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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
E. S. D.

’2).070
REF: Expediente 06-12-070

TITULO SOLICITADO: METODO PARA TRATAR LA ESCLEROSIS
MULTIPLE.

PUBLICACION: Gaceta 583 do 18 Diciembre 2007, NO do publicación
742.

PRIORIDAD: US 601576.993 do 04106/2004

SOLICITANTE: GENENTECH, INC.

APODERADO: JUAN PABLO CADENA SARMIENTO

TRAM1TE: SUSTENTACION DE OPOSICION

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al
. pie de ml firma, abogado en ejerciclo, titular de la tarjeta profesional n(Imero 44655
- del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad LAFRANCOL S.A., dentro del trÆmitede la referenda, en ejercicio de to dispuesto par el arUculo 42 inciso 2° de la Decision 486 de 2000, por medlo del presente escrito, procedo a sustentar y complementar la oposiciOn presentada en
los siguientes tØrminos:

I. RATIFICACION

Comedidamente me permito insistir en los argumentos planteados en la oposiciôn respetiva, los cuales, como se dijo en su momento, demuestran que la solicitud de la referenda incumple con algunos de los requisitos de patentabilidad establecidos en la Decision 486 de 2000, en especial el articulo 20 d) ya que se refiere un mØtodo terapØutico para el tratamiento de aterosclerosis multiple, lo cual incurre

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directamente en una improcedencia de patentabilidad puesto que coma se sabe, "No serân patentables: Los mØtodos terapØuticos a quirOrgicos para el tratamiento humano a animal, asl coma los mØtodos do diagnostico aplicados a los sores humanos o anima!es"

Asi mismo, et pretender protección sobre un mØtodo que se apbca para sujetos que tienen elevados los nivetes de MBP, MOG, et anticuerpo antineurofilamentoso o antigangliosido, y que dichos sujetos tienen niveles elevados de cØlulas B en el fluido cerebroespinal, en la lesion esteroclerOtica o en el suero sanguineo podria considerarse irrelevante toda vez que dichas caracteristicas son tan solo sintomatotogla caracteristica de los pacientes que padecen dicho trastomo esclerOtico, to que en consecuencia demuestra que ademÆs delNo cumplimiento del articulo 20 d) tambiØn podria encontrarse que dicha solicitud carece al menos de nivel inventivo.

IL COMPLEIVIENTO DE INFORMACION.

Si no fuera suficiente la directa improcedencia de patentabilidad en la que incurre la solicitud colombiana en trÆmite at reivindicar un mØtodo terapØutico, existen otros argumentos que pueden desvirtuar el nivel inventivo de dicha solicitud,

veamos:

) La publicación internacional WO 2004/035607 del 29 de abril de 2004 titulada "HUMAN MONOCLONAL ANTIBODIES AGAINST CD20" reivindica:
I.. An isolated human monoclonal antibody wbich binds to human
CD20

81. The method ofclaim 80, wherein Ireatment includes the killing of
B cells wbich produce antibodies against autoantigens.

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I..

82, The method ofclaim 73, wherein the disease or disorder is
selected from the group consisting ofpsoriasis, psoriatic arthritis, dermatitis, systemic scieroderma and sclerosis, inflammatory bowel disease (IBD), Croim’s disease,
ulcerative colitis, respiratory distress syndrome, meningitis, encephalitis, uveitis, glomemlonepbritis, eczema, asthma, atherosclerosis, leukocyte adhesion deficiency, multiple so eros, Raynaud’s syndrome, Sögren’s syndrome,juvenile onset diabetes, Relter’s disease, Behçet’s disease, immune complex nephritis, IgA nepliropathy, 1gM polyneuropathies, immune-mediated thrombocytopenias, such as acute idiopathic thrombocytopenic purpura and chronic idiopathic thrombocytopenic ptupura, belnoiyti4 anemia, myasthenia gravis, lupus nephritis, systemic lupus eiyth.ematosns, rheumatoid arthritis (RA), atopic dermatitis, pempbigtis, Graves’ disease, Hashimoto"s thyroiditis, Wegener’s granu.lomatosis, Omenn’s syndrome, chronic renal failure, acute infectious mononucleosis, HP!, and herpes virus associated diseases.
86. The method of any one ofclaims 7045, further comprising
separately administering another therapeutic agent to the subject

87. The method ofclaim 86, wherein the therapeutic agent is a
cy ooxic agent or a radiotoxic agent.

88. The method of claim 86, wherein the therapeutic agent is an
imrnunosuppressant

89. The method ofclaim 86, wherein the therapeutic agent is an
immunological modulating agent, such as a ctük inc or a cheinoicine.

90. The method ofclaim 86, wherein the therapeutic agent is selected
from the group consisting ofdoxorubicin, cisplatin, bleomycin, carmustine, chlorambudil, and cyclophosphamide.

Hasta aqul si bien es cierto no se revela el mismo regimen de dosificaciôn que el pianteado en la solicitud en trÆmite, se evidencia claramente que el anticuerpo CD20 (Rituximab) es empleado en el tratamiento de trastornos inmunologicos, explicitamente esclerosis miItipIe, ademÆs, se sugiere la combinaciôn de dichos anticuerpos con diversos fÆrmacos, algunos deellos del mismo tipo de los que menciona la solicitud cofombiana en trÆmite especificamente en sus reivindicaciones 18 y 39; de esta manera, quedaria demostrada la ausencia de nivel inventivo de la solicitud colombiana en trÆmite.

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Ahora bien, Si tenemos en cuenta to descrito en la pagina 53, lineas 20 a 36 de
la anterioridad WO 04/035,607 podemos observar que dicho documento reveta:
*

Los anticuerpos monoclonales son administrados en dosificación
semanalmente entre 250mg y 2000mg hasta 8 veces, preferiblemente entre 4y

6 veces.

* El regimen puede ser repetido una a mâs veces como sea necesaria, por ejemplo despuØs de 6 meses o 12 meses.

Por su parte, la solicitud colombiana revela:
*

una cantidad efectiva de un anticuerpo CD20 at sujeto para suministrar una exposición inicial a anticuerpo de aproximadamente 0.5 a 4 gramos.
*

una segunda exposición de anticuerpo de aproximadamente 0.5 a 4 gramos, se suministra luego de aproximadamente 16 a 60 semanas a partir de la exposición inicial, o entre 20 y 30 semanas, y cada una de las exposiciones de anticuerpo se suministra al sujeto como una o dos dosis de anticuerpo.

Si comparamos to descrito en la anterioridad tantas veces mencionadas con Ia revelado en la solicitud colombiana en trÆmite, vemos que existen similitudes entre ellos porque:
*

en los dos mØtodos se procura la administración inicial de dosis de anticuerpo monoclonal entre 250 y 2000mg, 4 a 6 veces para la WO 04/035,607 y entre 500 y 4000mg, 1 a 2 veces para la CO 06-120-070, que, vendrian a ser Sdosificaciones muy cercanas las unas de las otras.

* la segunda exposición se da luego de 6 meses o de 12 meses para la WO 04/035,607 y luego de 4 a 15 meses (16 a 60 semanas), o entre 5 y 7.5 meses (20 a 30 semanas) para la CO 06-120-070.

Par esta razOn, consideramos que la solicitud colombiana en trÆmitecarece at menos de nivel inventivo dada que el problema de proporcionar un regimen de dosificaciôn de un anticuerpo CD20 con distintas exposiciones o con repetición del regimen luego de varios meses para el tratamiento de la esclerosis mUltiple ya habla sido tenido en cuenta en el estado del arte, y ademâs, no representa un avance tØcnico sorprendente.

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> La publicación internacional WO 01/13945 publicada el 01 de marzo de 2001 y titulada "METHODS AND COMPOSITIONS FOR IMMUNOTHERAPY OF CELL INVOLVEMENT IN PROMOTION OF A DISEASE CONDITION COMPRISING MULTIPLE SCLEROSIS" revela:

Drug Action
Betaseron reduces T cells & gamma interferon
beta 1 -Alpha reduces # of circulating T cells
Cladribine - reduces #of circulating ’i’ cells
Copolymer 1 acts as decoy for T cells
Methotrexate reduces # of circulating T cells
Myloral desensitizes T cells to myelin
beta interferon suppresses microglial cells
methyiprednisolone suppresses macrophages
chiorambucil suppresses inflammation
cyclophospharnide suppresses inflammation

Accordingly, it is a primary object of the present
invention to provide compositions and methods for reducing a pro-MS immune response, wherein the treatment is directed to an individual’s immune cells, wherein the immune cells are B lymphocytes, a subpopulation of which may be involved in
the promotion of MS.

In a preferred embodiment, the determinant is selected from the group consisting of cDl9, CD20, CD21, CD22, Lym-1, CDIM, slg having binding specificity for shed antigen, and a combination thereof.

