

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

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Abogado
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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ASUNTO	Radicación	07-22892
	Trámite	11
	Evento	378
	Actuación	519
	Oficio	
	Folios	3

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (Fase Nacional)	☒	Capítulo I	☒
		Capítulo II	☐
No Solicitud Internacional		PCT/US2005/031907	
Fecha de Presentación Internacional		07/Septiembre/2005	

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 94 a 230	07/Marzo/2007
Reivindicaciones:	Folios 231 a 233	07/Marzo/2007
Dibujos:	Folios 235 a 271	07/Marzo/2007
Prioridad:	US 60/607,909	08/Septiembre/2004
	US 60/666,553	30/Marzo/2005

2. Análisis de la Prioridad

Se acepta la reivindicación de Prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486), y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: "Métodos para utilizar ligandos de receptor muerto y anticuerpos CD20".

El problema planteado en esta solicitud consiste en suministrar un método para tratar el cáncer y enfermedades relacionadas con el sistema inmune.

Para resolver este problema técnico la solicitud en estudio proporciona un método para utilizar el ligando/TRAIL Apo-2 o los anticuerpos de receptor muerto en combinación con los anticuerpos CD20.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C07K 14/705, C07K 16/28, A61P 35/02, A61K 39/395.

4. Excepción a la Patentabilidad (Art 20 D 486 literal (d))

El objeto de las reivindicaciones 1 – 21 no es patentable de acuerdo con el Art citado.

Sin embargo, esta Superintendencia pone en conocimiento que la combinación de Rituximab y una citoquina de la familia del factor de necrosis tumoral (TNF), como Apo2L ya se encuentra divulgada en los documentos US20030092631 (párrafo 199), publicado el 15 de Mayo de 2003 (Folios 459 y 460) y WO03/038043 (páginas 6-8 y página 54, líneas 8-14), publicado el 8 de Mayo de 2003 (Folios 461-465).

5. De la Solicitud de Patente

Título

El título no corresponde con un objeto patentable por lo cual se sugiere al Solicitante hacer la corrección necesaria.

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Las reivindicaciones 1 – 21 corresponden a materia no patentable porque corresponden a métodos terapéuticos para el tratamiento de mamíferos.

Las reivindicaciones 1 y 6 no son concisas porque utilizan los términos “polipéptido Apo2L/TRAIL”, “anticuerpo CD20”, “uno o más agentes inhibidores de crecimiento”, lo cual no permite determinar la extensión del objeto que se busca proteger.

En las reivindicaciones 1 – 4, 9, 10, 13 y 16, la invención no se divulga de forma completa para que la persona del oficio normalmente versada en la materia pueda ejecutarla cuando el polipéptido Apo2L/TRAIL es un fragmento o una variante y cuando el anticuerpo es un anticuerpo monoclonal CD20. Se requiere al Solicitante definir las características esenciales o estructurales, como la secuencia de aminoácidos.

Se requiere al Solicitante hacer las aclaraciones necesarias.

6. Examen de Patentabilidad (Art 14 D486)

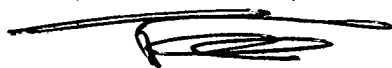
Aplicación industrial (Art 19 D 486)

Las reivindicaciones 1 – 21 no tienen aplicación industrial porque corresponden a métodos terapéuticos para mamíferos.

7. Conclusión

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ

Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha

_____, 19 FEB 2012

Elaborado por: Juan David Moncaleano.

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orlt

(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2003/0092631 A1**
Deshayes et al. (43) **Pub. Date: May 15, 2003**(54) **IGF ANTAGONIST PEPTIDES****Related U.S. Application Data**(75) **Inventors:** **Kurt D. Deshayes**, San Francisco, CA (US); **Henry B. Lowman**, El Granada, CA (US); **Michelle L. Schaffer**, Cambridge (GB); **Sachdev S. Sidhu**, San Francisco, CA (US)(60) **Provisional application No. 60/275,904**, filed on Mar. 14, 2001.**Publication Classification****Correspondence Address:****GENENTECH, INC.****1 DNA WAY****SOUTH SAN FRANCISCO, CA 94080 (US)**(51) **Int. Cl.⁷** **A61K 38/10; C07K 7 08**(52) **U.S. Cl.** **514/14; 530-326**(57) **ABSTRACT**(73) **Assignee: GENENTECH, INC.**(21) **Appl. No.: 10/098,093**(22) **Filed: Mar. 13, 2002**

Peptides are provided that antagonize the interaction of IGF-1 with its binding proteins, insulin receptor, and IGF receptor. These IGF antagonist peptides are useful in treating disorders involving IGF-1 as a causative agent, such as, for example, various cancers.

the alveoli. Other considerations such as construction of the delivery device, additional components in the formulation, and particle characteristics are important. These aspects of pulmonary administration of a drug are well known in the art, and manipulation of formulations, aerosolization means, and construction of a delivery device require at most routine experimentation by one of ordinary skill in the art.

