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DIRECCIÓN DE NUEVAS CREACIONES
PRESENTACIÓN DE OPOSICIÓN

1. Oposición a solicitud de:

- ☒ Patente de invención
☐ Registro de Diseño Industrial
☐ Patente de Modelo de Utilidad
Esquema de Trazado de Circuitos Integrados

Número de expediente: 13-025-485.

Solicitante: ABBVIE, INC.

Apoderado: ALICIA LLOREDA RICAURTE.

Título de la Nueva Creación: PROTEINAS DE UNION DE DOMINIO VARIABLE DUAL QUE SE UNEN A NGF Y AL MENOS A UN BLANCO ADICIONAL Y METODOS PARA HACER Y USAR DICHAS PROTEINAS DE UNION.

Gaceta: 667 de 15 de mayo de 2013, No. de publicación 522.

2. Datos del Opositor

Persona Natural ☐ Persona Jurídica ☒

TECNOQUIMICAS S.A.

Nombre o denominación / Razón social completa

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Autorizo expresamente a la Superintendencia de Industria y Comercio para que todas las comunicaciones sean enviadas a través de la dirección de correo electrónico

3. Datos del representante o apoderado:

REYES VILLAMIZAR JOSE LUIS

79'152.473

44655

Apellidos y Nombre

Documento de identificación

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Número telefónico

En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de Propiedad Industrial, sírvase indicar el número de su radicación

6. Fundamentos de la oposición

Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000)

Justificación: VER ANEXO

Prórroga: SI ☒ NO ☐

7. Anexos

☒ Comprobante de pago de la tasa para la presentación de la solicitud No. 79.152.473 Fecha: 44655

☒ Poder, si fuera el caso con el que se acredita la representación.

☒ Pruebas de los fundamentos de la oposición

☒ Copias para traslado

8. Firma

JOSÉ LUIS REYES VILLAMIZAR

Nombre y apellidos

Firma

79.152.473

44655

C.C.

T.P.

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF:

EXPEDIENTE 13-025-485

TÍTULO SOLICITADO:

“PROTEÍNAS DE UNIÓN DE DOMINIO VARIABLE DUAL QUE SE UNEN A NGF Y AL MENOS A UN BLANCO ADICIONAL, Y MÉTODOS PARA HACER Y USAR DICHAS PROTEÍNAS DE UNIÓN”

PUBLICACIÓN:

Gaceta 667 de 15 de mayo de 2013, N° de publicación 524.

PRIORIDAD:

US 61/363-120 09/07/2010

SOLICITANTE:

ABBVIE, INC.

APODERADO:

ALICIA LLOREDA RICAURTE

TRÁMITE:

PRESENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**, en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito formular la siguiente

I. PETICIÓN

Sírvase negar el beneficio patentario a la solicitud contenida en el expediente 13-025-485, por no cumplir con lo dispuesto en la Decisión 486 de 2000, con base en los fundamentos que se expondrán a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **TECNOQUÍMICAS S.A.**, legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias, derivados y procesos que a nuestro juicio carecen de nivel inventivo, en detrimento de sus legítimos intereses comerciales. De igual manera mis clientes están interesados, por su misma condición de industrias farmacéuticas, en evitar la concesión de privilegios de patente que incumplan los requisitos materiales de patentabilidad establecidos en las normas vigentes, y que supongan un riesgo para la libre competencia.

III. FUNDAMENTOS DE LA OPOSICIÓN

La solicitud colombiana en trámite 13-025-485, referida a Proteínas de unión multivalentes y multiespecíficas diseñadas, métodos para elaborarlasy, específicamente, sus usos en la prevención, el diagnóstico y/o el tratamiento de enfermedades, presenta defectos en la solicitud e incumple con los requisitos materiales de patentabilidad, tal como se demuestra a continuación:

Falta de claridad, concisión y soporte en la descripción:

La reivindicación 1 se encuentra dirigida a

1. *Una proteína de unión capaz de enlazar por lo menos un blanco, caracterizada porque la proteína de unión comprende una cadena de polipéptido, en donde dicha cadena de polipéptido comprende $VD1-(X1)_n-VD2-C-(X2)_n$, en donde*
 - VD1 es un primer dominio variable de cadena pesada;*
 - VD2 es un segundo dominio variable de cadena pesada;*
 - C es un dominio constante de cadena pesada;*
 - X1 es un conector con la condición que no sea CH1;*
 - X2 es una región Fc;*
 - N es 0 ó 1; y*

En donde la proteína de unión enlaza:

 - NGF y MTX,*
 - NNGF y NKG2D,*
 - NGF e IGF1;*
 - NGF e IGF2;*
 - NGF y RON;*
 - NGF y ErbB3;*
 - NGF y CD-3;*
 - NGF e IGFR;*
 - NGF y HGF;*

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NGF y VEGF;
 NGF y DLL4;
 NGF y P1GF;
 NGF y CD-20;
 NGF y EGFR;
 NGF y HER-2;
 NGF y CD-19;
 NGF y CD-22;
 NGF y CD-40;
 NGF y c-MET; o
 NGF y NRP1.

En primer término, debe anotarse que la solicitud carece de precisión y claridad, en tanto los anticuerpos en ella incorporados no han sido definidos según las técnicas aceptadas internacionalmente para esta clase de solicitudes, esto es, por su secuencia o por el número del certificado de depósito, sino mediante una definición de fórmula general conocida de anticuerpos duales que describen dominios variables de cadena pesada, ligados a un dominio constante de cadena pesada, un conector y una región Fc, definición ésta que resulta a todas luces insuficiente para delimitar el alcance de la materia pretendida, y dificulta en forma injustificada el debido entendimiento de la misma.

No existe, en efecto, caracterización técnica de los anticuerpos referidos, pues los mismos se han definido, o bien en función de un "resultado esperado", o bien de las moléculas a las que dichos anticuerpos han de unirse, pero no de acuerdo con sus propias secuencias o características. Aceptar esta redacción permitiría que cualquier molécula de unión que cumpla las condiciones de orden descriptivo antes mencionadas, se entienda amparada dentro de la reivindicación, y llevaría a amparar un número indeterminado de compuestos. Como ya se ha dicho, se considera que la simple sustitución de sitios de unión, no definidos por sus características, sino por sus antígenos o proteínas de unión, no constituye una identificación aceptable de la proteína reclamada.

Nótese cómo, en efecto, la estructura en cuestión puede ser tan amplia que entre los anticuerpos reclamados se incluyen compuestos de secuencias presentes en los anticuerpos *Rituximab* (que se unen a CD20), *Bevacizumab* (que se unen a VEGF), *Cetuximab* (que se unen a EGFR), entre otros, todos conocidos ampliamente en el estado de la técnica, e incluso con patentes que se encuentran próximas a expirar.

Pero aún si se definieran los anticuerpos correctamente y se presentaran debidamente sus secuencias, se estima que la solicitud presenta faltas graves en materia de unidad de invención, dadas por la existencia de proteínas de funciones diferentes y de estructuras en secuencias de aminoácidos igualmente distintas.

Es por ello, que al existir diferentes parejas de moléculas a las cuales se unen las proteínas de unión reclamadas, cada una de ellas debería emplearse para definir un grupo inventivo en función de su propia secuencia.

Carencia de Unidad de Invención

La Decisión 486 menciona en su Artículo 25 que *“La solicitud de patente sólo podrá comprender una invención o un grupo de invenciones relacionadas entre si, de manera que conformen un único concepto inventivo”*, si tenemos en cuenta lo anterior, la solicitud tampoco presenta un concepto único inventivo ya que cada uno de los anticuerpos duales resultantes de cada combinación posible dan una estructura única tal que el cambio en los CDRs modifica su actividad, su función y su afinidad, adicionalmente, su estructura tridimensional también varía con dichas modificaciones.

Un ejemplo de lo anterior se da en las reivindicaciones 1- 33 de la solicitud en trámite, las cuales están dirigidas a la proteína de unión donde la cadena de polipéptido comprende $VD-1(X1)_n-VD2-C-(X2)_n$ tal como se observó en la reivindicación 1 y donde la proteína de unión se selecciona de una que enlaza diferentes antígenos o sitios de unión como NGF y MTX, o NGF y NKG2D o NGF e IGF1, etc. De esta forma, el primer objeto inventivo se encuentra limitado por la proteína de unión que se une a los antígenos NGF y MTX. Así, cada proteína que sea capaz de ligarse a una pareja de antígenos o sitios de unión diferente presentará una estructura y función que no se une en un concepto común inventivo con las demás.

Por lo tanto, se llama la atención del Despacho sobre el hecho que la materia incluida en el capítulo reivindicatorio es muy amplia e cubija una gran variedad de proteínas duales posibles que no han sido completamente desarrolladas en la descripción.

Por otro lado, la inclusión de regiones Fc de diferentes inmunoglobulinas existentes en la proteína de unión, tal como las que se mencionan en la reivindicación 11 cambia diametralmente el enfoque de la solicitud ya que dichos compuestos de inmunoglobulina presentan una estructura y función diferentes a las reclamadas por el conjugado, en consecuencia, su inclusión hace que todo el efecto técnico demostrable varíe.

Reivindicaciones referidas a usos

La presente solicitud en sus reivindicaciones 59 a 61 revela el uso de las proteínas de unión para el tratamiento de enfermedades:

59. El uso de la proteína de unión de acuerdo con las reivindicaciones 1, 3, 6, 24, o 91-94, para tratar a un sujeto contra una enfermedad o un trastorno administrando al sujeto la proteína de unión de tal manera que se logre el tratamiento.

si tenemos en cuenta que el artículo 14 de la Decisión 486 dice: *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*; por lo tanto, las reivindicaciones 59 a 61 contienen materia que no se considera un elemento que pueda ser patentado.