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1. uee of an Æffinityligand in the manufacture of a Pharmaceutical composition for use in a procedure for depleting nonmalignant B cells associated with a disease .condition selected from the group consisting of multiple sclerosis and a pro-MS immune response, and a pro-MS immune response.; wherein the affinity ligand selectively contacts and binds to a B cell determinant; wherein the
pharmaceutical. composLtiou:is administered to an individual in an amount effective to deplete B cells; and wherein upon contact and binding to such B cells, the pharmaceutical
. . composition induces or. causes. B cell depletion.

* The use according to claim l. wherein the pharmaceutical cOmposition further comprises at least one additional component selected. from the group consisting of one or more chemotherapeutic agents, an anti-inflammatory agent, a
. ctolytic agent, a pharmaceutically acceptable carrier, and combination thereof.

13. The use according to claim 11, wherein the affinity ligand comprises a Æhimeric anti-CD20 monoclonal antibody.

Coma se puede apreciar, on estedocumento tamblØn se ye claramente que los anticuerpos CD20 son itiles on el tratamiento de trastomos inmunologicos coma to es la esclerosis mtltiple y qüe pueden combinarse fàrmacos de otro tipo para dicho tratamiento, lo que nuevamente nos muestra la ausencia de nivØt inventivode la solicitud on trmIte.

)’ Existen

. diversas pubticaciones de. carÆcter cientifico que con
anterioridad mencionan el uso de compuestos coma los mencionados on las

rØlvindicaciones 19 y38. en el tratamiento de la escierosis mcftipte, veamos:

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o Approved And Future Pharmacotherapy For Multiple Sclerosis’.

BACKGROUND: Pharmacotherapy for relapsing-remitting multiple sclerosis (MS) advanced with the demonstration that interferon beta and glatiramer acetate improve the clinical course of this disease. Mitoxantrone is the first drug approved by the Food and Drug Administration for treatment of secondary progressive MS. Despite this progress, the agents presently available are only partially effective, are difficult to administer, and may have significant side effects. Several orally administered Immunomodulatory agents are presently being evaluated for treatment of MS. One class of drugs, HMG CoA inhibitors Istatinsi, is safe and well-tolerated and could become another mainstay of MS therapy. SUMMARY:
This article reviews the clinical evidence for approved MS therapies and discusses
their mechanisms of action. Furthermore, the clinical and laboratory data suggesting a potential role for statins in MS therapy are discussed. CONCLUSIONS: Although treatment with interferon beta, glatiramer acetate, and mitoxantrone, the approved therapies, provide important treatment options for
. patients with relapsing-remitting MS and secondary progressive MS, the potential benefits of other medications, including statins, should be explored in controlled
clinical trials.

o Treatment Of Multiple Sclerosis With Gamma Interferon: Exacerbations

Associated With Activation Of The Immune System2.

Abstract: We treated 18 clinically definite relapsing-remitting MS patients with recombinant gamma interferon in a pilot study designed to evaluate toxicity and dosage. Patients received low (1 microgram), intermediate (30 micrograms), or
high (1,000 micrograms) doses of interferon by intravenous infusion twice a week
for 4 weeks. Serum levels of gamma interferon were proportional to dose and no interferon was detected in CSF. Seven of the 18 patients had exacerbations during treatment, a significant increase compared with the prestudy exacerbation rate (p
. less than 0.01). Exacerbations occurred in all three dosage groups and were not precipitated by fever or other dose-dependent side effects. There were significant increases in circulating monocytes bearing class ii (!-ILA-DR) surface antigen, in
the proliferative responses of peripheral blood leukocytes, and in natural killer cell
activity. These results show that systemic administration of gamma interferon has pronounced effects on cellular immunity in MS and on disease activity within the
CNS, suggesting that the attacks induced during treatment were immunologically mediated. Gamma interferon is unsuitable for use as a therapeutic agent in MS. Agents that specifically inhibit gamma interferon production or counteract its effects on immune cells should be investigated as candidates for experimental therapy.

o Extended Use Of Glatiramer Acetate (Copaxone) Is Well Tolerated And

Maintains Its Clinical Effect On Multiple Sclerosis Relapse Rate And

Degree Of Disability3.

St(ive 0, Cree BC, von Budingen HC, Yousef S, Bowen JD, Genain CP, Hauser SL, Steinman L, Zamvil SS. Neurologist. 2002 Sep;8(5):290-301.
2 Panitch 1-IS, Hirsch RL, Schindler J, Johnson KP. Neurology. 1987 JuI;37(7):1097-102.
K. P. Johnson, MD, B. R. Brooks, MD, J. A. Cohen, MD, C. C. Ford, MD, PhD, J. Goldstein, MD, R. P. Lisak, MD, L. W. Myers, MD, H. S. Panitch, MD, J. W. Rose, MD, R. B. Schiffer, MD, T. Vollmer, MD, L.

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Abstract: When 251 relapsing-remitting patients with multiple sclerosis were randomized to receive daily subcutaneous injections of glatiramer acetate, previously called copolymer I (Copaxone, n = 125) or placebo (n = 126) for 24 months, there were no laboratory abnormalities associated with glatiramer acetate treatment and it was well tolerated with few side effects. Patients receiving glatiramer acetate had significantly fewer relapses and were more likely to be neurologically improved, whereas those receiving placebo were more likely to worsen. This study was extended for I to 11 months (mean of 5.2 months for the glatiramer acetate group and 5.9 months for the placebo group). The blinding and study conditions used during the core 24-month study were unchanged throughout the extension. The results of this extension study confirm the excellent tolerance and safety profile of glatiramer acetate for injection. The clinical benefit of glatiramer acetate for both the relapse rate and for neurologic disability was sustained at the end of the extension trial.

o Treatment Of Multiple Sclerosis With Mitoxantrone4.

Abstract: Ten multiple sclerosis patients, all with a rapid deteriorating disease profile, were treated with 12 mg/m2 of the cytostatic agent mitoxantrone, administered every 3 months. This dosage is only 25% of what a patient with a solid tumour would normally receive during the same time period. In all treated patients the deterioration was stopped following the initial dosage; in four out often patients there was even an immediate improvement of the neurological status. Eight out of nine patients showed an improvement after 1 year as compared with their enrollment status; the other one remained stabile. In correlation with the
clinical improvement, the mean P100 latencies of visual evoked potentials showed
a reduction after 1 year. However, the changes identified through magnetic resonance imaging were even clearer than those seen clinically. At admission, this
group of patients presented with a total of 169 gadolinium (Gd)-enhancing lesions.
Only 10 lesions were enhancing in nine patients 12 months after the initiation of
. treatment. It appears that mitoxantrone accelerates the disappearance of Gd-enhancing lesions and prevents the development of new ones. Minimal side effects
such as mild nausea and a slight faintness were evident in six patients and then for
only 1-2 days.

o Low-Dose (7.5 Mg) Oral Methotrexate Reduces The Rate Of Progression In

Chronic Progressive Multiple Sclerosis5.

Abstract: A randomized, double-blinded, placebo-controlled, clinical trial of low-dose, weekly, oral methotrexate was performed in 60 patients with clinically definite chronic progressive multiple sclerosis (MS) attending a referral-based outpatient MS clinic. Study patients were 21 to 60 years old with a disease duration of longer than 1 year. Patients’ Expanded Disability Status Scale scores were 3.0 to 6.5

P. Weiner, MD, J. S. Wolinsky, MD and The Copolymer I Multiple Sclerosis Study Group. NEUROLOGY 1998;50:701-708 ' 1998 American Academy ofNeurology.
"Mauch E, Konthuber HH, Krapf H, Fetzer U, Laufen H. Eur Arch Psychiatry Clin Neurosci. 1992;242(2-
3):96-102. 992;242(23):96-I02.
Goodkin DE, Rudick RA, VanderBrug Medendorp S. Daughtry MM, Schwetz KM, Fischer J, Van Dyke C. Ann Neurol. 1995 Jan;37(1):30-40.

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(ambulatory with moderate disability). Patients were first stratified by Expanded Disability Status Scale scores, 3.0 to 5.5 and 6.0 to 6.5, and then were randomized to receive methotrexate or placebo treatment. Treatment consisted of weekly, oral, low-dose (7.5 mg) methotrexate or identical placebo for 2 years, followed by observation for as long as 1 year. A composite outcome measurement instrument was used and consisted of (1) Expanded Disability Status Scale, (2) ambulation index, (3) Box and Block Test, and (4) 9-Hole Peg Test. Failure of therapy was indicated by a designated change that was sustained for more than 2 months in one or more components of this composite measure. Significantly less progression of impairment as measured by validated tests of upper-extremity function was observed in the methotrexate treatment group in the absence of clinically significant toxicity. We conclude that low-dose, weekly, oral methotrexate offers a new, relatively nontoxic treatment option for patients with chronic progressive MS.

a Treatment Of Multiple Sclerosis With Cyclophosphamide: Critical Review

Of Clinical And Immunologic Effects6.

