

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
4 June 2009 (04.06.2009)

PCT

(10) International Publication Number
WO 2009/068628 A1

(51) International Patent Classification:
C07K 16/32 (2006.01)

(74) Agents: **HOFFMANN . EITL** et al.; Arabellastrasse 4,
81925 München (DE).

(21) International Application Number:
PCT/EP2008/066366

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(22) International Filing Date:
27 November 2008 (27.11.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/004,332 27 November 2007 (27.11.2007) US
61/005,265 4 December 2007 (04.12.2007) US
61/005,324 4 December 2007 (04.12.2007) US
61/005,331 4 December 2007 (04.12.2007) US

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): **ABL-YNX N.V.** [BE/BE]; Technologiepark 4, B-9052 Ghent-zwijnaarde (BE).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **HERMANS, Guy** [BE/BE]; Hundelgemsesteenweg 848, B-9052 Merelbeke (BE). **REVETS, Hilde** [BE/BE]; Kapellelaan 299, B-1860 Meise (BE).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(54) Title: CONSTRUCTS COMPRISING SINGLE VARIABLE DOMAINS AND AN FC PORTION DERIVED FROM LGE.

(57) Abstract: The present invention relates to protein and polypeptide constructs that comprise immunoglobulin single variable domains that are linked to an Fc portion that is derived from IgE. The invention also relates to polypeptide chains that form part of such constructs and/or that can be used to form such constructs. The invention further relates to nucleotide sequences and nucleic acids that encode or can be used to express such constructs or polypeptide chains; to methods for producing such constructs and polypeptides chains; to compositions (and in particular pharmaceutical compositions) that comprise such constructs or polypeptide chains; and to uses of such constructs, polypeptide chains or compositions.



WO 2009/068628 A1

Constructs comprising single variable domains and an Fc portion derived from IgE.

The present invention relates to protein and polypeptide constructs that comprise single variable domains that are linked to an Fc portion.

In particular, the invention relates to such constructs that comprise immunoglobulin single variable domains that are linked to an Fc portion that is derived from IgE (as further described herein). The immunoglobulin single variable domains may for example be a domain antibody (or an immunoglobulin variable domain that is suitable for use as a domain antibody), a single domain antibody (or an immunoglobulin variable domain that is suitable for use as a single domain antibody), a "dAb" (or an immunoglobulin variable domain that is suitable for use as a dAb) or a Nanobody (as defined herein, and including but not limited to a V_{HH} sequence); or any suitable fragment of any one thereof.

The invention also relates to polypeptide chains that form part of such constructs and/or that can be used to form such constructs.

The invention further relates to nucleotide sequences and nucleic acids that encode or can be used to express such constructs or polypeptide chains; to methods for producing such constructs and polypeptides chains; to compositions (and in particular pharmaceutical compositions) that comprise such constructs or polypeptide chains; and to uses of such constructs, polypeptide chains or compositions.

Other aspects, embodiments, uses, applications and advantages of the invention will become clear from the further disclosure herein.

It is also known that single variable domains can be linked to Fc portions. For example, as described in EP 0 698 097 and in Hamers-Casterman et al. (Nature 1993, June 3; 363 (6428): 446-8), the naturally occurring "heavy chain antibodies" from Camelidae comprise naturally occurring single variable domains (called " V_{HH} domains") that are linked via a hinge region to an Fc portion. Interestingly, as further described in these references, these heavy chain antibodies lack the C_{H1} domain that is present in conventional 4-chain antibodies, with the V_{HH} being directly linked – via the hinge – to the C_{H2} domain of the Fc portion.

EP 0 698 097 and its divisional application EP 1 621 554 also describe that V_{HH} domains can be linked to a human Fc portion. Reference is for example also made to WO 04/041862 which describes a fusion of a Nanobody against human TNF to the C_{H1} deleted Fc portion of human IgG1.

WO 04/068820 describes so-called "dAb's" that are linked to an effector group. The examples given are constructs that comprise dAb's linked to the Fc of IgG1.

WO 02/056910 also describes constructs in which binding domains that include at least one immunoglobulin variable region polypeptide are linked, via a suitable linker, to C_H2/C_H3 constant regions. In particular, the C_H2 and C_H3 regions of human IgG or human IgA are mentioned. The immunoglobulin variable region polypeptide may be all or a portion or fragment of heavy chain or light chain V-region, provided it is capable of specifically binding an antigen. It should however be noted that in the examples of WO 02/056910, the immunoglobulin variable region polypeptide is comprised of an ScFv fragment (in which the antigen binding site is formed jointly by the V_H and V_L domains that form the ScFv fragment).

The constructs described in these references all comprise two polypeptide chains, in which each polypeptide chain comprises one single variable domain that is linked, usually via a suitable hinge region or linker, to two constant domains that, in the final construct, form the Fc portion. These constructs bind to the intended antigen via the two antigen-binding sites that are present on each of the single variable domains.

It is commonly known that there are five general classes of immunoglobulin isotypes, namely IgG, IgA, IgM, IgE and IgD. All consist of heavy chains and light chains comprising variable domains and constant domains. However, whereas the heavy chains of immunoglobulins of the IgG, IgA and IgD isotypes contain 3 constant domains (referred to as C_H1, C_H2 and C_H3 in the case of IgG; as C_α1, C_α2 and C_α3 in the case of IgA; and as C_δ1, C_δ2 and C_δ3 in the case of IgD), the heavy chains of the IgM and IgE isotypes comprise 4 constant domains (referred to as C_μ1, C_μ2, C_μ3 and C_μ4 in the case of IgM and as C_ε1, C_ε2, C_ε3 and C_ε4 in the case of IgE).

Also, whereas IgM, IgG1, IgG3 and, to a lesser extent, IgG2 are capable of activating complement, IgG4, IgD and IgE are not. Instead, it is known that IgE binds to the Fc_ε receptors on mast cells and basophils (which are the main effectors of IgE-mediated immune reactions), as well as to Fc_ε receptors on other Fc_ε receptor-bearing cells, such as B-cells, T-cells, dendritic cells, monocytes, alveolar macrophages, eosinophils and platelets. It is also known that there are at least two IgE receptors, i.e. the high-affinity IgE receptor FcεRI (to which IgE binds with an affinity that is two to five orders greater than the affinity of IgG for its high-affinity receptor, FcγRI) and the low affinity receptor FcεRII (also known as CD23). It has been suggested that, of the IgE-mediated immune responses, binding of IgE to FcεRI

(as expressed on mast cells, basophils and eosinophils) triggers cytotoxic cell killing (ADCC) and that binding of IgE to CD23 is responsible for triggering phagocytosis (ADCP), and also facilitates antigen presentation and stimulates T helper cells and so a Th2 response.

In the art, there are various ways of that the constant regions of immunoglobulins are referred to. The term “Fc portion” is generally used to refer to a constant region dimer that lacks the C_H1 domain (in case of an IgG. This term will be used more generally herein to refer to the constant region dimer of an IgG that lacks C_H1, of an IgA that lacks C_α1, of an IgD that lacks C_δ1, of an IgM that lacks C_μ1, and of an IgE that lacks C_ε1. Thus, with respect to IgE, the Fc portion comprises C_ε2, C_ε3 and C_ε4). As the Fc portion of an immunoglobulin is also responsible for the effector functions (depending on the isotype and subtype of the immunoglobulin), the Fc portion (or at least the parts or domains thereof that are capable of providing the relevant effector functions) are also sometimes referred to as “effector groups”. Accordingly, depending on the context, the terms “Fc portion” and “effector group” will be used interchangeably herein.

Karagiannis et al. (Journal of Immunology, 2007, 2832-2843) describe a conventional 4-chain chimeric mouse-human IgE monoclonal antibody against the ovarian cancer antigen MOv18 and compare it to the corresponding chimeric IgG1 monoclonal antibody. They conclude that the efficacy of immunotherapy of solid tumors, in particular of ovarian carcinoma, may be improved by the use of IgE monoclonals instead of conventional IgG.

Riemer et al. (Cancer Res., 67:(7), April 2007) describe a vaccine and protocol for inducing tumor-specific IgE in vivo.

The present invention provides constructs that comprise two polypeptide chains, in which each polypeptide chain comprises at least one single variable domain that is linked, optionally via a suitable linker or hinge region, to one or more constant domains, wherein the constant domains from the first polypeptide chain and the second polypeptide chains together form (or are capable of forming) an Fc portion that is capable of effecting one or more IgE-mediated immune responses (as defined herein) and/or that is capable of binding to either the FcεRI receptor and/or the FcεRII receptor (as further described herein). Such an Fc portion will also be referred to herein as an “*IgE-derived Fc portion*”.

Thus, generally, the constructs provided by the invention (which are also generally referred to herein as “*constructs of the invention*”) comprise an IgE-derived Fc portion (as defined herein) that is linked (optionally via a suitable linker or hinge region) to two single variable domains (also as defined herein, with each polypeptide chain that forms the IgE-

derived Fc portion being linked to at least one single variable domain). Such constructs may for example be as described in EP 1 621 554, WO 02/056910 or WO 02/056910, but comprising an IgE-derived Fc portion (as defined herein) instead of an IgG- or IgA-derived Fc portion, as described in these references.

The invention also relates to a protein or polypeptide that comprises or essentially consists of a construct of the invention.

The invention further relates to a polypeptide chain that forms part of a construct of the invention and/or that is capable of forming (or can be used to form) a construct of the invention (i.e. together with another such polypeptide chain). Such polypeptide chains (which are also generally referred to herein as "*polypeptide chains of the invention*", and which may be as further described herein), and their use in forming the constructs of the invention, form further aspects of the invention. Also, in one specific aspect of the invention, as further described herein, these polypeptide chains of the invention may also be used as such (i.e. without interaction with another polypeptide chain and/or not as part of a construct of the invention).

