СУББОТА, 8 ДЕКАБРЯ 2012 Г.

Plagiatoren Apogenix und Deutsches Krebsforschungszentrum (DKFZ)

Mitteilung Krebsforschungszentrum

Diese Mitteilung informiert über Diebstahl meines geistigen Eigentums, und zwar der Erfindung neuartiger antitumoralen Fusionsproteine mit den Formeln Rezeptor-Fc (Fc-Rezeptor und Fc-Rezeptor-Region oder Fc-Exodomaine (extrazelluläre Domäne) eines Rezeptors) und Ligand-Fc (meine deutsche Patentdokumente bzw. meine deutsche Druckschriften vom Jahr 2001 DE10160248, z.B. Anspruch 1, Tabellen 1 und 3 sowie DE10162870, DE10161738 und DE10161899 (z.B. jeweils Anspruch 1)) durch Apogenix und Deutsches Krebsforschungszentrum (DKFZ) und über Betrug und absichtliche, bewusste, vorsätzliche Täuschung des Staates und der Investoren durch Apogenix und durch Deutsches Krebsforschungszentrum (DKFZ).
Apogenix GmbH (und zwar Henning Walczak) und DKFZ wurden (laut Depatisnet, Datenbank des Deutschen Patent - und Markenamtes (DPMA)) durch Recherchen der Prüfer Europäischen Patentamts zu ihren Patentanmeldungen aus dem Jahr 2004 EP1606318, WO2004/085478 und EP2004003239 informiert, dass diese Erfindung (DE10160248) mir gehört, aber Apogenix verschwieg und verschweigt meine Priorität und meine Autorenschaft und täuscht, bzw. betrügt den Staat und Investoren und sammelt Geld für diese meine Erfindung, die Apogenix (wegen möglicher Invalidierung oder fehlender Neuheit und erfinderischen Tätigkeit) nicht sicher (von Konkurrenz) schützen kann (mit entsprechenden Folgen, d.h. Verlusten für den Staat und Investoren). Apogenix verschönert, d.h. verzerrt bewusst, absichtlich die Sachlage und täuscht somit. Apogenix hat schon mehr als 58,5 Millionen Euro durch Betrug bzw. Verschweigung eingesammelt, davon 5 Millionen Euro vom Bundesministerium für Wissenschaft und Forschung (BMBF) bzw. vom Staat.
Mit falschen Informationen sucht Apogenix weiter nach Partnern und Investoren. Apogenix will nach Angaben auf seiner Internetseite, Lizenzen möglichst bald verkaufen, d.h. Apogenix bietet Lizenzen zum Verkaufen an für das, was dem Apogenix nicht gehört und was daher kein Wert hat, (weil das kein Wert von Apogenix ist). Es handelt sich daher auch um Betrug und Täuschung.

Deutsches Krebsforschungszentrum (DKFZ) wusste von dieser Recherche des Europäischen Patentamts bzw. wusste, dass Apogenix täuscht und hat trotzdem die „Spin-out"-Firma Apogenix GmbH im Jahr 2005 gegründet und finanziert.
Diese Gründung seitens DKFZ widerspricht auch der Behauptung der DKFZ-Mitarbeiterin aus dem Jahr 1998 (in ihrem Schreiben vom 28.05.1998) Dr. Ruth Herzog, dass DKFZ bei der Verwertung meiner Erfindung nicht unterstützen kann, und, dass DKFZ eine Forschungseinrichtung sei, „die keine Produkte herstellt bzw.

vertreibt." DKFZ agierte, (wie auf der Apogenix-Internetseite mitgeteilt wurde), als Investor von Apogenix.

Автор: Alexander Cherkasky в 6:30 Комментариев нет:

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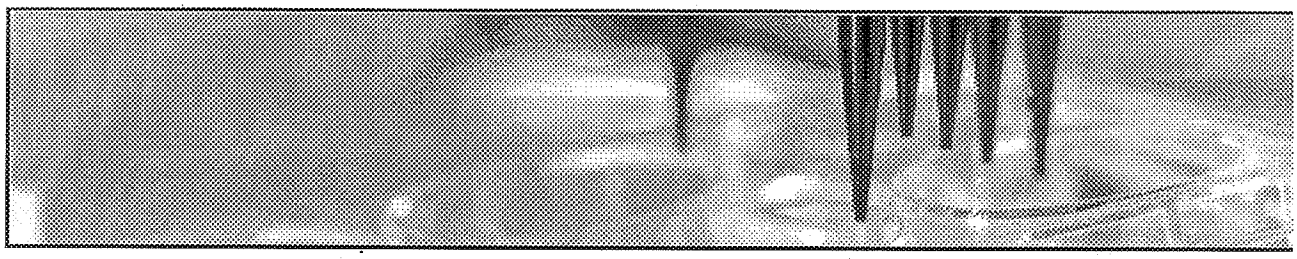

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CHERKASKY - FUSIONSPROTEINE ENTH/ ANTIKORPERBINDE-, ANTIGENBINDE - M UND IMMUNANTWORTAUSLOSENDE.

28.10.2004

Patent

Patentnummer:	WO2005040382
Anmeldedatum:	28. Oktober 2004
Veröffentlichungsdatum:	6. Mai 2005
Anmelder:	CHERKASKY, ALEXANDER, PRINZ-GEORG-STRASSE 5, 4047
Erfinder:	CHERKASKY, ALEXANDER
IPC-Klasse:	C12N015-62 (C12N015-62)

The invention relates to the fields of tumour physiology and biotechnology. The object of the inventi fusion proteins and fusion protein-antibody complexes against various types of leukaemia and solid t or tumour-specific ligands of the fusion proteins or by antibodies of the fusion protein-antibody com by the direct binding of the microtubules or cytoskeleton elements to the microtubule-binding region by the reinforcement of the immune reaction by regions that trigger the immune reaction on the targe

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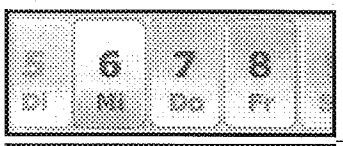

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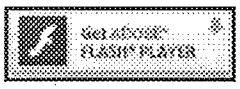

Investors

Apogenix has the support of committed long-term investors. Funds raised and grants awarded mainly from the BMBF will allow Apogenix to advance its programs through clinical proof of concept trials.

Bundesministerium für Bildung und Forschung

INVENTED IN GERMANY

dievini Hopp BioTech holding GmbG & Co. KG

The main investor in Apogenix is the Dietmar Hopp family. Dietmar Hopp, one of the co-founders of the leading software company SAP, supports biotech companies as a strategic investor. His family's biotechnology portfolio is managed by dievini Hopp BioTech holding GmbG & Co. KG.

German Cancer Research Center (DKFZ)

Apogenix was spun out from the renowned German Cancer Research Center (DKFZ), based in Heidelberg, in 2005. Apogenix concluded a comprehensive licensing agreement with the DKFZ covering exclusive worldwide rights to develop and market Apocept (APG101). DKFZ participated in the second and third financing round.

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Company

Apogenix is a clinical stage biopharmaceutical company developing novel protein therapeutics for the treatment of cancer and inflammatory diseases. The compound´s mechanism of action is either based on the targeted modulation of the programmed cell death (a.k.a. apoptosis - Απόπτωσις is used in Greek to describe the "falling off" of leaves from trees) or on the inhibition of tumour cell growth. The lead product candidate of the company, APG101, is currently in a controlled phase II proof of concept study with GBM patients (GBM: Glioblastoma multiforme). The primary endpoint of this study has been met. Data on secondary endpoints will become available in the next months.

Apogenix was founded as a spin-out from the German Cancer Research Center (DKFZ). Since its inception in fall 2005, the company has raised more than € 50 million in three financing rounds. In addition, the company has been awarded public funds totalling nearly € 8.5 million of which almost € 5 million have been granted as part of the so-called "Spitzencluster-Wettbewerb" initiated by the German Ministry for Research and Education (BMBF). Apogenix is based in Heidelberg, Germany, and currently employs some 25 people.

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Product

APG350 is one of several TRAIL-(TRAIL: Tumour necrosis factor related apoptosis inducing ligand) receptor agonists which have been developed by Apogenix. They are fully human Fc-fusion proteins consisting of two single chain TRAIL-molecules fused covalently to an Fc-part of a human IgG molecule. The proteins can be produced in very good yields using standard laboratory techniques and have a half-life of up to 24 hours. Preliminary toxicological investigations showed an excellent tolerability of these drug candidates. Currently, Apogenix works on the selection of the candidate which will be used for cell line development to be initiated in 2012. This is the first step towards the later GMP production.

****

Product

APG101 is a fully human fusion protein consisting of the extracellular domain of the CD95 receptor and the Fc domain of an IgG antibody. A controlled phase II study with APG101 was started in December 2009 in glioblastoma multiforme (GBM, the most aggressive brain tumour). Patient recruitment was completed in September. The primary endpoint of this study has been met in Q1/2012: the study objective of increasing the percentage of patients without a progress at six months after start of treatment by 100 % was substantially exceeded. Additional data on secondary endpoints will become available in the next months.
Preparations for another phase II study with APG101 are currently ongoing in the indication myelodysplastic syndromes (MDS). It is planned to initiate this trial in 2013.
An excellent tolerability of APG101 was shown in a randomized, double-blind, placebo-controlled phase I study in 34 healthy volunteers. Even the highest dose of 20 mg/kg body weight was tolerated very well and no anti-drug antibodies against APG101 were detected. The half-life was approximately 12 days. Preclinical toxicological long-term studies of up to 100 mg/kg bodyweight twice a week underline the excellent safety profile of the drug.

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Partnering

APG101

Apogenix wishes to establish a strategic partnership with a fully committed partner for late-stage clinical development and commercialisation of its lead product, APG101, on a worldwide basis. APG101 has been proven to be safe and well tolerated in preclinical and clinical trials. The substance is produced in a high-yield, proprietary production process which allows for the production of, e.g., phase III material. The company has built a comprehensive patent portfolio protecting APG101 until 2024 and beyond. With its most advanced drug candidate, Apogenix is targeting commercially attractive indications with high unmet medical needs. APG101 is currently being developed for the treatment of glioblastoma multiforme (GBM) and myelodysplastic syndrome (MDS).
In December 2009, a clinical phase II trial for the treatment of GBM was initiated. Enrolment was completed in September 2011 and final results regarding the primary study endpoint will be available in Q1/2012. It is planned to begin with an additional phase II trial in MDS next year.
Non-confidential information as well as preclinical and clinical data are available upon request.

APG350

Apogenix wishes to establish a partnership with a fully committed partner for clinical development and commercialisation of its TRAIL receptor agonist programme on a worldwide basis.
The TRAIL pathway has been shown to play an important role in many solid and hematopoietic cancers. There is a sound scientific rationale for the use of TRAIL receptor agonists especially in indications where new treatment options are much needed such as, e.g., lung and colon cancer, non-Hodgkin´s lymphoma, and multiple myeloma.
Apogenix has engineered novel TRAIL receptor agonists with improved efficacy and enhanced pharmacokinetic parameters to address this very attractive market. The fully human fusion proteins have been constructed to induce multimerisation of TRAIL receptors, thereby triggering apoptosis of established cancer cell lines, primary tumour cells and cancer stem cells at a much higher rate than other compounds. This has been shown not only in vitro but also in a number of in vivo tumour models.
In summary, Apogenix´ TRAIL receptor agonists are attractive candidates for future clinical development. Non-confidential information as well as preclinical and safety/tox data are available upon request.

If you are interested in further information, please contact

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juergen.gamer(at)apogenix.com

Press Releases

2012

July 26, 2012

Apogenix: APG101 Exceeds Expectations with Controlled Phase II Clinical Trial in Treatment of Recurrent Glioblastoma

May 29, 2012

Apogenix to Present Positive Phase II Results of APG101 in Glioblastoma Multiforme at ASCO

March 8, 2012

Apogenix Announces that APG101 Meets Primary Endpoint in a Controlled Phase II Trial with Glioblastoma Patients

January 5, 2012

Apogenix Raises € 7.5 Million to Further Advance APG101 to Treat Glioblastoma and other Tumors

January 3, 2012

Apogenix Receives Additional € 2.3 Million BMBF Grant as Partner of the Biotech Cluster Rhine-Neckar

2011

September 20, 2011

Apogenix Successfully Completes Patient Recruitment for Glioblastoma Phase II Trial with APG101

January 24, 2011

Apogenix Provides Update in the Ongoing Phase II Clinical Trial of APG101 to Treat Glioblastoma

2010

May 27, 2010

Data Published in "Nature" Confirms Development of APG101 to Treat Cancer

January 11, 2010

Apogenix Initiates Clinical Phase II Study with its Lead Compound APG101 in Glioblastoma

2009

November 16, 2009

Apogenix Receives Orphan Drug Designation for APG101 in the US and Positive Opinion on Orphan Product Designation in Europe

dkfz
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Krebsforschungszentrum
Stiftung des öffentlichen Rechts

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Ihr Zeichen	Ihre Nachricht vom	Unser Zeichen	Datum
		-zi	28. Mai 1998

Ihre Patentanmeldung „Therapeutisches Präparat"

Sehr geehrter Herr Cherkasky,

wir danken Ihnen für die Übersendung Ihrer Erfindung und Ihr Vertrauen, das Sie in uns setzen. Wir haben Ihre Unterlagen mit Interesse zur Kenntnis genommen und müssen Ihnen jedoch mitteilen, daß wir Sie bei der Verwertung nicht unterstützen können.