Abstract: Cyclophosphamide is an alkylating agent used to treat malignancies and immune-mediated inflammatory non-malignant processes such as lupus nephritis and immune-mediated neuropathies. It has been studied as a treatment for multiple sclerosis (MS) for the past 30 years and is used by physicians in selected cases ofprogressive or worsening MS. Review ofpublished reports suggests that it is efficacious in cases of worsening MS that have an inflammatory component as evidenced by relapses and/or gadolinium (Gd)-enhancing lesions on magnetic resonance imaging (MR1) or in patients in earlier stages of disease where inflammation predominates over degenerative processes in the central nervous
system (CNS). There is no evidence of efficacy in primary progressive MS or later
stages of secondary progressive MS. Although a general immunosuppressant that
affects both T- and B-cell function, cyclophosphamide has selective immune effects
In MS by suppressing IL-12 and Thi-type responses and enhancing Th2/Th3 responses (IL-4, IL-b, TGF-beta; eosinophils in peripheral blood). Side effects
. include nausea, alopecia, infertility, bladder toxicity and risk of malignancy. The most commonly used regimens involve every 4- to 8-week outpatient i. v. pulse therapy given with or without corticosteroids and are usually well-tolerated by patients. Cyclophosphamide is currently used in patients whose disease is not controlled by beta-interferon or glatiramer acetate and those with rapidly worsening
MS.

o Antegren (Natalizumab). A Promising New Approach To Therapy Of

Multiple Sclerosis".

Abstract: Antegren (Natalizumab) is a humanized monoclonal antibody directed against alpha 4-integrin. This antibody binds to the alpha 4 subunit of alpha 4 beta 1-integrin (VLA-4) and alpha 4 beta 7-integrin on leukocytes and blocks the interaction of these intogrins with their ligands (VCAM and MadCAM). Disruption of these cell adhesion molecule interactions inhibits the migration of leukocytes through the blood-brain barrier and the trafficking of leukocytes through the extracellular matrix. In clinical studies, short-term treatment ofpatients with multiple

Weiner HL, Cohen JA. Mutt Scler. 2002 Apr;8(2):142-54.
Kumpfel T, 1-leydari N, Hohifeld R. Nervenarzt. 2002 Jun;73(6):552-5.

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sclerosis (MS) with antegren resulted in a clear reduction of the number of new active brain lesions on magnetic resonance imaging (MRI). Antegren was safe and well tolerated. Two large phase Ill studies will help to determine the long-term effect of antegren on MRI and clinical outcome in relapsing-remitting MS patients.

Como se puede apreciar, en estos articulos cientificos se hace menciôn explicita de principios activos tales como interferon, glatiramer, mitoxantrone, metrotexate, ciclofosfamida, estatinas y natalizumab los cuates como dijimos anteriormente, se mencionan en las reivindicaciones 19 y 38 de la solicitud colombiana en trÆmitey que se reIaconan directamente en el tratamiento de esclerosis m(iltiple; esto demuestra que la asociaciôn y combinaciOn de dichos compuestos con anticuerpos CD20 para el tratamiento de este trastorno autoinmune resulta carente de nivel inventivo, ya que como cualquier persona medianamente versada en la materia reconoce, la asociación de compuestos con mecanismos de acciOn diferentes y eficientes sabre una misma disfunciôn a patologia pueden potenciar sus respectivas efectividades farrnacolOgicas; evidencia que se reveta a travØs de las publicaciones de carÆcter cientIficoexpuestas anteriormente.

Por todo Jo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales y que en consecuencia se decrete, ademÆs de la negación de la solicitud en comento, el archivo del expediente que la contiene.

III. ANCXOS

> La publicación internacional WO 2004/035607 publicada el 29 de abril de 2004 y titulada "HUMAN MONOCLONAL ANTIBODIES AGAINST CD20" capitulo reivindicatorio.

> La publicaciOn internacional WO 01/13945 publicada el 01 de marzo de 2001 y titulada "METHODS AND COMPOSITIONS FOR IMMUNOTHERAPY OF CELL INVOLVEMENT IN PROMOTION OF A DISEASE CONDITION COMPRISING MULTIPLE SCLEROSIS" pagina 3y capitula reivindicatorio.
Abstracts de todas las publicaciones cientificas mencionadas en el acÆpitede nuevos argumentos.

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We claim:

I. An isolated human monocloæal antibody which binds to human
CD2O.
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2. The antibody ofclaim 1, selected from the group consisting of an
IgGI, an JgG2) an IgG3, an IgG4, an 1gM, an igAl, an IgA2, a secretory IgA, an IgD,
and an IgE antibody.

10 3. The antibody ofclaim 2, wherein the antibody is an TgG1
antibody.

4. The antibody of claim 2, wherein the antibody is an IgG3
antibody.
15

5. The antibody ofclaim 2, wherein the antibody is an 1g04
antibody.

20 antibody.

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6. The antibody ofclaim 2, wherein the antibody is an IgAl or IgA2

7. The antibody ofany one ofthe preceding claims, wherein the
antibody dissociates from human CD20 with a dissociation rate constant (1c4) of about
10 sec’1 or less.

8. The antibody ofany one ofthe preceding claims, wherein the
antibody binds to human CD20 with an affinity constant (Kr) of about 5 nM or less.

9. The antibody of any one ofthe preceding claims, wherein the
30 antibody has one or more ofthe characteristics selected from the group consisting of-

(i) capable ofinducing complement dependent cytotoxicity (CDC) of(i)
cells expressing CD20 in the presence ofcomplement;
(ii) capable ofinducing complement dependent cytotoxicity (CDC) of
cells expressing CD20 and high levels ofCD55 and/or CD59 in the presence of
35 complement;
(iii) capable ofinducing apoptosis of cells expressing CD20;
(iv) capable ofinducing antibody dependent cellular cytotoxicity
(ADCC) ofcells expressing CD20 in the presence of effector cells;
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(v) capable ofinducing bomotypic adhesion of Is which..ecpress
CD2O; ..
(vi) capable oftrarislocating into lipid rafts upon binding to CB20,
(vii) capable ofprolonging the survival ofa subject having tumor cells
5 which express CD20;
(viii) capable of depleting cells expressing CD20; and
(ix) capable ofdepleting cells expressing low levels of CD20 (CD201°"z
cells)

10 10 The antibody ofchnm 9, which has one or more ofthe following
characteristics selected from the group consisting of
(i) capable ofinducing at least 20%, and preferably at least 30% CDC
mediated lyats ofB-CLL cells in the presence of33 vol/vol% plasma within 3 hours at
37 T at an antibody concentration of 10 igfml,
15 (ii) capable ofinducing at least

andpreferably at least 30% lysis of
B-CLL cells in the presence of33 voilvol% whole blood cells within 3 hours at 37°C at
an antibodyconcentration of 10 pg/nil,
(iii) capable ofprolonging the 50% survival late ofSCIL) mice injected
with Daudi cells by more than 30% at a dose of20ig; and

. :1.

20 (iv) capable ofdepleting peripheral 11 cells expressing low levels of........
CD20 (CD20 B cells) to undetectable levels for morc.tban 50 days in cynomolgus monkeys at a dosage of6.25 mg/kg per day for 4consccul–ve days.

11 The antibody of claim 10, which is capable of capable ofinducing
25 at least206, and preferably at least 30% CDC mediated lysis OfBCLL cells in the
presence of33 vollvol% plasma within 3 hoursat 37°C at an anti-CD20 antibody
concentration of 10 9fm1

12. The antibody ofany ofthcpeccding claims 1-11 encoded by_
30 human heavy chain and human kappa light chain nucleic acids comprising nucleotide

I) sequences in their variable regions as set forth mSEQ ID NO I and SEQ 1])
respectively, and conservative sequence modifications thereof.

13 The antibody ofany ofthe preceding claims 1-11 encoded by
35 human heavy chain and human kappa light chain nucleic acids comprising nucleotide
sequences in their variable regions as set forth in SEQ ID NO-5 and SEQ II) NO 7,
respectively, and conservative sequence modifications thereof.

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14 The antibody ofany ofthe preceding claims 1-Il encoded by
human heavy chain and human kappa light chain nucleic acids comprising nucicotide sequences in theirvariàble regions

forth in SEQ11DNO:9 and SEQ ID NO: 11,
respectively, and conservative sequence modifleations thereof.
5

15. The antibody ofany ofthe preceding claim i-li having a human
heavy chain and human kappa light chain variable regions comprising the amino acid sequences as set forth in SEQ ID NO2 and SEQ II) NO 4, respectively, and
conservative sequencemodificationsthereof.
10

16 The antibody of any ofthe preceding claims 1-11 having human
heavy chain and human kappa light chain variable regions which are at least 90%
tiomoiOgous,pTefºrably at least 95% homologous, andmore preferably at least 98%, or
at least 991/4 homologous to the amino acid sequences as set forth in SEQ ID NO:2 and
15 SEQ ID.N0:4,respectively;

. 17..Theantibodyofany ofthe preceding claims 1-11 having ahuman heavy chain and human kappa light chain variable regions comprising the amino acid
sequences as set forth in SEQ 11) NO:6 and SEQ ID NO 8, respectively, and
20 conservative sequence modifications thereof.

