn Tyr
20 25 30

Ala Val His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Val Ile Trp Ser Asp Gly Ser Thr Asp Tyr Asn Ala Ala Phe Ile
50 55 60

Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Lys Ser Gln Val Phe Phe
65 70 75 80

Lys Met Asn Ser Leu Gln Ala Asp Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Lys Lys Gly Gly Trp Phe Pro Trp Phe Ala Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ala
115

<210> 174
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 174
Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp His Ala
20 25 30

Gly Asp Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65 70 75 80

Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Ser Asn
85 90 95

Glu Asp Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105 110

<210> 175
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 175
Glu Val Gln Leu Gln Gln Ser Gly Pro Asp Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
20 25 30

Tyr Met His Trp Val Lys Gln Ser His Gly Lys Arg Leu Glu Trp Ile
35 40 45

Gly Arg Val Asn Pro Asn Asn Gly Gly Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Ile Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Ser Tyr Asp Asn Ala Glu Gly Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ala
115

<210> 176
<211> 107
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 176
Asp Ile Lys Met Thr Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Arg Tyr
20 25 30

Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
35 40 45

Tyr Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Tyr
65 70 75 80

Glu Asp Met Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Glu Phe Pro Phe
85 90 95

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 177
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 177
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Thr
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn Tyr
20 25 30

Leu Ile Glu Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Val Ile Asn Pro Gly Ser Gly Gly Thr Asn Ser Asn Glu Lys Phe
50 55 60

Lys Ala Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Ala Asp Ser Ala Val Tyr Phe Cys
85 90 95

Ala Arg Ser Asp Tyr Asp Tyr Ala Phe Tyr Ala Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 178
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 178
Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Glu Thr Val Thr Ile Thr Cys Arg Ala Ser Gly Asn Ile His Asn Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro His Leu Leu Val
35 40 45

Tyr Asn Ala Lys Thr Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Asn Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His Phe Trp Ser Thr Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 179
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 179

```
Glu Phe Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn Glu Lys Phe
    50                  55                  60

Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Arg Ser Gly Tyr Glu Asp Tyr Tyr Gly Met Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Ser Val Thr Val Ser Ser
        115                 120
```

<210> 180
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 180

```
Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Leu Gly
1               5                   10                  15

Glu Glu Ile Thr Leu Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
            20                  25                  30

His Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Leu Leu Ile Tyr
        35                  40                  45

Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    50                  55                  60

Gly Ser Gly Thr Phe Tyr Ser Leu Thr Ile Ser Ser Val Glu Ala Glu
65                  70                  75                  80
```

Asp Ala Ala Asp Tyr Tyr Cys His Gln Trp Ser Ser Tyr His Thr Phe
85 90 95

Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> 181
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 181
Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met Ser Trp Val Arg Gln Thr Pro Asp Lys Arg Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Ser Gly Gly Ser Tyr Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Arg Ala Asp Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
100 105 110

Val Thr Val Ser Ser
115

<210> 182
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 182
Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Gln Ser Ala Ser Leu Gly

1 5 10 15

Glu Ser Val Thr Ile Thr Cys Leu Ala Ser Gln Thr Ile Gly Thr Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro Gln Leu Leu Ile
35 40 45

Tyr Ser Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Lys Phe Ser Phe Lys Ile Ser Ser Leu Gln Ala
65 70 75 80

Glu Asp Phe Val Ser Tyr Tyr Cys Gln Gln Leu Tyr Ser Thr Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 183
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 183
Gln Val Gln Leu Lys Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Asp Tyr
20 25 30

Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Val Val Trp Gly Gly Gly Ser Thr Tyr Tyr Asn Ser Ala Leu Lys
50 55 60

Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Lys Ser Gln Val Phe Leu
65 70 75 80

Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Lys Gln Arg Gly Gln Tyr Gly Ala Tyr Trp Gly Gln Gly Thr Leu Val

100 105 110

Thr Val Ser Ala
115

<210> 184
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 184
Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Val Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Val Gln Ala
65 70 75 80

Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Ser Ser Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 185
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 185
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Thr Thr Ala Tyr
65 70 75 80

Met Ala Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Ala
85 90 95

Val Ala Tyr Tyr Ser Asn Trp Gly Phe Ala Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ala
115

<210> 186
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 186
Asp Ile Val Leu Thr Gln Ser Leu Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Lys Ser Val Ser Thr Ser
20 25 30

Gly Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65 70 75 80

Pro Val Glu Asp Glu Asp Ala Ala Thr Tyr Tyr Cys Gln His Ser Arg
85 90 95

Glu Leu Pro Phe Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105 110

<210> 187
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 187
Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Met Ile Asp Pro Ser Asn Ser Glu Thr Arg Leu Asn Gln Lys Phe
50 55 60

Lys Asp Lys Ala Thr Leu Asn Val Asp Lys Ser Ser Asn Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Val Met Asp Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu
100 105 110

Thr Val Ser Ser
115

<210> 188
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 188
Asp Ile Lys Met Thr Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Ser Tyr
20 25 30

Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
35 40 45

Tyr Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Tyr
65 70 75 80

Glu Asp Met Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Glu Phe Pro Phe
85 90 95

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 189
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 189
Gln Val Gln Leu Lys Gln Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15

Ser Leu Phe Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Tyr
20 25 30

Glu Ile Asn Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Val Ile Trp Thr Gly Gly Ser Thr Asn Tyr Asn Ser Ala Leu Ile
50 55 60

Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Lys Ser Leu Val Phe Leu
65 70 75 80

Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Val
85 90 95

Arg Gly Val Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr
100 105 110

Val Ser Ser
115

<210> 190
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 190

Asp	Ile	Lys	Met	Thr	Gln	Ser	Pro	Ser	Ser	Met	Tyr	Ala	Ser	Leu	Gly
1				5				10						15	
Glu	Arg	Val	Thr	Ile	Thr	Cys	Lys	Ala	Ser	Gln	Asp	Ile	Asn	Asn	Tyr
			20					25					30		
Leu	Ser	Trp	Phe	Gln	Gln	Lys	Pro	Gly	Lys	Ser	Pro	Lys	Thr	Leu	Ile
		35					40					45			
Tyr	Arg	Ala	Asn	Arg	Leu	Val	Asp	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55					60				
Ser	Gly	Ser	Gly	Gln	Asp	Tyr	Ser	Leu	Thr	Ile	Ser	Ser	Leu	Glu	Tyr
65					70					75					80
Glu	Asp	Met	Gly	Ile	Tyr	Tyr	Cys	Leu	Gln	Tyr	Asp	Glu	Phe	Pro	Tyr
				85					90					95	
Thr	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	Arg				
			100					105							

<210> 191
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 191

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

Gly Phe Phe Tyr Pro Tyr Asn Gly Asn Thr Val Tyr Ser Gln Lys Phe
50 55 60

Lys Ser Lys Ala Thr Leu Thr Val Asp Asn Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Leu Asn Trp Glu Gly Tyr Trp Gly Gln Gly Thr Thr Leu Thr
100 105 110

Val Ser Ser
115

<210> 192
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 192
Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
85 90 95

Ser His Val Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

<210> 193
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 193
Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Arg Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Ile His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Tyr Pro Gly Asn Gly Asn Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Ile Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
85 90 95

Ala Arg Glu Arg Trp Leu Leu Leu Trp Phe Ala Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ala
115

<210> 194
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 194
Ser Ile Val Met Thr Gln Thr Pro Lys Phe Leu Leu Val Ser Ala Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn Asp
20 25 30

Val Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Tyr Ala Ser Asn Arg Tyr Asn Gly Val Pro Asp Arg Phe Thr Gly

50 55 60

Ser Gly Tyr Gly Thr Asp Phe Thr Phe Thr Ile Ser Thr Val Gln Ala
65 70 75 80

Glu Asp Leu Ala Val Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 195
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 195
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Val
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Asp Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys
85 90 95

Ala Arg Val Gly Asp Tyr Val Gly Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Thr Leu Thr Val Ser Ser
115

<210> 196
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 196
Asp Ile Gln Met Thr Gln Thr Ala Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Asn Asn Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
35 40 45

Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Ile Leu Glu Gln
65 70 75 80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asp Thr Leu Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 197
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 197
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Thr Lys Pro Gly Glu
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Ser Leu His Trp Val Lys Gln Ala Leu Gly Lys Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Glu Thr Gly Glu Pro Ala Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Asn Asp Leu Lys Asn Glu Asp Thr Thr Thr Tyr Phe Cys
85 90 95

Gly Ile Tyr Asp Gly Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
100 105 110

Val Thr Val Ser Ser
115

<210> 198
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 198
Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Arg Leu Leu Ile Tyr
35 40 45

Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Met Glu Ala Glu
65 70 75 80

Asp Thr Ala Thr Tyr Tyr Cys Gln Glu Trp Ser Asn Asn Pro Leu Thr
85 90 95

Phe Gly Asp Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 199
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 199
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Leu Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Arg Ile Val Tyr
65 70 75 80

Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys
85 90 95

Ala Lys Tyr Glu Ala His Glu Gly Phe Val Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ala
115

<210> 200
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 200
Asp Ile Gln Met Asn Gln Ser Pro Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Thr Ile Thr Ile Thr Cys His Ala Ser Gln Asn Ile Asn Val Trp
20 25 30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Asn Ile Pro Lys Leu Leu Ile
35 40 45

Tyr Lys Ala Ser His Leu His Thr Gly Val Pro Ser Arg Leu Ser Gly
50 55 60

Ser Gly Ser Gly Thr Gly Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Gly Gln Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Ser Gly Thr Thr Leu Glu Ile Lys
100 105

<210> 201
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 201
Gln Val Gln Leu Lys Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15

Ser Leu Ser Ile Thr Cys Ala Val Ser Gly Phe Ser Leu Thr Ser Phe
20 25 30

Gly Val His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Tyr Ser Ala Leu Met
50 55 60

Ser Arg Leu Ser Ile Ser Ile Asp Asn Ser Lys Ser Gln Val Phe Leu
65 70 75 80

Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Asp Trp Glu Gly Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ala
115

<210> 202
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 202

```
Asp Ile Val Met Ser Gln Ser Pro Ser Ser Leu Thr Val Ser Val Gly
1               5                  10                  15

Glu Lys Val Thr Met Ser Cys Met Ser Ser Gln Ser Leu Leu Tyr Ser
            20                  25                  30

Ser Thr Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45

Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Ser Val Lys Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln
                85                  90                  95

Tyr Tyr Ser Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
            100                 105                 110

Lys Arg
```

<210> 203
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 203

```
Glu Ile Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1               5                  10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Ser Tyr
            20                  25                  30

Asn Met Tyr Trp Val Ser Gln Ser His Gly Lys Ser Leu Glu Trp Ile
        35                  40                  45

Gly Tyr Ile Asp Pro Tyr Asn Gly Gly Thr Ser Tyr Asn Gln Lys Phe
    50                  55                  60

Arg Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80
```

Met His Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Asn Tyr Arg Tyr Phe Asp Phe Trp Gly Gln Gly Thr Thr
100 105 110

Leu Thr Val Ser Ser
115

<210> 204
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 204
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
35 40 45

Leu Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Arg Ser Asn Pro Phe Thr
85 90 95

Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> 205
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 205
Gln Ile Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln

1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

Gly Met Gly Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
35 40 45

Trp Leu Ala His Ile Trp Trp Asp Asp Val Lys Arg Tyr Ser Pro Ser
50 55 60

Leu Lys Ser Arg Leu Thr Ile Thr Lys Asp Thr Ser Lys Asn Gln Val
65 70 75 80

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Arg Ile Val Ser Phe Asp Asn Asp Val Val Ser Ala Met Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 206
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 206
Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Asn Ile Tyr Tyr Asn
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Thr Ala Asn Ser Leu Glu Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Phe Cys Lys Gln Ala Tyr Asp Val Pro Pro

85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 207
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 207
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
20 25 30

Trp Ile His Trp Ile Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Tyr Ile Asn Pro Thr Thr Val Tyr Thr Glu Phe Asn Gln Asn Phe
50 55 60

Lys Asp Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Ser Asn Phe Phe Asp Tyr Trp Gly Gln Gly Thr Thr
100 105 110

Val Thr Val Ser Ser
115

<210> 208
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 208
Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val Thr Pro Lys
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
20 25 30

His Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro Lys Leu Leu Ile Lys
35 40 45

Asp Ser Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr
85 90 95

Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 209
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 209
Gln Ile Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

Gly Met Gly Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
35 40 45

Trp Leu Thr Asp Ile Trp Trp Asp Asp Asn Lys Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Leu Thr Ile Thr Lys Asp Thr Ser Lys Asn Gln Val
65 70 75 80

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Arg Arg Val Asn Tyr Tyr Tyr Asp Pro Tyr Tyr Ala Met Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 210
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 210
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn Asp
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu Ile
35 40 45

Tyr Tyr Ala Ser Asn Arg Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Val Ala Thr Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 211
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 211
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Asp Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ile Gly Gly Asn Ser Pro Ser Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Thr Val Thr Val Ser Ser
115

<210> 212
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 212
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Lys Ala Ser Gln Ser Val Ser Asn Asp
20 25 30

Val Val Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Tyr Ala Ser Asn Arg Tyr Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Asp Tyr Thr Ser Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> 213
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 213
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ile Gly Asp Ser Ser Pro Ser Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 214

<400> 214
000

<210> 215

<400> 215
000

<210> 216

<400> 216
000

<210> 217

<400> 217
000

<210> 218

<400> 218
000

<210> 219

<400> 219
000

<210> 220
<211> 325
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 220
caaattgttc tcacccagtc tccagcaatc atgtctgtat ctctagggga acgggtcacc 60

atgacctgca ctgccagctc aagtgtaagt tccagttact tgcactggta ccaacaaaag 120

ccaggatcct cccccaaact ctggatttat agcacatcca acctggcttc tggagtccca 180

gctcgcttca gtggcagtgg gtctgggacc tcttattttt tcacaatcag cagcatggag 240

gctgaagatg ctgccactta ttactgccac cagtatcatc gttccccatt cacgttcggc 300

gcggggacaa agttgaaaat aagac 325

<210> 221
<211> 369
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 221
caggttactc tgaaagagtc tggccctggg atattgcagc cctcccagac cctcagtctg 60

acttgttctt tctctgggtt ttcactgagc acttctggta tgggtgtagg ctggattcgt 120

cagccatcag ggaagggtct ggagtggctg gcacacattt ggtgggatga tgtcaagcgc 180

tataacccag ccctgaagag ccgactaact atctccaagg atacctccag cagccaggta 240

ttcctcaaga tcgccagtgt ggacactgca gatactgcca catactactg tgctcgaata 300

gctgactatg gcggagatta ctatgctatg gactactggg gtcaaggaac ctcagtcacc 360

gtctcctca 369

<210> 222
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 222
gatatccaga tgacacagac tacatcttcc ctgtctgcct ctctgggaga cagagtcacc 60

atcagttgca gggcaagtca ggacattagc aattatttaa actggtatca gcagaaacca 120

gatggaactg ttaaactcct gatctactac acatcaagat tacactcagg cgtcccatca 180

aggttcagtg gcagtgggtc tggaacagat tattctctca ccattagcaa cctggagcta 240

gaagatattg ccacttactt ttgccaacag ggtgatatgc ttccgtggac gttcggtgga 300

ggcaccaagc tggaaatcaa ac 322

<210> 223
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 223
cagatccagt tggtgcagtc tggacctgag ctgaagaagc ctggagagac agtcaagatc 60

tcctgcaagg cttctggtta taccttcaca gactattcaa tgcactgggt gaagcaggct 120

ccaggaaagg gtttaaagtg gatgggctgg ataaacactg agactggtga gccaggatat 180

gcagatgact tcaagggacg gtttgccttc tctttggaaa cctctgccag cactgcctat 240

ttgcagatca acaacctcaa aaatgaggac acggctacat atttctgtgc tcggtacgac 300

gggtatgcta tggactattg gggtcaagga acctcagtca ccgtctcctc a 351

<210> 224
<211> 319
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 224

caaattgttc tcacccagtc tccagcaatc atgtctgcat ctccagggga gaaggtcacc 60

atgacctgca gtgccagctc aagtgtaagt tacatgcact ggtaccagca gaagtcaggc 120

acctccccca aaagatggat ttatgacaca tccaaactgg cttctggagt ccctgctcgc 180

ttcagtggca gtgggtctgg gacctcttac tctctcacaa tcagcagcat ggaggctgaa 240

gatgctgcca cttattactg ccagcagtgg actagaaacc cgctcacgtt cggggctgga 300

accaagctgg agctgaaac 319

<210> 225
<211> 372
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 225
caggttactc tgaaagagtc tggccctggg atattgcagc cctcccagac cctcagtctg 60

acttgttctt tctctgggtt ttcactgagc acttctggta tgggtgtagg ctggattcgt 120

cagccttcag gagagggtct agagtggctg gcagacattt ggtgggatga caataagtac 180

tataacccat ccctgaagag ccggctcaca atctccaagg atacctccag caaccaggta 240

ttcctcaaga tcaccagtgt ggacactgca gatactgcca cttactactg tgctcgaaga 300

gttaactatg tttacgaccc gtactatgct atggactact ggggtcaagg aacctcagtc 360

accgtctcct ca 372

<210> 226
<211> 337
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 226
aacattatga tgacacagtc gccatcatct ctggctgtgt ctgcaggaga aaaggtcact 60

atgagctgta agtccagtca aagtgtttta tacagttcaa atcagaagaa ctacttggcc 120

tggtaccaac agaaaccagg gcagtctcct aaactgctga tctactgggc atccactagg 180

gaatctggtg tccctgatcg cttcacaggc agtggatctg ggacagattt tactcttacc 240

atcagcactg tacaagttga agacctggca gtttattact gtcatcaata cctctcctcg 300

tggacgttcg gtggaggcac caagctggaa atcaaac 337

<210> 227
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 227
gaggtccagc tgcaacagtc tggacctgag ctggtgaagc ctggggcttc agtgaagatt 60

tcctgcaagg cttctggtta ctcattcact ggctataaaa tgcactgggt gaagcaaagc 120

catgtaaaga gccttgagtg gattggacgt attaatcctt acaatggtgc tactagctac 180

aaccagaatt tcaaggacaa ggccaccttg actgtagata agtcctccag cacagcctac 240

atggacctcc acagcctgac atctgaggac tctgcagtct atttctgtgc aagaggggac 300

tataggtacg actggtttgc ttactggggc caagggactc tggtcactgt ctctgca 357

<210> 228
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 228
gaaatccaga tgacccagtc tccatcctct atgtctgcat ctctgggaga cagaataacc 60

atcacttgcc aggcaactca agacattgtt aagaatttaa actggtatca gcagaaacca 120

gggaaacccc cttcattcct gatctattat gcaattgaac tggcagaagg ggtcccatca 180

aggttcagtg gcagtgggtc tgggtcagac tattctctga caatcagcaa cctggagtct 240

gaagattttg cagactatta ctgtctacag ttttatgagt ttccgttcac gttcggtgct 300

gggaccaagc tggagctgaa ac 322

<210> 229
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 229
caggcccagc tgcagcagtc tggagctgag ctggtaaggc ctgggacttc agtgaaggtg 60

tcctgcaagg cttctggata cgccttcact aattacttga tagagtgggt aaagcagagg 120

cctggacagg gccttgagtg gattggagtg attaatcctg gaactggtgg tactaactac 180

aatgagaact tcaagggcaa ggcaactctg actgcagaca aatcctccag tactgcctac 240

atgcagctca gcagcctgac atctgatgac tctgcggtct atttctgtgc aagatccccc 300

tatgattacc acgagggtgc tatggactac tggggtcaag gaacctcagt caccgtctcc 360

tca 363

<210> 230
<211> 410
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 230
caaattgttc tcacccagtc tccagcaatc atgtctgcat ctctagggga acgggtcacc 60

atgacctgca ctgccagctc aagtgtaagt tccagttact tgcactggta ccagcagaag 120

ccaggatcat cccccaaact ctggatttat agcacttcca acctggcttc tggagtccca 180

actcgcttca gtggcagtgg gtctgggacc tcttactctc tcacaatcag cagcatggag 240

gctgaagatg ctgccactta ttactgccac cagtatcatc gttccccatt cacgttcggc 300

tcggggacaa agttggaaat aaaaccagca tggaggctga agatgctgcc acttattact 360

gccaccagta tcatcgttcc ccattcacgt tcggctcggg gacaaagttg 410

<210> 231
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 231
caggttactc tgaaagagtc tggccctggg atattgcagt cctcccagac cctcagtctg 60

acttgttctt tctctgggtt ttcactgagc acttctggta tgggtgtagg ctggattcgt 120

cagccatcag ggaagggtct ggagtggctg gcacacattt ggtgggatga tgtcaagcgc 180

tataacccag tcctgaagag ccgactgact atctccaagg atacctccag cagccaggta 240

ttcctcaaga tcgccagtgt ggacactgca gatactgcca catactattg tgctcgatta 300

gttgatgatc tgtactactt tgactactgg ggccaaggca ccactctcac agtctcctca 360

<210> 232
<211> 337

<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 232
gatgttgaga tgacccagac tccactcact ttgtcggtta ccattggaca accagcctcc 60

atctcttgca agtcaagtca gagcctctca gacagtgatg gaaagacata tttgaattgg 120

atgtttcaga ggccaggccg gtctccaaag cgcctaatct atctggtgtc taaactggac 180

tctggagtcc ctgacaggtt cactggcagt ggatcaggga cagatttcac actgaaaatc 240

agcagagtgg aggctgagga tttgggagtt tactattgct ggcaaggtaa acattttccg 300

tggacgttcg gtggaggcac caagctggaa atcaaac 337

<210> 233
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 233
cagatccagt tggtgcagtc tggacctgag ctgaagaagc ctggagagac agtcaagatc 60

tcctgcaagg cttctggtta taccttcaca gactattcaa tgcactgggt gaagcaggct 120

ccaggaaagg gtttaaagtg gatgggctgg ataaacactg agactgttga gccaacatat 180

gcagatgact tcatgggacg gtttgccttc tctttggaaa cctctgccag cactgccttt 240

ttgcagatca acaacctcga aaatgaggac acggctacat atttctgtgc tagatttggt 300

tcctatgcta tggactactg gggtcaagga acctcagtca ccgtctcctc a 351

<210> 234
<211> 319
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 234
caaattgttc tcacccagtc tccagcactc gtgtctgcat ctccagggga gaaggtcacc 60

atgacctgca gtgccagctc aagtgtaagt tacatgtact ggtaccagca gaaaccaaga 120

tcctccccca aaccctggat ttatctcaca tccaacctgg cttctggagt ccctgctcgc 180

ttcagtggca gtgggtctgg gacctcttac tctctcacaa tcagcagcat ggaggctgaa 240

gatgctgcca cttattactg ccagcagtgg cgtagtaacc cattcacgtt cggctcgggg 300

acaaagttgg aaataaaac 319

<210> 235
<211> 371
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 235
caggttactc tgaaagagtc tggccctggg atattgcagc cctcccagac cctcagtctg 60

acttgttctt tctctgggtt ttcactgagc acttctggta tgggtgtagg ctggattcgg 120

cagccatcag ggaagggtct ggagtggctg gcacacattt ggtgggatga tgtcaagcgc 180

tataacccag ccctgaagag ccgactgact atctccaagg atacctccag cagccaggta 240

ttcctcaaga tcgccagtgt ggacactgca gatactgcca catactactg tgctcgcata 300

gtttcctttg ataacgacgt tgtctctgct atggactact ggggtcaagg aacctcagtc 360

accgtctcct c 371

<210> 236
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 236
gacatccaga tgactcagtc tccagcctcc ctggctgcat ctgtgggaga aactgtcgcc 60

atcacatgtc gagcaagtga gaacatttac tacaatttag catggtatca gcagaaacaa 120

gggaaatctc ctcagctcct gatctatact gcaaacagtt tggaagatgg tgtcccatcg 180

aggttcagtg gcagtggatc tgggacacag tattctttga agatcaacag catgcagcct 240

gaagattccg caacttattt ctgtaaacag gcttatgacg ttcctccgac gttcggtgga 300

ggcaccaagc tggaaatcaa ac 322

<210> 237
<211> 351
<212> DNA
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 237
caggtccagc ttcagcagtc tggggctgaa ctggcaaaac ctggggcctc agtgaagatg 60

tcctgtaagg cttctggcta cacctttact cgctactgga tacactggat aaaacagagg 120

cctggacagg gtctggaatg gattggatac attaatccta caactgttta tactgagttc 180

aatcagaact tcaaggacaa ggccactttg actgcagaca aatcctccac cacagcctcc 240

atgcaactga gcagcctgac atctgaggac tctgcagtct attactgtgc aagaggcggt 300

agtaacttct ttgactactg gggccaaggc accactctca cagtctcctc a 351

<210> 238
<211> 323
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 238
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctttgggaga cagagtcacc 60

atcagttgca gggcaagtca gaatattatc aattatttaa actggtatca gcagaagcca 120

gatggaactg ttaaactcct gatctactac acatcaagat tacactcagg agtcccatca 180

aggttcagtg gcagtgggtc tgggacagat tattctctca ccatcagcaa cctggaacct 240

gaagatattg ccacttacta ttgtcaacag tatagtgagc gtccgtacac gttcgggggg 300

gggaccaagc tggaaataaa acg 323

<210> 239
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 239
gaagtgaagc tggaggagtc aggaggaggc ttggtacaac ctggagaatc catgaaactc 60

tcttgtgctg cttctggatt cacttttagt gatgcctgga tggactgggt ccgccagtct 120

ccagagaagg gacttgagtg ggttgctgaa attagaaaca aagctaataa tcatgcaaca 180

tattatgctg agtctgtgaa agggaaattc accatctcaa gagatgattc caaaagtaga 240

gtgtacctgc aaatgaacaa cttaagagct gcagacactg gcatttatta ctgtacggcc 300

tatagtaact ttgcttactg gggccaaggg actctggtca ctgtctctac a 351

<210> 240
<211> 320
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 240
gacatccaga tgacacagtc tccatcctca ctgtctgcat ctctgggagg caaagtcacc 60

ttcacttgca aggcaagcca agacattcac aagtatgtag cttggtacca acacaagcct 120

ggaaaaggtc ctaggctgct catacattac acatctacat tacagccagg catctcatca 180

aggttcagtg gaagtgggtc tgggagagat tattccttca gcatcagcaa cctggagcct 240

gaagatattg caacttatta ttgtctacag tataataatc tgtacacgtt cggaggggg 300

accaagctgg aaataaaacg 320

<210> 241
<211> 354
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 241
gaggttcagc tgcagcagtc tggggctgag cttgtgaggc caggggcctc agtcaagttg 60

tcctgcacag cttctggctt caacattaaa gacagccttt tgcactgggt gaagcagagg 120

cctgaaaagg gcctggagtg gattgggtgg attgatcctg aggatggtga aactaaatat 180

gccccgaact tccaggacaa ggccactata actacagact catcctccaa cacagcctac 240

ctgcaactca tcagcctgac atctgttgac actgccatct attactgtgc ctatggtaac 300

tacgtgcggc actttgacta ctggggccaa ggcaccactc tcacagtctc ctca 354

<210> 242
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 242
gaaatccaga tgacccagtc tccatcctct atgtctgcat ctctgggaga cagaataacc 60

atcacttgcc aggcaactca agacattgtt aagaatttaa actggtatca gcagaaacca 120

gggaaacccc cttcattcct gatctattat gcaactgaac tggcagaagg ggtcccatca 180

aggttcagtg gcagtgggtc tgggtcagac tattctctga caatcaggaa cctggagtct 240

gaagactttg cagaccatta ctgtctacag ttttatgagt ttccgttcac gttcggtgct 300

gggaccaagc tggagctgaa ac 322

<210> 243
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 243
caggtccagt tgcagcagtc tggaactgag ctggtaaggc ctgggacttc agtgagggtg 60

tcctgcaagg cttctggata cgccttcggt aatcacttga ttgagtgggt gaagcagagg 120

cctggacagg gccttgagtg gattggagtg attaatcctg gaactggtgg tactcactac 180

aatgagaagt tcaaggacaa ggcaagactg accgcagaca aatcctccaa cactgcctac 240

atgcacctca acagcctgac atctgatgac tctgcggtct atttctgtgc aagatccccc 300

tatgattacc acgagggtgc tatggactac tggggtcaag gaacctcagt caccgtctcc 360

tca 363

<210> 244
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 244
gacattgtga tgacacagtc tccatcctcc ctggctatgt cagtaggaca gaaggtcact 60

atgagctgca agtccagtca gagcctttta aatagtagca atcaaaagaa ttatttggcc 120

tggtatcagc aggaaccagg acagtctcct aaacttctgg tatcctttgc atccactagg 180

gaatctgggg tccctgatcg cttcacaggc agtggatctg ggacagattt cactcttacc 240

atcagcggtg tgcaggctga agacctggca gtttattact gtcagcaaca ttatagcatt 300

ccgctcacgt tcggtgctgg gaccaagctg gagctgaaa 339

<210> 245

<211> 372
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 245
caggttcagc tacaacagtc tggacctgag ctggtgaagc ctggggcctc agtgaagatt 60

tcctgcaagg cttctggcta tgcattcagt agctcctgga tgaactgggt gaagcagagg 120

cctggaaagg gtcttgagtg gattggacgg atttatcctg gagatggaga tactaactac 180

aatgggaagt tcaagggcaa ggccacactg actgcagaca aatcctccag cacagcctac 240

atgcaactca gcagcctgac atctgaggac tctgcggtct acttctgtgc aatgggtatt 300

tataactacg atggtagccg ttactattct atggactact ggggtcaagg aacctcagtc 360

accgtctcct ca 372

<210> 246
<211> 315
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 246
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagagtcacc 60

atcagttgca gggcaagtca ggacattaag aattatttaa actggtatca gcagaaacca 120

gatggaactg ttaaacccct gatctactac acatcaagag tacactcagg agtcccatca 180

aggttcagtg gcagtgggtc tggaacagat tattctctca ccattagcaa cctggagcaa 240

gaagatattg ccacttactt ttgccagcag ggttatacgc ttccattcac gttcggctcg 300

gggacaaagt tggaa 315

<210> 247
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 247
caggtccagc tgcagcagcc tggggctgaa ctggtgaagc ctggggcttc agtgaagctg 60

tcctgtaagg cttctggata caccttcact acctactgga tgcactgggt gaagcagagg 120

cctggacaag gccttgagtg gatcggagag attgatcctt ctgatagtta tacttactac 180

aatcaaaagt tcaagggcaa ggccacattg actgtagaca aatcctccag cacagcctac 240

atgcaactca gcagcctgac atctgaggac tctgcggtct attattgtgc aagaggggac 300

tatggtaacc cctatgctat ggactactgg ggtcaaggat cctcagtcac cgtctcctca 360

<210> 248
<211> 325
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 248
caaattgttc tcacccagtc tccagcaatc atgtctgcat ctcctgggga gaaggtcacc 60

ttgacctgca gtgccagctc aagtgtaagt tccaggtact tgtactggta ccagcagaag 120

ccaggatcct cccccaaact ctggatttat agcacatcca acctggcttc tggagtccct 180

gctcgcttca gtggcagtgg gtctgggacc tcttactctc tcataatcag cagcatggag 240

gctgaagatg ctgcctctta tttctgccat cagtggagta attacccact cacgttcggt 300

gctgggacca agctggagct gaaac 325

<210> 249
<211> 372
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 249
caggttactc tgaaagagtc tggccctggg atattgcagc cctcccagac cctcagtctg 60

acttgttctt tctctgggtt ttcactgagc acttctaata cgggcatagg ctggattcgt 120

cagccttcag ggacgggtct ggagtggctg gcacacattt ggtggaatga tgataagtac 180

tataatccat ccctgaagag ccggctcaca atctccaagg aaacctccaa caaccaggta 240

ttcctcaaga tcaccaatgt ggacactgca gatactgcct catacttctg tgttcaaatc 300

gggcgcgact acagtaacta cgcctggtat ttcgatgtct ggggcgcagg gaccacggtc 360

accgtctcct ca 372

<210> 250
<211> 319
<212> DNA

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 250
caaattgttc tcacccagtc tccagcaatc atgtctgcat ctccagggga gaaggtcacc 60

atgacctgca gtgccagctc aagtgtaagt tacatgcact ggtaccagca gaagtcaggc 120

acctccccca aaagatggat ttatgactca tccaaactgg cttctggagt ccctgctcgc 180

ttcagtggca gtgggtctgg gacctcttac tctctcacaa tcagcagcat ggaggctgaa 240

gatgctgcca cttattactg ccagcagtgg agtagtaacc cgctcacgtt cggtgctggg 300

accaagctgg agctgaaac 319

<210> 251
<211> 372
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 251
caggttactc tgaaagagtc tggccctggg atattgcagc cctcccagac cctcagtctg 60

acttgttctt tctctgggtt ttcactgagc acttctggta tgggtgtagg ctggattcgt 120

cagccttcag gagagggtct agagtggctg acagacattt ggtgggatga caataagtac 180

tataacccat ccctgaagag ccggctcaca atctccaagg atacctccag caaccaggta 240

ttcctcaata tcaccagtgt ggacactgca gatactgcca cttactactg tgctcgaaga 300

gttaactatt attacgaccc gtactatgct atggactact ggggtcaagg aacctcagtc 360

accgtctcct ca 372

<210> 252
<211> 337
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 252
gatgttgaga tgacccagac tccactcact ttgtcggtta ccattggaca accagcctcc 60

atctcttgca agtcaagtca gagcctctca gacagtgatg gaaagacata tttgaattgg 120

atgtttcaga ggccaggccg gtctccaaag cgcctaatct atctggtgtc taaactggac 180

tctggagtcc ctgacaggtt cactggcagt ggatcaggga cagatttcac actgaaaatc 240

agcagagtgg aggctgagga tttgggagtt tactattgct ggcaaggtaa acattttccg 300

tggacgttcg gtggaggcac caagctggaa atcaaac 337

<210> 253
<211> 337
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 253
cagatccagt tggtgcagtc tggacctgag ctgaagaagc ctggagagac agtcaagatc 60

tcctgcaagg cttctggtta ttccttcaca gactattcaa tgcactgggt gaagcaggct 120

ccaggaaagg gtttaaagtg gatgggctgg ataaacactg agactgttga gccaacatat 180

gcagatgact tcatgggacg gtttgccttc tctttggaaa cctctgccag cactgccttt 240

ttgcagatca acaacctcga aaatgaggac acggctacat atttctgtgc tagatttggt 300

tcctatgcta tggactactg gggtcaagga acctcag 337

<210> 254
<211> 320
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 254
caaattgttc tcacccagtc tccagcaatc atgtctgcat ctccagggga gaaggtcacc 60

ataacctgca gtgccagctc aagtgtaagt tacatgcact ggttccagca gaagccaggc 120

acttctccca aactctggat ttataccaca tccaacctgg cttctggagt ccctgctcgc 180

ttcagtggca gtggatctgg gacctcttac tctctcacag tcagccgaat ggaggctgaa 240

gatgctgcca cttattactg ccagcaaagg agtctttatc cgtacacgtt cggaggggggg 300

accaaggtgg aaataaaacg 320

<210> 255
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 255
caggttcagc tacagcagtc tggagctgag ctggcgaggc ccggggcttc agtgaagctg 60

tcctgcaagg cttcaggcta caccttcact gaccagtata taaactgggt gaagcagagg 120

actggacagg gccttgagtg gattggagag atttatcccg gaaggggtaa tacttactac 180

aatgagaagt tcaagggcaa ggccacactg actgcagaca aatcctccag cacagcctac 240

atgcaactca gcagcctgac atctgaggac tctgcagtct atttctgtgc aagagaggat 300

ggtggttacg acgatgcctg gtttgcttac tggggccaag ggactctggt cactgtctct 360

gca 363

<210> 256
<211> 325
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 256
caaattgttc tgacccagtc tccaacaatc atgtctgcat ctctagggga acgggtcacc 60

atgacctgca ctgccagctc aagtgtaact tccagttact tgcactggta ccagcagaag 120

ccaggatcct cccccaaact ctggatttat agcacatcca acctggcttc tggagtccca 180

gctcgcttca gtggcagtgg gtctgggacc tcttactctc tcacaatcag cagcatggag 240

gctgaagatg ctgccactta ttactgccac cagtttcatc gttccccatt cacgttcggc 300

tcggggacaa agttggaaat aaaac 325

<210> 257
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 257
caggttactc tgaaagagtc tggccctggg atattgcagc cctcccagac cctcagtctg 60

acttgttctt tctctgggtt ttcactgagc acttctggta tgggtgtagg ctggattcgt 120

cagccatcag ggaagggtct ggagtggctg gcacacattt ggtgggatga tgtcaagcgc 180

tataaaccag ccctgaagag ccgactgact gtctccaagg atacctccag caaccaggtt 240

ttcctcaaga tcgccactgt ggacgctgca gatactggca catactactg tgctcgaatc 300

gttgatggtc acccccccgtt tgcttactgg ggccaaggga ctctggtcac tgtctctgca 360

<210> 258
<211> 337
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 258
gacattgtgc tgacccagtc tccactctct ctgcctgtca atattggaga tcaagcctct 60

atctcttgca agtctactaa gagtcttctg aatagtgatg gattcactta tttggactgg 120

tatttgcaga ggccaggcca gtctccacaa ttcctaatat atttggtttc taatcgattt 180

tctggagttc cagacaggtt cagtggcagt gggtcaggaa cagatttcac actcaagatc 240

agcagagtgg aggctgagga tttgggagta tattattgct tccagagtaa ctatcttccg 300

ctcacgttcg gtgctgggac caagctggag ctgagac 337

<210> 259
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 259
gaggtccaac tgcagcagtc tggacctgag ctggtgaagc ctggggcttc agtgaagata 60

tcctgcaagg cttctggtta ctcattcagt cgtttctata tgcactgggt gaagcaaagt 120

cctgaaaata gtcttgagtg gattggagag attaatccta gcactggggg tacaagctac 180

aaccagaagt tcaagggcaa ggccacatta actgtagata aatcctccag cacagcctac 240

atgcagctca agagcctgac atctgaagag tctgcagtct attactgtac taggggttac 300

gggagcaact ggtacttcga tgtctggggc gcagggacca cggtcaccgt ctccaca 357

<210> 260
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 260

agtattgtga tgacccagac tcccaaattc ctgcttgtat cagcaggaga cagggttacc 60

ataacctgca aggccagtca gagtgtgagt aatgatgtag cttggtacca acagaagcca 120

gggcagtctc ctaaactgct gatatactat gcatccaatc gctacagtgg agtccctgat 180

cgcttcactg gcagtggata tgggacggat ttcactttca ccatcagcac tgtgcaggct 240

gaagacctgg cagtttattt ctgtcagcag gattatagct ctccgtggac gttcggtgga 300

ggcaccaagc tggaaatcaa ac 322

<210> 261
<211> 354
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 261
cagatccagt tggtgcagtc tggacctgag ctgaagaggc ctggagagac agtcaagatc 60

tcctgcaagg cttctggata taccttcaca aactatggaa tgaactgggt gaagcaggct 120

ccaggaaagg gtttaaagtg gatgggctgg ataaacacgt acactggaga cccaacatat 180

gctgatgact tcaagggacg gtttgccttc tctttggaaa cctctgccag cactgcctat 240

ttgcagatca acaacctcaa aaatgaggac acggctacat atttctgtgc aagaattggc 300

ggtaatagtc cctctgatta ctggggccaa ggcacctctc tcacagtctc ctca 354

<210> 262
<211> 323
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 262
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagagtcacc 60

atcagttgca gggcaagtca ggacattagc aattatttaa actggtatca gcagaaacca 120

gatggaactg ttaaactcct gatctactac acatcaagat tacactcagg agtcccatca 180

aggttcagtg gcagtgggtc tggaacagat tattctctca ccattagcaa cctggagcaa 240

gaagatattg ccacttactt ttgccaacag ggtaatacgc ttccgtacac gttcggaggg 300

gggaccaagc tggaaataaa acg 323

<210> 263
<211> 363

<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 263
tctgatgtgc agcttcagga gtcgggacct ggcctggtga aaccttctca gtctctgtcc 60

ctcacctgca ctgtcactgg ctactcaatc accagtgatt atgcctggaa ctggatccgg 120

cagtttccag gaaacaaact ggagtggatg ggctacataa gctacagtgg tagcactagc 180

tacaacccat ctctcaaaag tcgaatctct atcactcgag acacatccaa gaaccagttc 240

ttcctgcagt tgaattctgt gactactgag gacacagcca catattactg tgcaagattt 300

tactacggta gtagctatgc tatggactac tggggtcaag gaacctcagt caccgtctcc 360

tca 363

<210> 264
<211> 318
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 264
gaaacaactg tgacccagtc tccagcatcc ctgtccgtga ctacaggaga aaaagtcact 60

atcagatgca taaccacccc tgatattgat gatgatatga actggtacca gcagaagcca 120

ggggaacctc ctaacctcct tatttcagaa ggcaatagtc ttcgtcctgg agtcccatcc 180

cgattctcca gcagtggcta tggcacaaat tttgttttta caattgaaaa cacgctctca 240

gaagatgttg cagattacta ctgtttgcaa agtgataaca tgccattcac gttcggctcg 300

gggacaaagt tggaaata 318

<210> 265
<211> 352
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 265
caggtccagc tgcagcagtc tggggctgaa ctggcaaaac ctggggcctc agtgaagatg 60

tcctgcaagg cttctggcta cacctttact acctactgga tgcactgggt aaaacagagg 120

cctggacagg gtctggaatg gattggatac attaatccta gcagtggtta tactgagtac 180

aatcagaagt tcaaggacaa ggccacattg actgcagaca aatcctccag cacagcctac 240

atgcaactaa gcagcctgac atctgaggac tcttcagtct attactgtgc aagaaagggt 300

agtaacaggg ggtttgctta ctggggccaa gggactctgg tcactgtctc tg 352

<210> 266
<211> 313
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 266
caaattgttc tcacccagtc tccagcaatc atgtctgcat ctccagggga gaaggtcacc 60

atgacctgca gtgccagctc aagtataaat tacatgcact ggtaccagca gaagccaggc 120

acctccccca aaagatggat ttatgacaca tccaaactgg cttctggagt ccctgctcgc 180

ttcagtggca gtgggtctgg gacctcttat tctctcacaa tcagcagcat ggaggctgaa 240

gatgctgcca cttattactg ccatcagcgg agtacgtgga cgttcggtgg aggcaccaag 300

ctggaaatca aac 313

<210> 267
<211> 348
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 267
gaggttcagc tgcagcagtc tggggcagag cttgtgaagc caggggcctc agtcaagttg 60

tcctgcacag tttctggctt caacattaaa gacacctata tacactgggt gaagcagagg 120

cctgaacagg gcctggagtg gattggaagg attgatcctg cgaatggtaa tactaaatat 180

gacccgaagt tccagggcaa ggccactata acagcagaca catcctccaa cacagcctac 240

ctgcagctca gcagcctgac atctgaggac actgccgtct attactgtgc tagaccgacg 300

gggtactttg aatactgggg ccaaggcacc actctcacag tctcctca 348

<210> 268
<211> 323
<212> DNA
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 268
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctttgggaga cagagtcacc 60

atcagttgca gggcaagtca ggatgttatc aattatttaa actggtatca gcagaaacca 120

gatggaactg ttaaactcct gatctactac acatcaaggt tacactcagg agtcccatca 180

aggttcagtg gcagtgggtc taggacagat tattctctca ccatcagcaa cctggaacct 240

gaagatattg ccacttacta ttgtcagcag tatagtgagc gtccgtacac gttcggaggg 300

gggaccaagc tggaaataaa acg 323

<210> 269
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 269
gaagtgaagc ttgaggagtc tggaggaggc ttggtgcaat ttggaggatc catgaaactc 60

tcttgtgctg cttctggatt cacttttagt gatgcctgga tggactgggt ccgccagtct 120

ccagagaagg ggcttgagtg ggttgctgaa attagaaaca aagctaataa tcatgcaaca 180

tattatcctg agtctgtgaa agggaggttc accatctcaa gagatgattc caaaagtaga 240

gtgtacctgc aaatgaacaa cttaagagct gaagacactg gcatttatta ctgtacgggt 300

tactcctcgt ttgcttactg gggccaaggg actctggtca ctgtctctgc a 351

<210> 270
<211> 338
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 270
gatgttttga tgacacagtc tccactctcc ctgtctgtca gtcttggaga tcaagcctcc 60

atctcttgta gatctagtca gaacattgta cacagtgata gatacaccta tttagaatgg 120

tacctgcaga aaccaggcca gtcgccaaaa ctcctgatat atggggtttc caaccgattt 180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcagagtgg aggctgagga tatgggagtt tattactgct ttcaaggtac acatgttccg 300

tacacgttcg gaggggggac caagctggaa ataaaacg 338

<210> 271
<211> 354
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 271
cagatccagt tggtgcagtc tggacctgaa ctgaagaagc ctggagagac agtcaagatc 60

tcctgcaagg cttctgggta taccttcaca actgctggaa tgcagtgggt gcaaaagatg 120

ccaggaaagg gttttaagtg gattggctgg ataaacaccc actctggaga gccaaaatat 180

gcagatgact tcaagggacg gtttgccttc tctttggaaa cctctgccag cactgcctat 240

ttacagataa gcaacctcaa agacgaggac acggctacgt ttttctgtgc gcccctatgg 300

tccgatagta gttttgctta ctggggccaa ggaactctgg tcactgtctc tgca 354

<210> 272
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 272
gaaatccaga tgacccagtc tccatcctct atgtctgcat ctctgggaga cagaataacc 60

atcacttgcc aggcaactca agacattgtt aagaatttaa actggtatca gcagaaacca 120

gggaaacccc cttcattcct gatctattat gcaactgaac tggcagaagg ggtcccagca 180

aggttcagtg gcagtgggtc tgggtcagac tattctctga caatcagcaa cctggagtct 240

gaagattttg cagactatca ctgtctacag ttttatgagt ttccgttcac gttcggtgct 300

gggaccaagc tggagctgaa ac 322

<210> 273
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 273
caggtccagc tgcagcagtc tggagctgac ctggtaaggc ctgggacttc agtgaaggtg 60

tcctgcaagg cttctggata ctccttcact aattacctga tagagtgggt aaagcagagg 120

ccaggacagg gccttgagtg gattggagtg attaatcctg gaagtggtgg aactcactac 180

aatgagaaat tcaaggacaa ggcagttctg actgcagaca aatcctccac tactgcccac 240

atgcagctca gcagcctgac atctgatgac tctgcggtct atttctgtgc aagatccccc 300

tatgattata acgatggtgc tatggactac tggggtcaag gaacctcagt caccgtctct 360

tca 363

<210> 274
<211> 337
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 274
gatgttgttc tgacccagtc tccactctct ctgcctgtca tattggaga tcaagcctct 60

atctcttgca agtctactaa gagtcttctg aatagtgatg gattcactta tttggactgg 120

tatttgcaga ggccaggcca gtctccacaa ttcctaatat atttggtttc taatcgattt 180

tctggagttc cagacaggtt cagtggcagt gggtcaggaa cagatttcac actcaagatc 240

agcagagtgg aggctgagga tttgggagta tattattgct tccagagtaa ctatcttccg 300

ctcacgttcg gtgctgggac caagctggag ctgagac 337

<210> 275
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 275
gaggtccaac tgcagcagtc tggacctgag ctggtgaagc ctggggcttc agtgaagata 60