Pese a las anteriores consideraciones, se realizó una búsqueda del estado de la técnica encontrando documentos relevantes para objetar los requisitos de patentabilidad de la solicitud en estudio, veamos:

La solicitud no cumple con el requisito de novedad:

Además de la violación a la D. 486 en cuanto a claridad, soporte, unidad de invención y usos se refiere, la materia reclamada ha sido descrita en el arte anterior, de forma tal que ya se ha resuelto el problema técnico bajo las mismas características esenciales según la publicación US 2009/0304693 de Ghayur et al., publicada el 10 de diciembre de 2009, en la cual se enseñan proteínas de unión

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capaces de unirse a un par de antígenos, que comprenden una cadena polipeptídica que comprende $VD-1(X1)n-VD2-C-(X2)n$, en donde;

VD1 es un primer dominio variable de la cadena pesada;

VD2 es un segundo dominio variable de la cadena pesada;

C es un dominio constante de la cadena pesada;

X1 es un conector con la condición que no sea CH1 (párrafo 0014);

X2 es una región Fc y n es 0 o 1;

En el párrafo 0013 de la anterioridad puede observarse la esencia de lo solicitado así:

[0013] In one embodiment the invention provides a binding protein comprising a polypeptide chain, wherein the polypeptide chain comprises $VD1-(X1)n-VD2-C-(X2)n$, wherein VD1 is a first variable domain, VD2 is a second variable domain, C is a constant domain, X1 represents an amino acid or polypeptide, X2 represents an Fc region and n is 0 or 1. In an embodiment the VD1 and VD2 in the binding protein are heavy chain variable domains. In another embodiment, the heavy chain variable domain is selected from the group consisting of a murine heavy chain variable domain, a human heavy chain variable domain, a CDR grafted heavy chain variable domain, and a humanized heavy chain variable domain. In yet another, embodiment VD1 and VD2 are capable of binding the same antigen. In another embodiment VD1 and VD2 are capable of binding different antigens. In still another embodiment, C is a heavy chain constant domain. For example, X1 is a linker with the proviso that X1 is not CH1. For example, X1 is a linker selected from the group

De igual forma se observa en la anterioridad que X2 es una región Fc; y n es 0 o 1

[0014] In an embodiment the binding protein disclosed herein comprises a polypeptide chain, wherein the polypeptide chain comprises $VD1-(X1)n-VD2-C-(X2)n$, wherein VD1 is a first heavy chain variable domain, VD2 is a second heavy chain variable domain, C is a heavy chain constant domain, X1 is a linker with the proviso that it is not CH1, and X2 is an Fc region.

Se observa entonces, que la fórmula propuesta por la solicitud en trámite ha sido de uso recurrente en el estado de la técnica indicando incluso los sustituyentes comunes de cada uno de las cadenas variables.

Ahora bien, con respecto a los dominios variables de cadena pesada que son seleccionados alternativamente en la fórmula, los primeros en identificarse por el

documento del estado de la técnica son aquellos de NGF, de igual modo que en la solicitud en estudio. Esto puede observarse en el siguiente fragmento del párrafo 0019.

receptors, or tumor markers. For example, the DVD-Ig of the invention is capable of binding two or more of the following: Amyloid beta (Abeta) (seq. 1), Abeta (seq. 2), Abeta (seq. 3), Tumor Necrosis Factor alpha (TNF- α), interleukin 1 β (IL-1 β), Insulin-like Growth Factor 1 (IGF1), Insulin-like Growth Factor 2 (IGF2), Interleukin 18 (IL-18), Interleukin 6 (IL-6), Receptor for Advanced Glycation Endproducts (RAGE), Nerve Growth Factor (NGF), Epidermal Growth Factor Receptor (EGFR) (seq. 1), EGFR (seq. 2), CD-20, and Repulsive Guidance Molecule (RGMA) (see also Table 2). In a specific embodiment the binding protein is capable of binding pairs of targets selected from the group consisting of Abeta (seq. 1) and Abeta (seq. 3); TNF- α and Abeta (seq. 2); IL-1 and Abeta (seq. 2); Abeta (seq. 1) and Abeta (seq. 2); IGF1,2 and Abeta (seq. 2); Abeta (seq. 2) and IL-18; IL-6 and Abeta (seq. 2); TNF- α and Abeta (seq. 3); IL-1 β and Abeta (seq. 3); Abeta (seq. 1) and Abeta (seq. 3); IGF1,2 and Abeta (seq. 3); Abeta (seq. 3) and IL-18; IL-6 and Abeta (seq. 3); TNF- α and Abeta (seq. 1); IL-1 β and Abeta (seq. 1); IGF1,2 and Abeta (seq. 1); Abeta (seq. 1) and IL-18; IL-6 and Abeta (seq. 1); Abeta (seq. 1) and RAGE; NGF and IL-18; NGF and IL-1; NGF and IL-6; TNF- α and EGFR (seq. 2); TNF- α and RAGE; CD-20 and EGFR (seq. 1); CD-20 and EGFR (seq. 2); RGMA and TNF- α (see Examples 2.1 to 2.27).

En un ejemplo, la proteína de unión liga a un par de antígenos que consisten de NGF (párrafo 0019) y Aunque no es específico, D1 enseña composiciones farmacéuticas para tratar una enfermedad, que comprenden la proteína de unión y metotrexato (MTX):

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[0069] The invention also provides a pharmaceutical composition comprising a binding protein, as disclosed herein and a pharmaceutically acceptable carrier. In a further embodiment the pharmaceutical composition comprises at least one additional therapeutic agent for treating a disorder. For example, the additional agent is selected from the group consisting of: a therapeutic agent, an imaging agent, a cytotoxic agent, an angiogenesis inhibitor (including but not limited to an anti-VEGF antibody or a VEGF-trap), a kinase inhibitor (including but not limited to a KDR and a TIE-2 inhibitor), a co-stimulation molecule blocker (including but not limited to anti-B7.1, anti-B7.2, CTLA4-Ig, anti-CD20), an adhesion molecule blocker (including but not limited to an anti-LFA-1 antibody, an anti-E/L selectin antibody, a small molecule inhibitor), an anti-cytokine antibody or functional fragment thereof (including but not limited to an anti-IL-18, an anti-TNF, and an anti-IL-6/cytokine receptor antibody), methotrexate, cyclosporin, rapamycin, FK506, a detectable label or reporter, a TNF antagonist, an antirheumatic, a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antip-

Esto se reafirma en el párrafo 328 que menciona:

Mesopram. Combinations include methotrexate or leflunomide and in moderate or severe rheumatoid arthritis cases, cyclosporine.

En consecuencia, la solicitud no cumple con el requisito de novedad ya que no demuestra características técnicas esenciales novedosas e incluso reclama las mismas secuencias y proteínas de unión de anticuerpos conocidos en una fórmula también conocida de anticuerpos biespecíficos y bivalentes.

Por lo tanto, se ha demostrado que la solicitud no cumple con los requisitos de claridad, concisión, unidad de invención, excepciones de patentabilidad y requisitos de patentabilidad como Novedad; por lo que no puede ser objeto del beneficio de patente; rogamos se analicen los argumentos expuestos con el rigor y detenimiento habituales y que en consecuencia se decrete, además de la negación de la solicitud en comento, el archivo del expediente que la contiene.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

V. SOLICITUD DE PLAZO EXTRA PARA SUSTENTAR LA OPOSICIÓN

En desarrollo de lo dispuesto por el artículo 42, inciso 2º de la Decisión 486, solicito comedidamente a su Despacho el plazo adicional de sesenta días para sustentar la presente oposición. Para los anteriores efectos, me permito anexar la constancia de pago correspondiente.

VI. PRUEBAS

Ruego que se tenga como tal, sin perjuicio de las que puedan presentarse al vencimiento de la prórroga solicitada, y de aquellas que el Despacho considere oficiosamente, las siguientes:

- La publicación US 2009/0304693 A1 (GHAYUR et .al.) publicada el 10 Diciembre de 2009. Portada, página 1 – 5, 11, 54 y 236 - 238.

VII. ANEXOS

Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos:

1. Certificado de existencia y representación legal de Tecnoquímicas S.A.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Copia para correr traslado al solicitante.
5. Las mencionadas en el acápite de pruebas

VIII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 205, Fax (1) 621.25.42 de esta ciudad. Tecnoquímicas S.A. las recibirá en sus oficinas localizadas en la Calle 23 N° 7-39 de Cali.

REYES & REYES
A B O G A D O S

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79.152.473 de Usaquén

T.P.A. 44.655 de C.S.J.



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(19) **United States**

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(43) **Pub. Date: Dec. 10, 2009**

(54) **DUAL VARIABLE DOMAIN
IMMUNOGLOBULINS AND USES THEREOF**

Publication Classification
(51) **Int. Cl.**

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C12P 21/06 (2006.01)

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(52) **U.S. Cl. 424/133.1; 530/387.1; 530/391.3;**
435/184; 536/23.1; 435/320.1; 435/252.33;
435/358; 435/365; 435/254.2; 435/69.6; 424/130.1;
530/387.3

(21) **Appl. No.:** 12/477,668

(22) **Filed:** Jun. 3, 2009

(57) **ABSTRACT**

Related U.S. Application Data

(60) Provisional application No. 61/130,776, filed on Jun.
3, 2008, provisional application No. 61/132,951, filed
on Jun. 21, 2008.

The present invention relates to engineered multivalent and
multispecific binding proteins, methods of making, and spe-
cifically to their uses in the prevention, diagnosis, and/or
treatment of disease.

DUAL VARIABLE DOMAIN IMMUNOGLOBULINS AND USES THEREOF

REFERENCE TO RELATED APPLICATIONS

[0001] This application is a non-provisional application claiming priority to U.S. Provisional Application Ser. No. 61/130,776, filed Jun. 3, 2008 and U.S. Provisional Application Ser. No. 61/132,951, filed Jun. 24, 2008, the contents of which are hereby incorporated by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to multivalent and multispecific binding proteins, methods of making, and specifically to their uses in the, diagnosis, prevention and/or treatment of acute and chronic inflammatory diseases, cancer, and other diseases.

BACKGROUND OF THE INVENTION

[0003] Engineered proteins, such as multispecific antibodies capable of binding two or more antigens are known in the art. Such multispecific binding proteins can be generated using cell fusion, chemical conjugation, or recombinant DNA techniques.

[0004] Bispecific antibodies have been produced using quadroma technology (see Milstein, C. and A. C. Cuello (1983) *Nature* 305(5934):537-40) based on the somatic fusion of two different hybridoma cell lines expressing murine monoclonal antibodies (mAbs) with the desired specificities of the bispecific antibody. Because of the random pairing of two different immunoglobulin (Ig) heavy and light chains within the resulting hybrid-hybridoma (or quadroma) cell line, up to ten different Ig species are generated, of which only one is the functional bispecific antibody. The presence of mis-paired by-products, and significantly reduced production yields, means sophisticated purification procedures are required.

[0005] Bispecific antibodies can also be produced by chemical conjugation of two different mAbs (see Staerz, U. D., et al. (1985) *Nature* 314(6012): 628-31). This approach does not yield homogeneous preparation. Other approaches have used chemical conjugation of two different mAbs or smaller antibody fragments (see Brennan, M., et al. (1985) *Science* 229(4708): 81-3).

[0006] Another method used to produce bispecific antibodies is the coupling of two parental antibodies with a heterobifunctional crosslinker, but the resulting bispecific antibodies suffer from significant molecular heterogeneity because reaction of the crosslinker with the parental antibodies is not site-directed. To obtain more homogeneous preparations of bispecific antibodies two different Fab fragments have been chemically crosslinked at their hinge cysteine residues in a site-directed manner (see Glennie, M. J., et al. (1987) *J. Immunol.* 139(7): 2367-75). But this method results in Fab'2 fragments, not full IgG molecule.