18 The antibody of any ofthepreceding claims 1-11 having human
heavy chain and human kappa light chain variable regions which are at least 90%
homologous, preferably at least 95% homologous, andmore preferably at least 98%, or
25 at least99% homologous to the amino acid sequences as set forth in SEQ II) NO:6 and
SEQ IDNO:8, respectively.

19 The antibody ofany ofthe preceding claims I-iI having a human
heavy chain and human kappa light chain variable regions comprising the amino acid
30 sequences as setforthin SEQ IDNO I0and SEIQD)NO 12, respectively, and
conservative sequence modifications thereof.

20. The antibody of any olthe preceding claims 1-11 having human
heavy chain and human kappa light chain variable regions winch are at least 90%
35 homologous, preferably at least 95% homologous, andmore preferably at least 98%, or
at least 99% homologous to the amino acid sequences asset forth in SEQ ID $010 and SEQ II) NO 12, respectively.

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21. The antibody of any ofthe preceding claims 1-11 comprising at
least one human variable region selected from the group consisting of:
(1) SEQ ID NOs:2, 4, 6, 8, 10, or 12; and
(ii) a sequence which is at least 90% homologous, preferably at least 95%
homologous, and more preferably at least 98%, or at least 99% homologous toyone ofthe amino acid sequences as set forth in (i) above.

22. An isolated human monoclonal antibody which binds to an
epitope on human CD20 dened by the antibody of any one ofclaims 12-21.
10

23. An isolated human monoclonal antibody which binds to an
epitope on CL)20
(1) which does not comprise or require the amino acid residue proline at
position 172;
15 (ii) which does not comprise or require the amino acid residues alanine at position 170 or proline at position 172;
(iii) which comprises or requires the amino acid residues asparagine at
position 163 and asparagine at position 166;
(iv) which does not comprise or require the amino acid residue proline at
20 position 172, but which comprises or requires the amino acid residues asparagine at position 163 and asparagine at position 166; or
(v) which does not comprise or require the amino acid residues alanine at
position 170 or proline at position 172, but which comprises or requires the amino acid residues asparagine at position 163 and asparagine at position 166.
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24. An isolated human monoclonal antibody which binds to CD20,
wherein the antibody has one or more ofthe following characteristics:
(i) binds to mutant PI72S CD20 (proline at position 172 mutated to
serine) with at least the same affinity as to human CD20;
5 (ii) binds to mutant AxP (alanine at position 170 mutated to seririe, and
proline at position 172 mutated to serinc) with at least the same affinity as to human CD2O;
(iii) shows a reduced binding of50% or more to mutant N166D
(asparagino at position 166 mutated to aspartic acid) compared to human CD20 at an
10 antibody concentration of 10 Lg/m1; or
(iv) shows a reduced binding of 50% ormore to mutant N163D
(asparagine at position 163 mutated to aspartic acid) compared to human CD20 at an

antibody concentration of 10 4ml.

15 25. An isolated humanmonoclonal antibody which binds to an
epitope in the small first extracellular loop ofhuman CD20.

26. An isolated human monoclonal antibody which binds to a
discontinuous epitope on CD20.
20

27. An isolated human monoclonal antibody which binds to a
discontinuous epitope on CD20, wherein the epitope comprises part of the first small extracellular loop and part ofthe second extracellular loop.

25 28. An isolated human monoclonal antibody which binds to a
discontinuous epitope on CD20, wherein the epitope has residues AGJYAP ofthe small first extracellular loop and residues MESLNFIBAHTPYI ofthe second extracellular
loop.

30 29. An isolated human monoclonal antibody which has the binding
characteristics ofthe antibody of any one ofclaims 11 -28.

30. An isolated human monoclonal antibody which binds to human
CD20 comprising at least one CDR sequence selected from the group consisting of:
35 (1) SEQ B) NOs: 13, 14, 15, 16, 17, or 18;
(ii) conservative sequence modifications ofthe sequences listed in (i);
and

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(iii) fragments of any one ofthe sequences defined in (i) or (ii) which
retain the ability to bind to human CD20.

31 The àntibodyof

30, comprising SEQThNO:15.
5.

32. The antibody ofclaim 30, comprising at least four (DR
sequences selected from the group consisting of
SEQ ID NOs: 13, 14, 15, 16, 17, or 18;
(ii) conservative sequence modifications ofthe sequences listed in (i); 10 and . . ...

(iii) fragmonts of anyone ofthe sequences defined in (1) or (ii) which
retain the ability to bind to human cD2o.

33.. The antibody ofclaim 30, comprising SEQ B) NOs: 13, 14,. 15,
15.. 16, 17, and 18. ...,

34. An isolated human monoclonal antibody which bindsto human
CD20 comprising at.least one CDR. sequence selected from the group consisting of:
(1) SEQ ID NO: 19, 20, 21,22, 23, or 24;
20 (ii) conservative sequence modifications Ofthe sequences listed in (1); and :.
(iii) fragments of

one ofthe sequences defined in (i) or (ii) which
retain the ability to bind tobuman C1)20...

25 . 35 The antibody ofclaim 34, comprising at least four (DR
sequences selected from the group consisting o1
(i) SEQ ID N09: 19, 20,2i 22,23, or 24;
(ii) conservative sequence modifications ofthe sequences listed in (i);
and

30 .. (iii). fragments ofany one ofthe sequences defined in. (1) or (ii) which

5
:retain the ability tobthd human CD2O

36. The antibody ofclaim 34, comprising SEQ ID NOs: 19,20,21,
22,23, and 24.
.35

37,An isolated human monoclonal antibody which binds to human
CD20 comprising at least one CDR sequence selected from the group consisting of:
SEQ ID.NOs: 25,26,27, 28,29, or 30;
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() conservative sequencemodifications; ofthe sequences listed in (1);
and .

0

(iii).fragments ofany one ofthe sequences defined in (1) or (ii) which
retain the ability to bind

human CD20.
5

38. The antibody of claim 37, comprising SEQ B) NO:27.

39. The antibody ofclaim 37, comprising at least four CDR
sequences selected from.the group consisting of:.’.
10 (1) SEQ ID NOs: 25, 26, 27,28P29, or 30;
(ii) conservative sequence modifications ofthe sequences listed in (i); and.

(iii) fragments ofany one ofthe sequences defined in (i) or (ii) which retain the ability to bind to human CD20.
.1.5 .. .

40. The antibody ofclaim 39, comprising SEQ 11) NOs 25,26,27,
28,29, and 30.

41. The antibody ofany ofthe pxeeding claims i-Il comprising at
20 least one CDR selected from the group consisting of
(1) SEQ II) NOs.13, 19, or 25,.or a sequence having I amino acid
substitution, deletion or addition ofthe sequence ofSEQ ID NOs:13, 19 or 25;
(ii) SEQ 11) NOs-.14, 20, or 26, or a sequence having 1-4 amino acid
-substitutions, deletions or additions ofthe sequence ofSEQ II) NOs: 14, 20, or 26;
25 (iii) SEQ Ti) N0s15, or 27, era sequence having 1-4 amino acid
substitutions, deletions or additions ofthe sequence ofSEQ II) NOs:15, or 27;
(iv) SEQ 11) NO: 16, or a sequence having 1-2 amino acid substitutions,
deletions or additions ofthe sequence ofSEQ TDNO:16;
(v)SEQ ID.NO: 17, or a sequence having 1-2 amino acid substitutions,
30 deletions or additions ofthe sequence ofSEQ 11) NO:1 7; and
S. . ... (vi) SEQ ID NOs: 18, or 30, or, a sequence having 1-2 amino acid
substitutions, deletions or additions ofthe sequence ofSEQ ID NOs: 18, or 30.

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42. The antibody ofclaim 41 comprising at least four CDRs selected
from the group consisting of
(i) SEQ ID NOs:13, 19, or 25, or a sequence having 1 amino acid
substitution, deletion or addition ofthe sequence ofSEQ B) NOs: 13, 19 or 25;
(ii) SEQ ID NOs: 14, 20, or 26, or a sequence having 1-4 amino acid
substitutions, deletions or additions ofthe sequence ofSEQ ID NOs: 14, 20, or 26;
(ii) SEQ 11) NOs:IS, or 27, or a sequence having 1-4 amino acid
substitutions, deletions or additions ofthe sequence ofSEQ 1)) NOs: 15, or 27;
(iv) SEQ ID NO: 16, or a sequence having 1-2 amino acid substitutions,
10 deletions or additions ofthe sequence of SEQ ID NO: 16;

15

20

(v) SEQ ID NO: 17, or a.sequence having 1-2 amino acid substitutions,
deletions or additions ofthe sequence ofSEQ ID NO: 17; and
(vi) SEQ ID NOs: 18, or 30, or a sequence having 1-2 amino acid
substitutions, deletions or additions ofthe sequence of SEQ ID NOs: 18, or 30.

43. The antibody ofclaim 41 comprising one CDR selected from the
group consisting of
SEQ I]) NOs:IS, or 27, and a sequence having 1-4 amino acid
substitutions, deletions or additions ofthe sequence ofSEQ Ii) NOs: 15, or 27.