tcctgcaagg cttctggtta ctcattcagt cgtttctata tgcactgggt gaagcaaagt 120

cctgaaaata gtcttgagtg gattggagag attaatccta gcactggggg tacaagctac 180

aaccagaagt tcaagggcaa ggccacatta actgtagata aatcctccag cacagcctac 240

atgcagctca agagcctgac atctgaagag tctgcagtct attactgtac taggggttac 300

gggagcaact gttacttcga tgtctggggc gcagggacca cggtcaccgt ctccaca 357

<210> 276

<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 276
gacatcaaga tgacccagtc tccatcttcc atgtatgcat ctctaggaga gagagtcact 60

atcacttgca aggcgagtca ggacattaat agttatttaa gctggttcca gcagaaacca 120

gggaaatctc ctaagaccct gatctatcga gcaaacagat tggtagatgg ggtcccatca 180

aggttcagtg gcagtggatc tgggcaagat tattctctca ccatcaccag cctggagtat 240

gaagatatgg gaatttatta ttgtctacag tatgatgaat ttccgctcac gttcggtgct 300

gggaccaagc tggagctgaa ac 322

<210> 277
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 277
caggttcaac tgcagcagtc tggacctgag ctggtgaagc ctgggacttt agtgaagata 60

tcctgcaagg cttctggtta caccttcaca agctacgata taaactgggt gaagcagagg 120

cctggacagg gacttgaatg gattggatgg atttatcctg gagatggtaa tactaagtac 180

agtgagaaat tcaagggcaa ggccacactg actgcagaca aatcctccag cacagcctac 240

atgcagctca ccagcctgac ttctgagaac tctgcagtct atttctgtgc aagagactat 300

gattaccctt ttgcttactg gggccaaggg actctggtca ctgtctctgc a 351

<210> 278
<211> 319
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 278
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagagtcacc 60

atcagttgca gggcaagtca ggacattagc aattatttaa actggtatca gcagaaacca 120

gatggaactg ttaaactcct gatctactac acatcaagat tacactcagg agtcccatca 180

aggttcagtg gcagtgggtc tggtacagat tattctctca ccattagcaa cctggagcaa 240

gaagatattg ccacttactt ttgccaacag ggtaatacgc ttcggacgtt cggtggaggc 300

accaagctgg aaatcaaac 319

<210> 279
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 279
gaagtgcagc tggtggagtg tgggggatgc ttagtgaagc ctggagggta cctgaaactc 60

tcctgtgcag cctctggatt cactttcagt agctatgcca tgtcttgggt tcgccagtct 120

ccagagaaga ggctggagtg ggtcgcagaa atcagtattg gtggtagcta cacctactat 180

ccagacactg tgacgggccg attcaccatc tccagagaca atgccaagaa caccctgtac 240

ctggaaatga gcagtctgag gtctgaggac acggccatgt attactgtgc aagggagggc 300

tatgattacg acgtgagagc tatggactac tggggtcaag gaacctcagt caccgtctcc 360

tca 363

<210> 280
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 280
gacatccaga tgattcagtc tccatcgtcc atgtttgcct ctctgggaga cagagtcagt 60

ctctcttgtc gggctagtca gggcattaga gggactttag actggtatca acagaaacca 120

aatggaacta ttaaactcct gatctactcc acatccaatt taaattctgg tgtcccatca 180

aggttcagtg gcagtgggtc tgggtcagat tattctctca ccatcagcag cctagagtct 240

gaagattttg cagactatta ctgtctacag cgtaatgcgt atcctctcac gttcggtgct 300

gggaccaagc tggagctgaa ac 322

<210> 281
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 281
caggtgcagc tgaaggagtc aggacctggc ctggtggcgc cctcacagag cctgtccatc 60

acgtgcgctg tctctggatt ttcattaacc agctttgcaa tacactggtt tcgcaagcct 120

ccaggaaagg gtctggagtg gctgggagta atatggactg gtggaaccac aaattataat 180

tcggctctca tgtccagact gagcatcagc aaagacaact ccaagagcca agttttctta 240

aaaatgaaca gtctgcaaac tgatgacaca gccatgtact actgtgccag agacgattac 300

gacaataatt atgctatgga ctactggggt caaggaacct cagtcaccgt ctcctca 357

<210> 282
<211> 323
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 282
gacatcaaga tgacccagtc tccatcttcc atgtatgcat ctctaggaga gagagtcact 60

atcacttgca aggcgagtca ggacattaat agctatttaa actggttcca gcagaaacca 120

gggaaatctc ctaagaccct gatctatcgt gcaaacagat tggtagatgg ggtcccatca 180

aggttcagtg gcagtggatc tgggcaagat tattctctca ccatcagcag cctggagtat 240

gaagatatgg gaatttatta ttgtctacag tatgatgagt ttccgtacac gttcggaggg 300

gggaccaagc tggaaataaa acg 323

<210> 283
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 283
gaggtgcagc ttgttgagtc tggtggagga ttggtgcagc ctaaagggtc attgaaactc 60

tcatgtgcag tctctgcatt caccttcact acctacgcca tgaactgggt ccgccaggct 120

ccaggaaagg gtttggagtg ggttgctcgc ataagaaata aaagtaataa ttatgcaaca 180

tattatgccg attcagtgaa agacaggttc accatctcca gagatgattc acaaagcatg 240

ctctatctgc aaatgaacaa cttgaaaatt gaggacacag ccatgtatta ctgtgtgttc 300

tactatgatt acgtctactg gggccaaggg actctggtca ctgtctctgc a 351

<210> 284
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 284
agtattgtga tgacccagac tcccaaattc ctgcttgtat cagcaggaga cagggttacc 60

ataacctgca aggccagtca gagtgtgagt aatgatgtag tatggtacca acagaagcca 120

gggcagtctc ctaaactgct gatatactat gcatccaatc gctacactgg agtccctgat 180

cgcttcgctg gcagtggata tgggacggat ttctctttca ccatcagcac tgtgcaggct 240

gaagacctgg cagtttattt ctgtcagcag gattatacct ctccgtggac gttcggtgga 300

ggcaccaagc tggaaatcag ac 322

<210> 285
<211> 354
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 285
cagatccagt tggtgcagtc tggacctgaa ctgaagaagc ctggagagac agtcaagatc 60

tcctgcaagg cttctgggta taccttcaca aactatggaa tgaactgggt gaagcaggct 120

ccaggaaagg gtttaaagtg gatggcctgg ataaacacct acactggaga gccaacatat 180

gctgatgact tcaagggacg gtttgccttc tctttggaaa cctctgccag cactgcctct 240

ttgcagatca tcaacctcaa aaatgaggac acggctacat atttctgtgc aaggatcggc 300

gatagtagtc cctctgacta ctgggggcag ggcaccactc tcacagtctc ctca 354

<210> 286
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 286

gacattgtga tgacccagtc tcacaaattc atgtccatat cagtaggaga cagggtcagc 60

atcacctgca aggccagtca ggatgtgagt atttttgtag cctggtatca acagaaacca 120

ggacaatctc ctaaactact gatttactcg gcatcctacc ggtacactgg agtccctgat 180

cgcttcactg gcagtggatc tgggacggat ttcattttca ccatcagcag tgtgcaggct 240

gaagacctgg cagtttacta ctgtcagcaa cattatggta ctccattcac gttcggctcg 300

gggacaaagt tgaaaataag ac 322

<210> 287
<211> 354
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 287
gaagtgaaac tggtggagtc tgggggagac ttagtgaagc ctggagggtc cctaaaactc 60

tcctgtgcag cctctggatt cgctttcagt agttatgaca tgtcttgggt tcgccagact 120

ccggagaaga gactggagtg ggtcgcaacc attagcagtg gtggtagtta cacctattat 180

ccagacagtg tgaagggccg attcaccatc tccagagaca atgtcaggga caccctgtac 240

ctgcaaatga gcagtttgag gtctgaggac acggccttgt attactgtgc aagacaggca 300

attgggacgt actttgacta ctggggccaa ggcaccactc tcacagtctc ctca 354

<210> 288
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 288
gacatccaga tgactcagtc tccagcctcc ctatcttcat ctgtgggaga aactgtcacc 60

atcacatgtc gagcaagtga gaatatttac agttatttag catggtatca gcagaaacag 120

ggaaaatctc ctcagctcct ggtctataat gcaaaaactt tagcagaagg tgtgccatca 180

aggttcagtg gcagtggatc aggcacacag ttttctctga agatcaacag cctgcagcct 240

gaagattttg ggacttatta ctgtcaacat cattatgatt ctccgctcac gttcggtgct 300

gggaccaagc tggagctgag ac 322

<210> 289
<211> 360

<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 289
gatgtgcagc tggtggagtc tgggggaggc ttagtgcagc ctggagggtc ccggaaactc 60

tcctgtgcag cctctggatt cactttcagt agctttggaa tgcactgggt tcgtcaggct 120

ccagagaagg ggctggagtg ggtcgcatac attagtagtg gcagtagtaa catctactat 180

gcagacacag tgaagggccg attcaccatc tccagagaca atcccaagaa caccctgttc 240

ctgcaaatga ccagtctaag gtctgaggac acggccatgt attactgtgc aagaggctac 300

tatggtaact acgatgctat ggactactgg ggtcaaggaa cctcagtcac cgtctcctca 360

<210> 290
<211> 340
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 290
gatattgtga tgacacagtc tacatcctcc ctggctatgt cagtaggaca gaaggtcact 60

atgagctgca agtccagtca gagcctttta aatagtagca atcaaaagaa ttatttggcc 120

tggtaccagc aggaaccagg acagtctcct aaacttctgg tatcctttgc atccactagg 180

gaatctgggg tccctgatcg cttcacaggc agtggatctg ggacagattt cactcttacc 240

atcagcggtg tgcaggctga agacctggca gtttattact gtcagcaaca ttatagcatt 300

ccgctcacgt tcggtgctgg aaccaagctg gagctgaaac 340

<210> 291
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 291
gaggtcctgc tccaacggtc tggacctgac ctggtgaagc ctggggcttc agtgacgata 60

ccctgcaagg cttctggata cacattcact gactacaaca tggactgggt gaagcagagc 120

catggaaaga gccttgagtg gattggaaat attaatactt acaatggtgg tactatctac 180

aaccagaagt tcaagggcaa ggccacattg actgtagaca agccctccag cacagcctac 240

atggagctcc gcagcctgac atctgaggac actgcagtct attactgtgc aagacgtcta 300

cggtatgggg gacactactt tgactactgg ggccaaggca ccgctctcac agtctcctca 360

<210> 292
<211> 323
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 292
gacatcaaga tgacccagtc tccatcttcc atgtatgcat ctctaggaga gagagtcact 60

atcacttgca aggcgagtca ggacattaat agcttttaa gctggttcca gcggaaacca 120

gggaaatctc cgaagaccct gatctatcgt gcaaacagat tagtagatgg agtcccatca 180

aggttcactg gcagtggatc tgggcaagaa ttttctctca ccatcagcag cctggagtat 240

gaagatttgg gaatttatta ttgtcttcag tatgatgagt ttccgtacac gttcggaggg 300

gggaccaagc tggaaataaa acg 323

<210> 293
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 293
gaagtgatgc tggtagagtc tgggggagac ttagtgaagc ctggagggtc cctgaaactc 60

tcctgtgcag cctctggatt cactttcagt agctatgcca tgtcttgggt tcgccagact 120

ccggagaaga ggctggagtg ggtcgcatac attagcggtg gtggtgatca catctattat 180

ccagacagtg tgaggggccg attcaccatc tccagagaca atgccaagga caccctgtac 240

ctgcaaatga gcagtctgag gtctgaggac acggccttgt atgactgtgc aagagtgaga 300

gactggtact tcgatgtctg gggcgcaggg accacggtca ccgtctcctc a 351

<210> 294
<211> 316
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

polynucleotide"

<400> 294
caaattgttc tcacccagtc tccagcaatc atgtctgcat ctccagggga gaaggtcacc 60

atgacctgca gtgccagctc aagtgtcagt tacatgtact ggtaccagca gaagtcaggc 120

acctccccca aaagatggat ttatgacaca tccaaactgg cttctggagt ccctgctcgc 180

ttcagtggca gtgggtctgg gacctcttac tctctcacaa tcagcagcat ggaggctgaa 240

gatgctgcca cttattactg ccagcagtgg agtagtaacc cgtacacgtt cggaggggg 300

accaagctgg aaataa 316

<210> 295
<211> 342
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 295
caggttcagc tgcagcagtc tggaactgag ctgctgaggc ctggggcctc agtgaagata 60

tcctgcaagg ctactggcta cacattcagt agctactgga tggagtgggt aaagcagagg 120

cctggacatg gccttgagtg gattggagag attttacctg gaagtggtac tactcagtac 180

aatgagaagt tcaagggcaa ggccaccttc actgcagata catcctccaa cacagcctac 240

atgcatctca gcagcctgac atctgaggac tctgccgtct attactgtgc aagagggact 300

aactctctct ggggccaagg gactctggtc actgtctctg ca 342

<210> 296
<211> 304
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 296
caaattgttc tcacccagtc tccagcactc atgtctgcat ctccagggga gaaggtcacc 60

atgacctgca gtgtcacctc aagtgtaagt tacatgtact ggtaccagca gaagcctaga 120

tcctccccca aaccctggat ttatctcaca tccaacctgg cttctggagt ccctgctcgc 180

ttcagtggca gtgggtctgg gacctcttac tctctcacaa tcagcagcgt ggaggctgaa 240

gatgctgcca cttattactg ccagcagtgg aggaataacc cattcacgtt cggctcgggg 300

acaa 304

<210> 297
<211> 387
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 297
caggttactc tgaaagagtc tggccctggg atattgcagc cctcccagac cctcagtctg 60

acttgttctt tctctgggtt ttcactgagc acttctggta tgggtgtagg ctggattcgt 120

cagccatcag ggaagggtct ggagtggctg gcactcattt ggtgggatga tgtcaagcgc 180

tataatccag ccctgaagag tcgactgact atctccaagg atgcctccag cagccaggtc 240

ttcctcaaga tcgccagtgt ggacactgca gatactgcca catactactg tgctcgaata 300

gcttcctatg attacgacgt agtctatgct atggactact ggggtcaagg aacctcagtc 360

agcgtctcct caaggtggaa ataaaac 387

<210> 298
<211> 328
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 298
caggctgttg tgactcagga atctgcactc accacatcac ctggtgaaac agtcacactc 60

acttgtcgct caagtactgg ggctgttaca actagtaact atgccaactg gatccaagaa 120

aaaccagatc atttattcac tggtctaata ggtggtacca acaaccgagc tccaggtgtt 180

cctgccagat tctcaggctc cctgattgga gacaaggctg ccctcaccat cacaggggca 240

cagactgagg atgaggcaat atatttctgt ggtctatggt acagcaacca tttggtgttc 300

ggtggaggaa ccaaactgac tgtcctag 328

<210> 299
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 299
gaggtgcagc ttgttgagac tggtggagga ttggtgcagc ctaaagggtc attgaaactc 60

tcatgtgcag tctctgcatt caccttcact acctacgcca tgaactgggt ccgccaggct 120

ccaggaaagg gtttggagtg ggttgctcgc ataagaaata aaagtaataa ttatgcaaca 180

tattatgccg attcagtgaa agacaggttc accatctcca gagatgattc acaaagcatg 240

ctctatctgc aaatgaacaa cttgaaaatt gaggacacag ccatgtatta ctgtgtgttc 300

tactatgatt acgtctactg gggccaaggg actctggtca ctgtctctgc a 351

<210> 300
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 300
gaaacaactg tgacccagtc tccagcattc ctgtccgtgg ctacaggaga aaaagtcact 60

atcagatgca taaccagcac tgatattgat gatgatatga actggtacca gcagaagcca 120

ggggaacctc ctaatgtcct tatttcagaa ggcaatactc ttcgtcctgg agtcccatcc 180

cgattctcca gcagtggcta tggcacagat tttgttttta caattgaaaa cacgctctca 240

gaagatgttg cagattacta ctgtttgcaa agtgataaca tgcctctcac gttcggtgct 300

gggaccaagc tggagctgaa ac 322

<210> 301
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 301
caggtgcaac tgcagcagcc tggggctgag ctggtgaagc ctggggcctc agtgaagatg 60

tcctgcaagg cttctggcta cacatttacc aattacaata tgcactgggt aaagcagaca 120

cctggacagg gcctggaatg gattggggct atttttccag gaaatggtgg tacttcctac 180

aatcagaagt tcaaaggcaa ggccacattg actgcagaca aatcctccag cacagcctac 240

atgcagctca ccagtttgac atctggggac tctgcagtct attactgtgc aagatggggc 300

tacggtagtg gcctttatgc tatggactac tggggtcaag gaacctcagt caccgtctcc 360

tca 363

<210> 302

<211> 320
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 302
gaaaatgtac tcacccagtc tccagcaatc atgtctgcat ctctagggga gaaggtcacc 60

atgagctgca gggccagctc aagtgtaaat tacatgtcct ggtaccagca gaagtcagat 120

gcctccccca aactatggat ttattacaca tccaacctgg ctcctggagt cccagctcgc 180

ttcagtggca gtgggtctgg gaactcttat tctctcacaa tcagcagcat ggagggtgaa 240

gatgctgcca cttattactg ccagcagttt actagttccc cgtacacgtt cggaggggg 300

accaagctgg aaataaaacg 320

<210> 303
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 303
gaggtccagc tgcagcagtc tggacctgag ctggtaaagc ctggggcttc agtgaagatg 60

tcctgcaagg cttctggata cacattcact agctatgtta tgcactgggt gaagcagaag 120

cctgggcagg gccttgagtg gattggatat attaatcctt acaatgatgg tactaagtac 180

aatgagaagt tcaaaggcaa ggccacactg acttcagaca aatcctccag cacagcctac 240

atggagctca gcagcctgac ctctgaggac tctgcggtct attactgtgc aagattgagg 300

tcgagggcta tggactactg gggtcaagga acctcagtca ccgtctcctc a 351

<210> 304
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 304
gacatccaga tgacccagtc tccatcctcc ttatctgcct ctctgggaga gagagtcagt 60

ctcacttgtc gggcaagtca ggacattggt tatagcttaa actggcttca gcaggaacca 120

gatggaacta ttaaacgcct gatctacgcc acatccagtt tagattctgg tgtccccaaa 180

aggttcagtg gcagtaggtc tgggtcagat tattctctca ccatcagcag ccttgagtct 240

gaagattttg tagactatta ctgtctacaa tatgctagtt ctccgtggac gttcggtgga 300

ggcaccaagc tggaaatcaa ac 322

<210> 305
<211> 369
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 305
caggtgcagc tgcagcagtc tggagctgag ctgatgaagc ctggggcctc agtgaagata 60

tcctgcaagg ctaatggcta cacattcagt agctactgga tagagtggtt aaggcagagg 120

cctggacatg gccttgagtg gattggagag attttacctg gaagtgataa tagtaattat 180

aatgagaagt tcaagggcaa ggccacattc actgcagata catcctccaa cacagcctac 240

atgcaactca gcagcctgac atctgaggaa tctgccgtct attactgtac aaggggatta 300

cgacgagacg gctcatatta ctatgttatg gaacattggg gtcaaggaac ctcagtcacc 360

gtctcctca 369

<210> 306
<211> 312
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 306
gacatcaaga tgacccagtc tccatcttcc atgtatgcat ctctaggaga gagagtcact 60

atcacttgca aggcgagtca ggacattaat agctatttaa gctggttcca gcagaagcca 120

gggagatctc ctaagaccct gatctatcgt gcaaacagat tggtagatgg ggtcccatca 180

aggttcagtg gcagtggatc tgggcaagat tattctctca ccatcagcag cctggactat 240

gaagatatgg gaatttatta ttgtctacag tatgatgaat ttccattcac gttcggctcg 300

gggacaaagt tg 312

<210> 307
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 307
gaagtgaagc tggtggagtc tgggggaggc ttagtgaagc ctggagggtc cctgaaactc 60

tcctgtgcag cctctggatt cactttcggt cgctatgtca tgtcttgggt tcgccagact 120

ccagaaaaga aactggagtg ggtcgcatcc attactagtg gtggtactac ctactatcca 180

gacagtgtga agggccgatt caccatctcc agagataatg ccaggaacat cctgtaccta 240

caaatgagca gtctgaggtc tgaggacacg gccatgtatt actgtgcaag agtctactat 300

cattacgacg acatctttgc ttactggggc caagggactc tggtcactgt ctctgca 357

<210> 308
<211> 338
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 308
gacattgtga tgtcacagtc tccatcctcc ctggctgtgt cagcaggaga gaaggtcact 60

atgagctgca aatccagtca gagtctgctc aacagtagaa cccgaaagaa ctacttggct 120

tggtaccagc agaaaccagg gcagtctcct aaactgctga tctactgggc atccactagg 180

gaatctgggg tccctgatcg cttcacaggc agtggatctg ggacagattt cactctcacc 240

atcagcagtg tgcaggctga agacctggca gtttattact gcaagcaatc ttataatctt 300

tacacgttcg gaggggggac caagctgaaa ataaaacg 338

<210> 309
<211> 348
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 309
gaggtccagc tgcaacagtc tggacctgag ctggtgaagc ctggggcttc agtgaagata 60

tcctgcaaga cttctggata cacattcact gaatacacca tgcactgggt gaagcagagc 120

catggaaaga gccttgagtg gattggaggt attaatccta acaatggtgg tactagctac 180

aaccagaagt tcaagggcaa ggccacattg actgtagaca agtcctccag cacagcctac 240

atggagctcc gcagcctgac atctgaggat tctgcagtct attactgtgc aaggggtccc 300

gcctggtttg cttactgggg ccaagggact ctggtcactg tctctgca 348

<210> 310
<211> 323
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 310
gaaacaactg tgacccagtc tccagcatcc ctgtccatgg ctataggaga aaaagtcacc 60

atcagatgca taaccagcac tgatattgat gatgatatga tctggtacca gcagaagcca 120

ggggaacctc ctaagctcct tatttcagaa ggcaatactc ttcgtcctgg agtcccatcc 180

cgattctcca gcagtggcta tggtacagat tttgttttta caattgaaaa catgctctca 240

gaagatgttg ccgattacta ctgtttgaaa agggatgact tgccttacac gttcggcggg 300

gggacacagg tggaaattaa acg 323

<210> 311
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 311
gaggtccagc tgcaacagtc tggacctgag ctggtgaagc ctggaggttc aaagaagata 60

tcctgcaagg cttctggtta ctcattcact ggctacagta tgaactgggt gaagcagagc 120

catggaaaga accttgagtg gattggactt attaatcctt acagtggtgg tactatctac 180

aaccagaaat tcaagggcaa ggccacatta actgtagaca agtcatccag cacagcctac 240

atggagctcc tcagtctgac atctgaggac tctgcagtct attactgtgc aagaaggagt 300

gattacccgt tagtttactg gggccaaggg actctggtca ctgtctctgc a 351

<210> 312
<211> 325
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 312

caaattgttc tcacccagtc tccagcaatc atgtctgcat ctctagggga acgggtcacc 60

ctgacctgca ctgccagctc aagtgtaagt tccagttact tgcactggta ccagcagaag 120

ccaggatcct cccccaaact ctggatttat agcacatcca acctggcttc tggagtccca 180

actcgcttca gtggcagtgg gtctgggacc tcttactctc tcagaatcag cagcatggag 240

gctgaagatg ctgccactta ttactgccac cagtataatc gttccccgct cacgttcggt 300

gctgggacca agctggagct gaaac 325

<210> 313
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 313
caggtgcagc tgaaggagtc aggacctgtc ctggtggcgc cctcacagag cctgtccatc 60

acttgcactg tctctgggtt ttcattaacc agctatggtg tacactgggt tcgccagcct 120

ccaggaaagg gtctggagtg gctgggagta atttgggctg gtggaagtac aaattataat 180

tcagctctca tgtccagact gagcatcagc aaagacaact ccaagagcca agttttctta 240

aaaatgaaca gtctgcaaac tgatgacaca gccatgtact actgtgccaa acagggcaac 300

ttctatgcta tggactactg gggtcaagga acctcagtca ccgtctcctc a 351

<210> 314
<211> 319
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 314
gacatccaga tgacacagtc tccatcctca ctgtctgcat ctctgggagg caaagtcacc 60

atcacttgca aggcaagcca agacattaag aagtatatag cttggtacca acacaagcct 120

ggaaaaggtc ctaggctact catacattac acatctacat tagagccagg catcccatca 180

aggttcagtg gaagtgggtc tgggagagat tattccttca gcatcagcaa cctggagcct 240

gaagatattg caacttatta ttgtctacaa tatgatattc tgtggacgtt cggtggaggc 300

accaagctgg aaatcaaac 319

<210> 315
<211> 363

<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 315
gaggtccagc tgcaacagtc tggacctgag ctggtgaagc ctggagcttc aatgaagata 60

tcctgcaagg cttctggtta ctcattcact ggctacacca tgaactgggt gaagcagagc 120

catggaaaga accttgagtg gattggactt attaatcctt acaatggtgg tactacctac 180

aaccagaagt tcaagggcaa ggccacatta actgtagaca agtcatccag cacagcctac 240

atggagctcc tcagtctgac atctgaggac tctgcagtct attactgtgc attaggttac 300

tatggtaact acaggaggta cttcgatgtc tggggcgcag ggaccacggt caccgtctcc 360

tca 363

<210> 316
<211> 325
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 316
gaaaatgtgc tcacccagtc tccagcaata atggctgcct ctctggggca gaaggtcacc 60

atgacctgca gtgccagctc aagtgtaagt tccagttact tgcactggta ccagcagaag 120

tcaggcgctt cccccaaacc cttgattcat aggacatcca acctggcttc tggagtccca 180

gctcgcttca gtggcagtgg gtctgggacc tcttactctc tcacaatcag cagcgtggag 240

gctgaagatg atgcaactta ttactgccgg cagtggagtg gttacccgtg gacgttcggt 300

ggaggcacca agctggaaat caaac 325

<210> 317
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 317
caggttcagc tgcagcagtc tggggctgag ctggcaagac ctggggcttc agtgaagttg 60

tcctgcaagg cttctggcta cacctgtact agctactgga tgcagtgggt aaaacagagg 120

cctggacagg gtctggaatg gattggggct atttatcctg gagatggtga tactaggtac 180

actcagaagt tcaagggcaa ggccacattg actgcagata aatcctccag cacagcctac 240

atgcaactca gcagcttggc atctgaggac tctgcggtct attactgtgc aaggggggagg 300

cggacggagg cctggtttgc ttactggggc caagggactc tggtcactgt ctctgca 357

<210> 318
<211> 325
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 318
caaattgttc tcacccagtc tccagcaatc atgtctgcat ctctagggga acgggtcacc 60

atgacctgca ctgccagctc aagtgtaagt tccagttact tgcactggta ccagcagaag 120

ccaggatcct cccccaaact ctggatttat agcacatcca acctggcttc tggagtccca 180

gctcgcttca gtggcagtga gtctgggacc tcttactctc tcacaatcag caacatggag 240

gctgaggatg ctgccactta ttactgccac cagtatcatc gttccccatt cacgttcggc 300

tcggggacaa agttggaaat aaaac 325

<210> 319
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 319
caggttactc tgaaagagtc tggccctggg atattgcagc cctcccagac cctcagtctg 60

acttgttctt tctctggatt ttcactgagc acttctggta tgggcgtagg ctggattcgt 120

cagccatcag ggaagggtct ggagtggctg gcacacattt ggtgggatga tgtcaagcgc 180

tataacccag cccttaagag ccgactgact atctccaagg atgcctccag cagccaggta 240

ttcctcaaga tcgccagtgt ggacactgca gaaactgcca catactactg tgcccacatc 300

ctcgaccggg cttactactt tgactactgg ggccaaggca ccactctcac agtcacctca 360

<210> 320
<211> 334
<212> DNA
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 320
gacattgtgc tgacacagtc tcctgcttcc ttagctgtat ctctggggca gagggccacc 60

atctcatgca gggccagcaa aagtgtcagt acatctggct atagttatat gcactggtac 120

caacagaaac caggacagcc acccaaactc ctcatctatc ttgcatccaa cctagaatct 180

ggggtccctg ccaggttcag tggcagtggg tctgggacag acttcaccct caacatccat 240

cctgtggagg aggaggatgc tgcaacctat tactgtcagc acagtaggga gcttcctctc 300

acgttcggtg ctgggaccaa gctggagctg aaac 334

<210> 321
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 321
caagttactc taaaagagtc tggccctggg atattgaagc cctcacagac cctcagtctg 60

acttgttctt tctctgggtt ttcactgagc acttctggta tgggtatagg ctggattcgt 120

cagccttcag ggaagggtct ggagtggctg gcacacattt ggtgggatga tgataagtac 180

tataacccat ccctgaagag ccagctcaca atctccaagg attcctccag aaaccaggtt 240

ttcctcaaga tcaccagtgt ggacactgca gatactgcca cttactactg tgctcgaaga 300

gggactgcgt actactttga ctactggggc caaggcacca ctctcacagt ctcctca 357

<210> 322
<211> 319
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 322
caaattgttc tctcccagtc tccagcaatc ctgtctgcat ctccagggga gaaggtcaca 60

atgacttgca gggccagttc aagtgtaagt tacattcact ggtaccggca gaagccagga 120

tcctcccccа aaccctggat ttatgccaca tccaacctgg cttctggagt ccctgctcgc 180

ttcagtggca gtgggtctgg gacctcttac tctctcacaa tcagcagagt ggaggctgaa 240

gatgctgcca cttattactg ccagcagtgg agcagtaatc cacccacgtt cggtgctggg 300

accaagctgg agctgaaac 319

<210> 323
<211> 345
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 323
caggtgcagc tgaaggagtc aggacctgac cttgtgcagc cctcacagac cctgtctctc 60

acctgcactg tctctgggtt ctcattaacc ttctatggtg ttcactgggt tcgccagcct 120

ccaggaaagg gactggagtg ggtgggaaca atgggctggg atgacaaaaa atattataat 180

tcagctctaa aatctcgact gagcatcagc agggatacct ccaagaacca ggttttctta 240

aaactgagca gtctgcaaac tgaagacaca gccatgtact actgtactag aggtgggacg 300

gggtttgact actggggcca aggcaccact ctcacagtct cctca 345

<210> 324
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 324
gacattgtga tgacccagtc gcacaaattc atgtccacat cagtaggaga cagggtcagc 60

atcacctgca aggccagtca ggatgtgggt actgctgtag cctggtatca acagaaacca 120

gggcaatctc ctaaactact gatttactgg gcatccatcc ggcacactgg agtccctgat 180

cgcttcacag gcagtggatc tgggacagat ttcactctca ccattagcaa tgtgcagtct 240

gaagacttgg cagattattt ctgtcagcaa tatagcagct atccgctcac gttcggtgct 300

gggaccaagc tggagctgaa ac 322

<210> 325
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 325
caggtccaac tgcagcagcc tggggctgag cttgtgaagc ctggggcttc agtgaagctg 60

tcctgcaagg cttctggcta caccttcacc agctactgga tgcactgggt gaagcagagg 120

cctggacaag gccttgagtg gattggagtg attaatccta gcaacggtcg tactaactac 180

aatgagaagt tcaagagcaa ggccacactg actgtagaca aatcctccag cacagcctac 240

atgcaactca gcagcctgac atctgaggac tctgcggtct attactgtgc aagaagaagg 300

gaactgggaa ccctctatgc tatggactac tggggtcaag gaacctcagt caccgtctcc 360

tca 363

<210> 326
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 326
gacatcaaga tgacccagtc tccatcttcc atgtatgcat ctctaggaga gagagtcact 60

atcacttgca aggcgagtca ggacattaat agctatttaa gctggttcca gcagaaacca 120

gggaaatctc ctaagaccct gatctatcgt gcaaacagat tggtagatgg ggtcccatca 180

aggttcagtg gcagtggatc tgggcaagat tattctctca ccatcagcag cctggagtat 240

gaagatatgg gaatttatta ttgtctacag tatgatgagt ttccattcac gttcggctcg 300

gggacaaagt tggaaataaa ac 322

<210> 327
<211> 345
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 327
caggtgcaac tgaagcagtc aggacctggc ctggtggcgc cctcacagag cctgttcatc 60

acatgcaccg tctcagggtt ctcattaacc agctatgaaa taaactgggt tcgccagcct 120

ccaggaaagg gtctggagtg gctgggagtg atatggactg gtggaagcac aaattataat 180

tcagctctca tatccagact gagcatcagc aaagacaact ccaagagcct agttttctta 240

aaaatgaaca gtctgcaaac tgatgacaca gccatatatt actgtgtaag aggtgtttat 300

gctatggact actggggtca aggaacctca gtcaccgtct cctca 345

<210> 328

<211> 323
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 328
gacattgtga tgacccagtc tcacaaattc atgtccacat cagtaggaga cagggtcagc 60

atcacctgca aggccagtca ggatgtgaat actgctgtag gctggtatca acagaaacca 120

ggacaatctc ctaaactact gatttactcg gcatcctacc ggtacactgg agtccctgat 180

cgcttcactg gcagtggatc tgggacggat ttcactttca ccatcagcag tgtgcaggct 240

gaagacctgg cagtttatta ctgtcagcaa cattatagta gtccgtacac gttcggaggg 300

gggaccaagg tggaaataaa acg 323

<210> 329
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 329
gaggtccagc tgcagcagtc tggacctgag ctggtaaagc ctggggcttc agtgaagatg 60

tcctgcaagg cttctggata cacattcact aactatgtta tgcactgggt gaagcagaag 120

cctgggcagg gccttgagtg gattggatat attaatcctt acaatgatgg tactaaatac 180

aatgagaagt tcaaaggcaa ggccacactg acttcagaca aatcctccac cacagcctac 240

atggcgctca gcagcctgac ctctgaggac tctgcggtct attactgtgc agtagcctac 300

tatagtaact gggggtttgc ttactggggc caagggactc tggtcactgt ctctgca 357

<210> 330
<211> 323
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 330
gacatccaga tgactcagtc tccagcctcc ctatctgcat ctgtgggaga aactgtcacc 60

atcacatgtc gagcaagtga gaatatttac agttatttag catggtatca gcagaaacag 120

ggaaaatctc ctcagctcct ggtctataat gcaaaaacct tagcagaagg tgtgccatca 180

aggttcagtg gcagtagatc aggctcacag ttttctctga agatcaacag cctgcagcct 240

gaagattttg ggagttatta ctgtcaacat cattatggta ctccgtacac gttcggaggg 300

gggaccaagc tggaaataaa acg 323

<210> 331
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 331
caggttcagc tggaggagtc aggggctgag ctggcaagac ctggggcttc agtgaagttg 60

tcctgcaagg cttctggcta tagctactgg atgcagtgga taaaacagag gcctggacag 120

ggtctggaat ggattggggc tatttatcct ggaaatggtg atactaggta cactcagaag 180

ttcaagggca aggccacatt gactgcagat aaatcctcca gcacagccta catgcaactc 240

agcagcttgg catctgagga ctctgcggtc tattactgtg caagatctcc ggcctactat 300

aggtacggcg agggctactt tgactactgg ggccaaggca ccactctcac agtctcctca 360

<210> 332
<211> 319
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 332
caaattgttc tcacccagtc tccagcaatc atgtctgcat ctccagggga gaaggtcacc 60

atgacctgca gtgccagctc aagtgtaagt tacatgtact ggtaccagca gaagccagga 120

tcctccccca gactcctgat ttatgacaca tccaacctgg cttctggagt ccctgttcgc 180

ttcagtggca gtgggtctgg gacctctttc tctctcacaa tcagccgaat ggaggctgaa 240

gatactgcca cttattactg ccaggagtgg agtggtaatc cgctcacgtt cggtgatggg 300

accaagctgg agctgaaac 319

<210> 333
<211> 354
<212> DNA
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 333
cagatccagt tggtgcagtc tggacctgag ctgaagaagc ctggagagac agtcaagatc 60

tcctgcaagg cttctgggta taccttcaca aactatggaa tgaactgggt gaagcaggct 120

ccaggaaagg gtttaaagtg gatgggctgg ataaacacct acactggaga gccagcatat 180

gctgatgact tcaagggacg gtttgccttc tctttggaaa cctctgccag cgctgcctat 240

ttgcagatca acaacctcaa aaatgaggac acggctactt ttttctgtgc aaatatgagg 300

cccacgaggg ggtttgctta ctgggggcaa gggactctgg gcactgtctc tgca 354

<210> 334
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 334
aatattgtga tgacccagac tcccaaattc ctgcttgtat cagcaggaga cagggttacc 60

ataacctgca aggccagtca gagtgtgagt aatgatgtag cttggtacca acagaagcca 120

gggcagtctc ctaaactgct gatatactat gcatccaatc gctacactgg agtccctgat 180

cgcttcactg gcagtggata tgggacggat ttcactttca ccatcagcac tgtgcaggct 240

gaagacctgg cagtttattt ctgtcagcag gattatagct ctcctccgac gttcggtgga 300

ggcaccaagc tggaaatcaa ac 322

<210> 335
<211> 354
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 335
gaggtccagc tgcagcagtc tggacctggg ctagtgagga ctggggcttc agtgaagata 60

tcctgcaagg cttctggtta ctcattcact ggttactaca tgcactgggt caagcagagc 120

catggaaaga gccttgagtg gattggatat attagttgtt acaatggtgc tactacctac 180

aaccagaact tcaagggcaa ggccacattt attgtagaca catcctccag cacagcctac 240

atgcagttca acagcctgac atctgaggac tctgcggtct attactgtgc aagatccgac 300

ggggggcatg ctatggacta ctggggtcaa ggaacctcag tcaccgtctc ctca 354

<210> 336
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 336
gacatccaga tgactcagtc tccagcctcc ctggctgcat ctgtgggaga aactgtcacc 60

atcacatgtc gagcaagtga gaacatttac tacagtttag catggtatca gcagaagcaa 120

gggaaatctc ctcagctcct gatctataat gcaaacagct tggaagatgg tgtcccatcg 180

aggttcagtg gcagtggatc tgggacacag tattctatga agatcaacag catgcagcct 240

gaagataccg caacttattt ctgtaagcag acttatgacg ttccgctcac gttcggtgct 300

gggaccaagc tggagctgaa ac 322

<210> 337
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 337
gaggttcagc tgcagcagtc tggacctgag ctggagaagc ctggcgcttc agtgaagata 60

tcctgcaagg cttctggtta ctcattcact ggctacaaca tgaactgggt gaagcagagc 120

aatggaaaga gccttgagtg gattggaaat attgatcctt attatggtgg ttctagctac 180

aaacagaagt tcgagggcaa ggccacattg actgtagaca aatcctccag cacagcctac 240

atgcagctca agagcctgac atctgaggac tctgcagtct attactgtgc aagaggtggt 300

agtaacttct ttgactactg gggccaaggc accactctca cagtctcctc a 351

<210> 338
<211> 337
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 338
gatgttgtga tgacccagac tccactcact ttgtcggtta ccattggaca accagcctcc 60

atctcttgca agtcaagtca gagcctctta gatagtgatg gaacgacata tttgaattgg 120

ttgttacaga ggccaggcca gtctccaaag cgcctaatct atctggtgtc taaactggac 180

tctggagtcc ctgacaggtt cactggcagt ggatcaggga cagatttcac actgaaaatc 240

agcagagtgg aggctgagga tttgggagtt tattattgct ggcaaggtac acattttccg 300

ctcacgttcg gtgctgggac caagctggag ctgaaac 337

<210> 339
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 339
gacgtgaagc tggtggagtc tgggggaggc ttagtgaagc ctggagggtc cctgaaactc 60

tcctgtgcag cctctggatt cactttcagt agctatacca tgtcttgggt tcgccagact 120

ccggagaaga ggctggagtg ggtcgcaacc attagtagtg gtggtagtta cccctactat 180

ccagacagtg tgaagggccg attcaccatc tccagagaca atgccaagaa caccctgtac 240

ctgcaaatga gcagtctgaa gtctgaggac acagccatgt attactgtac aagagatgtc 300

tatgatggtt actcctactg gggccaaggc accactctca cagtctcctc a 351

<210> 340
<211> 320
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 340
caaattgttc tctcccagtc tccagcaatc ctgtctgcat ctccagggga gaaggtcaca 60

atgacttgca gggccagctc aagtgtaagt tacatgcact ggtaccagca gaagccagga 120

tcctccccca aaccctggat ttatgccaca tccaacctgg cttctggagt ccctgctcgc 180

ttcagtggca gtgggtctgg gacctcttac tctctcacaa tcagcagagt ggaggctgaa 240

gatgctgcca cttattactg ccagcagtgg agtagtaacc catacacgtt cggaggggag 300

accaagctgg aaataaaacg 320

<210> 341
<211> 369
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 341
gaggttcagc tgcagcagtc tggggcagaa cttgtgaagc caggggcctc agtcaaattg 60

tcctgcacag cttctggctt caacattaaa gacacctata tacactgggt gaaacagagg 120

cctgaacagg gcctggagtg gattggaagg attgatcctg cgaatggtaa tactaaatat 180

gacccgaagt tccagggcaa ggccactata acaccagaca catcctccaa cacagcctac 240

ctgcagctca gcagcctgac atctgaggac actgccgtct attactgtgc tagaagctgg 300

cgaaactacg gtagtagttt ctggtacttc gatgtctggg gcgcagggac cacggtcacc 360

gtctcctca 369

<210> 342
<211> 337
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 342
gatgttgtga tgacccagac tccactcact ttgtcggtta ccattggaca accagcctcc 60

atctcttgca agtcaagtca gagcctctta gatagtgatg gaacgacata tttgaattgg 120

ttgttacaga ggccaggcca gtctccaaag cgcctaatct atctggtgtc taaactggac 180

tctggagtcc ctgacaggtt cactggcagt ggatcaggga cagatttcac actgaaaatc 240

agcagagtgg aggctgagga tttgggagtt tattattgct ggcaaggtac acattttccg 300

ctcacgttcg gtgctgggac caagctggag ctgaaac 337

<210> 343
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 343
gacgtgaagc tggtggagtc tgggggaggc ttagtgaagc ctggagggtc cctgaaactc 60

tcctgtgcag cctctggatt cactttcagt agctatacca tgtcttgggt tcgccagact 120

ccggagaaga ggctggagtg ggtcgcaacc attagtagtg gtggtagtta cccctactat 180

ccagacagtg tgaagggccg attcaccatc tccagagaca atgccaagaa caccctgtac 240

ctgcaaatga gcagtctgaa gtctgaggac acagccatgt attactgtac aagagatgtc 300

tatgatggtt actcctactg gggccaaggc accactctca cagtctcctc a 351

<210> 344
<211> 334
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 344
gacattgtga tgacacagtc tccatcctcc ctgactgtga cagcaggaga gaaggtcact 60

atgagctgca cgtccagtca gagtctgtta accagtggaa atcaaaagaa ctacttgacc 120

tggtaccagc agaaaccagg gcagcctcct aaactgttga tctactgggc atccactagg 180

gaatctgggg tccctgatcg cttcacaggc agtggatctg gaacagattt cactctcacc 240

atcagcagtt tgcaggctga agacctggca gtttattact gtcagaatga ttatagtctc 300

acgttcggtg ctgggaccaa gctggagctg aaac 334

<210> 345
<211> 354
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 345
caggtgcagc tgaagcagtc aggacctggc cgagtgcagc cctcacagag cctgtccatc 60

acctgcacag tctctggttt ttcattaact agcaatggtg tacactgggt tcgccagtct 120

ccaggaaagg gtctggagtg gctgggagtg ctatggagtg gtggaagcac agactataat 180

gcagctttca tatccagact gagcatcagc aaggacaatt acaagagcca agttttcttt 240

aaaatgaaca gtctgcaagc taatgacaca gccatatatt actgtgccag aaataataat 300

aggtacggag ctatggacta ctggggtcaa ggaacctcag tcaccgtctc ctca 354

<210> 346
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

polynucleotide"