Das Deutsche Krebsforschungszentrum ist eine Forschungseinrichtung, die keine Produkte herstellt bzw. vertreibt.

Zu unserer Entlastung reichen wir Ihnen deshalb die Unterlagen zurück.

Wir wünschen Ihnen viel Erfolg bei der Verwertung und verbleiben

mit freundlichen Grüßen

Dr. Ruth Herzog

Trefferliste Expertenrecherche

Suchanfrage:

CT=DE10160248

Neue Suche (verfeinert) Zurück zur Recherche Familienmitglieder löschen

TREFFERLISTE: TREFFER 1 - GESAMTTREFFER 4 | ANGEZEIGTE TREFFERLISTE HERUNTERLADEN

Nr.	Veröffentlichungs-Nummer	Original-dokument	Recherchier-barer Text	Familien-Recherche
1	DE000010202191A1			Suchen
2	DE000010161899B4			Suchen
3	DE000010161738B4			Suchen
4	EP000001606318A2			Suchen

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Bibliographische Daten

Dokument EP000001606318A2 (Seiten: 1)

Blättern in der Trefferliste |< < > >| (4 / 4)

BIBLIOGRAPHISCHE DATEN ABSTRACT EPÜ-INFORMATIONEN KORRIGIERT

Kriterium	Feld	Inhalt
Titel	TI	[DE] VERBESSERTE FC-FUSIONSPROTEINE [EN] IMPROVED FC FUSION PROTEINS [FR] PROTEINES HYBRIDES FC AMELIOREES
Anmelder/Inhaber	PA	APOGENIX GMBH, DE ; DEUTSCHES KREBSFORSCH, DE
Erfinder	IN	WALCZAK HENNING, DE
Anmeldedatum	AD	26.03.2004
Anmeldenummer	AN	04723552
Anmeldeland	AC	EP
Veröffentlichungsdatum	PUB	21.12.2005
Priorität	PRC PRN PRD	EP 2004003239 20040326
	PRC PRN PRD	EP 03006949 20030326
IPC-Hauptklasse	ICM	C07K 19/00
IPC-Nebenklasse	ICS	C07K 14/47 C07K 14/475 C07K 14/52 C07K 14/525 C07K 14/54 C07K 14/705 C07K 14/715
IPC-Zusatzklasse	ICA	
IPC-Indexklasse	ICI	
MCD-Hauptklasse	MCM	
MCD-Nebenklasse	MCS	A61P 31/12 (2006.01) A61P 31/16 (2006.01) C07K 14/47 (2006.01) C07K 14/475 (2006.01) C07K 14/52 (2006.01) C07K 14/525 (2006.01) C07K 14/54 (2006.01) C07K 14/705 (2006.01) C07K 14/715 (2006.01) C07K 16/28 (2006.01) C07K 19/00 (2006.01)
MCD-Zusatzklasse	MCA	
Abstract	AB	
Korrekturinformation	KORRINF	
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Entgegengehaltene Patentdokumente, vom Anmelder genannt	CT	
Entgegengehaltene Nichtpatentliteratur, in Recherche ermittelt	CTNP	See also references of WO 2004085478A2 4

Kriterium	Feld	Inhalt
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Prüfstoff-IPC	ICP	

Deutsches
Patent- und Markenamt

Hinweis des DPMA zu einer EuroPCT-Anmeldung

Information provided by the DPMA concerning a Euro-PCT application

Information du DPMA concernant une demande euro-PCT

(11) Veröffentlichungsnummer:
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Numéro de publication:

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21.12.2005

Internationale Anmeldung veröffentlicht durch die Weltorganisation für geistiges Eigentum,

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siehe / see / voir:

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(07.10.2004 Gazette 2004/10)

1. (WO2004085478) IMPROVED FC FUSION PROTEINS

PCT Biblio. Data | Description | Claims | National Phase | Notices | Documents

Latest bibliographic data on file with the International Bureau

Pub. No.: WO/2004/085478 **International Application No.:** PCT/EP2004/003239
Publication Date: 07.10.2004 **International Filing Date:** 26.03.2004

IPC: ***C07K 14/705*** (2006.01), ***C07K 16/28*** (2006.01)

Applicants: **APOGENIX GMBH** [DE/DE]; Im Neuenheimer Feld 581, 69120 Heidelberg (DE) *(For All Designated States Except US)*.
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Priority Data: 03006949.6 26.03.2003 EP

Title
(EN) IMPROVED FC FUSION PROTEINS
(FR) PROTEINES HYBRIDES FC AMELIOREES

Abstract:
(EN) The invention relates to fusion proteins comprising at least a first domain and a second domain selected from a constant Fc immunoglobulin domain.
(FR) La présente invention a trait à des protéines hybrides comprenant au moins un premier domaine et un deuxième domaine choisis à partir d'un domaine d'immunoglobuline Fc.

Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
African Regional Intellectual Property Org. (ARIPO) (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW)
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European Patent Office (EPO) (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR)
African Intellectual Property Organization (OAPI) (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Publication Language: English (EN)
Filing Language: English (EN)

1. (WO2004085478) IMPROVED FC FUSION PROTEINS

Query
FP:(WO2004085478)

Improved Fc Fusion Proteins

Description

The invention relates to fusion proteins comprising at least a biologically active polypeptide domain and a second domain immunoglobulin domain.

Fusion proteins comprising an immunoglobulin heavy and/or light chain dimer or an immunoglobulin heavy and/or light cha amino acid sequence of a ligand-binding partner which is a receptor, a carrier protein, a hormone, a growth factor or an en variable region of at least one immunoglobulin chain, are described in EP-A-0 526 452. A fusion protein comprising the ex death receptor CD95 (APO-1 ; Fas) fused to an immunoglobulin Fc fragment is described in WO 95/27735. N-terminally tr APO-1 molecule optionally fused to immunoglobulin Fc fragments are disclosed in EP-A-0 965 637. A fusion protein consi and Fc fragments is disclosed in WO 98/36768. A fusion protein consisting of an antagonist IL-15 mutant and an Fc IgG2a Kim et al. (J. Immunol. 160 (1998), 5742-5748). These documents are incorporated herein by reference.

Although it has been shown that fusion proteins as described above have high biological activity in vitro and in vivo, there the immunogenic potential of such molecules since there is a fusion region between two protein domains of different origin ocurring amino sequence which may elicit an undesired immune response in an organism to which the fusion protein is ad

WO 02/066514 describes artificial fusion proteins having a reduced immunogenicity compared to the parent non-modified a species in vivo. These proteins essentially consist of an immunoglobulin molecule or a fragment thereof covalently fusec terminus of a biologically active non-immunoglobulin molecule, preferably a polypeptide or protein or a biologically active f molecules have amino acid sequences which are altered in one or more amino acid residue positions but, in principle, hav activity as compared with the non-altered molecules. The changes are made in regions of the molecules which are identifi contribute to an immune reaction in a living host. A disadvantage of this procedure, however, is that not all epitopes, partic can be reliably eliminated. Furthermore, the introduction of non-naturally occurring amino acid sequences can lead to the

Thus, it was an object of the present invention to provide fusion proteins with at least two domains of different origin havin potential.

Thus, the present invention relates to a fusion protein comprising
(i) at least one first domain comprising a biologically active polypeptide and (ii) a heterologous second domain comprising constant immunoglobulin domain,
wherein there is at least one amino acid overlap between the first domain and the second domain in the fusion region.

The fusion protein may be a monomeric protein or a multimeric protein, e.g. a dimeric or tetrameric protein, which may be via the constant immunoglobulin domain.

According to the present invention, the design of a fusion protein comprises i) the selection of at least one first domain anc heterologous to the first domain and ii) the selection of at least one terminal amino acid which is common to the first and th last amino acid(s) of the first domain is (are) selected such that they are identical with the first amino acid(s) of the second overlap has a length of one, two or three amino acids. Thus, a fusion protein is obtained which is free from a non-naturally between the last amino acid of one domain and the first amino acid of another domain.

In an embodiment of the invention, the first domain(s) is (are) located at the N-terminus of the fusion protein, whereas the at the C-terminus. Thus, in this embodiment, at least one carboxy terminal amino acid of a first domain overlaps with at lea of the second domain.

In a further embodiment the second domain is located at the N-terminus of the fusion protein and the first domain(s) is (are terminus. Thus, in this embodiment, at least one carboxy terminal amino acid of the second domain overlaps with at least a first domain.

In cases where the fusion protein comprises more than one, e.g. two or three, first domains, these domains are preferably N-terminus or the C-terminus of the fusion protein and the second domain at the C-terminus or at the N-terminus, respecti the first domains in such proteins may be the same or different. Transitions between individual first domains are preferably is also at least one amino acid overlap (and thus not a non-naturally occurring transition between the last amino acid of on amino acid of the other domain) between the individual first domains. Fusion proteins comprising multiple first domains are

which is incorporated herein by reference.

The first domain of the fusion protein comprises a biologically active polypeptide, i.e. a polypeptide which is capable of inte to, a binding partner, e.g. another polypeptide, in its natural environment in a cell or an organism and which is preferably c pharmacological activity. The first domain is preferably a non-immunoglobulin polypeptide. The first domain may be a natu or a variant thereof having desired, e.g. increased or reduced, biological activity or a fragment of a naturally occurring poly The first domain is preferably selected from the ligand-binding domain of a receptor and a receptor-binding domain of a lig and ..receptor" are understood in this context such that ligands are defined as proteins known to function to bind specifical The term ..receptor" includes soluble or membrane-anchored receptor proteins having a hydrophobic transmembrane regi anchor. Further, the term ..receptor" encompasses carrier prote ns as well as hormones, cellular adhesive proteins, lectins etc.

In a preferred embodiment of the invention the first domain is a ligand-binding receptor domain comprising the extra-cellul anchored receptor or a ligand-binding fragment thereof. The receptor is preferably selected from death receptors, growth f cytokine receptors. More preferably, the receptor is selected from CD95 (APO-1 ; Fas), TRAIL receptors, TNF receptors, V interleukin receptor such as IL-15Rα. Most preferably the receptor is CD95, a TRAIL receptor, e.g. the TRAIL receptor-1 , TRAIL receptor-3 or the TRAIL receptor-4 or a TNF receptor, e.g. the TNF receptor-1 or the TNF receptor-2.

In a further embodiment, the first domain is a receptor-binding ligand domain. The ligand is preferably selected from death ligand, TRAIL, TNF, e.g. TNF-α or TNF-β, growth factors, e.g. VEGF and cytokines, such as interferons or interleukins, e.g

In a still further embodiment, the fusion protein comprises multiple first domains which may be the same or different. A pre multiple fusion protein is a VEGF Trap fusion protein comprising the second extracellular domain of the VEGF receptor 1 (of the VEGF receptor 2 (KDR/FIK-1) and an IgG constant region.

The first domain protein is preferably a mammalian protein, more preferably a human protein. For therapeutic purposes in human proteins is preferred.

The second domain of the fusion protein comprises at least a portion of a constant immunoglobulin domain, e.g. a constar domain or a constant light immunoglobulin domain. Preferably, the second domain comprises at least a portion of a consta domain. The constant heavy immunoglobulin domain is preferably an Fc fragment comprising the CH2 and CH3 domain a part of the hinge region. The immunoglobulin domain may be an IgG, IgM, IgD or IgE immunoglobulin domain or a modifie derived , therefrom. Preferably, the second domain comprises at least a portion of a constant IgG immunoglobulin domain domain may be selected from IgG1 , IgG2, IgG3 of IgG4 domains or from modified domains such as are described in US 5 immunoglobulin domain may exhibit effector functions, particularly effector functions selected from ADCC and/or CDC. In s however, modified immunoglobulin domains having modified, e.g. at least partially deleted, effector functions may be used

Designing the fusion protein of the present invention comprises a selection of the terminal amino acid(s) of the first domair in order to create an at least one amino acid overlap between both domains. In order to achieve this goal it is usually nece several amino acids from a first and/or second domain and/or to add one or several amino acids from the naturally occurri first and/or second domain. For example, it may be necessary to provide a first domain having a deletion of preferably up t up to 6 amino acids, e.g. 1 , 2, 3, 4, 5 or 6 amino acids from naturally occurring domain boundaries. On the other hand, it r preferably up to 10 and, more preferably, up to 6 amino acids, e.g. 1 , 2, 3, 4, 5 or 6 amino acids from a naturally occurring first and/or second domain. When deleting and/or adding amino acids, however, one has to take care that the biological ac and/or the second domain is not detrimentally affected.

The fusion protein of the invention may comprise an N-terminal signal sequence which allows secretion from a host cell aft The signal sequence may be a signal sequence which is homologous to the first domain of the fusion protein. Alternatively also be a heterologous signal sequence, e.g. the Igκ or the Igλ signal peptide sequence. In a different embodiment, the fus N-terminal sequence, thus representing the mature form of the fusion protein.