44. The antibody of any one ofthe preceding claims which is an
intact antibody selected from the group consisting of: an intact I:gG 1 antibody, an intact IgG2 antibody, an intact IgG3 antibody, an intact IgG4 antibody, an intact 1gM
antibody, an intact IgAl antibody, an intact IgA2 antibody, an intact secretory IgA
25 antibody, an intact Ig]) antibody, and an intact IglE antibody, wherein the antibody is

IJ

glycosylated in a eukaryotic cell.

45. The antibody ofany one ofthe preceding claims which is an
antibody fragment or a single chain antibody.

46. The antibody ofany one ofthe preceding claims which is a
binding-domain immunoglobulin fusion protein comprising (i) a binding domain polypeptide in the form of a heavy chain variable region or a light chain variable region
as defined in claim 24 that is fused to an immunoglobulin hinge region polypeptide, (ii)
35 an immunoglobulin heavy chain CH2 constant region fused to the hinge region, and (iii)
an immunoglobulin heavy chain CH3 constant region fused to the CH2 constant region.

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47. The antibody ofanyone ofthe preceding claims produced by
hybridoma which includes aB cell obtained from a trausgenic non-human animal, in which V-(D)-J gene segment rearrangements have resulted in the formation ofa
functional human heavy chain iranagenc and a functional human light chain tranagenc,
5 fused to an immortalized cell.

48. A hybridorna comprising aB cell obtained from a transgenic non-
human animal in which V-(D)-J gene segment rearrangements have resulted in the formation ofa fimctional human heavy chain transgene and a functional light chain
10 tranagene fused to an immortalized cell, wherein the bybridoma produces a detectable
amount ofthe monoclonal antibody ofany one ofthe preceding claims.

49. A hybridoma which produces a human monoclonal antibody
encoded by human IgG heavy chain and human kappa light chain nucleic acids
15 comprising.nucleotide sequencesin their variable regions as set forth in.SEQ ID NOs: 1,
5, or 9 and SEQ 11) N0s3, 7, or 11, respectively, and conservative sequence
modifications thereof.

SO. Ahybridoma which produces a human monoclonal having lgG
20

heavy chain and kappa light chain variable regions which comprise the amino acid
sequences as set forth in SEQ ID NOs:2, 6, or 10 and SEQ U) NOs: 4, 8, or 12,
respectively, and conservative sequence modificationsthereof.

..

SI. The antibody ofany one ofclaims 1-45 produced by a
25 iransfectoma comprising nucleic acids encoding a.human heavy chain and a human light
chain. ...

$2 Atransfectoma comprising nucleic acids encoding a human heavy
chain and a human light chain, wherein the transfectoma produces a detectable amount
30 ofthe antibody of any one ofclaims 1-45.

53. Atrausfectoma.which produces ahuman monoclonal antibody.
encoded by human IgU heavy chain and human kappa light chain nucleic acids
comprising nucleotide sequences in their variable regions as set forth in SEQ Ii) N09:1,
35 5, or 9 and SEQ II) llOs:3, 7, or 11, respectively, and conservative sequence
modifications thereof

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54. A transfectQma which produces a human monoclonal antibody
having IgO heavy chain and kappa light chain variable regions which comprise the
amino acid sequences as set forth in SEQ II) NOs:2, 6, or 10 and SEQ ID NOs:4, 8, or
12, respectively, and conservative sequence modifications thereof.
5

. . 55.. A eukaryotic or prokaEyodc host cell which produces a human
. S monoclonal antibody having heavy chain and light chain variable regions which
. . . . comprise the amino acid sequences as

forth in SEQ Ii) NOs:2, 6, or 10 and SEQ ID
NOs:4, 8, or 12, respectively, and conservative sequence modifications thereof.
10

56. A transgenic non-human animal or plant which produces a human
monoclonal antibody having heavy chain and light chain variable regions which
comprise the amino acid sequences asset forth in SEQ ID NOs:2, 6, or 10 and SEQ II)
NOs:4, 8, or 12, respectively, and conservative sequence modifications thereof.
15

57.. Amethod ofproducing a human monoclonal antibody which

 . bindsto human CDZO, comprising: AP
imniunizing a transgenic non-human animal having a genome comprising
 . a human heavy chain transgene and a human light chain transgene with human CD20 or
20 a cell expressing human CD20, such that antibodies are produced by B cells ofthe
animal

isolating B cells ofthe animal;
the B cells withmycloma cellsto form immortal, hybridoma cells
that secrete human monoclonal antibodies specific for human CD20; and
25 isolating the human.monoclonal antibodies specific for CD20 from the
culture supernatant ofthe bybridonia, orthe.iransfectoma derived from such hybridoma.

58. A method according to claim 57, wherein the immunization is
performed with cells which have been transfected with human C))20.
30

59. An isolated human monoclonal antibody which binds to human
CD2O obtained by:

immunizing a transgenic non-human animal having a genome comprising . a human heavy chain transgene and a human light chain transgene with a cell which has
35 been transfected with human CD20, such that antibodies are produced byB cells ofthe
animal;

 ’ isolating B cells ofthe animal;

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4,;

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fusing the B cells witb myeloma cellsto form hybdoma cells
thatsecrete human monoclonal antibodies specific forJmrnan CD20; and
isolating the human monoclonal antibodies specific for CDZO from the
culture mqxmdant ofthe hybridoma, or the transfectoma derived from such hybridoma.
5

.

60. An isolated human antibody comprising a heavy chain variable
regiouaniino acid sequence derived from a human V3-13IDP-44 gcrniline sequence (SEQ mNO:54) and a light chain variable region amino acid sequence derived from a
S

human L6/JK4-CK (SEQ U) NO:55) germlinc sequence, wherein the human antibody
10 binds to human CD20.

61. An isolated human antibody comprising a heavy chain variable
region amino acid sequence derived from a human VH3-09/JH6b.gennline sequence (SEQ U) NO:56) and a light chain variable region amino acid sequence derived from a
15 human VL-L6/3K5 germlinc sequence (SEQ Ii) NO:57), wherein the human antibody
binds to human CD20.

62. Acomposition comprising the human antibody ofany one of
claims 1-45 and a pharmaceutically acceptable carrier.
20

63. A composition comprising a combination oftwo ormore human
antibodies according to any one ofclaims 1-45, which have complementary functional
activities.

25

64. A composition according to claim 61 comprising a first antibody
.

according to claim IS and a second antibody according to claim 19.

65. A composition according to any of claims 62-64 further
 . comprising a therapeutic agent.
30

66. The antibody.accordingto any one ofclaims 1-45, further ....
comprising a chelator linker for attaching a radioisotope.

67. An inimunoconjugate comprising an antibody according to any
35 one of claims 145 linked to a cytotoxic agent, a radioisotope, or a drug.

., ...

68. A bispecific molecule comprising an antibody according to any
one of claims 1-45 and a binding specificity for a human effector cell.
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69. A bispecific molecule comprising an antibody according to.any
one ofclaims 145 and a binding specificity for a human Pc receptor or a binding specificity for aT cell receptor, such,as CD3.
5

70. Amethod ofinhibiting growth ofa cell expressing CD20,
comprising contacting the cell with an affective amount of an antibody according to any one ofclaims 1-45 such that the growth ofthe cell is inhibited.

10 71. A method ofkilling a cell expressing CD20, comprising
contacting the cell with the antibody,of any one of claims 145, such that killing ofthe
cell expressing CD20 occurs.

72. The method ofany one ofclaims 70 or 71, wherein the cell is a B
.15 lymphocyte or a tumor cell.

73. A method oftreating or preventing a disease or disorder involving
cells expressing CD20, comprising administering to a subject a human antibody, composition, ioconjgate, or bibpecific molee according to any one of claims
20 1-45 or 60-69, an expression vector according to any one ofthe claims 94-97, in an
amount effective to treat or prevent the disease.

74. Themethod ofclaim 73, wherein the disease is a B cell

25

75. Themethod ofclaim 73, wherein the disease is B cell non-
Hodgkin’s lymphoma.

76. The method ofclaim 73, wherein the disease is selected from the
30 group consislmg ofprecursor B cell lymphoblastic leukeiniaflymphoma and mature B
cell neoplasms, such, as B cell chronic lymhocytic leukemia (CLL)/sniall lymphocytic lymphoma (SLL), B cell prolyrnphocytic leukemia, lymphoplasmacytic lymphoma,
mantle cell lymphoma (MCL), follicular lymphoma (FL), cutaneous follicle center lymphoma, marginal zone B cell lymphoma (MALT type, nodal and splenic type), hairy
35 cell leukemia, diffuse large B cell lymphoma, J3urldtt’s lymphoma, plasmacytoma,
plasma cell myeloma, post-transplant lboproliferative disorder, Waidenös macrogl6bulinemia, and anaplastic large-cell lymphoma (ALCL).

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77. The method of claim 76, wherein the disease is follicular
lymphoma (FL).

78. The method ofclaim 76, wherein the disease is B cell chronic
5 lymhocytic leukemia (CLL)/small lympbocytic lymphoma (SLL).