<400> 346
gacatccaga tgaaccagtc tccatccagt ctgtctgcat cccttggaga cacaattacc 60

atcacttgcc atgtcagtca gaacattaat gtttggttaa gctggtacca gcagaaacca 120

ggaaatattc ctaaactatt gatccaaaag gcttccaact tgcacacagg cgtcccctca 180

aggtttagtg gcagtggatc tggaacaggt ttcacattaa ccatcagcag cctgcagcct 240

gaagacattg ccacttacta ctgtcaacag ggtcaaagtt atccattcac gttcggctcg 300

gggacaaagt tggaaataaa ac 322

<210> 347
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 347
caggtgcagc tgaaggagtc aggacctggc ctggtggcgc cctcacagag cctgtccatc 60

acttgcactg tctctgggtt ttcattaacc aactatggtg tacactgggt tcgccagcct 120

ccaggaaagg gtctggagtg gctgggagta atatgggctg gtggaatcac aaattataat 180

tcggctctca tgtccagact gagcatcagc gaagacaact ccaagagcca agttttctta 240

aaaatgaaca gtctgcaaac tgatgacaca gccatgtact actgtgccag aaatttaggt 300

ccctatgcta tggactactg gggtcaagga acctcagtca ccgtctcctc a 351

<210> 348
<211> 335
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 348
gacattgtgc tgacccaatc tccagcttct ttggctgtgt ctctagggca gagggccacc 60

atctcctgca aggccagcca aagtgttgat tatgatggtg atagttattt gacctggtac 120

caacagaaac caggacagcc acccaaactc ctcatctatg ctgcatccaa tctagaatct 180

gggatcccag ccaggtttag tggcagtggg tctgggacag acttcaccct caacatccat 240

cctgtggagg aggaggacgc tgcaacctat tactgtcagc aaagtaatga ggatccgtac 300

acgttcggag gggggaccaa gctggaaata aaacg 335

<210> 349
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 349
gaggtccagc tgcagcagtc tggacctgac ctggtgaagc ctggggcttc agtgaagata 60

tcctgcaagg cttctggtta ctcattcact ggctactaca tgcactgggt gaagcagagc 120

catggaaaga gccttgagtg gattggacgt gttaatccta acaatggtgg tactagctac 180

aaccagaagt tcaagggcaa ggccatatta actgcagaca agtcatccag cacagcctac 240

atggagctcc gcagcctgac atctgaggac tctgcggtct attactgtgc aagagggagt 300

tatgattacg ccgagggctg gggccaaggg actctggtca ctgtctctgc a 351

<210> 350
<211> 341
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 350
gacattgtga tgtcacagtc tccatcctcc ctagctgtgt cagttggaga gaaggttact 60

atgagctgca agtccagtca gagcctttta tatagtagca ctcaaaagaa ctacttggcc 120

tggtaccagc agaaaccagg gcagtctcct aaactgctga tttactgggc atccactagg 180

gaatctgggg tccctgatcg cttcacaggc agtggatctg ggacagattt cactctcacc 240

atcagcagtg tgaaggctga agacctggca gtttattact gtcagcaata ttatagctat 300

ccgtacacgt tcggaggggg gaccaagctg gaaataaaac g 341

<210> 351
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 351
gagatccagc tgcagcagtc tggacctgag ctggtgaagc ctggggcttc agtgaaggta 60

tcctgcaagg cttctggtta tgcattcact agctacaaca tgtactgggt gatgcagagc 120

catggaaaga gccttgagtg gattggatat gttgatcctt acaatggtgg tactagctac 180

aaccagaagt tcaagggcaa ggccacattg actgttgaca agtcctccag cacagcctac 240

atgcatctca acagcctgac atctgaggac tctgcagtct attactgtgc aagagaaaac 300

tataggtact ttgactactg gggccaaggc accactctca cagtctcctc a 351

<210> 352
<211> 316
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 352
caaattgttc tcacccagtc tccagcaatc atgtctgcat ctccagggga gaaggtcacc 60

ataacctgca gtgccagctc aagtgtaagt tacatgcact ggttccagca gaagccaggc 120

acttctccca aactctggat ttatagcaca tccaacctgg cttctggagt ccctgctcgc 180

ttcagtggca gtggatctgg gacctcttac tctctcacaa tcagccgaat ggaggctgaa 240

gatgctgcca cttattactg ccagcaaagg agtagttacc cacccacgtt cggaggggg 300

accaagctgg aaataa 316

<210> 353
<211> 372
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 353
gaggtgcagc ttgttgagtc tggtggagga ttggtgcagc ctaaagggtc attgaaactc 60

tcatgtgcag cctctggatt caccttcaat acctacgcca tgaactgggt ccgccaggct 120

ccaggaaagg gtttggaatg ggttgctcgc ataagaatta aaagtaataa ttatgcaaca 180

tattatgccg attcagtaaa agacaggttc accatctcca gagatgattc acaaaacatg 240

ctctatctgc aaatgaacaa cttgaaaact gaggacacag ccgtgtatta ctgtgtgaga 300

caaggctata gttacgactg gggaccctgg tttgcttact ggggccaagg gactctggtc 360

actgtctctg ca 372

<210> 354
<211> 320
<212> DNA

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 354
caaattgttc tcacccagtc tccagcaatc atgtctgcat ctccagggga gaaggtcacc 60

ataacctgca gtgccagctc aagtgtaagt tacatgcact ggttccagca gaagccaggc 120

acttctccca aactctggat ttatagcaca tccaacctgg cttctggagt ccctgctcgc 180

ttcagtggca gtggatctgg gacctcttac tctctcacaa tcagccgaat ggaggctgaa 240

gatgctgcca cttattactg ccagcaaagg agtagttacc cacccacgtt cggaggggg 300

accaagctgg aaataaaacg 320

<210> 355
<211> 354
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 355
gaagtgcagc tggtggagtc tgggggaggc ttagtgaagc ctggagggtc cctgaaactc 60

tcctgtgcag cctctggatt cactttcagt gactattaca tgttttgggt tcgccagact 120

ccggaaaaga ggctggagtg ggtcgcaacc attagtgatg gtggtagtta cacctacttt 180

ccagacagtg tgaaggggcg attcaccatc tccagagaca atgcccagaa caacctgtac 240

ctgcaaatga gcagtctgaa gtctgaggac acagccatgt attactgtgc aagagccggg 300

accctctatg ctatggacta ctggggtcaa ggaacctcag tcaccgtctc ctca 354

<210> 356
<211> 325
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 356
caaattgttc tcacccagtc tccagcaatc atgtctgcat ctctagggga acgggtcacc 60

atgacctgca ctgccagctc aagtgtaagt tccagttact tgcactggta ccagcagaag 120

ccaggatcct cccccaaact ctggatttat agcacatcca acctggcttc tggagtccca 180

gctcgcttca gtggcagtgg gtctgggacc tcttactctc tcacaatcag cagcatggag 240

actgaagatg ctgccactta ttactgccac cagtatcatc gttccccctt cacgttcggc 300

tcggggacaa agttggaaat aaaac 325

<210> 357
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 357
caggttgctc tgaaagagtc tggccctggg atattgcagc cctcccagac cctcagtctg 60

acttgttctt tctctgggtt ttcactgagc acttctggta tgggtgtagg ctggattcgt 120

cagccatcag ggaagggtct ggagtggctg gcacacattt ggtgggatga tgtcaagcgc 180

tataacccag ccctgaagag ccgactgact atctccaagg atacctccag cagccaggta 240

ttcctcaaga tcgccagtgt ggacactgca gatactgcca catactactg tgctcgaatg 300

gaggactacg gtagtagctc ctactttgac ttctggggcc acggcaccac tctcacagtc 360

tcctca 366

<210> 358
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 358
gacattcaga tgacccagtc tcctgcctcc cagtctgcat ctctgggaga aagtgtcacc 60

atcacatgcc tggcaagtca gaccattggt acatggttag catggtatca gcagaaacca 120

gggaaatctc ctcagctcct gatttctgct gcaaccagct tggcagatgg ggtcccatca 180

aggttcagtg gtagtggatc tggcacaaaa ttttctttca agatcagcag cctacaggct 240

gaagattttg taagttatta ctgtcaacaa ctttacagta ctccgtggac gttcggtgga 300

ggcaccaagc tggaaatcaa ac 322

<210> 359
<211> 369
<212> DNA
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 359
gaggtccagc tgcagcagtc tggacctgag ctggtaaagc ctggggcttc agtgaagatg 60

tcctgcaagg cttctggata cacattcact agctatgtta tgcactgggt gaagcagaag 120

cctgggcagg gccttgagtg gattggatat attaatcctt acaatgatgg tactaagtac 180

aatgagaagt tcaaaggcaa ggccacactg acttcagaca aatcctccag cacagcctac 240

atggagctca gcagcctgac ctctgaggac tctgcggtct attactgtgc aagaggggct 300

ctctactatg gtaactacct cgggtacttc gatgtctggg gcgcagggac cacggtcacc 360

gtctcctca 369

<210> 360
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 360
gacatccaga tgaaccagtc tccatccagt ctgtctgcat cccttggaga cacaattacc 60

atcacttgcc atgccagtca gaacattaat gtttggttaa gctggtacca gcagaaacca 120

ggaaatattc ctaaactatt gatctataag gcttccatct tacacacagg cgtcccatca 180

aggtttagtg gcagtggatc tggaacaggt ttcacattaa ccatcagcag cctgcagcct 240

gaagacattg ccacttactc ctgtcaacag ggtcaaagtt atccgtacac gttcggaggg 300

gggaccaagc tggaaataaa a 321

<210> 361
<211> 355
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 361
tctgatgtgc agcttcagga gtcaggacct gacctggtga aaccttctca gtcactttca 60

ctcacctgca ctgtcactgg ctactccatc accagtggtt atagctggca ctggatccgg 120

cagtttccag gaaacaaact ggaatggatg ggctacatac actacagtgg tagcactaac 180

tacaacccat ctctcaaaag tcgaatctct atcactcgag acacatccaa gaaccagttc 240

ttcctgcagt tcaaatctgt gactactgaa gactcagcca catattactg tgccctagag 300

gggaattacg acgggtttgc ttactggggc caagggactc tggtcactgt ctctg 355

<210> 362
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 362
gacatccaga tgaaccagtc tccatccagt ctgtctgcat cccttggaga cacaattacc 60

atcacttgcc atgccagtca gaacataaat gtttggttaa gctggtacca gcagaaacca 120

ggaaatattc ctaaactatt gatctataag gcttccaact tgcacacagg cgtcccatca 180

aggtttagtg gcagtggatc tggaacaggt ttcacattaa ccatcagcag cctgcagcct 240

gaagacattg ccacttacta ctgtcaacag ggtcaaagtt atccattcac gttcggctcg 300

gggacaaagt tggaaataaa ac 322

<210> 363
<211> 348
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 363
caggtgcaga tgaaggagtc aggacctggc ctggtggcgc cctcacagag cctgtccatc 60

acttgcactg tctctgggtc ttcattaacc aactatggtg tacactgggt tcgccagcct 120

ccaggaaagg gtctagagtg gctgggagta atatgggctg gtggaagcac aaattataat 180

tcggctctca tgtccagact gagtatcagc aaagacaact ccaagagcca agttttctta 240

aaaatgaaca gtctgcaaac tgatgacaca gccatgtact actgtgccag agactgggag 300

ggctggtttg cttactgggg ccaagggact ctggtcactg tctctgca 348

<210> 364
<211> 323
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 364

gacattcaga tgacccagtc tcctgcctcc cagtctgcat ctctgggaga aagtgtcacc 60

atcacatgcc tggcaagtca gaccattggt acatggttag catggtatca gcagaaacca 120

gggaaatctc ctcagctcct gatttatgct gcaaccagct tggcagatgg ggtcccatca 180

aggttcagtg gtagtggatc tggcacaaaa ttttctttca agatcagcag cctacaggct 240

gaagattttg taagttatta ctgtcaacaa ctttacagta ctccgtacac gttcggaggg 300

gggaccaagc tggaaataaa acg 323

<210> 365
<211> 348
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 365
caggtgcagc taaaggagtc aggacctggc ctggtggcgc cctcacagag cctgtccatc 60

acatgcactg tctcagggtt ctcattaacc gactatggtg taagctggat tcgccagcct 120

ccaggaaagg gtctggagtg gctgggagta atatggggtg gtggaagcac atactataat 180

tcagctctca aatccagact gagcatcagc aaggacaact ccaagagcca agttttctta 240

gaactgaaca gtctgcaaac tgatgacaca gccatttact actgtgccaa acattatggt 300

cactacgctg cttactgggg ccaagggact ctggtcactg tctctgca 348

<210> 366
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 366
gacatccagt tgactcagtc tccagcctcc ctatctgcat ctgtgggaga aactgtcacc 60

atcacatgtc gagcaagtgg gagtattcac aattatttag catggtatca gcagaaacag 120

ggaaagtctc ctcagctcct ggtctataat gcaaaaacct tagtagatgg tgtgccatca 180

aggttcagtg gcagtggatc aggaacacaa tattctctca agatcaacag cctgcagcct 240

gaagattttg ggtattatta ctgtcaacat ttttggacta ctccgtggac attcggtgga 300

ggcaccaagc tggaaatcaa ac 322

<210> 367
<211> 360

<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 367
gaggtccagc tgcagcagtc tggacctgag ctggtaaagc ctggggcttc agtgaagatg 60

tcctgcaagg cttctggata cacattcact agctatgtta tgcactgggt gaagcagaag 120

cctgggcagg gccttgagtg gattggatat attaatcctt acaatgatgg tactgagtac 180

aatgagaagt tcaaaggcaa ggccacactg acttcagaca aatcctccag cacagcctac 240

atggagctca gcagcctgac ctctgaggac tctgcggtct attactgtgc aagaggggtc 300

tatgatggtt actcttactt tgactactgg ggccaaggca ccactctcac agtctcctca 360

<210> 368
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 368
gacatccaga tgaaccagtc tccatccagt ctgtctgcat cccttggaga cacaattacc 60

atcacttgcc atgtcagtca gaacattaat gtttggttaa gctggtacca gcagaaacca 120

ggaaatattc ctaaactatt gatccaaaag gcttccaact tgcacacagg cgtcccctca 180

aggtttagtg gcagtggatc tggaacaggt ttcacattaa ccatcagcag cctgcagcct 240

gaagacattg ccacttacta ctgtcaacag ggtcaaagtt atccattcac gttcggctcg 300

gggacaaagt tggaaataaa ac 322

<210> 369
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 369
caggtgcagc tgaaggagtc aggacctggc ctggtggcgc cctcacagag cctgtccatc 60

acttgcactg tctctgggtt ttcattaacc aactatggtg tacactgggt tcgccagcct 120

ccaggaaagg gtctggagtg gctgggagta atatgggctg gtggaatcac aaattataat 180

tcggctctca tgtccagact gagcatcagc gaagacaact ccaagagcca agttttctta 240

aaaatgaaca gtctgcaaac tgatgacaca gccatgtact actgtgccag aaatttaggt 300

ccctatgcta tggactactg gggtcaagga acctcagtca ccgtctcctc a 351

<210> 370
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 370
gacattcaga tgacccagtc tcctgcctcc cagtctgcat ctctgggaga aagtgtcacc 60

atcacatgcc tggcaagtca gaccattggt acatggttag catggtatca gcagaaacca 120

gggaaatctc ctcagctcct gatttatgct gcaaccagct tggcagatgg ggtcccatca 180

aggttcagtg gtagtggatc tggcacaaaa ttttctttca agatcagcag cctacaggct 240

gaagattttg taagttatta ctgtcaacaa ctttacagta ctccgtggac gttcggtgga 300

ggcaccaagc tggagatcaa ac 322

<210> 371
<211> 348
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 371
caggtgcagc tgaaggagtc aggacctggc ctggtggcgc cctcacagag cctgtccatc 60

acatgcactg tctcagggtt ctcattaacc gactatggtg taagctggat tcgccagcct 120

ccaggaaagg gtctggagtg gctgggagta gtatggggtg gtggaagcac atactataat 180

tccgctctca aatccagact gagcatcacc aaggacaact ccaagagcca agttttctta 240

aaaatgaaca gtctgcaaac tgatgacaca gccatgtact actgtgccaa acagaggggt 300

cagtacgggg cttactgggg ccaagggact ctggtcactg tctctgca 348

<210> 372
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

polynucleotide"

<400> 372
agtattgtga tgacccagac tcccaaattc ctgcttgttt cagcaggaga cagggttacc 60

ataacctgca aggccagtca gagtgtgagt aatgatgtag cttggtacca acagaagcca 120

gggcagtctc ctaaactgct gatatactgt gcatccaatc gctacactgg agtccctgat 180

cgcttcactg gcagtggata tgggacggat ttcactttca ccatcagcac tgtgcaggct 240

gaagacctgg cagtttattt ctgtcagcag gattatagct ctccgctcac gttcggtgct 300

gggaccaagc tggagctgaa ac 322

<210> 373
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 373
caggtgcagc tgaaggagtc aggacctggc ctggtggcgc cctcacagag cctgtccatc 60

acctgcacag tctctggttt ctcattaacc aactatgctg tacactgggt tcgccagtct 120

ccaggaaagg gtctggagtg gctgggagtg atatggagtg atggaagcac agactataat 180

gcagctttca tatctagact gagcatcagc aaggacaact ccaagagcca agttttcttt 240

aagatgaaca gtctgcaagc tgatgacaca gccatgtact actgtgcccg aaagaaagga 300

ggatggtttc cctggtttgc ttactggggc caagggactc tggtcactgt ctctgca 357

<210> 374
<211> 335
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 374
gacattgtgc tgacccaatc tccagcttct ttggctgtgt ctctagggca gagggccacc 60

atctcctgca aggccagcca aagtgttgat catgctggtg atagttatat gaactggtac 120

caacagaaac caggacagcc acccaaactc ctcatctatg ctgcatccaa tctagaatct 180

gggatcccag ccaggtttag tggcagtggg tctgggacag acttcaccct caacatccat 240

cctgtggagg aggaggatgc tgcaacctat tactgtcagc aaagtaatga ggatccgtac 300

acgttcggag gggggaccaa gctggaaatc aaacg 335

<210> 375
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 375
gaggtccagc tgcagcagtc tggacctgac ctggtgaagc ctggggcttc agtgaagata 60

tcctgcaagg cttctggtta ctcattcact ggctactaca tgcactgggt gaagcagagc 120

catggaaaga ggcttgagtg gattggacgt gttaatccta acaatggtgg tactaactac 180

aaccagaaat tcaagggcaa ggccatatta actgtagaca agtcatccag cacagcctac 240

atggagctcc gcagcctgac atctgaggac tctgcggtct attactgtgc aagagggagt 300

tatgataacg ccgagggctg gggccaaggg actctggtca ctgtctctgc a 351

<210> 376
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 376
gacatcaaga tgacccagtc tccatcttcc atgtatgcat ctctaggaga gagagtcact 60

atcacttgca aggcgagtca ggacattaat aggtatttaa gctggttcca gcagaaacca 120

gggaaatctc ctaagaccct gatctatcgt gcaaacagat tggtagatgg ggtcccatca 180

aggttcagtg gcagtggatc tgggcaagat tattctctca ccatcagcag cctggagtat 240

gaagatatgg gaatttatta ttgtctacag tatgatgagt ttccattcac gttcggctcg 300

gggacaaagt tggaaataaa ac 322

<210> 377
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 377
caggtccagt tgcagcagtc tggagctgag ctggtaaggc ctgggacttc agtgaaggtg 60

tcctgcaagg cttctggata cgccttcact aattacttga tagagtgggt aaagcagagg 120

cctggacagg gccttgagtg gattggggtg attaatcctg gaagtggtgg tactaactcc 180

aatgagaagt tcaaggccaa ggcaacactg actgcagaca aatcctccag cactgcctac 240

atgcagctca gcagcctgac atctgctgac tctgcggtct atttctgtgc aagatcggac 300

tatgattacg ccttctatgc tatggactac tggggtcaag gaacctcagt caccgtctcc 360

tca 363

<210> 378
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 378
gacatccaga tgactcagtc tccagcctcc ctatctgcat ctgtgggaga aactgtcacc 60

atcacatgtc gagcaagtgg gaatattcac aattatttag catggtatca gcagaaacag 120

ggaaaatctc ctcacctcct ggtctataat gcaaaaacct tagcagatgg tgtgccatca 180

aggttcagtg gcagtggatc aggaacacaa tattctctca agatcaacag cctgcagcct 240

gaagattttg ggagttatta ctgtcaacat ttttggagta ctccgtggac gttcggtgga 300

ggcaccaagc tggaaatcaa ac 322

<210> 379
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 379
gagttccagc tgcagcagtc tggacctgag ctggtaaagc ctggggcttc agtgaagatg 60

tcctgcaagg cttctggata cacattcact agctatgtta tgcactgggt gaagcagaag 120

cctgggcagg gccttgagtg gattggatat attaatcctt acaatgatgg tactaagtac 180

aatgagaagt tcaaaggcaa ggccacactg acttcagaca aatcctccag cacagcctac 240

atggagctca gcagcctgac ctctgaggac tctgcggtct attactgtgc aagagacagg 300

tcgggctacg aagattacta tggtatggac tactggggtc aaggaacctc agtcaccgtc 360

tcctca 366

<210> 380

<211> 318
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 380
caaattgttc tcacccagtc tccagcaatc atgtctgcat ctctagggga ggagatcacc 60

ctaacctgca gtgccagctc gagtgtaagt tacatgcact ggtaccagca gaagtcaggc 120

acttctccca aactcttgat ttatagcaca tccaacctgg cttctggagt cccttctcgc 180

ttcagtggca gtgggtctgg gacctttttat tctctcacaa tcagcagtgt ggaggctgaa 240

gatgctgccg attattactg ccatcagtgg agtagttatc acacgttcgg agggggggacc 300

aagctggaaa taaaacgg 318

<210> 381
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 381
gaggtgcagc tggtggagtc tgggggagac ttagtgaagc ctggagggtc cctgaaactc 60

tcctgtgcag cctctggatt cactttcagt agctatggca tgtcttgggt tcgccagact 120

ccagacaaga ggctggagtg ggtcgcaacc attagtagtg gtggtagtta cacctactat 180

ccagacagtg tgaaggggcg attcaccatc tccagagaca atgccaagaa caccctgtac 240

ctgcaaatga gcagtctgaa gtctgaggac acagccatgt attactgtgc aagacgaaga 300

gccgatgcta tggactactg gggtcaagga acctcagtca ccgtctcctc a 351

<210> 382
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 382
gacattcaga tgacccagtc tcctgcctcc cagtctgcat ctctgggaga aagtgtcacc 60

atcacatgcc tggcaagtca gaccattggt acatggttag catggtatca gcagaaacca 120

gggaaatctc ctcagctcct gatttattct gcaaccagct tggcagatgg ggtcccatca 180

aggttcagtg gtagtggatc tggcacaaaa ttttctttca agatcagcag cctacaggct 240

gaagattttg taagttatta ctgtcaacaa ctttacagta ctccgtggac gttcggtgga 300

ggcaccaagc tggaaatcaa ac 322

<210> 383
<211> 348
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 383
caggtgcagc tgaaggagtc aggacctggc ctggtggcgc cctcacagag cctgtccatc 60

acatgcactg tctcagggtt ctcattaacc gactatggtg taagctggat tcgccagcct 120

ccaggaaagg gtctggagtg gctgggagta gtatggggtg gtggaagcac atactataat 180

tccgctctca aatccagact gagcatcagc aaggacaact ccaagagcca agttttctta 240

aaaatgaaca gtctgcaaac tgatgacaca gccatgtact actgtgccaa acagaggggt 300

cagtacgggg cttactgggg ccaagggact ctggtcactg tctctgca 348

<210> 384
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 384
gacattgtga tgacccagtc tcacaaattc atgtccacat cagtaggaga cagggtcagc 60

atcacctgca aggccagtca ggatgtgaat actgctgtag gctggtatca acagaaacca 120

ggacaatctc ctaaactact gatttactcg gcatcctacc ggtacactgg agtccctgat 180

cgcttcactg gcagtggatc tgggacggat ttcactttca ccatcagcag tgtgcaggct 240

gaagacctgg cagtttatta ctgtcagcaa cattatagta gtccgtacac gttcggaggg 300

gggaccaagc tggaaattaa a 321

<210> 385
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 385
gaggtccagc tgcagcagtc tggacctgag ctggtaaagc ctggggcttc agtgaagatg 60

tcctgcaagg cttctggata cacattcact aactatgtta tgcactgggt gaagcagaag 120

cctgggcagg gccttgagtg gattggatat attaatcctt acaatgatgg tactaaatac 180

aatgagaagt tcaaaggcaa ggccacactg acttcagaca aatcctccac cacagcctac 240

atggcgctca gcagcctgac ctctgaggac tctgcggtct attactgtgc agtagcctac 300

tatagtaact gggggtttgc ttactggggc caagggactc tggtcactgt ctctgca 357

<210> 386
<211> 335
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 386
gacattgtgc tgacacagtc tcttgcttcc ttagctgtat ctctggggca gagggccacc 60

atctcatgca gggccagcaa aagtgtcagt acatctggct atagttatat gcactggtac 120

caacagaaac caggacagcc acccaaactc ctcatttatc ttgcatcctc ggaggggga 180

ccaagctgga aataaagcga acctagaatc tggggtccct gccaggttca gtggcagtgg 240

gtctgggaca gacttcaccc tcaacatcca tcctgtggaa gacgaagatg ctgcaaccta 300

ttactgtcag cacagtaggg agcttccgtt cacgt 335

<210> 387
<211> 348
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 387
caggtccaac tgcagcagtc tgggcctgag ctggtgaggc ctggggcttc agtgaagatg 60

tcctgcaagg cttcaggcta taccttcacc agctactgga tgcactgggt gaaacagagg 120

cctggacaag gccttgagtg gattggcatg attgatcctt ccaatagtga aactaggtta 180

aatcagaagt tcaaggacaa ggccacattg aatgtagaca aatcctccaa cacagcctac 240

atgcagctca gcagcctgac atctgaggac tctgcagtct attactgtgc agtaatggac 300

tactactttg actactgggg ccaaggcacc actctcacag tctcctca 348

<210> 388
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 388
gacatcaaga tgacccagtc tccatcttcc atgtatgcat ctctaggaga gagagtcact 60

atcacttgca aggcgagtca ggacattaat agctatttaa gctggttcca gcagaaacca 120

gggaaatctc ctaagaccct gatctatcgt gcaaacagat tggtagatgg ggtcccatca 180

aggttcagtg gcagtggatc tgggcaagat tattctctca ccatcagcag cctggagtat 240

gaagatatgg gaatttatta ttgtctacag tatgatgagt ttccattcac gttcggctcg 300

gggacaaagt tggaaataaa ac 322

<210> 389
<211> 345
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 389
caggtgcaac tgaagcagtc aggacctggc ctggtggcgc cctcacagag cctgttcatc 60

acatgcaccg tctcagggtt ctcattaacc agctatgaaa taaactgggt tcgccagcct 120

ccaggaaagg gtctggagtg gctgggagtg atatggactg gtggaagcac aaattataat 180

tcagctctca tatccagact gagcatcagc aaagacaact ccaagagcct agttttctta 240

aaaatgaaca gtctgcaaac tgatgacaca gccatatatt actgtgtaag aggtgtttat 300

gctatggact actggggtca aggaacctca gtcaccgtct cctca 345

<210> 390
<211> 323
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 390
gacatcaaga tgacccagtc tccatcttcc atgtatgcat ctctaggaga gagagtcact 60

atcacttgca aggcgagtca ggacattaat aattatttaa gctggttcca gcagaaacca 120

gggaaatctc ctaagaccct gatctatcgt gcaaacagat tggtagatgg ggtcccatca 180

aggttcagtg gcagtggatc tgggcaagat tattctctca ccatcagcag cctggagtat 240

gaagatatgg gaatttatta ttgtctacag tatgatgagt ttccgtacac gttcggaggg 300

gggaccaagc tggaaataaa acg 323

<210> 391
<211> 333
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 391
gaggtccagc ttcagcagtc aggacctgag ctggtgaaac ctggggcctc agtgaagata 60

tcctgcaagg cttctggata cacattcact gactacaaca tgcactgggt gaagcagagc 120

catggaaaga gccttgagtg gattggattc ttttatcctt acaacggtaa tactgtctac 180

agccagaagt tcaagagcaa ggccacattg actgtagaca attcctccag cacagcctac 240

atggagctcc gcagcctgac atctgaggac tctgcagtct attactgtgc aagacttaac 300

tgggagggct actggggcca aggcaccacc ctc 333

<210> 392
<211> 337
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 392
gatgttttga tgacccaaac tccactctcc ctgcctgtca gtcttggaga tcaagcctcc 60

atctcttgca gatctagtca gagcattgta catagtaatg gaaacaccta tttagaatgg 120

tacctgcaga aaccaggcca gtctccaaag ctcctgatct acaaagtttc caaccgattt 180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcagagtgg aggctgagga tctgggagtt tattactgct ttcaaggttc acatgttccg 300

ctcacgttcg gtgctgggac caagctggag ctgaaac 337

<210> 393
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 393
caggtccagc tgcagcagtc tggacctgag ctggtgaagc ctggggcttc agtgaggata 60

tcctgcaagg cttctggcta caccttcaca agctactata tacactgggt gaagcagagg 120

cctggacagg gacttgagtg gattggatgg atttatcctg gaaatggtaa tactaagtac 180

aatgagaagt tcaagggcaa ggccacactg actgcagaca aatcctccag cacagcctac 240

atgcagatca gcagcctgac ctctgaggac tctgcggtct atttctgtgc aagagagaga 300

tggttactac tatggtttgc ttactggggc caagggactc tggtcactgt ctctgca 357

<210> 394
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 394
agtattgtga tgacccagac tcccaaattc ctgcttgtat cagcaggaga cagggttacc 60

ataacctgca aggccagtca gagtgtgagt aatgatgtag gttggtacca acagaagcca 120

gggcagtctc ctaaactgct gatatactat gcatccaatc gctacaatgg agtccctgat 180

cgcttcactg gcagtggata tgggacggat ttcactttca ccatcagcac tgtgcaggct 240

gaagacctgg cagtttattt ctgtcagcag gattatagct ctccgtggac gttcggtgga 300

ggcaccaagc tggaaatcaa ac 322

<210> 395
<211> 354
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 395
cagatccagt tggtgcagtc tggacctgag ctgaagaagc ctggagagac agtcaagatc 60

tcctgcaagg cttctgggta taccttcaca aactatggaa tgaactgggt gaagcaggct 120

ccaggaaagg gtttaaagtg ggtgggctgg ataaacacct acactggaga gccaacatat 180

gctgatgact tcaagggacg gtttgccttc tctttggaaa cctctgccag cactgcctat 240

ttgcagatcg acaacctcaa aaatgaggac acggctacat atttctgtgc aagagtgggg 300

gattacgtcg gctttgacta ctggggccaa ggcaccactc tcacagtctc ctca 354

<210> 396
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 396
gatatccaga tgacacagac tgcatcctcc ctgtctgcct ctctgggaga cagagtcacc 60

atcagttgca gggcaagtca ggacattaac aattatttaa actggtatca gcagaaacca 120

gatggaactg ttaaactcct gatctactac acatcaagat tacactcagg agtcccatca 180

aggttcagtg gcagtgggtc tggaacagat tattctctca ccattagcat cctggaacaa 240

gaagatattg ccacttactt ttgccaacag ggtgatacgc ttccgtggac gttcggtgga 300

ggcaccaagc tggaaatcaa ac 322

<210> 397
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 397
cagatccagt tggtgcagtc tggacctgag ctgacgaagc ctggagagac agtcaagatc 60

tcctgcaagg cctctggata taccttcaca gactattcat tgcactgggt gaagcaggct 120

ctaggaaagg gtttaaagtg gatgggctgg ataaacactg agactggtga gccagcatat 180

gcagatgact tcaagggacg gtttgccttc tctttggaaa cctctgccag cactgcctat 240

ttgcagatca acgacctcaa aaatgaggac acgactacat atttctgtgg tatttacgac 300

gggtatgcta tggactactg gggtcaagga acctcagtca ccgtctcctc a 351

<210> 398
<211> 319
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 398
caaattgttc tcacccagtc tccagcaatc atgtctgcat ctccagggga gaaggtcacc 60

atgacctgca gtgccagctc aagtgtaagt tacatgtact ggtaccagca gaagccagga 120

tcctccccca gactcctgat ttatgacaca tccaacctgg cttctggagt ccctgttcgc 180

ttcagtggca gtgggtctgg gacctcttac tctctcacaa tcagccgaat ggaggctgaa 240

gatactgcca cttattattg ccaggagtgg agtaataatc cgctcacgtt cggtgatggg 300

accaagctgg agctgaaac 319

<210> 399
<211> 354
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 399
cagatccagt tggtgcagtc tggacctgag ctgaagaagc ctggagagac agtcaagatc 60

tcctgcaagg cttctgggta taccctcaca aactatggaa tgaactgggt gaagcaggct 120

ccaggaaagg gtttaaagtg gatgggctgg ataaacacct acactggaga gccaacatat 180

gctgatgact tcaagggacg gtttgccttc tctttggaaa cctctgccag gattgtctat 240

ttgcagatca acaacctcaa aaatgaggac acggctacat atttctgtgc aaaatatgag 300

gcccacgagg ggtttgttta ttggggccaa gggactctgg tcactgtctc tgca 354

<210> 400
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 400
gacatccaga tgaaccagtc tccatccagt ctgtctgcat cccttggaga cacaattacc 60

atcacttgcc atgccagtca gaacattaat gtttggttaa gctggtacca gcagaaacca 120

ggaaatattc caaaactatt gatctataag gcttcccact tgcacacagg cgtcccatca 180

aggttgagtg gcagtggatc tggaacaggt ttcacattaa ccatcagcag cctgcagcct 240

gaagacattg ccacttacta ctgtcaacag ggtcaaagtt atccattcac gttcggctcg 300

gggacaacgt tggaaataaa ac 322

<210> 401

<211> 348
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 401
caggtgcagc tgaaggagtc aggacctggc ctggtggcgc cctcacagag cctgtccatc 60

acttgcgctg tctctgggtt ttcattaacc agctttggtg tacactgggt tcgccagcct 120

ccaggaaagg gtctggagtg gctgggagtt atatgggctg gtggaagcac aaattattat 180

tcggctctca tgtccagact gagcatcagc atagacaact ccaagagcca agttttctta 240

aagatgaaca gtctgcaaac tgatgacaca gccatgtact actgtgccag agactgggag 300

ggctggtttg cttactgggg ccaagggact ctggtcactg tctctgca 348

<210> 402
<211> 341
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 402
gacattgtga tgtcacagtc tccatcctcc ctaactgtgt cagttggaga gaaggttact 60

atgagctgca tgtccagtca gagcctttta tatagtagca ctcaaaagaa ctacttggcc 120

tggtaccagc agaaaccagg gcagtctcct aaactgctga tttactgggc atccactagg 180

gaatctgggg tccctgatcg cttcacaggc agtggatctg ggacagattt cactctcacc 240

atcagcagtg tgaaggctga agacctggca gtttattact gtcagcaata ttatagctat 300

ccgtacacgt tcggaggggg gaccaagctg gaaataaaac g 341

<210> 403
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 403
gagatccagc tgcagcagtc tggacctgag ctggtgaagc ctggggcttc agtgaaggta 60

tcctgcaagg cttctggtta tgcattcact agctacaaca tgtactgggt gagtcagagc 120

catggaaaga gccttgagtg gattggatat attgatcctt acaatggtgg cactagctac 180

aaccagaagt tcaggggcaa ggccacattg actgttgaca agtcctcaag cacagcctac 240

atgcatctca acagcctgac atctgaggac tcggcagtct attattgtgc aagagagaac 300

tataggtact ttgacttctg gggccaaggc accactctca cagtctcctc a 351

<210> 404
<211> 319
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 404
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgca gtgcaagtag cagcgttagc tatatgtatt ggtatcagca gaaaccaggg 120

aaagccccta agctcctgat ctacctcact agtaacttgg caagtggggt cccatcaagg 180

ttcagtggca gtggatctgg gacagatttc actctcacca tcagcagtct gcaacctgaa 240

gattttgcaa cttactactg tcaacagtgg cgtagtaacc cattcacgtt cggccagggg 300

acaaagttgg aaataaaac 319

<210> 405
<211> 373
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 405
cagatcacct tgaaggagtc tggtcctacg ctggtgaaac ccacacagac cctcacgctg 60

acctgcacct tctctgggtt ctcactcagc actagtggaa tgggtgtggg ctggatccgt 120

cagcccccag gaaaggccct ggagtggctt gcacacattt ggtgggatga tgttaagcgc 180

tacagcccat ctctgaagag caggctcacc atcaccaagg acacctccaa aaaccaggtg 240

gtccttacaa tgaccaacat ggaccctgtg gacacagcca catattactg tgcacgcata 300

gtttcctttg ataacgacgt tgtctctgct atggactact ggggtcaagg aaccctagtc 360

accgtctcct ccg 373

<210> 406
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 406
gccatccagt tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtga gaacatttat tataatttag cctggtatca gcagaaacca 120

gggaaagctc ctaagctcct gatctatact gccaatagtt tggaagatgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagattttg caacttattt ttgtaaacag gcttatgacg ttcctccgac gttcggtgga 300

ggcaccaagc tggaaatcaa ac 322

<210> 407
<211> 352
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 407
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctggata caccttcacc aggtactgga tacactggat acgacaggcc 120

cctggacaag ggcttgagtg gatgggatac atcaacccta caactgttta tactgagttc 180

aatcagaact tcaaggacag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaggcggt 300

agtaacttct ttgactactg gggccaaggc accactgtca cagtctcctc ag 352

<210> 408
<211> 319
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 408
gaaattgtgc tgactcagtc tccagacttt cagtctgtga ctccaaagga gaaagtcacc 60

atcacctgca gtgccagtag cagtgtgagc tacatgcact ggtaccagca gaaaccagat 120

cagtctccaa agctcctcat caaggatagt tccaaactcg cctcaggggt cccctcgagg 180

ttcagtggca gtggatctgg gacagatttc accctcacca tcaatagcct ggaagctgaa 240

gatgctgcaa cgtattactg tcagcagtgg agtagtaacc cgctcacgtt cggtcagggg 300

accaagctgg agatcaaac 319

<210> 409
<211> 354
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 409
cagatcacct tgaaggagtc tggtcctacg ctggtgaaac ccacacagac cctcacgctg 60

acctgcacct tctctgggtt ctcactcagc actagtggaa tgggtgtggg ctggatccgt 120

cagcccccag gaaaggccct ggagtggctt acagacattt ggtgggatga taataagtac 180

tacaacccat ctctgaagag caggctcacc atcaccaagg acacctccaa aaaccaggtg 240

gtccttacaa tgaccaacat ggaccctgtg gacacagcca catattactg tgcacgaaga 300

gttaactatt attacgaccc gtactatgct atggactact ggggtcaagg aacc 354

<210> 410
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 410
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgca aggcgagtca gagcgttagc aatgatgtag cctggtatca gcagaaacca 120

gggaaagttc ctaagctcct gatctattat gcatccaata ggtactcagg ggtcccatct 180

cggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagatgttg caacttattt ctgtcagcag gattatagct ctccgtggac gttcggtgga 300

ggcaccaagg tggaaatcaa ac 322

<210> 411
<211> 355
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 411

caggtccagc ttgtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg cttctggata caccttcact aactatggta tgaattgggt gcgccaggcc 120

cccggacaaa ggcttgagtg gatgggatgg atcaacactt acactggtga cccaacatat 180

gcagatgatt tcaagggcag agtcaccatt accagggaca catccgcgag cacagcctac 240

atggagctga gcagcctgag atctgaagac acggctgtgt attactgtgc gagaattggc 300

ggtaatagtc cctctgatta ctggggccaa ggcaccactg tcacagtctc ctcag 355

<210> 412
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 412
gagatcgtga tgacccagtc ccctgccaca ctgtccgtgt cccctggaga gagggccacc 60

ctgtcctgca aggcctccca gtccgtgtcc aacgacgtgg tgtggtacca gcagaagccc 120

ggacaggctc ccaggctgct gatctactac gcctccaaca ggtacaccgg catccctgcc 180

aggttctccg gatccggatc cggcaccgag ttcaccctga ccatctcctc cctgcagtcc 240

gaggacttcg ccgtgtacta ctgccagcag gactacacct ccccctggac ctttggccag 300

ggcaccaagc tggagatcaa gagg 324

<210> 413
<211> 353
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 413
caggtgcagc tggtgcagtc cggcgccgaa gtgaagaaac ccggcgcctc cgtgaaggtg 60

tcctgcaagg cctccggcta caccttcacc aactacggca tgaactgggt gaggcaggct 120

cctggacagg gactggagtg gatgggctgg atcaacacct acaccggcga acccacctac 180

gccgacgact tcaagggcag ggtgaccatg accaccgaca cctccacctc caccgcctac 240

atggagctga ggtccctgag gtccgacgac accgccgtgt actactgcgc taggattggc 300

gactcctccc cctccgatta ctggggacag ggcaccctcg tgaccgtctc ctc 353

Claims

1. An antibody that specifically binds to an epitope within the DSL domain of a DLL3 protein set forth as SEQ ID NO: 3 or 4, wherein the antibody is a chimeric antibody, CDR-grafted antibody, human antibody, humanized antibody, primatized antibody, multispecific antibody, bispecific antibody, multivalent antibody, or diabody.

2. The antibody of claim 1, wherein the antibody is a chimeric antibody, CDR-grafted antibody, human antibody, or humanized antibody.

3. The antibody of claim 1 or 2, wherein the epitope comprises amino acids G203, R205, and P206 (SEQ ID NO: 10).

4. The antibody of any one of claims 1-3, wherein the antibody is an internalizing antibody.

5. The antibody of any one of claims 1-4, wherein the antibody comprises or competes for binding to human DLL3 protein with an antibody comprising a light chain variable region set forth as SEQ ID NO: 60 and a heavy chain variable region set forth as SEQ ID NO: 61.

6. The antibody of any one of claims 1-5, wherein the antibody comprises three complementarity determining regions of a light chain variable region set forth as SEQ ID NO: 60, and three complementarity determining regions of a heavy chain variable region set forth as SEQ ID NO: 61.

7. The antibody of any one of claims 1-6, wherein the antibody comprises residues 23-34 of SEQ ID NO: 60 for CDR-L1, residues 50-56 of SEQ ID NO: 60 for CDR-L2, residues 89-97 of SEQ ID NO: 60 for CDR-L3, residues 26-32 of SEQ ID NO: 61 for CDR-H1, residues 50-58 of SEQ ID NO: 61 for CDR-H2 and residues 95-102 of SEQ ID NO: 61 for CDR-H3, wherein the residues are numbered according to Chothia.

8. The antibody of any one of claims 1-6, wherein the antibody comprises residues 30-36 of SEQ ID NO: 60 for CDR-L1, residues 46-55 of SEQ ID NO: 60 for CDR-L2, residues 89-96 of SEQ ID NO: 60 for CDR-L3, residues 30-35 of SEQ ID NO: 61 for CDR-H1, residues 47-58 of SEQ ID NO: 61 for CDR-H2 and residues 93-101 of SEQ ID NO: 61 for CDR-H3, wherein the residues are numbered according to MacCallum.

9. The antibody of any one of claims 1-6, wherein the antibody comprises residues 24-34 of SEQ ID NO: 60 for CDR-L1, residues 50-56 of SEQ ID NO: 60 for CDR-L2, residues 89-97 of SEQ ID NO: 60 for CDR-L3, residues 31-35 of SEQ ID NO: 61 for CDR-H1, residues 50-65 of SEQ ID NO: 61 for CDR-H2 and residues 95-102 of SEQ ID NO: 61 for CDR-H3, wherein the residues are numbered according to Kabat.

10. The antibody of any one of claims 1-4, wherein the antibody comprises a light chain variable region comprising an amino acid sequence set forth as SEQ ID NO: 210 and a heavy chain variable region comprising an amino acid sequence set forth as SEQ ID NO: 211.

11. The antibody of any one of claims 1-4, wherein the antibody comprises or competes for binding to human DLL3 protein with an antibody comprising a light chain variable region set forth as SEQ ID NO: 84 and a heavy chain variable region set forth as SEQ ID NO: 85.

12. The antibody of any one of claims 1-4 or 11, wherein the antibody comprises three complementarity determining regions of a light chain variable region set forth as SEQ ID NO: 84, and three complementarity determining regions of a heavy chain variable region set forth as SEQ ID NO: 85.

13. The antibody of any one of claims 1-4, 11 or 12, wherein the antibody comprises residues 24-34 of SEQ ID NO: 84 for CDR-L1, residues 50-56 of SEQ ID NO: 84 for CDR-L2, residues 89-97 of SEQ ID NO: 84 for CDR-L3, residues 31-35 of SEQ ID NO: 85 for CDR-H1, residues 50-65 of SEQ ID NO: 85 for CDR-H2 and residues 95-102 of SEQ ID NO: 85 for CDR-H3, wherein the residues are numbered according to Kabat.

14. The antibody of any one of claims 1-4, 11 or 12, wherein the antibody comprises residues 23-34 of SEQ ID NO: 84 for CDR-L1, residues 50-56 of SEQ ID NO: 84 for CDR-L2, residues 89-97 of SEQ ID NO: 84 for CDR-L3, residues 26-32 of SEQ ID NO: 85 for CDR-H1, residues 50-58 of SEQ ID NO: 85 for CDR-H2 and residues 95-102 of SEQ ID NO: 85 for CDR-H3, wherein the residues are numbered according to Chothia.

15. The antibody of any one of claims 1-4, 11 or 12, wherein the antibody comprises residues 30-36 of SEQ ID NO: 84 for CDR-L1, residues 46-55 of SEQ ID NO: 84 for CDR-L2, residues 89-96 of SEQ ID NO: 84 for CDR-L3, residues 30-35 of SEQ ID NO: 85 for CDR-H1, residues 47-58 of SEQ ID NO: 85 for CDR-H2 and residues 93-101 of SEQ ID NO: 85 for CDR-H3, wherein the residues are numbered according to MacCallum.

16. The antibody of any one of claims 1-4, wherein the antibody comprises a light chain variable region comprising an amino acid sequence set forth as SEQ ID NO: 212 and a heavy chain variable region comprising an amino acid sequence set forth as SEQ ID NO: 213.

17. The antibody of any one of claims 1-16, wherein the antibody comprises human constant regions, such as a human IgG1 heavy chain constant region and/or a human kappa light chain constant region.

18. The antibody of any one of claims 1-17, wherein the antibody is conjugated, linked, or otherwise associated with a cytotoxic agent.

19. The antibody of claim 18, wherein the cytotoxic agent is a pyrrolobenzodiazepine (PBD), an auristatin, a maytansinoid, a calicheamicin, or a radioisotope.

20. The antibody of claim 19, wherein the cytotoxic agent is a pyrrolobenzodiazepine (PBD).

21. The antibody of claim 19, wherein the cytotoxic agent is a radioisotope.

22. A pharmaceutical composition comprising the antibody of any one of claims 1-21.

23. An antibody according to any one of claims 18-21 for use as a pharmaceutical product.

24. An antibody according to any one of claims 18-21 for use in a method of treating cancer.

25. An antibody for use according to claim 24, wherein the cancer comprises a neuroendocrine tumor.

26. An antibody for use according to claim 24, wherein the cancer is small cell lung cancer, prostate cancer, thyroid cancer or large cell neuroendocrine carcinoma.

27. An antibody according to any one of claims 18-21 for use in a method of reducing the frequency of tumor initiating cells in a subject.

28. A nucleic acid comprising:

(a) a nucleic acid encoding a light chain variable region or a heavy chain variable region of the antibody of any one of claims 1-21;
(b) a nucleic acid encoding a light chain variable region comprising the amino acid sequence of SEQ ID NO: 212;
(c) a nucleic acid encoding a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 213;
(d) a nucleic acid comprising the nucleotide sequence of SEQ ID NO: 412; and/or
(e) a nucleic acid comprising the nucleotide sequence of SEQ ID NO: 413.

29. A vector comprising at least one of (a) a nucleic acid encoding a light chain variable region comprising the amino acid sequence set forth as SEQ ID NO: 212, and (b) a nucleic acid encoding a heavy chain variable region comprising the amino acid sequence set forth as SEQ ID NO: 213.

30. The vector of claim 29, further comprising a promoter that controls expression of the nucleic acid of (a) and/or the nucleic acid of (b).

31. A host cell comprising at least one of (a) a nucleic acid encoding a light chain variable region comprising the amino acid sequence set forth as SEQ ID NO: 212, and (b) a nucleic acid encoding a heavy chain variable region comprising the amino acid sequence set forth as SEQ ID NO: 213, and which optionally further comprises a vector comprising the nucleic acid of (a) and/or the nucleic acid of (b).

32. The host cell of claim 31, wherein the host cell is a mammalian host cell selected from the group consisting of a

CHO cell, HEK 293 cell, BHK cell, NSO cell, SP2/0 cell, YO myeloma cell, P3X63 mouse myeloma cell, PER cell, and PER.C6 cell.

33. The host cell of claim 32, wherein the host cell is a CHO cell.

34. The host cell of any one of claims 31-33, wherein the host cell expresses the light chain variable region comprising the amino acid sequence set forth as SEQ ID NO: 212 and/or the heavy chain variable region comprising the amino acid sequence set forth as SEQ ID NO: 213.

35. The host cell of any one of claims 31-34, wherein the host cell expresses an antibody comprising the light chain variable region comprising an amino acid sequence set forth as SEQ ID NO: 212 and the heavy chain variable region comprising an amino acid sequence set forth as SEQ ID NO: 213.