[0191] With regard to construction of the delivery device, any form of aerosolization known in the art, including but not limited to nebulization, atomization, or pump aerosolization of a liquid formulation, and aerosolization of a dry powder formulation, can be used in the practice of the invention. A delivery device that is uniquely designed for administration of solid formulations is envisioned. Often, the aerosolization of a liquid or a dry powder formulation will require a propellant. The propellant may be any propellant generally used in the art. Specific nonlimiting examples of such useful propellants include a chlorofluorocarbon, a hydrofluorocarbon, a hydrochlorofluorocarbon, or a hydrocarbon, including trifluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethanol, and 1,1,1,2-tetrafluoroethane, or combinations thereof.

[0192] In a preferred aspect of the invention, the device for aerosolization is a metered dose inhaler. A metered dose inhaler provides a specific dosage when administered, rather than a variable dose depending on administration. Such a metered dose inhaler can be used with either a liquid or a dry powder aerosol formulation. Metered dose inhalers are well known in the art.

[0193] Once the peptide reaches the lung, a number of formulation-dependent factors affect the drug absorption. It will be appreciated that in treating a disease or disorder that requires circulatory levels of the peptide, such factors as aerosol particle size, aerosol particle shape, the presence or absence of infection, lung disease, or emboli may affect the absorption of the peptides. For each of the formulations described herein, certain lubricators, absorption enhancers, protein stabilizers or suspending agents may be appropriate. The choice of these additional agents will vary depending on the goal. It will be appreciated that in instances where local delivery of the peptides is desired or sought, such variables as absorption enhancement will be less critical.

[0194] The liquid aerosol formulations of the present invention will typically be used with a nebulizer. The nebulizer can be either compressed air driven or ultrasonic. Any nebulizer known in the art can be used in conjunction with the present invention such as but not limited to the ULTRAVENT™ nebulizer (Mallinckrodt, Inc., St. Louis, Mo.) or the ACORN II™ nebulizer (Marquest Medical Products, Englewood CO). Other nebulizers useful in conjunction with the present invention are described in U.S. Pat. Nos. 4,624,251; 3,703,173; 3,561,444; and 4,635,627.

[0195] The liquid aerosol formulation may include a carrier. The carrier is a macromolecule that is soluble in the circulatory system and that is physiologically acceptable where physiological acceptance means that those of skill in the art would accept injection of said carrier into a patient as part of a therapeutic regime. The carrier preferably is relatively stable in the circulatory system with an acceptable plasma half life for clearance. Such macromolecules include but are not limited to soya lecithin, oleic acid, and sorbitan trioleate, with sorbitan trioleate preferred.

[0196] The liquid aerosol formulations herein may also include other agents useful for protein stabilization or for the regulation of osmotic pressure. Examples of the agents include but are not limited to salts, such as sodium chloride or potassium chloride, and carbohydrates, such as glucose, galactose or mannose, and the like.

[0197] It is also contemplated that the present pharmaceutical formulation will be used as a dry powder inhaler formulation comprising a finely divided powder form of the peptide and a dispersant. The form of the peptide will generally be a lyophilized powder. Lyophilized forms of peptides can be obtained through standard techniques.

[0198] In another embodiment, the dry powder formulation will comprise a finely divided dry powder containing one or more peptides of the present invention, a dispersing agent and also a bulking agent. Bulking agents useful in conjunction with the present formulation include such agents as lactose, sorbitol, sucrose, or mannitol, in amounts that facilitate the dispersal of the powder from the device.

[0199] The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Hence, the present application contemplates combining the peptide with one or more other therapeutic agent(s), which depend on the particular indication being treated. While the agent may be an endocrine agent such as a GH, a GHRP, a GHRH, a GH secretagogue, an IGFBP, ALS, a GH complexed with a GHBP, it is preferably a cytotoxic agent, especially for treating cancer. For instance, the peptide may be co-administered with another peptide (or multivalent antibodies), a monovalent or bivalent antibody (or antibodies), chemotherapeutic agent(s) (including cocktails of chemotherapeutic agents), other cytotoxic agent(s), anti-angiogenic agent(s), cytokines, and/or growth inhibitory agent(s). Where the peptide induces apoptosis, it may be particularly desirable to combine the peptide with one or more other therapeutic agent(s) that also induce apoptosis. For instance, the peptide may be combined with pro-apoptotic antibodies (e.g., bivalent or multivalent antibodies) directed against B-cell surface antigens (e.g., RITUXAN®, ZEVALIN® or BEXXAR® anti-CD20 antibodies) and/or with (1) pro-apoptotic antibodies (e.g., bivalent or multivalent antibodies directed against a receptor in the TNF receptor superfamily, such as anti-DR4 or anti-DR5 antibodies) or (2) cytokines in the TNF family of cytokines (e.g., Apo2L). Likewise, the peptide may be administered along with anti-ErbB antibodies (e.g., HERCEPTIN® anti-HER2 antibody) alone or combined with (1) and/or (2). Alternatively, or additionally, the patient may receive combined radiation therapy (e.g., external beam irradiation or therapy with a radioactive labeled agent, such as an antibody), ovarian ablation, chemical or surgical, or high-dose chemotherapy along with bone marrow transplantation or peripheral-blood stem-cell rescue or transplantation. Such combined therapies noted above include combined administration (where the two or more agents are included in the same or separate formulations), and separate administration, in which case, administration of the peptide can occur prior to, and/or following, administration of the adjunct therapy or therapies. The effective amount of such other agents depends on the amount of peptide present in the formulation, the type of disorder or treatment, and other factors discussed above. These are