The invention further relates to nucleotide sequences or nucleic acids that encode and/or that can be used to express a construct of the invention and/or a polypeptide chain of the invention. Such nucleotide sequences or nucleic acids (which are also generally referred to herein as "*nucleic acids of the invention*") may be as further described herein.

The invention further relates to methods for producing the constructs and polypeptides of the invention; to compositions (and in particular pharmaceutical compositions) that comprise one or more constructs or polypeptide chains of the invention; and to uses of the constructs or polypeptide chains of the invention or of compositions comprising them. Such methods, compositions and uses may be as further described herein.

Other aspects, embodiments, uses, applications and advantages of the invention will become clear from the further disclosure herein.

Figure 1 schematically shows a preferred, but non-limiting example of a construct of the invention, which construct comprises two polypeptide chains of the invention (1) and (2), which each comprise a single variable domain (3) that is linked via an optional hinge or linker (4) to three constant domains (5), (6) and (7), which together with the constant domains from the other polypeptide chain of the invention form the IgE derived Fc portion (8). As further described herein, in the constructs of the invention in their simplest form, the three constant domains (5), (6) and (7) are preferably the constant domains C_ε2, C_ε3 and C_ε4 of human IgE, respectively, so that the IgE derived Fc portion (8) is the Fc portion of human IgE.

Figure 2 schematically shows a specific, but non-limiting example of a construct of the invention, which construct comprises two polypeptide chains of the invention (1) and (2), which each comprise two single variable domains (3) and (9) that are linked to each other via an optional linker (10) and that are linked via an optional hinge or linker (4) to three constant domains (5), (6) and (7), which together with the constant domains from the other polypeptide chain of the invention form the IgE derived Fc portion (8). As further described herein, in the constructs of the invention in their simplest form, the three constant domains (5), (6) and (7) are preferably the constant domains C_ε2, C_ε3 and C_ε4 of human IgE, respectively, so that the IgE derived Fc portion (8) is the Fc portion of human IgE. Such a construct may for example be as further described in the co-pending International patent application by Ablynx N.V. entitled "*Immunoglobulin constructs*", which has the same filing date as the present application. Alternatively, in such a construct, the two single variable domains (3) and (9) may be essentially the same (i.e. directed against the same target or antigen, such as against the same antigenic determinant, epitope, part or domain on the same target) to allow for high(er) avidity binding to the intended antigen.

Figure 3 schematically shows a non-limiting example of a polypeptide of the invention, comprising a single variable domain (3) that is linked via an optional hinge or linker (4) to three constant domains (5), (6) and (7). As further described herein, such a polypeptide chain may be used to form a construct of the invention (i.e. with another polypeptide chain of the invention), but may also be used as such (i.e. without interaction with another polypeptide chain of the invention), for example when the Fc_ε chain (or an variant, analog, part of fragment thereof) that is formed by the constant domains is monomeric (i.e. non self-associating).

Figure 4 schematically shows a non-limiting example of a specific, but non-limiting polypeptide of the invention, comprising two single variable domains (3) and (9) that are linked to each other via an optional linker (10) and that are linked via an optional hinge or linker (4) to three constant domains (5), (6) and (7). Again, such a polypeptide chain may be used to form a construct of the invention (i.e. with another polypeptide chain of the invention), but may also be used as such (i.e. without interaction with another polypeptide chain of the invention), for example when the Fc_ε chain that is formed by the constant domains is monomeric (i.e. non self-associating). Also, the two single variable domains (3) and (9) may be different (as described in the co-pending International patent application by Ablynx N.V. entitled "*Immunoglobulin constructs*") or may be the same.

It should also be noted that, unless specifically defined otherwise herein, all terms used in the present specification either have the meaning given to them in the prior art cited herein (and in particular given to them in WO 06/122 825 or WO 06/122786), or otherwise have their usual meaning in the art, which will be clear to the skilled person. Reference is for example made to the standard handbooks, such as Sambrook et al, "Molecular Cloning: A Laboratory Manual" (2nd.Ed.), Vols. 1-3, Cold Spring Harbor Laboratory Press (1989); F. Ausubel et al, eds., "Current protocols in molecular biology", Green Publishing and Wiley Interscience, New York (1987); Lewin, "Genes II", John Wiley & Sons, New York, N.Y., (1985); Old et al., "Principles of Gene Manipulation: An Introduction to Genetic Engineering", 2nd edition, University of California Press, Berkeley, CA (1981); Roitt et al., "Immunology" (6th. Ed.), Mosby/Elsevier, Edinburgh (2001); Roitt et al., Roitt's Essential Immunology, 10th Ed. Blackwell Publishing, UK (2001); and Janeway et al., "Immunobiology" (6th Ed.), Garland Science Publishing/Churchill Livingstone, New York (2005), as well as to the further prior art cited herein, such as WO 04/068820 and WO 02/056910. Also, all methods, steps, techniques and manipulations that are not specifically described in detail in the present specification can be performed in a manner known per se to the skilled person, for which reference is again made to the prior art cited herein (including WO 04/068820 and WO 02/056910) as well as to the standard handbooks cited above.

The single variable domains that are present in the constructs of the invention may be any variable domain that forms a single antigen binding unit. Generally, such single variable domains will be amino acid sequences that essentially consist of 4 framework regions (FR1 to FR4 respectively) and 3 complementarity determining regions (CDR1 to CDR3 respectively); or any suitable fragment of such an amino acid sequence (which will then usually contain at least some of the amino acid residues that form at least one of the CDR's, as further described herein). Such single variable domains and fragments are most preferably such that they comprise an immunoglobulin fold or are capable for forming, under suitable conditions, an immunoglobulin fold. As such, the single variable domain may for example comprise a light chain variable domain sequence (e.g. a V_L-sequence) or a suitable fragment thereof; or a heavy chain variable domain sequence (e.g. a V_H-sequence or V_{HH} sequence) or a suitable fragment thereof; as long as it is capable of forming a single antigen binding unit (i.e. a functional antigen binding unit that essentially consists of the single variable domain, such that the single antigen binding domain does not need to interact with another variable domain to form a functional antigen binding unit, as is for example the case for the variable domains that are present in for example conventional antibodies and ScFv fragments that need to

interact with another variable domain – e.g. through a V_H/V_L interaction – to form a functional antigen binding domain).

For example, the single variable domain may be a domain antibody (or an amino acid sequence that is suitable for use as a domain antibody), a single domain antibody (or an amino acid sequence that is suitable for use as a single domain antibody), a "dAb" (or an amino acid sequence that is suitable for use as a dAb) or a Nanobody (as defined herein, and including but not limited to a V_{HH} sequence); other single variable domains, or any suitable fragment of any one thereof. For a general description of (single) domain antibodies, reference is also made to the prior art cited above, as well as to EP 0 368 684. For the term "dAb's", reference is for example made to Ward et al. (Nature 1989 Oct 12; 341 (6242): 544-6), to Holt et al. (Trends Biotechnol., 2003, 21(11):484-490); as well as to for example WO 04/068820, WO 06/030220, WO 06/003388 and other published patent applications of Domantis Ltd. It should also be noted that, although less preferred in the context of the present invention because they are not of mammalian origin, single domain antibodies or single variable domains can be derived from certain species of shark (for example, the so-called "IgNAR domains", see for example WO 05/18629).

In particular, the amino acid sequence of the invention may be a Nanobody™ or a suitable fragment thereof. *[Note: Nanobody®, Nanobodies® and Nanoclone® are trademarks of Ablynx N.V.]* For a further description of V_{HH} 's and Nanobodies, reference is made to the review article by Muyldermans in Reviews in Molecular Biotechnology (74(2001), 277-302); as well as to the following patent applications, which are mentioned as general background art: WO 94/04678, WO 95/04079 and WO 96/34103 of the Vrije Universiteit Brussel; WO 94/25591, WO 99/37681, WO 00/40968, WO 00/43507, WO 00/65057, WO 01/40310, WO 01/44301, EP 1134231 and WO 02/48193 of Unilever; WO 97/49805, WO 01/21817, WO 03/035694, WO 03/054016 and WO 03/055527 of the Vlaams Instituut voor Biotechnologie (VIB); WO 03/050531 of Algonomics N.V. and Ablynx N.V.; WO 01/90190 by the National Research Council of Canada; WO 03/025020 (= EP 1 433 793) by the Institute of Antibodies; as well as WO 04/041867, WO 04/041862, WO 04/041865, WO 04/041863, WO 04/062551, WO 05/044858, WO 06/40153, WO 06/079372, WO 06/122786, WO 06/122787 and WO 06/122825, by Ablynx N.V. and the further published patent applications by Ablynx N.V. Reference is also made to the further prior art mentioned in these applications, and in particular to the list of references mentioned on pages 41-43 of the International application WO 06/040153, which list and references are incorporated herein by reference. As described in these references, Generally, Nanobodies (in particular V_{HH} sequences and partially

humanized Nanobodies) can in particular be characterized by the presence of one or more “*Hallmark residues*” in one or more of the framework sequences.

The single variable domains used in the constructs of the invention may be directed against (as defined in WO 06/122 825) any suitable antigen. Examples of suitable antigens and of single variable domains directed against those antigens will be clear to the skilled person based on the disclosure herein, and for example include the antigens and single variable domains mentioned in the prior art cited herein as well as the antigens and “dAb’s” mentioned and described in the patent applications of Domantis Ltd. or Domantis Inc..