Homo sapiens delta-like 3(DLL3), transcript variant 1, mRNA
>gi|189163470|ref|NM_016941.3|

SEQ ID NO:1

AGATATAAGGCTTGGAAGCCAGCAGCTGCGACTCCCGAGACCCCCCCCACCAGAAGGCCATGGTCTCCCCACGGATGT
CCGGGCTCCTCTCCCAGACTGTGATCCTAGCGCTCATTTTCCTCCCCCAGACACGGCCCGCTGGCGTCTTCGAGCTG
CAGATCCACTCTTTCGGGCCGGGTCCAGGCCCTGGGGCCCCGCGGTCCCCCTGCAGCGCCCGGCTCCCCTGCCGCCT
CTTCTTCAGAGTCTGCCTGAAGCCTGGGCTCTCAGAGGAGGCCGCCGAGTCCCCGTGCGCCCTGGGCGCGGCGCTGA
GTGCGCGCGGACCGGTCTACACCGAGCAGCCCGGAGCGCCCGCGCCTGATCTCCCACTGCCCGACGGCCTCTTGCAG
GTGCCCTTCCGGGACGCCTGGCCTGGCACCTTCTCTTTCATCATCGAAACCTGGAGAGAGGAGTTAGGAGACCAGAT
TGGAGGGCCCGCCTGGAGCCTGCTGGCGCGCGTGGCTGGCAGGCGGCGCTTGGCAGCCGGAGGCCCGTGGGCCCGGG
ACATTCAGCGCGCAGGCGCCTGGGAGCTGCGCTTCTCGTACCGCGCCGCGCTGCGAGCCGCCTGCCGTCGGGACCGCG
TGCACGCGCCTCTGCCGTCCGCGCAGCGCCCCCTCGCGGTGCGGTCCGGGACTGCGCCCCTGCGCACCGCTCGAGGA
CGAATGTGAGGCGCCGCTGGTGTGCCGAGCAGGCTGCAGCCCTGAGCATGGCTTCTGTGAACAGCCCGGTGAATGCC
GATGCCTACAGGGCTGGACTGGACCCCTCTGCACGGTCCCTGTCTCCACCAGCAGCTGCCTCAGCCCCAGGGGCCCG
TCCTCTGCTACCACCGGATGCCTTGTCCCTGGGCCTGGGCCCTGTGACGGGAACCCGTGTGCCAATGGAGGCAGCTG
TAGTGAGACACCCAGGTCCTTTGAATGCACCTGCCCGCGTGGGTTCTACGGGCTGCGGTGTGAGGTGAGCGGGGTGA
CATGTGCAGATGGACCCTGCTTCAACGGCGGCTTGTGTGTCGGGGGTGCAGACCCTGACTCTGCCTACATCTGCCAC
TGCCCACCCGGTTTCCAAGGCTCCAACTGTGAGAAGAGGGTGGACCGGTGCAGCCTGCAGCCATGCCGCAATGGCGG
ACTCTGCCTGGACCTGGGCCACGCCCTGCGCTGCCGCTGCCGCGCCGGCTTCGCGGGTCCTCGCTGCGAGCACGACC
TGGACGACTGCGCGGGCCGCCGCCTGCGCTAACGGCGGCACGTGTGTGGAGGGCGGCGGCGCGCACCGCTGCTCCTGC
GCGCTGGGCTTCGGCGGCCCGCGACTGCCGCGAGCGCGCGGACCCGTGCGCCGCGCGCCCCTGTGCTCACGGCGGCCG
CTGCTACGCCCACTTCTCCGGCCTCGTCTGCGCTTGCGCTCCCGGCTACATGGGAGCGCGGTGTGAGTTCCCAGTGC
ACCCCGACGGCGCAAGCGCCTTGCCCGCGGCCCCGCCGGGCCTCAGGCCCGGGGACCCTCAGCGCTACCTTTTGCCT
CCGGCTCTGGGACTGCTCGTGGCCGCGGGCGTGGCCGGCGCTGCGCTCTTGCTGGTCCACGTGCGCCGCCGTGGCCA
CTCCCAGGATGCTGGGTCTCGCTTGCTGGCTGGGACCCCGGAGCCGTCAGTCCACGCACTCCCGGATGCACTCAACA
ACCTAAGGACGCAGGAGGGTTCCGGGGATGGTCCGAGCTCGTCCGTAGATTGGAATCGCCCTGAAGATGTAGACCCT
CAAGGGATTTATGTCATATCTGCTCCTTCCATCTACGCTCGGCAGGTAGCGACGCCCCTTTTCCCCCCGCTACACAC
TGGGCGCGCTGGGCAGAGGCAGCACCTGCTTTTTCCCTACCCTTCCTCGATTCTGTCCGTGAAATGAATTGGGTAGA
GTCTCTGGAAGGTTTTAAGCCCATTTTCAGTTCTAACTTACTTTCATCCTATTTTGCATCCCTCTTATCGTTTTGAG
CTACCTGCCATCTTCTCTTTGAAAAACCTATGGGCTTGAGGAGGTCACGATGCCGACTCCGCCAGAGCTTTTCCACT
GATTGTACTCAGCGGGGAGGCAGGGGAGGCAGACGGGCAGCCTCTCTAATGCTTCCTACTCATTTTGTTTCTAGGCC
TGACGCGTCTCCTCCATCCGCACCTGGAGTCAGAGCGTGGATTTTTGTATTTGCTCGGTGGTGCCCAGTCTCTGCCC
CAGAGGCTTTGGAGTTCAATCTTGAAGGGGTGTCTGGGGGAACTTTACTGTTGCAAGTTGTAAATAATGGTTATTTA
TATCCTATTTTTTCTCACCCCATCTCTCTAGAAACACCTATAAAGGCTATTATTGTGATCAGTTTTGACTAACAAAA

FIG. 1A

Homo sapiens delta-like 3(DLL3), transcript variant 2, mRNA
>gi|189163469|ref|NM_203486.2|

SEQ ID NO. 2

AGATATAAGGCTTGGAAGCCAGCAGCTGCGACTCCCGAGACCCCCCCCACCAGAAGGCCATGGTCTCCCCCACGGATGTC
CGGGCTCCTCTCCCAGACTGTGATCCTAGCGCTCATTTTCCTCCCCCAGACACGGCCCGCTGGCGTCTTCGAGCTGCA
GATCCACTCTTTCGGGCCGGGTCCAGGCCCTGGGGCCCCGCGGTCCCCCTGCAGCGCCCGGCTCCCCTGCCGCCTCTT
CTTCAGAGTCTGCCTGAAGCCTGGGCTCTCAGAGGAGGCCGCCGAGTCCCCGTGCGCCCTGGGCGCGGCGCTGAGTGC
GCGCGGACCGGTCTACACCGAGCAGCCCGGAGCGCCCGCGCCTGATCTCCCACTGCCCGACGGCCTCTTGCAGGTGCC
CTTCCGGGACGCCTGGCCTGGCACCTTCTCTTTCATCATCGAAACCTGGAGAGAGGAGTTAGGAGACCAGATTGGAGG
GCCCGCCTGGAGCCTGCTGGCGCGCGTGGCTGGCAGGCGGCGCTTGGCAGCCGGAGGCCCGTGGGCCCGGGACATTCA
GCGCGCAGGCGCCTGGGAGCTGCGCTTCTCGTACCGCGCGCGCTGCGAGCCGCCTGCCGTCGGGACCGCGTGCACGCG
CCTCTGCCGTCCGCGCAGCGCCCCCTCGCGGTGCGGTCCGGGACTGCGCCCCTGCGCACCGCTCGAGGACGAATGTGA
GGCGCCGCTGGTGTGCCGAGCAGGCTGCAGCCCTGAGCATGGCTTCTGTGAACAGCCCGGTGAATGCCGATGCCTAGA
GGGCTGGACTGGACCCCTCTGCACGGTCCCTGTCTCCACCAGCAGCTGCCTCAGCCCCAGGGGCCCGTCCTCTGCTAC
CACCGGATGCCTTGTCCCTGGGCCTGGGCCCTGTGACGGGAACCCGTGTGCCAATGGAGGCAGCTGTAGTGAGACACC
CAGGTCCTTTGAATGCACCTGCCCGCGTGGGTTCTACGGGCTGCGGTGTGAGGTGAGCGGGGTGACATGTGCAGATGG
ACCCTGCTTCAACGGCGGCTTGTGTGTCGGGGGTGCAGACCCTGACTCTGCCTACATCTGCCACTGCCCACCCGGTTT
CCAAGGCTCCAACTGTGAGAAGAGGGTGGACCGGTGCAGCCTGCAGCCATGCCGCAATGGCGGACTCTGCCTGGACCT
GGGCCACGCCCTGCGCTGCCGCTGCCGCGCCGGCTTCGCGGGTCCTCGCTGCGAGCACGACCTGGACGACTGCGCGGG
CCGCGCCTGCGCTAACGGCGGCACGTGTGTGGAGGGCGGCGGCGCGCACCGCTGCTCCTGCGCGCTGGGCTTCGGCGG
CCGCGACTGCCGCGAGCGCGCGGACCCGTGCGCCGCGCGCCCCTGTGCTCACGGCGGCCGCTGCTACGCCCACTTCTC
CGGCCTCGTCTGCGCTTGCGCTCCCGGCTACATGGGAGCGCGGTGTGAGTTCCCAGTGCACCCCGACGGCGCAAGCGC
CTTGCCCGCGGCCCCGCCGGGCCTCAGGCCCGGGGACCCTCAGCGCTACCTTTTGCCTCCGGCTCTGGGACTGCTCGT
GGCCGCGGGCGTGGCCGGCGCTGCGCTCTTGCTGGTCCACGTGCGCCGCCGTGGCCACTCCCAGGATGCTGGGTCTCG
CTTGCTGGCTGGGACCCCGGAGCCGTCAGTCCACGCACTCCCGGATGCACTCAACAACCTAAGGACGCAGGAGGGTTC
CGGGGATGGTCCGAGCTCGTCCGTAGATTGGAATCGCCCTGAAGATGTAGACCCTCAAGGGATTTATGTCATATCTGC
TCCTTCCATCTACGCTCGGGAGGCCTGACGCGTCTCCTCCATCCGCACCTGGAGTCAGAGCGTGGATTTTTGTATTTG
CTCGGTGGTGCCCAGTCTCTGCCCCAGAGGCTTTGGAGTTCAATCTTGAAGGGGTGTCTGGGGGAACTTTACTGTTGC
AAGTTGTAAATAATGGTTATTTATATCCTATTTTTTCTCACCCCATCTCTCTAGAAACACCTATAAAGGCTATTATTG
TGATCAGTTTTGACTAACAAAAAA

FIG. 1B

Homo sapiens delta-like protein 3 (DLL3)isoform 1 precursor
>gi|8393264|ref|NP_058637.1|

SEQ ID NO. 3

MVSPRMSGLLSQTVILALIFLPQTRPAGVFELQIHSFGPGPGPGAPRSPCSARLPCRLFFRVCLKPGLSE
EAAESPCALGAALSARGPVYTEQPGAPAPDLPLPDGLLQVPFRDAWPGTFSFIIETWREELGDQIGGPAW
SLLARVAGRRRLAAGGPWARDIQRAGAWELRFSYRARCEPPAVGTACTRLCRPRSAPSRCGPGLRPCAPL
EDECEAPLVCRAGCSPEHGFCEQPGECRCLEGWTGPLCTVPVSTSSCLSPRGPSSATTGCLVPGPGPCDG
NPCANGGSCSETPRSFECTCPRGFYGLRCEVSGVTCADGPCFNGGLCVGGADPDSAYICHCPPGFQGSNC
EKRVDRCSLQPCRNGGLCLDLGHALRCRCRAGFAGPRCEHDLDDCAGRACANGGTCVEGGGAHRCSCALG
FGGRDCRERADPCAARPCAHGGRCYAHFSGLVCACAPGYMGARCEFPVHPDGASALPAAPPGLRPGDPQR
YLLPPALGLLVAAGVAGAALLLVHVRRRGHSQDAGSRLLAGTPEPSVHALPDALNNLRTQEGSGDGPSSS
VDWNRPEDVDPQGIYVISAPSIYAREVATPLFPPLHTGRAGQRQHLLFPYPSSILSVK

FIG. 1C

Homo sapiens delta-like protein 3 (DLL3)isoform 2 precursor
>gi|45243561|ref|NP_982353.1|

SEQ ID NO. 4

MVSPRMSGLLSQTVILALIFLPQTRPAGVFELQIHSFGPGPGPGAPRSPCSARLPCRLFFRVCLKPGLSE
EAAESPCALGAALSARGPVYTEQPGAPAPDLPLPDGLLQVPFRDAWPGTFSFIIETWREELGDQIGGPAW
SLLARVAGRRRLAAGGPWARDIQRAGAWELRFSYRARCEPPAVGTACTRLCRPRSAPSRCGPGLRPCAPL
EDECEAPLVCRAGCSPEHGFCEQPGECRCLEGWTGPLCTVPVSTSSCLSPRGPSSATTGCLVPGPGPCDG
NPCANGGSCSETPRSFECTCPRGFYGLRCEVSGVTCADGPCFNGGLCVGGADPDSAYICHCPPGFQGSNC
EKRVDRCSLQPCRNGGLCLDLGHALRCRCRAGFAGPRCEHDLDDCAGRACANGGTCVEGGGAHRCSCALG
FGGRDCRERADPCAARPCAHGGRCYAHFSGLVCACAPGYMGARCEFPVHPDGASALPAAPPGLRPGDPQR
YLLPPALGLLVAAGVAGAALLLVHVRRRGHSQDAGSRLLAGTPEPSVHALPDALNNLRTQEGSGDGPSSS
VDWNRPEDVDPQGIYVISAPSIYAREA

FIG. 1D

Alignment of two human DLL3 isoforms (NP_058637 = var 1; NP_928353 = var 2)

```
                    1                                                                                80
NP_058637     (1)   MVSPRMSGLLSQTVILALIFLPQTRPAGVFELQIHSFGPGPGPGAPRSPCSARLPCRLFFRVCLKPGLSEEAAESPCALG
NP_982353     (1)   MVSPRMSGLLSQTVILALIFLPQTRPAGVFELQIHSFGPGPGPGAPRSPCSARLPCRLFFRVCLKPGLSEEAAESPCALG

                    81                                                                               160
NP_058637    (81)   AALSARGPVYTEQPGAPAPDLPLPDGLLQVPFRDAWPGTFSFIIETWREELGDQIGGPAWSLLARVAGRRRLAAGGPWAR
NP_982353    (81)   AALSARGPVYTEQPGAPAPDLPLPDGLLQVPFRDAWPGTFSFIIETWREELGDQIGGPAWSLLARVAGRRRLAAGGPWAR

                   161                                                                               240
NP_058637   (161)   DIQRAGAWELRFSYRARCEPPAVGTACTRLCRPRSAPSRCGPGLRPCAPLEDECEAPLVCRAGCSPEHGFCEQPGECRCL
NP_982353   (161)   DIQRAGAWELRFSYRARCEPPAVGTACTRLCRPRSAPSRCGPGLRPCAPLEDECEAPLVCRAGCSPEHGFCEQPGECRCL

                   241                                                                               320
NP_058637   (241)   EGWTGPLCTVPVSTSSCLSPRGPSSATTGCLVPGPGPCDGNPCANGGSCSETPRSFECTCPRGFYGLRCEVSGVTCADGP
NP_982353   (241)   EGWTGPLCTVPVSTSSCLSPRGPSSATTGCLVPGPGPCDGNPCANGGSCSETPRSFECTCPRGFYGLRCEVSGVTCADGP

                   321                                                                               400
NP_058637   (321)   CFNGGLCVGGADPDSAYICHCPPGFQGSNCEKRVDRCSLQPCRNGGLCLDLGHALRCRCRAGFAGPRCEHDLDDCAGRAC
NP_982353   (321)   CFNGGLCVGGADPDSAYICHCPPGFQGSNCEKRVDRCSLQPCRNGGLCLDLGHALRCRCRAGFAGPRCEHDLDDCAGRAC

                   401                                                                               480
NP_058637   (401)   ANGGTCVEGGGAHRCSCALGFGGRDCRERADPCAARPCAHGGRCYAHFSGLVCACAPGYMGARCEFPVHPDGASALPAAP
NP_982353   (401)   ANGGTCVEGGGAHRCSCALGFGGRDCRERADPCAARPCAHGGRCYAHFSGLVCACAPGYMGARCEFPVHPDGASALPAAP

                   481                                                                               560
NP_058637   (481)   PGLRPGDPQRYLLPPALGLLVAAGVAGAALLLVHVRRRGHSQDAGSRLLAGTPEPSVHALPDALNNLRTQEGSGDGPSSS
NP_982353   (481)   PGLRPGDPQRYLLPPALGLLVAAGVAGAALLLVHVRRRGHSQDAGSRLLAGTPEPSVHALPDALNNLRTQEGSGDGPSSS

                   561                                                                  618
NP_058637   (561)   VDWNRPEDVDPQGIYVISAPSIYAREVATPLFPPLHTGRAGQRQHLLFPYPSSILSVK                SEQ ID NO. 3
NP_982353   (561)   VDWNRPEDVDPQGIYVISAPSIYAREA----------------------------                  SEQ ID NO. 4
```

FIG. 1E

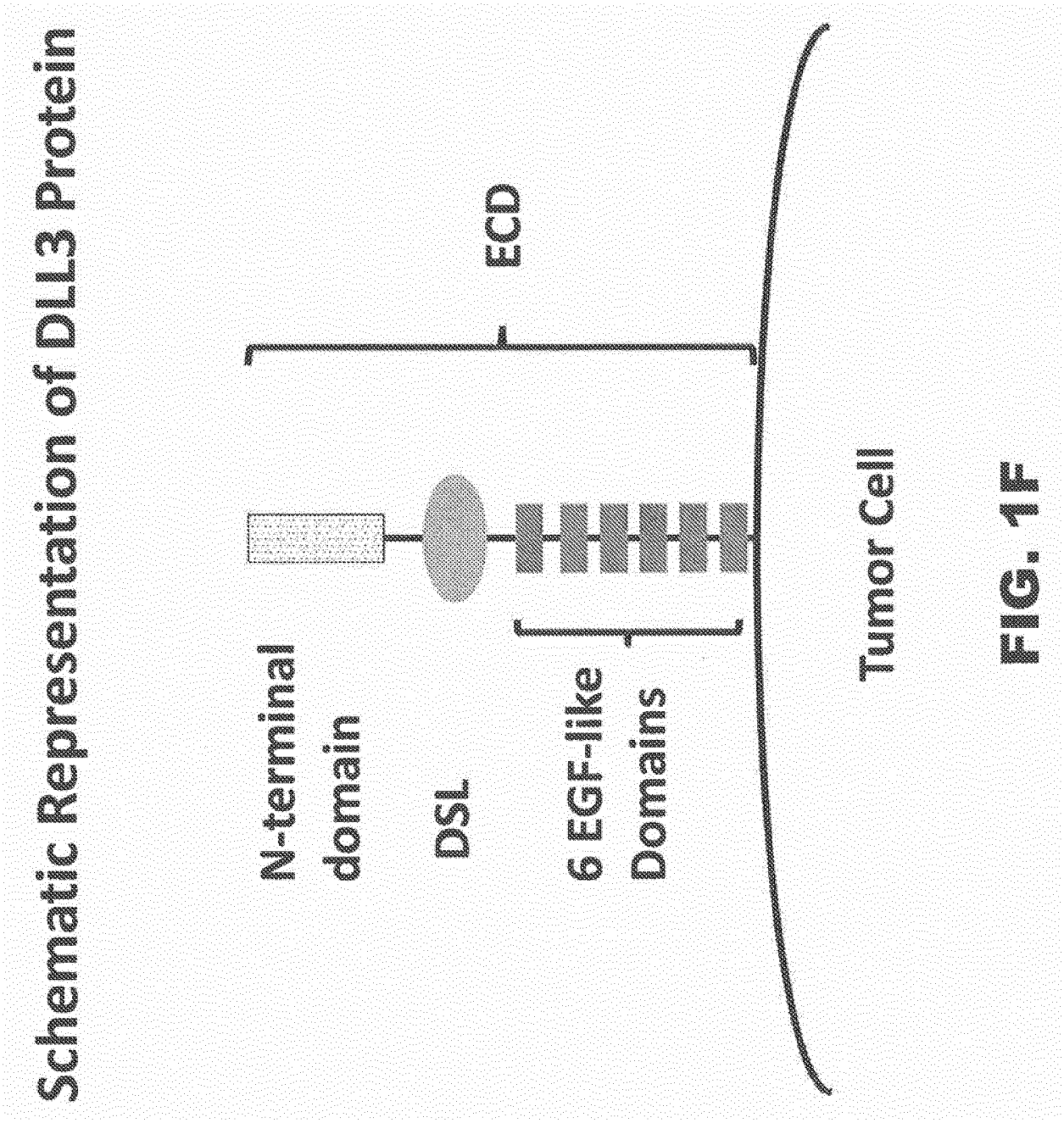

Schematic Representation of DLL3 Protein
ECD
N-terminal domain
DSL
6 EGF-like Domains
Tumor Cell

FIG. 1F

Percent Identity Between Homo sapiens DLL Family Member Proteins

DLL Family Homo sapiens	Complete protein DLL1 (NP_005609)	DLL3v1 (NP_058637)	DLL3v2 (NP_982353)
DLL3v1 (NP_058637)	28.8%		
DLL3v2 (NP_982353)	28.0%	94.8%	
DLL4 (NP_061947)	48.1%	28.0%	28.8%

DLL Family Homo sapiens	ECD DLL1 (NP_005609)	DLL3v1 (NP_058637)	DLL3v2 (NP_982353)
DLL3v1 (NP_058637)	33.8%		
DLL3v2 (NP_982353)	33.8%	100.0%	
DLL4 (NP_061947)	52.0%	32.6%	32.6%

FIG. 2A

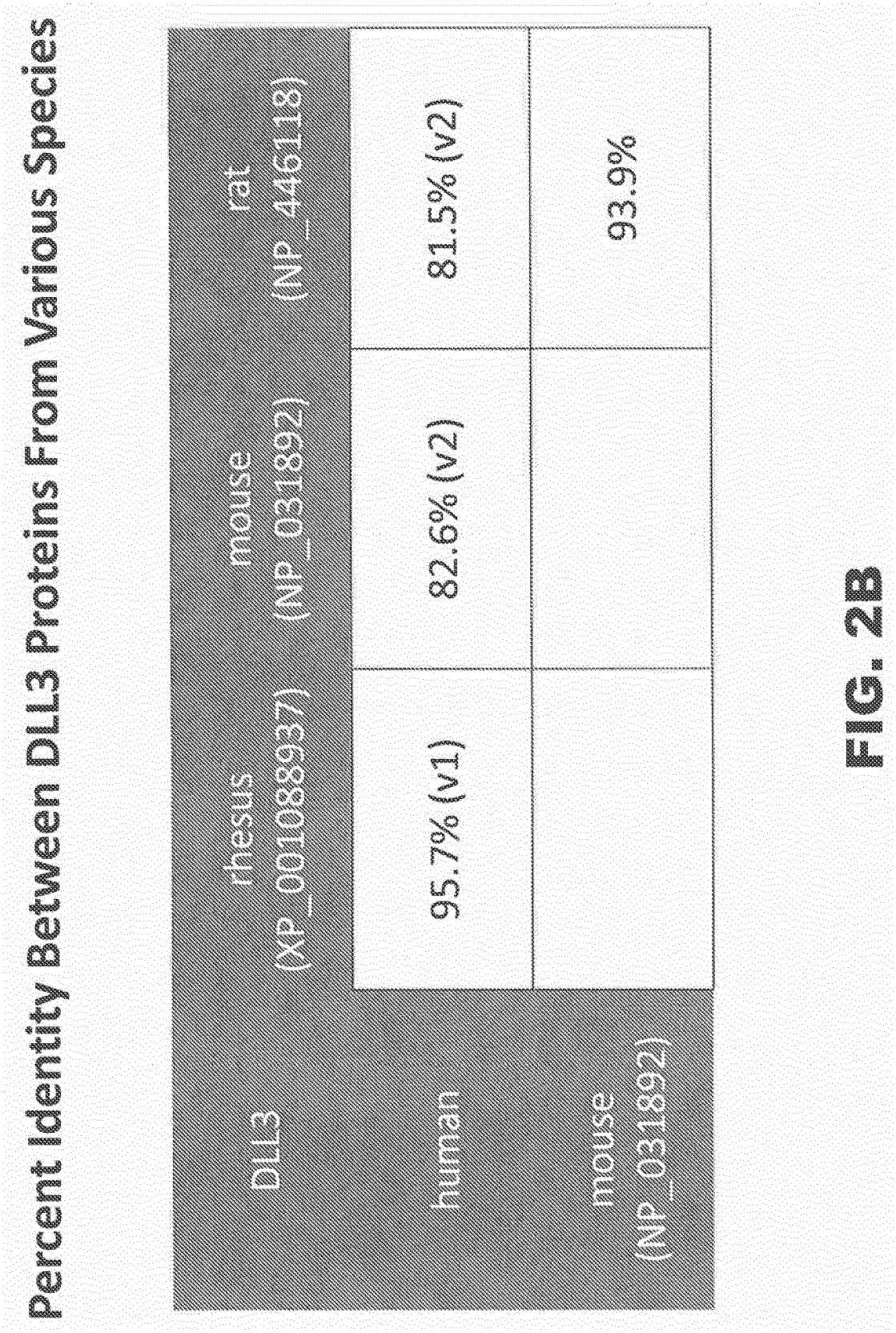

Percent Identity Between DLL3 Proteins From Various Species
DLL3
rhesus (XP_001088937)
mouse (NP_031892)
rat (NP_446118)
human
95.7% (v1)
82.6% (v2)
81.5% (v2)
mouse (NP_031892)
93.9%

FIG. 2B

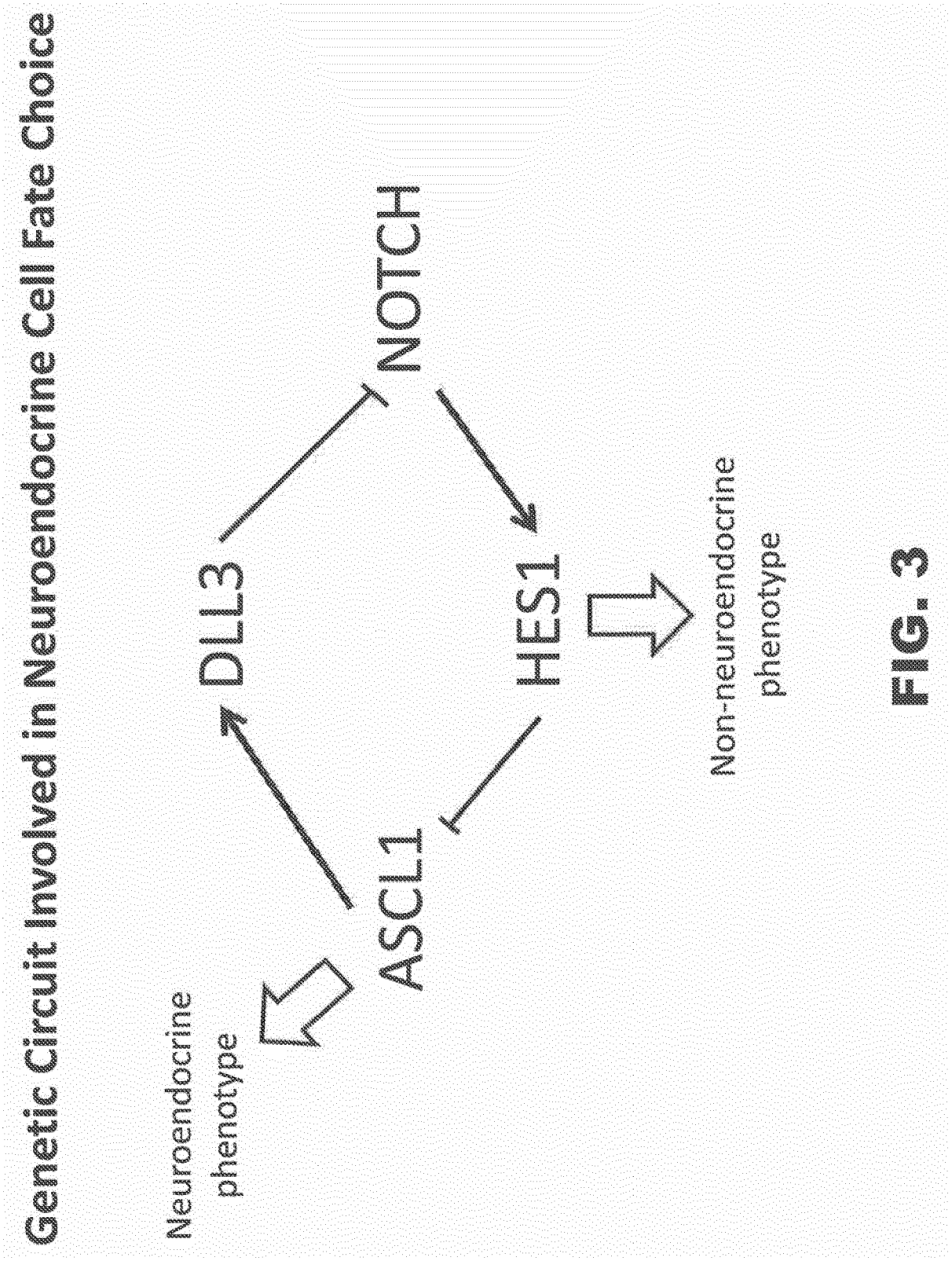

Genetic Circuit Involved in Neuroendocrine Cell Fate Choice
Neuroendocrine phenotype
ASCL1
DLL3
NOTCH
HES1
Non-neuroendocrine phenotype

FIG. 3

Relative Expression Values for Selected mRNA Transcripts in Various Samples as Determined by Whole Transcriptome Sequencing

	DLL1	DLL3	DLL4	NOTCH1	NOTCH2	NOTCH3	NOTCH4	ASCL1	NCAM1	CHGA	HES1	HES6	HEY1
LU37p3 - LCNEC	36.2	93.7	4.5	0.1	14.4	7.8	0.7	2690.8	72.0	94.0	2.7	55.1	5.6
LU64p2 - SCLC	10.9	34.3	10.8	8.2	0.2	0.7	5.7	418.4	57.8	729.5	6.3	2605.8	2.0
LU73p1 - SCLC	176.1	227.6	16.6	4.2	0.0	33.0	79.7	3429.1	77.5	515.0	34.5	3270.6	33.9
LU86p3 - SCLC	4.7	11.9	12.2	18.7	176.8	14.5	0.5	0.4	284.5	17.7	13.9	285.2	9.9
LU95p2 - SCLC	2.4	16.0	1.6	2.1	0.4	8.5	12.2	273.2	171.5	18.2	2.8	72.6	9.3
LU137p0 -LU_Ad	1.8	0.0	4.3	10.6	247.7	27.5	0.4	0.0	0.0	0.0	54.6	1.5	1.7
LU146p0 - LU_Ad	0.0	0.0	0.3	5.6	56.8	37.9	3.9	0.0	0.8	0.0	42.9	0.8	0.3
LU153p0 - LU_Ad	0.8	0.0	5.7	8.1	195.1	8.0	6.5	0.2	4.4	0.0	4.8	0.2	1.4
LU49p4 -- LU_SCC	2.6	0.7	0.0	7.6	104.2	0.0	1.3	0.0	0.0	0.0	62.1	4.3	0.0
LU70p4 - LU_SCC	4.7	0.0	0.8	12.6	123.2	1.8	0.1	0.0	0.0	0.3	42.3	2.1	0.0
LU76p5 - LU_SCC	0.8	0.0	4.8	20.0	32.5	0.1	0.0	3.4	0.3	0.3	23.0	0.8	0.0
OV26p3 - OV	34.2	65.4	15.7	0.0	101.0	17.4	0.6	2253.7	128.8	23.1	4.3	35.1	7.1
OV100p0 - OV	0.0	0.5	0.4	3.6	154.2	16.3	0.5	0.0	2.0	0.0	[redacted]	0.0	17.3
OV45p3 - OV	1.7	1.9	0.1	14.9	53.2	84.5	2.7	0.0	60.4	0.1	14.6	2.4	[redacted]
OV55p5 - OV	0.3	0.2	0.0	31.0	139.8	71.7	1.4	0.0	11.4	0.0	19.4	1.9	6.7
OV72METp0 - OV	0.0	0.1	0.2	1.6	201.1	46.8	0.2	0.3	34.5	0.1	17.1	1.9	2.0
OV91METp0 - OV	0.3	1.6	0.1	10.5	240.1	345.3	2.3	0.0	3.9	0.0	31.7	1.2	1.0
Normal Lung 1	1.7	0.0	5.7	8.2	85.9	33.1	11.4	0.4	3.4	0.0	13.8	0.1	11.4
Normal Lung 2	17.0	0.1	8.8	24.0	81.5	54.0	62.8	5.3	4.6	0.4	23.2	2.4	43.0
Normal Lung 3	26.9	0.2	61.6	146.0	25.6	239.3	91.7	0.8	1.8	1.3	11.9	8.1	40.2
Normal Lung 4	0.2	0.0	6.0	11.8	81.5	40.4	15.8	0.0	1.2	0.0	11.4	0.3	14.1
Normal Ovary	0.3	0.0	5.1	7.8	250.9	44.1	5.1	0.6	175.5	0.2	8.5	0.7	0.4

FIG. 4A

Relative Expression Values for DLL3 Transcripts in Various Samples as Determined by Whole Transcriptome Sequencing

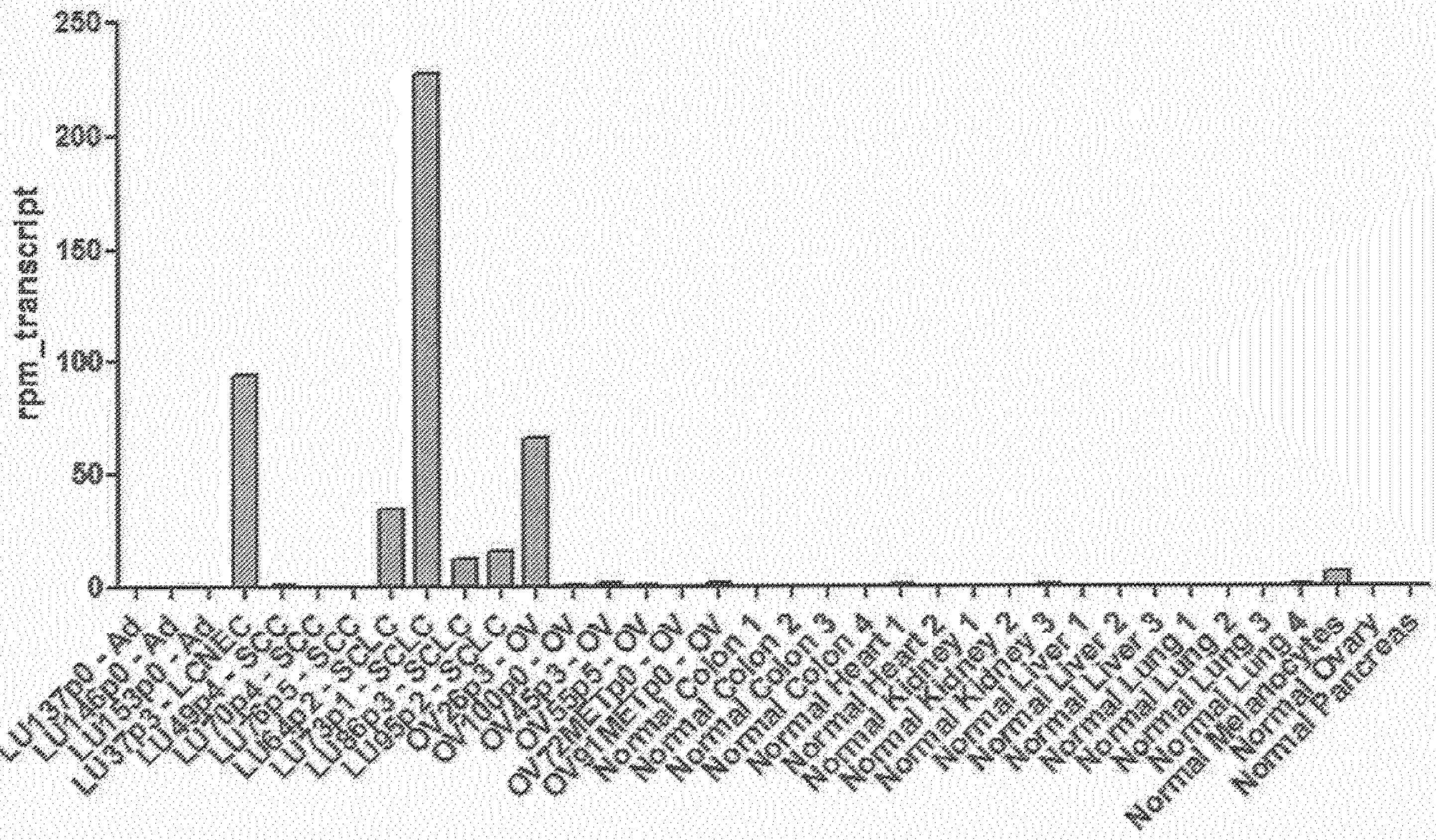


FIG. 4B

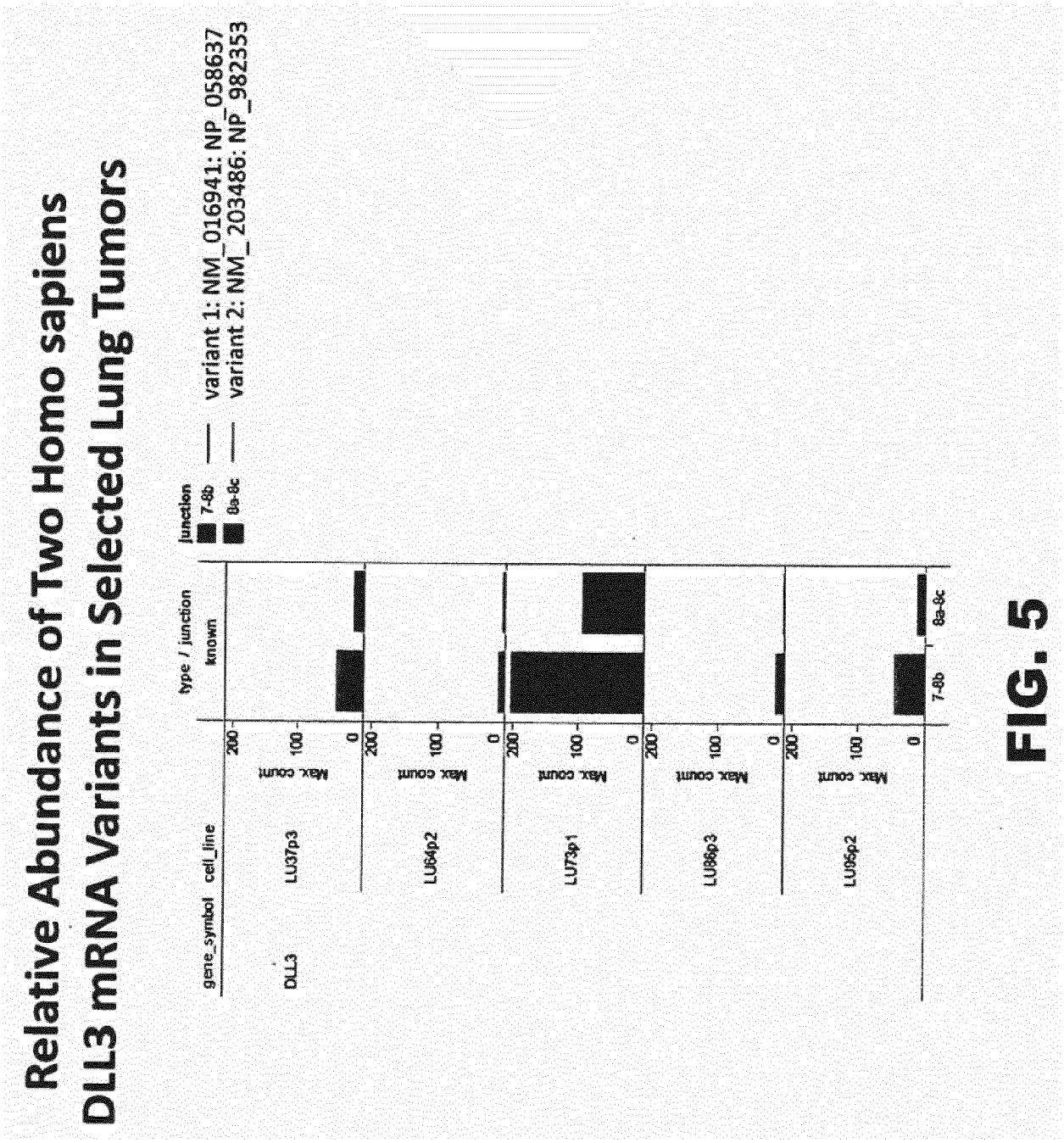

Relative Abundance of Two Homo sapiens
DLL3 mRNA Variants in Selected Lung Tumors
junction
7-8b
8a-8c
variant 1: NM_016941: NP_058637
variant 2: NM_203486: NP_982353
type / junction
known
gene_symbol cell_line
DLL3
LU37p3
LU64p2
LU73p1
LU86p3
LU95p2
Max. count
200
100
0
7-8b
8a-8c

FIG. 5

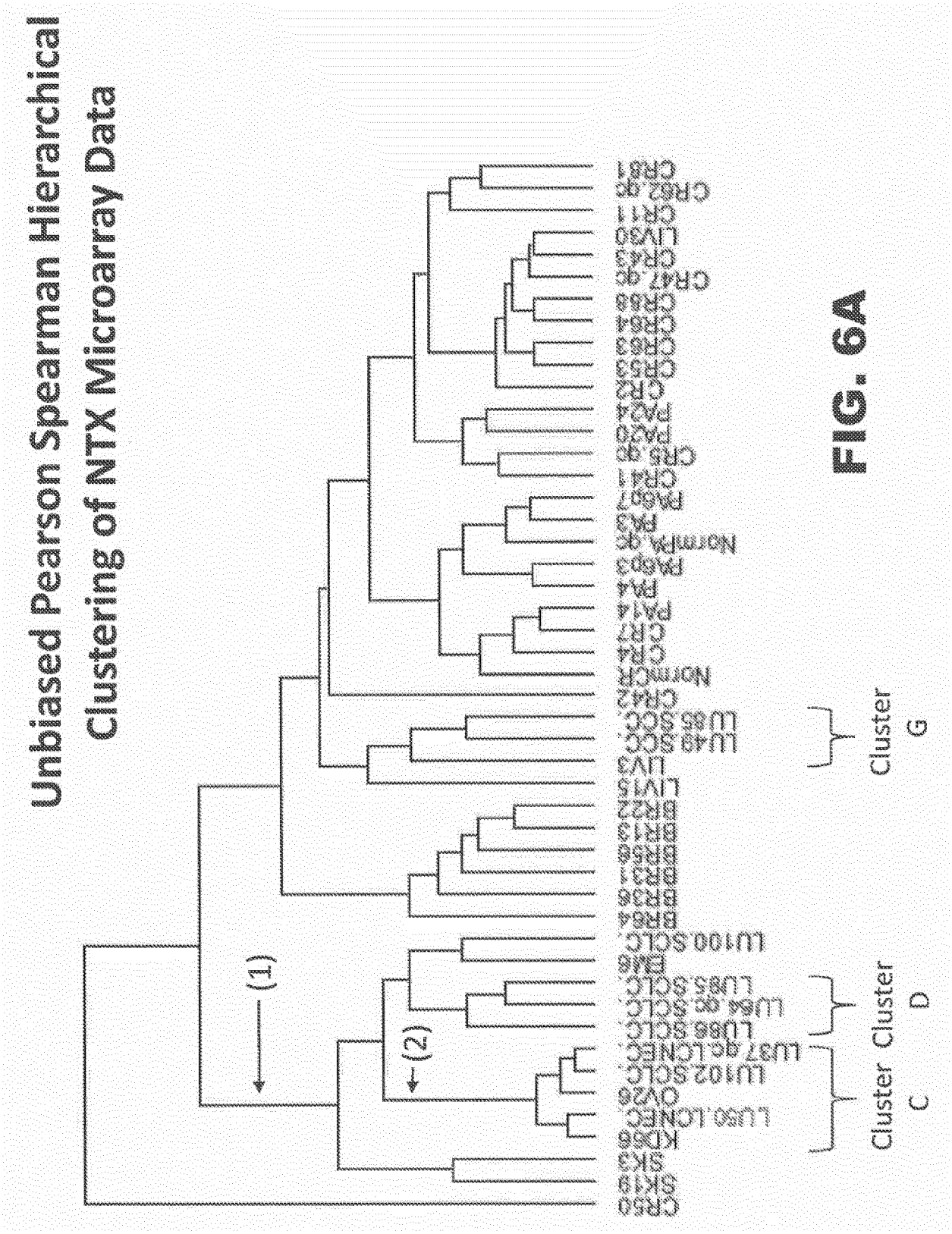

Unbiased Pearson Spearman Hierarchical
Clustering of NTX Microarray Data
(1)
(2)
Cluster C
Cluster D
Cluster G
CR50
SK19
SK3
KD56
LU60_LCNEC
OV26
LU102_SCLC
LU37ae_LCNEC
LU86_SCLC
LU64_qc_SCLC
LU85_SCLC
EA16
LU100_SCLC
BR64
BR36
BR31
BR56
BR13
BR22
LIV15
LIV3
LU49_SCC
LU85_SCC
CR42
NormCR
CR4
CR7
PA14
PA4
PAep3
NormPA_qc
PA23
PA697
CR41
CR5_qc
PA20
PA24
CR2
CR53
CR63
CR64
CR38
CR47_qc
CR43
LIV30
CR11
CR52_qc
CR31

FIG. 6A

Average Normalized Intensity Values for Common Markers of Neuroendocrine Phenotype

			Cluster C					Cluster D			Cluster G	
	Gene Symbol	Median (48 samples)	KD66	LU50(LCNEC)	OV26	LU102(SCLC)	LU37 (LCNEC)	LU86(SCLC)	LU64(SCLC)	LU95(SCLC)	LU49(SCC)	LU85(SCC)
Achaete-scute complex homolog 1	ASCL1	9	6589	8238	9382	12169	9664	11	3390	10298	8	5
Calcitonin	CALCA	73	16138	8352	10035	14633	14547	70	24	2477	52	39
CGRP	CALCB	143	2534	1147	1547	2584	2757	13189	433	1264	65	81
CD117, Kit receptor	KIT	343	5978	4907	3561	6416	6254	12760	11215	15187	34	301
Chromogranin A	CHGA	53	6167	8902	12848	8206	7408	7950	19869	35715	1249	2364
Chromogranin B	CHGB	22	1615	2152	1516	1456	1242	2365	1362	4151	32	24
Dopa decaroxylase	DDC	2441	21606	24512	23595	31824	25707	1498	4234	9297	134	286
Gamma (Neural) Enolase	ENO2	1910	2054	1881	1911	1573	1262	4043	4737	11120	2472	2241
GDNF family receptor alpha 1	GFRA1	9	263	29	37	146	133	90	4	6	9	4
CD56	NCAM1	82	551	875	801	999	727	2618	2519	3296	425	106
PGP9.5	UCHL1	415	16415	13168	12862	24212	19977	13414	9749	25738	122	8251
Proopiomelanocortin	POMC	94	751	427	590	750	657	66	560	5204	213	160
Somatostatin	SST	67	27000	1316	19913	5869	12189	35	9	62	90	28
Somatostatin Receptor 5	SSTR5	613	733	906	875	636	633	907	344	622	918	401
Synaptophysin	SYP	19	15	15	9	17	15	27	53	91	11	19
Thyroid Transcription Factor 1	NKX2-1	18	3137	3508	2734	5180	3315	1258	3585	2229	85	8