The overlap between the first and the second domain or between two first domains has a length of preferably 1 , 2 or 3 am the overlap has a length of one amino acid. Examples of overlapping amino acids are S, E, K, H, T, P and D.

The present invention is explained in detail below with regard to several specific preferred embodiments. It should be note fusion proteins of the invention may be manufactured by analogous means.

In a first preferred embodiment the first domain is the extracellular domain of human CD95. The extracellular domain of th comprises the amino acid sequence up to amino acid 170, 171, 172 or 173 of human CD95. Preferably, the extracellular d with a human IgG Fc fragment, e.g. a human IgG1 Fc fragment. The amino acid sequence of the human CD95 molecule is amino acid sequence of the human IgG1 chain constant domain is shown in Figure 2. Especially preferred is the fusion pro acid sequence as shown in Figures 3A and 3B, wherein the overlapping amino acid sequence is S.

In a further especially preferred embodiment the first domain is the extracellular domain of a human TRAIL receptor, e.g. tl 1 , the human TRAIL receptor-2, the human TRAIL receptor-3 and the human TRAIL receptor-4. The extracellular domain amino acid sequence up to amino acid 232, 233, 234, 235, 236, 237 238, 239 (TRAILR-1), 204, 205, 206, 207, 208, 209, 186, 187, 188, 189, 190, 191 (TRAILR-2 long - without repeat), 179 180, 181 , 182, 183, 184 (TRAILR-2 short), 228, 229, 2

235, 236, (TRAILR-3), 151 , 152, 153, 154, 155, 156, 157, 158, 159 160, 161 (TRAILR-3 without repeat) and 201 , 202, 2C 209, 210, 211 (TRAILR-4). Especially preferred is the human TRAIL receptor-2. The extracellular human TRAIL receptor c human IgG-1 Fc fragment. The amino acid sequences of human TRAIL receptors are shown in Figure 4 (TRAILR-1), Figu Figure 9 (TRAILR-2 short), Figure 11 (TRAIL-3) and Figure 14 (TRAILR-4). Specific examples of preferred fusion proteins sequences as shown in Figure 5, 7, 8, 10, 12, 13 and 15.

In still a further preferred embodiment the fusion protein comprises a first domain which is the extracellular domain of a hu human TNF receptor-1 or a human TNF receptor-2. The extracellular domain preferably comprises the amino acid sequen 204, 205, 206, 207, 208, 209, 210, 211 (TNF-R1) or 248, 249, 250, 251 , 252, 253, 254, 255, 256, 257 (TNF-R2). The extr human TNF receptor may be fused to a human IgG-1 Fc fragment. The amino acid sequence of human TNF receptors are R1) and 18 (TNF-R2). Specific examples of preferred fusion protein comprise amino acid sequences as shown in Figures

A further aspect of the present invention relates to a nucleic acid molecule encoding a fusion protein as described above. may be a DNA molecule, e.g. a double-stranded or single-stranded DNA molecule, or an RNA molecule. The nucleic acid fusion protein or a precursor thereof, e.g. a pro- or pre-proform of the fusion protein which may comprise a signal sequenc amino acid portions for secretion or purification which are preferably located at the N- and/or C-terminus of the fusion prot amino acid portions may be linked to the first and/or second domain via a protease cleavage site, e.g. a Factor X_a, thromb site.

The nucleic acid molecule may be operatively linked to an expression control sequence, e.g. an expression control sequer expression of the nucleic acid molecule in a desired host cell. The nucleic acid molecule may be located on a vector, e.g. a a viral vector, a chromosal integration vector, etc. Examples of suitable expression control sequences and vectors are des Sambrook et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, and Ausubel et al. (1989), Cu Biology, John Wiley & Sons.

Various expression vector/host cell systems may be used to express the nucleic acid sequences encoding the fusion prote invention. Suitable host cells include, but are not limited to, prokaryotic cells such as bacteria, e.g. E.coli, eukaryotic host c insect cells, plant cells or animal cells, preferably mammalian cells and, more preferably, human cells.

Further, the invention relates to a non-human organism transformed or transfected with a nucleic acid molecule as describ organisms may be generated by known methods of genetic transfer including homologous recombination.

A further aspect of the present invention relates to a pharmaceutical composition comprising as an active agent at least or nucleic acid molecule coding thereof as described above. In an especially preferred embodiment, the first domain is a solu extracellular domain of a death receptor as described above for use in the prophylaxis and/or treatment of disorders assoc preferably, the first domain is the extracellular CD95 domain.

In this embodiment of the invention the composition may be used in the prophylaxis and/or treatment of disorders selectec disorders, AIDS, heart disorders, e.g. myocardial infarction, graft-versus-host-disorders, transplant rejection, brain damage injuries, e.g. paraplegia, sepsis, hepatitis, disorders associated with inflammation, ischemic reperfusion injury and renal dis and further disorders which may be treated by administration of death receptor fusion proteins, particularly CD95 fusion pr 95/27735, WO 99/50413, WO 01/41803, EP-A-0 965 637 and EP-A-0 992 243 which are herein incorporated by reference

The fusion protein is administered to a subject in need thereof, particularly a human patient, in a sufficient dose for the trea conditions by suitable means. For example, the fusion protein may be formulated as a pharmaceutical composition togeth acceptable carriers, diluents and/or adjuvants. Therapeutic efficacy and toxicity may be determined according to standard pharmaceutical composition may be administered systemically, e.g. intraperitoneally, intramuscularly or intravenously or lc subcutaneously or intrathecally. Preferred is intravenous administration.

Especially preferred is a death ligand inhibitor, e.g. a soluble extracellular CD95 or TRAIL receptor domain fused to an Fc

The dose of the fusion protein administered will of course be dependent on the subject to be treated, on the subject's weig the injury, the manner of administration and the judgement of the prescribing physician. For the administration of CD95 or daily dose of 0,001 to 100 mg/kg is suitable.

Moreover, the invention relates to a method for manufacturing a fusion protein comprising
(i) at least one first domain comprising a biologically active protein fused to
(ii) a second domain comprising at least a portion of a constant immunoglobulin domain with reduced immunogenic potent is fused to the second domain with at least one amino acid overlap.

Still a further aspect of the present relates to a fusion protein comprising:

(i) at least one first domain comprising a biologically active polypeptide fused to
(ii) a heterologous second domain which is capable of oligomerising the fusion protein wherein there is at least one amino first and the second domain in the fusion region.

Fusion proteins comprising heterologous second domains which are capable or oligomerising the fusion proteins in the ab described in WO 01/49866 and in WO 02/090553, for example, which are incorporated herein by reference. The presence overlap, e.g. one, two or three amino acids overlap, between the first and the second domain in the fusion proteins leads - fusion proteins with reduced immunogenic potential.

The first domain in this oligomerising fusion protein is defined as above. Preferably, the first domain is an extracellular don anchored receptor, or a ligand-binding fragment thereof. Especially preferred is that the receptor is selected from CD95, a the TRAIL receptor-2 and a TNF receptor, particularly the TNF receptor-2. Alternatively, the first domain may be a recepto wherein the ligand is preferably selected from CD95 ligand, TRAIL and TNF. Specific examples of preferred first domains

The second domain of the fusion protein comprises an oligomerising portion of a protein. Preferably, the second domain is pentamerising the fusion protein. In this context, particular reference is made to the disclosure of WO 01/49866 and WO 0 incorporated by reference. Preferred examples of second domains are C1q, MBP (Mannose Binding Protein), SP-A (Lung D (Lung Surfactant Protein-D), BC (Bovine Serum Conglutinine), CL43 (Bovine Collectine-43), ACRP-30 (a protein from th (Cartilage Oligomeric Matrix Protein) or the collagen domain of EDA or a functionally active derivative thereof. Especially p ACRP-30, particularly of the human ACRP-30 protein, e.g. amino acids 18 to 108, or 18 to 110 or of COMP.

As described above, the first domain(s) of the fusion protein may be located at the N- or C-terminus and the second doma Further, both the first and the second domains are preferably from the same species, more preferably of human origin. Fu relating to preferred embodiments of the fusion proteins based on immunoglobulins also apply to the oligomerising fusion

The reduced immunogenic potential of the fusion protein results from the lack of non-naturally occurring transitions betwee domain in the fusion proteins, which in turn leads to a decreased potential for the formation of neo-epitopes resulting from heterologous polypeptides.

The present invention is illustrated further by the following Figures and Examples.

Figure Legend
Figure 1: the amino acid sequence of the human CD95 (APO-1, Fas) protein;
Figure 2: the amino acid sequence of the human IgG-1 chain C-region;
Figures 3A and 3B: a preferred example of a CD95-Fc IgG1 fusion protein with an overlapping amino acid;
Figure 4: the amino acid sequence of the human TRAIL receptor-1 ;
Figure 5: preferred examples of TRAILR-1 Fc IgG1 fusion proteins with overlapping amino acids;
Figure 6: the amino acid sequence of human TRAIL receptor-2 (long form);

Figure 7: preferred examples of TRAILR-2 (long) Fc IgG1 fusion proteins with overlapping amino acids, including a repeat
Figure 8: preferred examples of TRAILR-2 (long form) Fc fusion proteins with overlapping amino acids (without repeat seq
Figure 9: the amino acid sequence of human TRAILR-2 (short form);
Figure 10: preferred examples of TRAILR-2 (short) Fc IgG1 fusion proteins with overlapping amino acids;
Figure 11 : the amino acid sequence of human TRAIL receptor R-3;
Figure 12: preferred examples of TRAILR-3 Fc IgG1 fusion proteins with overlapping amino acids (repeats included);
Figure 13: preferred examples of TRAILR-3 Fc IgG1 fusion proteins with overlapping amino acids (repeats not included);
Figure 14: the amino acid sequence of human TRAIL receptor-4;
Figure 15: preferred examples of TRAILR-4 Fc IgG1 fusion proteins with overlapping amino acids;
Figure 16: the amino acid sequence of human tumor necrosis factor receptor-1 ;
Figure 17: preferred examples of TNFR-1 Fc IgG1 fusion proteins with overlapping amino acids;
Figure 18: the amino acid sequence of human tumor necrosis factor receptor-2;
Figure 19: preferred examples of TNF-R2 Fc IgG1 fusion proteins with overlapping amino acids.

Example 1
Fusion protein consisting of the human CDS5 extracellular domain and the human IgG1 Fc domain with overlapping amin

Human CD85 extracellular domain

Bases 221-736 of Human CD95 (Genbank Ace. No. X63717). Utilized Sequence from Oehm, A., "Purification and Molecul Cell Surface Antigen, a Member of the Tumour Necrosis Factor/Nerve Growth Factor Receptor Superfamily," Journal of Bi No.15, pp.10709-10715, 1992. cDNA was created from total RNA isolated from Peripheral Blood Lymphocytes (PBL) from using Oligo dT primer. PCRs were used to amplify the cDNA of the extracellular domain of CD95 by including a restriction Sequence at the 5' of the Extracellular domain and at the 3' a Bgl II site (termination of the extracellular domain).

PCR primers for the amplification of CD95 cDNA with Taq polymerase:
Sense huCD95-Hind III: TATA AAGCTT GCC ACC ATG CTG GGC ATC TG (SEQ ID NO:21)
Antisense huCD95-Bgl II: TATA AGATCT GGA TCC TTC CTC TTT GC (SEQ ID NO:2)

Human IgG1 Fc domain

Sequence: 2050-2745 bp. Sequence used from, Ellison, J., "The nucleotide sequence of human immunoglobulin C gene",

Volume 10 Number 13, 1982. cDNA was created from total RNA isolated from Peripheral Blood Lymphocytes (PBL) from (using Oligo dT primer. A PCR was used to amplify the cDNA of human IgG1 Fc (partial hinge-CH3) by including a restricti(primer and at the 3' primer after the stop codon, an Xho I site.

PCR primers for the amplification of IgGI Fc cD A with Taq polymerase: Sense hulgG1Fc-BglII: TATA AGATCT TGT GAC (SEQ ID NO: 3)
Antisense hulgGI Fc-XhoI: TATA CTCGAG TCA TTT ACC CGG AGA CAG GG (SEQ ID NO: 4)

Clonin Procedure:
Following amplification the IgG1 Fc PCR product was digested with Bgl II and Xho I. The CD95 PCR product was digestec pcDNA3.1 (with CMV promoter) with Hind III and Xho I. The products were purified via gel extraction (Qiagen Kit).

The hulgGI Fc and CD95 fragments were ligated with T4 ligase into pcDNA3.1. After transfection of One Shot Top 10 cher (E.coli) from Invitrogen Ordering # C4040-10 and amplification, a plasmid preparation was performed with Qiagen Plasmic

A three point ligation was performed by digesting pcDNA3.1 with HindIII and XhoI, CD95EC with HindIII and BglII, and hulg The presence of the CD95-hulgG1 Fc insert in pcDNA3.1 was verified by sequencing and restriction enzyme analysis. The was digested with HindIII and XbaI and the insert was ligated into pcDNA3.1 containing the EF-1 promoter.

The Kozak sequence of the original CD95-Fc construct was changed from GCCACCATGC to GCCGCCACCATGG by am CD95-Fc product with the primers SEQ ID 5 and SEQ ID 6.