The single variable domains used in the constructs of the invention may in particular be directed against one or more antigens that are expressed by cancer cells and/or that are associated with cancer cells, such as the antigens that are commonly used as targets for cancer therapy (such as for cancer immunotherapy using antibodies or antibody-based therapeutics). Such antigens will be clear to the skilled person, and for example include, but are not limited to B-cell or T-cell lymphoma B- and T-cell receptor idiotypic sequences, respectively, CD19, CD23 (low affinity IgE receptor), Prostate specific antigen (PSA), prostate specific membrane antigen (PSMA), CD52 (CAMPATH-1 antigen), CD80 (B7-1), GD3 (ganglioside cancer marker), MUC1 (glycoprotein cancer marker), EpCAM (epithelial cell adhesion molecule cancer marker), RAAG12 (glycoprotein cancer marker), CD55 (Decay Accelerating Factor (DAF), binds complement C3b), MAGE-1 (“melanoma antigen gene-1, a cancer associated antigen-1” presented to cytotoxic anti-cancer T-cells), MAGE-3, MAGE-10, NY-ESO-1, HER-2, EGFR, IGFR, VEGFR, CEA, CD38, CD138 and CD56 and other antigens that are expressed by and/or associated with tumors and tumor cells (including but not limited to solid tumors). For examples of single variable domains that are directed against such antigens (and for methods of generating such single variable domains), reference is again made to in the prior art cited herein as well as to for example WO 03/055527, WO 07/042289, WO 07/066109, WO 07/080392 and WO 07/066106 and the co-pending International patent application of Ablynx N.V. with the same filing date as the present application, entitled “*Amino acid sequences directed against HER2 and polypeptides comprising the same for the treatment of cancers and/or tumors*”.

For example, when the single variable domains are directed against HER-2, they may for example be (a Nanobody that is) directed against the Herceptin® binding site on HER2 (and in particular against domain IV of HER2, and more in particular against the C-terminus of domain IV of HER2) and/or that is capable of competing with Herceptin® for binding to HER-2; or be (a Nanobody that is) directed against the Omnitarg® binding site on HER2 (and

in particular against domain II of HER2, and more in particular against the middle of domain II of HER2) and/or that is capable of competing with Omnitarg® for binding to HER-2. For examples of such single variable domains, reference is again made to the co-pending International patent application of Ablynx N.V. with the same filing date as the present application, entitled "*Amino acid sequences directed against HER2 and polypeptides comprising the same for the treatment of cancers and/or tumors*".

Alternatively, single domain antibodies may in particular be directed against antigens associated with activated and/or autoreactive T- or B-lymphocytes. Such antigens will be clear to the skilled person, and for example include, but are not limited to CD25 (IL2 receptor), CD69 (early activation antigen), CD152 (CTLA4), CD154 (CD40L), CD95 (Apo-1, Fas), CD178 (Fas ligand, FasL), CD134 (OX-40), CD96 (T cell ACTivation Increased Late Expression (TACTILE)), CD97 (GR1), CD26 (Dipeptidyl peptidase IV). For examples of single variable domains that are directed against such antigens (and for methods of generating such single variable domains), reference is again made to the prior art cited herein and other applications by Ablynx N.V. and Domantis Ltd..

In a specific, but non-limiting aspect of the invention, each polypeptide chain of the invention may comprise not one, but two or more (such as three and preferably two) single variable domains, which may be directly linked to each other or optionally be linked to each other via one or more suitable linkers. A construct of the invention (in which each polypeptide chain comprises two single variable domains) is schematically shown in Figure 2, with the corresponding polypeptide chain of the invention being schematically shown in Figure 4. In the constructs and polypeptide chains according to this aspect of the invention, the single variable domains in each polypeptide chain may be essentially the same (in which case the constructs and polypeptide chains may for example bind with higher affinity to the intended or desired target or antigen, compared to corresponding constructs of the invention that comprise only a single variable domain in each polypeptide chain; or they may be different from each other (i.e. may be directed against different antigens or targets, and may in particular be directed against different epitopes, antigenic determinants, parts, domains or subunits of the same target or antigen). In the latter case, such a construct or polypeptide chain may for example be as further described in the co-pending International patent application by Ablynx N.V. entitled "*Immunoglobulin constructs*", which has the same filing date as the present application, but comprising an IgE-derived Fc portion.

For example, the polypeptide chains in such a construct may each comprise at least one single variable domain (such as a Nanobody) that is directed against the Herceptin®

binding site on HER2 (and in particular against domain IV of HER2, and more in particular against the C-terminus of domain IV of HER2) and/or that is capable of competing with Herceptin® for binding to HER-2, that is linked (directly or via a suitable linker) to at least one single variable domain (such as a Nanobody) that is directed against the Omnitarg® binding site on HER2 (and in particular against domain II of HER2, and more in particular against the middle of domain II of HER2) and/or that is capable of competing with Omnitarg® for binding to HER-2. Such a construct or polypeptide chain is further preferably such that it capable of (simultaneously) binding to both the Omnitarg® binding site on HER2 (and in particular against domain II of HER2, and more in particular against the middle of domain II of HER2) as well as the Herceptin® binding site on HER2 (and in particular against domain IV of HER2, and more in particular against the C-terminus of domain IV of HER2), most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition. For example, for this purpose, the two single variable domains in each polypeptide chain may be linked to each other via a suitable linker, for which reference is made to the International patent application of Ablynx N.V. with the same filing date as the present application, entitled "*Amino acid sequences directed against HER2 and polypeptides comprising the same for the treatment of cancers and/or tumors*" (see for example Example 19).

Besides the single variable domain(s), each of the polypeptide chains that together form the construct of the invention also comprise one or more constant domains that, together with the constant domains of the other polypeptide chain present in the construct, forms an Fc portion that is capable of effecting one or more IgE-mediated immune responses (as defined herein) and/or that is capable of binding to either the FcεRI receptor and/or the FcεRII receptor (as further described herein). Such an Fc portion will also be referred to herein as an "*IgE-derived Fc portion*".

In its simplest and most preferred form, the IgE-derived Fc portion used in the constructs of the invention is the Fc portion of IgE, in particular of human IgE.

However, more generally, the IgE-derived Fc portion may be any dimer formed by two polypeptide chains that is capable of binding to either the FcεRI receptor and/or the FcεRII receptor, and in particular of binding to either the FcεRI receptor and/or the FcεRII receptor so as to induce receptor-mediated signalling and/or more generally one or more cellular responses and/or immune responses that are mediated by these receptors (i.e. one or more of the cellular or immune responses that are usually triggered by the binding of IgE to

the receptor. These cellular and/or immune responses are also referred to herein as “*IgE-mediated immune responses*”). Such polypeptide chains will usually be comprised of one or more (and in particular two and preferably three) immunoglobulin constant domains (and in particular heavy chain constant domains) that are capable of forming such an Fc portion.

In particular, the IgE-derived Fc portion present in the constructs of the invention may be such that it is capable of binding to FcεRI with an affinity (expressed as the K_a value) better than 10^6 M^{-1} , preferably better than 10^8 M^{-1} , more preferably better than 10^9 M^{-1} , such as with a K_a value of about 10^{10} M^{-1} or 10^{11} M^{-1} ; and/or such that that it is capable of binding to FcεRII with an affinity (expressed as the K_a value) better than 10^6 M^{-1} , preferably better than 10^7 M^{-1} , such as with a K_a value of about 10^8 M^{-1} .

For example, and although the use of the Fc portion of human IgE is preferred, the IgE-derived Fc portion may also be a chimeric Fc portion that is capable of effecting one or more IgE-mediated immune responses and/or of binding to FcεRI and/or FcεRII (as described herein). Such a chimeric Fc portion will usually be comprised of one or more immunoglobulin constant domains (and preferably essentially consist of two constant domains, and more preferably three constant domains), and will usually at least comprise at least one or more parts, fragments, amino acid stretches or domains of the Fc portion of IgE (i.e. those parts, fragments, amino acid stretches or domains of the Fc portion of IgE that allow IgE to bind to its receptors) and further comprise one or more parts, fragments, amino acid stretches or domains of the Fc portion of one or more other immunoglobulins (for example, from the Fc portions of an IgG, IgA, IgM or IgD) so as to form an Fc portion that is capable of effecting one or more IgE-mediated immune responses and/or of binding to FcεRI and/or FcεRII (as described herein). Suitable chimeric Fc portions will be clear to the skilled person based on the disclosure herein, and/or can be generated by the skilled person based on the disclosure herein, optionally after a limited degree of routine experimentation. Usually, such a chimeric Fc portion will at least comprise C_ε4 (or a suitable part of fragment thereof) and may also comprise C_ε3 (or a suitable part of fragment thereof) and/or C_ε2 (or a suitable part of fragment thereof).

The IgE-derived Fc portion may also be a part or fragment of the Fc portion of IgE (or suitable combination of two or more parts or fragments from the Fc portion of IgE) that is still capable of (forming an Fc portion that is capable of) effecting one or more IgE-mediated immune responses and/or of binding to FcεRI and/or FcεRII (as described herein). Such parts or fragments will usually at least comprise C_ε4 (or a suitable part of fragment thereof) and

may also comprise C_ε3 (or a suitable part of fragment thereof) and/or C_ε2 (or a suitable part of fragment thereof). It is also possible to use suitable (naturally occurring, semi-synthetic or synthetic) analogs, homologs, variants or orthologs of the Fc portion of (human) IgE, as long as these are capable of (forming an Fc portion that is capable of) effecting one or more IgE-mediated immune responses and/or of binding to FcεRI and/or FcεRII (as described herein).