FIG. 6B

Average Normalized Intensity Values for Selected Genes in the Notch Pathway and ASCL1

		Cluster C					Cluster D			Cluster G	
	Median (48 samples)	KD66	LU50(LCNEC)	OV26	LU102(SCLC)	LU37(LCNEC)	LU86(SCLC)	LU64(SCLC)	LU95(SCLC)	LU49(SCC)	LU85(SCC)
ASCL1	9	6589	8238	9382	12169	9664	11	3390	10298	8	5
DLL1	51	348	565	406	497	179	218	98	514	29	120
DLL3	350	4584	3985	6232	5884	5233	1686	3137	5814	601	492
DLL4	614	601	445	592	301	280	763	198	673	357	469
HES1	670	128	129	160	92	82	551	137	335	2665	2024
HES6	117	196	361	481	416	279	5456	2716	3535	28	33
HEY1	89	86	101	116	103	77	1660	680	2502	3776	231
HEYL	87	157	132	128	148	132	2645	102	267	333	80
JAG1	630	159	114	110	95	111	743	521	311	9131	678
JAG2	125	335	529	398	420	247	324	513	611	159	153
NOTCH1	666	34	23	41	17	14	1039	381	202	4720	438
NOTCH2	26	6	11	12	16	12	105	11	1	37	5
NOTCH3	101	13	27	91	81	72	302	37	136	1474	322
NOTCH4	14	6	7	13	9	5	14	15	69	14	7
RBPJ	1289	1891	2255	1933	2717	2278	4502	2678	5167	1226	1029

FIG. 6C

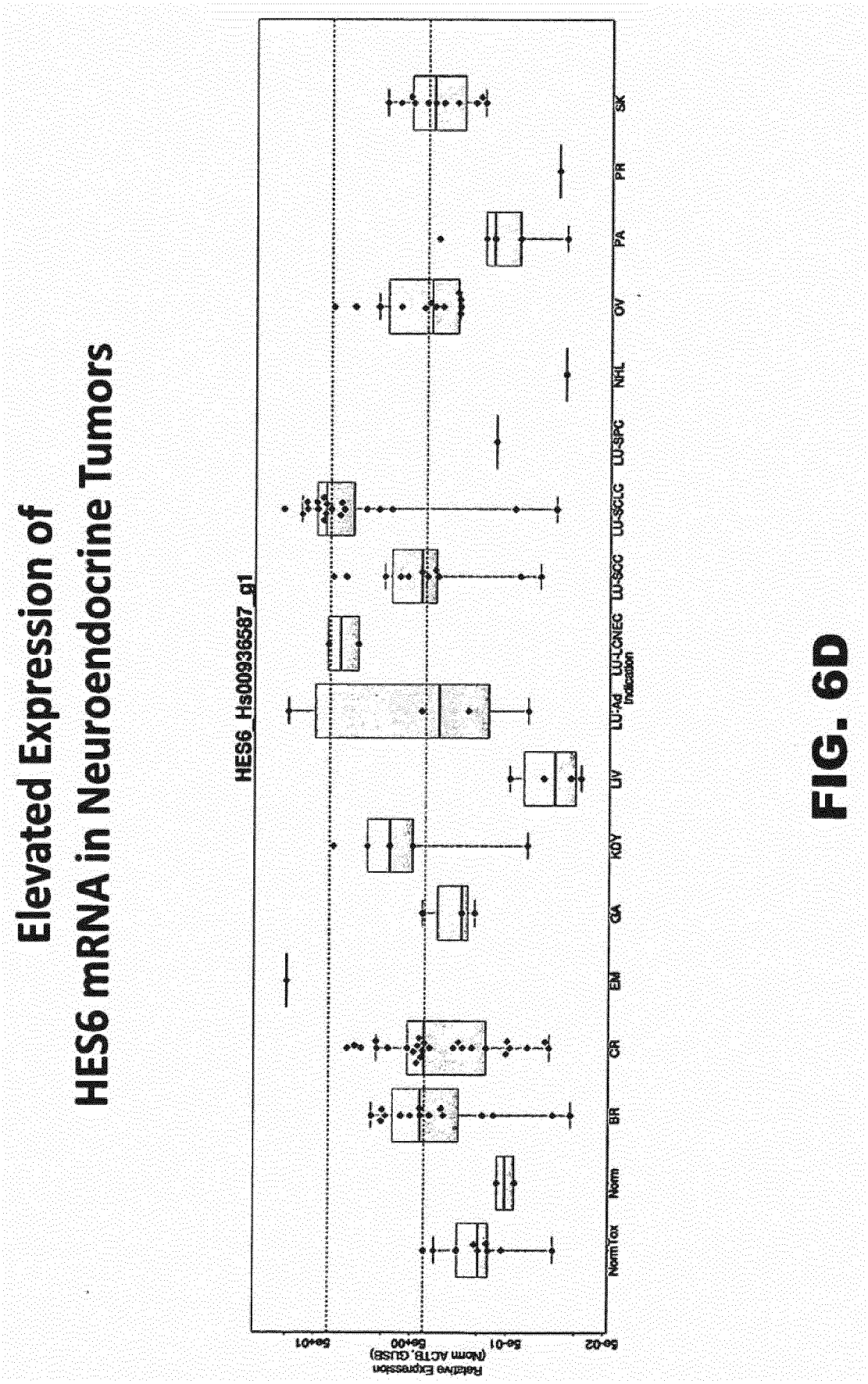

Elevated Expression of
HES6 mRNA in Neuroendocrine Tumors
HES6_Hs00936587_g1
Relative Expression
(Norm ACTB, GUSB)
5e-02
5e-01
5e+00
5e+01
Norm/Tox
Norm
BR
CR
EM
GA
KDY
LIV
LU-Ad
LU-CNEC
LU-SCC
LU-SCLC
LU-SPC
NHL
OV
PA
PR
SK
Indication

FIG. 6D

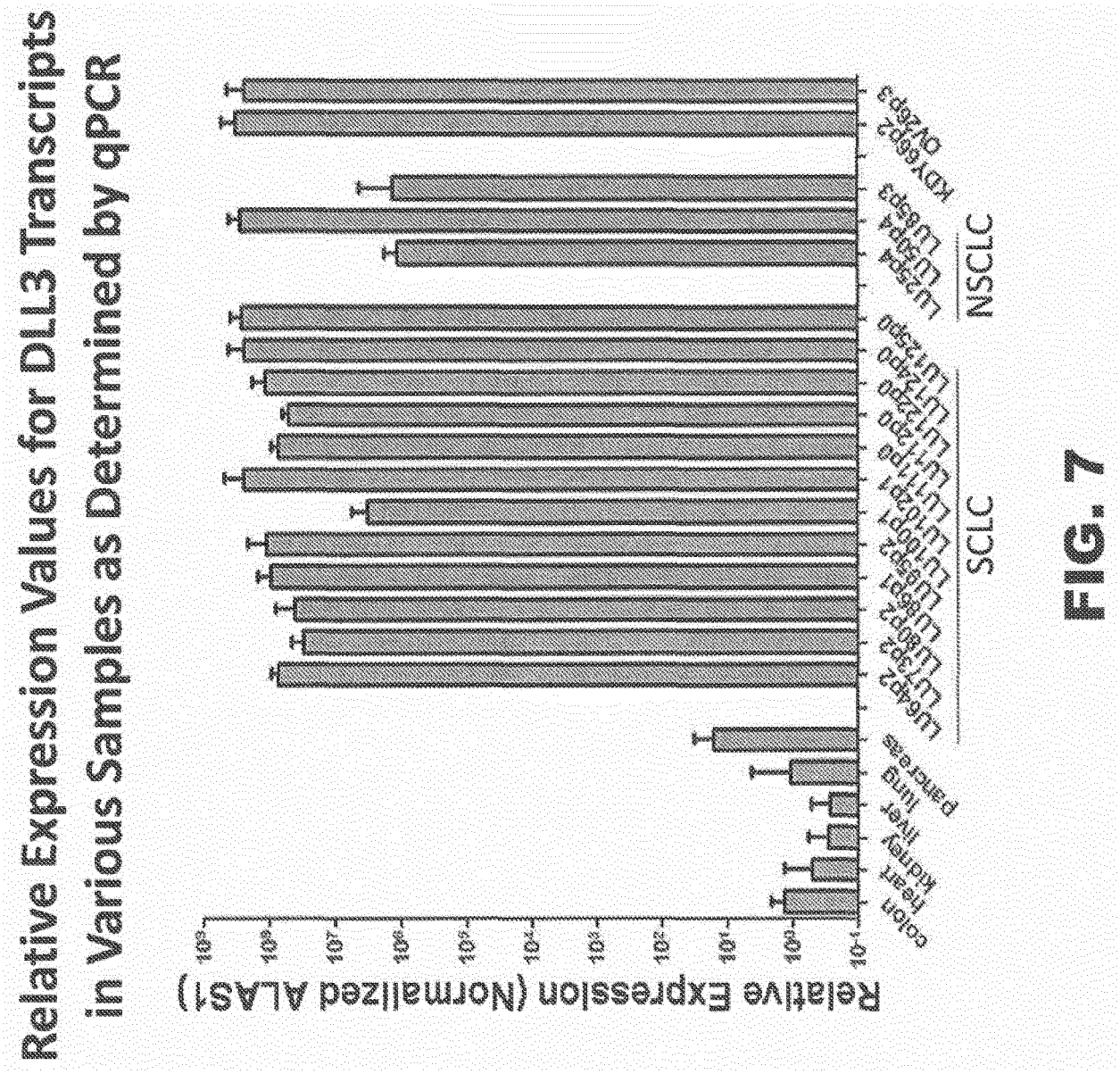

Relative Expression Values for DLL3 Transcripts
in Various Samples as Determined by qPCR
Relative Expression (Normalized ALAS1)
colon
heart
kidney
liver
lung
pancreas
LU64P2
LU73P2
LU80P2
LU85P1
LU85P2
LU100P1
LU102P1
LU111P3
LU120P
LU122P0
LU124P0
LU125P0
LU125P4
LU85P4
LU85P3
KDY66P2
OV26P3
SCLC
NSCLC

FIG. 7

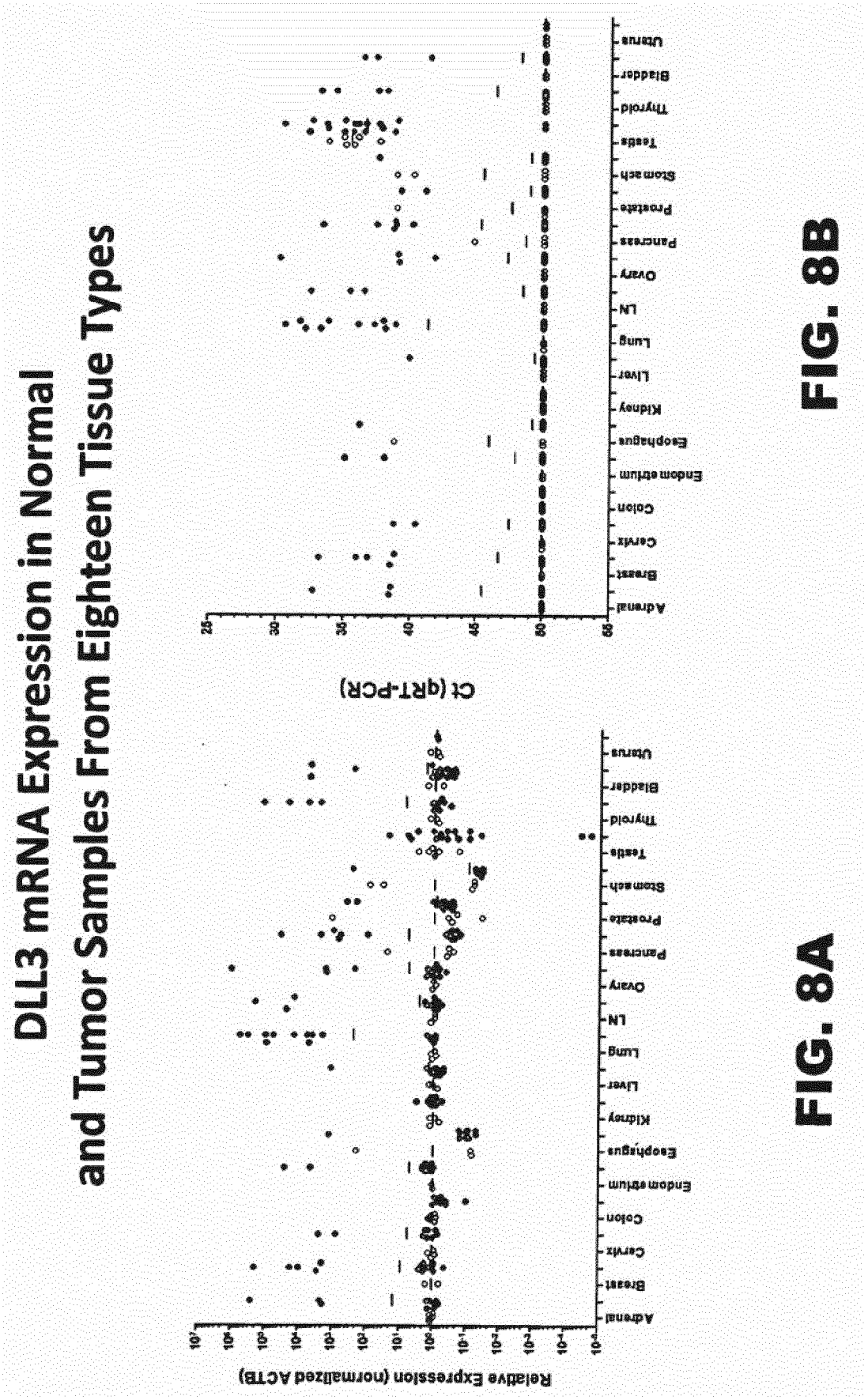

DLL3 mRNA Expression in Normal
and Tumor Samples From Eighteen Tissue Types
Ct (qRT-PCR)
Relative Expression (normalized ACTB)
Adrenal
Breast
Cervix
Colon
Endometrium
Esophagus
Kidney
Liver
Lung
LN
Ovary
Pancreas
Prostate
Stomach
Testis
Thyroid
Bladder
Uterus

FIG. 8B

FIG. 8A

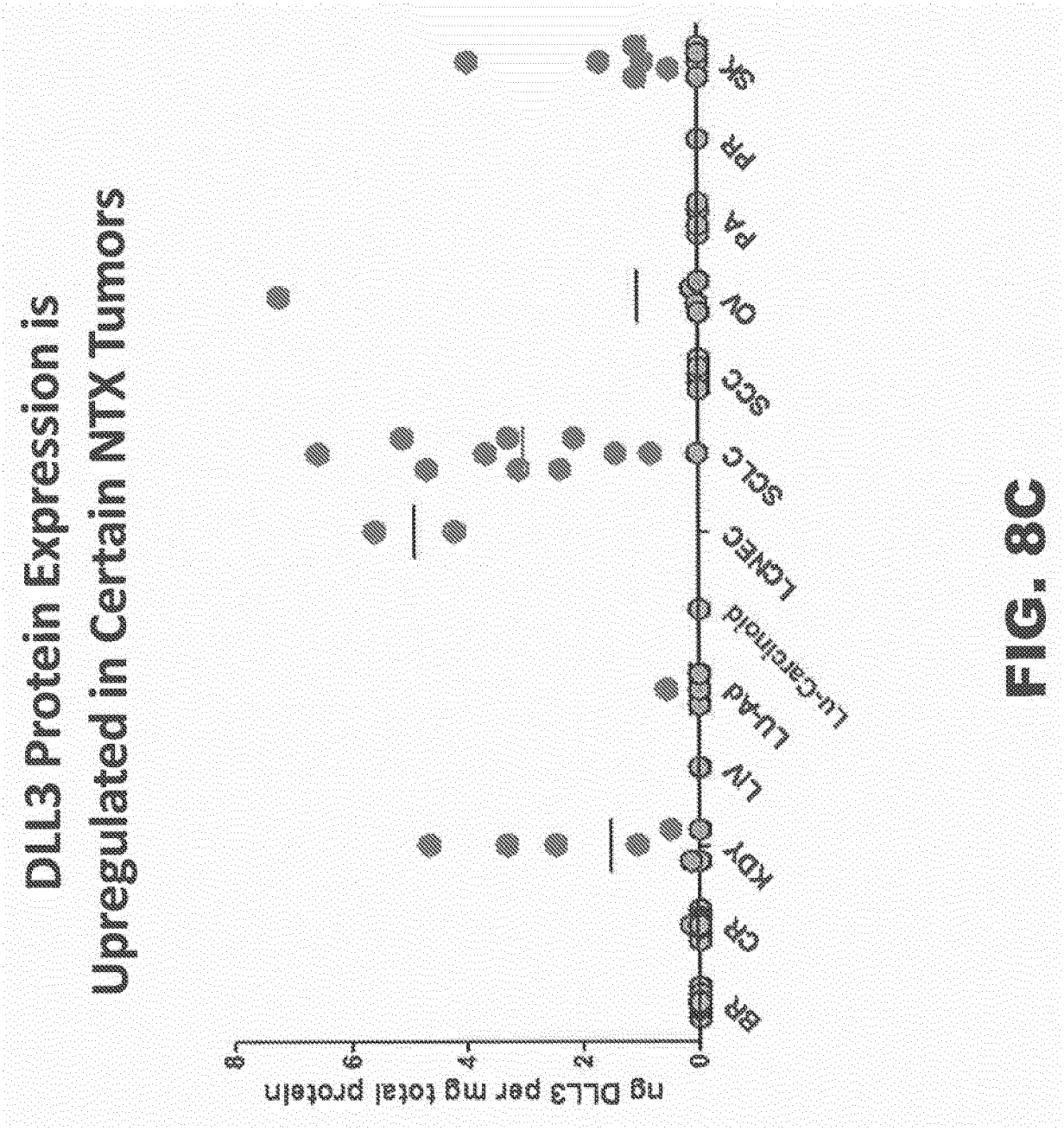

DLL3 Protein Expression is
Upregulated in Certain NTX Tumors
ng DLL3 per mg total protein
0
2
4
6
8
BR
CR
KDY
LIV
Lu-Ad
Lu-Carcinoid
LCNEC
SCLC
SCC
OV
PA
PR
GK

FIG. 8C

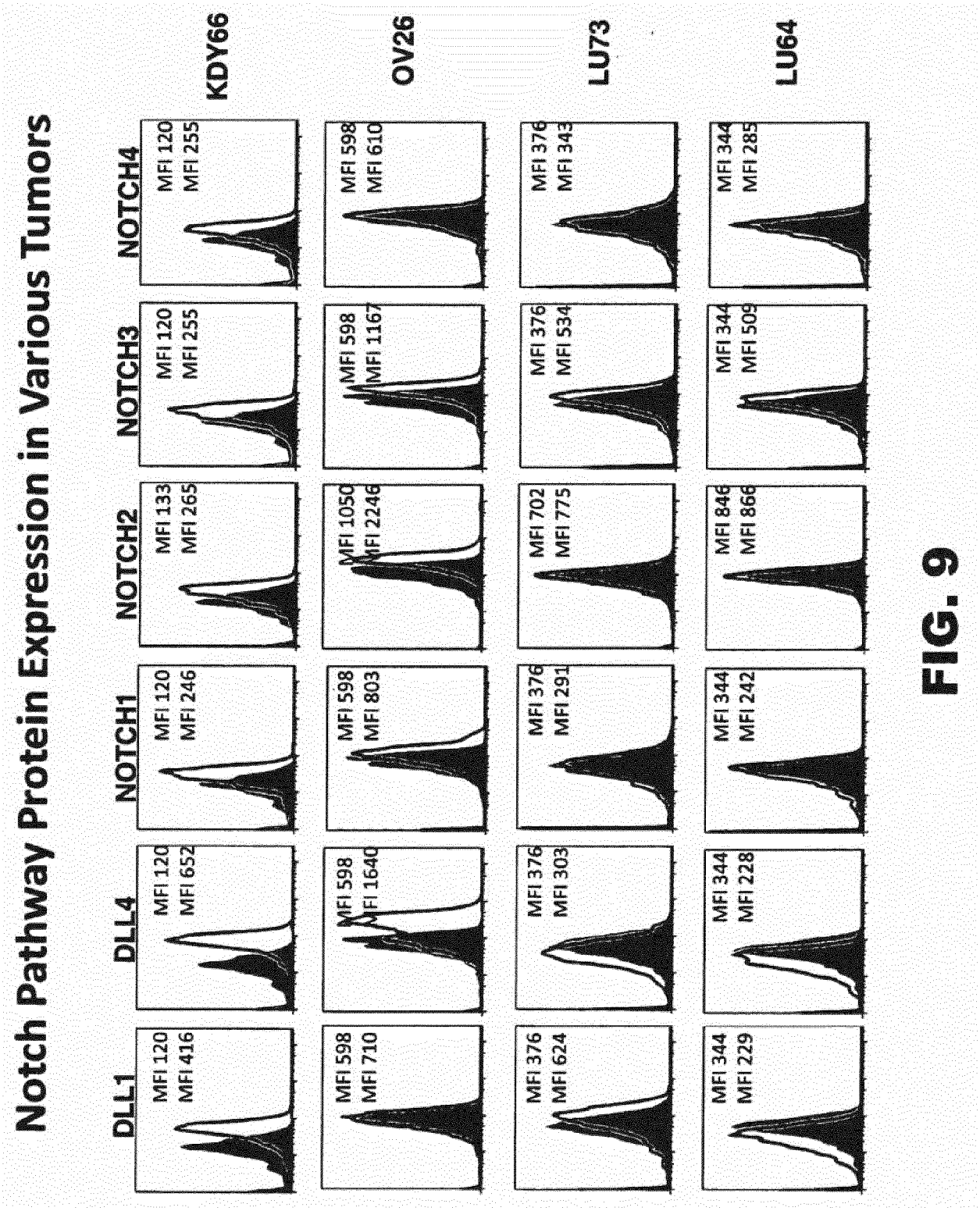

Notch Pathway Protein Expression in Various Tumors
DLL1
DLL4
NOTCH1
NOTCH2
NOTCH3
NOTCH4
KDY66
OV26
LU73
LU64
MFI 120 MFI 416
MFI 120 MFI 652
MFI 120 MFI 246
MFI 133 MFI 265
MFI 120 MFI 255
MFI 120 MFI 255
MFI 598 MFI 710
MFI 598 MFI 1640
MFI 598 MFI 803
MFI 1050 MFI 2246
MFI 598 MFI 1167
MFI 598 MFI 610
MFI 376 MFI 624
MFI 376 MFI 303
MFI 376 MFI 291
MFI 702 MFI 775
MFI 376 MFI 534
MFI 376 MFI 343
MFI 344 MFI 229
MFI 344 MFI 228
MFI 344 MFI 242
MFI 846 MFI 866
MFI 344 MFI 509
MFI 344 MFI 285

FIG. 9

>mature murine DLL3 DNA in lentiviral vector

SEQ ID NO. 5

GCTGGTGTCTTCGAGCTACAAATTCATTCTTTCGGGCCAGGCCCAGGCCTCGGGACCCCACGCT
CCCCCTGCAACGCCCGAGGCCCTTGCCGCCTCTTCTTCAGGGTCTGCCTGAAGCCCGGAGTCTC
CCAGGAGGCCACCGAGTCCCTGTGCGCCCTGGGCGCAGCACTGAGCACGAGCGTCCCGGTCTAT
ACGGAGCACCCCGGAGAGTCAGCGGCTGCCCTGCCGCTGCCTGATGGCCTCGTACGTGTGCCCT
TCCGCGATGCTTGGCCGGGCACCTTCTCCCTCGTCATTGAAACCTGGAGAGAGCAGCTGGGAGA
GCATGCTGGAGGGCCCGCCTGGAACCTGCTAGCACGTGTGGTCGGCCGTAGACGCCTGGCGGCT
GGGGGCCCGTGGGCCCGCGATGTGCAGCGCACAGGCACATGGGAGTTGCACTTCTCCTACCGCG
CGCGGTGCGAGCCGCCCGCCGTCGGGGCCGCCTGCGCGCGCCTGTGCCGCTCACGCAGTGCCCC
CTCGCGGTGTGGCCCGGGACTGCGACCCTGCACGCCATTCCCAGACGAGTGCGAAGCCCCGTCT
GTGTGTCGACCAGGCTGCAGCCCCGAGCACGGCTACTGTGAAGAGCCTGATGAATGCCGTTGCC
TGGAGGGCTGGACTGGACCCCTCTGCACGGTCCCTGTCTCCACCAGTAGCTGCCTGAACTCCAG
GGTTCCTGGTCCTGCCAGCACTGGATGCCTTTTACCTGGGCCTGGACCTTGTGATGGGAACCCA
TGTGCCAATGGGGGCAGCTGTAGTGAAACCTCTGGCTCCTTTGAATGTGCCTGTCCCCGGGGAT
TCTACGGGCTTCGATGTGAGGTGAGCGGGGTCACGTGCGCAGATGGACCCTGCTTCAATGGCGG
CTTGTGTGTTGGCGGTGAAGATCCTGACTCTGCCTATGTCTGTCATTGCCCACCTGGTTTCCAA
GGCTCTAACTGTGAGAAGAGGGTGGACCGCTGTAGCCTGCAGCCATGTCAGAATGGCGGCCTCT
GCCTGGACCTGGGCCACGCGTTGCGCTGCCGCTGTCGCGCGGGATTCGCCGGGCCGCGCTGCGA
GCACGACCTGGACGACTGCGCCGGCCGCGCCTGTGCCAACGGCGGCACGTGCGTGGAGGGCGGC
GGCTCGCGCCGCTGCTCCTGTGCGCTGGGCTTCGGCGGGCGCGACTGCCGAGAACGCGCCGACC
CCTGCGCCTCCCGCCCCTGCGCGCATGGAGGCCGTTGCTACGCCCACTTCTCTGGCCTGGTCTG
CGCCTGCGCGCCCGGCTACATGGGCGTGAGATGCGAGTTCGCTGTGCGCCCGGACGGCGCGGAC
GCGGTGCCCGCCGCCCCGCGGGGCCTGAGGCAGGCGGATCCACAGCGCTTTCTTCTGCCTCCCG
CCTTGGGGCTGCTGGTGGCCGCCGGTTTGGCTGGCGCCGCACTCTTGGTCATCCACGTTCGCCG
CCGAGGTCCTGGCCAGGATACCGGGACTCGCCTGCTTTCTGGGACCCGGGAGCCTTCGGTCCAC
ACGCTCCCGGATGCACTCAACAACCTGAGGTTACAAGACGGTGCTGGGGATGGCCCCAGTTCGT
CGGCTGACTGGAATCATCCTGAAGATGGAGACTCTAGATCCATTTATGTCATACCAGCCCCTTC
CATTTATGCACGAGAGGCCTGA

FIG. 10A

EP 3 095 797 A1

>translation of mature murine DLL3 in lentiviral vector

SEQ ID NO. 6

AGVFELQIHSFGPGPGLGTPRSPCNARGPCRLFFRVCLKPGVSQEATESLCALGAALSTS
VPVYTEHPGESAAALPLPDGLVRVPFRDAWPGTFSLVIETWREQLGEHAGGPAWNLLARV
VGRRRLAAGGPWARDVQRTGTWELHFSYRARCEPPAVGAACARLCRSRSAPSRCGPGLRP
CTPFPDECEAPSVCRPGCSPEHGYCEEPDECRCLEGWTGPLCTVPVSTSSCLNSRVPGPA
STGCLLPGPGPCDGNPCANGGSCSETSGSFECACPRGFYGLRCEVSGVTCADGPCFNGGL
CVGGEDPDSAYVCHCPPGFQGSNCEKRVDRCSLQPCQNGGLCLDLGHALRCRCRAGFAGP
RCEHDLDDCAGRACANGGTCVEGGGSRRCSCALGFGGRDCRERADPCASRPCAHGGRCYA
HFSGLVCACAPGYMGVRCEFAVRPDGADAVPAAPRGLRQADPQRFLLPPALGLLVAAGLA
GAALLVIHVRRRGPGQDTGTRLLSGTREPSVHTLPDALNNLRLQDGAGDGPSSSADWNHP
EDGDSRSIYVIPAPSIYAREA

FIG. 10B

EP 3 095 797 A1

>Deduced mature cynomolgus DLL3 DNA

SEQ ID NO. 7

CCCCAAGCCAGGCCCGCTGGCGTGTTCGAACTGCAGATCCATAGCTTCGGCCCTGGCCCTGGACCCGGAGCCCCT
AGAAGCCCTTGTTCCGCTAGAGGCCCCTGCAGACTGTTCTTCAGAGTCTGCCTGAAGCCTGGCCTGAGCGAGGAG
GCTGCTGAGAGCCCTTGTGCTCTGGGAGCTGCCCTCAGCGCTAGGGGCCCTGTCTACACCGAGCAACCTGAGGCT
CCCGCTCCCGATCTGCCTCTCCCTAACGGCCTGCTGCAGGTGCCCTTCAGGGATGCTTGGCCCGGAACCTTCAGC
CTCATCATCGAGACCTGGAGGGAGGAACTCGGAGACCAGATTGGAGGACCCGCCTGGTCCCTGCTCGCTAGAGTG
ACAAGAAGAAGAAGGCTGGCTGCTGGCGGACCTTGGGCTAGAGATATCCAGAGAGCTGGCGCCTGGGAGCTCAGG
TTCAGCTACAGGGCCAGATGTGAGCTCCCTGCCGTGGGCACCGCTTGTACCAGGCTGTGTAGGCCCAGATCCGCC
CCTTCCAGATGTGGCCCCGGACTCAGACCTTGCGCTCCTCTCGAGGACGAGTGTGAAGCTCCTCCCGTCTGTAGG
GCCGGATGCAGCCTCGAGCACGGCTTCTGTGAGCAGCCTGGCGAATGTAGGTGCCTCGAAGGCTGGACCGGCCCT
CTCTGTATGGTGCCTGTCTCCACCTCCTCCTGTCTCGGACTGAGGGGCCCTTCCTCCGCTACAACCGGATGTCTG
GTCCCTGGACCTGGACCTTGCGACGGAAACCCTTGTGCCAACGGAGGCTCCTGTAGCGAGACCCCCGGAAGCTTT
GAATGTACCTGCCCCAGGGGCTTTTACGGCCTCAGATGCGAGGTCAGCGGAGTCACATGCGCCGACGGACCCTGC
TTTAATGGAGGACTCTGCGTGGGAGGAGCCGACCCTGATAGCGCTTACATCTGTCACTGTCCCCCCGGCTTTCAG
GGCTCCAACTGCGAGAAGAGGGTCGACAGGTGCTCCCTGCAACCCTGTAGAAATGGCGGCCTCTGCCTGGATCTG
GGACATGCTCTCAGGTGCAGATGTAGAGCTGGATTCGCCGGACCCAGGTGCGAGCATGATCTCGACGATTGTGCT
GGCAGGGCCTGCGCTAATGGAGGAACATGTGTGGAAGGAGGCGGAGCCCACAGATGCAGCTGCGCTCTCGGCTTC
GGCGGAAGAGACTGCAGAGAGAGGGCTGACCCTTGTGCCGCCAGGCCTTGTGCTCATGGCGGAAGGTGCTACGCC
CATTTCTCCGGACTCGTGTGCGCCTGCGCCCCTGGATATATGGGCGCTAGGTGCGAGTTTCCCGTCCACCCTGAT
GGAGTCAGCGCTCTCCCTGCCGCTCCTCCTGGACTGAGACCTGGAGATCCTCAGAGATACCTGCTCCCTCCTGCC
CTCGGACTCCTGGTCGCTGCTGGAGTCGCTGGAGCCGCTCTCCTCCTGGGACACGTCAGGAGAAGAGGCCACGCC
CAGGATGCTGGAAGCAGACTGCTGGCCGGAACACCCGAGCCTTCCGTCCATGCCCTGCCTGACGCCCTCAACAAC
CTGAGGACCCAGGAGGGCCCTGGAGATGTGCCTAGCAGCTCCGTCGACTGGAACAGACCTGAGGATGTGGACTCC
AGGGGCATCTACGTGATCAGCGCCCCCTCCATCTATGCCAGGGAGGTCGCCATGCCCCTCTTTCCTCCTCTGCAT
ACAGGCAGAGCCGGCCAGAGACAGAACCTGCTCTTCCCCTACCCCAGCAGCATCCTGTCCGTGAAGTGA

FIG. 10C

EP 3 095 797 A1

>translation of mature cynomolgus DLL3

SEQ ID NO. 8

PQARPAGVFELQIHSFGPGPGAPRSPCSARGPCRLFFRVCLKPGLSEEAAESPCALGA
ALSARGPVYTEQPEAPAPDLPLPNGLLQVPFFRDAWPGTFSLIIETWREELGDQIGGPAWS
LLARVTRRRRLAAGGPWARDIQRAGAWELRFSYRARCELPAVGTACTRLCRPRSAPSRCG
PGLRPCAPLEDECEAPPVCRAGCSLEHGFCEQPGECRCLEGWTGPLCMVPVSTSSCLGLR
GPSSATTGCLVPGPGPCDGNPCANGGSCSETPGSFECTCPRGFYGLRCEVSGVTCADGPC
FNGGLCVGGADPDSAYICHCPPGFQGSNCEKRVDRCSLQPCRNGGLCLDLGHALRCRCRA
GFAGPRCEHDLDDCAGRACANGGTCVEGGGAHRCSCALGFGGRDCRERADPCAARPCAHG
GRCYAHFSGLVCACAPGYMGARCEFPVHPDGVSALPAAPPGLRPGDPQRYLLPPALGLLV
AAGVAGAALLLGHVRRRGHAQDAGSRLLAGTPEPSVHALPDALNNLRTQEGPGDVPSSSV
DWNRPEDVDSRGIYVISAPSIYAREVAMPLFPPLHTGRAGQRQNLLFPYPSSILSVK

FIG. 10D

Protein Sequences of Exemplary DLL3 Modulator Light Chain Variable Regions

mAb	FR1	CDR1	FR2	CDR2	FR3	CDR3	SEQ ID NO.
SC16.3	QIVLTQSPAIMSVSLGERVTMTC	TASSSVSSSY	LHWYQQKPGSSPKLWIY	STSNLAS	GVPARFSGSGSGTSYFFTISSMEAEDAATYYC	HQYHRSPFTFGAGTKLKIR	20
SC16.4	DIQMTQTTSSLSASLGDRVTISC	RASQDISNY	LNWYQQKPDGTVKLLIY	YTSRLHS	GVPSRFSGSGSGTDYSLTISNLELEDIATYFC	QQGDMLPWTFGGGTKLEIK	22
SC16.5	QIVLTQSPAIMSASPGEKVTMTC	SASSSVSY	MHWYQQKSGTSPKRWIY	DTSKLAS	GVPARFSGSGSGTSYSLTISSMEAEDAATYYC	QQWTRNPLTFGAGTKLELK	24
SC16.7	NIMMTQSPSSLAVSAGEKVTMSC	KSSQSVLYSSNQKNY	LAWYQQKPGQSPKLLIY	WASTRES	GVPDRFTGSGSGTDFTLTISTVQVEDLAVYYC	HQYLSSWTFGGGTKLEIK	26
SC16.8	EIQMTQSPSSMSASLGDRITITC	QATQDIVKN	LNWYQQKPGKPPSFLIY	YAIELAE	GVPSRFSGSGSGSDYSLTISNLESEDFADYYC	LQFYEFPFTFGAGTKLELK	28
SC16.10	QIVLTQSPAIMSASLGERVTMTC	TASSSVSSSY	LHWYQQKPGSSPKLWIY	STSNLAS	GVPTRFSGSGSGTSYSLTISSMEAEDAATYYC	HQYHRSPFTFGSGTKLEIK	30
SC16.11	DVEMTQTPLTLSVTIGQPASISC	KSSQSLSDSDGKTY	LNWMFQRPGRSPKRLIY	LVSKLDS	GVPDRFTGSGSGTDFTLKISRVEAEDLGVYYC	WQGKHFPWTFGGGTKLEIK	32
SC16.13	QIVLTQSPALVSASPGEKVTMTC	SASSSVSY	MYWYQQKPRSSPKPWIY	LTSNLAS	GVPARFSGSGSGTSYSLTISSMEAEDAATYYC	QQWRSNPFTFGSGTKLEIK	34
SC16.15	DIQMTQSPASLAASVGETVAITC	RASENIYYN	LAWYQQKQGKSPQLLIY	TANSLED	GVPSRFSGSGSGTQYSLKINSMQPEDSATYFC	KQAYDVPPTFGGGTKLEIK	36
SC16.18	DIQMTQTTSSLSASLGDRVTISC	RASQNIINY	LNWYQQKPDGTVKLLIY	YTSRLHS	GVPSRFSGSGSGTDYSLTISNLEPEDIATYYC	QQYSERPYTFGGGTKLEIKR	38
SC16.19	DIQMTQSPSSLSASLGGKVTFTC	KASQDIHKY	VAWYQHKPGKGPRLLIH	YTSTLQP	GISSRFSGSGSGRDYSFSISNLEPEDIATYYC	LQYNNLYTFGGGTKLEIKR	40
SC16.20	EIQMTQSPSSMSASLGDRITITC	QATQDIVKN	LNWYQQKPGKPPSFLIY	YATELAE	GVPSRFSGSGSGSDYSLTIRNLESEDFADHYC	LQFYEFPFTFGAGTKLELK	42
SC16.21	DIVMTQSPSSLAMSVGQKVTMSC	KSSQSLLNSSNQKNY	LAWYQQEPGQSPKLLVS	FASTRES	GVPDRFTGSGSGTDFTLTISGVQAEDLAVYYC	QQHYSIPLTFGAGTKLELK	44
SC16.22	DIQMTQTTSSLSASLGDRVTISC	RASQDIKNY	LNWYQQKPDGTVKPLIY	YTSRVHS	GVPSRFSGSGSGTDYSLTISNLEQEDIATYFC	QQGYTLPFTFGSGTKLE	46
SC16.23	QIVLTQSPAIMSASPGEKVTLTC	SASSSVSSRY	LYWYQQKPGSSPKLWIY	STSNLAS	GVPARFSGSGSGTSYSLIISSMEAEDAASYFC	HQWSNYPLTFGAGTKLELK	48
SC16.25	QIVLTQSPAIMSASPGEKVTMTC	SASSSVSY	MHWYQQKSGTSPKRWIY	DSSKLAS	GVPARFSGSGSGTSYSLTISSMEAEDAATYYC	QQWSSNPLTFGAGTKLELK	50
SC16.26	DVEMTQTPLTLSVTIGQPASISC	KSSQSLSDSDGKTY	LNWMFQRPGRSPKRLIY	LVSKLDS	GVPDRFTGSGSGTDFTLKISRVEAEDLGVYYC	WQGKHFPWTFGGGTKLEIK	52
SC16.29	QIVLTQSPAIMSASPGEKVTITC	SASSSVSY	MHWFQQKPGTSPKLWIY	TTSNLAS	GVPARFSGSGSGTSYSLTVSRMEAEDAATYYC	QQRSLYPYTFGGGTKVEIK	54
SC16.30	QIVLTQSPTIMSASLGERVTMTC	TASSSVTSSY	LHWYQQKPGSSPKLWIY	STSNLAS	GVPARFSGSGSGTSYSLTISSMEAEDAATYYC	HQFHRSPFTFGSGTKLEIK	56
SC16.31	DIVLTQSPLSLPVNIGDQASISC	KSTKSLLNSDGFTY	LDWYLQRPGQSPQFLIY	LVSNRFS	GVPDRFSGSGSGTDFTLKISRVEAEDLGVYYC	FQSNYLPLTFGAGTKLELR	58
SC16.34	SIVMTQTPKFLLVSAGDRVTITC	KASQSVSND	VAWYQQKPGQSPKLLIY	YASNRYS	GVPDRFTGSGYGTDFYFTISTVQAEDLAVYFC	QQDYSSPWTFGGGTKLEIK	60
SC16.35	DIQMTQTTSSLSASLGDRVTISC	RASQDISNY	LNWYQQKPDGTVKLLIY	YTSRLHS	GVPSRFSGSGSGTDYSLTISNLEQEDIATYFC	QQGNTLPYTFGGGTKLEIK	62
SC16.36	ETTVTQSPASLSVTTGEKVTIRC	ITTPDIDDD	MNWYQQKPGEPPNLLIS	EGNSLRP	GVPSRFSSSGYGTNFVFTIENTLSEDVADYYC	LQSDNMPFTFGSGTKLEIK	64

FIG. 11A

EP 3 095 797 A1

Protein Sequences of Exemplary DLL3 Modulator Light Chain Variable Regions

mAb	FR1	CDR1	FR2	CDR2	FR3	CDR3	SEQ ID NO.
SC16.38	QIVLTQSPAIMSASPGEKVTMTC	SASSSINY	MHWYQQKPGTSPKRWIY	DTSKLAS	GVPARFSGSGSGTSYSLTISSMEAEDAATYYC	HQRSTWTFGGGTKLEIK	66
SC16.41	DIQMTQTTSSLSASLGDRVTISC	RASQDVINY	LNWYQQKPDGTVKLLIY	YTSRLHS	GVPSRFSGSGSRTDYSLTISNLEPEDIATYYC	QQYSERPYTFGGGTKLEIKR	68
SC16.42	DVLMTQSPLSLSVSLGDQASISC	RSSQNIVHSDRYTY	LEWYLQKPGQSPKLLIY	GVSNRFS	GVPDRFSGSGSGTDFTLKISRVEAEDMGVYYC	FQGTHVPYTFGGGTKLEIK	70
SC16.45	EIQMTQSPSSMSASLGDRITITC	QATQDIVKN	LNWYQQKPGKPPSFLIY	YATELAE	GVPARFSGSGSGSDYSLTISNLESEDFADYHC	LQFYEFPFTFGAGTKLELK	72
SC16.47	DVVLTQSPLSLPVNIGDQASISC	KSTKSLLNSDGFTY	LDWYLQRPGQSPQFLIY	LVSNRFS	GVPDRFSGSGSGTDFTLKISRVEAEDLGVYYC	FQSNYLPLTFGAGTKLELR	74
SC16.49	DIKMTQSPSSMYASLGERVTITC	KASQDINSYL	SWFQQKPGKSPKTLIY	RANRLVD	GVPSRFSGSGSGQDYSLTITSLEYEDMGIYYC	LQYDEFPLTFGAGTKLELK	76
SC16.50	DIQMTQTTSSLSASLGDRVTISC	RASQDISNY	LNWYQQKPDGTVKLLIY	YTSRLHS	GVPSRFSGSGSGTDYSLTISNLEQEDIATYFC	QQGNTLRTFGGGTKLEIK	78
SC16.52	DIQMIQSPSSMFASLGDRVSLSC	RASQGIRGT	LDWYQQKPNGTIKLLIY	STSNLNS	GVPSRFSGSGSGSDYSLTISSLESEDFADYYC	LQRNAYPLTFGAGTKLELK	80
SC16.55	DIKMTQSPSSMYASLGERVTITC	KASQDINSY	LNWFQQKPGKSPKTLIY	RANRLVD	GVPSRFSGSGSGQDYSLTISSLEYEDMGIYYC	LQYDEFPYTFGGGTKLEIKR	82
SC16.56	SIVMTQTPKFLLVSAGDRVTITC	KASQSVSND	VVWYQQKPGQSPKLLIY	YASNRYT	GVPDRFAGSGYGTDFSFTISTVQAEDLAVYFC	QQDYTSPWTFGGGTKLEIR	84
SC16.57	DIVMTQSHKFMSISVGDRVSITC	KASQDVSIF	VAWYQQKPGQSPKLLIY	SASYRYT	GVPDRFTGSGSGTDFIFTISSVQAEDLAVYYC	QQHYGTPFTFGSGTKLKIR	86
SC16.58	DIQMTQSPASLSSSVGETVTITC	RASENIYSY	LAWYQQKQGKSPQLLVY	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGTYYC	QHHYDSPLTFGAGTKLELR	88
SC16.61	DIVMTQSTSSLAMSVGQKVTMSC	KSSQSLLNSSNQKNY	LAWYQQEPGQSPKLLVS	FASTRES	GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC	QQHYSIPLTFGAGTKLELK	90
SC16.62	DIKMTQSPSSMYASLGERVTITC	KASQDINSF	LSWFQRKPGKSPKTLIY	RANRLVD	GVPSRFTGSGSGQEFSLTISSLEYEDLGIYYC	LQYDEFPYTFGGGTKLEIKR	92
SC16.63	QIVLTQSPAIMSASPGEKVTMTC	SASSSVSY	MYWYQQKSGTSPKRWIY	DTSKLAS	GVPARFSGSGSGTSYSLTISSMEAEDAATYYC	QQWSSNPYTFGGGTKLEIK	94
SC16.65	QIVLTQSPALMSASPGEKVTMTC	SVTSSVSY	MYWYQQKPRSSPKPWIY	LTSNLAS	GVPARFSGSGSGTSYSLTISSVEAEDAATYYC	QQWRNNPFTFGSGTKVEIK	96
SC16.67	QAVVTQESALTTSPGETVTLTC	RSSTGAVTTSNY	ANWIQEKPDHLFTGLIG	GTNNRAP	GVPARFSGSLIGDKAALTITGAQTEDEAIYFC	GLWYSNHLVFGGGTKLTVL	98
SC16.68	ETTVTQSPAFLSVATGEKVTIRC	ITSTDIDDD	MNWYQQKPGEPPNVLIS	EGNTLRP	GVPSRFSSSGYGTDFVFTIENTLSEDVADYYC	LQSDNMPLTFGAGTKLELK	100
SC16.72	ENVLTQSPAIMSASLGEKVTMSC	RASSSVNY	MSWYQQKSDASPKLWIY	YTSNLAP	GVPARFSGSGSGNSYSLTISSMEGEDAATYYC	QQFTSSPYTFGGGTKLEIKR	102
SC16.73	DIQMTQSPSSLSASLGERVSLTC	RASQDIGYS	LNWLQQEPDGTIKRLIY	ATSSLDS	GVPKRFSGSRSGSDYSLTISSLESEDFVDYYC	LQYASSPWTFGGGTKLEIK	104
SC16.78	DIKMTQSPSSMYASLGERVTITC	KASQDINSY	LSWFQQKPGRSPKTLIY	RANRLVD	GVPSRFSGSGSGQDYSLTISSLDYEDMGIYYC	LQYDEFPFTFGSGTKLEIK	106
SC16.79	DIVMSQSPSSLAVSAGEKVTMSC	KSSQSLLNSRTRKNY	LAWYQQKPGQSPKLLIY	WASTRES	GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC	KQSYNLYTFGGGTKLKIKR	108
SC16.80	ETTVTQSPASLSMAIGEKVTIRC	ITSTDIDDD	MIWYQQKPGEPPKLLIS	EGNTLRP	GVPSRFSSSGYGTDFVFTIENMLSEDVADYYC	LKRDDLPYTFGGGTQVEIKR	110
SC16.81	QIVLTQSPAIMSASLGERVTLTC	TASSSVSSSY	LHWYQQKPGSSPKLWIY	STSNLAS	GVPTRFSGSGSGTSYSLRISSMEAEDAATYYC	HQYNRSPLTFGAGTKLELK	112
SC16.84	DIQMTQSPSSLSASLGGKVTITC	KASQDIKKY	IAWYQHKPGKGPRLLIH	YTSTLEP	GIPSRFSGSGSGRDYSFSISNLEPEDIATYYC	LQYDILWTFGGGTKLEIK	114
SC16.88	ENVLTQSPAIMAASLGQKVTMTC	SASSSVSSSY	LHWYQQKSGASPKPLIH	RTSNLAS	GVPARFSGSGSGTSYSLTISSVEAEDDATYYC	RQWSGYPWTFGGGTKLEIK	116

FIG. 11A (Cont.)