[0007] A wide variety of other recombinant bispecific antibody formats have been developed (see Kriangkum, J., et al. (2001) *Biomol. Eng.* 18(2): 31-40). Amongst them tandem single-chain Fv molecules and diabodies, and various derivatives thereof, are the most widely used. Routinely, construction of these molecules starts from two single-chain Fv (scFv) fragments that recognize different antigens (see Economides, A. N., et al. (2003) *Nat. Med.* 9(1): 47-52). Tandem scFv molecules (taFv) represent a straightforward format simply

connecting the two scFv molecules with an additional peptide linker. The two scFv fragments present in these tandem scFv molecules form separate folding entities. Various linkers can be used to connect the two scFv fragments and linkers with a length of up to 63 residues (see Nakanishi, K., et al. (2001) *Ann. Rev. Immunol.* 19: 423-74). Although the parental scFv fragments can normally be expressed in soluble form in bacteria, it is, however, often observed that tandem scFv molecules form insoluble aggregates in bacteria. Hence, refolding protocols or the use of mammalian expression systems are routinely applied to produce soluble tandem scFv molecules. In a recent study, in vivo expression by transgenic rabbits and cattle of a tandem scFv directed against CD28 and a melanoma-associated proteoglycan was reported (see Gracie, J. A., et al. (1999) *J. Clin. Invest.* 104(10): 1393-401). In this construct, the two scFv molecules were connected by a CH1 linker and serum concentrations of up to 100 mg/L of the bispecific antibody were found. Various strategies including variations of the domain order or using middle linkers with varying length or flexibility were employed to allow soluble expression in bacteria. A few studies have now reported expression of soluble tandem scFv molecules in bacteria (see Leung, B. P., et al. (2000) *J. Immunol.* 164(12): 6495-502; Ito, A., et al. (2003) *J. Immunol.* 170(9): 4802-9; Karni, A., et al. (2002) *J. Neuroimmunol.* 125(1-2): 134-40) using either a very short Ala3 linker or long glycine/serine-rich linkers. In another recent study, phage display of a tandem scFv repertoire containing randomized middle linkers with a length of 3 or 6 residues was employed to enrich for those molecules that are produced in soluble and active form in bacteria. This approach resulted in the isolation of a tandem scFv molecule with a 6 amino acid residue linker (see Arndt, M. and J. Krauss (2003) *Methods Mol. Biol.* 207: 305-21). It is unclear whether this linker sequence represents a general solution to the soluble expression of tandem scFv molecules. Nevertheless, this study demonstrated that phage display of tandem scFv molecules in combination with directed mutagenesis is a powerful tool to enrich for these molecules, which can be expressed in bacteria in an active form.

[0008] Bispecific diabodies (Db) utilize the diabody format for expression. Diabodies are produced from scFv fragments by reducing the length of the linker connecting the VH and VL domain to approximately 5 residues (see Peipp, M. and T. Valerius (2002) *Biochem. Soc. Trans.* 30(4): 507-11). This reduction of linker size facilitates dimerization of two polypeptide chains by crossover pairing of the VH and VL domains. Bispecific diabodies are produced by expressing, two polypeptide chains with, either the structure VHA-VLB and VHB-VLA (VH-VL configuration), or VLA-VHB and VLB-VHA (VL-VH configuration) within the same cell. A large variety of different bispecific diabodies have been produced in the past and most of them are expressed in soluble form in bacteria. However, a recent comparative study demonstrates that the orientation of the variable domains can influence expression and formation of active binding sites (see Mack, M. et al. (1995) *Proc. Natl. Acad. Sci. USA* 92(15): 7021-5). Nevertheless, soluble expression in bacteria represents an important advantage over tandem scFv molecules. However, since two different polypeptide chains are expressed within a single cell inactive homodimers can be produced together with active heterodimers. This necessitates the implementation of additional purification steps in order to obtain homogenous preparations of bispecific diabodies. One approach to force the generation of bispecific diabodies is the

production of knob-into-hole diabodies (see Holliger, P., T. Prospero, and G. Winter (1993) *Proc. Natl. Acad. Sci. USA* 90(14): 6444-8.18). This approach was demonstrated for a bispecific diabody directed against HER2 and CD3. A large knob was introduced in the VH domain by exchanging Val37 with Phe and Leu45 with Trp and a complementary hole was produced in the VL domain by mutating Phe98 to Met and Tyr87 to Ala, either in the anti-HER2 or the anti-CD3 variable domains. By using this approach the production of bispecific diabodies could be increased from 72% by the parental diabody to over 90% by the knob-into-hole diabody. Importantly, production yields only slightly decrease as a result of these mutations. However, a reduction in antigen-binding activity was observed for several constructs. Thus, this rather elaborate approach requires the analysis of various constructs in order to identify those mutations that produce heterodimeric molecule with unaltered binding activity. In addition, such approach requires mutational modification of the immunoglobulin sequence at the constant region, thus creating non-native and non-natural form of the antibody sequence, which may result in increased immunogenicity, poor in vivo stability, as well as undesirable pharmacokinetics.

[0009] Single-chain diabodies (scDb) represent an alternative strategy for improving the formation of bispecific diabody-like molecules (see Holliger, P. and G. Winter (1997) *Cancer Immunol. Immunother.* 45(3-4): 128-30; Wu, A. M., et al. (1996) *Immunotechnology* 2(1): p. 21-36). Bispecific single-chain diabodies are produced by connecting the two diabody-forming polypeptide chains with an additional middle linker with a length of approximately 15 amino acid residues. Consequently, all molecules with a molecular weight corresponding to monomeric single-chain diabodies (50-60 kDa) are bispecific. Several studies have demonstrated that bispecific single chain diabodies are expressed in bacteria in soluble and active form with the majority of purified molecules present as monomers (see Holliger, P. and G. Winter (1997) *Cancer Immunol. Immunother.* 45(3-4): 128-30; Wu, A. M., et al. (1996) *Immunotechnol.* 2(1): 21-36; Pluckthun, A. and P. Pack (1997) *Immunotechnol.* 3(2): 83-105; Ridgway, J. B., et al. (1996) *Protein Engin.* 9(7): 617-21). Thus, single-chain diabodies combine the advantages of tandem scFvs (all monomers are bispecific) and diabodies (soluble expression in bacteria).

[0010] More recently diabodies have been fused to Fc to generate more Ig-like molecules, named di-diabodies (see Lu, D., et al. (2004) *J. Biol. Chem.* 279(4): 2856-65). In addition, multivalent antibody construct comprising two Fab repeats in the heavy chain of an IgG and capable of binding four antigen molecules has been described (see WO 0177342A1, and Miller, K., et al. (2003) *J. Immunol.* 170(9): 4854-61).

[0011] There is a need in the art for improved multivalent binding proteins capable of binding two or more antigens. U.S. patent application Ser. No. 11/507,050 provides a novel family of binding proteins capable of binding two or more antigens with high affinity, which are called dual variable domain immunoglobulins (DVD-Ig™). The present invention provides further novel binding proteins capable of binding two or more antigens.

SUMMARY OF THE INVENTION

[0012] This invention pertains to multivalent binding proteins capable of binding two or more antigens. The present

invention provides a novel family of binding proteins capable of binding two or more antigens with high affinity.

[0013] In one embodiment the invention provides a binding protein comprising a polypeptide chain, wherein the polypeptide chain comprises VD1-(X1)_n-VD2-C-(X2)_n, wherein VD1 is a first variable domain, VD2 is a second variable domain, C is a constant domain, X1 represents an amino acid or polypeptide, X2 represents an Fc region and n is 0 or 1. In an embodiment the VD1 and VD2 in the binding protein are heavy chain variable domains. In another embodiment, the heavy chain variable domain is selected from the group consisting of a murine heavy chain variable domain, a human heavy chain variable domain, a CDR grafted heavy chain variable domain, and a humanized heavy chain variable domain. In yet another, embodiment VD1 and VD2 are capable of binding the same antigen. In another embodiment VD1 and VD2 are capable of binding different antigens. In still another embodiment, C is a heavy chain constant domain. For example, X1 is a linker with the proviso that X1 is not CH1. For example, X1 is a linker selected from the group consisting of AKTTPKLEEGEFSEAR (SEQ ID NO: 1); AKTTPKLEEGEFSEARV (SEQ ID NO: 2); AKTTPKLGG (SEQ ID NO: 3); SAKTTPKLGG (SEQ ID NO: 4); SAKTTP (SEQ ID NO: 5); RADAAP (SEQ ID NO: 6); RADAAPTVS (SEQ ID NO: 7); RADAAAAGGPGS (SEQ ID NO: 8); RADAAA(G₄S)₄ (SEQ ID NO: 9); SAKTTPKLEEGEFSEARV (SEQ ID NO: 10); ADAAP (SEQ ID NO: 11); ADAAPTVSIFPP (SEQ ID NO: 12); TVAAP (SEQ ID NO: 13); TVAAPSVFIFPP (SEQ ID NO: 14); QPKAAP (SEQ ID NO: 15); QPKAAPSVTLFPP (SEQ ID NO: 16); AKTTPP (SEQ ID NO: 17); AKTTPPSVTPLAP (SEQ ID NO: 18); AKTTAP (SEQ ID NO: 19); AKTTAPSVYPLAP (SEQ ID NO: 20); ASTKGP (SEQ ID NO: 21); ASTKGPSVFPLAP (SEQ ID NO: 22); GGGGSGGGGSGGGGS (SEQ ID NO: 23); GENKVEYAPALMALS (SEQ ID NO: 24); GPAKELT-PLKEAKVS (SEQ ID NO: 25); and GHEAAAVMQVQY-PAS (SEQ ID NO: 26). In an embodiment, X2 is an Fc region. In another embodiment, X2 is a variant Fc region.

[0014] In an embodiment the binding protein disclosed herein comprises a polypeptide chain, wherein the polypeptide chain comprises VD1-(X1)_n-VD2-C-(X2)_n, wherein VD1 is a first heavy chain variable domain, VD2 is a second heavy chain variable domain, C is a heavy chain constant domain, X1 is a linker with the proviso that it is not CH1, and X2 is an Fc region.

[0015] In an embodiment, VD1 and VD2 in the binding protein are light chain variable domains. In an embodiment, the light chain variable domain is selected from the group consisting of a murine light chain variable domain, a human light chain variable domain, a CDR grafted light chain variable domain, and a humanized light chain variable domain. In one embodiment VD1 and VD2 are capable of binding the same antigen. In another embodiment VD1 and VD2 are capable of binding different antigens. In an embodiment, C is a light chain constant domain. In another embodiment, X1 is a linker with the proviso that X1 is not CL1. In an embodiment, X1 is a linker selected from the group consisting of AKTTPKLEEGEFSEAR (SEQ ID NO: 1); AKTTPKLEEGEFSEARV (SEQ ID NO: 2); AKTTPKLGG (SEQ ID NO: 3); SAKTTPKLGG (SEQ ID NO: 4); SAKTTP (SEQ ID NO: 5); RADAAP (SEQ ID NO: 6); RADAAPTVS (SEQ ID NO: 7); RADAAAAGGPGS (SEQ ID NO: 8); RADAAA(G₄S)₄ (SEQ ID NO: 9); SAKTTPKLEEGEFSEARV (SEQ ID NO: 10); ADAAP (SEQ ID NO: 11); ADAAPTVSIFPP (SEQ ID

NO: 12); TVAAP (SEQ ID NO: 13); TVAAPSVFIFPP (SEQ ID NO: 14); QPKAAP (SEQ ID NO: 15); QPKAAPSVTLFPP (SEQ ID NO: 16); AKTTTPP (SEQ ID NO: 17); AKTTTPSVTPLAP (SEQ ID NO: 18); AKTIAP (SEQ ID NO: 19); AKTTAPSVYPLAP (SEQ ID NO: 20); ASTKGP (SEQ ID NO: 21); ASTKGPSVFPLAP (SEQ ID NO: 22); GGGGSGGGGSGGGGS (SEQ ID NO: 23); GENKVEYAPALMALS (SEQ ID NO: 24); GPAKELTPLKEAKVS (SEQ ID NO: 25); and GHEAAAVMQVQYPAS (SEQ ID NO: 26). In an embodiment, the binding protein does not comprise X2.