79. The method ofclaim 73, wherein the disease is selected from the
group consisting oflyniphomatoid granulomatosis, primary effusion lymphoma, intravascular large B cell lymphoma, mediastinal large B cell lymphoma, heavy chain
10 diseases (including y, it, and a disease), lymphomas induced by therapy with
immunosuppressive agents, such as cyclosporine-induced lyniphorna, and methotrexate-
induced lymphoma.

80. A method oftreating or preventing an immune disease involving
15 CD20 expressing immune cells, comprising administering to a subject the antibody,
composition, inimunoconjugate, or bispecific molecule according to any one of claims
. 1-45 or 60-67 or an expression vector according to any one ofthe claims 94-97, in an
amount effective to treat or prevent the immune disease.

20 81. The method ofclaim 80, wherein treatment includes the killing of
B cells which produce antibodies against autonntigens.

82. The method ofclaim 73, wherein the disease or disorder is
selected from the group consisting ofpsoriasis, psoiiatic arthritis, dermatitis, systemic
25 scieroderma and sclerosis, inflammatory bowel disease (1W)), Crohn’s disease,
ulcerative colitis, respiratory distress syndrome, meningitis, encephalitis, uveitis, glomeralonhritis, eczema, asthma, atherosclerosis, leukocyte adhesion deficiency, multiple sclerosis, Raynaud’s syndrome, Sjogren’s syndrome, juvenile onset diabetes, Reiter’s disease, Bebçet’s disease, immune complex nephritis, IgA nephropathy, 1gM
30 polyneuropathies, immune-mediated thrembocytopenias, such as acute idiopathic
thrombocytopenic purpura and chronic idiopathic thrombocytopenic purpura, hemolytic anemia, myasthenia gravis, lupus nephritis, systemic lupus crythematosus, rheumatoid arthritis (RA), atopic dermatitis, pemphigus, Graves’ disease, Hashimoto’s thyroiditis, Wegener’s granulomatosis, Omenu’s syndrome, chronic renal failure, acute infectious
35 mononucleosis, H1V, and herpes virus associated diseases.

83. The method ofclaim 82, wherein the autoirmnunc disease is
rheumatoid arthritis (RA).
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84.. The method ofclaim 73, wherein the disease is an inflammatory,
immune and/or autoimmune disorder selected from ulcerative colitis, Crobn’s disease juvenile onset diabetes, multiple sclerosis,.immuue-mediated throxnbooytopenias, such
5 as acute idiopathic thrombocytopenic purpura and chronic idiopathic thrombocytopenic
purpmT4 hemolytic anerma, msthetha.s, systemic sclerosis, and pps
ValflS.

85. The method ofclaim 73, wherein the disease is an inflammatory,
10 immune and/or autoimmune disorder selected from inflammatory bowel disease
ulcerative colitis, Crohn’s disease, and multiple sclerosis.

86.. The method ofany one ofclaims 70-85, farther comprising
separately administering another therapeutic agent to the subject
15.

87. The method ofclaim 86, wherein the therapeutic agent is a
cytotoxic agent or a radiotoxic agent.

.88. The method ofclaim 86 wherein the therapeutic agent is an
20 imxrnmosuppressant.

89. Themethod of claim 86, wherein the therapeutic agent is an
immunological modulating agent, such as a cytokixie or a chemokine.

25.

90. The method ofclaim 86, wherein the therapeutic agent isselected
from the group consisting ofdoxorubicin,eisplatin, bleomycin, carmustine,
dulorambudil, and cyclophosphamide.

91. The method ofclaim 86, wherein the therapeutic agent is selected
30 from the group consisting ofanti-CD25 antibodies, anti-CD19 antibodies, anti-CD2I
antibodies, anti-M22 antibodies anti-CD37 antibodies, anfi-38 antibodieq, anti-
IL6R antibodies, anti-1L8 antibodies, anti-ILlS antibodies, anti-)LI5Rantibodies, anti-CD4 antibodies, anti4M13a antibodies, and-alpha-4/beta-1 integrixi (VLA4) antibodies, CTLA4-Ig, and anti-C3b(i) antibodies.
35.

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92 An in vitro method for detecting the presence ofCD20 antigen, or
a cell expressing 0)20, in a sample comprising
contacting the sample with the antibody of any one ofclaims 1-45 under
conditions that allow for formation ofa complex between the antibody and CD20, and
5 detecting the formation ofa complex

93 A kit for detecting the presence ofCD20 antigen, or a cell
expressing CD20, in a sample comprising the antibody of any one of claims 1-45

10 94 An in vivo method for detecting CD20 antigen, or a cell
expressing CD20, in an subject comprising
adnimistermg the antibody of any one of claims 145 under conditions
that allow for formation of a complex between the antibody and CD20, and
detecting the formed complex
15

95 An expression vector comprising a nucleotide sequence encoding
the variable region ofa tight chain, heavy chain or both light and heavy chains ofa
human antibody winch binds human CD20

20 96 fle expression vector ofclaim 95, further comprising a
nucleotide sequence encoding the constant region of a light chain, heavy chain or both light and heavy chains ofa human antibody winch binds human CD20

97 An expression vector comprising a nucleotide sequence encoding
25 a heavy chain variable region comprising a nucleotide selected from the group consisting ofthe nucleotide sequences as set forth in SEQ II) NOs 1, 5, and 9, and a
tight variable region comprising a nucleotide sequence selected from the group
consisting ofthe nucleotide sequences as set forth in SEQ ID NOs 3, 7, and 11, and
conservative modifications thereof
30

98 An expression vector comprising a nucleotide sequence encoding
a heavy chain variable region comprising an ammo acid sequence selected from the
group consisting ofthe amino acid sequences as set forth in SEQ ID NOs 2,6, and 10,
and a light chain variable region comprising the amino acid sequence selected from the
35 group consisting ofthe amino acid sequences as set forth in shown in SEQ ID NOs 4,8, and 12, and conservative sequence modifications thereof:

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iDrug

Action

Betaseron reducesT cells & gamma interferon
beta 1 -Alpha reduces # of circulating T cells
Cladribinà reduces * of circulating T cells
Copolymer 1 acts as

decoy for cells
Methotrexate reduces.# of circulating T cells
Myloral - desensitizes T cells to myelin
beta interferon suppresses microgli.al cells
methyiprednisolone suppresses macrophages
ch1àrÆmbüi1 suppresses inflammation
cyclo.phospharnide suppresses inflammation

Known pathology involving B cells is limited to such
diseases as B cell lymphoma There are numerous approaches
S and successes in treating B cell lymphoma (cancer cells of B
cell origin) Such treatments include administration of immunologically active anti-CD20 antibodies to B cell
lymphoma patients, administration of an immunoconjugate comprising mAb Lym-1 coupled to ricin toxin A chain,
10 administration of an immunoconjugate comprising mAb LL2
(anti-CD22) coupled to chemotherapeutic agent, and adminis-tration of an mAb alone, or an i.mmunocon)ugate comprising
anti-CDI9 mAb coupled to a chemotherapeutic agent
We have discovered that certain soluble antigens,
15 shed from central nervous system (CS) tissue damaged by an
inflam-matory process, are capable of inducing an immune
response which promotes one or more of the development,
, relapse, or progression of MS (promotion of 145") We have
demonstrated that a similar phenomenon promotes a chronic
20 inflammatory process which enables progression of solid,
nonlymphoid tumors

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1. Use of an affinity ligand in the manufacture of a
pharmaceutical composition for use in a procedure for
depleting nonmalignant B cells associated with a disease condition selected from the group consisting of multiple
5 sclerosis and a pro-MS immune response, and a pro -MS immune
response; wherein the affinity ligand selectively contacts
and binds to a B cell determinant; wherein the
pharmaceutical composition is administered to an individual
in an amount effective to deplete B cells; and wherein upon
10 contact and binding to such B cells, the pharmaceutical
composition induces or causes B cell depletion.

2. The use according to

1, wherein the pharmaceutical
composition further comprises at least one additional
15 component selected from the group consisting of one or more
chemotherapeutic agents, an anti-inflammatory agent, a cytolytic agent, a pharmaceutically acceptable carrier, and
a combination thereof.

20 3. The use according to claim 1, wherein the nonmalignant B
cells are B cells selected from the group consisting of
mature B cells and memory B cells, CD19+sTh+ B cells, CD19+CD21+sTh+ B cells, cD19+CD5+sTn+ B cells, and a combination thereof.
25

4. The use according to claim 1, wherein the affinity
ligand comprises a chimeric anti-CD20 monoclonal antibody.

S. The use according to claim 1, wherein the pharmaceutical
30 composition is administered by a mode selected from the
group consisting of parenterally, and in a site -directed
method in which the pharmaceutical composition is delivered

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into an. access that directly supplies central nervous tissue undergoing dernyalination.

6. Use of an affinity ligand in the manufacture of.a
5 pharmaceutical.óomposition. for use in a method for reducing
. a pro-MS immune response in an individual, the method
comprising administering to an individual the pharmaceutical composition, wherein the. pharmaceutical composition
comprises an affinity ligand which selectively binds to a B
10 cell determinant, wherein the B ells. targeted by the method
and by the pharmaceutical. composit-ion are nonmalignant B
cells, and wherein the pharmaceutical composition is
administered in an amount effective to deplete B cells..