Primers for Changing the Kozak Sequence from GCCACCATGC to
GCCGCCACCATGG:
ShuCD95EC_altKθZal TATA AAGCTT GCC GCC ACC ATG GTG GGC ATC (SEQ ID NO. 5)
AS698 hulgGI Fc-Xho 1 TATA CTCGAG TCA TTT ACC CGG AGA CAG GG (SEQ ID NO:6)

The PCR product was cloned in pcDNA3.1/V5 His Topo vector from
Invitrogen (Ordering # K4800-01), digested with Hind III and Xba I as well as pcDNA3.1 containing the pEF promoter and I

Expression and Isolation
The construct encoding the final product was transfected into cell lines suitable for protein expression. Transfection can be standard method know to those skilled in the art. Examples include electroporation, liposomal mediated transfer, calcium p transfection. Cell lines suitable for the expression include 293T cells, COS-1, COS-7 and CHO cells. Other cell lines may b

In this example, 293T cells were transiently transfected by the calcium phosphate method. Alternatively, CHO cells were tr FuGeneθ and stable clones were selected.

The desired protein can be purified from the cell culture medium by chromatographic methods. Methods include but are nc chromatography on protein-G or protein-A columns, ion-exchange
chromatography, hydrophobic interaction chromatography, size exclusion chromatograpy or a combination of these metho In the example the supernatant was purified on IgG columns (Amersham Pharmacia) according to the manufacturers instr purified product in a single step.

Example 2.
Fusion protein consisting of the TRAIL receptor-2 and the human IgG1

Fc domain with overlapping amino acids

Human IgıG1 Fc domain:

Sequence used from, Ellison, J., "The nucleotide sequence of human immunoglobulin C gene", Nucleic Acid Research, Vc cDNA was created from total RNA isolated from Peripheral Blood Lymphocytes (PBL) from donor blood by RT-PCR using was used to amplify the cDNA of human IgG1 Fc (partial hinge-CH3) with an overlapping sequence to TRAILR2 at the 5' e the stop codon an EcoRI site.

I. Primer: Sense_hulgG1 (SEQ ID NO: 7)
cca ggg act cct gcc TCT TGT GAG AAA ACT CAC ACA TG (Capital letters => part of hulgGI)

II. Primer: Antisense_ERIhulgG1 (SEQ ID NO: 8)
TATA gaa ttc tea ttt ace egg aga cag gg

TRAILR2:
Utilized Sequence from Walczak H., "TRAIL-R2: a novel apoptosis-mediating receptor for TRAIL" The EMBO Journal Vol. 1997. (Accession number DDBJ/EMBL/GenBank: AF016849) cDNA was created from total RNA isolated from Peripheral I

from donor blood by RT-PCR using an Oligo dT primer. A PCR was used to amplify the cDNA of TRAILR2 domain by inclu
III and a Kozak Sequence at the 5' end and at the 3' end an
overlapping sequence to human IgG1.

III. Primer: Sense _HIII_J AILR2 (SEQ ID NO: 9)
TATA aag ctt gcc gcc ace atg gaa caa egg gga cag aac IV. Primer: Antisense_TRAILR2 (SEQ ID NO: 10)
gtg agt ttt gtc aca aga GGC AGG AGT CCC TGG (Capital letters => part huTRAIL-R2, in reverse)

Clonina Procedure:
Following the amplification a gel extraction was performed to isolate the modified inserts. Then a third PCR utilizing both fr
Due to the overlap of both fragments and the primers at the end, this PCR joins in one product. Afterwards the product wa
EcoR I and ligated in a suitable expression vector, e.g. pcDNA3.1
(Invitrogen).

III. Primer: Sense_HH._TRAILR2 (SEQ ID NO: 11)
TATA aag ctt gcc gcc ace atg gaa caa egg gga cag aac

II. Primer: Antisense_ERIhuIgG1 (SEQ ID NO: 12)
TATA gaa ttc tea ttt ace egg aga cag gg

Expression
The construct was cloned and expressed in suitable host cells as described in Example 1.

Example 3.
Use of a CD95-Fc construct for the regeneration and functional recovery after spinal cord injury.

The CD95-Fc construct with overlapping amino acids as described in Example 1 was used for the treatment of spinal cord
described by Demjen et al., Nat Med. (March 7, 2004). It was found that administration of the construct promotes regenera
recovery after spinal cord injury.

Example 4.
Use of CD95-Fc construct for the attenuation of brain damage in stroke.

The CD95-Fc construct with overlapping amino acids was investigated for its influence on primary ischemic death and sec
in a mouse model as described by Martin-Villalba et al. (Cell Death Differ. 8 (2001), 679-68.6). It was found that administra
construct resulted in a significant decrease in both infarct volumes and mortality.

1. (WO2004085478) IMPROVED FC FUSION PROTEINS

Query
FP:(WO2004085478)

Claims

1. A fusion protein comprising
(i) at least one first domain comprising a biologically active polypeptide fused to
(ii) a heterologous second domain comprising at least a portion of a constant immunoglobulin domain wherein there is at l
between the first domain and the second domain in the fusion region.

2. The fusion protein of claim 1, wherein the first domain is selected from a ligand-binding domain of a receptor and a rece
ligand.

3. The fusion protein of claims 1 or 2, wherein the first domain is a ligand- binding receptor domain comprising an extracell
membrane-anchored receptor or a ligand-binding fragment thereof.

4. The fusion protein of claims 2 or 3, wherein the receptor is selected from death receptors, growth factor receptors and c

5. The fusion protein of claim 4, wherein the receptor is selected from CD95, a TRAIL receptor, a TNF receptor and a VEG

6. The fusion protein of claims 1 or 2, wherein the first domain is a receptor-binding ligand domain.

7. The fusion protein of claims 1 or 6, wherein the ligand is selected from death ligands, growth factors and cytokines.

8. The fusion protein of claim 7, wherein the ligand is selected from CD95 ligand, TRAIL, TNF, VEGF and IL-15.

9. The fusion protein of any one of claims 1 to 8 wherein the at least one first domain is derived from a human protein.

10. The fusion protein of any one of claims 1 to 9, wherein the second s domain comprises at least a portion of a constant
domain.

11. The fusion protein of any one of claims 1 to 9, wherein the second domain is an Fc fragment of a constant heavy immu
comprising the CH2 and CH3 domain and optionally at least a part of the hinge region.

12. The fusion protein of any one of claims 1 to 11 , wherein the second domain comprises at least a portion of a constant
domain.

13. The fusion protein of any one of claims 1 to 12, wherein the second domain comprises at least a portion of a constant l
immunoglobulin domain or a variant thereof.
0
14. The fusion protein of any one of claims 1 to 13 wherein the immunoglobulin domain exhibits effector functions, particul
selected from ADCC and/or CDC.

5 15. The fusion protein of any one of claims 1 to 14, wherein the second domain is derived from a human immunoglobulir

16. The fusion protein of any one of claims 1 to 15 wherein the overlap has a length of 1 , 2 or 3 amino acids.
0
17. The fusion protein of any one of claims 1 to 16 wherein at least one carboxy terminal amino acid of the first domain ov
amino terminal amino acid of the second domain.

18. The fusion protein of any one of claims 1 to 17 wherein the fusion region is free from a non-naturally occurring transitic
acid of one domain and the first amino acid of the other domain.

19. The fusion protein of any one of claims 1 to 18 wherein the first domain and/or second domain comprises a deletion of
acids.

20. The fusion protein of any one of claims 1 to 19 wherein the first domain and/or second domain comprises an addition c
acids.

21. The fusion protein of any one of claims 1 to 20 which comprises an N- terminal signal sequence.

22. The fusion protein of any one of claims 1 to 20 which lacks an N- terminal signal sequence.

23. The fusion protein of any one of claims 1 to 22 wherein the overlapping amino acid sequence is selected from S, E, K,

24. The fusion protein of any one of claims 1 to 23 wherein the first domain is the extracellular domain of human CD95.

25. The fusion protein of claim 24 wherein the extracellular domain of CD95 has the amino acid sequence up to amino aci human CD 95.

26. The fusion protein of claim 25 comprising an amino acid sequence as shown in Figures 3A and 3B.

27. The fusion protein of any one of claims 1 to 23 wherein the first domain is the extracellular domain of a human TRAIL r

28. The fusion protein of claim 22, wherein the human TRAIL receptor is selected from human TRAIL receptor-1, human T TRAIL receptor-3 and human TRAIL receptor-4.

29. The fusion protein of claim 28 comprising an amino acid sequence as shown in Figures 5, 7, 8, 10, 12, 13 or 15.

30. The fusion protein of any one of claims 1 to 23 wherein the first domain is the extracellular domain of a human TNF re

31. The fusion protein of claim 30, wherein the human TNF receptor is selected from human TNF receptor-1 and human T

32. The fusion protein of claim 31 comprising the amino acid sequence as shown in Figures 17 or 19.

33. A nucleic acid molecule encoding a fusion protein of any one of claims 1 to 32 or a precursor thereof.

34. The nucleic acid molecule of claim 33 which is operatively linked to an expression control sequence.

35. The nucleic acid molecule of claims 33 or 34 which is located on a vector.

36. A cell transformed or transfected with a nucleic acid molecule of any one of claims 33 to 35.

37. The cell of claim 36 which is a prokaryotic cell.

38. The cell of claim 37 which is a eukaryotic cell, preferably a mammalian cell and more preferably a human cell.

39. A non-human organism transformed or transfected with a nucleic acid molecule of any one of claims 33 to 35.

40. A pharmaceutical composition comprising as an active agent a fusion protein of any one of claims 1 to 32 or a nucleic claims 33 to 35.

41. The composition of claim 40 wherein the first domain is a soluble death receptor for use in the prophylaxis and/or treat associated with apoptosis.

42. The composition of claim 41 wherein the first domain is the extracellular CD95 domain.

43. The composition of claims 41 or 42 for use in the prophylaxis and/or treatment of disorders selected from autoimmune disorders, e.g. myocardial infarction, graft-versus-host-disorders, e.g. transplant rejection, spinal cord injuries, e.g. paraple disorders associated with inflammation, ischemic reperfusion injury and renal disorders.

44. A method for manufacturing a fusion protein comprising
(i) at least one first domain comprising a biologically active polypeptide fused to
(ii) a second domain comprising at least a portion of a constant immunoglobulin domain with reduced immunogenic potent is fused to the second domain with at least one amino acid overlap.

45. A fusion protein comprising
(i) at least one first domain comprising a biologically active polypeptide fused to
(ii) a heterologous second domain which is capable of oligomerising the fusion protein wherein there is at least one amino first and the second domain in the fusion region.

46. The fusion protein of claim 45, wherein the first domain comprises an extracellular domain of a membrane-anchored re fragment thereof.

47. The fusion protein of claim 46, wherein the receptor is selected from CD95, a TRAIL receptor and a TNF receptor.

48. The fusion protein of claim 48, wherein the first domain comprises a receptor-binding ligand domain.

49. The fusion protein of claim 48, wherein the ligand is selected from CD95 ligand, TRAIL and TNF.

50. The fusion protein of any one of claims 45 to 49, wherein the second domain comprises an oligomerising portion of a p MBP, SP-A, SP-D, BC, CL43 and ACRP30 and COMP or the collagen domain of EDA or a functionally active derivative th

51. The fusion protein of any one of claims 45 to 50, wherein the second domain is capable of di-, tri-, tetra- or pentameris

Press Release

Apogenix: Death Receptor CD95 Promotes Tumour Growth

Data Published in "Nature" Confirms Development of APG101 to Treat Cancer

Peer-Reviewed Publication by Professor Marcus Peter of the University of Chicago Shows Cancer Cells Depend on the Constitutive Activity of CD95, Stimulated by Cancer-Produced CD95L.

Heidelberg, May 27, 2010 – Apogenix GmbH, a protein therapeutic-based biopharmaceutical company specializing in malignant and inflammatory diseases, today announced the publication of an independent Nature article. This publication describes *in vitro* and *in vivo* studies of CD95: "CD95 promotes tumour growth" (Nature, May 27, 2010) by Professor Marcus Peter and his team, previously at the Ben May Department for Cancer Research, The University of Chicago Cancer Research Center, now in the Department of Medicine at the Northwestern Feinberg School of Medicine, Chicago, IL.

In vitro and *in vivo* data in this publication showed that cancer cells in general, regardless of their CD95 apoptosis sensitivity, depend on constitutive activity of CD95, stimulated by cancer-produced CD95L, for optimal growth. Results demonstrated that CD95 has a growth-promoting role during tumorigenesis and indicate that efforts to inhibit its activity rather than to enhance it should be considered during cancer therapy.

Professor Peter told Apogenix: "Our data indicate that the CD95/CD95L system, rather than being tumour suppressive, drives cancer growth - joining the ranks of TNFR1 and TNF-*alpha* in stimulating tumour growth. In line with our results, studies by other groups suggest that CD95 activates neuronal stem cells and acts as a tumour promoter for glioblastoma."

Apogenix is developing APG101: a soluble CD95-Fc fusion protein that blocks CD95L from binding to the CD95 receptor, thus inhibiting tumour cell migration and invasive growth. APG101 is currently in Phase II trials to treat Glioblastoma multiforme (GBM), the most common and aggressive type of primary brain tumour. Results from the trial are expected in 2011.