[0016] In an embodiment, both the variable heavy and variable light chain comprise the same linker. In another embodiment, the variable heavy and variable light chain comprise different linkers. In another embodiment, both the variable heavy and variable light chain comprise a short (about 6 amino acids) linker. In another embodiment, both the variable heavy and variable light chain comprise a long (greater than 6 amino acids) linker. In another embodiment, the variable heavy chain comprises a short linker and the variable light chain comprises a long linker. In another embodiment, the variable heavy chain comprises a long linker and the variable light chain comprises a short linker.

[0017] In an embodiment the binding protein disclosed herein comprises a polypeptide chain, wherein said polypeptide chain comprises VD1-(X1)_n-VD2-C-(X2)_n, wherein VD1 is a first light chain variable domain, VD2 is a second light chain variable domain, C is a light chain constant domain, X1 is a linker with the proviso that it is not CH1, and X2 does not comprise an Fc region.

[0018] In another embodiment the invention provides a binding protein comprising two polypeptide chains, wherein said first polypeptide chain comprises VD1-(X1)_n-VD2-C-(X2)_n, wherein VD1 is a first heavy chain variable domain, VD2 is a second heavy chain variable domain, C is a heavy chain constant domain, X1 is a linker with the proviso that it is not CH1, and X2 is an Fc region; and said second polypeptide chain comprises VD1-(X1)_n-VD2-C-(X2)_n, wherein VD1 is a first light chain variable domain, VD2 is a second light chain variable domain, C is a light chain constant domain, X1 is a linker with the proviso that it is not CH1, and X2 does not comprise an Fc region. In a particular embodiment, the Dual Variable Domain (DVD) binding protein comprises four polypeptide chains wherein the first two polypeptide chains comprises VD1-(X1)_n-VD2-C-(X2)_n, respectively wherein VD1 is a first heavy chain variable domain, VD2 is a second heavy chain variable domain, C is a heavy chain constant domain, X1 is a linker with the proviso that it is not CH1, and X2 is an Fc region; and the second two polypeptide chain comprises VD1-(X1)_n-VD2-C-(X2)_n respectively, wherein VD1 is a first light chain variable domain, VD2 is a second light chain variable domain, C is a light chain constant domain, X1 is a linker with the proviso that it is not CH1, and X2 does not comprise an Fc region. Such a Dual Variable Domain (DVD) protein has four antigen binding sites.

[0019] In another embodiment the binding proteins disclosed herein are capable of binding one or more targets. In an embodiment, the target is selected from the group consisting of cytokines, cell surface proteins, enzymes and receptors. In another embodiment, the binding protein is capable of modulating a biological function of one or more targets. In another embodiment, the binding protein is capable of neutralizing one or more targets. The binding protein of the invention is capable of binding cytokines selected from the group consist-

ing of lymphokines, monokines, polypeptide hormones, receptors, or tumor markers. For example, the DVD-Ig of the invention is capable of binding two or more of the following: Amyloid beta (Abeta) (seq. 1), Abeta (seq. 2), Abeta (seq. 3), Tumor Necrosis Factor alpha (TNF-α), interleukin 1β (IL-1β), Insulin-like Growth Factor 1 (IGF1), Insulin-like Growth Factor 2 (IGF2), Interleukin 18 (IL-18), Interleukin 6 (IL-6), Receptor for Advanced Glycation Endproducts (RAGE), Nerve Growth Factor (NGF), Epidermal Growth Factor Receptor (EGFR) (seq. 1), EGFR (seq. 2), CD-20, and Repulsive Guidance Molecule (RGMA) (see also Table 2). In a specific embodiment the binding protein is capable of binding pairs of targets selected from the group consisting of Abeta (seq. 1) and Abeta (seq. 3); TNF-α and Abeta (seq. 2); IL-1 and Abeta (seq. 2); Abeta (seq. 1) and Abeta (seq. 2); IGF1,2 and Abeta (seq. 2); Abeta (seq. 2) and IL-18; IL-6 and Abeta (seq. 2); TNF-α and Abeta (seq. 3); IL-1β and Abeta (seq. 3); Abeta (seq. 1) and Abeta (seq. 3); IGF1,2 and Abeta (seq. 3); Abeta (seq. 3) and IL-18; IL-6 and Abeta (seq. 3); TNF-α and Abeta (seq. 1); IL-1β and Abeta (seq. 1); IGF1,2 and Abeta (seq. 1); Abeta (seq. 1) and IL-18; IL-6 and Abeta (seq. 1); Abeta (seq. 1) and RAGE; NGF and IL-18; NGF and IL-1; NGF and IL-6; TNF-α and EGFR (seq. 2); TNF-α and RAGE; CD-20 and EGFR (seq. 1); CD-20 and EGFR (seq. 2); RGMA and TNF-α (see Examples 2.1 to 2.27).

[0020] In an embodiment, the binding protein capable of binding Abeta (seq. 1) and Abeta (seq. 3) comprises a DVD heavy chain amino acid sequence selected from the group consisting of SEQ ID NO. 62 and SEQ ID NO. 64; and a DVD light chain amino acid sequence selected from the group consisting of SEQ ID NO. 63 and SEQ ID NO. 65. In an embodiment, the binding protein capable of binding Abeta (seq. 1) and Abeta (seq. 3) comprises a DVD heavy chain amino acid sequence of SEQ ID NO. 62 and a DVD light chain amino acid sequence of SEQ ID NO. 63. In another embodiment, the binding protein capable of binding Abeta (seq. 1) and Abeta (seq. 3) has a reverse orientation and comprises a DVD heavy chain amino acid sequence of SEQ ID NO. 64 and a DVD light chain amino acid sequence of SEQ ID NO. 65.

[0021] In an embodiment, the binding protein capable of binding TNF-α and Abeta (seq. 2) comprises a DVD heavy chain amino acid sequence selected from the group consisting of SEQ ID NO. 66 and SEQ ID NO. 68; and a DVD light chain amino acid sequence selected from the group consisting of SEQ ID NO. 67 and SEQ ID NO. 69. In an embodiment, the binding protein capable of binding TNF-α and Abeta (seq. 2) comprises a DVD heavy chain amino acid sequence of SEQ ID NO. 66 and a DVD light chain amino acid sequence of SEQ ID NO. 67. In another embodiment, the binding protein capable of binding TNF-α and Abeta (seq. 2) has a reverse orientation and comprises a DVD heavy chain amino acid sequence of SEQ ID NO. 68 and a DVD light chain amino acid sequence of SEQ ID NO. 69.

[0022] In an embodiment, the binding protein capable of binding IL-1β and Abeta (seq. 2) comprises a DVD heavy chain amino acid sequence selected from the group consisting of SEQ ID NO. 70 and SEQ ID NO. 72; and a DVD light chain amino acid sequence selected from the group consisting of SEQ ID NO. 71 and SEQ ID NO. 73. In an embodiment, the binding protein capable of binding IL-1β and Abeta (seq. 2) comprises a DVD heavy chain amino acid sequence of SEQ ID NO. 70 and a DVD light chain amino acid sequence of SEQ ID NO. 71. In another embodiment, the binding protein

of SEQ ID NO. 90 and SEQ ID NO. 92; and a DVD light chain amino acid sequence selected from the group consisting of SEQ ID NO. 91 and SEQ ID NO. 93. In an embodiment, the binding protein capable of binding TNF- α and Abeta (seq. 3) comprises a DVD heavy chain amino acid sequence of SEQ ID NO. 90 and a DVD light chain amino acid sequence of SEQ ID NO. 91. In another embodiment, the binding protein capable of binding TNF- α and Abeta (seq. 3) has a reverse orientation and comprises a DVD heavy chain amino acid sequence of SEQ ID NO. 92, and a DVD light chain amino acid sequence of SEQ ID NO. 93.

[0028] In an embodiment, the binding protein capable of binding IL-1 β and Abeta (seq. 3) comprises a DVD heavy chain amino acid sequence selected from the group consisting of SEQ ID NO. 94 and SEQ ID NO. 96; and a DVD light chain amino acid sequence selected from the group consisting of SEQ ID NO. 95 and SEQ ID NO. 97. In an embodiment, the binding protein capable of binding IL-1 β and Abeta (seq. 3) comprises a DVD heavy chain amino acid sequence of SEQ ID NO. 94 and a DVD light chain amino acid sequence of SEQ ID NO. 95. In another embodiment, the binding protein capable of binding IL-1 β and Abeta (seq. 3) has a reverse orientation and comprises a DVD heavy chain amino acid sequence of SEQ ID NO. 96 and a DVD light chain amino acid sequence of SEQ ID NO. 97.

[0029] In an embodiment, the binding protein capable of binding Abeta (seq. 1) and Abeta (seq. 3) comprises a DVD heavy chain amino acid sequence selected from the group consisting of SEQ ID NO. 98 and SEQ ID NO. 100; and a DVD light chain amino acid sequence selected from the group consisting of SEQ ID NO. 99 and SEQ ID NO. 101. In an embodiment, the binding protein capable of binding Abeta (seq. 1) and Abeta (seq. 3) comprises a DVD heavy chain amino acid sequence of SEQ ID NO. 98 and a DVD light chain amino acid sequence of SEQ ID NO. 99. In another embodiment, the binding protein capable of binding Abeta (seq. 1) and Abeta (seq. 3) has a reverse orientation and comprises a DVD heavy chain amino acid sequence of SEQ ID NO. 100 and a DVD light chain amino acid sequence of SEQ ID NO. 101.

[0030] In an embodiment, the binding protein capable of binding IGF1,2 and Abeta (seq. 3) comprises a DVD heavy chain amino acid sequence selected from the group consisting of SEQ ID NO. 102 and SEQ ID NO. 104; and a DVD light chain amino acid sequence selected from the group consisting of SEQ ID NO. 103 and SEQ ID NO. 105. In an embodiment, the binding protein capable of binding IGF1,2 and Abeta (seq. 3) comprises a DVD heavy chain amino acid sequence of SEQ ID NO. 102 and a DVD light chain amino acid sequence of SEQ ID NO. 103. In another embodiment, the binding protein capable of binding IGF1,2 and Abeta (seq. 3) has a reverse orientation and comprises a DVD heavy chain amino acid sequence of SEQ ID NO. 104 and a DVD light chain amino acid sequence of SEQ ID NO. 105.