15 7. The use according to claim 1, wherein the nonmalignant B.
cells are B cells selected from the group consisting of

S mature 3 cells and memory B cells, 19+sTh+ B cells,

D19+CD2.1+sTh+ B cells,. cD19+cD5+sTn+. B cells, and a
combination thereof. .
20

8 The use according to claim 3., whereIn the affinity
ligand comprises.a.chimeric anti -D20 monoclonal antibody.

9.. The use according to claim 1,- wherein, the pharmaceutical
25 composition is administered by a mode selected from the
group consisting of parenterally, and in a site -directed
method in which the pharmaceutical composition is delivered into an access that directly supplies central nervous tissue undergoing demyelination.

30

10 The use according to claim 6, wherein the
pharmaceutical composition further comprises an additional component selected.fromü. the group...consisting of one or more ’chemotherapeutic agents, an anti-inflammatory agent, a
35

cytolytic agent, a pharmaceutically acceptable carrier, and combination thereof. .
33

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11. Use of an affinity ligarid in the manufacture of.a
pharmaceutical composition for use in a site-directed method for reducing a pro-MS immune response in an individual, the
5- method comprising administering to an individual, the
pharmaceutical compositiqn, wherein the pharmaceutical composition comprises an affinity, ’ligand which selectively binds to a B cØll determinant,, wherein the H cells targeted
by the method and by the pharmaceutical composition are
10.. nonmalignant B cells, which the pharmaceutical composition
is delivered into an access that directly supplies central nervous tissue undergoing denryelination, and wherein, the pharmaceutical: composition is administered in an amount effective, to. deplete B cells.

12. The use according.to claim 11, wherein the nonmalignant
B cells are B cells selected from the group consisting of mature.B cella.and memory B cells, 19an+ B’cells, CD19’+CD21+sTi+’ B. cells, cD19+cDS+sTh+ B cells, and a
20 combination thereof.

130 The use according to claim 11, wherein the affinity
l.igard comprises a chimeric anti-c20monoclonal antibody.

25 14. The use according to claim Il "wherein the
pharmaceutical composition further comprises an additional component selected from: the group consisting of one or more. chemother.apeutic agents, an anti-inflammatory agent, a cytolytic agent, a pharmaceutically acceptable carrier, and
30 "a’combination’thereof.’.

. I5.. Use.of..an.affinitynl.igand in the manufacture of a
pharmaceutical composition for use in a method for reducing
a pro -MS immune response’ in an individual, the method
35 ’comprising administering, to an individual the pharmaceutical
composition, ’wherein the ’pharmaceutical composition

34

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comprises an affinity ligand.which selectively binds to a B...
cell determinant,, wherein the B cells targeted by the method:
and by the composition are nonmalignant B cells, wherein the .5 pharmaceutical composition is administered intravenously,.
5 and wherein the pharmaceutical composition is administered
in an amount effective to deplete ’B cells.

16. The use according

claim 15, wherein the nonmalignant
B cells are B cells selected from the group consisting of
10 mature Bcell8 and memory B cells, CD19+sTn+ B cells,
CD19+Cb21+sTh+Bce1lsCb19+CD54-sTzi+ B. cells, and a combination thereof. .

17. The use according to claim 15, wherein the affinity
15: ligand comprises.a chimeric anti-CD20 monoclonal antibody.

18. The useaccording to claim 15, wherein the
pharmaceutical composition further comprises an additional component selected from the group consisting of one or more

20
chemotherapeutic agents, an anti-inflaüunatory agent,, a cyt.Olytic agent, a.pharmaceutically acceptable carrier, and
a combination thereo!

19... Use Of an:affinity ligandin the manufacture of a
25 pharmaceutical composition forusein a method for treating
an.individual having a disease condition selected from the group consisting of multiple sclerosis:(MS) and a pro-MS
immune respOnse, and a pro-MS immune response; wherein the pharmaceutical composition comprises an. affinity ligand
30 Which selectively binds to a B.Cell determinant, wherein the.
B cells targeted..by the method and:by the pharmaceutical composition are nonmalignant B cells, and wherein the.. pharmaceutical composition is administered in an amount to effect a reduction in inflammation underlying clinical
35 manifestations of MS.

35

Approved and future phÆrmacotherapy for multiples...[Neurologist. 2002] - PubMed R... Pâgtha I de I

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epartmcnt of Neurology, University of CalUOrnia, San Francisco 94143-0114, USA.

astUve@ttsa.ucsf.edu iu?M, ry,p,.’::s:c, f :r, miiir!e..
BACKGROUND: Pharrnacotherapy for relapsing-remitting muitiplesclerosls(MS) W.
advanced with the demonstration that interferon beta and glatiramar. acetate
O irat a- S improve the clinical course of this disease Mitoxantrone Is the first drug approved by the iood and Drug Administration for treatment of secondary progressive MS.
Despite this progress, the. agents presently available are only partially effective, rnncrr,:iv therry ri ettuit4
are difficult to administer, and may have significant side effects; Severai.Oraily U1Y’.:.ix.tl administered- immunomodulatory agents are presently being.evaivated for
treatment of MS One class of drugs HMG CoA inhibitors (statins), is sateand. AN$ well-tolerated’and could become another mainstay of:MStherapy. EVIEW

SUMMARY: This article reviews the clinical evidence for approved MS therapies And discusses their mechanisms:f action. Furthermore, the clinical and

1 Related Reviews

laboratory data suggesting a potential role for statins in MS therapy. are
discussed CONCLUSIONS Although treatment with interferon beta, glatiramer
acetate, and mitoxantrone, the approved therapies, provide importaflt treatment
options for patients with relapsing-remitting MS and secondary progressive MS, P tins a.r;;t op t U;I.4tipKf I’
the potential. benefits of other medications, Including statins,should be explored

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in controlled clinical trials.

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Treatment of multiple sclerosis with gamma interferon: exacerbations

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We.treatŁd 1 clinicallydefinite. relapsing-remitting MS patients with recombinant in çmtia:n n nbinMłn thy 1th FN.bat. gamma Interferon In a pilot study designed to evaluate toxicity and dosage. aOi4atS)n1P3Id
Patients received low (1 microgram), Intermediate (30 micrograms), or high
(1,000 micrograms) doses of interferon by intravenous Infusion twice a week for
4 weeks, Serum levels of gamma interferon were proportional to dose and no ah.2 id"-e alon:e. din’ o,
interferon was detected in CSFi Seven of the 18 patients had exacerbations diase iivity, an1 iypncxi ioit;4’nma
during treatment, a significant Increase compared with the prestudy exacerbation
rate (p less th:0.01). Exacerbations occurred in all three dosage groups and.Inteft. .
were not.preclpitated by fever or other dose-dependent side effects There wereun,ii s
significant increases in circulating monocytes bearing class fl (HtA-DR) surface . b:4ve oi.’k and nnet a00
. antigen, in the proliferative responses of peripheral blood leukocytes, and In natural killer cell activity. These results show that systCmkadrnifllstratlon of

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gamma interferon has pronounced effects on cellular immunity In MS and on ; disease activity within the CNS, suggesting that the attacks induced during MtA. I30il0d, c"

treatment were immunologicaily mediated. Gamma Interferon is unsuitable for
use as a therapeutic agent..inMS. Agents that specifically inhibIt gamma . tee al: eias
interferon production or counteract its effects on immune cells should be
investigated as candidates for experimental therapy. .

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Extended use of glatiramer acetate (Copaxone) is well tolerated and maintains its clinic... Pªgina I de 11

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NEUROLOGY 1998;50:701-708
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Extended use of glatiramer acetate
(Copaxone) is well tolerated and
maintains its clinical effect on

multiple sclerosis relapse rate and degree of disability

K. P. Johnson, MID, B. R. Brooks, MID, J. A. Cohen, MD, C. C. Ford, MD, PhD, J. Goldstein, MID,
U. P. Lisak, MD, L. W. Myers, MD, IL S. Panitch, MD, J. W. Rose, MD, R. B. Schiffer, MD, T. Vollmer, MD, L. P. Weiner, MD, J. S. Wolinsky, MID and
The Copolymer I Multiple Sclerosis Study Group*

From the Department ofNeurology (Drs. Johnson and Panitch), University of Maryland, Baltimore, MD; the Department of Neurology (Dr. Brooks), University of Wisconsin, Madison, WI; the Department of Neurology (Dr. Cohen), University of Pennsylvania, Philadelphia, PA; the Department of Neurology (Dr. Ford), University of New Mexico, Albuquerque, NM; the Department of Neurology (Drs. Goldstein and Vollmer), Yale University, New Haven, CT; the Department of Neurology (Dr. Lisak), Wayne State University, Detroit, MI; the Department of Neurology (Dr. Myers), University of California, Los Angeles, CA; the Department of Neurology (Dr. Rose), University of Utah/VAMC, Salt Lake City, UT; the Department of Neurology (Dr. Schiffer), University ofRochester, NY; the Department of Neurology (Dr. Weiner), University of Southern California, Los Angeles, CA; and the Department of Neurology (Dr. Wolinsky), University of Texas, Houston, TX.