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(54) Title: COMBINATIONS OF ANTIBODIES SELECTIVE FOR A TUMOR NECROSIS FACTOR-RELATED APOPTOSIS-INDUCING LIGAND RECEPTOR AND OTHER THERAPEUTIC AGENTS

(57) Abstract: An antibody of the invention interacts with human DR5 or with human DR4 to produce agonistic or antagonistic effects downstream of the receptor including inhibition of cell proliferation and apoptosis. Methods and uses for the antibodies, optionally in combination with various therapeutic agents, are detailed, including treatment of apoptosis-related disease and treatment of dysregulated cell growth.

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Summary of the Invention

In one embodiment, the invention relates to an antibody which recognizes a TRAIL receptor DR5 and which induces apoptosis in a DR5-expressing cell *in vivo* or *in vitro*. Further disclosed is an antibody that recognizes DR5 but not DR4, DcR1, or DcR2. Specifically detailed is a monoclonal antibody to DR5 produced by a hybridoma.

In another embodiment, the invention relates to an antibody which recognizes a TRAIL receptor DR4 and which induces apoptosis in a DR4-expressing cell *in vivo* or *in vitro*. Further disclosed is an antibody that recognizes DR4 but not DR5, DcR1, or DcR2. Specifically detailed is a monoclonal antibody to DR4 produced by a hybridoma.

A method provided is induction of apoptosis in target cells or inhibition of target cell proliferation by contacting a cell with a therapeutic quantity of an antibody capable of binding to DR5 or DR4. In various embodiments of the method, the apoptosis can be induced or the cell proliferation inhibited by contacting the target cells with antibodies against other death receptors.

Also disclosed is a pharmacological composition that includes a therapeutic amount of monoclonal antibody active against a DR5, a pharmaceutically acceptable carrier and, optionally, a container enclosing the antibody and the carrier. Further provided by the invention is the use of an antibody recognizing DR5 or an antibody recognizing DR4 for preparing a therapeutic for selective apoptosis of abnormal or dysregulated cells.

An antibody of the present invention interacts with a tumor necrosis factor related apoptosis-inducing ligand receptor such as DR4, DR5, DrR1, DrR2 and OPG, inducing apoptosis in a cell expressing such a receptor. Disclosed is an antibody of the invention capable of selectively binding an agonistic or antagonistic tumor necrosis factor ligand receptor epitope.

The present invention provides a treatment for an apoptosis related disease, cancer, inflammatory disease, or an autoimmune disease by a method that includes

contacting a target tissue having the disease to a therapeutic quantity of an antibody of the invention, singly or in combination with other apoptosis inducing antibodies, and/or other therapeutic agents or treatments.

Further described is a fusion protein that includes an antigenic TRAIL
5 receptor amino acid sequence having at least ten bases, coupled to an immunoglobulin protein or fragment thereof capable of eliciting an immune response within a subject.

The present invention provides a method of gene therapy in which a target
10 cell is transfected with a TRAIL receptor nucleic acid sequence in an expression vector so that the TRAIL receptor is expressed on the target cell. The target cell is then exposed to an antibody that selectively binds the TRAIL receptor.

Provided are nucleic acid sequences and amino acid sequences encoding the
heavy and light chain immunoglobulins of an antibody selective for DR5. Sequences
are also provided for an antibody that selectively binds DR4. Also detailed are
15 vectors that include a nucleic acid sequence of the invention and host cells transformed with a vector of the invention.

The present invention provides a humanized DR5 antibody (e.g., TRA-8) and
a humanized DR4 (e.g., 2E12), as well as a transfected cell producing the humanized
DR5 antibody and a transfected cell producing the humanized DR4 antibody.