[0031] In an embodiment, the binding protein capable of binding Abeta (seq. 3) and IL-18 comprises a DVD heavy chain amino acid sequence selected from the group consisting of SEQ ID NO. 106 and SEQ ID NO. 108; and a DVD light chain amino acid sequence selected from the group consisting of SEQ ID NO. 107 and SEQ ID NO. 109. In an embodiment, the binding protein capable of binding Abeta (seq. 3) and IL-18 comprises a DVD heavy chain amino acid sequence of SEQ ID NO. 106 and a DVD light chain amino acid sequence of SEQ ID NO. 107. In another embodiment, the binding

arthropathies, shock, sickle cell anemia, skin allograft rejection, skin changes syndrome, small bowel transplant rejection, solid tumors, specific arrhythmias, spinal ataxia, spinocerebellar degenerations, streptococcal myositis, structural lesions of the cerebellum, Subacute sclerosing panencephalitis, Syncope, syphilis of the cardiovascular system, systemic anaphylaxis, systemic inflammatory response syndrome, systemic onset juvenile rheumatoid arthritis, T-cell or FAB ALL, Telangiectasia, thromboangitis obliterans, thrombocytopenia, toxicity, transplants, trauma/hemorrhage, type III hypersensitivity reactions, type IV hypersensitivity, unstable angina, uremia, urosepsis, urticaria, valvular heart diseases, varicose veins, vasculitis, venous diseases, venous thrombosis, ventricular fibrillation, viral and fungal infections, viral encephalitis/aseptic meningitis, vital-associated hemaphagocytic syndrome, Wernicke-Korsakoff syndrome, Wilson's disease, xenograft rejection of any organ or tissue.

[0071] In an embodiment, diseases that can be treated or diagnosed with the compositions and methods of the invention include, but are not limited to, primary and metastatic cancers, including carcinomas of breast, colon, rectum, lung, oropharynx, hypopharynx, esophagus, stomach, pancreas, liver, gallbladder and bile ducts, small intestine, urinary tract (including kidney, bladder and urothelium), female genital tract (including cervix, uterus, and ovaries as well as choriocarcinoma and gestational trophoblastic disease), male genital tract (including prostate, seminal vesicles, testes and germ cell tumors), endocrine glands (including the thyroid, adrenal, and pituitary glands), and skin, as well as hemangiomas, melanomas, sarcomas (including those arising from bone and soft tissues as well as Kaposi's sarcoma), tumors of the brain, nerves, eyes, and meninges (including astrocytomas, gliomas, glioblastomas, retinoblastomas, neuromas, neuroblastomas, Schwannomas, and meningiomas), solid tumors arising from hematopoietic malignancies such as leukemias, and lymphomas (both Hodgkin's and non-Hodgkin's lymphomas).

[0072] The DVD-Igs of the invention may also treat one or more of the following diseases: Acute coronary syndromes, Acute Idiopathic Polyneuritis, Acute Inflammatory Demyelinating Polyradiculoneuropathy, Acute ischemia, Adult Still's Disease, Alopecia areata, Anaphylaxis, Anti-Phospholipid Antibody Syndrome, Aplastic anemia, Arteriosclerosis, Atopic eczema, Atopic dermatitis, Autoimmune dermatitis, Autoimmune disorder associated with *Streptococcus* infection, autoimmune enteropathy, Autoimmune hearing loss, Autoimmune Lymphoproliferative Syndrome (ALPS), Autoimmune myocarditis, autoimmune thrombocytopenia (AITP), autoimmune premature ovarian failure, Blepharitis, Bronchiectasis, Bullous pemphigoid, Cardiovascular Disease, Catastrophic Antiphospholipid Syndrome, Celiac Disease, Cervical Spondylosis, Chronic ischemia, Cicatricial pemphigoid, Clinically isolated Syndrome (CIS) with Risk for Multiple Sclerosis, Conjunctivitis, Childhood Onset Psychiatric Disorder, Chronic obstructive pulmonary disease (COPD), Dacryocystitis, dermatomyositis, Diabetic retinopathy, Diabetes mellitus, Disk herniation, Disk prolaps, Drug induced immune hemolytic anemia, Endocarditis, Endometriosis, endophthalmitis, Episcleritis, Erythema multiforme, erythema multiforme major, Gestational pemphigoid, Guillain-Barré Syndrome (GBS), Hay Fever, Hughes Syndrome, Idiopathic Parkinson's Disease, idiopathic interstitial pneumonia, IgE-mediated Allergy, Immune hemolytic anemia, Inclusion Body Myositis, Infectious ocular inflam-

matory disease, Inflammatory demyelinating disease, Inflammatory heart disease, Inflammatory kidney disease, IPF/UIP, Iritis, Keratitis, Keratoconjunctivitis sicca, Kussmaul disease or Kussmaul-Meier Disease, Landry's Paralysis, Langerhan's Cell Histiocytosis, Livedo reticularis, Macular Degeneration, malignancies, Microscopic Polyangiitis, Morbus Bechterev, Motor Neuron Disorders, Mucous membrane pemphigoid, Multiple Organ failure, Myasthenia Gravis, Myelodysplastic Syndrome, Myocarditis, Nerve Root Disorders, Neuropathy, Non-A Non-B Hepatitis, Optic Neuritis, Osteolysis, Ovarian cancer, Pauciarticular JRA, peripheral artery occlusive disease (PAOD), peripheral vascular disease (PVD), peripheral artery disease (PAD), Phlebitis, Polyarteritis nodosa (or periarteritis nodosa), Polychondritis, Polymyalgia Rheumatica, Poliosis, Polyarticular JRA, Polyendocrine Deficiency Syndrome, Polymyositis, polymyalgia rheumatica (PMR), Post-Pump Syndrome, primary Parkinsonism, prostate and rectal cancer and hematopoietic malignancies (leukemia and lymphoma), Prostatitis, Pure red cell aplasia, Primary Adrenal Insufficiency, Recurrent Neuromyelitis Optica, Restenosis, Rheumatic heart disease, SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis), Scleroderma, Secondary Amyloidosis, Shock lung, Scleritis, Sciatica, Secondary Adrenal Insufficiency, Silicone associated connective tissue disease, Sneddon-Wilkinson Dermatositis, spondylitis ankylosans, Stevens-Johnson Syndrome (SJS), Systemic inflammatory response syndrome, Temporal arteritis, toxoplasmic retinitis, toxic epidermal necrolysis, Transverse myelitis, TRAPS (Tumor Necrosis Factor Receptor, Type 1 allergic reaction, Type II Diabetes, Urticaria, Usual interstitial pneumonia (UIP), Vasculitis, Vernal conjunctivitis, viral retinitis, Vogt-Koyanagi-Harada syndrome (VKH syndrome), Wet macular degeneration, Wound healing, *yersinia*, and *salmonella* associated arthropathy.

[0073] In an embodiment, the antibodies of the invention or antigen-binding portions thereof, are used to treat cancer or in the prevention of metastases from the tumors described herein either when used alone or in combination with radiotherapy and/or other chemotherapeutic agents.

[0074] In another aspect the invention provides a method of treating a patient suffering from a disorder comprising the step of administering any one of the binding proteins disclosed herein before, concurrent, or after the administration of a second agent, as discussed herein. In a particular embodiment the second agent is selected from the group consisting of budenoside, epidermal growth factor, corticosteroids, cyclosporin, sulfasalazine, aminosalicylates, 6-mercaptopurine, azathioprine, metronidazole, lipoxigenase inhibitors, mesalamine, olsalazine, balsalazide, antioxidants, thromboxane inhibitors, IL-1 receptor antagonists, anti-IL-1 β mAbs, anti-IL-6 or IL-6 receptor mAbs, growth factors, elastase inhibitors, pyridinyl-imidazole compounds, antibodies or agonists of TNF, LT, IL-1, IL-2, IL-6, IL-7, IL-8, IL-12, IL-13, IL-15, IL-16, IL-18, IL-23, EMAP-II, GM-CSF, FGF, and PDGF, antibodies of CD2, CD3, CD4, CD8, CD-19, CD25, CD28, CD30, CD40, CD45, CD69, CD90 or their ligands, methotrexate, cyclosporin, FK506, rapamycin, mycophenolate mofetil, leflunomide, NSAIDs, ibuprofen, corticosteroids, prednisolone, phosphodiesterase inhibitors, adenosine agonists, antithrombotic agents, complement inhibitors, adrenergic agents, IRAK, NIK, IKK, p38, MAP kinase inhibitors, IL-1 β converting enzyme inhibitors, TNF α converting enzyme inhibitors, T-cell signalling inhibitors, metalloproteinase inhibitors, sulfasalazine, azathio-

ylprednisolone sodium succinate, diphenoxylate/atrop sulfate, loperamide hydrochloride, methotrexate, omeprazole, folate, ciprofloxacin/dextrose-water, hydrocodone bitartrate/apap, tetracycline hydrochloride, fluocinonide, metronidazole, thimerosal/boric acid, cholestyramine/sucrose, ciprofloxacin hydrochloride, hyoscyamine sulfate, meperidine hydrochloride, midazolam hydrochloride, oxycodone hcl/acetaminophen, promethazine hydrochloride, sodium phosphate, sulfamethoxazole/trimethoprim, celecoxib, polycarbophil, propoxyphene napsylate, hydrocortisone, multivitamins, balsalazide disodium, codeine phosphate/apap, colesvelam hcl, cyanocobalamin, folic acid, levofloxacin, methylprednisolone, natalizumab and interferon-gamma

[0333] Non-limiting examples of therapeutic agents for multiple sclerosis with which binding proteins of the invention can be combined include the following: corticosteroids; prednisolone; methylprednisolone; azathioprine; cyclophosphamide; cyclosporine; methotrexate; 4-aminopyridine; tizanidine; interferon- β 1a (AVONEX; Biogen); interferon- β 1b (BETASERON; Chiron/Berlex); interferon α -n3 (Interferon Sciences/Fujimoto), interferon- α (Alfa Wassermann/J&J), interferon β 1A-IF (Serono/Inhale Therapeutics), Peginterferon α 2b (Enzon/Schering-Plough), Copolymer 1 (Cop-1; COPAXONE; Teva Pharmaceutical Industries, Inc.); hyperbaric oxygen; intravenous immunoglobulin; clabribine; antibodies to or antagonists of other human cytokines or growth factors and their receptors, for example, TNF, LT, IL-1, IL-2, IL-6, IL-7, IL-8, IL-23, IL-15, IL-16, IL-18, EMAP-II, GM-CSF, FGF, and PDGF. Binding proteins of the invention can be combined with antibodies to cell surface molecules such as CD2, CD3, CD4, CD8, CD19, CD20, CD25, CD28, CD30, CD40, CD45, CD69, CD80, CD86, CD90 or their ligands. Binding proteins of the invention, may also be combined with agents, such as methotrexate, cyclosporine, FK506, rapamycin, mycophenolate mofetil, leflunomide, NSAIDs, for example, ibuprofen, corticosteroids such as prednisolone, phosphodiesterase inhibitors, adenosine agonists, anti-thrombotic agents, complement inhibitors, adrenergic agents, agents which interfere with signalling by proinflammatory cytokines such as TNF α or IL-1 (e.g., IRAK, NIK, IKK, p38 or MAP kinase inhibitors), IL-1 β converting enzyme inhibitors, TACE inhibitors, T-cell signaling inhibitors such as kinase inhibitors, metalloproteinase inhibitors, sulfasalazine, azathioprine, 6-mercaptopurines, angiotensin converting enzyme inhibitors, soluble cytokine receptors and derivatives thereof (e.g., soluble p55 or p75 TNF receptors, sIL-1RI, sIL-1RII, sIL-6R), antiinflammatory cytokines (e.g., IL-4, IL-10, IL-13 and TGF β) and bcl-2 inhibitors.