Harald Fricke, CMO of Apogenix, said: "This is an independent confirmation of our approach to treating glioblastoma and potentially other tumours. Professor Peter and his team at the University of Chicago are highly respected for their studies on the activities of death receptors and the related signaling components in cell death as well as for the relevance of non-apoptotic activities in cancer development."

With APG101 Apogenix intends to fundamentally improve the treatment of GBM. The goal of the current Phase II study is to achieve clinical proof-of-concept for APG101.

About Apogenix

Apogenix, a spin-out from the German Cancer Research Center (DKFZ), is developing novel protein therapeutics for the treatment of cancer and inflammatory diseases, based either on the targeted modulation of apoptosis (programmed cell death) or by blocking the invasive growth of tumour cells. The company is developing APG101, its lead product candidate, to treat Glioblastoma multiforme (GBM), the most common and aggressive type of primary brain tumour. APG101 is in preparation to enter Phase II trials for the treatment of acute Graft-versus-Host Disease (aGvHD), the rejection of recipient tissue by transplanted bone marrow. In preclinical studies, Apogenix is focusing on Interleukin-4 (IL-4) blockers. IL-4 plays an essential role in the development of apoptosis resistance in cancer cells and cancer stem cells. Since its inception in autumn 2005, the company has raised €43 million and has been awarded public grants totalling nearly €5.8 million. Apogenix is based in Heidelberg, Germany.

About APG101

The company's lead product candidate, APG101, a soluble fusion protein combining the extracellular domain of the CD95-receptor and the Fc-portion of IgG, completed Phase I studies in 2009. In December 2009, APG101 entered a controlled Phase II trial for the treatment of Glioblastoma multiforme (GBM) and is in preparation to enter Phase II trials for the treatment of acute Graft-versus-Host Disease (aGvHD). Apogenix plans to out-license APG101 no later than the completion of proof of concept Phase II trials. Apogenix has been granted orphan drug status for APG101 to treat GBM in Europe and the U.S and for the prevention of aGvHD in Europe.

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Company

Apogenix is a clinical stage biopharmaceutical company developing novel protein therapeutics for the treatment of cancer and inflammatory diseases. The compound´s mechanism of action is either based on the targeted modulation of the programmed cell death (a.k.a. apoptosis - □πόπτωσις is used in Greek to describe the "falling off" of leaves from trees) or on the inhibition of tumour cell growth. The lead product candidate of the company, Apocept (APG101), is currently in a controlled phase II proof of concept study with GBM patients (GBM: Glioblastoma multiforme). The primary endpoint of this study has been met. Data on secondary endpoints will become available in the next months.

Apogenix was founded as a spin-out from the German Cancer Research Center (DKFZ). Since its inception in fall 2005, the company has raised more than € 50 million in three financing rounds. In addition, the company has been awarded public funds totalling nearly € 8.5 million of which almost € 5 million have been granted as part of the so-called "Spitzencluster-Wettbewerb" initiated by the German Ministry for Research and Education (BMBF). Apogenix is based in Heidelberg, Germany, and currently employs some 25 people.

The Apogenix Management Team

The Apogenix management team combines entrepreneurial experience with a strong track record in pharmaceutical research and clinical development.

Thomas Höger, Ph.D.

Chief Executive Officer & Chief Financial Officer
Dr. Thomas Höger joined Apogenix GmbH as Chief Executive Officer and Chief Financial Officer in November 2005. Prior to this, he worked as a stock analyst for DZ BANK, Frankfurt (Germany) for five years. From 1997 to 2000, he headed the CNS research at BASF AG and Knoll AG. From 1992 to 1996, he held various research and management positions at BASF AG.
Dr. Thomas Höger obtained his Ph.D. in 1991 for the doctoral work performed at the German Cancer Research Center (DKFZ) after having studied biology at the Universities of Kiel and Heidelberg, and the Massachusetts Institute of Technology (MIT, Cambridge, USA) as a Fulbright Scholar. In 2001, he gained a certification as a CEFA-analyst ("Certified European Federation of Financial Societies Financial Analyst").
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Harald Fricke, M.D./Ph.D.

Chief Medical Officer & Chief Operating Officer
Dr. Harald Fricke joined Apogenix GmbH as Chief Medical Officer and Chief Operating Officer in January 2006. Previously, he was responsible for global clinical development at Fresenius Biotech GmbH. Prior to this, he was head of Baxter Oncology's clinical development department. From 1996 to 2001 he held various national and international management positions at SmithKline Beecham and GlaxoSmithKline, respectively.
Dr. Fricke obtained his M.D. in 1987 after having studied medicine at the University of Aachen and the University Lübeck. From 1987 to 1990, he worked as a postdoc at the Weizman Institute of Science in Israel. Following his accreditation as a specialist in internal medicine in 1993, he was awarded his 'Habilitation' in 1996 by Ludwig-Maximilian-University in Munich.
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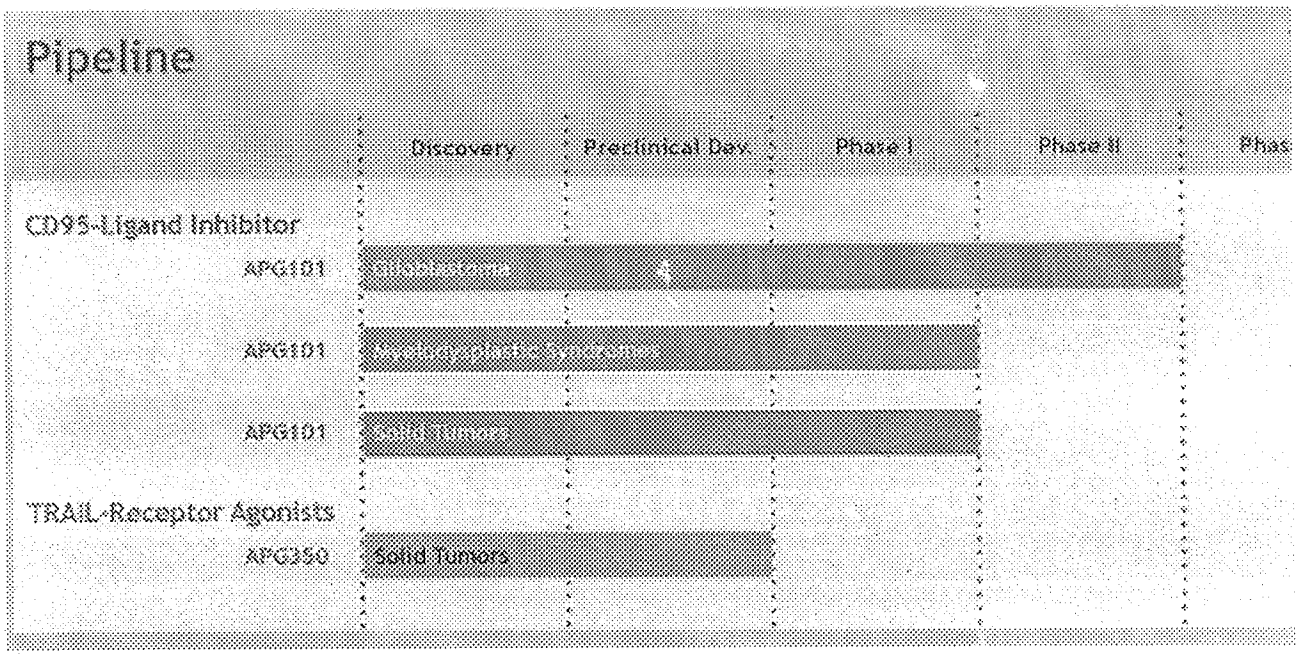
Milestones

2012	Primary endpoint of phase II GBM study with Apocept met
2011	Completion of patient recruitment of phase II GBM study with Apocept
2010	„Orphan Drug Designation“ for Apocept in EU and USA (Indication: GBM)
2009	Start of phase II with Apocept (Indication: GBM)
2008	Start of phase I with Apocept; 2nd financing round: € 28 million
2007	Establishment of GMP-production for Apocept
2006	„Orphan Drug Designation“ for Apocept (APG101) in EU (Indication: acute Graft-versus-Host Disease, aGvHD)
2005	Foundation of Apogenix; 1st financing round: € 15 million

Overview

Since its foundation in 2005, the Apogenix team has built a promising product pipeline with currently two product candidates having a huge potential for the treatment of various diseases. Main focus is on the development of novel cancer treatments.
The CD95L blocker Apocept (APG101) is currently in clinical development for GBM and MDS. In addition, inhibition of the CD95L offers a novel treatment option for solid tumours beyond GBM. Apogenix owns an extensive patent portfolio covering Apocept at least until 2024. Furthermore, the company has been granted „orphan drug" designations in US and Europe for the treatment of glioma and glioblastoma, respectively. The product is manufactured in an efficient GMP process well-suited for the production of clinical phase III material and market supply. Apogenix is the owner of this production process.
TRAIL receptor agonists such as, e.g., APG350, will be developed for the treatment of solid tumours. The novel mode of action of these compounds is protected by a series of patent applications filed by Apogenix in the last years. Apogenix´ TRAIL receptor agonists can be produced with excellent yields at laboratory scale. It is planned to initiate the development of a GMP cell line in 2012.



Partnering

Apocept

Apogenix wishes to establish a strategic partnership with a fully committed partner for late-stage clinical development and commercialisation of its lead product, Apocept (APG101), on a worldwide basis.
Apocept has been proven to be safe and well tolerated in preclinical and clinical trials. The substance is produced in a high-yield, proprietary production process which allows for the production of, e.g., phase III material. The company has built a comprehensive patent portfolio protecting Apocept until 2024 and beyond. With its most advanced drug candidate, Apogenix is targeting commercially attractive indications with high unmet medical needs. Apocept is currently being developed for the treatment of glioblastoma multiforme (GBM) and myelodysplastic syndrome (MDS).
In December 2009, a clinical phase II trial for the treatment of GBM was initiated. Enrolment was completed in September 2011 and final results regarding the primary study endpoint will be available in Q1/2012. It is planned to begin with an additional phase II trial in MDS next year.
Non-confidential information as well as preclinical and clinical data are available upon request.

APG350

Apogenix wishes to establish a partnership with a fully committed partner for clinical development and commercialisation of its TRAIL receptor agonist programme on a worldwide basis.
The TRAIL pathway has been shown to play an important role in many solid and hematopoietic cancers. There is a sound scientific rationale for the use of TRAIL receptor agonists especially in indications where new treatment options are much needed such as, e.g., lung and colon cancer, non-Hodgkin´s lymphoma, and multiple myeloma.
Apogenix has engineered novel TRAIL receptor agonists with improved efficacy and enhanced pharmacokinetic parameters to address this very attractive market. The fully human fusion proteins have been constructed to induce multimerisation of TRAIL receptors, thereby triggering apoptosis of established cancer cell lines, primary tumour cells and cancer stem cells at a much higher rate than other compounds. This has been shown not only in vitro but also in a number of in vivo tumour models.
In summary, Apogenix´ TRAIL receptor agonists are attractive candidates for future clinical development. Non-confidential information as well as preclinical and safety/tox data are available upon request.

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Press Releases

2012

November 6, 2012

Apogenix's Apocept™ for Glioblastoma Multiforme Named One of "Top 10 Projects to Watch"

July 26, 2012

Apogenix: APG101 Exceeds Expectations with Controlled Phase II Clinical Trial in Treatment of Recurrent Glioblastoma

May 29, 2012

Apogenix to Present Positive Phase II Results of APG101 in Glioblastoma Multiforme at ASCO

March 8, 2012

Apogenix Announces that APG101 Meets Primary Endpoint in a□Controlled Phase II Trial with Glioblastoma Patients

January 5, 2012

Apogenix Raises € 7.5 Million to Further Advance APG101 to Treat Glioblastoma and other Tumors

January 3, 2012

Apogenix Receives Additional € 2.3 Million BMBF Grant as Partner of the Biotech Cluster Rhine-Neckar

2011

September 20, 2011

Apogenix Successfully Completes Patient Recruitment for Glioblastoma Phase II Trial with APG101

January 24, 2011

Apogenix Provides Update in the Ongoing Phase II Clinical Trial of APG101 to Treat Glioblastoma

2010

May 27, 2010

Data Published in "Nature" Confirms Development of APG101 to Treat Cancer

January 11, 2010

Apogenix Initiates Clinical Phase II Study with its Lead Compound APG101 in Glioblastoma

2009

November 16, 2009

Apogenix Receives Orphan Drug Designation for APG101 in the US and Positive Opinion on Orphan Product Designation in Europe

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Prüfungsantrag gem. § 44 PatG ist gestellt

(54) Fusionsproteinen enthaltend Fc-Regionen

(57) Die Erfindung betrifft die Bereiche der Immunologie, Molekularbiologie und Onkologie.
Die Aufgabe der Erfindung ist, Immunreaktionen auf Viren, Tumore, autoreaktive Proteine und Zellen wie z. B. Autoantikörper, autoantigen-spezifische T-Zell-Rezeptoren (TZR) der autoreaktiven T-Zellen, autoantigen-spezifische B-Zell-Rezeptoren (BZR) der autoreaktiven B-Zellen und autoantigen-spezifische MHC der "unprofessionellen" antigen-präsentierenden Zellen (APZ), zu verbessern.
Die Aufgabe der Erfindung wird dadurch gelöst, dass Fc Regionen mit spezifischen Domänen fisioniert werden.