In one specific, but non-limiting, aspect, the Fc portion may also (be used to) confer upon the constructs the invention an increased half-life in vivo. According to this aspect, the IgE-derived Fc portion may still have some or all of the effector functions of the IgE-derived Fc portion (or have these effector functions, but at a reduced level still suitable for the intended use), but when the IgE-derived Fc portion is solely used to provide for increased half-life, also a suitable mutant, variant part or fragment of an IgE-derived Fc portion may be used that has no or essentially no effector functions. Half-life can generally be defined as the time taken for the serum concentration of the polypeptide to be reduced by 50%, in vivo, for example due to degradation of the ligand and/or clearance or sequestration of the ligand by natural mechanisms. Methods for pharmacokinetic analysis and determination of half-life are familiar to those skilled in the art. Details may be found in Kenneth, A et al: *Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists* and in Peters et al, *Pharmacokinetic analysis: A Practical Approach* (1996). Reference is also made to "Pharmacokinetics", M Gibaldi & D Perron, published by Marcel Dekker, 2nd revised edition (1982). For example, the constructs or polypeptides of the invention may have a half-life in a mammal (such as a mouse, rat or monkey) and/or in man that is at least 25%, preferably at least 50%, more preferably at least 70%, such as about 80% or 90% or more, of a naturally occurring IgE in said mammal or in man.

In another one specific, but non-limiting, aspect, the constant domains used in a polypeptide chain of the invention may be such that they allow the polypeptide chain of the invention to be used (i.e. for antigen-binding, for example for therapeutic purposes) as such, i.e. without forming part of a construct of the invention. Generally, according to this aspect of the invention, the constant domains may be naturally occurring, synthetic or semisynthetic analogs, variants, parts or fragments of constant domains (e.g. derived from IgE or other immunoglobulins) that, when combined in a polypeptide chain of the invention, confer upon the polypeptide chain a reduced (or essentially no) tendency to self-associate into dimers (i.e. compared to the constant domains that naturally occur in the Fc portion of IgE). Such monomeric (i.e. not self-associating) Fc chain variants, or fragments thereof, may for

example be as described in Helm et al., J Biol Chem 1996 271 7494. Also, such monomeric Fc ϵ chain variants are preferably such that they are still capable of binding to the high and/or low affinity IgE receptor (as described herein for the IgE-derived Fc portion), and/or such that they still have some or all of the effector functions of the IgE –derived Fc portion (or at a reduced level still suitable for the intended use). Alternatively, in such a polypeptide chain of the invention, the monomeric Fc ϵ chain may be used to confer increased half-life upon the polypeptide chain, in which case the monomeric Fc ϵ chain may also have no or essentially no effector functions.

Again, suitable parts, fragments, analogs, homologs, variants or orthologs will be clear to the skilled person based on the disclosure herein, and/or can be generated by the skilled person based on the disclosure herein, optionally after a limited degree of routine experimentation.

In the constructs of the invention, the parts, fragments, amino acid stretches or domains that make up the IgE-derived Fc portion are preferably all or essentially all derived from human Fc portions, including human IgE Fc portions. For example, the constant domains may be the C ϵ 2, C ϵ 3 and C ϵ 4 domains of human IgE.

However, it is also possible that some or all of the parts, fragments, amino acid stretches or domains that make up the IgE-derived Fc portion are derived from one or more other species of mammal, such as rat, mouse, rabbit, or primates such as rhesus monkey, baboon or cynomolgous monkey. For example, for testing of the constructs of the invention in an animal model, the IgE-derived Fc portion may be in full or in part be derived from parts, fragments, amino acid stretches or domains of the Fc portion of IgE from the species of mammal used in said animal model. Thus, for example, the IgE-derived Fc portion may also be the Fc portion of IgE from another species of mammal, such as rat, mouse, rabbit, or primates such as rhesus monkey, baboon or cynomolgous monkey.

In the polypeptide chains that form the constructs of the invention, the constant domains that form the IgE-derived Fc portion (as defined herein) may be suitably linked to the single variable domains, either directly (which is less preferred), via a suitable hinge region or linker (which is most preferred), or even (although much less preferred) via a suitable constant domain (such as a C α 1, C δ 1, C μ 1 or preferably C H 1 or C ϵ 1 domain, which may in turn be linked to the Fc portion via a suitable linker).

The hinge region or linker may be any suitable hinge region or linker, and suitable hinge regions and linkers, which will usually comprise or essentially consist of a suitable

amino acid sequence, will be clear to the skilled person based on the disclosure herein. Some preferred, but non-limiting examples include the hinge regions that naturally occur in immunoglobulins (such as the hinge region of IgG's or the hinge region from Camelid heavy chain antibodies, see for example EP 0 698 097 or the linkers described in WO 96/34103), suitable analogs, variants, homologs, parts or fragments thereof (including synthetic or semi-synthetic analogs, variants, homologs, parts or fragments, for example hinge regions that have been engineered so as not to contain cysteine residues, see for example WO 07/085814), as well as the synthetic and semi-synthetic linkers mentioned in WO 04/068820 and WO 02/056910. Also, a naturally occurring C_H1 domain or a suitable variant thereof may be used as (or instead of) a hinge region.

Usually, in the practice of the invention, the single variable domains that are present in the two polypeptide chains that form the construct of the invention will be the essentially same (i.e. be comprised of essentially the same amino acid sequence), or at least directed to the same antigen. Also, usually, in the practice of the invention, the constant domains that are present in both of the polypeptide chains that form the construct of the invention will be essentially the same (i.e. be comprised of essentially the same amino acid sequence). Thus, usually, both polypeptide chains that form the construct of the invention will comprise essentially the same single variable domains and essentially the same constant domains, so that the constructs of the invention will usually be comprised of two polypeptide chains that have essentially the same (variable and constant) domains and more in particular essentially the same sequence. However, the invention in its broadest sense is not limited thereto, and for example also comprises constructs in which the single variable domains in each of the two polypeptide chains are directed against different epitopes on the same target or antigen, constructs in which the two polypeptide chains that form the construct of the invention comprise different hinge regions or linkers, or even constructs in which the two polypeptide chains that form the construct of the invention comprise different constant domains (as long as the constant domains of the two polypeptide chains are still capable of forming an IgE-derived Fc portion as defined herein).

The constructs of the invention may be prepared in any suitable manner known per se. Usually, such methods will either comprise joining two suitable polypeptide chains of the invention so as to form a construct of the invention (in which these polypeptide chains will usually be essentially identical in sequence, although the invention in its broadest sense is not limited thereto). For the purposes of this method, the polypeptide chains of the invention may

be prepared in any suitable manner, usually by suitably expressing, in a suitable host or host organism, a nucleic acid of the invention that encodes the desired polypeptide chain.

Alternatively, the constructs of the invention may be prepared by suitably co-expressing, in a suitable host or host organism, (suitable nucleic acids of the invention that encode) two suitable polypeptide chains of the invention (in which these polypeptide chains will again usually be essentially identical in sequence) so as to form a construct of the invention.

For the purposes of the above methods, the nucleic acids encoding the polypeptide chains of the invention may be prepared in any suitable manner, for example using PCR assembly using overlapping primers, by suitably linking (naturally occurring, synthetic or semi-synthetic) nucleotide sequences that encode the various parts of the desired polypeptide chain, or by de novo synthesis of the desired nucleic acid of the invention using an automated apparatus for synthesizing nucleic acid sequences with a predefined amino acid sequence. The particular codons used may also be chosen and/or optimized for the host or host organism to be used for the expression. Also, for the purposes of the invention, the nucleic acids of the invention may be provided and/or used in the form of a suitable genetic construct (such as a plasmid or expression vector), that may for example comprise – in addition to the nucleotide sequences that encodes the desired polypeptide chain – one or more regulatory elements and/or other suitable components of such constructs known per se. All this can be performed using methods and techniques known per se, for which reference is made to the prior art cited herein, such as WO 04/068820 and WO 02/056910. For example, a nucleotide sequence encoding the desired single variable domain can be suitably linked to a nucleotide sequence that encodes the C_ε2, C_ε3 and C_ε4 domains of human IgE, optionally via a nucleotide sequence that encodes a suitable linker or hinge region.

The further expression, production, purification and isolation (including any steps for joining the two polypeptide chains of the invention so as to form a construct of the invention, or for co-expressing two polypeptide chains of the invention so as to form a construct of the invention) may be performed using techniques, vectors, host cells or host organisms known per se, for which reference is again made to for example WO 04/068820 and WO 02/056910.

In a further aspect, the invention relates to a host or host cell that expresses or is capable of expressing a construct of the invention or a polypeptide chain of the invention, or that contains a nucleotide sequence or nucleic acid that encodes a construct of the invention or a polypeptide chain of the invention. The invention further relates to methods for producing a construct of the invention or a polypeptide chain of the invention, comprising maintaining or

cultivating such a host or host cell under conditions such that said host or host cell expresses or produces a construct of the invention or a polypeptide chain of the invention, and optionally comprising isolating the construct of the invention or polypeptide chain of the invention so expressed or produced.

The invention further relates to compositions that comprise at least one construct of the invention or a polypeptide chain of the invention. Such a composition may in particular be a pharmaceutical composition that comprises at least one construct of the invention and one or more pharmaceutically acceptable carriers, adjuvants or excipients. Reference is again made to for example WO 04/068820 and WO 02/056910, as well as to the further prior art cited herein. Usually, such a pharmaceutical composition will be a (usually liquid and aqueous) composition that is suitable for injection or infusion, essentially similar to the formulations that are used for injection or infusion of conventional monoclonal antibodies, but containing one or more constructs of the invention instead of a conventional 4-chain monoclonal antibody.