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Address correspondence and reprint requests to Dr. Kenneth P. Johnson, Department of Neurology, University of Maryland Hospital, 22 S. Greene Street, Baltimore, MD 21201.

When 251 relapsing-remitting patients with multiple sclerosis were randomized to receive daily subcutaneous injections ofglatiramer acetate, previously called copolymer 1 (Copaxone; n = 125) or placebo (n = 126) for 24 months, there were no laboratory abnormalities associated with glatiramer acetate treatment and it was well tolerated with few side effects. Patients receiving glatiramer acetate

had significantly fewer relapses and were more likely to be neurologically improved, whereas those receiving placebo were more likely to worsen. This study was extended for ito 11 months (mean of 5.2 months for the glatiramer acetate group and 5.9 months for the placebo group). The blinding and study conditions used during the core 24-month study were unchanged throughout the extension. The results ofthis extension study confirm the excellent tolerance and safety profile of glatiramer acetate for

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Extended use of glatiramer acetate (Copaxone) is well tolerated and maintains its clinic... Vagina 2 de 11

injection. The clinical benefit of glatiramer acetate for both the relapse rate and for neurologic disability was sustained at the end ofthe extension trial.

*See the Appendix on page 707 for a complete listing ofthe Copolymer 1 Multiple Sclerosis Study

Group.

Supported by the Federal Food and Drug Administration Orphan Drug Program no. FD-4000559-01, the National Multiple Sclerosis Society no. RG 2202-A-6, and Teva Pharmaceutical Industries Ltd., Petab

Tiqva, Israel.

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Rheumatoid Arthritis-Associated H LA-DR Molecules
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Treatment of multiple sclerosis with mitoxantrone [Eur Arch Psychiatry Clin Neurosci Pagina 1 de I jPY
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Treatment of multiple sclerosis with mitoxantrone.

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Department of Neutoloqy, Ulm University, DletenbronnfSchwend Federal Republic of
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Ten

patients, all with a rapid deteriorating disease profile, were
treated with 12 mg/m2 of. the cytostatic agent mitoxantrone, administered every tosr’e f.
3 months. This. dosage

Only 25% of what a patient with

solid tumour would
.... normally receive during the same time period Zn all treated patients the

deterioration was stopped following the initial dosage; In four out often patients.. there was even an immediate improvement of the neurological status.. Eight Out

of nine patients showed an Improvement after. 1 as compared with their

year
enrollment status the other one remained stabile. In correlation with the clinical

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improvement, the meafl P100 latencies of visual evoked potentials shoWect a reduction after 1 year, However, thi changesidentified through magnetic resonance imaging were even clearer than those seen dlnically At admission, this group of -patients presented with a total Of 169 gadolinium (Gd).enhancing. leSiOnS Only 10 leslonaWere enhancing in nine patients, t2.months after the initiation of treatment. It appears that mitoxantrone accelerates the. disappearance of GO-enhancing lesions and prevents the development of new ones. Minimal side effects such as mild nausea and a slight: faintness were evident in six patients and then for only 1-2 days.
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Low-dose (7.5 mg) oral methotrexate reduces the ra... (Ann Neurol. 1995] - PUbMed Re... Pâgina 1 del

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Low-dose (7.5 mg) oral methotrexate reduces the rate of progression in chronic.
progressive multiple sclerosis.

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Schwez KM. Fischet2 Von Dyke C. ..

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University of California, San frandsco/Mt. Zion Multiple Sclerosis Center, 94115. fli fl

A randomized, double blinded, placebo-controlled, clinical trial of low-dose, :. 1 a weekly, oral methotrexate was performed in 60 patients with clinically definite
chronic progressive -multiple sclerosis (MS) attending a referral-based outpatient-. ’’ia d.uhia .lacb
M$ clinic Study patients were 21 to 60 years old with a disease duration of
longer than 1 Patients’ Expanded Disability Status Scale scores were 3.0 to

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6.5 (ambulatory with moderate disability) Patients were first stratified by Disability-Statue Scale scores, 3.0 to 5.5 and 6.0 to 6.5, and then were
randomized to receive methotrexate or placebo treatment. Treatment consisted
of weekly, oral, 1owdose (7.5 my) methotrexate or Identical placebo foi’ 2 years,
followed by observation for as long as 1 year. A composite

D9 1ofii.Uon

measurOmeflt Instrument was used and consisted of (1) Expanded Disability
Status Stile, (2) ambulation index, (3) Boxand Block Test, and (4) 9-Hole Peg Shr XO. T)CIO) ’?CJr:’ia
Test. Failure of therapy was Indicated by a designated change that wassustainedt;V fflat4f I
for more than

months In one or more components

composite measure
Significantly less progression of Impairment as measured

validated tests

upper-extremity function

observed in the methotrexate treatment

in
the absOnce of

significant toxicity. We conclude that low-dose, weekly,
methotrexte offers a new, relatively. nontoxic treatment option for patients progressive

Treatment of multiple scleiosis with cyclophospham... [Mult Scler. 2002]

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Treatment of multiple sclerosis with cyclophosphamlde: critical review of
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YJelner ML., Cohen 3A.

Multiple Sclerosis Center, Brigham and Womens Hospital, Massachusetts General Hospital, UIU
Harvard Medical School, Boston 02115, USA, hwelner@rtc5.bwh.harvard.edu r M;
Ht It zoas

Cyciophosphamide Wan alkylating agent used to treat malignancies and Immune- mediated inflammatory non-malignant processes such as lupus nephritis and

immune-mediated neuropathies. It has been studied as a treatment for multiple.
sclerosis (MS) for the past 30 years and is used by physicians In selected cases of
progressive or worsening MS. Review of published reports suggests that It Is
efficacious in cases of worsening MS that have an inflammatory component as
evidenced by relapses and/or gadolinium (Gd)-enhanelng lesions on magnetic
resonance imaging (MRfl or in patients in earlier stages of disease where
inflammation predominates over degenerative processes In the central nervous
systen (CNS). There is no evidence of efficacy in primary progressive MS Or later

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stages of secondary progresslve.MS. Although a general lmmunosuppressant that vcr affects both 1- and B-cell function, cyclophosphamide has selective Immune CWWhas r3 the Ju9oyhlt effects in MS by suppressing IL-12 and Thi-type responses and enhancing..
Th2th3 responses (IL-4, IL-b, TGF-bete; easinophlls in peripheral blood), Side rthi;j icrr or i’s ii uyir4cilun lcloa effects include nausea, alopecia, Infertility, bladder toxicity and risk of
malignancy. The most commonly used regimens involve every 4 to 8-week
outpatient l.v. pulse therapy given with or without corticosterolds and are usually
well-tolerated by patients..Cyclophosphamide is currently used in patients whose
disease Is not controlled by beta-interferon or glatlramer acetate and those with
rapidly worsening MS.

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[Antegren (natalizumab). A promising new approach to therapy of multiple sclerosis]

[Article in German]

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Neurologisehe Klinik, Institut fir Klinische Neuroimmunologie, Klinikum, Universitat MUnchen-Grosshadern. taniakuempfel@nro.med.uni-muenchen.de

Antegren (Natalizumab) is a humanized monoclonal antibody directed against alpha 4-integrin. This antibody binds to the alpha 4 subunit of alpha 4 beta 1-integrin (VLA-4) and alpha 4 beta 7-integrin on leukocytes and blocks the interaction ofthese integrins with their ligands (VCAM and MadCAM). Disruption ofthese cell adhesion molecule interactions inhibits the migration of leukocytes through the blood-brain barrier and the trafficking ofleukocytes through the extracellular matrix. In clinical studies, short-term treatment of patients with multiple sclerosis (MS) with antegren resulted in a clear reduction ofthe number of new active brain lesions on magnetic resonance imaging (MRT). Antegren was safe and well tolerated. Two large phase 111 studies will help to determine the long-term effect of antegren on MRI and clinical outcome in relapsing-remitting MS patients.

PMID: 12243004 [PubMed - indexed for MFDLINE]

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OficioN°: 10353

Con fundamento en Jo previsto pot el articulo 43 de la Decision 486 de la ComisiOn de la Comunidad Andina, se le comunica que la oposición presentada por el doctor JosØ Luis Reyes Villamizar, en su calidad de apoderado do Laboratorio Franco Colombiano Lafrancol S.A., re(ine los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de Jo dispuesto en la citada norma, se le concede el tØrmino de sesenta (60) dias hÆbilessiguientes a la fecha de notificaciOn del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifiquese el presente oficio conforme a 10 dispuesto en el numeral 5.2, literal e), del capitulo quinto del tItulo primero dp-I Circular Unica NO 10 de 2001.

ALIX CARMEN CESPEDES DE VERGEL
Jefe de la Divisin de Nuevas Creaciones.

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El anterior oficio fue notificado por fijaciOn en lista de fecha,______________

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