[0334] Examples of therapeutic agents for multiple sclerosis in which binding proteins of the invention can be combined to include interferon- β , for example, IFN β 1a and IFN β 1b; copaxone, corticosteroids, caspase inhibitors, for example inhibitors of caspase-1, IL-1 inhibitors, TNF inhibitors, and antibodies to CD40 ligand and CD80.

[0335] The binding proteins of the invention, may also be combined with agents, such as alemtuzumab, dronabinol, Unimed, daclizumab, mitoxantrone, xaliproden hydrochloride, fampridine, glatiramer acetate, natalizumab, sinnabidol, a-immunokine NNSO3, ABR-215062, AnergiX.MS, chemokine receptor antagonists, BBR-2778, calagualine, CPI-1189, LEM (liposome encapsulated mitoxantrone), THC.CBD (cannabinoid agonist) MBP-8298, mesopram (PDE4 inhibitor), MNA-715, anti-IL-6 receptor antibody,

neurovax, pirfenidone allotrap 1258 (RDP-1258), sTNF-R1, talampanel, teriflunomide, TGF-beta2, tiplimotide, VLA-4 antagonists (for example, TR-14035, VLA4 Ultrahaler, Antegran-ELAN/Biogen), interferon gamma antagonists, IL-4 agonists.

[0336] Non-limiting examples of therapeutic agents for Angina with which binding proteins of the invention can be combined include the following: aspirin, nitroglycerin, isosorbide mononitrate, metoprolol succinate, atenolol, metoprolol tartrate, amlodipine besylate, diltiazem hydrochloride, isosorbide dinitrate, clopidogrel bisulfate, nifedipine, atorvastatin calcium, potassium chloride, furosemide, simvastatin, verapamil hcl, digoxin, propranolol hydrochloride, carvedilol, lisinopril, spironolactone, hydrochlorothiazide, enalapril maleate, nadolol, ramipril, enoxaparin sodium, heparin sodium, valsartan, sotalol hydrochloride, fenofibrate, ezetimibe, bumetanide, losartan potassium, lisinopril/hydrochlorothiazide, felodipine, captopril, bisoprolol fumarate.

[0337] Non-limiting examples of therapeutic agents for Ankylosing Spondylitis with which binding proteins of the invention can be combined include the following: ibuprofen, diclofenac and misoprostol, naproxen, meloxicam, indomethacin, diclofenac, celecoxib, rofecoxib, Sulfasalazine, Methotrexate, azathioprine, minocyclin, prednisone, etanercept, infliximab.

[0338] Non-limiting examples of therapeutic agents for Asthma with which binding proteins of the invention can be combined include the following: albuterol, salmeterol/fluticasone, montelukast sodium, fluticasone propionate, budesonide, prednisone, salmeterol xinafoate, levalbuterol hcl, albuterol sulfate/ipratropium, prednisolone sodium phosphate, triamcinolone acetonide, beclomethasone dipropionate, ipratropium bromide, azithromycin, pirbuterol acetate, prednisolone, theophylline anhydrous, methylprednisolone sodium succinate, clarithromycin, zafirlukast, formoterol fumarate, influenza virus vaccine, methylprednisolone, amoxicillin trihydrate, flunisolide, allergy injection, cromolyn sodium, fexofenadine hydrochloride, flunisolide/menthol, amoxicillin/clavulanate, levofloxacin, inhaler assist device, guaifenesin, dexamethasone sodium phosphate, moxifloxacin hcl, doxycycline hyclate, guaifenesin/d-methorphan, p-ephedrine/cod/chlorphenir, gatifloxacin, cetirizine hydrochloride, mometasone furoate, salmeterol xinafoate, benzonatate, cephalixin, pe/hydrocodone/chlorphenir, cetirizine hcl/pseudoephed, phenylephrine/cod/promethazine, codeine/promethazine, cefprozil, dexamethasone, guaifenesin/pseudoephedrine, chlorpheniramine/hydrocodone, nedocromil sodium, terbutaline sulfate, epinephrine, methylprednisolone, metaproterenol sulfate.

[0339] Non-limiting examples of therapeutic agents for COPD with which binding proteins of the invention can be combined include the following: albuterol sulfate/ipratropium, ipratropium bromide, salmeterol/fluticasone, albuterol, salmeterol xinafoate, fluticasone propionate, prednisone, theophylline anhydrous, methylprednisolone sodium succinate, montelukast sodium, budesonide, formoterol fumarate, triamcinolone acetonide, levofloxacin, guaifenesin, azithromycin, beclomethasone dipropionate, levalbuterol hcl, flunisolide, ceftriaxone sodium, amoxicillin trihydrate, gatifloxacin, zafirlukast, amoxicillin/clavulanate, flunisolide/menthol, chlorpheniramine/hydrocodone, metaproterenol sulfate, methylprednisolone, mometasone furoate, p-ephedrine/cod/chlorphenir, pirbuterol acetate, p-eph-

tion efficiency, immunogenicity, pharmacokinetics, bioavailability, tissue cross reactivity, and orthologous antigen binding.

24. A binding protein capable of binding two antigens comprising four polypeptide chains, wherein two polypeptide chains comprise VD1-(X1)_n-VD2-C-(X2)_n, wherein

VD1 is a first heavy chain variable domain;

VD2 is a second heavy chain variable domain;

C is a heavy chain constant domain;

X1 is a linker with the proviso that it is not CH1; and

X2 is an Fc region; and

wherein two polypeptide chains comprise VD1-(X1)_n-

VD2-C-(X2)_n, wherein

VD1 is a first light chain variable domain;

VD2 is a second light chain variable domain;

C is a light chain constant domain;

X1 is a linker with the proviso that it is not CH1;

X2 does not comprise an Fc region; and

n is 0 or 1; wherein the VD1 and VD2 heavy chain variable

domains comprise an amino acid sequence selected

from the group consisting of SEQ ID NOs: 28, 30, 32,

34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, and 56 and

wherein the VD1 and VD2 light chain variable domains

comprise an amino acid sequence selected from the

group consisting of SEQ ID NOs: 29, 31, 33, 35, 37, 39,

41, 43, 45, 47, 49, 51, 53, 55, and 57.

25. A binding protein capable of binding two antigens comprising four polypeptide chains, wherein two polypeptide chains comprise VD1-(X1)_n-VD2-C-(X2)_n, wherein

VD1 is a first heavy chain variable domain;

VD2 is a second heavy chain variable domain;

C is a heavy chain constant domain;

X1 is a linker with the proviso that it is not CH1;

X2 is an Fc region; and

n is 0 or 1; and

wherein two polypeptide chains comprise VD1-(X1)_n-

VD2-C-(X2)_n, wherein

VD1 is a first light chain variable domain;

VD2 is a second light chain variable domain;

C is a light chain constant domain;

X1 is a linker with the proviso that it is not CH1;

X2 does not comprise an Fc region; and

n is 0 or 1;

wherein the DVD-Ig binds at least one antigen selected from the group consisting of Amyloid beta (Aβeta) (seq. 1), Aβeta (seq. 2), Aβeta (seq. 3), Tumor Necrosis Factor alpha (TNF-α), interleukin 1β (IL-1β), Insulin-like Growth Factor 1 (IGF1), Insulin-like Growth Factor 2 (IGF2), Interleukin 18 (IL-18), Interleukin 6 (IL-6), Receptor for Advanced Glycation Endproducts (RAGE), Nerve Growth Factor (NGF), Epidermal Growth Factor Receptor (EGFR) (seq. 1), EGFR (seq. 2), CD-20, and Repulsive Guidance Molecule (RGMA).

26. The binding protein according to claim 1, 3, 6, 24, or 25, wherein said binding protein has an on rate constant (K_{on}) to said one or more targets selected from the group consisting of: at least about 10²M⁻¹s⁻¹; at least about 10³M⁻¹s⁻¹; at least about 10⁴M⁻¹s⁻¹; at least about 10⁵M⁻¹s⁻¹; and at least about 10⁶M⁻¹s⁻¹, as measured by surface plasmon resonance.

27. The binding protein according to claim 1, 3, 6, 24, or 25, wherein said binding protein has an off rate constant (K_{off}) to said one or more targets selected from the group consisting of: at most about 10⁻³s⁻¹; at most about 10⁻⁴s⁻¹; at most about 10⁻⁵s⁻¹; and at most about 10⁻⁶s⁻¹, as measured by surface plasmon resonance.

28. The binding protein according to claim 1, 3, 6, 24, or 25, wherein said binding protein has a dissociation constant (K_D) to said one or more targets selected from the group consisting of: at most about 10⁻⁷M; at most about 10⁻⁸M; at most about 10⁻⁹M; at most about 10⁻¹⁰M; at most about 10⁻¹¹M; at most about 10⁻¹²M; and at most 10⁻¹³M.

29. A binding protein conjugate comprising a binding protein according to any one of claims 1, 3, 6, 24, or 25, said binding protein conjugate further comprising an agent selected from the group consisting of; an immunoadhesion molecule, an imaging agent, a therapeutic agent, and a cytotoxic agent.

30. The binding protein conjugate according to claim 29, wherein said agent is an imaging agent selected from the group consisting of a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, and biotin.

31. The binding protein conjugate according to claim 30, wherein said imaging agent is a radiolabel selected from the group consisting of: ³H, ¹⁴C, ³⁵S, ⁹⁰Y, ⁹⁹Tc, ¹¹¹In, ¹²⁵I, ¹³¹I, ¹⁷⁷Lu, ¹⁶⁶Ho, and ¹⁵³Sm.

32. The binding protein conjugate according to claim 30, wherein said agent is a therapeutic or cytotoxic agent selected from the group consisting of; an anti-metabolite, an alkylating agent, an antibiotic, a growth factor, a cytokine, an anti-angiogenic agent, an anti-mitotic agent, an anthracycline, toxin, and an apoptotic agent.

33. The binding protein according to claim 1, 3, 6, 24, or 25, wherein said binding protein is a crystallized binding protein.