The constructs and compositions of the invention may be used for any suitable purpose, mainly depending upon the antigen(s) against which the single variable domains that are present in the construct are directed. For example, when the single variable domains that are present in the construct are directed against a pharmaceutically relevant target or antigen, the constructs and compositions of the invention may be used in the prevention and/or treatment of diseases and disorders that are associated with said target or antigen, i.e. by suitably administering the constructs or compositions to a subject that is at risk of and/or suffering from said disease or disorder. Such diseases and disorders, and suitable routes of administration and treatment regimens, will be clear to the skilled person based on the disclosure herein. Generally, it is envisaged that constructs of the invention can be made that are analogous to conventional therapeutic monoclonal antibodies (i.e. directed against the same target or antigen, but only containing two polypeptide chains as described herein, in which the single variable domains in each chain are directed against the relevant target or antigen), and that such constructs (and pharmaceutical compositions comprising the same) can be used for the prevention and/or treatment of the essentially same diseases and disorders as these conventional monoclonals, using essentially similar routes of administration and treatment regimens, which can easily be determined by the treating physician.

Thus, in another aspect, the invention relates to (the use of) a construct of the invention that is directed against a desired or intended (therapeutically relevant) target or

antigen (or of a pharmaceutical composition comprising the same) for the prevention or treatment of a disease or disorder associated with said target or antigen.

The invention further relates to the use of a construct of the invention that is directed against a desired or intended (therapeutically relevant) target or antigen in the preparation of a pharmaceutical composition for the prevention or treatment of a disease or disorder associated with said target or antigen.

The invention also relates to a method for preventing or treating a disease or disorder that is associated with a target or antigen, which method comprises administering, to a subject in need of such prevention or treatment, of a therapeutically active amount of a construct of the invention that is directed against said target or antigen (or of a pharmaceutical composition comprising the same).

As mentioned above, in one specifically preferred, but non-limiting aspect, the construct of the invention is directed against a target or antigen that is associated with cancer or tumors, such as those described above. Such constructs of the invention are particularly suited for the treatment of various forms of cancer and tumors (including solid tumors), e.g. by slowing, stopping or reversing the growth of a tumor and/or by slowing, stopping or reversing the spread of metastases caused by the tumor; and it is envisaged that such constructs of the invention may have improved efficacy and/or other improved properties compared to similar constructs based on single variable domains (i.e. directed against the same antigen and/or comprising the same single variable domains) that comprise an IgG-derived Fc portion (as described in EP 1 621 554, WO 04/068820 or WO 02/056910) instead of an IgE-derived Fc portion, and may also have improved properties (such as improved stability, ease of production, efficacy per gram of material, or tumor penetration) compared to 4-chain monoclonals that comprise an IgE-derived Fc portion, such as those described in Karagiannis et al., *supra*. The efficacy of the constructs of the invention may be determined using suitable cellular assays (for example using a suitable tumor cell line) or animal models known per se, which may be suitably chosen by the skilled person.

Again, for use of the constructs of the invention in the prevention and/or treatment of cancer, suitable tumor-associated antigens, constructs of the invention, pharmaceutical compositions, routes of administration and treatment regimens will be clear to the skilled person based on the disclosure herein, and may for example also include suitable combination treatments with other cytostatic agents and/or with surgery and/or radiation treatment.

Thus, in another aspect, the invention relates to (the use of) a construct of the invention that is directed against a tumor-associated target or antigen (or of a pharmaceutical

composition comprising the same) for the prevention or treatment of cancer (and in particular, for the prevention or treatment of tumors that express said tumor-associated target or antigen).

The invention further relates to the use of a construct of the invention that is directed against a tumor-associated target or antigen in the preparation of a pharmaceutical composition for the prevention or treatment of cancer (and in particular, of tumors that (over)express said tumor-associated target or antigen).

The invention also relates to a method for preventing or treating a cancer, which method comprises administering, to a subject in need of such prevention or treatment, of a therapeutically active amount of a construct of the invention that is directed against a tumor-associated target or antigen (i.e. a target or antigen expressed by the tumor to be treated) or of a pharmaceutical composition comprising the same.

The invention also relates to a polypeptide chain that comprises at least one single variable domain that is linked, optionally via a suitable linker or hinge region, to one or more constant domains, in which the constant domains are capable of forming (i.e. with the constant domains of another such polypeptide chain) an Fc portion that is capable of effecting one or more IgE-mediated immune responses and/or that is capable of binding to either the FcεRI receptor and/or the FcεRII receptor. Again, the constant domains are preferably such that they are capable of forming (i.e. with the constant domains of another such polypeptide chain) an IgE-derived Fc portion as further defined herein. For example, the constant domains may be the C_ε2, C_ε3 and C_ε4 domains of a mammalian IgE, and in particular of human IgE.

SEQ ID NO's 1 to 12 (see also Table 1) and Figures 5 to 10 give some non-limiting examples of amino acid sequences and nucleic acid sequences of polypeptide chains of the invention that can be used to form constructs of the invention:

- SEQ ID NO:1 and Figure 5A give an example of an amino acid sequence of a polypeptide chain of the invention comprising a humanized Nanobody against the carcinoembryonic antigen associated with cancer (CEA) that is fused via a C_ε1 domain, serving here as native sequence variable region-Fc linker, to C_ε2, C_ε3 and C_ε4 domains of human IgE. The corresponding nucleotide sequence is given in SEQ ID NO:2 and Figure 5B.
- SEQ ID NO:3 and Figure 6A give an example of an amino acid sequence of a polypeptide chain of the invention comprising a Nanobody against EGFR that is linked via a glycine-serine linker and the native C_ε1- C_ε2 linking sequence to the C_ε2, C_ε3 and

C_ε4 domains of human IgE. The corresponding nucleotide sequence is given in SEQ ID NO:4 and Figure 6B.

- SEQ ID NO:5 and Figure 7A give an example of an amino acid sequence of a polypeptide chain of the invention comprising a Nanobody against HER-2 (47D5, which is competitive for binding to HER-2 with pertuzumab (Omnitarg®)) that is linked via a glycine-serine linker and the native C_ε1- C_ε2 linking sequence to the C_ε2, C_ε3 and C_ε4 domains of human IgE,. The corresponding nucleotide sequence is given in SEQ ID NO:6 and Figure 7B.
- SEQ ID NO:7 and Figure 8A give an example of an amino acid sequence of a polypeptide chain of the invention comprising a Nanobody against HER-2 (2D3, which is competitive for binding to HER-2 with trastuzumab (Herceptin®)) that is linked via a glycine-serine linker and the native C_ε1- C_ε2 linking sequence to the C_ε2, C_ε3 and C_ε4 domains of human IgE. The corresponding nucleotide sequence is given in SEQ ID NO:8 and Figure 8B.
- SEQ ID NO:9 and Figure 9A give an example of an amino acid sequence of a polypeptide chain of the invention comprising two different Nanobodies against HER-2 (i.e. 47D5 and 2D3, which together form a biparatopic Nanobody construct), that are linked via a glycine-serine linker and the native C_ε1- C_ε2 linking sequence to the C_ε2, C_ε3 and C_ε4 domains of human IgE. In this construct, 47D5 and 2D3 are linked to each other via 35 a.a. Gly/Ser linker, which should allow both Nanobodies to bind to HER-2 (i.e. essentially simultaneously). The corresponding nucleotide sequence is given in SEQ ID NO:10 and Figure 9B.
- SEQ ID NO:11 and Figure 10A give another example of an amino acid sequence of a polypeptide chain of the invention comprising two different Nanobodies against HER-2 (i.e. 47D5 and 2D3, which together form a biparatopic Nanobody construct), that are linked via a glycine-serine linker and the native C_ε1- C_ε2 linking sequence to the C_ε2, C_ε3 and C_ε4 domains of human IgE. In this construct, 47D5 and 2D3 are again linked to each other via 35 a.a. Gly/Ser linker, which should allow both Nanobodies to bind to HER-2 (i.e. essentially simultaneously); however, compared to the construct of SEQ ID NO:9/Figure 9A, the order of the 2 anti-HER-2 Nanobodies 47D5 and 2D3 is reversed. The corresponding nucleotide sequence is given in SEQ ID NO:12 and Figure 10B.

Table 1: Non-limiting examples of amino acid sequences and nucleic acid sequences of polypeptide chains of the invention.