DE 101 60 248 A 1

Beschreibung

[0001] Die Erfindung betrifft die Bereiche der Immunologie, Molekularbiologie und Onkologie. Die Aufgabe der Erfindung ist Immunreaktionen auf Viren Tumoren, autoreaktive Proteinen und Zellen wie z. B. Autoantikörper, Autoantigen-spezifische T-Zell-Rezeptoren (TZR) der autoreaktiven T-Zellen, Autoantigen-spezifische B-Zell-Rezeptoren (BZR) der autoreaktiven B-Zellen und autoantigen-spezifische MHC der "unprofessionellen" Antigen-präsentierenden Zellen (APZ), zu verbessern. Die Aufgabe der Erfindung wird dadurch gelöst, dass Fc Regionen mit spezifischen Domänen fisioniert werden.

[0002] Die Kombinationen zur Herstellung rekombinanter Fusionsproteinen, sowie deren konkrete Beispiele und Anwendungen sind in den Tabellen 1, 2, 3 und 4 dargestellt.

[0003] Das Fc Fragment bzw. die Fc. Region eines Antikörpers bindet sein Rezeptor, welches meistens von Makrophagen exprimiert wird, und dadurch wird der Antigen-Antikörper-Komplex vom Makrophagen aufgenommen.

[0004] Durch Fusionen von Fc-Fragmenten mit spezifischen Bindedomänen kann man zielgerichteter pathogene Proteinen oder andere Substanzen, die von diesen spezifischen Bindedomänen erkannt und gebunden werden, entfernen, bzw. zur Phagozytose durch Makrophagen führen.

[0005] In der Tabelle 1 sind Fc Fusionen verallgemeinert dargestellt. Das sind also Fusionsproteinen enthaltend Liganden, Rezeptoren, Antigene, Autoantigene oder andere Domänen die mit Fc Regionen fusioniert sind.

[0006] Die Fusionsproteinen können His-tag oder andere Tags für die Reinigung, sowie Tyr oder Ser-tag für die Phosphorylierung durch Kinasen bzw. zur Erhöhung des energetischen Niveaus, enthalten zwischen Domänen können sich Gelenkdomänen, wie z. B. fünf Glyzine (5G) befinden.

[0007] In der Tabelle 2 sind Fc-Ligand-Fusionen bzw. Fusionsproteinen gegen Tumoren dargestellt. Fc Regionen werden entweder mit kompletten Liganden oder ihren spezifischen Binderegionen fusioniert.

[0008] Die Fc-CD 153-Fusion soll gegen die Hodgkin-Krankheit wirken. Die Hodgkin-Krankheit ist eine Erkrankung, bei der anscheinend antigenpräsentierende Zellen verändert sind, die den dendritischen Zellen ähneln. Beim Hodgkin-Lymphom herrschen Lymphocyten vor. Diese Form der Hodgkin-Krankheit hat weitaus bessere Heilungsaussichten als die noduläre Sklerose genannte form, bei der nichtlymphatische Zellen dominieren. (C. A. Janeway und P. Travers, 1995 Immunologie, Spektrum akademischer Verlag, S. 606)

[0009] Der Standort der Krankheit ist die Peripherie. Der charakteristische Oberflächenmarker ist CD 30. (C. A. Janeway und P. Travers, 1995 Immunalogie, Spektrum akademischer Verlag, S. 273).

[0010] CD 30 wird also von Monozyten bzw. Makrophagen exprimiert.

[0011] CD 153 (38–40 kDa) oder CD 30L (Ligand für CD 30) bindet CD 30 und ist ein Mitglied der TNF (tumor necrosis factor)-Familie. (I. Roitt, J. Brostoff, D. Male, 1998 Immunology, S. 398, 401).

[0012] Die Fusionsproteinen Fc-FK 506, Fc-CD 58 und Fc-CD 72 sollen gegen T-Zellen-Tumoren wirken.

[0013] T-Zell-Tumoren repräsentieren monoklonale Auswünchse normaler Zell-populationen. Jeder einzelne T-Zell-Tumor hat ein normales Äquivalent und behält viele der Eigenschaffen der Zelle bei, von der er abstammt. Einige von diesen Tumoren repräsentieren massive Answünchse eines seltenen Zelltyps wie z. B. die allgemeine akute lymphatische Leukämie, die von einer lymphalischen Vorläuferzelle abstammt.

[0014] Es gibt unterschiedliche T-Zell-Tumoren, die durch entsprechende charakteristische Oberflächenmarker gekennzeichnet sind. Bei allgemeinen akuten lymphatischen Leukämie sind die Moleküle CD 10, CD 19 und CD 20 charakteristische Oberflachenmarker.

[0015] Thymome leiten sich von Thymusstroma- oder Thymusepithelzellen ab und ihre charakterische Oberflächenmarker sind Cytokeratine. Bei der akuten lymphatischen Leukämie (T-ALL) ist CD 1 charakterisches oberflächenmarker.

[0016] Bei Sezary-Syndrom, adulten T-Zell-Leukämie und chronischer lymphocytischen Leukämie (C LL) sind CD 3/TZR, CD 4 oder CD 8 charakterische Oberflächenmarker. (C. A. Janeway und P. Travers, 1995 Immunologie, Spertrum akademischer Verlag, S. 273). T-Zell-spezifische Liganden sind z. B. CD 58, FK 506 und CD 72 bzw. ihre extrazellulären Regionen CD 58 oder LFA-3 wiegt 55–70 kd, bindet CD 2 und ist ein Adhäsionsmolekül. Seine Exodomäne bindet CD 2. CD 2 wird von T-Zellen, aber auch von Thymocyten und natürlichen Killerzellen bzw. ihren Subpopulationen exprimiert.

[0017] FK 506 ist ein immunsuppressives Polypeptid, das T-Zellen inaktiviert, in dem es die Signalübermittlung über den T-Zel-Rezeptoren (TZR) hemmt. FK 506 und Cyclosporin A sind die bei der Organtransplantation meistverwerdeten Immunsuppressiva.

[0018] CD 72 ist ein C-Typ-Lektin wiegt 42 kd, und ist Ligand bzw. seine Exodomäne ist Ligand für CD 5.

[0019] CD 5 wird von T-Zellen, Thymocyten und einer Untergruppe von B-Zellen exprimiert. (C. A. Janeway und P. Travers, 1995 Immunologie, Spektrum akademischer Verlag, S. 589–604 und I. Roitt, J. Brostoff, D. Male 1998 Immunology, S. 398–401). Die Fusionsproteinen Fc-CD5 Fc-CD 28 sollen gegen B-Zell-Tumoren wirken.

[0020] B-Zell-Tumoren stellen klonale Auswüchse, von B-Zellen verschiedener Entwicklungsstadien dar. Es gibt unterschiedliche B-Zell-Tumoren, wie z. B. multiples Myelom bzw. Leukämie der Plasmazellen verschiedener Isotypen, Waldström-Makroglobulinämie bzw. Leukämie der IgM-sezernirernden B-Zellen, Follikel Zentrum-Lymphom, Burkitt-Lymphom bzw. Leukämie reifer B-Zellen, Prä-B-Leukämie etc. (C. A. Janeway und P. Travers, 1995 Immunologie, Spektrum akademischer Verlag, S. 233). B-Zell-spezifische Liganden sind z. B. CD 5 und CD 8 bzw. ihre extrazelluläre Regionen. CD 5 wiegt 67 kd und bindet an CD 72. CD 72 wird von B-Zellen exprimiert und ist ein C-Typ-Lektin.

[0021] CD 28 wiegt 44 kd und bindet CD 80 (B7.1) und B7.2. CD 80 wird von einer Untergruppe von B-Zellen exprimiert. CD 80 bindet CD 28 und CD 152 (CTLA-4). (C. A. Janeway und P. Travers, 1995 Immunologie, Spektrum akademischer Verlag S. 589–593 und I. Roitt, J. Brostoff, D. Male 1998, Immunology, S. 398–401).

[0022] In der Tabelle 3 sind Fc-Fusionen gegen Autoimmunerkrankungen und zwar Fc-Autoantigen, Fc-autoantigenes Peptid, Fc-Rezeptor, Fc-Rezeptor-Exo bzw. Ligand-Binde-Domäne dargestellt.

[0023] Die Fc-MBP (82–104)-Fusion soll gegen Multiple Sklerose (MS) wirken.

[0024] MBP(Myelin-basisches Protein) bzw. seine immundominante Region 82–104 ist das Autoantigen bei der MS.

[0025] Ein MBP-spezifisches Antikörper bindet die MBP (82–104)-Domäne der Fc-MBP (82–104)-Fusion und wird vom Makrophagen aufgenommen.

[0026] Eine MBP-spezifische T-Zelle bzw. ihr MBP-spezifischer Z-Zell-Rezeptor(TZR) bindet die MBP(82–104)-Domäne der Fc-MBP(82–104)-Fusion und diese autoreak-

teve T-Zelle wird vom Makrophagen vernichtet. Also führt die Fc-MBP-Fusion dazu, dass Makropfagen MBP-spezifische T-Zellen vernichten.

[0027] Die Fc-GAD bzw. Fc-GSD (Glutaminsäuredecarboxylase) und Fc-GAD autoantigenes Peptid-Fusionen, soure Fc-Insulinrezeptor-Fusion sollen gegen Diabetes mellitus wirken. GAD ist das initiierende Autoantigen bei dieser Krankheit (H. von Boehmer and A. Sarukhan, 1999 Science Vol. 284, 14 May. S. 1135–1137 und J. W. Yoon et al. 1999. Science Vol. 284, 14 May, S. 1183–1187).

[0028] Ein GAD-spezifisches Antikörper bindet GAD. Domäne der Fc-GAD-Fusion und wird vom Makrophagen aufgenommen. Eine GAD-spezifische T-Zelle bzw. ihr GAD-spezifischer TZR bindet GAD-Domäne der Fc-GAD-Fusion und wird ebenfalls von Makrophagen vernichtet.

[0029] Die Fc-DNA-Bindedomäne (DBD) die mit einer bestimmter DNA-Sequenz ein Komplex bildet sowie Fc-RNA-Binde Domäne mit RNA, Fc-Histon-Fusionen, und Fc-Ribonucleoprotein-Fusionen sollen gegen die systemische Lupus erythematosus (SLE) wirken.

[0030] ds DNA ist das Autoantigen bei dieser Krankheit. Es gibt auch andere Autoantigene, wie z. B. RNA, Histone und Ribonukleoproteinen.

[0031] Das Wirkungsmechanismus ist das selbe, wie bei den oben beschriebenen Fusionen.

[0032] Die Fusionen Fc-TSHR oder Fc-TSHR-Exo- bzw. Ligandbindedomäne sollen gegen die Basedow-Krankheit wirken. TSHR ist das entsprechende Autoantigen.

[0033] Die Fusionen Fc-AchR (Acetylcholin-Rezeptor) bzw. Fc-AchR-Alpha-Untereinheit, Region 125–147 oder 131–147 sollen gegen die Krankheit Myastenia gravis wirken. AchR bzw. AchR-Alpha-Untereinheit, Region 125–147 oder 131–147 ist das Autoantigen bei dieser Krankheit.

[0034] Die Fusionen Fc-Desmoglein 1, Fc-Desmoglein 3, Fc-BP 180 und Fc-Kollagen-Typ 7 sollen gegen die Autoimmunerkrankungen der Haut, und zwar Pemphigus foliaceus, Pemphigus vulgaris, bullöses Pemphigoid und Epidermolyse bullosa aquesita wirken.

[0035] Desmoglein 1 ist das Autoantigen bei Pemphigus foliacens. Desmoglein 3 ist das Autoantigen bei Pemphigus vulgaris.

[0036] BP-180 ist das Autoantigen beibullösem Pemphigoid, und Kollagen-Typ 7 ist das Autoantigen bei der Epidermolyse bullosa aquesita.

[0037] Die Fusion bestehend aus Fc Region und der nichtkollagenösen Domäne des Basalmembran -Kollagens-Typ-4, soll gegen die Krankheit Good-Pasture-Syndrom wirken.

[0038] Nicht-kollagenöse Domäne des Basal-membran-Kollagens-Typ-4 ist das Autoantigen bei dieser Krankheit.

[0039] Die Fusion bestehend aus Fc Region und dem Oberflächenantigen des Hepatitis-B-Virus oder seiner Region soll gegen die Krankheit Polyarteriitis nodosa wirken. Das Oberflächen antigen des Hepatitis-B-Virus induziert diese Autoimmunerkrankung.

[0040] Die Fusion bestehend aus Fc Region und dem Hitzeschockprotein (HSP) soll gegen die rheumatische Arthritis wirken. HSP ist vermutlich das Autoantigen bei dieser Krankheit. Die Fusion bestehend aus Fc Region und dem Integrin gp IIb–IIIa aus Blutplättchen soll gegen die autoimmunen Thrombopenie wirken.

[0041] Dieses Protein aus Bluttplättchen ist das Autoantigen bei dieser Krankheit.

[0042] Die Fusion bestehend aus Fc Region und Rhesus-Antigene und Fc-I-Antigen-Fusion sollen gegen die hämolytische Anämie wirken.