34. The binding protein according to claim 33, wherein said crystal is a carrier-free pharmaceutical controlled release crystal.

35. The binding protein according to claim 33, wherein said binding protein has a greater half life in vivo than the soluble counterpart of said binding protein.

36. The binding protein according to claim 33, wherein said binding protein retains biological activity.

37. An isolated nucleic acid encoding a binding protein amino acid sequence according to any one of claims 1, 3, 6, 24, or 25.

38. A vector comprising an isolated nucleic acid according to claim 37.

39. The vector according to claim 38, wherein said vector is selected from the group consisting of pcDNA, pTT, pTT3, pEFBOS, pBV, pJV, pcDNA3.1 TOPO, pEF6 TOPO, and pBJ.

40. A host cell comprising a vector according to claim 38.

41. The host cell according to claim 40, wherein said host cell is a prokaryotic cell.

42. The host cell according to claim 41, wherein said host cell is *E. Coli*.

43. The host cell according to claim 40, wherein said host cell is a eukaryotic cell.

44. The host cell according to claim 43, wherein said eukaryotic cell is selected from the group consisting of protist cell, animal cell, plant cell and fungal cell.

45. The host cell according to claim 43, wherein said eukaryotic cell is an animal cell selected from the group consisting of; a mammalian cell, an avian cell, and an insect cell.

46. The host cell according to claim 45, wherein said host cell is a CHO cell.

47. The host cell according to claim 45, wherein said host cell is COS.

48. The host cell according to claim 43, wherein said host cell is a yeast cell.

49. The host cell according to claim 48, wherein said yeast cell is *Saccharomyces cerevisiae*.

50. The host cell according to claim 45, wherein said host cell is an insect Sf9 cell.

51. A method of producing a binding protein, comprising culturing a host cell described in any one of claims 40-50 in culture medium under conditions sufficient to produce the binding protein

52. The method according to claim 51, wherein 50%-75% of the binding protein produced is a dual specific tetravalent binding protein.

53. The method according to claim 51, wherein 75%-90% of the binding protein produced is a dual specific tetravalent binding protein.

54. The method according to claim 51, wherein 90%-95% of the binding protein produced is a dual specific tetravalent binding protein.

55. A protein produced according to the method of claim 51.

56. A pharmaceutical composition comprising the binding protein of any one of claims 1-36 and 55, and a pharmaceutically acceptable carrier.

57. The pharmaceutical composition of claim 56 further comprising at least one additional therapeutic agent.

58. The pharmaceutical composition of claim 57, wherein said additional therapeutic agent is selected from the group consisting of: Therapeutic agent, imaging agent, cytotoxic agent, angiogenesis inhibitors; kinase inhibitors; co-stimulation molecule blockers; adhesion molecule blockers; anti-cytokine antibody or functional fragment thereof; methotrexate; cyclosporin; rapamycin; FK506; detectable label or reporter; a TNF antagonist; an antirheumatic; a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteroid, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a growth hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, and a cytokine antagonist.

59. A method for treating a subject for a disease or a disorder by administering to the subject the binding protein of any one of claims 1-36 and 55 such that treatment is achieved.

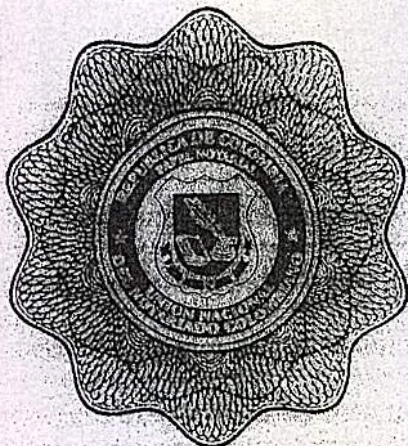
60. The method of claim 59, wherein said disorder is selected from the group comprising rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, septic arthritis, Lyme arthritis, psoriatic arthritis, reactive arthritis, spondyloarthritis, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, inflammatory bowel disease, insulin dependent diabetes mellitus, thyroiditis, asthma, allergic diseases, psoriasis, dermatitis scleroderma, graft versus host disease, organ transplant rejection, acute or chronic immune disease associated with organ transplantation, sarcoidosis, atherosclerosis, disseminated intravascular coagulation, Kawasaki's disease, Grave's disease, nephrotic syndrome, chronic fatigue syndrome, Wegener's granulomatosis, Henoch-Schoenlein purpura, microscopic vasculitis of the kidneys, chronic active hepatitis, uveitis, septic shock, toxic shock syndrome, sepsis syndrome, cachexia, infectious diseases, parasitic diseases, acquired immunodeficiency syndrome,

acute transverse myelitis, Huntington's chorea, Parkinson's disease, Alzheimer's disease, stroke, primary biliary cirrhosis, hemolytic anemia, malignancies, heart failure, myocardial infarction, Addison's disease, sporadic, polyglandular deficiency type I and polyglandular deficiency type II, Schmidt's syndrome, adult (acute) respiratory distress syndrome, alopecia, alopecia areata, seronegative arthropathy, arthropathy, Reiter's disease, psoriatic arthropathy, ulcerative colitic arthropathy, enteropathic synovitis, *chlamydia*, *yersinia* and *salmonella* associated arthropathy, spondyloarthritis, atheromatous disease/arteriosclerosis, atopic allergy, autoimmune bullous disease, pemphigus vulgaris, pemphigus foliaceus, pemphigoid, linear IgA disease, autoimmune haemolytic anaemia, Coombs positive haemolytic anaemia, acquired pernicious anaemia, juvenile pernicious anaemia, myalgic encephalitis/Royal Free Disease, chronic mucocutaneous candidiasis, giant cell arteritis, primary sclerosing hepatitis, cryptogenic autoimmune hepatitis, Acquired Immunodeficiency Disease Syndrome, Acquired Immunodeficiency Related Diseases, Hepatitis B, Hepatitis C, common varied immunodeficiency (common variable hypogammaglobulinaemia), dilated cardiomyopathy, female infertility, ovarian failure, premature ovarian failure, fibrotic lung disease, cryptogenic fibrosing alveolitis, post-inflammatory interstitial lung disease, interstitial pneumonitis, connective tissue disease associated interstitial lung disease, mixed connective tissue disease associated lung disease, systemic sclerosis associated interstitial lung disease, rheumatoid arthritis associated interstitial lung disease, systemic lupus erythematosus associated lung disease, dermatomyositis/polymyositis associated lung disease, Sjögren's disease associated lung disease, ankylosing spondylitis associated lung disease, vasculitic diffuse lung disease, haemosiderosis associated lung disease, drug-induced interstitial lung disease, fibrosis, radiation fibrosis, bronchiolitis obliterans, chronic eosinophilic pneumonia, lymphocytic infiltrative lung disease, postinfectious interstitial lung disease, gouty arthritis, autoimmune hepatitis, type-1 autoimmune hepatitis (classical autoimmune or lupoid hepatitis), type-2 autoimmune hepatitis (anti-LKM antibody hepatitis), autoimmune mediated hypoglycaemia, type B insulin resistance with acanthosis nigricans, hypoparathyroidism, acute immune disease associated with organ transplantation, chronic immune disease associated with organ transplantation, osteoarthritis, primary sclerosing cholangitis, psoriasis type 1, psoriasis type 2, idiopathic leucopenia, autoimmune neutropenia, renal disease NOS, glomerulonephritides, microscopic vasculitis of the kidneys, lyme disease, discoid lupus erythematosus, male infertility, idiopathic or NOS, sperm autoimmunity, multiple sclerosis (all subtypes), sympathetic ophthalmia, pulmonary hypertension secondary to connective tissue disease, Goodpasture's syndrome, pulmonary manifestation of polyarteritis nodosa, acute rheumatic fever, rheumatoid spondylitis, Still's disease, systemic sclerosis, Sjögren's syndrome, Takayasu's disease/arteritis, autoimmune thrombocytopenia, idiopathic thrombocytopenia, autoimmune thyroid disease, hyperthyroidism, goitrous autoimmune hypothyroidism (Hashimoto's disease), atrophic autoimmune hypothyroidism, primary myxoedema, phacogenic uveitis, primary vasculitis, vitiligo, acute liver disease, chronic liver diseases, alcoholic cirrhosis, alcohol-induced liver injury, cholelithiasis, idiosyncratic liver disease, Drug-Induced hepatitis, Non-alcoholic Steatohepatitis, allergy and asthma, group B streptococci (GBS) infection, mental disorders (e.g., depression and schizophrenia),

Th2 Type and Th1 Type mediated diseases, acute and chronic pain (different forms of pain), and cancers such as lung, breast, stomach, bladder, colon, pancreas, ovarian, prostate and rectal cancer and hematopoietic malignancies (leukemia and lymphoma) Abetalipoproteinemia, Acrocyanosis, acute and chronic parasitic or infectious processes, acute leukemia, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), acute or chronic bacterial infection, acute pancreatitis, acute renal failure, adenocarcinomas, aerial ectopic beats, AIDS dementia complex, alcohol-induced hepatitis, allergic conjunctivitis, allergic contact dermatitis, allergic rhinitis, allograft rejection, alpha-1-antitrypsin deficiency, amyotrophic lateral sclerosis, anemia, angina pectoris, anterior horn cell degeneration, anti cd3 therapy, antiphospholipid syndrome, anti-receptor hypersensitivity reactions, aortic and peripheral aneurysms, aortic dissection, arterial hypertension, arteriosclerosis, arteriovenous fistula, ataxia, atrial fibrillation (sustained or paroxysmal), atrial flutter, atrioventricular block, B cell lymphoma, bone graft rejection, bone marrow transplant (BMT) rejection, bundle branch block, Burkitt's lymphoma, Burns, cardiac arrhythmias, cardiac stun syndrome, cardiac tumors, cardiomyopathy, cardiopulmonary bypass inflammation response, cartilage transplant rejection, cerebellar cortical degenerations, cerebellar disorders, chaotic or multifocal atrial tachycardia, chemotherapy associated disorders, chronic myelocytic leukemia (CML), chronic alcoholism, chronic inflammatory pathologies, chronic lymphocytic leukemia (CLL), chronic obstructive pulmonary disease (COPD), chronic salicylate intoxication, colorectal carcinoma, congestive heart failure, conjunctivitis, contact dermatitis, cor pulmonale, coronary artery disease, Creutzfeldt-Jakob disease, culture negative sepsis, cystic fibrosis, cytokine therapy associated disorders, Dementia pugilistica, demyelinating diseases, dengue hemorrhagic fever, dermatitis, dermatologic conditions, diabetes, diabetes mellitus, diabetic atherosclerotic disease, Diffuse Lewy body disease, dilated congestive cardiomyopathy, disorders of the basal ganglia, Down's Syndrome in middle age, drug-induced movement disorders induced by drugs which block CNS dopamine receptors, drug sensitivity, eczema, encephalomyelitis, endocarditis, endocrinopathy, epiglottitis, epstein-barr virus infection, erythromelalgia, extrapyramidal and cerebellar disorders, familial hemaphagocytic lymphohistiocytosis, fetal thymus implant rejection, Friedreich's ataxia, functional peripheral arterial disorders, fungal sepsis, gas gangrene, gastric ulcer, glomerular nephritis, graft rejection of any organ or tissue, gram negative sepsis, gram positive sepsis, granulomas due to intracellular organisms, hairy cell leukemia, Hallervorden-Spatz disease, hashimoto's thyroiditis, hay fever, heart transplant rejection, hemachromatosis, hemodialysis, hemolytic uremic syndrome/thrombolytic thrombocytopenic purpura, hemorrhage, hepatitis (A), His bundle arrhythmias, HIV infection/HIV neuropathy, Hodgkin's disease, hyperkinetic movement disorders, hypersensitivity reactions, hypersensitivity pneumonitis, hypertension, hypokinetic movement disorders, hypothalamic-pituitary-adrenal axis evaluation, idiopathic Addison's disease, idiopathic pulmonary fibrosis, antibody mediated cytotoxicity, Asthenia, infantile spinal muscular atrophy, inflammation of the aorta, influenza a, ionizing radiation exposure, iridocyclitis/uveitis/optic neuritis, ischemia-reperfusion injury, ischemic stroke, juvenile rheumatoid arthritis, juvenile spinal muscular atrophy, Kaposi's sarcoma, kidney transplant rejection, *legionella*, leishmania-