Protein Sequences of Exemplary DLL3 Modulator Light Chain Variable Regions

mAb	FR1	CDR1	FR2	CDR2	FR3	CDR3	SEQ ID NO.
SC16.101	QIVLTQSPAIMSASLGERVTMTC	TASSSVSSSY	LHWYQQKPGSSPKLWIY	STSNLAS	GVPARFSGSESGTSYSLTISNMEAEDAATYYC	HQYHRSPFTFGSGTKLEIK	118
SC16.103	DIVLTQSPASLAVSLGQRATISC	RASKSVSTSGYSY	MHWYQQKPGQPPKLLIY	LASNLES	GVPARFSGSGSGTDFTLNIHPVEEEDAATYYC	QHSRELPLTFGAGTKLELK	120
SC16.104	QIVLSQSPAILSASPGEKVTMTC	RASSSVSY	IHWYRQKPGSSPKPWIY	ATSNLAS	GVPARFSGSGSGTSYSLTISRVEAEDAATYYC	QQWSSNPPTFGAGTKLELK	122
SC16.105	DIVMTQSHKFMSTSVGDRVSIT	KASQDVGTA	VAWYQQKPGQSPKLLIY	WASIRHT	GVPDRFTGSGSGTDFTLTISNVQSEDLADYFC	QQYSSYPLTFGAGTKLELK	124
SC16.106	DIKMTQSPSSMYASLGERVTITC	KASQDINSY	LSWFQQKPGKSPKTLIY	RANRLVD	GVPSRFSGSGSGQDYSLTISSLEYEDMGIYYC	LQYDEFPFTFGSGTKLEIK	126
SC16.107	DIVMTQSHKFMSTSVGDRVSITC	KASQDVNTA	VGWYQQKPGQSPKLLIY	SASYRYT	GVPDRFTGSGSGTDFTFTISSVQAEDLAVYYC	QQHYSSPYTFGGGTKLEIKR	128
SC16.108	DIQMTQSPASLSASVGETVTITC	RASENIYSY	LAWYQQKQGKSPQLLVY	NAKTLAE	GVPSRFSGSRSGSQFSLKINSLQPEDFGSYYC	QHHYGTPYTFGGGTKLEIKR	130
SC16.109	QIVLTQSPAIMSASPGEKVTMTC	SASSSVSY	MYWYQQKPGSSPRLLIY	DTSNLAS	GVPVRFSGSGSGTSFSLTISRMEAEDTATYYC	QEWSGNPLTFGDGTKLELK	132
SC16.110	NIVMTQTPKFLLVSAGDRVTITC	KASQSVSND	VAWYQQKPGQSPKLLIY	YASNRYT	GVPDRFTGSGYGTDFTFTISTVQAEDLAVYFC	QQDYSSPPTFGGGTKLEIK	134
SC16.111	DIQMTQSPASLAASVGETVTITC	RASENIYYS	LAWYQQKQGKSPQLLIY	NANSLED	GVPSRFSGSGSGTQYSMKINSMQPEDTATYFC	KQTYDVPLTFGAGTKLELK	136
SC16.113	DVVMTQTPLTLSVTIGQPASISC	KSSQSLLDSDGTTY	LNWLLQRPGQSPKRLIY	LVSKLDS	GVPDRFTGSGSGTDFTLKISRVEAEDLGVYYC	WQGTHFPLTFGAGTKLELK	138
SC16.114	QIVLSQSPAILSASPGEKVTMTC	RASSSVSY	MHWYQQKPGSSPKPWIY	ATSNLAS	GVPARFSGSGSGTSYSLTISRVEAEDAATYYC	QQWSSNPYTFGGGTKLEIKR	140
SC16.115	DVVMTQTPLTLSVTIGQPASISC	KSSQSLLDSDGTTY	LNWLLQRPGQSPKRLIY	LVSKLDS	GVPDRFTGSGSGTDFTLKISRVEAEDLGVYYC	WQGTHFPLTFGAGTKLELK	142
SC16.116	DIVMTQSPSSLTVTAGEKVTMSC	TSSQSLLTSGNQKNY	LTWYQQKPGQPPKLLIY	WASTRES	GVPDRFTGSGSGTDFTLTISSLQAEDLAVYYC	QNDYSLTFGAGTKLELK	144
SC16.117	DIQMNQSPSSLSASLGDTITITC	HVSQNINVW	LSWYQQKPGNIPKLLIQ	KASNLHT	GVPSRFSGSGSGTGFTLTISSLQPEDIATYYC	QQGQSYPFTFGSGTKLEIK	146
SC16.118	DIVLTQSPASLAVSLGQRATISC	KASQSVDYDGDSY	LTWYQQKPGQPPKLLIY	AASNLES	GIPARFSGSGSGTDFTLNIHPVEEEDAATYYC	QQSNEDPYTFGGGTKLEIKR	148
SC16.120	DIVMSQSPSSLAVSVGEKVTMSC	KSSQSLLYSSTQKNY	LAWYQQKPGQSPKLLIY	WASTRES	GVPDRFTGSGSGTDFTLTISSVKAEDLAVYYC	QQYYSYPYTFGGGTKLEIKR	150
SC16.121	QIVLTQSPAIMSASPGEKVTITC	SASSSVSY	MHWFQQKPGTSPKLWIY	STSNLAS	GVPARFSGSGSGTSYSLTISRMEAEDAATYYC	QQRSSYPPTFGGGTKLEIKR	152
SC16.122	DIVMTQSQKFMSTSVGDRVSVTC	KASQNVGTN	VAWYQQKPGQSPKVLIY	SASYRYS	GVPDRFTGSGSGTDFTLTISNVQSEDLAEFFC	QQYNSYPLTFGGGTKLEIK	154
SC16.123	QIVLTQSPAIMSASLGERVTMTC	TASSSVSSSY	LHWYQQKPGSSPKLWIY	STSNLAS	GVPARFSGSGSGTSYSLTISSMETEDAATYYC	HQYHRSPFTFGSGTKLEIK	156
SC16.124	DIQMTQSPASQSASLGESVTITC	LASQTIGTW	LAWYQQKPGKSPQLLIS	AATSLAD	GVPSRFSGSGSGTKFSFKISSLQAEDFVSYYC	QQLYSTPWTFGGGTKLEIK	158
SC16.125	DIQMNQSPSSLSASLGDTITITC	HASQNINVW	LSWYQQKPGNIPKLLIY	KASILHT	GVPSRFSGSGSGTGFTLTISSLQPEDIATYSC	QQGQSYPYTFGGGTKLEIK	160

FIG. 11A (Cont.)

EP 3 095 797 A1

Protein Sequences of Exemplary DLL3 Modulator Light Chain Variable Regions

mAb	FR1	CDR1	FR2	CDR2	FR3	CDR3	SEQ ID NO.
SC16.126	DIQMNQSPSSLSASLGDTITITC	HASQNINVW	LSWYQQKPGNIPKLLIY	KASNLHT	GVPSRFSGSGSGTGFTLTISSLQPEDIATYYC	QQGQSYPFTFGSGTKLEIK	162
SC16.129	DIQMTQSPASQSASLGESVTITC	LASQTIGTW	LAWYQQKPGKSPQLLIY	AATSLAD	GVPSRFSGSGSGTKFSFKISSLQAEDFVSYYC	QQLYSTPYTFGGGTKLEIKR	164
SC16.130	DIQLTQSPASLSASVGETVTITC	RASGSIHNY	LAWYQQKQGKSPQLLVY	NAKTLVD	GVPSRFSGSGSGTQYSLKINSLQPEDFGYYYC	QHFWTTPWTFGGGTKLEIK	166
SC16.131	DIQMNQSPSSLSASLGDTITITC	HVSQNINVW	LSWYQQKPGNIPKLLIQ	KASNLHT	GVPSRFSGSGSGTGFTLTISSLQPEDIATYYC	QQGQSYPFTFGSGTKLEIK	168
SC16.132	DIQMTQSPASQSASLGESVTITC	LASQTIGTW	LAWYQQKPGKSPQLLIY	AATSLAD	GVPSRFSGSGSGTKFSFKISSLQAEDFVSYYC	QQLYSTPWTFGGGTKLEIK	170
SC16.133	SIVMTQTPKFLLVSAGDRVTITC	KASQSVSND	VAWYQQKPGQSPKLLIY	CASNRYT	GVPDRFTGSGYGTDFTFTISTVQAEDLAVYFC	QQDYSSPLTFGAGTKLELK	172
SC16.134	DIVLTQSPASLAVSLGQRATISC	KASQSVDHAGDSY	MNWYQQKPGQPPKLLIY	AASNLES	GIPARFSGSGSGTDFTLNIHPVEEEDAATYYC	QQSNEDPYTFGGGTKLEIKR	174
SC16.135	DIKMTQSPSSMYASLGERVTITC	KASQDINRY	LSWFQQKPGKSPKTLIY	RANRLVD	GVPSRFSGSGSGQDYSLTISSLEYEDMGIYYC	LQYDEFPFTFGSGTKLEIK	176
SC16.136	DIQMTQSPASLSASVGETVTITC	RASGNIHNY	LAWYQQKQGKSPHLLVY	NAKTLAD	GVPSRFSGSGSGTQYSLKINSLQPEDFGSYYC	QHFWSTPWTFGGGTKLEIK	178
SC16.137	QIVLTQSPAIMSASLGEEITLTC	SASSSVSY	MHWYQQKSGTSPKLLIY	STSNLAS	GVPSRFSGSGSGTFYSLTISSVEAEDAADYYC	HQWSSYHTFGGGTKLEIKR	180
SC16.138	DIQMTQSPASQSASLGESVTITC	LASQTIGTW	LAWYQQKPGKSPQLLIY	SATSLAD	GVPSRFSGSGSGTKFSFKISSLQAEDFVSYYC	QQLYSTPWTFGGGTKLEIK	182
SC16.139	DIVMTQSHKFMSTSVGDRVSITC	KASQDVNTA	VGWYQQKPGQSPKLLIY	SASYRYT	GVPDRFTGSGSGTDFTFTISSVQAEDLAVYYC	QQHYSSPYTFGGGTKLEIK	184
SC16.140	DIVLTQSLASLAVSLGQRATISC	RASKSVSTSGYSY	MHWYQQKPGQPPKLLIY	LASNLES	GVPARFSGSGSGTDFTLNIHPVEDEDAATYYC	QHSRELPFTFGGGTKLEIKR	186
SC16.141	DIKMTQSPSSMYASLGERVTITC	KASQDINSY	LSWFQQKPGKSPKTLIY	RANRLVD	GVPSRFSGSGSGQDYSLTISSLEYEDMGIYYC	LQYDEFPFTFGSGTKLEIK	188
SC16.142	DIKMTQSPSSMYASLGERVTITC	KASQDINNY	LSWFQQKPGKSPKTLIY	RANRLVD	GVPSRFSGSGSGQDYSLTISSLEYEDMGIYYC	LQYDEFPYTFGGGTKLEIKR	190
SC16.143	DVLMTQTPLSLPVSLGDQASISC	RSSQSIVHSNGNTY	LEWYLQKPGQSPKLLIY	KVSNRFS	GVPDRFSGSGSGTDFTLKISRVEAEDLGVYYC	FQGSHVPLTFGAGTKLELK	192
SC16.144	SIVMTQTPKFLLVSAGDRVTITC	KASQSVSND	VGWYQQKPGQSPKLLIY	YASNRYN	GVPDRFTGSGYGTDFTFTISTVQAEDLAVYFC	QQDYSSPWTFGGGTKLEIK	194
SC16.147	DIQMTQTASSLSASLGDRVTISC	RASQDINNY	LNWYQQKPDGTVKLLIY	YTSRLHS	GVPSRFSGSGSGTDYSLTISILEQEDIATYFC	QQGDTLPWTFGGGTKLEIK	196
SC16.148	QIVLTQSPAIMSASPGEKVTMTC	SASSSVSY	MYWYQQKPGSSPRLLIY	DTSNLAS	GVPVRFSGSGSGTSYSLTISRMEAEDTATYYC	QEWSNNPLTFGDGTKLELK	198
SC16.149	DIQMNQSPSSLSASLGDTITITC	HASQNINVW	LSWYQQKPGNIPKLLIY	KASHLHT	GVPSRLSGSGSGTGFTLTISSLQPEDIATYYC	QQGQSYPFTFGSGTTLEIK	200
SC16.150	DIVMSQSPSSLTVSVGEKVTMSC	MSSQSLLYSSTQKNY	LAWYQQKPGQSPKLLIY	WASTRES	GVPDRFTGSGSGTDFTLTISSVKAEDLAVYYC	QQYYSYPYTFGGGTKLEIKR	202

FIG. 11A (Cont.)

EP 3 095 797 A1

Protein Sequences of Exemplary Humanized DLL3 Modulator Light Chain Variable Regions

hmAb	FR1	CDR1	FR2	CDR2	FR3	CDR3	SEQ ID NO.
hSC16.13	DIQMTQSPSSLSASVGDRVTITC	SASSSVSY	MYWYQQKPGKAPKLLIY	LTSNLAS	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	QQWRSNPFTFGQGTKLEIKR	204
hSC16.15	AIQLTQSPSSLSASVGDRVTITC	RASENIYYN	LAWYQQKPGKAPKLLIY	TANSLED	GVPSRFSGSGSGTDFTLTISSLQPEDFATYFC	KQAYDVPPTFGGGTKLEIK	206
hSC16.25	EIVLTQSPDFQSVTPKEKVTITC	SASSSVSY	MHWYQQKPDQSPKLLIK	DSSKLAS	GVPSRFSGSGSGTDFTLTINSLEAEDAATYYC	QQWSSNPLTFGQGTKLEIK	208
hSC16.34	DIQMTQSPSSLSASVGDRVTITC	KASQSVSND	VAWYQQKPGKVPKLLIY	YASNRYS	GVPSRFSGSGSGTDFTLTISSLQPEDVATYFC	QQDYSSPWTFGGGTKVEIK	210
hSC16.56	EIVMTQSPATLSVSPGERATLSC	KASQSVSND	VVWYQQKPGQAPRLLIY	YASNRYT	GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC	QQDYTSPWTFGQGTKLEIKR	212

FIG. 11A (Cont.)

Protein Sequences of Exemplary DLL3 Modulator Heavy Chain Variable Regions

mAb	FR1	CDR1	FR2	CDR2	FR3	CDR3	SEQ ID NO.
SC16.3	QVTLKESGPGILQPSQTLSLTCSFS	GFSLSTSGMG	VGWIRQPSGKGLEWLAH	IWWDDVK	RYNPALKSRLTISKDTSSSQVFLKIASVDTADTATYYC	ARIADYGGDYYAMDYWGQGTSVTVSS	21
SC16.4	QIQLVQSGPELKKPGETVKISCKAS	GYTFTDYS	MHWVKQAPGKGLKWMGW	INTETGEP	GYADDFKGRFAFSLETSASTAYLQINNLKNEDTATYFC	ARYDGYAMDYWGQGTSVTVSS	23
SC16.5	QVTLKESGPGILQPSQTLSLTCSFS	GFSLSTSGMG	VGWIRQPSGEGLEWLAD	IWWDDNK	YYNPSLKSRLTISKDTSSNQVFLKITSVDTADTATYYC	ARRVNYVYDPYYAMDYWGQGTSVTVSS	25
SC16.7	EVQLQQSGPELVKPGASVKISCKAS	GYSFTGYK	MHWVKQSHVKSLEWIGR	INPYNGAT	SYNQNFKDKATLTVDKSSSTAYMDLHSLTSEDSAVYFC	ARGDYRYDWFAYWGQGTLVTVSA	27
SC16.8	QAQLQQSGAELVRPGTSVKVSCKAS	GYAFTNYL	IEWVKQRPGQGLEWIGV	INPGTGGT	NYNENFKGKATLTADKSSSTAYMQLSSLTSDDSAVYFC	ARSPYDYHEGAMDYWGQGTSVTVSS	29
SC16.10	QVTLKESGPGILQSSQTLSLTCSFS	GFSLSTSGMG	VGWIRQPSGKGLEWLAH	IWWDDVK	RYNPVLKSRLTISKDTSSSQVFLKIASVDTADTATYYC	ARLVDDLYYFDYWGQGTTLTVSS	31
SC16.11	QIQLVQSGPELKKPGETVKISCKAS	GYTFTDYS	MHWVKQAPGKGLKWMGW	INTETVEP	TYADDFMGRFAFSLETSASTAFLQINNLENEDTATYFC	ARFGSYAMDYWGQGTSVTVSS	33
SC16.13	QVTLKESGPGILQPSQTLSLTCSFS	GFSLSTSGMG	VGWIRQPSGKGLEWLAH	IWWDDVK	RYNPALKSRLTISKDTSSSQVFLKIASVDTADTATYYC	ARIVSFDNDVVSAMDYWGQGTSVTVSS	35
SC16.15	QVQLQQSGAELAKPGASVKMSCKA	SGYTFTRYW	IHWIKQRPGQGLEWIGY	INPTTVYT	EFNQNFKDKATLTADKSSTTASMQLSSLTSEDSAVYYC	ARGGSNFFDYWGQGTTLTVSS	37
SC16.18	EVKLEESGGGLVQPGESMKLSCAAS	GFTFSDAW	MDWVRQSPEKGLEWVAE	IRNKANNHAT	YYAESVKGKFTISRDDSKSRVYLQMNNLRAADTGIYYC	TAYSNFAYWGQGTLVTVST	39
SC16.19	EVQLQQSGAELVRPGASVKLSCTAS	GFNIKDSL	LHWVKQRPEKGLEWIGW	IDPEDGET	KYAPNFQDKATITTDSSSNTAYLQLSLTSVDTAIYYC	AYGNYVRHFDYWGQGTTLTVSS	41
SC16.20	QVQLQQSGTELVRPGTSVRVSCKA	SGYAFGNHL	IEWVKQRPGQGLEWIGV	INPGTGGT	HYNEKFKDKARLTADKSSNTAYMHLNSLTSDDSAVYFC	ARSPYDYHEGAMDYWGQGTSVTVSS	43
SC16.21	QVQLQQSGPELVKPGASVKISCKAS	GYAFSSSW	MNWVKQRPGKGLEWIGR	IYPGDGDT	NYNGKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYFC	AMGIYNYDGSRYYSMDYWGQGTSVTVSS	45
SC16.22	QVQLQQPGAELVKPGASVKLSCKAS	GYTFTTYW	MHWVKQRPGQGLEWIGE	IDPSDSYT	YYNQKFKGKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGDYGNPYAMDYWGQGSSVTVSS	47
SC16.23	QVTLKESGPGILQPSQTLSLTCSFS	GFSLSTSNTG	IGWIRQPSGTGLEWLAH	IWWNDDK	YYNPSLKSRLTISKETSNNQVFLKITNVDTADTASYFC	VQIGRDYSNYAWYFDVWGAGTTVTVSS	49
SC16.25	QVTLKESGPGILQPSQTLSLTCSFS	GFSLSTSGMG	VGWIRQPSGEGLEWLTD	IWWDDNK	YYNPSLKSRLTISKDTSSNQVFLNITSVDTADTATYYC	ARRVNYYYDPYYAMDYWGQGTSVTVSS	51
SC16.26	QIQLVQSGPELKKPGETVKISCKAS	GYSFTDYS	MHWVKQAPGKGLKWMGW	INTETVEPT	YADDFMGRFAFSLETSASTAFLQINNLENEDTATYFC	ARFGSYAMDYWGQGTS	53
SC16.29	QVQLQQSGAELARPGASVKLSCKAS	GYTFTDQY	INWVKQRTGQGLEWIGE	IYPGRGNT	YYNEKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYFC	AREDGGYDDAWFAYWGQGTLVTVSA	55
SC16.30	QVTLKESGPGILQPSQTLSLTCSFS	GFSLSTSGMG	VGWIRQPSGKGLEWLAH	IWWDDVK	RYKPALKSRLTVSKDTSSNQVFLKIATVDAADTGTYYC	ARIVDGHPPFAYWGQGTLVTVSA	57
SC16.31	EVQLQQSGPELVKPGASVKISCKAS	GYSFSRFY	MHWVKQSPENSLEWGE	INPSTGGT	ISYNQKFKGKATLTVDKSSSTAYMQLKSLTSEESAVYYC	TRGYGSNWYFDVWGAGTTVTVST	59
SC16.34	QIQLVQSGPELKRPGETVKISCKAS	GYTFTNYG	MNWVKQAPGKGLKWMGW	INTYTGDP	TYADDFKGRFAFSLETSASTAYLQINNLKNEDTATYFC	ARIGGNSPSDYWGQGTSLTVSS	61
SC16.35	SDVQLQESGPGLVKPSQSLSLTCTVT	GYSITSDYA	WNWIRQFPGNKLEWMGY	ISYSGST	SYNPSLKSRISITRDTSKNQFFLQLNSVTTEDTATYYC	ARFYYGSSYAMDYWGQGTSVTVSS	63
SC16.36	QVQLQQSGAELAKPGASVKMSCKAS	GYTFTTYW	MHWVKQRPGQGLEWIGY	INPSSGYT	EYNQKFKDKATLTADKSSSTAYMQLSSLTSEDSVYYC	ARKGSNRGFAYWGQGTLVTVS	65
SC16.38	EVQLQQSGAELVKPGASVKLSCTVS	GFNIKDTY	IHWVKQRPEQGLEWIGR	IDPANGNT	KYDPKFQGKATITADTSSNTAYLQLSSLTSEDTAVYYC	ARPTGYFEYWGQGTTLTVSS	67

FIG. 11B

EP 3 095 797 A1

Protein Sequences of Exemplary DLL3 Modulator Heavy Chain Variable Regions

mAb	FR1	CDR1	FR2	CDR2	FR3	CDR3	SEQ ID NO.
SC16.41	EVKLEESGGGLVQFGGSMKLSCAAS	GFTFSDAW	MDWVRQSPEKGLEWVAE	IRNKANNHAT	YYPESVKGRFTISRDDSKSRVYLQMNNLRAEDTGIYYC	TGYSSFAYWGQGTLVTVSA	69
SC16.42	QIQLVQSGPELKKPGETVKISCKAS	GYTFTTAG	MQWVQKMPGKGFKWIGW	INTHSGEP	KYADDFKGRFAFSLETSASTAYLQISNLKDEDTATFFC	APLWSDSSFAYWGQGTLVTVSA	71
SC16.45	QVQLQQSGADLVRPGTSVKVSCKAS	GYSFTNYL	IEWVKQRPGQGLEWIGV	INPGSGGT	HYNEKFKDKAVLTADKSSTTAHMQLSSLTSDDSAVYFC	ARSPYDYNDGAMDYWGQGTSVTVSS	73
SC16.47	EVQLQQSGPELVKPGASVKISCKAS	GYSFSRFY	MHWVKQSPENSLEWIGE	INPSTGGT	SYNQKFKGKATLTVDKSSSTAYMQLKSLTSEESAVYYC	TRGYGSNCYFDVWGAGTTVTVST	75
SC16.49	QVQLQQSGPELVKPGTLVKISCKAS	GYTFTSYD	INWVKQRPGQGLEWIGW	IYPGDGNT	KYSEKFKGKATLTADKSSSTAYMQLTSLTSENSAVYFC	ARDYDYPFAYWGQGTLVTVSA	77
SC16.50	EVQLVECGGCLVKPGGYLKLSCAAS	GFTFSSYA	MSWVRQSPEKRLEWVAE	ISIGGSYT	YYPDTVTGRFTISRDNAKNTLYLEMSSLRSEDTAMYYC	AREGYDYDVRAMDYWGQGTSVTVSS	79
SC16.52	QVQLKESGPGLVAPSQSLSITCAVS	GFSLTSFA	IHWFRKPPGKGLEWLGV	IWTGGTT	NYNSALMSRLSISKDNSKSQVFLKMNSLQTDDTAMYYC	ARDDYDNNYAMDYWGQGTSVTVSS	81
SC16.55	EVQLVESGGGLVQPKGSLKLSCAVS	AFTFTTYA	MNWVRQAPGKGLEWVAR	IRNKSNNYAT	YYADSVKDRFTISRDDSQSMLYLQMNNLKIEDTAMYYC	VFYYDYVYWGQGTLVTVSA	83
SC16.56	QIQLVQSGPELKKPGETVKISCKAS	GYTFTNYG	MNWVKQAPGKGLKWMAW	INTYTGEP	TYADDFKGRFAFSLETSASTASLQINNLKNEDTATYFC	ARIGDSSPSDYWGQGTTLTVSS	85
SC16.57	EVKLVESGGDLVKPGGSLKLSCAAS	GFAFSSYD	MSWVRQTPEKRLEWVAT	ISSGGSYT	YYPDSVKGRFTISRDNVRDTLYLQMSSLRSEDTALYYC	ARQAIGTYFDYWGQGTTLTVSS	87
SC16.58	DVQLVESGGGLVQPGGSRKLSCAAS	GFTFSSFG	MHWVRQAPEKGLEWVAY	ISSGSSNI	YYADTVKGRFTISRDNPKNTLFLQMTSLRSEDTAMYYC	ARGYYGNYDAMDYWGQGTSVTVSS	89
SC16.61	EVLLQRSGPDLVKPGASVTIPCKAS	GYTFTDYN	MDWVKQSHGKSLEWIGN	INTYNGGT	IYNQKFKGKATLTVDKPSSTAYMELRSLTSEDTAVYYC	ARRLRYGGHYFDYWGQGTALTVSS	91
SC16.62	EVMLVESGGGDLVKPGGSLKLSCAAS	GFTFSSYA	MSWVRQTPEKRLEWVAY	ISGGGDHI	YYPDSVRGRFTISRDNAKDTLYLQMSSLRSEDTALYDC	ARVRDWYFDVWGAGTTVTVSS	93
SC16.63	QVQLQQSGTELLRPGASVKISCKAT	GYTFSSYW	MEWVKQRPGHGLEWIGE	ILPGSGTT	QYNEKFKGKATFTADTSSNTAYMHLSSLTSEDSAVYYC	ARGTNSLWGQGTLVTVSA	95
SC16.65	QVTLKESGPGILQPSQTLSLTCSFS	GFSLSTSGMG	VGWIRQPSGKGLEWLAL	WWDDVK	RYNPALKSRLTISKDASSSQVFLKIASVDTADTATYYC	ARIASYDYDVVYAMDYWGQGTSVSVSS	97
SC16.67	EVQLVETGGGLVQPKGSLKLSCAVS	AFTFTTYA	MNWVRQAPGKGLEWVAR	IRNKSNNYAT	YYADSVKDRFTISRDDSQSMLYLQMNNLKIEDTAMYYC	VFYYDYVYWGQGTLVTVSA	99
SC16.68	QVQLQQPGAELVKPGASVKMSCKAS	GYTFTNYN	MHWVKQTPGQGLEWIGA	IFPGNGGT	SYNQKFKGKATLTADKSSSTAYMQLTSLTSGDSAVYYC	ARWGYGSGLYAMDYWGQGTSVTVSS	101
SC16.72	EVQLQQSGPELVKPGASVKMSCKAS	GYTFTSYV	MHWVKQKPGQGLEWIGY	INPYNDGT	KYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYC	ARLRSRAMDYWGQGTSVTVSS	103
SC16.73	QVQLQQSGAELMKPGASVKISCKAN	GYTFSSYW	IEWLRQRPGHGLEWIGE	ILPGSDNS	NYNEKFKGKATFTADTSSNTAYMQLSSLTSEESAVYYC	TRGLRRDGSYYYVMEHWGQGTSVTVSS	105
SC16.78	EVKLVESGGGLVKPGGSLKLSCAAS	GFTFGRYV	MSWVRQTPEKKLEWVAS	ITSGGTT	YYPDSVKGRFTISRDNARNILYLQMSSLRSEDTAMYYC	ARVYYHYDDIFAYWGQGTLVTVSA	107
SC16.79	EVQLQQSGPELVKPGASVKISCKTS	GYTFTEYT	MHWVKQSHGKSLEWIGG	INPNNGGT	SYNQKFKGKATLTVDKSSSTAYMELRSLTSEDSAVYYC	ARGPAWFAYWGQGTLVTVSA	109
SC16.80	EVQLQQSGPELVKPGGSKKISCKAS	GYSFTGYS	MNWVKQSHGKNLEWIGL	INPYSGGT	IYNQKFKGKATLTVDKSSSTAYMELLSLTSEDSAVYYC	ARRSDYPLVYWGQGTLVTVSA	111
SC16.81	QVQLKESGPVLVAPSQSLSITCTVS	GFSLTSYG	VHWVRQPPGKGLEWLGV	IWAGGST	NYNSALMSRLSISKDNSKSQVFLKMNSLQTDDTAMYYC	AKQGNFYAMDYWGQGTSVTVSS	113
SC16.84	EVQLQQSGPELVKPGASMKISCKAS	GYSFTGYT	MNWVKQSHGKNLEWIGL	INPYNGGT	TYNQKFKGKATLTVDKSSSTAYMELLSLTSEDSAVYYC	ALGYYGNYRRYFDVWGAGTTVTVSS	115
SC16.88	QVQLQQSGAELARPGASVKLSCKAS	GYTCTSYW	MQWVKQRPGQGLEWIGA	IYPGDGDT	RYTQKFKGKATLTADKSSSTAYMQLSSLASEDSAVYYC	ARGRRTEAWFAYWGQGTLVTVSA	117

FIG. 11B (Cont.)

EP 3 095 797 A1

Protein Sequences of Exemplary DLL3 Modulator Heavy Chain Variable Regions

mAb	FR1	CDR1	FR2	CDR2	FR3	CDR3	SEQ ID NO.
SC16.101	QVTLKESGPGILQPSQTLSLTCSFS	GFSLSTSGMG	VGWIRQPSGKGLEWLAH	IWWDDVK	RYNPALKSRLTISKDASSSQVFLKIASVDTAETATYYC	AHILDRAYYFDYWGQGTTLTVTS	119
SC16.103	QVTLKESGPGILKPSQTLSLTCSFS	GFSLSTSGM	IGWIRQPSGKGLEWLAH	IWWDDDK	YYNPSLKSQLTISKDSSRNQVFLKITSVDTADTATYYC	ARRGTAYYFDYWGQGTTLTVSS	121
SC16.104	QVQLKESGPDLVQPSQTLSLTCTVS	GFSLTFYG	VHWVRQPPGKGLEWVGT	MGWDDKK	YYNSALKSRLSISRDTSKNQVFLKLSSLQTEDTAMYYC	TRGGTGFDYWGQGTTLTVSS	123
SC16.105	QVQLQQPGAELVKPGASVKLSCKAS	GYTFTSYW	MHWVKQRPGQGLEWIGV	INPSNGRT	NYNEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARRRELGTLYAMDYWGQGTSVTVSS	125
SC16.106	QVQLKQSGPGLVAPSQSLFITCTVS	GFSLTSYE	INWVRQPPGKGLEWLGV	IWTGGST	NYNSALISRLSISKDNSKSLVFLKMNSLQTDDTAIYYC	VRGVYAMDYWGQGTSVTVSS	127
SC16.107	EVQLQQSGPELVKPGASVKMSCKAS	GYTFTNYV	MHWVKQKPGQGLEWIGY	INPYNDGT	KYNEKFKGKATLTSDKSSTTAYMALSSLTSEDSAVYYC	AVAYYSNWGFAYWGQGTLVTVSA	129
SC16.108	QVQLEESGAELARPGASVKLSCKAS	GYSYW	MQWIKQRPGQGLEWIGA	IYPGNGDT	RYTQKFKGKATLTADKSSSTAYMQLSSLASEDSAVYYC	ARSPAYYRYGEGYFDYWGQGTTLTVSS	131
SC16.109	QIQLVQSGPELKKPGETVKISCKAS	GYTFTNYG	MNWVKQAPGKGLKWMGW	INTYTGEP	AYADDFKGRFAFSLETSASAAYLQINNLKNEDTATFFC	ANMRPTRGFAYWGQGTLGTVSA	133
SC16.110	EVQLQQSGPGLVRTGASVKISCKAS	GYSFTGYY	MHWVKQSHGKSLEWIGY	ISCYNGAT	TYNQNFKGKATFIVDTSSSTAYMQFNSLTSEDSAVYYC	ARSDGGHAMDYWGQGTSVTVSS	135
SC16.111	EVQLQQSGPELEKPGASVKISCKAS	GYSFTGYN	MNWVKQSNGKSLEWIGN	IDPYYGGS	SYKQKFEGKATLTVDKSSSTAYMQLKSLTSEDSAVYYC	ARGGSNFFDYWGQGTTLTVSS	137
SC16.113	DVKLVESGGGLVKPGGSLKLSCAAS	GFTFSSYT	MSWVRQTPEKRLEWVAT	ISSGGSYP	YYPDSVKGRFTISRDNAKNTLYLQMSSLKSEDTAMYYC	TRDVYDGYSYWGQGTTLTVSS	139
SC16.114	EVQLQQSGAELVKPGASVKLSCTAS	GFNIKDTY	IHWVKQRPEQGLEWIGR	IDPANGNT	KYDPKFQGKATITPDTSSNTAYLQLSSLTSEDTAVYYC	ARSWRNYGSSPWYFDVWGAGTTVTVSS	141
SC16.115	DVKLVESGGGLVKPGGSLKLSCAAS	GFTFSSYT	MSWVRQTPEKRLEWVAT	ISSGGSYP	YYPDSVKGRFTISRDNAKNTLYLQMSSLKSEDTAMYYC	TRDVYDGYSYWGQGTTLTVSS	143
SC16.116	QVQLKQSGPGRVQPSQSLSITCTVS	GFSLTSNGV	VHWVRQSPGKGLEWLGV	LWSGGST	DYNAAFISRLSISKDNYKSQVFFKMNSLQANDTAIYYC	ARNNNRYGAMDYWGQGTSVTVSS	145
SC16.117	QVQLKESGPGLVAPSQSLSIPCTVS	GFSLTNYG	VHWVRQPPGKGLEWLGV	IWAGGIT	NYNSALMSRLSISEDNSKSQVFLKMNSLQTDDTAMYYC	ARNLGPYAMDYWGQGTSVTVSS	147
SC16.118	EVQLQQSGPDLVKPGASVKISCKAS	GYSFTGYY	MHWVKQSHGKSLEWIGR	VNPNNGGT	SYNQKFKGKAILTADKSSSTAYMELRSLTSEDSAVYYC	ARGSYDYAEGWGQGTLVTVSA	149
SC16.120	EIQLQQSGPELVKPGASVKVSCKAS	GYAFTSYN	MYWVMQSHGKSLEWIGY	VDPYNGGT	SYNQKFKGKATLTVDKSSSTAYMHLNSLTSEDSAVYYC	ARENYRYFDYWGQGTTLTVSS	151
SC16.121	EVQLVESGGGLVQPKGSLKLSCAAS	GFTFNTYA	MNWVRQAPGKGLEWVARR	IKSNNYAT	YYADSVKDRFTISRDDSQNMLYLQMNNLKTEDTAVYYC	VRQGYSYDWGPWFAYWGQGTLVTVSA	153
SC16.122	EVQLVESGGGLVKPGGSLKLSCAAS	GFTFSDYY	MFWVRQTPEKRLEWVAT	ISDGGSY	TYFPDSVKGRFTISRDNAQNNLYLQMSSLKSEDTAMYYC	ARAGTLYAMDYWGQGTSVTVSS	155
SC16.123	QVALKESGPGILQPSQTLSLTCSFS	GFSLSTSGMG	VGWIRQPSGKGLEWLAH	IWWDDVK	RYNPALKSRLTISKDTSSSQVFLKIASVDTADTATYYC	ARMEDYGSSSYFDFWGHGTTLTVSS	157
SC16.124	EVQLQQSGPELVKPGASVKMSCKAS	GYTFTSYV	MHWVKQKPGQGLEWIGY	INPYNDGT	KYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYC	ARGALYYGNYLGYFDVWGAGTTVTVSS	159
SC16.125	SDVQLQESGPDLVKPSQSLSLTCTVT	GYSITSGYS	WHWIRQFPGNKLEWMGY	IHYSGST	NYNPSLKSRISITRDTSKNQFFLQFKSVTTEDSATYYC	ALEGNYDGFAYWGQGTLVTVS	161

FIG. 11B (Cont.)

EP 3 095 797 A1

Protein Sequences of Exemplary DLL3 Modulator Heavy Chain Variable Regions

mAb	FR1	CDR1	FR2	CDR2	FR3	CDR3	SEQ ID NO.
SC16.126	QVQMKESGPGLVAPSQSLSITCTVS	GSSLTNYG	VHWVRQPPGKGLEWLGV	IWAGGST	NYNSALMSRLSISKDNSKSQVFLKMNSLQTDDTAMYYC	ARDWEGWFAYWGQGTLVTVSA	163
SC16.129	QVQLKESGPGLVAPSQSLSITCTVS	SGFSLTDYG	VSWIRQPPGKGLEWLGV	IWGGGST	YYNSALKSRLSISKDNSKSQVFLELNSLQTDDTAIYYC	AKHYGHYAAYWGQGTLVTVSA	165
SC16.130	EVQLQQSGPELVKPGASVKMSCKAS	GYTFTSYV	MHWVKQKPGQGLEWIGY	INPYNDGT	EYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYC	ARGVYDGYSYFDYWGQGTTLTVSS	167
SC16.131	QVQLKESGPGLVAPSQSLSITCTVS	GFSLTNYGV	VHWVRQPPGKGLEWLGV	IWA6GIT	NYNSALMSRLSISEDNSKSQVFLKMNSLQTDDTAMYYC	ARNLGPYAMDYWGQGTSVTVSS	169
SC16.132	QVQLKESGPGLVAPSQSLSITCTVS	GFSLTDYG	VSWIRQPPGKGLEWLGV	VWGGGST	YYNSALKSRLSITKDNSKSQVFLKMNSLQTDDTAMYYC	AKQRGQYGAYWGQGTLVTVSA	171
SC16.133	QVQLKESGPGLVAPSQSLSITCTVS	GFSLTNYA	VHWVRQSPGKGLEWLGV	IWSDGST	DYNAAFISRLSISKDNSKSQVFFKMNSLQADDTAMYYC	ARKKGGWFPWFAYWGQGTLVTVSA	173
SC16.134	EVQLQQSGPDLVKPGASVKISCKAS	GYSFTGYY	MHWVKQSHGKRLEWIGR	VNPNNGGT	NYNQKFKGKAILTVDKSSSTAYMELRSLTSEDSAVYYC	ARGSYDNAEGWGQGTLVTVSA	175
SC16.135	QVQLQQSGAELVRPGTSVKVSCKAS	GYAFTNYL	IEWVKQRPGQGLEWIGV	INPGSGGT	NSNEKFKAKATLTADKSSSTAYMQLSSLTSADSAVYFC	ARSDYDYAFYAMDYWGQGTSVTVSS	177
SC16.136	EFQLQQSGPELVKPGASVKMSCKAS	GYTFTSYV	MHWVKQKPGQGLEWIGY	INPYNDGT	KYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYC	ARDRSGYEDYYGMDYWGQGTSVTVSS	179
SC16.137	EVQLVESGGDLVKPGGSLKLSCAAS	GFTFSSYG	MSWVRQTPDKRLEWVAT	ISSGGSYT	YYPDSVKGRFTISRDNAKNTLYLQMSSLKSEDTAMYYC	ARRRADAMDYWGQGTSVTVSS	181
SC16.138	QVQLKESGPGLVAPSQSLSITCTVS	GFSLTDYG	VSWIRQPPGKGLEWLGV	VWGGGST	YYNSALKSRLSISKDNSKSQVFLKMNSLQTDDTAMYYC	AKQRGQYGAYWGQGTLVTVSA	183
SC16.139	EVQLQQSGPELVKPGASVKMSCKAS	GYTFTNYV	MHWVKQKPGQGLEWIGY	INPYNDGT	KYNEKFKGKATLTSDKSSTTAYMALSSLTSEDSAVYY	AVAYYSNWGFAYWGQGTLVTVSA	185
SC16.140	QVQLQQSGPELVRPGASVKMSCKAS	GYTFTSYW	MHWVKQRPGQGLEWIGM	IDPSNSET	RLNQKFKDKATLNVDKSSNTAYMQLSSLTSEDSAVYYC	AVMDYYFDYWGQGTTLTVSS	187
SC16.141	QVQLKQSGPGLVAPSQSLFITCTVS	GFSLTSYE	INWVRQPPGKGLEWLGV	IWTGGST	NYNSALISRLSISKDNSKSLVFLKMNSLQTDDTAIYYC	VRGVYAMDYWGQGTSVTVSS	189
SC16.142	EVQLQQSGPELVKPGASVKISCKAS	GYTFTDYN	MHWVKQSHGKSLEWIGF	FYPYNGNT	VYSQKFKSKATLTVDNSSSTAYMELRSLTSEDSAVYYC	ARLNWEGYWGQGTTLTVSS	191
SC16.143	QVQLQQSGPELVKPGASVRISCKAS	GYTFTSYY	IHWVKQRPGQGLEWIGW	IYPGNGNT	KYNEKFKGKATLTADKSSSTAYMQISSLTSEDSAVYFC	ARERWLLLWFAYWGQGTLVTVSA	193
SC16.144	QIQLVQSGPELKKPGETVKISCKAS	GYTFTNYG	MNWVKQAPGKGLKWVGW	INTYTGEP	TYADDFKGRFAFSLETSASTAYLQIDNLKNEDTATYFC	ARVGDYVGFDYWGQGTTLTVSS	195
SC16.147	QIQLVQSGPELTKPGETVKISCKAS	GYTFTDYS	LHWVKQALGKGLKWMGW	INTETGEP	AYADDFKGRFAFSLETSASTAYLQINDLKNEDTTTYFC	GIYDGYAMDYWGQGTSVTVSS	197
SC16.148	QIQLVQSGPELKKPGETVKISCKAS	GYTLTNYG	MNWVKQAPGKGLKWMGW	INTYTGEP	TYADDFKGRFAFSLETSARIVYLQINNLKNEDTATYFC	AKYEAHEGFVYWGQGTLVTVSA	199
SC16.149	QVQLKESGPGLVAPSQSLSITCAVS	GFSLTSFG	VHWVRQPPGKGLEWLGV	IWAGGSTN	YYSALMSRLSISIDNSKSQVFLKMNSLQTDDTAMYYC	ARDWEGWFAYWGQGTLVTVSA	201
SC16.150	EIQLQQSGPELVKPGASVKVSCKAS	GYAFTSYN	MYWVSQSHGKSLEWIGY	IDPYNGGT	SYNQKFRGKATLTVDKSSSTAYMHLNSLTSEDSAVYYC	ARENYRYFDFWGQGTTLTVSS	203

FIG. 11B (Cont.)

EP 3 095 797 A1

Protein Sequences of Exemplary Humanized DLL3 Modulator Heavy Chain Variable Regions

hmAb	FR1	CDR1	FR2	CDR2	FR3	CDR3	SEQ ID NO.
hSC16.13	QITLKESGPTLVKPTQTLTLTCTFS	GFSLSTSGMG	VGWIRQPPGKALEWLAH	IWWDDVK	RYSPSLKSRLTITKDTSKNQVVLTMTNMDPVDTATYYC	ARIVSFDNDVVSAMDYWGQGTLVTVSS	205
hSC16.15	QVQLVQSGAEVKKPGASVKVSCKAS	GYTFTRYW	IHWIRQAPGQGLEWMGY	INPTTVYT	EFNQNFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYC	ARGGSNFFDYWGQGTTVTVSS	207
hSC16.25	QITLKESGPTLVKPTQTLTLTCTFS	GFSLSTSGMG	VGWIRQPPGKALEWLTD	IWWDDNK	YYNPSLKSRLTITKDTSKNQVVLTMTNMDPVDTATYYC	ARRVNYYYDPYYAMDYWGQGTTLVTVSS	209
hSC16.34	QVQLVQSGAEVKKPGASVKVSCKAS	GYTFTNYG	MNWVRQAPGQRLEWMGW	INTYTGDP	TYADDFKGRVTITRDTSASTAYMELSSLRSEDTAVYYC	ARIGGNSPSDYWGQGTTVTVSS	211
hSC16.56	QVQLVQSGAEVKKPGASVKVSCKAS	GYTFTNYG	MNWVRQAPGQGLEWMGW	INTYTGEP	TYADDFKGRVTMTTDTSTSTAYMELRSLRSDDTAVYYC	ARIGDSSPSDYWGQGTLVTVSS	213

FIG. 11B (Cont.)