CEA1_Hu-C1-C2-C3-C4 IgE; SEQ ID NO:1 EVQLLESGGGLVQPGGSLRLSCAASGFTFSKYDMSWVRQAPGKGLEWVSRIS SGGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKPTYSSD YRGLPPGQGTQVTVSSTQSPSVFPLTRCCKNIPSNATSVTLGCLATGYFPEPVM VTCDTGSLNGTTMTLPATTLTSLGHYATISLLTVSGAWAKQMFTCRVAHTPSS TDWVDNKTFVCSRDFTPPTVKILQSSCDGGGHFPPTIQLLCLVSGYTPGTINIT WLEDGQVMDVDLSTASTTQEGELASTQSEL TLSQKHWLSDRTYTCQVTYQG HTFEDSTKKCADSNPRGVSA YLSRPSFDL FIRKSPTITCLVVDLAPSKGTVNL TWSRASGKPVNHSTRKEEKQRNGTLTVTSTLPVGTRDWIEGETYQCRVTHPH LPRALMRSTTKTSGPRAAPEVYAFATPEWPGSRDKRTLACLIQNFMPEDISVQ WLHNEVQLPDARHSTTQPRKTKGSGFFVFSRLEVTRAWEQKDEFICRAVHE AASPSQTVQRAVSVNPGK
CEA1_Hu-C1-C2-C3-C4 IgE; SEQ ID NO:2 gaggtgcagctgctcagctctgggggaggttggtgcagcctggggggtctctgagactctctgtgcagcctctggatc acattcagtaaatacagacatgagctgggtccgccaggtccagggaaggggctcagtggtctcacgtattagtagtggt ggtgtagcacatactatgcagactccgtgaagggccgattcaccatctccagagacaacagtaagaacacgctgtatctg caaatgaacagtttgcgggcccaggacactgcccgtgtattactgcgccaaagccaacctacagtagcgactatcgaggcctc ccccggggccagggggaccaggtcaccgtctcctcaacacagagcccacccgtcttccccctgacccgctgctgcaaaaa cattccctccaatgccacctccgtgactctgggctgcctggccacgggctacttcccggagccgggtgatggtgacctgcga cacaggtccctcaacgggacaactatgacctaccagccaccacctcacgctctctggtcactatgccaccatcagcttg ctgacctctcgggtgctgggccaagcagatgttcacctgccgtgtggcacacactccatcgtccacagactgggtgcag aacaaaaccttcagcgtctgctccagggaactcaccgcccccaccgtgaagatcttacagtcgtcctgcgacggcgccgg geacttcccccgaccatccagctcctgtgcctcgtctctgggtacaccccagggactatcaacatcacctggctggaggac gggcaggtcatgagcgtggacttgtccaccgccctctaccacgcaggagggtgagctggcctccacacaaagcgagctca ccctcagccagaagcactggctgtcagaccgcacctacacctgccagggtcacctatcaaggtcacaccttgaggacagca ccaagaagtgtgcagattccaacccgagagggggtgagcgcctacctaagccggcccagcccgttcgacctgttcateccg aagtcgcccacgatacctgtctgtgtgggtgacctggcaccacagcaaggggaccgtgaacctgacctggtccgggcca gtgggaagcctgtgaaccactccaccagaaaggaggagaagcagcgaatggcacgttaaccgtcacgtccacctgcc ggtgggcacccgagactggatcgagggggagacctaccagtgcagggtgacccacccccacctgcccagggccctcat gcggtccacgaccaagaccagcggcccgcgtgctgccccggaagtctatgcgtttgcagccggagtgccgggggag ccgggacaagcgcacctcgcctgacctgacagaaactcatgctgaggacatctcgggtcagtggtgcacaacgagg tgcagctcccgagcggccggcacagcagcagcagccccgaagaccaagggtccgggttcttcgtcttcagccgct ggagggtgaccagggccgaatgggagcagaaagatgagttcatctgccgtgcagtcagtgaggcagcagccctcaca gacctccagcagcgggtgtctgtaaatcccgtaaatga
EGFR 7H10-G/S-C2-3-4 IgE; SEQ ID NO:3 QVQLVESGGGLVQAGGSLRLSCAASGRTFSTYTMAWFRQAPGKEREVQGIS RSDGGTYDADSVKGRFTISRDN AKNTVYLQMNSLKPEDTAVYFCAAASVKL VYVNP NRYSYWGQGTQVTVSSGGGSGGGSGGGSDVNDKTFVCSRDFTPPTV KILQSSCDGGGHFPPTIQLLCLVSGYTPGTINITWLEDGQVMDVDLSTASTTQE GELASTQSEL TLSQKHWLSDRTYTCQVTYQGHTFEDSTKKCADSNPRGVSA Y LSRPSFDL FIRKSPTITCLVVDLAPSKGTVNL TWSRASGKPVNHSTRKEEKQR NGTLTVTSTLPVGTRDWIEGETYQCRVTHPHLPRALMRSTTKTSGPRAAPEVY AFATPEWPGSRDKRTLACLIQNFMPEDISVQWLHNEVQLPDARHSTTQPRKT KSGGFFVFSRLEVTRAWEQKDEFICRAVHEAASPSQTVQRAVSVNPGK

Table 1 (continued)

EGFR 7H10-G/S-C2-3-4 IgE; SEQ ID NO:4

CAGGTACAGCTGGTGGAGTCTGGGGGAGGATTGGTGCAGGCTGGGGGCTC
 TCTGAGACTCTCCTGTGCAGCCTCTGGACGCACCTTCAGTACTTATACCAT
 GGCCTGGTTCCGCCAGGCTCCAGGAAAGGAGCGTGAGTTTGTACAAGGTA
 TTAGCCGGAGTGATGGAGGCACATACGACGCAGACTCCGTGAAGGGCCGG
 TTCACCATCTCCAGAGACAACGCCAAGAACACGGTGTATCTGCAAATGAA
 CAGCCTGAAACCTGAGGACACGGCCGTTTATTTTTGTGCAGCAGCGAGTGT
 AAAGTTGGTCTATGTGAATCCTAATCGCTATAGTTACTGGGGCCAGGGGAC
 CCAGGTCACCGTCTCCTCAGGCGGCGGCAGCGGCGGCGGCAGCGGCGGCG
 GCAGCGctcgacaacaaaacctcagcgtctgctccagggacttcacccgcccaccgtgaagatcttacagtcgtcctg
 cgacggcgggcgggcacttcccccgaccatccagctcctgtgcctcgtctctgggtacacccagggactataacatcac
 ctggctggaggacgggcaggtcatggacgtggactgtccaccgcctctaccacgcaggaggggtgagctggcctccaca
 caaagcgagctcaccctcagccagaagcactggctgtcagaccgcacctacacctgccaggtcacctatcaaggtcacac
 ctttgaggacagcaccaagaagtgtgcagattccaacccgagaggggtgagcgcctacctaaagccggcccagcccgttc
 gacctgttcacccgaagtcgccacgatcacctgtctgggtgggtggacctggcaccagcaaggggacctgaacctgac
 ctggctccggggcagtggaagcctgtgaaccactccaccagaaaggaggagaagcagcgcgaatggcacgttaacctg
 cacgtccacctgcccgggtgggcacccgagactggatcgaggggggagacctaccagtcaggggtgacccacccccacct
 gccaggggcccctcatgcggtccacgaccaagaccagcggcccgcgtgctgccccggaagtctatgctgttgagacgccg
 gagtggccgggggagccgggacaagcgcacctcgcctgctgacccagaactcatgctgaggacatctcgggtcagtg
 ggctgcacaacgaggtgcagctcccgacgcccggcacagcacgacgcagccccgaagaccaagggctccggcttc
 ttcgtcttcagccgcctggaggtgaccagggccgaatgggagcagaaagatgagttcatctgccgtgcagtcctatgaggc
 agcgagccccctcacagaccgtccagcgagcgggtgtctgtaaatcccggtaaatga

Her2 47D5-G/S-C2-3-4 IgE; SEQ ID NO:5

KVQLVESGGGLVQPGGSLRLSCAASGSIFFGNDMAWYRQAPGKQRELVALIS
 RVGVTTSSADSVKGRFTISRVDNAKDTVYQLQMNSLKPEDTAVYYCYMDQRLDG
 STLAYWGQGTQVTVSSGGGSGGGSGGGSVDNKTFSVCSRDFTPPTVKILQSSC
 DGGGHFPPTIQLLCLVSGYTPGTINITWLEDGQVMDVDLSTASTTQEGELAST
 QSELTLSQKHWLSDRTYTCQVTYQGHTFEDSTKKCADSNPRGVSAAYLSRPSPF
 DLFIRKSPTITCLVVDLAPSKGTVNLTWSRASGKPVNHSTRKEEKQRNGTLTV
 TSTLPVGTRDWIEGETYQCRVTHPHLPRALMRSTTKTSGPRAAPEVYAFATPE
 WPGSRDKRTLACLIQNFMPEDISVQWLHNEVQLPDARHSTTQPRKTKGSGFF
 VFSRLEVTRAWEQKDEFICRAVHEAASPSQTVQRAVSVNPGK

Table 1 (continued)

Her2 47D5-G/S-C2-3-4 IgE; SEQ ID NO:6

AAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTGCAGCCTGGGGGGTC
 TCTGAGACTCTCCTGTGCAGCCTCTGGAAGCATCTTCGGTTTCAATGACAT
 GGCCTGGTACCGCCAGGCTCCAGGGAAGCAGCGGAGTTGGTCGCACTAA
 TTAGTAGGGTTGGTGTCAACAAGTTCTGCAGACTCCGTGAAGGGCCGATTCA
 CCATCTCCAGAGTCAACGCCAAGGACACGGTGTATCTGCAAATGAACAGC
 CTGAAACCTGAGGATACGGCCGTCTATTATTGTTATATGGATCAGCGACTC
 GACGGTAGTACTTTAGCGTACTGGGGCCAGGGGACCCAGGTCACCGTATC
 GAGTGGCGGCGGCAGCGGCGGCGGCAGCGGCGGCGGCAGCgtcgacaacaaaacc
 ttcagcgtctgtccagggaacttcaccccgcccaccgtgaagatcttacagtcgtcctgcgacggcggcgggcacttcccc
 ccgaccatccagctcctgtgcctcgtctctgggtacaccccagggaactatcaacatcacctggctggaggacgggcaggtc
 atggacgtggacttgtccaccgctctaccacgcaggaggggtgagctggcctccacacaaagcgagctcacctcagcca
 gaagcactggctgtcagaccgcacctacacctgccaggtcacctataaggtcacacctttgaggacagcaccaagaagt
 gtgcagattccaacccgagaggggtgagcgctacctaagccggcccagcccgttcgacctgttcacccaagtcgccc
 acgatcacctgtctgggtgtggacctggcaccagcaaggggaccgtgaacctgacctggctccgggcccagtgaggaaagc
 ctgtgaaccactccaccagaaaggaggagaagcagcgcaatggcagcttaaccgtcacgtccacctgccgggtgggcac
 ccgagactggatcgaggggggagacctaccagtgacaggggtgacccacccccacctgccaggggcccctcatcggtccac
 gaccaagaccagcgggcccgctgtgccccggaagtctatgcgtttgcgacgccggagtggccggggagccggggaca
 agcgcacctcgcctgctgatccagaactcatgcctgaggacatctcgggtcagtggtgcacaacgaggtgcagctcc
 cggacgcccggcacagcagcagcagccccgcaagaccaagggctccggcttcttcgtcttcagcgccttgagggtgac
 cagggccgaatgggagcagaaagatgagttcatctgccgtgcagtcctcatgaggcagcagccctcacagaccgtccag
 cgagcgggtgtctgtaaatcccggtaaatga