sis, leprosy, lesions of the corticospinal system, lipedema, liver transplant rejection, lymphedema, malaria, malignant Lymphoma, malignant histiocytosis, malignant melanoma, meningitis, meningococcemia, metabolic/idiopathic, migraine headache, mitochondrial multi.system disorder, mixed connective tissue disease, monoclonal gammopathy, multiple myeloma, multiple systems degenerations (Mencel Dejerine-Thomas Shi-Drager and Machado-Joseph), myasthenia gravis, *mycobacterium avium* intracellulare, *mycobacterium tuberculosis*, myelodysplastic syndrome, myocardial infarction, myocardial ischemic disorders, nasopharyngeal carcinoma, neonatal chronic lung disease, nephritis, nephrosis, neurodegenerative diseases, neurogenic I muscular atrophies, neutropenic fever, non-hodgkins lymphoma, occlusion of the abdominal aorta and its branches, occlusive arterial disorders, okt3 therapy, orchitis/epididymitis, orchitis/vasectomy reversal procedures, organomegaly, osteoporosis, pancreas transplant rejection, pancreatic carcinoma, paraneoplastic syndrome/hypercalcemia of malignancy, parathyroid transplant rejection, pelvic inflammatory disease, perennial rhinitis, pericardial disease, peripheral atherosclerotic disease, peripheral vascular disorders, peritonitis, pernicious anemia, *pneumocystis carinii* pneumonia, pneumonia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), post perfusion syndrome, post pump syndrome, post-MI cardiomyopathy syndrome, preeclampsia, Progressive supranucleo Palsy, primary pulmonary hypertension, radiation therapy, Raynaud's phenomenon and disease, Raynaud's disease, Refsum's disease, regular narrow QRS tachycardia, renovascular hypertension, reperfusion injury, restrictive cardiomyopathy, sarcomas, scleroderma, senile chorea, Senile Dementia of Lewy body type, seronegative arthropathies, shock, sickle cell anemia, skin allograft rejection, skin changes syndrome, small bowel transplant rejection, solid tumors, specific arrhythmias, spinal ataxia, spinocerebellar degenerations, streptococcal myositis, structural lesions of the cerebellum, Subacute sclerosing panencephalitis, Sympcope, syphilis of the cardiovascular system, systemic anaphalaxis, systemic inflammatory response syndrome, systemic onset juvenile rheumatoid arthritis, T-cell or FAB ALL, Telangiectasia, thromboangitis obliterans, thrombocytopenia, toxicity, transplants, trauma/hemorrhage, type III hypersensitivity reactions, type IV hypersensitivity, unstable angina, uremia, urosepsis, urticaria, valvular heart diseases, varicose veins, vasculitis, venous diseases, venous thrombosis, ventricular fibrillation, viral and fungal infections, vital encephalitis/aseptic meningitis, vital-associated hemaphagocytic syndrome, Wernicke-Korsakoff syndrome, Wilson's disease, xenograft rejection of any organ or tissue, acute coronary syndromes, acute idiopathic polyneuritis, acute inflammatory demyelinating polyradiculoneuropathy, acute ischemia, adult Still's disease, alopecia areata, anaphylaxis, anti-phospholipid antibody syndrome, aplastic anemia, arteriosclerosis, atopic eczema, atopic dermatitis, autoimmune dermatitis, autoimmune disorder associated with *streptococcus* infection, autoimmune enteropathy, autoimmune hearing loss, autoimmune lymphoproliferative syndrome (ALPS), autoimmune myocarditis, autoimmune premature ovarian failure, blepharitis, bronchiectasis, bullous pemphigoid, cardiovascular disease, catastrophic antiphospholipid syndrome, celiac disease, cervical spondylosis, chronic ischemia, cicatricial pemphigoid, clinically isolated syndrome (cis) with risk for multiple sclerosis, conjunctivitis,

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 RAMIREZ MARANTO
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 NOTARIA TERCERA
 ENMIENDA



ESCRITURA NUMERO CUATRO MIL QUINTIENTOS -
 TREINTA Y NUEVE (No. 4.539) -----

En la ciudad de Cali, Capital del Departamento del Valle del Cauca, República de Colombia, a los VEINTITRES (23) días -
 del mes de OCTUBRE del año DOS MIL UNO --

(2.001), ante mí, JORGE ENRIQUE CAICEDO ZAMORANO, Notario
 T E R C E R O (3o.) del Circulo de Cali, - - - - -

compareció JUAN MANUEL BARBERI OSPINA mayor de edad, vecino de Cali,
 identificado con la cédula de ciudadanía número 14.949.561 de Cali, y dijo: ----

PRIMERO.- Que obra en su carácter de Representante Legal de en nombre y
 representación de TECNOQUIMICAS S.A. sociedad comercial organizada y existente
 conforme a las leyes colombianas, con domicilio y sede principal en Cali constituida
 mediante escritura pública número 2670 de la Notaría Segunda de Cali de fecha 12 de
 junio de 1957, reformada en distintas oportunidades, según consta en el certificado
 expedido por la Cámara de Comercio de Cali -----

SEGUNDO: Que en tal carácter, por este público instrumento, concede Poder Especial
 pero amplio y suficiente a JOSE LUIS REYES VILLAMIZAR, mayor de edad, vecino de
 Bogotá, identificado con C.C. # 79.152.473 de Bogotá, abogado en ejercicio, portador
 de la T.P. 44655 del C.S. de la J., domiciliado en Bogotá, D.C., República de Colombia
 con dirección carrera 7 No. 88.23 oficina 205, de la misma ciudad, como su representante
 con poder especial, amplio y suficiente, para obtener la protección de nuestra propiedad
 industrial y contra la competencia desleal, a cuyo efecto lo autorizo, para que nos
 represente ante cualesquiera entidad o persona, ejerzan o no jurisdicción, especialmente
 ante las del orden administrativo, contencioso-administrativo y judicial, en todo lo
 concerniente a los siguientes asuntos: a) Obtención, formulación de observaciones y
 oposición a patentes de invención, modelos y dibujos industriales y el registro de
 licencias de uso de esos derechos; b) Las acciones de oposición, cancelación, nulidad,
 medidas cautelares, concesión de licencias y en general los procesos civiles, penales,
 administrativos o contencioso-administrativos relacionados con estos derechos u otros de
 diferente naturaleza; acciones y procesos que promovamos o se nos promuevan; y c) para

Como Notario Veintitres de este Circulo
 hago constar que esta fotocopia
 con su fotocopia autentica a
 la vista.
 13 AGO 2007
 WILLY VALEK
 NOTARIO
 13 AGO 2007

4539
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LUZ MERY CORDELL
 ELABORACION DE ESCRITURAS
 Notaria 3 de Cali

que en todos los asuntos arriba determinados, , tanto en los términos señalados por los artículos 42 y complementarios de la Decisión 486 de la Comunidad Andina como del artículo 70 del C.P.C pueda sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos y ceder a título gratuito y/o oneroso, licenciar, inscribir contratos de cesión y de licencia, inscripción de prendas, levantamiento de prendas, inscribir derechos de retención y en general todos los asuntos que se deban tramitar ante la Superintendencia de Industria y Comercio.-----

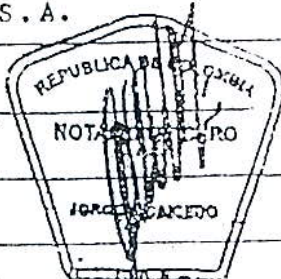
Leído el presente instrumento al otorgante, lo aprobó y en constancia firma conmigo el Notario de todo lo cual doy fe.-----

Se agregan comprobantes. Derechos \$30.000.00 Decreto 1681 de Septiembre 16 de 1996. Reformado mediante Resolución No.5839 de Diciembre 27 del año 2.000 y Decreto 1326 de Julio 06 del año 2.001. Se corrió en la hoja número AA 3286877. ENMENDADO "OCTUBRE" VALE.

Juan m. Barberi

JUAN MANUEL BARBERI OSPINA

En rep. de TECNOQUIMICAS S.A.



El Notario Tercero de Cali

Dr. JORGE ENRIQUE CAICEDO ZAMORANO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

- / -

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Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 13 - 0079589

Bogotá D.C., Agosto 09 de 2013 - 15:56:20

RECIBIDO DE : REYES Y REYES ABOGADOS

NI 900.048.328

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	559958604	09/08/2013	1.284.000.00

*** Conceptos Pagados ***

CANT	RENTISTICO	CONCEPTO	Vr UNDITARIO	Vr CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES A SOLICITUDES	12 OPOSICION POR CADA CLASE-MARCAS Y LEMAS COMERCIALES	325.000.00	325.000.00
				\$325.000.00

SON: **TRESCIENTOS VEINTICINCO MIL PESOS MONEDA CORRIENTE**

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 13-025485- -00006-0000

Fecha: 2013-08-12 16:09:41 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 21

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mai: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

, Agosto 9 de 2013 - 15:56:21

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

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RECIBO DE CAJA

No. 13 - 0079592

Bogotá D.C., Agosto 09 de 2013 - 15:56:20

RECIBIDO DE : REYES Y REYES ABOGADOS

NI 900.048.328

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	559958604	09/08/2013	1.284.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr. UNDITARIO	Vr. CONCEPTO
1	50005-01-08	PRORROGA DE TERMINOS	103.000.00	103.000.00
		1608 N. CREACION PRORROGA DE TERMINOS O PLAZO ADICIONAL		\$103.000.00

SON: **CIENTO TRES MIL PESOS MONEDA CORRIENTE**

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 13-025485- -00006-0000

Fecha: 2013-08-12 16:09:41 Dep. 2020 DIR.NUEVASCR
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Agosto 9 de 2013 - 15:56:21