EP 3 095 797 A1

Biochemical Characteristics of Selected DLL3 Modulators

Clone	Bin	Domain	Affinity (nM)	% Live Cells (*in vitro*)	Cyno XR	Mouse & Rat XR
SC16.4	F	EGF4	0.5[F]	49	N.D.	Yes
SC16.8	A	EGF5	0.5[F]	82	N.D.	Yes
SC16.10	E	EGF2	4.0[F]	18	N.D.	No
SC16.13	B	EGF2	2.0[B]	31	No[Y]	No
SC16.15	G	N-terminal	0.5[B]	24	Yes[B]	Yes
SC16.25	C	N-terminal	0.2[B]	28	Yes[B]	No
SC16.34	D	DSL	0.2[B]	12	Yes[B]	Yes
SC16.39	I	EGF6	1.0[F]	98	N.D.	Yes
SC16.46	A	EGF1	0.5[F]	19	No[Y]	Yes
SC16.51	H	N-terminal	2.0[F]	56	Yes[B]	Yes
SC16.56	D	DSL	1.0[B]	16	Yes[B]	Yes
SC16.65	B	EGF2	0.9[B]	13	No[B]	No
SC16.67	D	EGF3	0.5[F]	37	Yes[Y]	No

[B] Biacore; [F] ForteBio; [Y] Yeast Display

FIG. 12

EP 3 095 797 A1

Binding Characteristics of Exemplary DLL3 Modulators

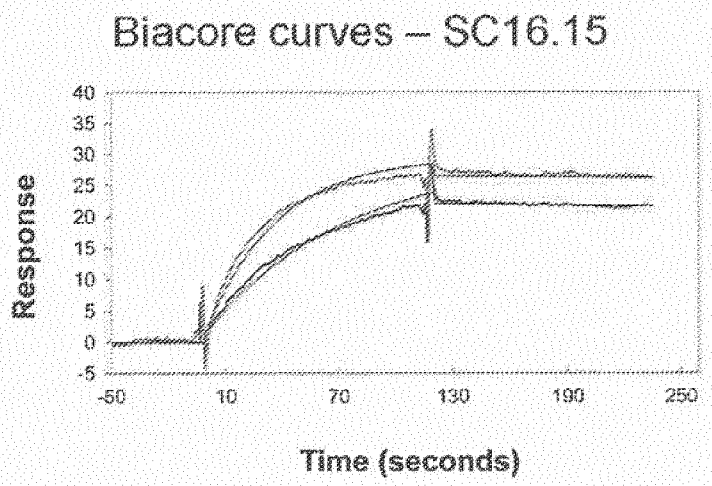


FIG. 13A

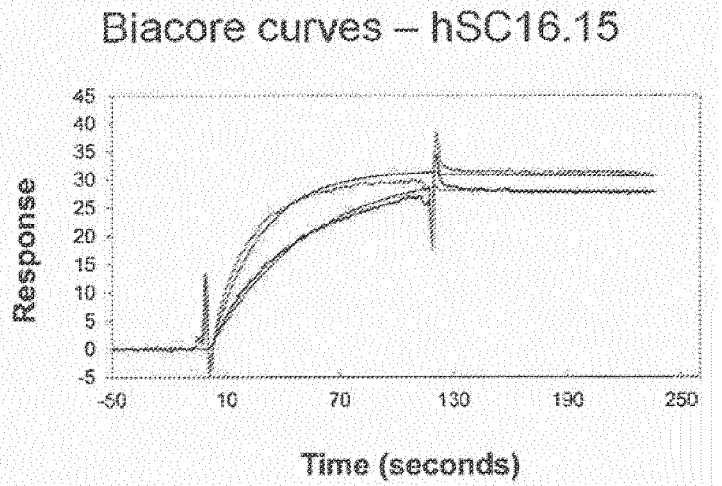


FIG. 13B

hClone	Bin	Mouse Ag Binding	Hu Ag Affinity (Murine mAb)	Hu Ag Affinity (Human mAb)
SC16.13	B	No	0.3nM	0.5nM
SC16.15	G	Yes	0.2nM	0.2nM
SC16.25	C	No	<0.2nM	<0.2nM
SC16.34	D	Yes	0.6nM	0.9nM
SC16.56	D	Yes	0.5nM	0.5nM

FIG. 13C

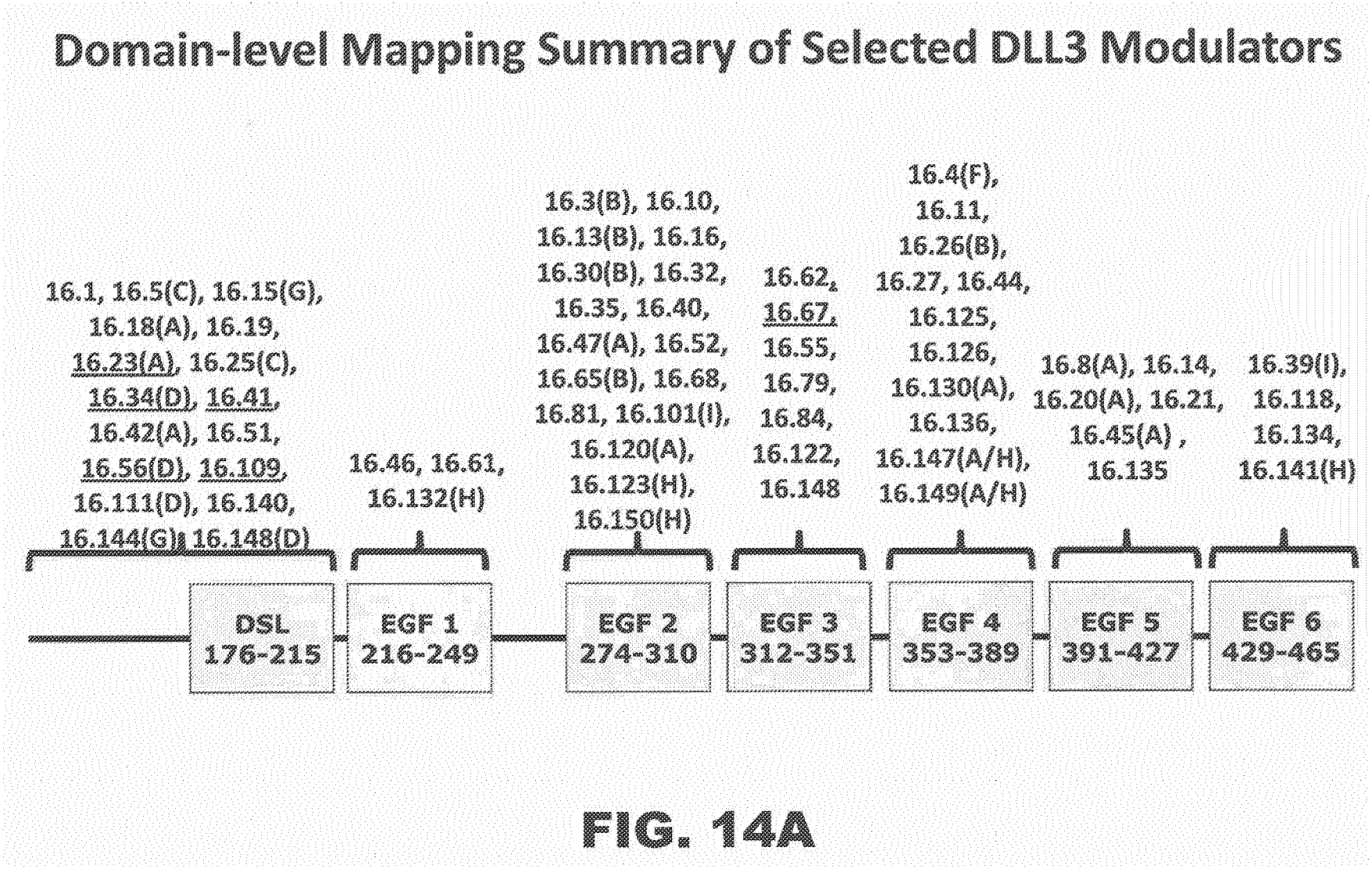

Domain-level Mapping Summary of Selected DLL3 Modulators
16.1, 16.5(C), 16.15(G), 16.18(A), 16.19, 16.23(A), 16.25(C), 16.34(D), 16.41, 16.42(A), 16.51, 16.56(D), 16.109, 16.111(D), 16.140, 16.144(G), 16.148(D)
16.46, 16.61, 16.132(H)
16.3(B), 16.10, 16.13(B), 16.16, 16.30(B), 16.32, 16.35, 16.40, 16.47(A), 16.52, 16.65(B), 16.68, 16.81, 16.101(I), 16.120(A), 16.123(H), 16.150(H)
16.62, 16.67, 16.55, 16.79, 16.84, 16.122, 16.148
16.4(F), 16.11, 16.26(B), 16.27, 16.44, 16.125, 16.126, 16.130(A), 16.136, 16.147(A/H), 16.149(A/H)
16.8(A), 16.14, 16.20(A), 16.21, 16.45(A), 16.135
16.39(I), 16.118, 16.134, 16.141(H)
DSL 176-215
EGF 1 216-249
EGF 2 274-310
EGF 3 312-351
EGF 4 353-389
EGF 5 391-427
EGF 6 429-465

FIG. 14A

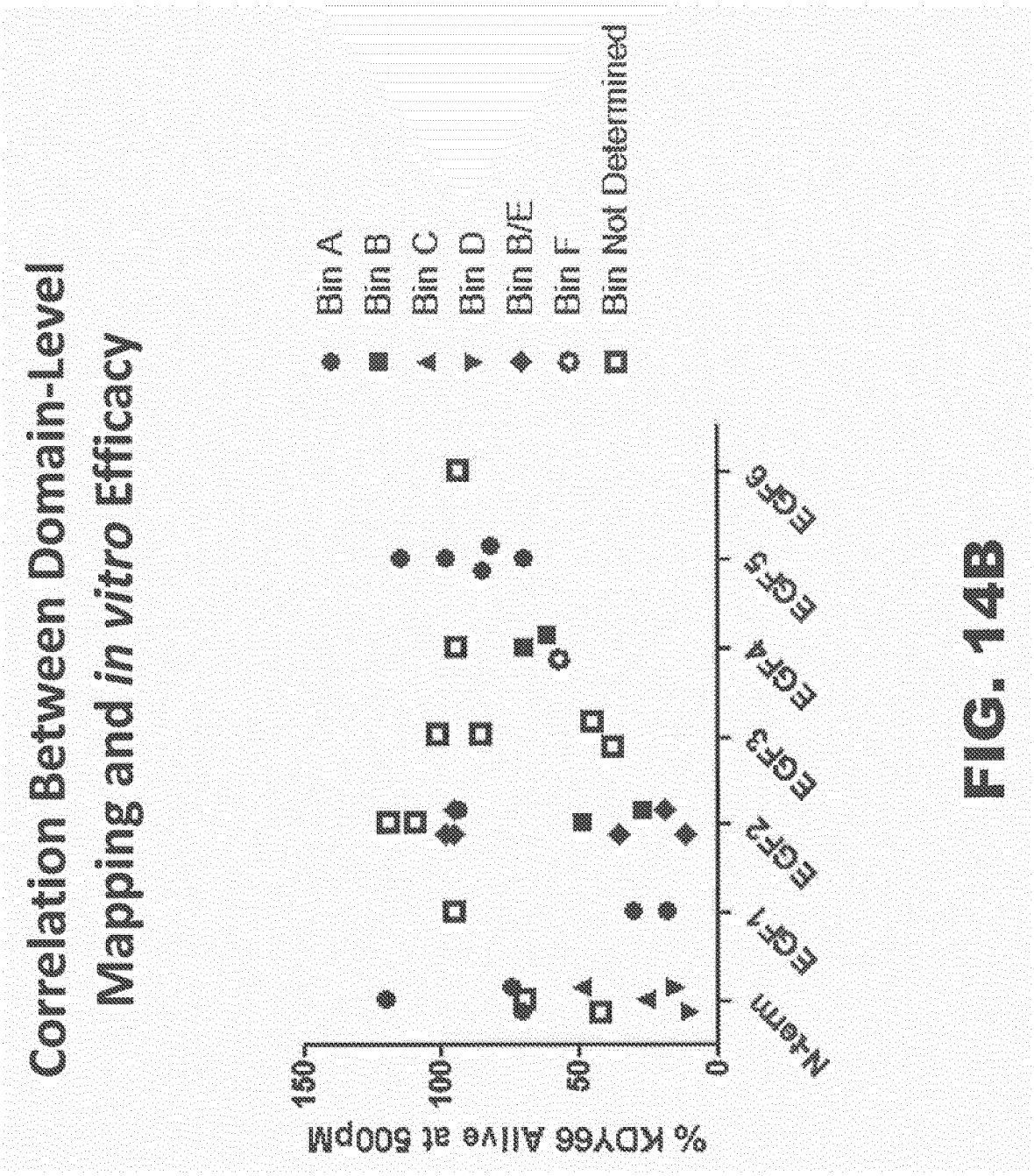

Correlation Between Domain-Level
Mapping and in vitro Efficacy
Bin A
Bin B
Bin C
Bin D
Bin B/E
Bin F
Bin Not Determined
% KDY66 Alive at 500pM
150
100
50
0
N-term
EGF1
EGF2
EGF3
EGF4
EGF5
EGF6

FIG. 14B

Selected DLL3 Modulators Detect Surface Expression of DLL3 in Engineered Lines

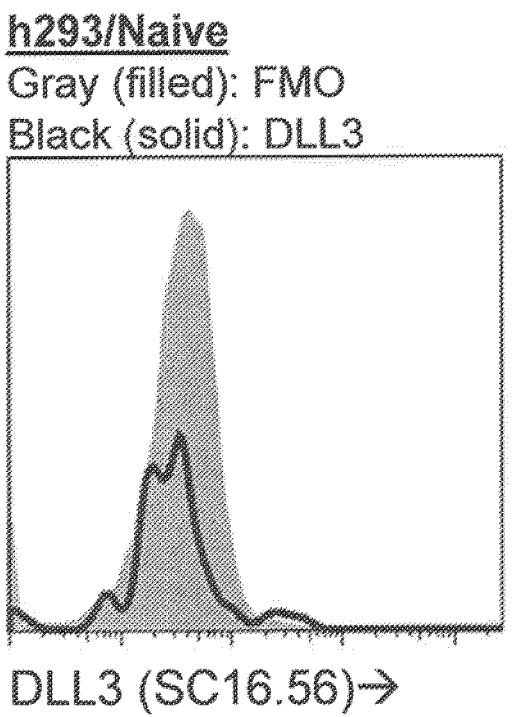


FIG. 15A

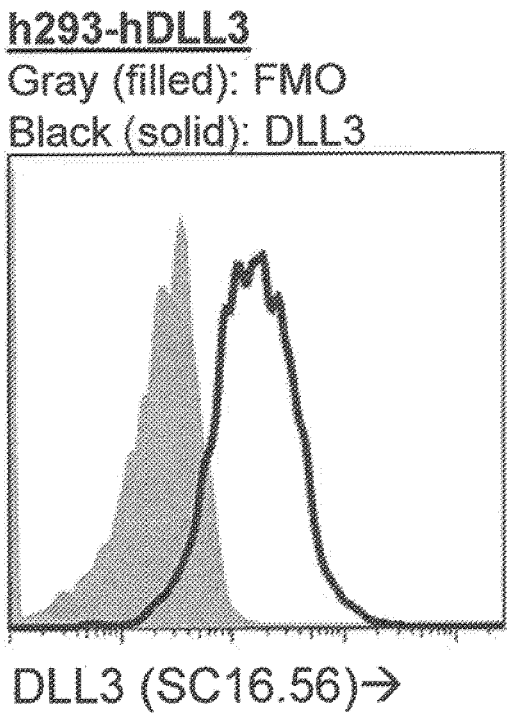


FIG. 15B

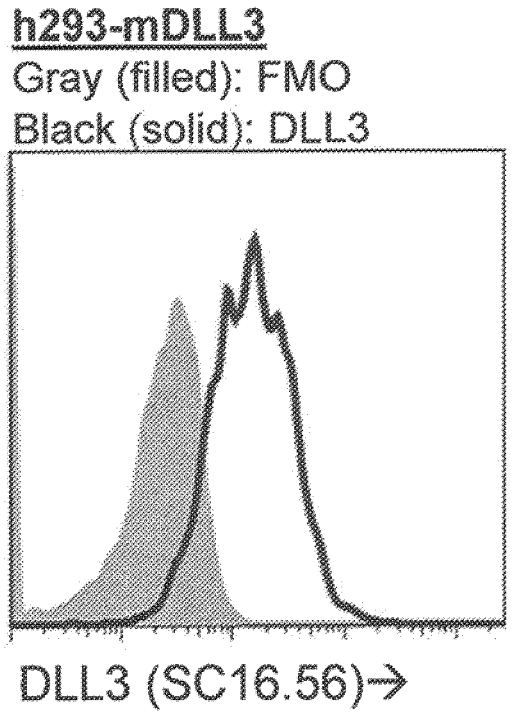


FIG. 15C

Selected DLL3 Modulators Detect Surface Expression of DLL3 in NTX Tumors

OV26	MFI
FMO (gray filled)	72
SC16.56 (black line)	493

FIG. 16A

KDY66	MFI
FMO (gray filled)	62
SC16.56 (black line)	262

FIG. 16B

LU37	MFI
FMO (gray filled)	29
SC16.56 (black line)	313

FIG. 16C

Immunohistochemistry Staining of DLL3 in NTX Tumors and Normal Human Tissues

NTX Tumor	SC16.65
KDY27p3	-
KDY66p4	+++, 80%
KDY67p2	+++, 70%
LU100p1	-
LU102p1	+++, 70%
LU109p2	+++, 70%
LU111p1	-/+, 10%
LU117p2	-/+, 70%
LU124p1	-/+, 10%
LU126p2	-
LU135p3	-
LU37p5	+++, 70%
LU50p1	-
LU64p1	+, 60%
LU73p2	-/+, 20%
LU80p3	-
LU86p1	+, 70%
LU95p1	+, 30%
LU49p2	-
OV26p2	-
SK11p4	-
SK13p3	-
SK19p3	+, 70%
SK23p1	-
SK29p2	-
SK6p4	-

FIG. 16D

Organ	SC16.65
Skin	-
Skin	-
Subcutis	-
Subcutis	-
Breast	-
Breast	-
Spleen	-
Spleen	-
Lymphnode	-
Lymphnode	-
Skeletal muscle	-
Skeletal muscle	-
Lung	-
Lung	-
Heart	-
Heart	-
Aorta	-
Aorta	-
Salivary gland	-
Salivary gland	-
Liver	-
Liver	-
Gallbladder	-
Gallbladder	-
Pancreas	-
Pancreas	-
Tonsil	-
Tonsil	-
Esophagus	-
Esophagus	-

Organ	SC16.65
Stomach	-
Stomach	-
Small intestine	-
Small intestine	-
Colon	-
Colon	-
Kidney, cortex	-
Kidney, cortex	-
Kidney, medulla	-
Kidney, medulla	-
Uterus	-
Uterus	-
Prostate	-
Prostate	-
Placenta	-
Placenta	-
Umbilical cord	-
Umbilical cord	-
Adrenal	-
Adrenal	-
Thyroid	-
Thyroid	-
Thymus	-
Thymus	-
Gray matter, cerebrum	-
Gray matter, cerebrum	-
White matter, cerebrum	-
White matter, cerebrum	-
Cerebellum	-
Cerebellum	-

FIG. 16E

EP 3 095 797 A1

Immunohistochemistry Staining of DLL3 in Human Tumors

Core	Tissues/Diagnosis	stage	SC16.65	CHGA
A1	Small cell carcinoma	I	-/+, 20%	+
A2	Small cell carcinoma	I	-/+, 10%	+
A3	Small cell carcinoma	I	-	-
A4	Small cell carcinoma	I	+, 40%	+
A5	Small cell carcinoma	I	++, 90%	+
A6	Small cell carcinoma	II	-	-
A7	Small cell carcinoma	I	-/+, 20%	-
A8	Small cell carcinoma	I	+/++, 70%	+
A9	Small cell carcinoma	I	++, 80%	+
B1	Small cell carcinoma	I	-	-
B2	Small cell carcinoma	I	-	-
B3	Small cell carcinoma	I	+, 70%	-
B4	Small cell carcinoma	II	+, 10%	+
B5	Small cell carcinoma	II	++, 70%	+
B6	Small cell carcinoma	I	++/+++, 90%	+
B7	Small cell carcinoma	II	+++, 90%	+
B8	Small cell carcinoma	II	++, 80%	+
B9	Small cell carcinoma	II	++, 70%	+
C1	Small cell carcinoma	II	-	-
C2	Small cell carcinoma	II	+, 40%	+
C3	Small cell carcinoma	II	+, 10%	+
C4	Small cell carcinoma	II	+, 50%	+
C5	Small cell carcinoma	II	-	-
C6	Small cell carcinoma	II	++/+++, 90%	+
C7	Small cell carcinoma	II	+++, 90%	+
C8	Small cell carcinoma	II	+, 50%	+
C9	Small cell carcinoma	I	++/+++, 80%	+

Core	Tissues/Diagnosis	stage	SC16.65	CHGA
D1	Small cell carcinoma	II	-	-
D2	Small cell carcinoma	II	+, 20%	+
D3	Small cell carcinoma	II	+, 30%	+
D4	Small cell carcinoma	IIIa	+, 10%	+
D5	Small cell carcinoma	IIIa	-	-
D6	Small cell carcinoma	II	++/+++, 90%	+
D7	Small cell carcinoma	II	+, 70%	+
D8	Small cell carcinoma	II	+++, 90%	+
D9	Small cell carcinoma	IIIa	+, 70%	-
E1	Small cell carcinoma	IIIa	+, 20%	+
E2	Small cell carcinoma	IIIa	+, 10%	+
E3	Small cell carcinoma	IIIb	+, 20%	+
E4	Small cell carcinoma	IIIa	+, 70%	+
E5	Empty core		-	-
E6	Small cell carcinoma	IIIb	+, 70%	+
E7	Small cell carcinoma	IIIa	++, 70%	-
E8	Small cell carcinoma	IIIb	++, 80%	+
E9	Small cell carcinoma	IIIb	++, 90%	+

FIG. 16F

EP 3 095 797 A1

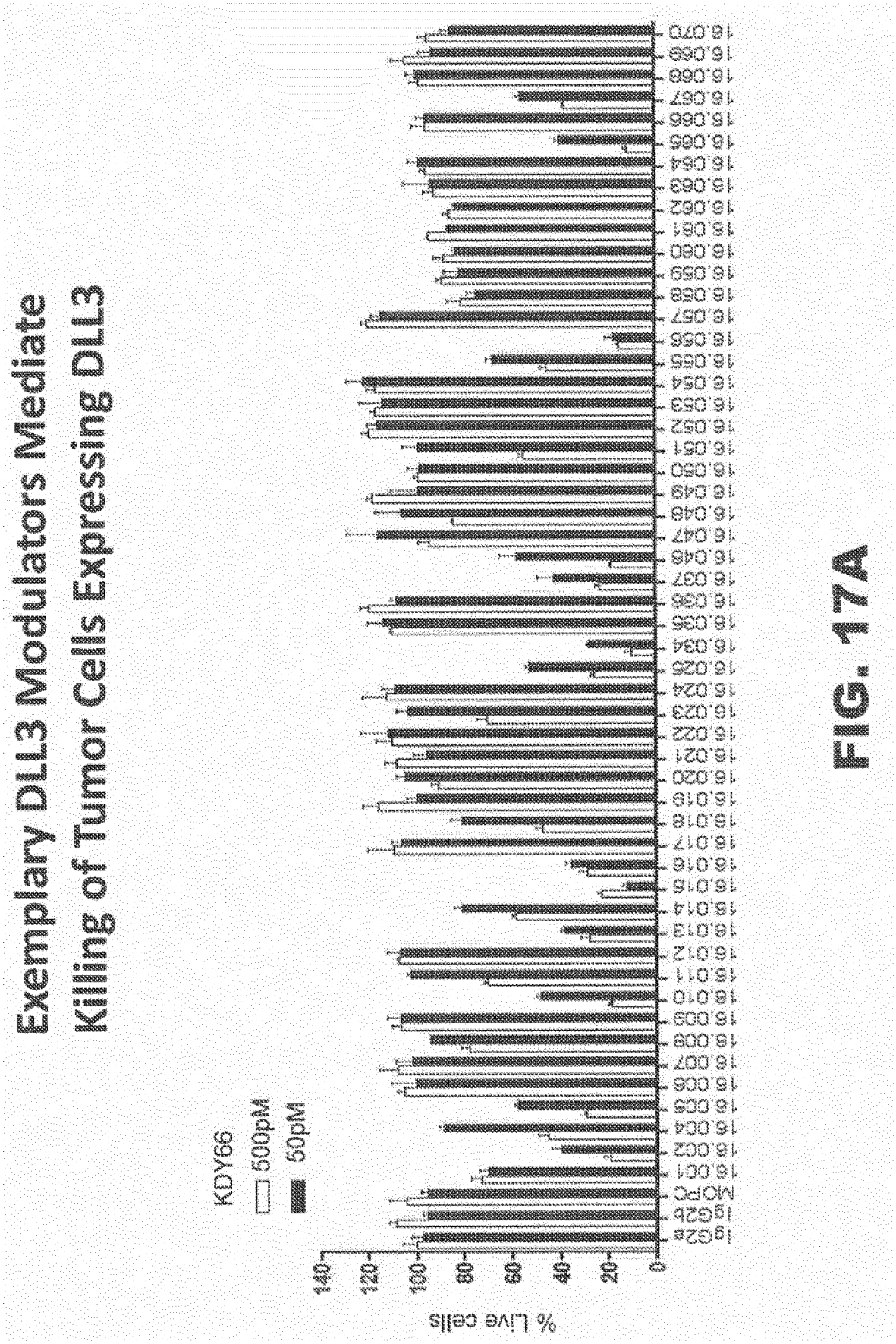

Exemplary DLL3 Modulators Mediate
Killing of Tumor Cells Expressing DLL3
KDY66
500pM
50pM
% Live cells
140
120
100
80
60
40
20
0
IgG2a
IgG2b
MOPC
16.001
16.002
16.004
16.005
16.006
16.007
16.008
16.009
16.010
16.011
16.012
16.013
16.014
16.015
16.016
16.017
16.018
16.019
16.020
16.021
16.022
16.023
16.024
16.025
16.034
16.035
16.036
16.037
16.046
16.047
16.048
16.049
16.050
16.051
16.052
16.053
16.054
16.055
16.056
16.057
16.058
16.059
16.060
16.061
16.062
16.063
16.064
16.065
16.066
16.067
16.068
16.069
16.070

FIG. 17A

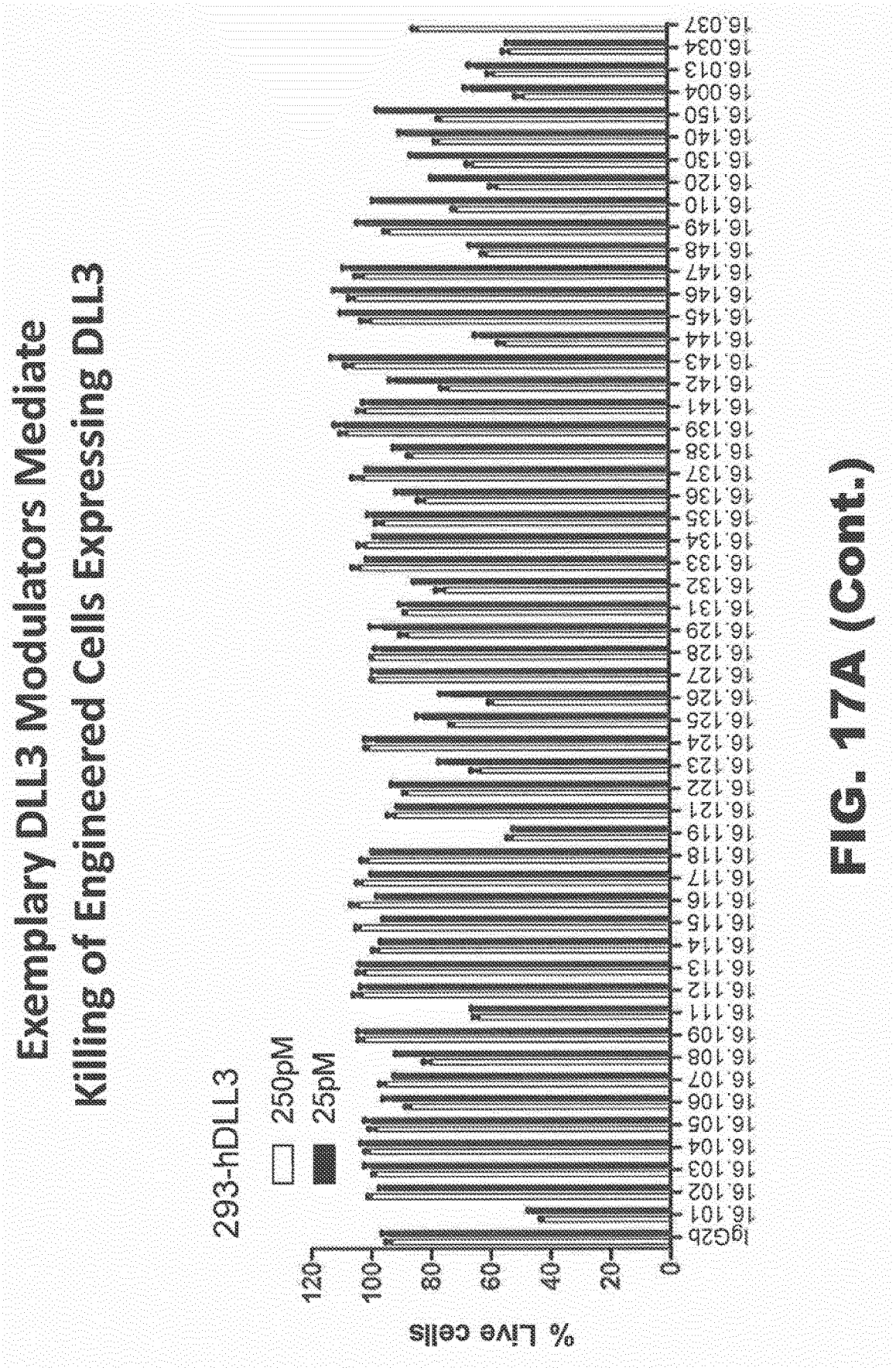

Exemplary DLL3 Modulators Mediate
Killing of Engineered Cells Expressing DLL3
293-hDLL3
250pM
25pM
% Live cells
120
100
80
60
40
20
0
IgG2b
16.101
16.102
16.103
16.104
16.105
16.106
16.107
16.108
16.109
16.111
16.112
16.113
16.114
16.115
16.116
16.117
16.118
16.119
16.121
16.122
16.123
16.124
16.125
16.126
16.127
16.128
16.129
16.131
16.132
16.133
16.134
16.135
16.136
16.137
16.138
16.139
16.141
16.142
16.143
16.144
16.145
16.146
16.147
16.148
16.149
16.110
16.120
16.130
16.140
16.150
16.004
16.013
16.034
16.037

FIG. 17A (Cont.)

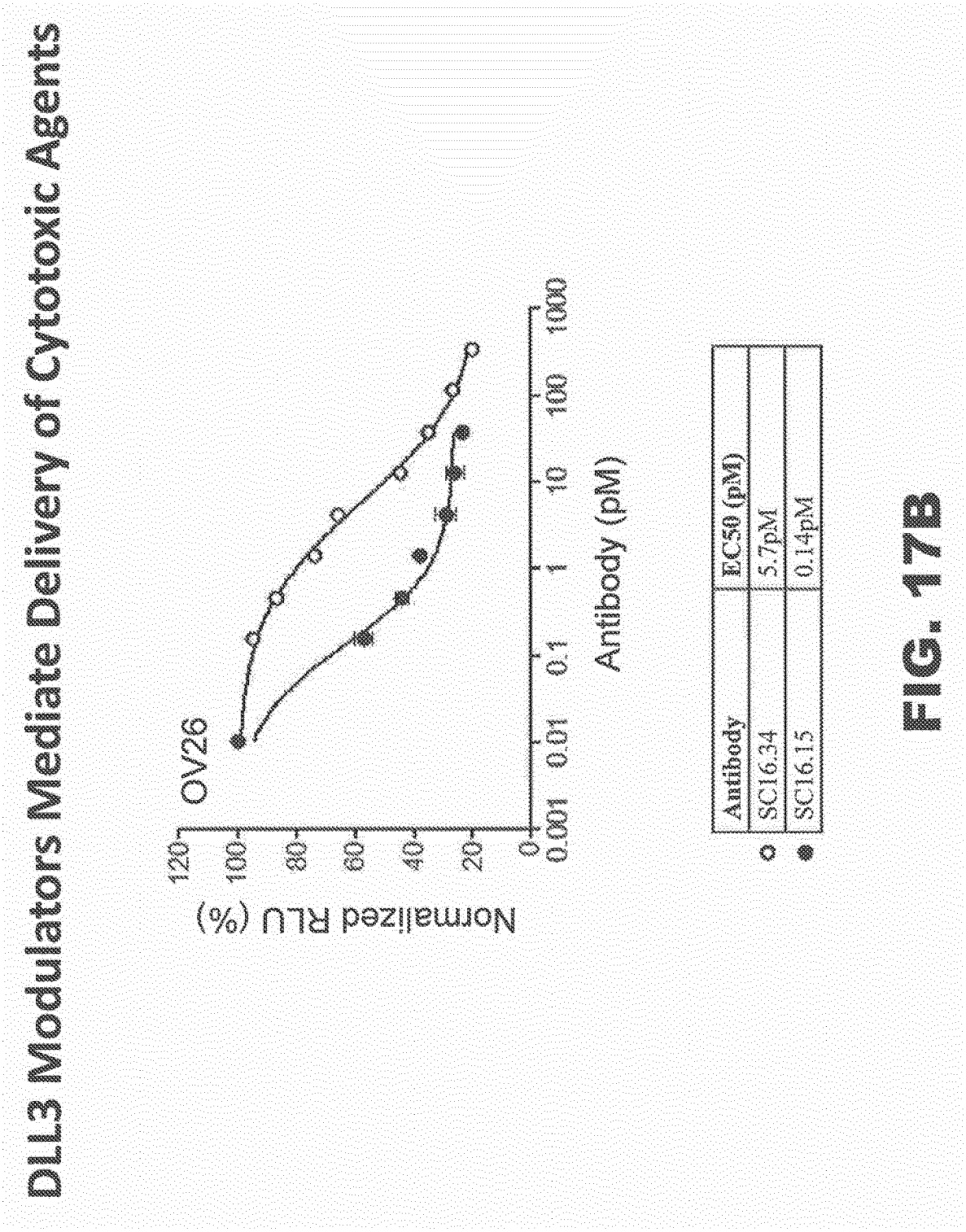

DLL3 Modulators Mediate Delivery of Cytotoxic Agents
OV26
Normalized RLU (%)
120
100
80
60
40
20
0
0.001
0.01
0.1
1
10
100
1000
Antibody (pM)
Antibody
EC50 (pM)
SC16.34
5.7pM
SC16.15
0.14pM

FIG. 17B

DLL3 Modulator ADCs Mediate Delivery of Cytotoxic Agents

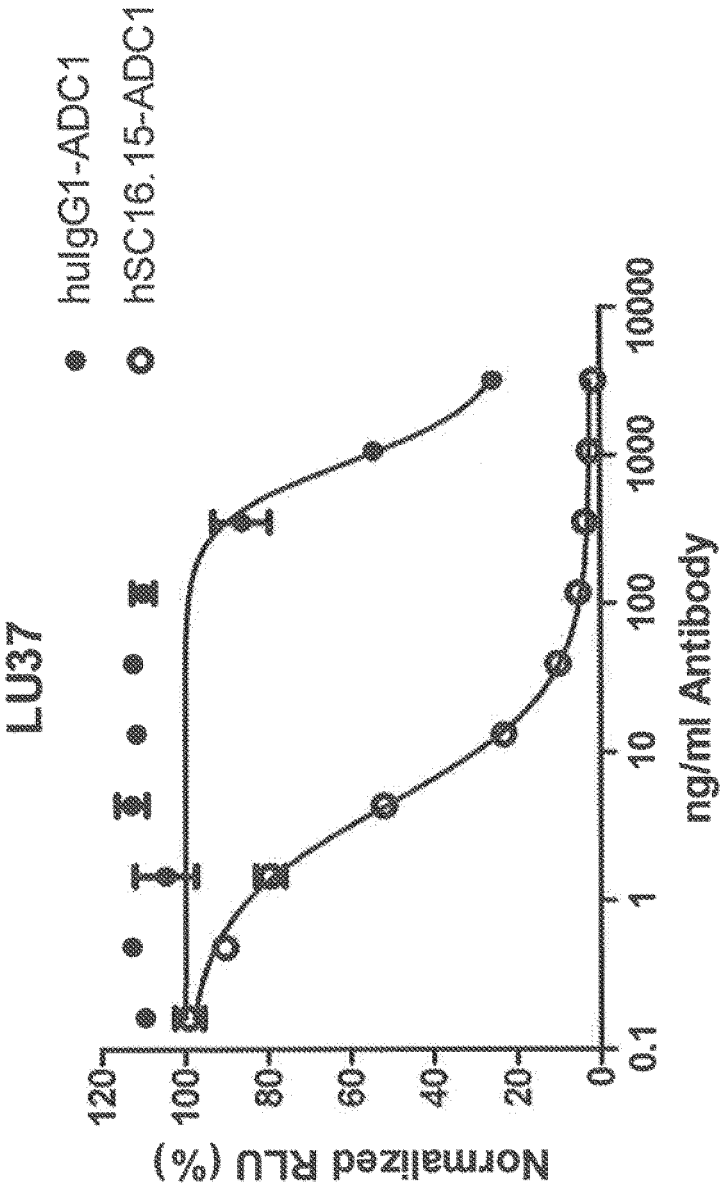


FIG. 17C

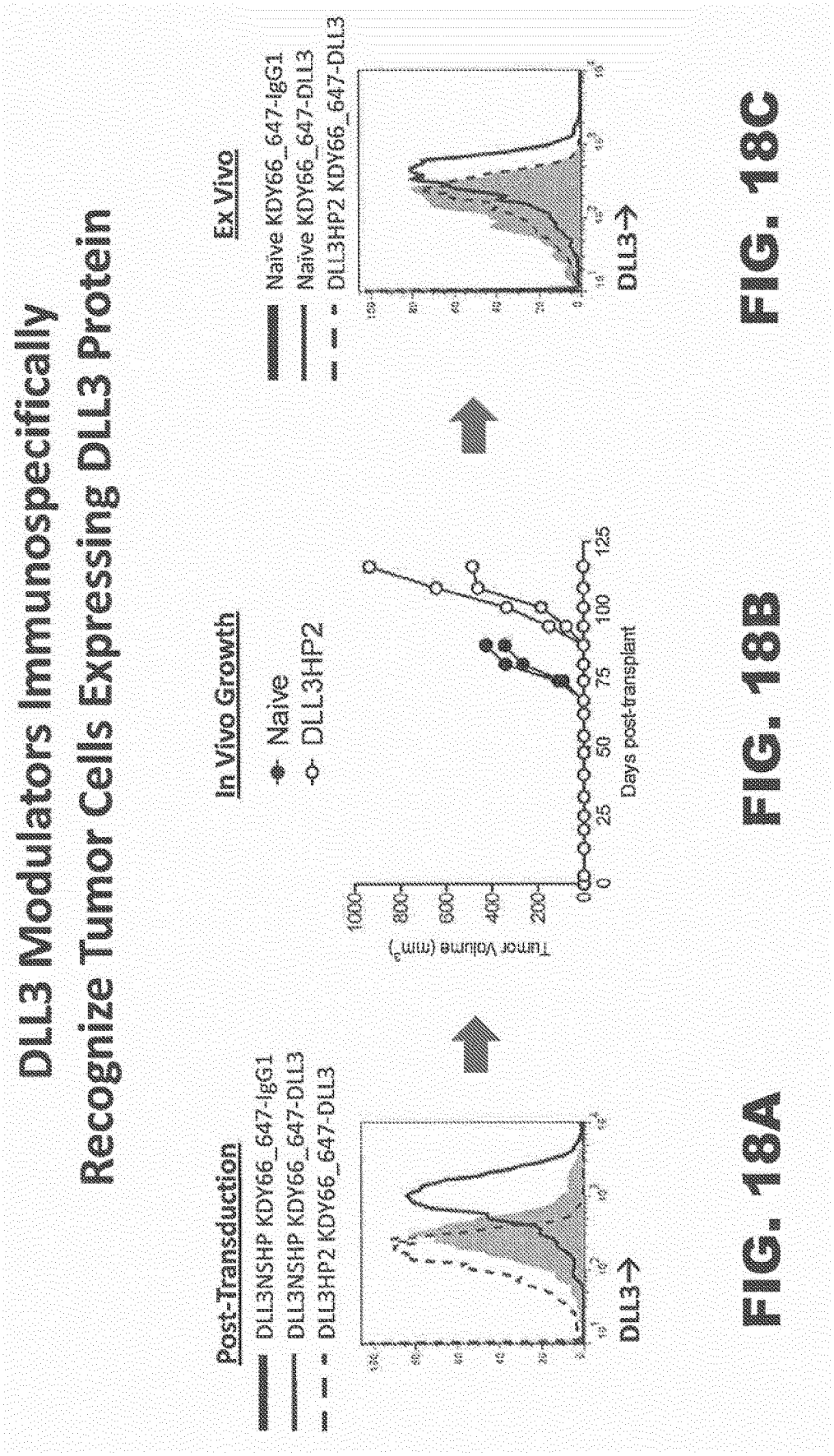


FIG. 18A FIG. 18B FIG. 18C

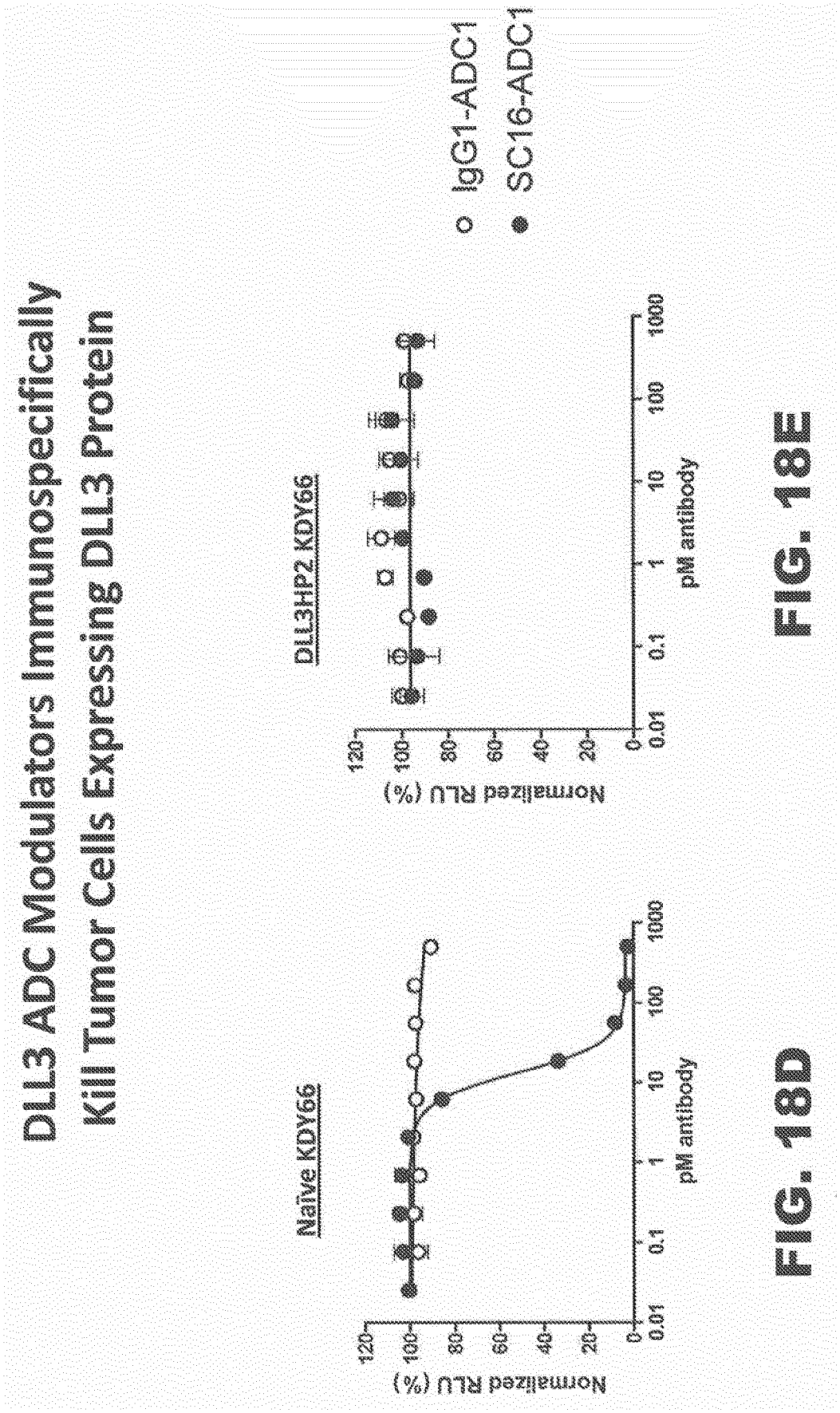
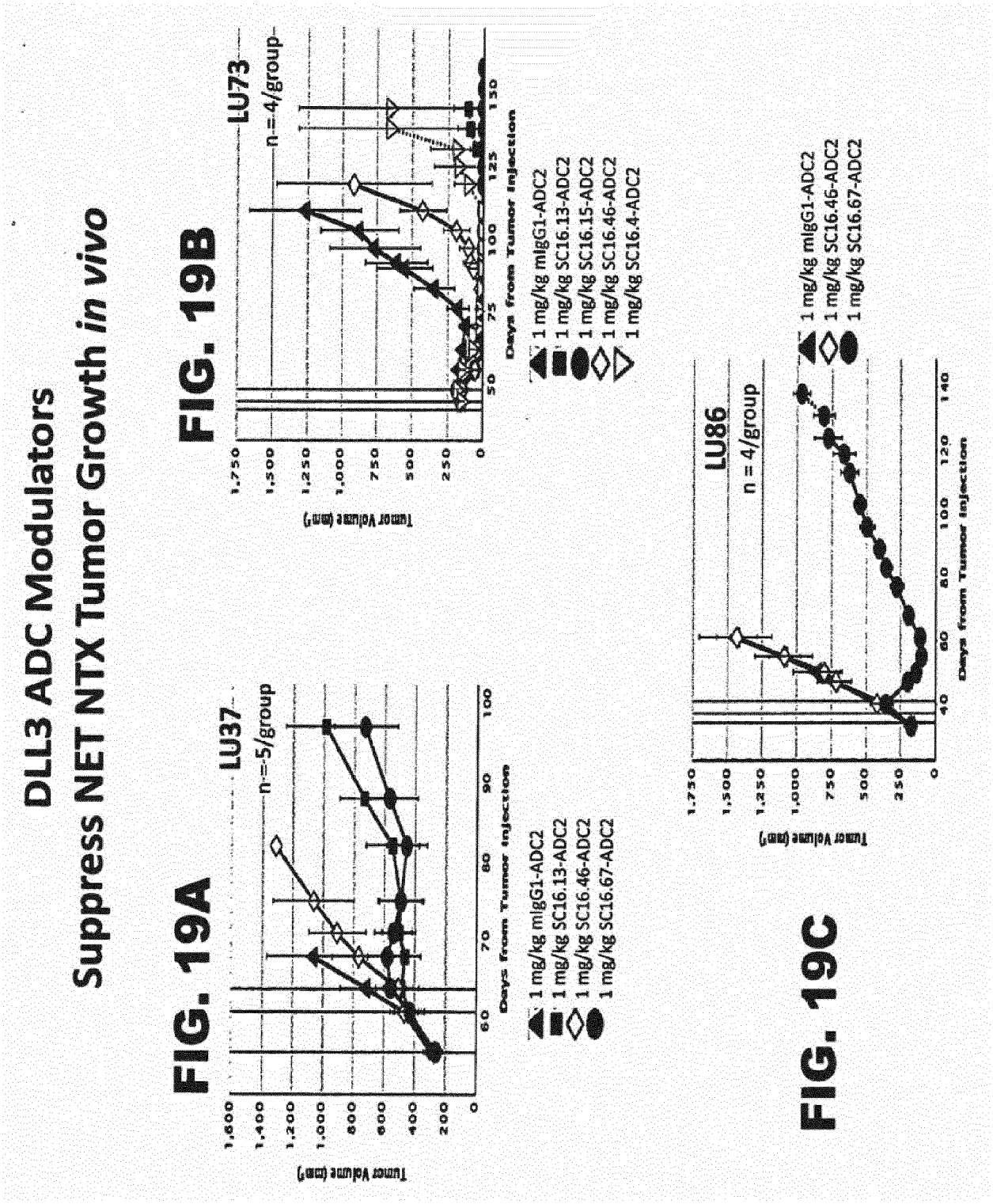