Her2 2D3-G/S-C2-3-4 IgE; SEQ ID NO:7

EVQLVESGGSLVQPGGSLRLSCAASGFTFDDYAMSWVRQVPGKGLEWVSSIN
 WSGTHTDYADSVKGRFTISRNNANNTLYLQMNSLKSEDTAVYYCAKNWRD
 AGTTWFEKSGSAGQGTQVTVSSGGGSGGGSGGGSVDNKTFSVCSRDFTPPTV
 KILQSSCDGGGHFPPTIQLLCLVSGYTPGTINITWLEDGQVMDVDLSTASTTQE
 GELASTQSELTLQKHWLSDRTYTCQVTYQGHTFEDSTKKCADSNPRGVSA
 YLSRPSPFDLFIRKSPTITCLVVDLAPSKGTVNLTWSRASGKPVNHSTRKEEKQR
 NGTLTVTSTLPVGTRDWIEGETYQCRVTHPHLPRALMRSTTKTSGPRAAPEVY
 AFATPEWPGSRDKRTLACLIQNFMPEDISVQWLHNEVQLPDARHSTTQPRKT
 KGSGFFVFSRLEVTRAWEQKDEFICRAVHEAASPSQTVQRAVSVNPGK

Table 1 (continued)

Her2 2D3-G/S-C2-3-4 IgE; SEQ ID NO:8 gaagtgcagttagtcgagtcaggggtagcttggtgcagccgggggtagcctgcgcctgagctgcgccgcgagcggct tcacctcgacgattatgcgatgtcatgggtcagacaggtccctggtaaagggttgaatgggttccctcaataaactggagc ggcaccatacggattatgcggatagcgtgaaaggacgtttaccattagccgcaataacgctaataacactctgtacctaca aatgaactcgtcaaatctgaagatactgctgtctactattgtccaagaattggcgtgacgcagggaccacatggttgaga aatccggtagcgcgggccaaggcactcaggtgacagtgagcagcGGCGGCGGCAGCGGCGGCGGC AGCGGCGGCGGCAGCgtcgacaacaaaacctcagcgtctgtcaccagggaacttccccgccaccgtgaa gatcttacagtcgtcctgcgacggcgggcacttcccccgaccatccagtcctgtgctcgtctctgggtacacccca gggactatcaacatcacctggctggaggacgggcaggtcatggacgtggacttgtccaccgcctctaccacgcaggagg gtgagctggcctccacaaaagcgagctcaccctcagccagaagcactggctgtcagaccgcactacacctgccaggtc acctatcaaggtcacacctttgaggacagcaccagaagtgtgcagattccaaccgagaggggtgagcgctacctaaag ccggcccagcccggttcagctgttcacgcaagtcgccacgacacctgtctggtggtggacctggcaccagcaagg ggaccgtgaacctgacctggctcccgggcagtggaagcctgtgaaccactccaccagaaaggaggagaagcagcgca atggcacgttaaccgtcacgtccaccctgccggtgggcacccgagactggatcaggggggagacctaccagtgcagggt gaccacccccacctgcccagggccctcatcggtccacgaccaagaccagcggcccgctgctgccccggaagtctat gcgtttgcgacgccggagtggccggggagccgggacaagcgccacctgcctgctgatccagaacttcatgctgagg acatctcggtgcagtggtgcacaacgaggtgcagctcccgagccggcagcagcagcagcagcccgcaagacca agggtcctcggtctctcgtcttcagccgctggaggtgaccagggccgaatgggagcagaaagatgagttcatctgccgtg cagtcctagaggcagcagccctcagacaccgtccagcgagcggtgtctgtaaatccccggtaaatga	Her2 47D5-G/S-2D3-G/S-C2-3-4 IgE; SEQ ID NO:9 KVQLVESGGGLVQPGGSLRLSCAASGSIQGFNDMAWYRQAPGKQRELVALIS RVGVTSSADSVKGRFTISRNVNAKDTVYLMNSLKPEDTAVYYCYMDQRLDG STLAYWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGG SEVQLVESGGSLVQPGGSLRLSCAASGFTFDDYAMSWVRQVPGKGLEWVSSI NWSGTHTDYADSVKGRFTISRNNANNTLYLMNSLKSEDTAVYYCAKNWR DAGTTWFEKSGSAGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGG VKILQSSCDGGGHFPPTIQLLCLVSGYTPGTINITWLEDGQVMDVDLSTASTTQ EGELASTQSELTLQKHWLSDRTYTCQVTYQGHTFEDSTKKCADSNPRGVSA YLSRPSPFDFIRKSPITITCLVVDLAPSKGTVNLTWSRASGKPVNHSTRKEEKQ RNGTLTVTSTLPVGTDRDWIEGETYQCRVTHPHLPRALMRSTTKTSGPRAAPEV YAFATPEWPGSRDKRTLACLIQNFMPEDISVQWLHNEVQLPDARHSTTQPRK TKGSGFFVFSRLEVTRAWEQKDEFICRAVHEAASPSQTVQRAVSVNPGK
---	---

Table 1 (continued)

Table 1 (continued)

Her2 2D3-G/S-47D5-G/S-C2-3-4 IgE; SEQ ID NO:12

gaggtgcagctgggtggagctctggggctccttgggtgcagcctgggggtctctgagactctcctgtgcagcctctggcttca
 cttttgatgattatgccatgagctgggtccgacaggttccaggggaaggggttggagtgggtttcatctattaattggtctgttac
 tcacacagactatgcagactccgtgaagggccgattaccatctccagaacaacgccataaacacgctgtatctacaaatg
 aacagtctgaaatctgaggacacggccgtgtattactgtgcaaaaaactggagagacgcaggtactacctggttcgaaaag
 tccggctccgcccaggggacccaggtcaccgtatcagtggtggggcgggggaagtggcggaggtgggtccggtgg
 cggaggcagcgggtggaggaggtagtggcgggtggcggtagtggcgggtggcggcagtgaggcggaggatccgaggtg
 cagctgggtggagctctgggggagggcttgggtgcagcctgggggtctctgagactctcctgtgcagcctctggaagcatctt
 ggtttcaatgacatggcctggtagccaggtccaggggaagcagcgcgagttggctgcactaattagtagggttggtgtc
 acaagtctgcagactccgtgaagggccgattaccatctccagagtaacgccaaaggacacgggtgtatctgcaaatgaac
 agcctgaaacctgaggatacggccgtctattattgttatatggatcagcgcactgcagcggtagtactttagcgtactggggcca
 ggggaccaggtcaccgtctctcaGGCGGCGGCAGCGGCGGCGGCAGCGGCGGCGGCA
 GCgtcgacaacaaaacctcagcgtctgtccagggacttccccgccaccgtgaagatcttacagtcgtctgcgac
 ggcggcgggcacttccccccgaccatccagctcctgtgectgtctctgggtacaccccagggaactatcaacatcacctgg
 ctggaggacgggcaggtcatggacgtggactgtccaccgcctctaccacgcaggagggtgagctggcctccacacaaa
 gcgagctcacctcagccagaagcactggctgtcagaccgcacctacacctgccaggtcacctatcaaggtcacacctttg
 aggacagcaccaagaagtgtgcagattccaacccgagaggggtgagcgctacctaagccggcccagcccgttcgacct
 gttcatccgcaagtcgcccacgatcacctgtctgggtgggtggacctggcaccagcaaggggaccgtgaacctgacctggt
 cccggggcagtggaagcctgtgaaccactccaccagaaaggaggagaagcagcgcgaatggcacgttaacctgcacgt
 ccacctgccggtgggcacccgagactggatcgagggggagacctaccagtgcagggtgacccacccccacctgccc
 gggccctcatcggtccacgaccaagaccagcggcccgctgtgccccggaagtctatgcgtttgcgacgcccggagt
 gccggggagccgggacaagcgcacctcgcctgcctgatccagaactcctgcctgaggacatctcgggtcagtggtg
 cacaacgaggtgcagctcccgacgcccggcacagcagcgcagccccgcaagaccaagggtccggcttcttcgtc
 ttacgcccttgaggtgaccagggccgaatgggagcagaaagatgagttcatctgccgtgcagtcacatgaggcagcga
 gccccacagaccgtccagcgcgggtgtctgtaaatcccggttaaatga

CLAIMS

1. Polypeptide construct comprising two single variable domains and an Fc portion that is capable of effecting one or more IgE-mediated immune responses and/or that is capable of binding to either the FcεRI receptor and/or the FcεRII receptor.
2. Polypeptide construct according to claim 1, in which the single variable domains are linked to the Fc portion via a linker or hinge region.
3. Polypeptide construct, comprising two polypeptide chains, in which each polypeptide chain comprises at least one single variable domain that is linked, optionally via a suitable linker or hinge region, to one or more constant domains, in which the constant domains from the first polypeptide chain and the second polypeptide chains together form an Fc portion that is capable of effecting one or more IgE-mediated immune responses and/or that is capable of binding to either the FcεRI receptor and/or the FcεRII receptor.
4. Polypeptide construct according to any of the preceding claims, in which the Fc portion is capable of binding to FcεRI with an affinity (expressed as the K_a value) better than 10^6 M^{-1} , preferably better than 10^8 M^{-1} , more preferably better than 10^9 M^{-1} , such as with a K_a value of about 10^{10} M^{-1} or 10^{11} M^{-1} .
5. Polypeptide construct according to any of the preceding claims, in which the Fc portion is capable of binding to FcεRII with an affinity (expressed as the K_a value) better than 10^6 M^{-1} , preferably better than 10^7 M^{-1} , such as with a K_a value of about 10^8 M^{-1} .
6. Polypeptide construct according to any of the preceding claims, in which the Fc portion comprises at least one or more parts, fragments, amino acid stretches or domains of the Fc portion of IgE.
7. Polypeptide construct according to any of the preceding claims, in which the Fc portion comprises at least one or more of those parts, fragments, amino acid stretches or domains of the Fc portion of IgE that allow IgE to bind to its receptors.
8. Polypeptide construct according to any of the preceding claims, in which the Fc portion at least comprises Cε4 (or a suitable part of fragment thereof), and optionally also comprises Cε3 (or a suitable part of fragment thereof) and/or Cε2 (or a suitable part of fragment thereof).
9. Polypeptide construct according to any of the preceding claims, in which the Fc portion essentially consist of three constant domains.