[0043] Rhesus-Antigene und das I-Antigen sind Autoantigene bei dieser Krankheit.

[0044] Der Wirkungsmechanismus der Fc Fusionen ist identisch. Fc-Autoantigen, bzw. Fc-autoantigenes Peptid-Fusionen wirken nicht mehr gegen Autoantikörper und autoreaktive T-Zellen, sondern auch gegen autoreaktive B-Zellen und unprofessionelle autoreaktive Antigen -Präsentierende Zellen (APZ), wie z. B. Makrophagen.

[0045] Ein Autoantikörper bindet die autoantigene Domäne einer Fc-Autoantigen-Fusion. Fc-Region wird von einem Fc-Rezeptor eines Makrophagen erkannt und danach nimmt Makrophage den Komplex bestehend aus dieser Fc-Autoantigen-Fusion und dem für dieses Autoantigen spezifischen Auto-Antikörper auf. So wird die Zahl der Autoantikörper vermindert und dies führt zur Linderung.

[0046] Eine autoreaktive T-Zelle besitzt ein Autoantigen-spezifisches T-Zell-rezeptor (TZR). Dieses autoreaktives TZR bindet die autoantigene Domäne einer Fc-Autoantigen-Fusion. Die Fc-Region wird von einem Makrophagen erkannt und somit wird ein Kampf eines Makrophagen und einer autoreaktiven T-Zelle hervorgerufen. Der Makrophage kann diese T -Zelle vernichten und aufnehmen.

[0047] Dieses Mechanismus kann zur Ausrottung autoreaktiven T-Zellen führen. Im Falle der Multiplen Sklerose, bedeutet die Ausrottung der MBP-spezifischen T-Zellen eine Heilung dieser Krankheit.

[0048] Eine autoreaktive B-Zelle besitzt ein Autoantigen-spezifisches B-Zell-Rezeptor (BZR). Dieses autoreaktives BZR bindet die autoantigene Domäne einer Fc-Autoantigen-Fusion. Die Fc Region wird von einem Makrophagen erkannt und somit wird ein Kampf eines Makrophagen und einer autoreaktiven B-Zelle hevor gerufen. Der Makrophage kann diese B -Zelle vernichten und aufnehmen. Dies kann zur Ausrottung autoreaktiver B-Zellen führen. Eine unprofessionelle autoreaktive APZ besitzt ein Autoantigen-spezifisches MHC. Dieses autoreaktives MHC bindet die autoantigene Domäne einer Fc-Autoantigen-Fusion. Die Fc-Region wird von einem Makrophagen erkannt und somit wird ein Kampf eines Makrophagen und einer unprofessionellen autoreaktiven APZ hervorgerufen.

[0049] Also können Fc-Autoantigen Fusionen zur völligen Bekämpfung und Ausrottung der Autoimmunerkrankungen führen.

[0050] In der Tabelle 4 sind antivirale Fc Fusionen dargestellt. Viren haben Rezeptoren bzw. Oberflächen Wirtszell-Schlüssel moleküle, über die ein Virus in diese Zelle gelangen kann. Für Epstein-Barr-Virus (EBV) ist CR 2(CD 21) das Rezeptor. Für Poliovirus ist CD/55 das Rezeptor. Für HIV ist CD 4 das Rezeptor. Influenza-Viren werden von bestimmten T- und B-Zell rezeptoren sowie bestimmten MHC erkannt.

[0051] Also können die Fusionsproteinen Fc-CR 2 bzw. Fc-CD 21, Fc-CD 155, Fc-CD 4, Fc-TZR. FC-BZR und Fc-MHC entsprechend gegen EBV, Polioviren, HIV und Influenza wirken. Betrachtet man als Beispiel die Wirkung des Fusionsproteins Fc-CR 2 bzw. Fc-CD21. Die CR 2 bzw. CD 21-Domäne der Fc-CR 2 bzw. Fc-CD 21-Fusion erkannt die Oberfläche des EBV. Fc Region wird vom Fc Rezeptor eines Makrophagen erkannt und dieser Makrophage nimmt den Komplex bestehend aus der Fc-CR 2 bzw. Fc-CD 21-Fusion und dem EBV auf, wonach die Vernichtung des EBV bzw. die Virolyse (ein Fachausdruck des Erfinders) stattfindet.

Tabelle 1

1. Fc-L (ein Ligand)
2. Fc-R (ein Rezeptor)
3. Fc-A (ein Antigen)
4. Fc-Auto A (ein Autoantigen oder eine autoantigene Region)

5. Fc D (eine beliebige Domäne)

1. a Fc-L(Ligand)
b 1 Fc-L-His tag
b 2 His tag-Fc-L
c 1 Fc-5G-L-His tag
c 2 His tag-Fc-5G-L
d 1 Fc-5G-L5G His tag
d 2 His-tag-5G-Fc-5G-L

2. a Fc-R (Rezeptor oder Rezeptor-Exodomäne)
b 1 Fc-R-His tag
b 2 His tag-Fc-R
c 1 Fc-5G-R-His tag
c 2 His tag-Fc-5G-R
d 1 Fc-5G-R-5G-His tag
d 2 His tag-5G-Fc-5G-R

3. a Fc-A
b 1 Fc-A-His tag
b 2 His tag-Fc-A
c 1 Fc-5G-A-His tag
c 2 His tag-Fc-5G-A
d 1 Fc-5G-A-5G-His tag
d 2 His tag-5G-Fc-5G-A

4. a Fc-Auto A
b 1 Fc-Auto A-His tag
b 2 His tag-Fc-Auto A
c 1 Fc-5G-Auto A-His tag
c 2 His tag-Fc-5G-AutoA
d 1 Fc-5G-Auto A-5G-His tag
d 2 His tag-5G-Fc-5G-Auto A

5. a Fc-D
b 1 Fc-D-His tag
b 2 His tag-Fc-D
c 1 Fc-5G-D-His tag
c 2 His tag-fc-5G-D
d 1 Fc-5G-D-5G-His tag
d 2 His tag-5G-Fc-5G-D

Tabelle 2

Anti-tumor: Fc-L (Ligand)
Anti Hodgkin-Krankheit: Fc-CD 153
Anti-T-Zell-Tumoren: Fc-FK 506
Fc-CD 58
Fc-CD 72
Anti-B-Zell-Tumoren:
Fc-CD 5
Fc-CD 28
Fc-CTLA-4

Tabelle 3

Antiautoimmun: Fc-Autoantigen
Fc-autoantigenes Peptid bzw. immunodominante Region des Autoantigens
Fc-Rezeptor
Fc-Rezeptor-Region z. B. Exo- bzw. Ligand-Bindedomäne

Anti-Multiple-Sklerose:
Fc-MBP (82–104)(Myelin-Basisches Protein, Region 82–104)
Fc-MBP

Anti-Diabetes mellitus: Fc-GAD oder
Fe-GSD (Glutaminsäure-Decaorboxylase)
Fc-GAD-autoantigenes Peptid
Fc-Insulinrezeptor

Anti-Lupus: (Anti-SLE (Systemisches Lupus erythematosus))
Fc-DBD + DNA Komplex
Fc-RBD + RNA Komplex
Fc-ein Histon
Fc-RNP, ein Ribonukleoproteinen

Anti-Basedow-Krankheit:
Fc-TSHR
Fc-TSHR-Exodomäne

Anti-myastenia gravis:
Fc-AchR
Fc-AchR-Alpha – unter einheit – Region 125–147 oder 131–147

Anti-Pemphigus foliaceus:
Fc-Desmoglein 1

Anti-Pemphigus vulgaris:
Fc-Desmoglein 3
Anti-bullöses Pemphigoid:
Fc-BP 180

Anti-Epidermolyse bullosa aquesita:
Fc-Kollagen-Typ-7

Anti-Goodpasture-Syndrom:
Fc-nichtkollagenöse Domäne des Basalmembran-kollagens-Typ-4

Anti-Polyarteriitis nodosa:
Fc-Oberflächenantigen des Hepatitis-B-Virus oder seine Region

Anti-rheumatische Arthitis:
Fc-Hsp (Hitze-schockproteinen)

Anti-autoimmune Thrombopenie:
Fc-Integrin gp II b : II a aus Blutplättchen

Anti-hämolytische Anämie:
Fc-Rhesus-Antigene
Fc-I-Antigen

Tabelle 4

Antiviral
Anti-Epstein-Barr-Virus (EBV):
Fc-CR 2(Fc-CD21)

Anti Polio virus: Fc-CD 155

Anti-HIV: Fc-CD 4

Anti Influenza: Fc-TZR
Fc-BZR
Fc-MHC

Patentansprüche

1. Fusionen, enthaltend mindestens eine Fc-Region und mindestens eine andere Domäne wie z. B. ein Autoantigen oder seine Region bzw. ein autoantigenes

Peptid z. B. MBP (82–104)-Peptid, ein Rezeptor wie z. B. T-Zell-Rezeptor oder seine Region, B-Zell-Rezeptor oder seine Region, MHC oder seine Region Bindedomäne, Rezeptor-Exodomäne bzw. Ligand-Binde-Domäne, ein Ligand wie z. B. CD 153, CD 72, CD 58, CD 5, CR 2(CD 21), CD 4, CD 155, CR 1(CD 35), CD 28, CTLA 4, FK 506 etc., ein Allergen, eine DNA- oder RNA Bindedomäne etc.

2. Alle in den Tabellen 1, 2, 3 und 4 dargestellten Kombinationen.

3. Fusionsproteinen nach dem Ansprüchen 1 und 2, die Histag oder ein anderes Tag zur Reinigung, Ser/Tyr-tag zur Phosphorylierung, eine Gelenkdomäne wie z. B. 5G (fünf Glyzine) oder mindenstens eine andere Domäne enthalten.

4. Nukleinsäure sequenzen, Vektoren, Klonierung- und Expressionsystemen für Fusionsproteinen nach den Ansprüchen 1–3.

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Prüfungsantrag gem. § 44 PatG ist gestellt

(54) Fusionsproteinen gegen B-Zell-Tumoren

(57) Die Erfindung betrifft die Bereiche der Immunologie, Molekularbiologie und Onkologie.
Die Aufgabe der Erfindung ist B-Zell-Tumore effektiv und selektiv zu heilen.
Die Aufgabe der Erfindung wird dadurch gelöst, dass Fusionen, enthaltend B-Zell-spezifische Liganden und zytotoxische oder immunoreaktionsfördernde Domänen von B-Zellen bzw. malignanten B-Zellen aufgenommen werden, und danach entweder sterben oder werden von Makrophagen vernichtet oder werden von zytotoxischen T-Zellen vernichtet oder sie können sich nicht mehr teilen oder sie werden auf eine andere Weise spezifisch bzw. zielgerichtet und selektiv geschädigt.

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Fusionsproteinen gegen B-Zell-Zumoren

Tabelle 1

MBD-CD 5
MBD-CD-MPD
HLA-B 7-CD 5 bzw.
CD 81-CD 5
CD 86-CD 5
DD-CD 5
DD-CD 5-MPD
DED-CD 5
DED-CD 5-MPD
Zytochrom c-CD 5
Zytochrom c-CD 5-MRD
GTPase/GTP Hydrolase-CD 5
GTPase/GTP Hydrolase-CD 5-MPD
Endotoxin-CD 5
Endotoxin-CD 5-MPD
Protease-CD 5
Protease-CD 5-MPD
Fc-CD5
Nuklease-CD 5
MBD-CD 28
MBD-CD 28-MPD
HLA-B 7-CD 28 bzw.
CD 81-CD 28
CD 86-CD 28
DD-CD28
DD-CD28-MPD
DED-CD 28
DED-CD 28-MPD
Zytochrom c-CD 28
Zytochrom c-CD 28-MPD
GTPase/GTP Hydrolase-CD 28
GTPase/GTP Hydrolase-CD 28-MPD
Endotoxin-CD 28
Entotoxin-CD 28-MPD
Portease-CD 28
Protease-CD 28-MPD
Fc-CD28
Nuklease-CD 28
MBD-CTLA-4
MBD-CTLA-4
HLA-B 7-CTLA 4 bzw.
CD 81-CTLA-4
CD 86-CTLA-4
DD-CTLA-4
DD-CTLA-4-MPD
DED-CTLA-4
DED-CTLA-4-MPD
Zytochrome c-CTLA-4
Zytochrome c-CTLA-4-MPD
GTPase/GTP-Hydrolase-CTLA-4
GTPase/GTP Hydrolase-CTLA-4-MPD
Endotoxin-CTLA-4
Endotoxin-CTLA-4-MPD
Protease-CTLA-4
Protease-CTLA-4-MPD
Fc-CTLA-4
Nuklease-CTLA-4

Tabelle 2

A D-L (Domäne, wie z. B. MBD und Ligand, wie z. B. CD 5)
B1 D-L-His-tag
B2 His-tag-D-L
C1 D-5G-L-His-tag
C2 His-tag-D-5G-L
D1 D-5G-L-5G-His-tag
D2 His-tag-5G-D-5G-L
E1 His-tag-D-L-MPD
E2 His-tag-5G-D-L-MPD
E3 His-tag-D-5G-L-MPD
E4 His-tag-5G-D-5G-L-MPD
Es His-tag-D-L-5G-MPD
E6 His-tag-5G-D-L-5G-MPD
E7 His-tag-D-5G-L-5G-MPD
E8 His-tag-5G-D-5G-L-5G-MPD
F1 Tyr/Ser-tag-D-L-His-tag
F2 Tyr/Ser-tag-5G-D-L-His-tag
F3 Tyr/Ser-tag-5G-D-5G-L-His-tag
F4 Tyr/Ser-tag-5G-D-L-5G-His-tag
F5 Tyr/Ser-tag-5G-D-L-5G-His-tag
F5 Tyr/Ser-tag-5G-D-5G-L-5G-His-tag
G1 Tyr/Ser-tag-D-L-MPD-His-tag
G2 Tyr/Ser-tag-D-L-His-tag-MPD

Patentansprüche

1. Fusionsproteienen **dadurch gekennzeichnet**, dass sie mindestens ein B-Zell-spezifisches Ligand wie z. B. Cd 5, CD 28, CTLA-4 etc. oder seine Region, ein anderes Ligand oder eine andere Domäne und mindestens eine zellschädigende Domäne, wie z. B. Mikrotubuli-Bindedomäne (MBD), HLA-B7 bzw. CD 81, CD 86; Endotoxin, GTPase bzw. GTP-Hydrolase, Protease, Nuklease oder ein anderes Enzym, Zytochrom c, DD, DED, Fc Region oder eine andere Domäne, enthalten.