FIG. 18D

FIG. 18E


DLL3 ADC Modulators
Suppress NET NTX Tumor Growth in vivo
FIG. 19A
LU37
n=5/group
Tumor Volume (mm³)
Days from Tumor Injection
1 mg/kg mIgG1-ADC2
1 mg/kg SC16.13-ADC2
1 mg/kg SC16.46-ADC2
1 mg/kg SC16.67-ADC2
FIG. 19B
LU73
n=4/group
Tumor Volume (mm³)
Days from Tumor Injection
1 mg/kg mIgG1-ADC2
1 mg/kg SC16.13-ADC2
1 mg/kg SC16.15-ADC2
1 mg/kg SC16.46-ADC2
1 mg/kg SC16.4-ADC2
FIG. 19C
LU86
n = 4/group
Tumor Volume (mm³)
Days from Tumor Injection
1 mg/kg mIgG1-ADC2
1 mg/kg SC16.46-ADC2
1 mg/kg SC16.67-ADC2

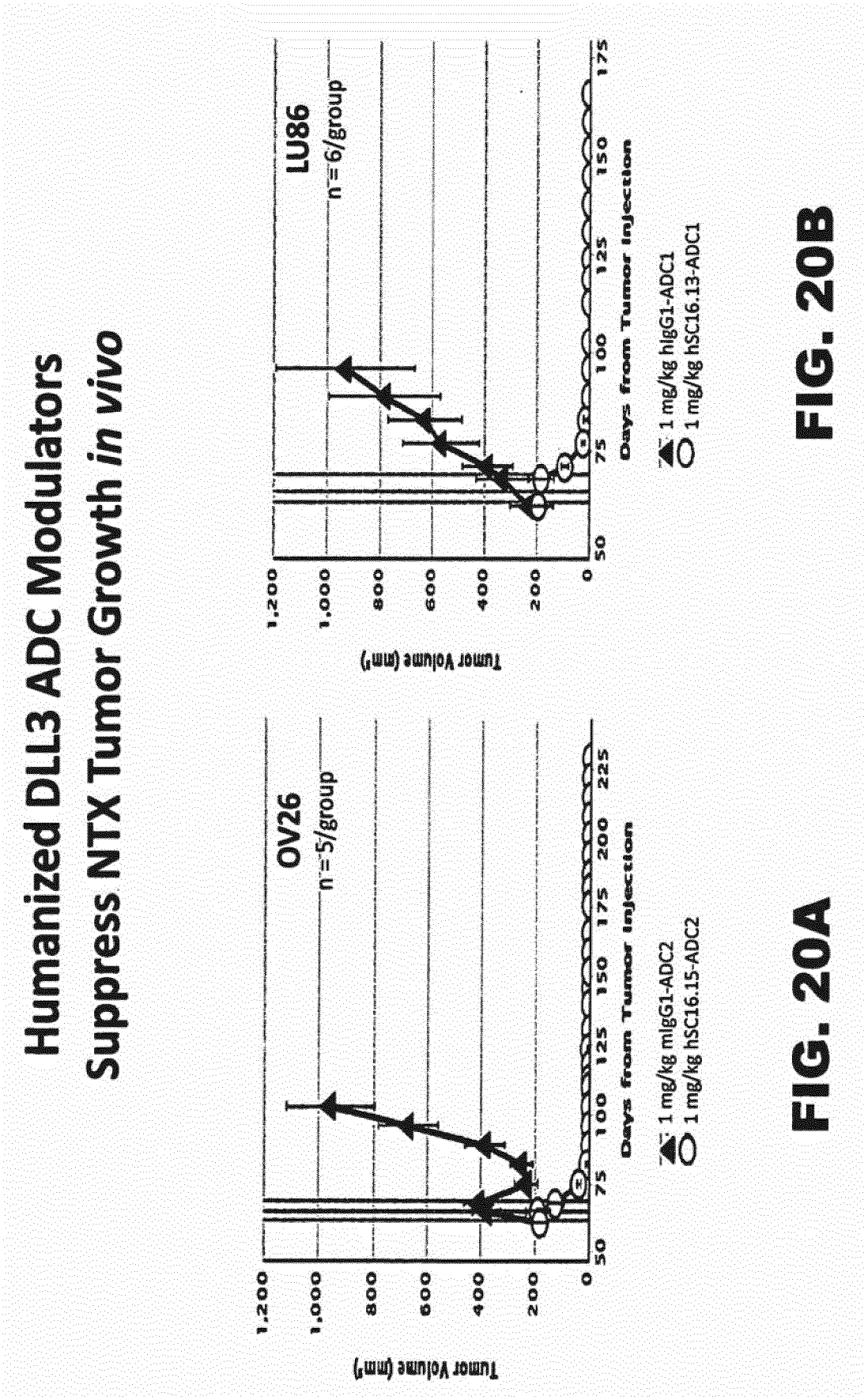


FIG. 20A

FIG. 20B

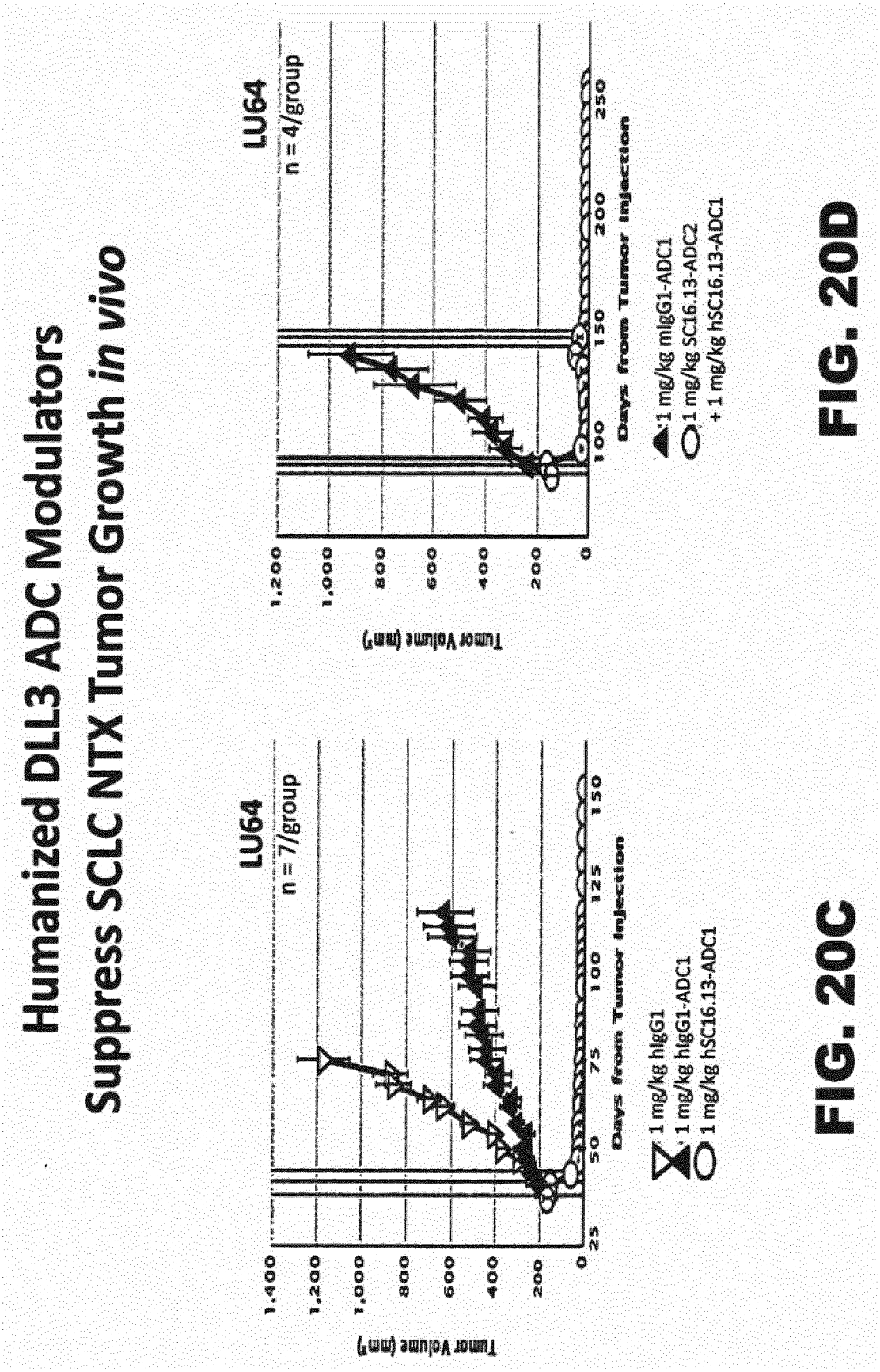


FIG. 20C

FIG. 20D

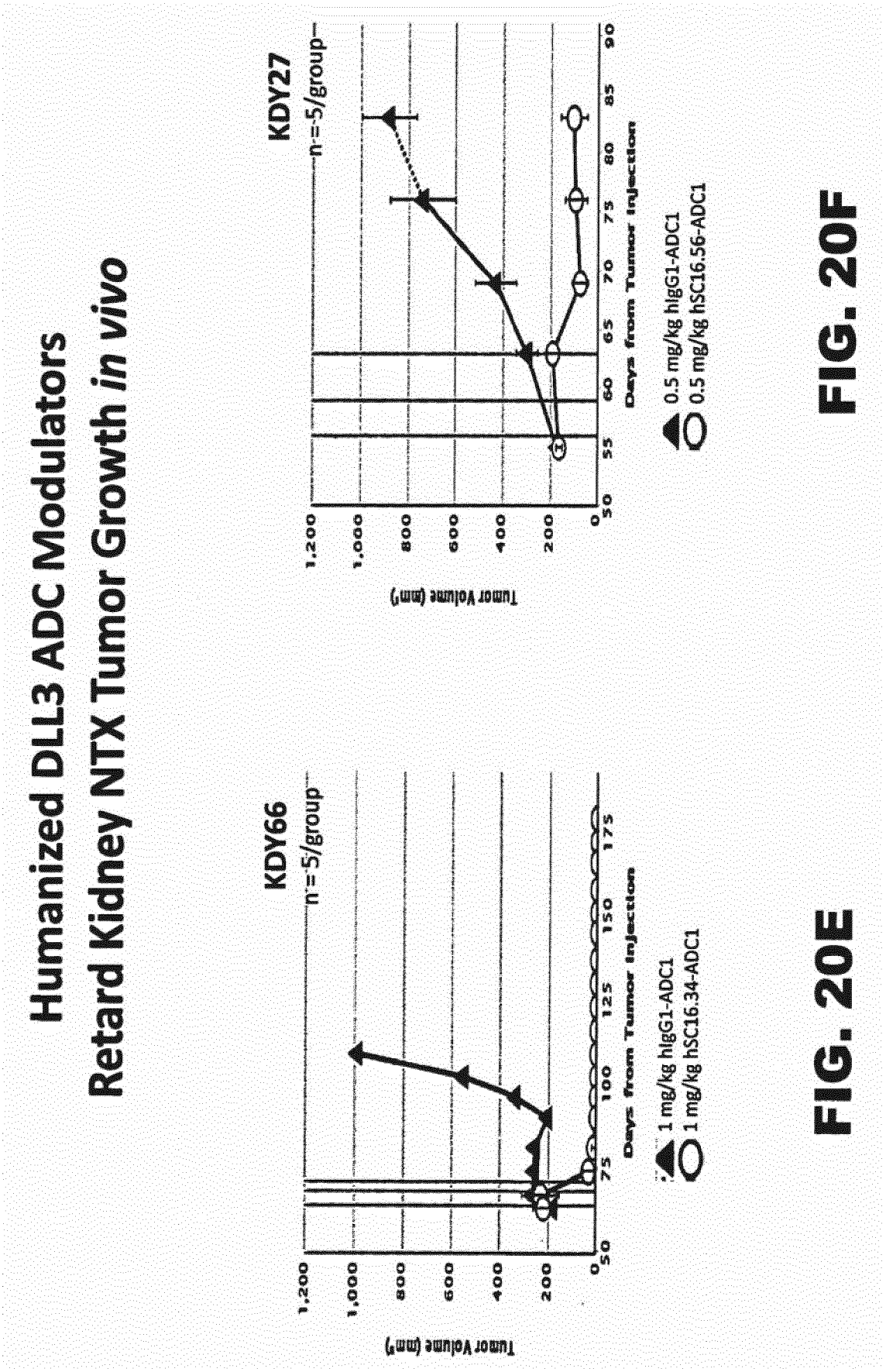


FIG. 20E

FIG. 20F

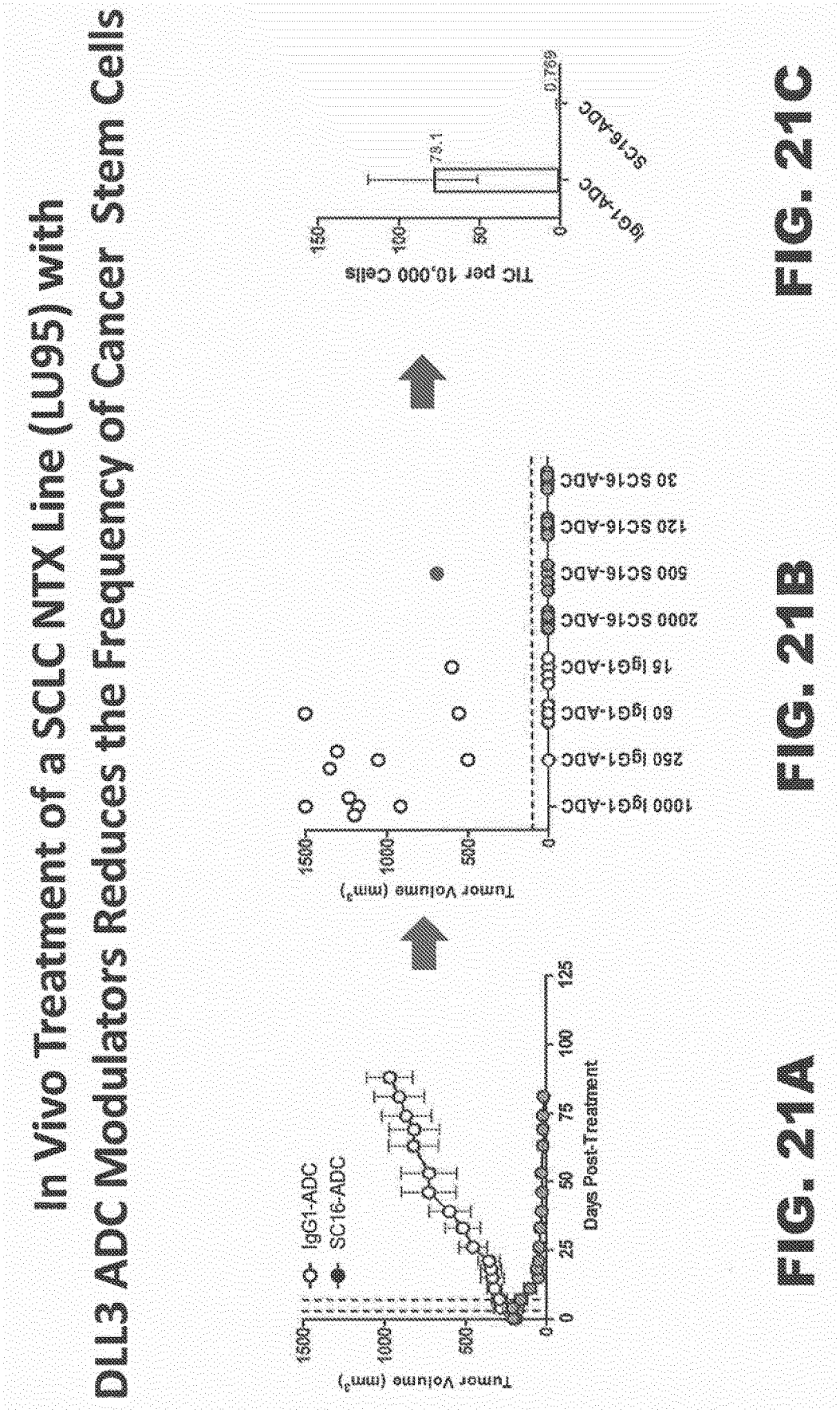


FIG. 21A

FIG. 21B

FIG. 21C

In Vivo Treatment of a SCLC NTX Line (LU64) with DLL3 ADC Modulators Reduces the Frequency of Cancer Stem Cells

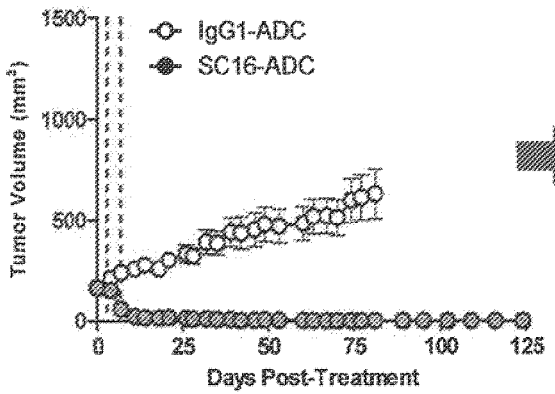


FIG. 21D

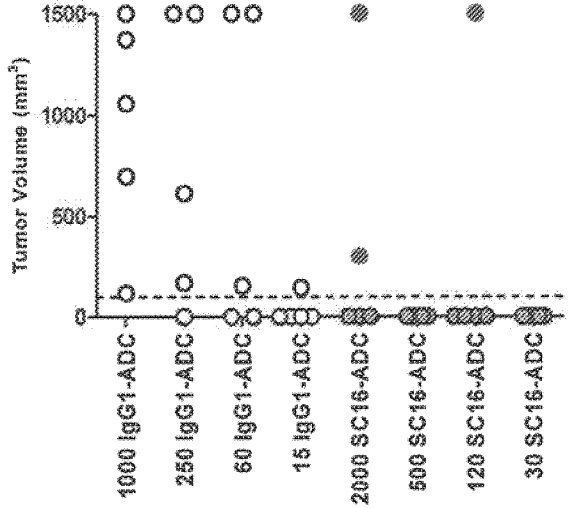


FIG. 21E

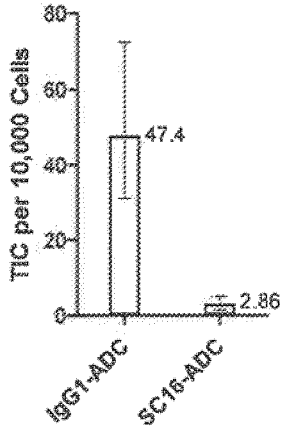


FIG. 21F

Europäisches Patentamt
European Patent Office
Office européen des brevets

EUROPEAN SEARCH REPORT

Application Number
EP 16 16 4567

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X A X,P	WO 2011/093097 A1 (FORERUNNER PHARMA RES CO LTD [JP]; UNIV TOKYO [JP]; YOSHIDA KENJI [JP]) 4 August 2011 (2011-08-04) * paragraph [0011]; claims 1-13; figures 4,11,12; examples 3,4,7,8 * & EP 2 530 091 A1 (FORERUNNER PHARMA RES CO LTD [JP]; UNIV TOKYO [JP]) 5 December 2012 (2012-12-05) -----	1-5,11, 16-34 6-10, 12-15,35 1-5,11, 16-34	INV. C07K16/28 A61K47/48 C07K16/30 C07K14/47 A61P35/00
X	R&D Systems: "Human DLL3 Antibody Monoclonal Mouse IgG2B Clone # 378703, Catalog Number: MAB4315", R&D System catalog , 5 May 2010 (2010-05-05), pages 1-1, XP002697358, Retrieved from the Internet: URL:http://www.rndsystems.com/pdf/MAB4315.pdf [retrieved on 2012-05-18] * the whole document * -----	1-5,11, 16-34	
X	Millipore: "Anti-Delta3, clone 1E7.2", , 15 July 2008 (2008-07-15), pages 1-3, XP002697359, usa Retrieved from the Internet: URL:http://www.millipore.com/catalogue/item/MABT189?cid=bios-a-antr-1012-1206 [retrieved on 2013-05-14] * the whole document * -----	1-5,11, 16-34	TECHNICAL FIELDS SEARCHED (IPC) C07K A61K
X	US 2003/180784 A1 (MCCARTHY SEAN A [US] ET AL) 25 September 2003 (2003-09-25) * paragraph [0318] - paragraph [0342]; claims 21-22 * -----	1-5,11, 16-34	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	22 September 2016	Siaterli, Maria

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 16 16 4567

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

22-09-2016

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011093097 A1	04-08-2011	EP 2530091 A1	05-12-2012
		JP 5918540 B2	18-05-2016
		US 2012328624 A1	27-12-2012
		US 2015368355 A1	24-12-2015
		WO 2011093097 A1	04-08-2011
US 2003180784 A1	25-09-2003	NONE	

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US 61603173 A **[0001]**
- US 61719803 A **[0001]**
- WO 2012031280 A **[0073]**
- US 7632678 B **[0074]**
- US 20070292414 A **[0074] [0492]**
- US 20080175870 A **[0074]**
- US 20100275280 A **[0074]**
- US 20100162416 A **[0074]**
- US 20110020221 A **[0074]**
- US 20080138313 A **[0075]**
- US 4816567 A **[0099]**
- US 6180370 B **[0102]**
- US 5693762 A **[0102]**
- US 20050008625 A **[0102]**
- WO 9852976 A **[0102]**
- WO 0034317 A **[0102]**
- US 6300064 B **[0103]**
- US 5223409 A **[0106]**
- WO 9218619 A **[0106]**
- WO 9117271 A **[0106]**
- WO 9220791 A **[0106]**
- WO 9215679 A **[0106]**
- WO 9301288 A **[0106]**
- WO 9201047 A **[0106]**
- WO 9209690 A **[0106]**
- WO 9607754 A **[0108]**
- US 7700302 B **[0109]**
- US 12404059 B **[0109]**
- US 5545807 A **[0110]**
- US 5545806 A **[0110]**
- US 5569825 A **[0110]**
- US 5625126 A **[0110]**
- US 5633425 A **[0110]**
- US 5661016 A **[0110]**
- US 6075181 A **[0110]**
- US 6150584 A **[0110]**
- US 5750373 A **[0110]**
- US 7709611 B **[0114]**
- WO 8605807 A **[0126]**
- WO 8901036 A **[0126]**
- US 5122464 A **[0126]**
- EP 0216846 A **[0129]**
- EP 0256055 A **[0129]**
- EP 0323997 A **[0129]**
- EP 0338841 A **[0129]**
- US 5591639 A **[0129]**
- US 5879936 A **[0129]**
- US 6417429 B **[0134]**
- US 20090130105 A **[0145]**
- US 20090155255 A **[0146] [0276]**
- WO 9404690 A **[0146]**
- WO 9627011 A **[0146]**
- US 4676980 A **[0147]**
- WO 9100360 A **[0147]**
- WO 92200373 A **[0147]**
- EP 03089 A **[0147]**
- WO 9734631 A **[0151]**
- WO 04029207 A **[0151]**
- US 6737056 B **[0151]**
- US 20030190311 A **[0151]**
- WO 200042072 A **[0151]**
- US 5714350 A **[0153]**
- US 6350861 B **[0153]**
- WO 2012117002 A **[0154]**
- US 7619068 B **[0161]**
- WO 0348731 A **[0167]**
- US 20040101920 A **[0175]**
- WO 9321232 A **[0187]**
- EP 439095 A **[0187]**
- US 5474981 A **[0187]**
- US 6214345 B **[0190] [0568]**
- US 20120078028 A **[0190] [0568]**
- US 5122368 A **[0191]**
- US 5824805 A **[0191]**
- US 5622929 A **[0191] [0423]**
- US 20050238649 A **[0192]**
- US 20110256157 A **[0193] [0277] [0278] [0568]**
- US 7521541 B **[0254]**
- WO 2005082023 A **[0266]**
- WO 9315199 A **[0270]**
- WO 9315200 A **[0270]**
- WO 0177137 A **[0270]**
- EP 0413622 A **[0270]**
- US 4703004 A **[0273]**
- FR 901464 **[0275]**
- US 7825267 B **[0275]**
- WO 03075957 A **[0276]**
- US 6362331 B **[0277]**
- US 7049311 B **[0277]**
- US 7189710 B **[0277]**
- US 7429658 B **[0277]**
- US 7407951 B **[0277]**
- US 7741319 B **[0277]**
- US 7557099 B **[0277]**
- US 8034808 B **[0277]**
- US 8163736 B **[0277]**
- WO 2011130613 PCT **[0277]**
- WO 2011128650 A **[0277]**

- WO 2011130616 A **[0277]**
- WO 0012507 A **[0388]**
- WO 9733899 A **[0423]**
- WO 9734911 A **[0423]**
- WO 9923105 A **[0423]**
- US 5336603 A **[0423]**
- US 5359046 A **[0423]**
- US 5349053 A **[0423]**
- US 5447851 A **[0423]**
- US 5112946 A **[0423]**
- EP 307434 A **[0423]**
- EP 367166 A **[0423]**
- WO 9604388 A **[0423]**
- WO 9106570 A **[0423]**
- WO 20120128801 A **[0429] [0481]**
- US 7744877 B **[0446]**
- US 7422739 B **[0476]**

Non-patent literature cited in the description

- **ABBAS.** Cellular and Molecular Immunology. W.B. Saunders Company, 2010 **[0084]**
- **MURPHEY et al.** Janeway's Immunobiology. Garland Science, 2011 **[0084]**
- **KABAT et al.** NIH Publication 91-3242. National Technical Information Service, 1991 **[0089]**
- **CHOTHIA et al.** *J. Mol. Biol.,* 1987, vol. 196, 901-917 **[0091]**
- **MACCALLUM et al.** *J. Mol. Biol.,* 1996, vol. 262, 732-745 **[0091]**
- **CHOTHIA et al.** *Nature,* 1989, vol. 342, 877-883 **[0091]**
- Handbook of Therapeutic Antibodies. WILEY-VCH Verlag GmbH and Co, 2007 **[0091]**
- **BHASKARAN R. ; PONNUSWAMY P. K.** *Int. J. Pept. Protein Res.,* 1988, vol. 32, 242-255 **[0096]**
- **DELEAGE, G. ; ROUX B.** *Protein Engineering,* 1987, vol. 1, 289-294 **[0096]**
- Therapeutic Monoc/onal Antibodies: Frorn Bench to Clinic. John Wiley and Sons, 2009 **[0098]**
- Current Trends in Monoclonal Antibody Development and Manufacturing. Springer Science + Business Media LLC, 2010 **[0098]**
- **HARLOW et al.** Antibodies: A Laboratory Manual. Cold Spring Harbor Laboratory Press, 1988 **[0098]**
- **HAMMERLING et al.** Monoclonal Antibodies and T-Cell Hybridomas. Elsevier, 1981, 563-681 **[0098]**
- **MORRISON et al.** *Proc. Natl. Acad. Sci. USA,* 1984, vol. 81, 6851-6855 **[0099]**
- **JONES et al.** *Nature,* 1986, vol. 321, 522-525 **[0102]**
- **TOMLINSON, I. A. et al.** *J. Mol, Biol.,* 1992, vol. 227, 776-798 **[0103]**
- **COOK, G. P. et al.** *Immunol. Today,* 1995, vol. 16, 237-242 **[0103]**
- **CHOTHIA, D. et al.** *J. Mol. Biol.,* 1992, vol. 227, 799-817 **[0103]**
- **TOMLINSON et al.** *EMBO J,* 1995, vol. 14, 4628-4638 **[0103]**
- **RETTER et al.** *Nucleic Acid Res.,* 2005, vol. 33, 671-674 **[0103]**
- **BARBAS et al.** *Proc. Natl. Acad. Sci. USA,* 1991, vol. 88, 7978-7982 **[0106]**
- **LEUNG et al.** *Technique,* 1989, vol. 1, 11-15 **[0108]**
- **MARKS.** *Biotechnol.,* 1992, vol. 10, 779-783 **[0108]**
- **VAUGHAN et al.** *Nature Biotechnology,* 1996, vol. 14, 309-314 **[0109]**
- **SHEETS et al.** *Proc. Natl. Acad. Sci. USA,* 1998, vol. 95, 6157-6162 **[0109]**
- **LONBERG ; HUSZAR.** *Intern. Rev. Immunol.,* 1995, vol. 13, 65-93 **[0110]**
- **COLE et al.** Monoclonal Antibodies and Cancer Therapy. Alan R. Liss, 1985, 77 **[0110]**
- **BOERNER et al.** *J Immunol,* 1991, vol. 147 (1), 86-95 **[0110]**
- **SAMBROOK J. ; RUSSELL D.** Molecular Cloning: A Laboratory Manual. Cold Spring Harbor Laboratory Press, 2000 **[0113]**
- **AUSUBEL et al.** Short Protocols in Molecular Biology: A Compendium of Methods from Current Protocols in Molecular Biology. Wiley, John & Sons, Inc, 2002 **[0113]**
- **SAMBROOK ; FRITSCH ; MANIATIS.** Molecular Cloning: A Laboratory Manual. Cold Spring Harbor Laboratory Press, 1989 **[0119]**
- Current Protocols in Molecular Biology. John Wiley & Sons, Inc, 1995 **[0119]**
- **DURBIN.** Biological Sequence Analysis: Probabilistic models of proteins and nucleic acids. Cambridge Press, 1998 **[0120]**
- **ALTSCHUL et al.** *J. Mol. Biol.,* 1990, vol. 215, 403-410 **[0121]**
- **ALTSCHUL et al.** *Nucleic Acids Res.,* 1997, vol. 25, 3389-402 **[0121]**
- Guide to Molecular Cloning Techniques. **BERGER ; KIMMEL.** Methods in Enzymology. Academic Press, Inc, vol. 152 **[0123]**
- **SAMBROOK et al.** Molecular Cloning-A Laboratory Manual. Cold Spring Harbor Laboratory, 2000, vol. 1-3 **[0123]**
- Current Protocols in Molecular Biology. Greene Publishing Associates, Inc. and John Wiley & Sons, Inc, 2006 **[0123]**
- **CREIGHTON.** Proteins: Structures and Molecular Principles. W.H. Freeman & Co, 1983 **[0132]**
- **HUNKAPILLER, M. et al.** *Nature,* 1984, vol. 310, 105-111 **[0132]**
- **HOGAN et al.** Manipulating the Mouse Embryo: A Laboratory Manual. Cold Spring Harbor Press, 1999 **[0134]**

- **JACKSON et al.** Mouse Genetics and Transgenics: A Practical Approach. Oxford University Press, 2000 **[0134]**
- **PINKERT.** Transgenic Animal Technology: A Laboratory Handbook. Academic Press, 1999 **[0134]**
- **LINDMARK et al.** *J Immunol Meth,* 1983, vol. 62, 1 **[0137]**
- **GUSS et al.** *EMBO J,* 1986, vol. 5, 1567 **[0137]**
- Fundamental Immunology. Raven Press, 1999 **[0143]**
- **MILLSTEIN et al.** *Nature,* 1983, vol. 305, 537-539 **[0146]**
- **SURESH et al.** *Methods in Enzymology,* 1986, vol. 121, 210 **[0146]**
- **RAVETCH ; KINET.** *Annu. Rev. Immunol,* 1991, vol. 9, 457-92 **[0150]**
- **CAPEL.** *Immunomethods,* 1994, vol. 4, 25-34 **[0150]**
- **DE HAAS et al.** *J. Lab. Clin. Med.,* 1995, vol. 126, 330-41 **[0150]**
- **SHIELDS et al.** *J. Biol. Chem.,* 2001, vol. 9 (2), 6591-6604 **[0151]**
- **SHIELDS, R. L. et al.** *J. Biol. Chem.,* 2002, vol. 277, 26733-26740 **[0153]**
- **COCHRAN et al.** *J Immunol Methods.,* 2004, vol. 287 (1-2), 147-158 **[0174]**
- **REINEKE.** *Methods Mol Biol,* 2004, vol. 248, 443-63 **[0175]**
- **TOMER.** *Protein Science,* 2000, vol. 9, 487-496 **[0175]**
- **BJELLQVIST et al.** *Electrophoresis,* 1993, vol. 14, 1023 **[0183]**
- **VERMEER et al.** *Biophys. J.,* 2000, vol. 78, 394-404 **[0183]**
- **VERMEER et al.** *Biophys. J.,* 2000, vol. 79, 2150-2154 **[0183]**
- **NARAMURA et al.** *Immunol. Lett.,* 1994, vol. 39, 91-99 **[0187]**
- **GILLIES et al.** *PNAS,* 1992, vol. 89, 1428-1432 **[0187]**
- **FELL et al.** *J. Immunol.,* 1991, vol. 146, 2446-2452 **[0187]**
- **HERMANSON, G.T.** Bioconjugate Techniques. Academic Press, 1996, 234-242 **[0189]**
- **JOHNSON et al.** *Anticancer Res.,* 1995, vol. 15, 1387-93 **[0192]**
- **LAU et al.** *Bioorg-Med-Chem.,* 1995, vol. 3 (10), 1299-1304 **[0192]**
- **LAU et al.** *Bioorg-Med-Chem,* 1995, vol. 3 (10), 1305-12 **[0192]**
- **DUBOWCHIK et al.** *Bioconjugate Chemistry,* 2002, vol. 13, 855-869 **[0222]**
- **DENARDO et al.** *Clin Cancer Res.,* 1998, vol. 4, 2483 **[0268]**
- **PETERSON et al.** *Bioconjug. Chem.,* 1999, vol. 10, 553 **[0268]**
- **ZIMMERMAN et al.** *Nucl. Med. Biol.,* 1999, vol. 26, 943 **[0268]**
- **GARNETT.** *Adv Drug Deliv Rev,* 2002, vol. 53, 171 **[0269] [0423]**
- Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy. **AMON et al.** Monoclonal Antibodies And Cancer Therapy. Alan R. Liss, Inc, 1985, 243-56 **[0269]**
- Antibodies For Drug Delivery. **HELLSTROM et al.** Controlled Drug Delivery. Marcel Dekker, Inc, 1987, 623-53 **[0269]**
- Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review. **THORPE et al.** Monoclonal Antibodies '84: Biological And Clinical Applications. 1995, 475-506 **[0269]**
- Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy. Monoclonal Antibodies For Cancer Detection And Therapy. Academic Press, 1985, 303-16 **[0269]**
- **THORPE et al.** *Immunol. Rev.,* 1982, vol. 62, 119 **[0269]**
- **WILSON et al.** *Cell,* 1984, vol. 37, 767 **[0273]**
- **FUHRMANN, S.** *Annual Meeting ofAACR Abstract No. 5625,* 2010 **[0275]**
- **TAKAHASHI et al.** *J. Immunol.,* 1994, vol. 6, 1567 **[0423]**
- **ASHKENAZI et al.** *PNAS USA,* 1991, vol. 88, 10535 **[0423]**
- **ZHENG et al.** *J Immunol,* 1995, vol. 154, 5590 **[0423]**
- **VIL et al.** *PNAS USA,* 1992, vol. 89, 11337 **[0423]**
- **DENARDO et al.** *Clin Cancer Res,* 1998, vol. 4, 2483 **[0423]**
- **PETERSON et al.** *Bioconjug Chem,* 1999, vol. 10, 553 **[0423]**
- **ZIMMERMAN et al.** *Nucl Med Biol,* 1999, vol. 26, 943 **[0423]**
- **PINHASOV et al.** *Comb. Chem. High Throughput Screen.,* 2004, vol. 7, 133 **[0435]**
- **MOCELLIN ; ROSSI.** *Adv. Exp. Med. Biol,* 2007, vol. 593, 19 **[0435]**
- **GENNARO.** Remington: The Science and Practice of with Facts and Comparisons: Drugfacts Plus. 2003 **[0437]**
- **ANSEL et al.** Pharmaceutical Dosage Forms and Drug Delivery Systems. Lippencott Williams and Wilkins, 2004 **[0437]**
- **KIBBE et al.** Handbook of Pharmaceutical Excipients. Pharmaceutical Press, 2000 **[0437]**
- **REMINGTON.** The Science and Practice of Pharmacy. Mack Publishing, 2000 **[0439]**
- **GAIDONO et al.** Lymphomas. *IN CANCER: PRINCIPLES & PRACTICE OF ONCOLOGY,* vol. 2, 2131-2145 **[0473]**
- **ABBAS et al.** Cellular and Molecular Immunology. W.B. Saunders Company, 2010 **[0484]**
- **SAMBROOK J. ; RUSSELL D.** Molecular Cloning: A Laboratory Manual. Cold Spring Harbor Laboratory Press, 2000 **[0484]**

- Short Protocols in Molecular Biology. **AUSUBEL et al.** A Compendium of Methods from Current Protocols in Molecular Biology. Wiley, John & Sons, Inc, 2002 **[0484]**
- **HARLOW ; LANE.** Using Antibodies: A Laboratory Manual. Cold Spring Harbor Laboratory Press, 1998 **[0484]**
- **COLIGAN et al.** Short Protocols in Protein Science. Wiley, John & Sons, Inc, 2003 **[0484]**
- **APELQVIST A et al.** Notch signalling controls pancreatic cell differentiation. *Nature,* 1999, vol. 400, 877-81 **[0485]**
- **BIGAS A ; ESPINOSA L.** Hematopoietic stem cells: to be or Notch to be. *Blood,* 2012 **[0485]**
- **CABRERA CV.** Lateral inhibition and cell fate during neurogenesis in Drosophila: the interactions between scute. *Notch and Delta. Development,* 1990, vol. 110, 733-42 **[0485]**
- **CHAPMAN G et al.** Notch inhibition by the ligand DELTA-LIKE 3 defines the mechanism of abnormal vertebral segmentation in spondylocostal dysostosis. *Hum Mol Genet.,* 2011, vol. 20, 905-16 **[0485]**
- **CHEN H et al.** Conservation of the Drosophila lateral inhibition pathway in human lung cancer: a hairy-related protein (HES-1) directly represses achaete-scute homolog-1 expression. *Proc Natl Acad Sci U S A.,* 1997, vol. 94, 5355-60 **[0485]**
- **COOK M et al.** Notch in the development of thyroid C-cells and the treatment of medullary thyroid cancer. *Am J Transl Res.,* 2010, vol. 2, 119-25 **[0485]**
- **DE LA POMPA JL et al.** Conservation of the Notch signaling pathway in mammalian neurogenesis. *Development,* 1997, vol. 124, 1139-48 **[0485]**
- **D'SOUZA B et al.** Canonical and non-canonical Notch ligands. *Curr Top Dev Biol.,* 2010, vol. 92, 73-129 **[0485]**
- **DUNWOODIE SL.** The role of Notch in patterning the human vertebral column. *Curr Opin Genet Dev.,* 2009, vol. 19, 329-37 **[0485]**
- **DUTTA S et al.** Notch signaling regulates endocrine cell specification in the zebrafish anterior pituitary. *Dev Biol.,* 2008, vol. 319, 248-57 **[0485]**
- **FRE S et al.** Notch signals control the fate of immature progenitor cells in the intestine. *Nature,* 2005, vol. 435, 964-8 **[0485]**
- **FRE S et al.** Notch and Wnt signals cooperatively control cell proliferation and tumorigenesis in the intestine. *Proc Natl Acad Sci U S A.,* 2009, vol. 106, 6309-14 **[0485]**
- **GALLUZZO P ; BOCCHETTA M.** Notch signaling in lung cancer. *Expert Rev Anticancer Ther.,* 2011, vol. 11, 533-40 **[0485]**
- **GEFFERS I et al.** Divergent functions and distinct localization of the Notch ligands DLL1 and DLL3 in vivo. *J Cell Biol.,* 2007, vol. 178, 465-76 **[0485]**
- **GLITTENBERG M et al.** Role of conserved intracellular motifs in Serrate signalling, cis-inhibition and endocytosis. *EMBO J.,* 2006, vol. 25, 4697-706 **[0485]**
- **GOLDBETER A ; POURQUIÉ O.** Modeling the segmentation clock as a network of coupled oscillations in the Notch, Wnt and FGF signaling pathways. *J Theor Biol.,* 2008, vol. 252, 574-85 **[0485]**
- **HABENER JF et al.** Minireview: transcriptional regulation in pancreatic development. *Endocrinology,* 2005, vol. 146, 1025-34 **[0485]**
- **HARRIS PJ et al.** Targeting embryonic signaling pathways in cancer therapy. *Expert Opin Ther Targets,* 2012 **[0485]**
- **HENKE RM et al.** AscII and Neurog2 form novel complexes and regulate Delta-like3 (DLL3) expression in the neural tube. *Dev Biol.,* 2009, vol. 328, 529-40 **[0485]**
- **HOYNE GF et al.** A cell autonomous role for the Notch ligand Delta-like 3 in $\alpha\beta$ T-cell development. *Immunol Cell Biol.,* 2011, vol. 89, 696-705 **[0485]**
- **HUBER K et al.** Development of chromaffin cells depends on MASHI function. *Development,* 2002, vol. 129, 4729-38 **[0485]**
- **ITO T et al.** Basic helix-loop-helix transcription factors regulate the neuroendocrine differentiation of fetal mouse pulmonary epithelium. *Development,* 2000, vol. 127, 3913-21 **[0485]**
- **JENSEN J et al.** Control of endodermal endocrine development by Hes-1. *Nat Genet.,* 2000, vol. 24, 36-44 **[0485]**
- **KAGEYAMA R et al.** Oscillator mechanism of Notch pathway in the segmentation clock. *Dev Dyn.,* 2007, vol. 236, 1403-9 **[0485]**
- **KAMEDA Y et al.** Mashl regulates the development of C cells in mouse thyroid glands. *Dev Dyn.,* 2007, vol. 236, 262-70 **[0485]**
- **KLEIN T et al.** An intrinsic dominant negative activity of serrate that is modulated during wing development in Drosophila. *Dev Biol.,* 1997, vol. 189, 123-34 **[0485]**
- **KLIMSTRA DS et al.** The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. *Pancreas,* 2010, vol. 39, 707-12 **[0485]**
- **KLÖPPEL G.** Classification and pathology of gastroenteropancreatic neuroendocrine neoplasms. *Endocr Relat Cancer,* 2011, vol. 1, 1-16 **[0485]**
- **KOCH U ; RADTKE F.** Notch signaling in solid tumors. *Curr Top Dev Biol.,* 2010, vol. 92, 411-55 **[0485]**
- **KUSUMI K et al.** The mouse pudgy mutation disrupts Delta homologue DLL3 and initiation of early somite boundaries. *Nat Genet,* 1998, vol. 19, 274-8 **[0485]**
- **LADI E et al.** The divergent DSL ligand DLL3 does not activate Notch signaling but cell autonomously attenuates signaling induced by other DSL ligands. *J Cell Biol.,* 2005, vol. 170, 983-92 **[0485]**
- **LIU J et al.** Notch signaling in the regulation of stem cell self-renewal and differentiation. *Curr Top Dev Biol.,* 2010, vol. 92, 367-409 **[0485]**

- **NAGASE H et al.** γ-Secretase-regulated signaling pathways, such as notch signaling, mediate the differentiation of hematopoietic stem cells, development of the immune system, and peripheral immune responses. *Curr Stem Cell Res Ther,* 2011, vol. 6, 131-41 **[0485]**
- **RAETZMAN LT.** Developmental regulation of Notch signaling genes in the embryonic pituitary: Prop1 deficiency affects Notch2 expression. *Dev Biol.,* 2004, vol. 265, 329-40 **[0485]**
- **REBAY I et al.** Specific EGF repeats of Notch mediate interactions with Delta and Serrate: implications for Notch as a multifunctional receptor. *Cell.,* 1991, vol. 67, 687-99 **[0485]**
- **SAKAMOTO K et al.** Intracellular cell-autonomous association of Notch and its ligands: a novel mechanism of Notch signal modification. *Dev Biol.,* 2002, vol. 241, 313-26 **[0485]**
- **SCHONHOFF SE et al.** Minireview: Development and differentiation of gut endocrine cells. *Endocrinology,* 2004, vol. 145, 2639-44 **[0485]**
- **SHIMIZU K et al.** Mouse jagged1 physically interacts with notch2 and other notch receptors. Assessment by quantitative methods. *J Biol Chem.,* 1999, vol. 274, 32961-9 **[0485]**
- **SHINKAI Y et al.** New mutant mouse with skeletal deformities caused by mutation in delta like 3 (DLL3) gene. *Exp Anim.,* 2004, vol. 53, 129-36 **[0485]**
- **SPRINZAK D et al.** Cis-interactions between Notch and Delta generate mutually exclusive signalling states. *Nature,* 2010, vol. 465, 86-90 **[0485]**
- **SRIURANPONG V et al.** Notch signaling induces rapid degradation of achaete-scute homolog 1. *Mol Cell Biol.,* 2002, vol. 22, 3129-39 **[0485]**
- **STERNBERG PW.** Lateral inhibition during vulval induction in Caenorhabditis elegans. *Nature,* 1988, vol. 335, 551-4 **[0485]**
- **WHARTON KA et al.** Nucleotide sequence from the neurogenic locus notch implies a gene product that shares homology with proteins containing EGF-like repeats. *Cell,* 1985, vol. 43, 567-81 **[0485]**
- **YAO JC et al.** One hundred years after ''carcinoid'': epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol.,* 2008, vol. 26, 3063-72 **[0485]**
- **ZAREBCZAN B ; CHEN H.** Signaling mechanisms in neuroendocrine tumors as targets for therapy. *Endocrinol Metab Clin North Am.,* 2010, vol. 39, 801-10 **[0485]**
- **COCHRAN et al.** *J Immunol Methods,* 2004, vol. 287 (1-2), 147-158 **[0547]**
- **CHAO et al.** *Nat Protoc.,* 2007, vol. 1 (2), 755-768 **[0558]**

摘要

本发明提供了新型调节剂，包括抗体和其衍生物；及使用这些调节剂治疗增生性病症的方法。