20 A process for producing a humanized DR5 antibody or DR4 antibody is described in which a host is transformed with nucleic acid sequences encoding a humanized immunoglobulin light chain and a humanized immunoglobulin heavy chain after which the transformed host is incubated for a predetermined period of time.

25 Also described is a process for inducing apoptosis in target cells or for inhibiting cell proliferation that includes contacting a target cell with a pharmaceutically effective amount of a humanized DR5 antibody, a humanized DR4 antibody, or a combination of a DR5 antibody and an antibody to another death

receptor(e.g., an antibody to DR4), in the presence or absence of other therapeutic agents and treatments.

A commercial kit is provided for inducing apoptosis that includes a humanized TRA-8 antibody selective for DR5 or a humanized antibody for DR4
5 (e.g., humanized 2E12), packaged in a suitable container, and optionally with instructions for use.

Brief Description of the Drawings

Figure 1. Characterization of TRA-8. (a.) Binding specificity of TRA-8:
10 Western blot analysis (upper panel): Recombinant fusion proteins of the TNFR family probed with TRA-8 or anti-human IgG. Lane 1: DR5/hIgG1 fusion protein (immunogen); Lane 2: DR4/hIgG1 (TRAIL-R1); Lane 3: DR5/hIgG1; Lane 4: TRAIL-R3 (DcR-1)/hIgG1; Lane 5: TRAIL-R4 (DcR-2)/hIgG1; Lane 6, CD95/hIgG1; Lane 7: soluble TNFRI. ELISA analysis (lower panel): The well
15 numbers match those of the Western blot except well 8 which is a murine DR5/hIgG1 fusion protein. (b.) Binding activity of soluble TRAIL and TRA-8 to DR5 and DR4: ELISA plates were coated with DR5/hIgG1 (left panel) or DR4/hIgG1 (middle panel) and then incubated with TRAIL or TRA-8. (c.) Flow cytometry analysis of the surface expression of DR5. Cos-7 cells transfected with
20 pcDNA3 expression vector containing the full-length DR5 cDNA (solid histogram), DR4 cDNA (open histogram, solid line) or empty vector (open histogram, dashed line). Forty-eight hours after transfection, cells were stained with TRA-8 followed by PE-conjugated anti-mouse IgG1. (d.) in situ immunohistochemistry reactivity for DR5: Cytospin slides of Cos-7 cells transfected with DR5 expression or control
25 vector were stained with TRA-8 at 48 hours after transfection, (e.) Killing activity of TRA-8: Jurkat cells were incubated with the indicated concentrations of TRA-8. Cell viability was determined by ATPLite, MTT, and PI exclusion assays after overnight culture. The results of ATPLite and MTT assays are presented as percent of medium control, and PI assay are presented as percent of PI negative cells (f.)

For example, an antibody can be administered in conjunction with other therapeutic agents like anti-inflammatory agents, DMARDs, chemotherapeutic agents, methotrexate, bisindolylmaleimide VIII or other sensitizing agents, and the like.

5 Radiotherapy can also be combined with other therapeutic agents in the treatment of inflammatory and autoimmune diseases. One skilled in the art would adapt the form of radiotherapy to the specific inflammatory or autoimmune disease (e.g., radiation synovectomy in the treatment of arthritis).

Therapy using an antibody of the present invention can also be combined with therapy using another antibody. For example, an antibody to DR5 can be
10 administered to a subject in need thereof along with, prior to, or following administration of an antibody to DR4, TNF, B7, CD40 ligand, CD40, CD20 (e.g., rituximab), Fas, or a combination thereof. Such combined antibody therapy can be further combined with administration of one or more therapeutic agents (e.g., chemotherapeutics, doxorubicin, and/or methotrexate), radiotherapy, or both.

15 Thus, the invention provides a method of selectively inducing apoptosis or inhibiting proliferation in target cells expressing DR5, comprising the steps of (a) contacting the target cells with a therapeutic quantity of an antibody that specifically binds a TRAIL receptor DR5, wherein said antibody, in its soluble form, has *in vivo* and *in vitro* apoptosis-inducing activity in target cells expressing DR5 and (b)
20 contacting the target cells with a therapeutic quantity of one or more therapeutic agents. In one embodiment, one or both of the contacting steps are optionally performed *in vivo*. In another embodiment, one or both contacting steps are performed *in vitro*. The target cells can be selected from cells showing dysregulation of the apoptosis system, neutrophils, activated lymphocytes or other activated
25 immune cells (e.g., lymphoid cells and myeloid cells), virally infected cells, and abnormally proliferating synovial cells (e.g., rheumatoid arthritis synovial cells, including inflammatory synovial cells, activated lymphoid and myeloid cells in the synovium, macrophage-like synoviocytes, and fibroblast-like synoviocytes) of autoimmune diseases. Compared to previously published anti-DR5 antibody (24),