2. Fusionsproteinen nach dem Anspruch 1, dadurch gekennzeichnet, dass sie mindestens einen die His-tag oder ein anderes Tag zur Reinigung, Ser/Tyr -tag zur Phosphorylierung, eine Gelenkdomäne wie z. B. 5G (fünf Glyzine) oder mindestens eine andere Domäne enthalten.

3. Nukleinsäuresequenzen, Vektoren, Klonierungs- und Expressions-Systeme für alle Fusionsproteinen nach den Ansprüchen 1 und 2, und in den Tabelle 1 und 2.

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Prüfungsantrag gem. § 44 PatG ist gestellt

(54) Fusionsproteinen gegen T-Zell-Tumoren

(57) Die Erfindung betrifft die Bereiche der Immunologie, Molekularbiologie und Onkologie.
Die Aufgabe der Erfindung ist, T-Zell-Tumoren effektiv und selektiv zu heilen.
Die Aufgabe der Erfindung wird dadurch gelöst, dass Fusionen, enthaltend T-Zell-spezifische Liganden und zytotoxische oder immunoreaktionsfördernde Domänen von T-Zellen bzw. malignanten T-Zellen, aufgenommen werden und danach entweder sterben oder von Makrophagen vernichtet werden oder sich nicht mehr teilen können oder sie werden auf eine andere Weise spezifisch bzw. zielgerichtet und selektiv geschädigt.

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teine bzw. CD 2, oder TZR die CD 58, CD 72 oder FK 506-Domäne der CD 58-MBD, CD 72-MBD oder FK 506-MBD erkannt und an das gebunden hat.

[0033] Nach der Aufnahme bzw. Internalisierung der CD 58-MBD-Fusion bindet die MBD Mikrotubuli bzw. Zytoskelett.

[0034] Nach der Internalisierung mehrerer CD 58-MBD-Fusionsproteinen wird sich eine malignante T-Zelle nicht mehr teilen können. Sobald eine Tumor-Zelle sich nicht mehr teilen kann, stirbt sie.

[0035] Man soll diese Therapie mit Blut-Filtrationen bzw. Aufreinigungen kombinieren um getötete malignante Zellen aus dem Blut-Kreislauf zu entfernen und somit eine Blut Verschmutzung und Vergiftung von Patienten zu verhindern.

[0036] In den Tabellen 1 und 2 sind einige Kombinationen bzw. Fusionsproteinen gegen T-Zell-Tumoren dargestellt.

[0037] Die Fusionsproteinen können His-tag oder andere Tags für die Reinigung, sowie Tyr oder Ser-tag für die Phosphorylierung durch Kinasen bzw. zur Erhöhung des energetischen Niveaus, enthalten zwischen Domänen können sich Gelenkdomänen, wie z. B. fünf Glyzine (5G) befinden.

[0038] Die Fusionsproteinen werden rekombinant hergestellt.

Fusionsproteinen gegen T-Zell-Tumoren

Tabelle 1

MBD-FK 506
MBD-FK 506-MPD
HLA-B 7-FK 506 bzw.
CD 81-FK 506
CD 86-FK 506
DD-FK 506
DD-FK 506-MPD
DED-FK 506
DED-FK 506-MPD
Zytochrom c-FK 506
Zytochrom c-FK 506-MPD
GTPase/GTP Hydrolase-FK 506
GTPase/GTP Hydrolase-FK-506-MPD
Endotoxin-FK 506
Endotoxin-FK 506-MPD
Protease-FK 506
Protease-FK 506-MPD
Fc-FK 506
Nuklease-FK 506
MBD-CD 5 8
MBD-CD 58-MPD
HLA-B 7-CD 58 bzw.
CD 81-CD 58
CD 86-CD 58
DD-CD 58
DD-CD 58-MPD
DED-CD 58
DED-CD 58-MPD
Zytochrom c-CD 58
Zytochrom c-CD 58-MPD
GTPase/GTP Hydroktse-CD 58
GTPase/GTP Hydrolose-CD 58-MPD
Endotoxin-CD 58
Endotoxin-CD 58-MPD
Protease-CD 58
Protease-CD 58-MPD
Fc-CD 58
Nuklease-CD 58
MBD-CD 72
MBD-CD 72-MPD
HLA-B 7-CD 72 bzw.
CD 81-CD 72
CD-CD 86-CD 72
DD-CD 72
DD-CD 72-MPD
DED-CD 72
DED-CD 72-MPD
Zytochrom c-CD 72
Zytochrom c-CD 72-MPD
GTPase/GTP Hydrolase-CD 72
GTPase/GTP Hydrolase-CD 72-MPD
Endotoxin-CD 72
Endotoxin-CD 72-MPD
Protease-CD 72
Protease-CD 72-MPD
Fc-CD 72
Nuklease-CD 72

Tabelle 2

A D-L (Domäne, wie z. B. MBD und Ligand, wie z. B. CD 5)
B 1 D-L-His-tag
B 2 His-tag-D-L
C 1 D-5G-L-His-tag
C 2 His-tag-D-5G-L
D 1 D-5G-L-5G-His-tag
D 2 His-tag-5G-D-5G-L
E 1 His-tag-D-L-MPD
E 2 His-tag-5G-D-L-MPD
E 3 His-tag-D-5G-L-MPD
E 4 His-tag-5G-D-5G-L-MPD
E 5 His-tag-D-L-5G-MPD
E 6 His-tag-5G-D-L-5G-MPD
E 7 His-tag-D-5G-L-5G-MPD
E 8 His-tag-5G-D-5G-L-5G-MPD
F 1 Tyr/Ser-tag-D-L-His-tag
F 2 Tyr/Ser-tag-5G-D-L-His-tag
F 3 Tyr/Ser-tag-5G-D-5G-L-His-tag
F 4 Tyr/Ser-tag-5G-D-L-5G-His-tag
F 5 Tyr/Ser-tag-5G-D-5G-L-5G-His-tag
G 1 Tyr/Ser-tag-D-L-MPD-His-tag
G 2 Tyr/Ser-tag-D-L-His-tag-MPD

Patentansprüche

1. Fusionsproteinen, **dadurch gekennzeichnet**, dass sie mindestens ein T-Zell-spezifisches Ligand wie z. B. CD 58, CD 72, FK 506, CD 29 Kollagen Laminin etc. oder seine Region und mindestens eine Zell-schädigende Domäne, wie z. B. Mikrotubuli-Bindedomäne (MBD), HLA-B7 bzw. CD 81, CD 86; Endotoxin, GTP ase bzw. GTP-Hydrolase, Protease, Nuklease, oder ein anderes Enzym, Zytochrom c, DD, DED, Fc Region eines Antikörpers oder eine andere Domäne, enthalten.

2. Fusionsproteinen nach dem Anspruch 1, dadurch gekennzeichnet, dass sie His-tag oder ein anderes Tag zur Reinigung, Ser/Tyr-tag zur Phosphorylierung, eine Gelenkdomäne wie z. B. 5G (fünf Glyzine) oder mindestens eine andere Domäne enthalten.

3. Nukleinsäuresequenzen, Vektoren, Klonierungs- und Expressionssysteme für alle Fusionsproteinen nach den Ansprüchen 1 und 2, und in den Tabellen 1 und 2.

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Prüfungsantrag gem. § 44 PatG ist gestellt

(54) Fusionsproteinen gegen die Hodgkin-Krankheit

(57) Die Erfindung betrifft die Bereiche der Immunologie, Molekularbiologie und Onkologie.
Die Aufgabe der Erfindung ist die Hodgkin-Krankheit effektiv und selektiv zu heilen.
Die Aufgabe der Erfindung wird dadurch gelöst, dass Fusionen, enthaltend APZ-spezifisches Ligand oder seine Region und zytotoxische oder immunreaktionfördernde Domänen, nur von Hodgkin-Zellen aufgenommen werden und danach entweder sterben oder von zytotoxischen T-Zellen vernichtet oder können sich nicht mehr heilen, oder sie werden auf eine andere Weise spezifisch bzw. zielgerichtet und selektiv geschädigt.

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tischen Niveaus, enthalten.

[0032] Zwischen Domänen können sich Gelenkdomänen wie z. B. fünf Glyzine (5G) befinden.

[0033] Die Fusionsproteinen werden rekombinant hergestellt.

Fusionsproteinen gegen die Hodgkin-Krankheit

Tabelle 1

MBD-CD153
MBD-CD153-MPD
HLA-B7-CD153 bzw.
CD-81-CD153
CD-86-CD153
DD-CD153
DD-CD153-MPD
DED-CD15 DED-CD153 MPD
Zytochrom c-CD153
Zytochrom c CD153-MPD
GTPASE/GTP-Hydgrolase-CD153
GTPASE/GTP-Hydrolase-CD153-MPD
Endotoxin-CD153
Endotoxin-CD153-MPD
Protease-CD153
Protease-CD153-MPD
Fc-CD153
Nuklease-CD153

Tabelle 2

A D(Domäne)-CD153
B1 D-CD153-His-tag
B2 His-tag-D-CD153
C1 D-5G-CD153-His-tag
C2 His-tag-D-5G-CD153
D1 D-5G-CD153-5G-His-tag
D2 His-tag-5G-D-5G-CD153
E1 His-tag-D-CD153-MPD
E2 His-tag-5G-D-CD153-MPD
E3 His-tag-D-5G-CD153-MPD
E4 His-tag-5G-D-5G-CD153-MPD
E5 His-tag-D-CD153-5G-MPD
E6 His-tag-5G-D-CD153-5G-MPD
E7 His-tag-D-5G-CD153-5G-MPD
E8 His-tag-5G-D-5G-CD153-5G-MPD
F1 Tyr/Ser-tag-D-CD153-His-tag
F2 Tyr/Ser-tag-5G-D-CD153-His-tag
F3 Tyr/Ser-tag-5G-D-5G-CD153-His-tag
F4 Tyr/Ser-tag-5G-D-CD153-5G-His-tag
F5 Tyr/Ser-tag-5G-D-5G-CD153-5G-His-tag
G1 Tyr/Ser tag-D-CD153-MPD-His-tag
G2 Tyr/Ser tag-D-CD153-His-tag-MPD

Patentansprüche

1. Fusionsproteinen, **dadurch gekennzeichnet**, dass sie mindestens ein APZ-spezifisches Ligand wie z. B. CD153, TNF etc. oder seine Region und mindestens eine Zell-schädigende Domäne, wie z. B. Mikrotubuli-Bindedomäne (MBD), HLA-B7 bzw. CD81, CD86; Endotoxin, GTPase bzw. GTP-Hydrolase, Protease, Nuklease oder ein anderes Enzym, Zytochrom C, DD, DED, Fc Region eines Antikörpers oder eine andere Domäne, enthalten.

2. Fusionsproteinen nach dem Anspruch 1, dadurch gekennzeichnet, dass sie His-tag oder einen anderen Tag zur Reinigung, Ser/Tyr-tag zur Phosphorylierung, eine Gelenkdomäne wie z. B. 5G (fünf Glyzine) oder mindestens eine andere Domäne enthalten.

3. Nukleinsäuresequenzen, Vektoren, Klonierung- und Expressionsysteme für alle Fusionsproteinen nach den Ansprüchen 1 und 2, und in der Tabellen 1 und 2.

4. GTPase bzw. GTP Hydrolase mit ihrer antitumoraler Aktivität, bzw. dadurch gekennzeichnet, dass dieses Enzym eine antitumorale Aktivität besitzt.

5. Nukleinsäuresequenzen, Vektoren, Klonierungs und Expressionssysteme für GTP Hydrolase(n) nach dem Anspruch 4.

6. Serin- oder Tyrosin-tags oder tags für die Phosphorylierung.

7. Nukleinsäuresequenzen, Vektoren, Klonierungs- und Expressions-Systemen für Peptide nach dem Anspruch 6.