10. Polypeptide construct according to any of the preceding claims, in which the parts, fragments, amino acid stretches or domains that make up the IgE-derived Fc portion are preferably all or essentially all derived from human Fc portions.

11. Polypeptide construct according to any of the preceding claims, in which the IgE-derived Fc portion is from human IgE.

12. Polypeptide construct according to any of the preceding claims, in which the single variable domains are directed against a pharmaceutically relevant target or antigen.

13. Polypeptide construct according to any of the preceding claims, in which the single variable domains are directed against tumor antigen.

14. Polypeptide construct according to any of the preceding claims, in which the single variable domains are directed against activated and/or autoantigen specific T- or B-cell associated antigens.

15. Polypeptide construct according to any of the preceding claims, in which each polypeptide chain comprises two or more single variable domains.

16. Polypeptide construct according to claim 15, in which the number of single variable domains in each polypeptide construct is two.

17. Polypeptide construct according to any of claims 15 or 16, in which said two or more single variable domains are linked via one or more linkers.

18. Polypeptide construct according to any of claims 15 or 16, in which said two or more single variable domains are directly linked.

19. Polypeptide construct according to any of claims 15 to 18, in which said two or more single variable domains are directed against the same target or antigen.

20. Polypeptide construct according to any of claims 15 to 18, in which said two or more single variable domains are directed against a different target or antigen.

21. Polypeptide construct according to any of the preceding claims, in which the single variable domains are a domain antibody (or an amino acid sequence that is suitable for use as a domain antibody), a single domain antibody (or an amino acid sequence that is suitable for use as a single domain antibody), a "dAb" (or an amino acid sequence that is suitable for use as a dAb) or a Nanobody (including but not limited to a V_{HH} sequence), or any suitable fragment thereof.

22. Polypeptide construct according to any of the preceding claims, in which the single variable domains are Nanobodies.

23. Polypeptide, comprising at least one single variable domain that is linked, optionally via a suitable linker or hinge region, to one or more constant domains, in which the

constant domains are capable of forming (e.g. with the constant domains of a second such polypeptide chain) an Fc portion that is capable of effecting one or more IgE-mediated immune responses and/or that is capable of binding to either the FcεRI receptor and/or the FcεRII receptor, or form a monomeric Fc portion that is capable of effecting one or more IgE-mediated immune responses and/or that is capable of binding to either the FcεRI receptor and/or the FcεRII receptor.

24. Polypeptide according to claim 23, in which the constant domains are the C_ε2, C_ε3 and C_ε4 of human IgE.

25. Polypeptide according to claim 23 or 24, in which the single variable domain is directed against a pharmaceutically relevant target or antigen.

26. Polypeptide according to any of claims 23 to 25, in which the single variable domain is directed against a tumor antigen.

27. Polypeptide according to any of claims 23 to 25, in which the single variable domain is directed against activated and/or autoantigen specific T- or B-cell associated antigens.

28. Polypeptide according to any of claims 23 to 27, which comprises two or more single variable domains.

29. Polypeptide according to claim 28, in which the number of single variable domains is two.

30. Polypeptide according to any of claims 28 or 29, in which said two or more single variable domains are linked via one or more linkers.

31. Polypeptide according to any of claims 28 or 29, in which said two or more single variable domains are directly linked.

32. Polypeptide according to any of claims 28 to 31, in which said two or more single variable domains are directed against the same target or antigen.

33. Polypeptide according to any of claims 28 to 31, in which said two or more single variable domains are directed against a different target or antigen.

34. Polypeptide according to any of claims 23 to 33, in which the single variable domain is a domain antibody (or an amino acid sequence that is suitable for use as a domain antibody), a single domain antibody (or an amino acid sequence that is suitable for use as a single domain antibody), a "dAb" (or an amino acid sequence that is suitable for use as a dAb) or a Nanobody (including but not limited to a V_{HH} sequence), or any suitable fragment thereof.

35. Polypeptide according to any of claims 23 to 34, in which the single variable domain is a Nanobody.

36. Nucleotide sequence or nucleic acid that encodes and/or that can be used to express a polypeptide construct according to any of claims 1 to 22 or a polypeptide according to any of claims 23 to 35.

37. Method for preparing a polypeptide construct according to any of claims 1 to 22, which method comprises joining two polypeptides according to any of claims 23 to 35 so as to form a polypeptide construct according to any of claims 1 to 22.

38. Method for preparing a polypeptide construct according to any of claims 1 to 22, which method comprises co-expressing, in a suitable host or host organism, two polypeptides according to any of claims 23 to 35 so as to form a polypeptide construct according to any of claims 1 to 22.

39. Host or host cell that expresses or is capable of expressing a polypeptide construct according to any of claims 1 to 22 or a polypeptide according to any of claims 23 to 35, or that comprises a nucleotide sequence or nucleic acid according to claim 36.

40. Method for producing a polypeptide construct according to any of claims 1 to 22 or a polypeptide according to any of claims 23 to 35, said method comprising maintaining or cultivating a host or host cell according to claim 39 under conditions such that said host or host cell expresses or produces a polypeptide construct according to any of claims 1 to 22 or a polypeptide according to any of claims 23 to 35, respectively, and optionally further comprising isolating the polypeptide construct according to any of claims 1 to 22 or the polypeptide according to any of claims 23 to 35 so expressed or produced.

41. Composition comprising at least one polypeptide construct according to any of claims 1 to 22.

42. Composition according to claim 41, which is a pharmaceutical composition comprising at least one polypeptide construct according to any of claims 1 to 22 and one or more pharmaceutically acceptable carriers, adjuvants or excipients.

43. Polypeptide construct according to any of claims 1 to 22, which is directed against a desired or intended target or antigen, or pharmaceutical composition comprising such a polypeptide construct, for the prevention or treatment of a disease or disorder associated with said target or antigen.

44. Polypeptide construct according to any of claims 1 to 22, which is directed against a tumor antigen, or pharmaceutical composition comprising such a polypeptide construct, for the prevention or treatment of cancer.

45. Polypeptide construct according to any of claims 1 to 22, which is directed against a self-reactive and/or activated T- or B-lymphocyte associated antigen, or pharmaceutical composition comprising such a polypeptide construct, for the prevention or treatment of inflammatory disorders and/or autoimmunity.

46. Use of a polypeptide construct according to any of claims 1 to 22 which is directed against a desired or intended target or antigen for use in the preparation of a pharmaceutical composition for the prevention or treatment of a disease or disorder associated with said target or antigen.

47. Use of a polypeptide construct according to any of claims 1 to 22 which is directed against a tumor antigen for use in the preparation of a pharmaceutical composition for the prevention or treatment of cancer.

48. Method for preventing or treating a disease or disorder that is associated with a target or antigen, which method comprises administering, to a subject in need of such prevention or treatment, of a therapeutically active amount of a polypeptide construct according to any of claims 1 to 22 that is directed against said target or antigen, or of a pharmaceutical composition comprising such a polypeptide construct.

49. Method for preventing or treating cancer, which method comprises administering, to a subject in need of such prevention or treatment, of a therapeutically active amount of a polypeptide construct according to any of claims 1 to 22 that is directed against a tumor antigen, or of a pharmaceutical composition comprising such a polypeptide construct.

Figure 1

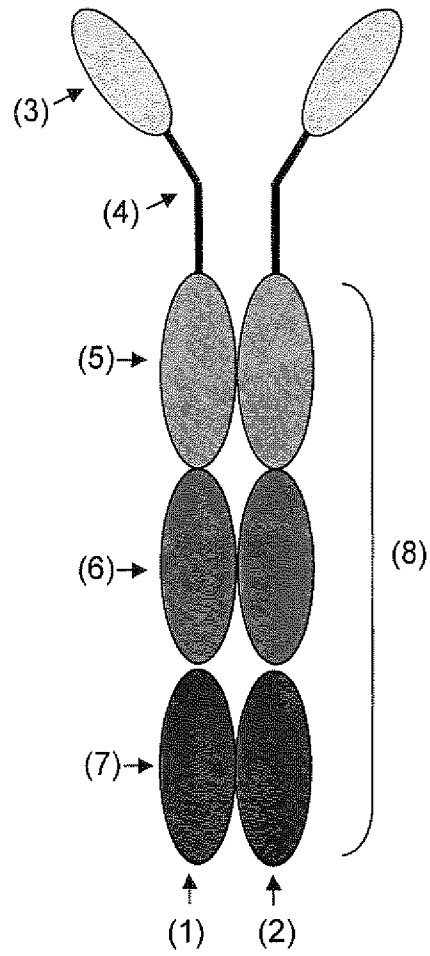


Figure 2

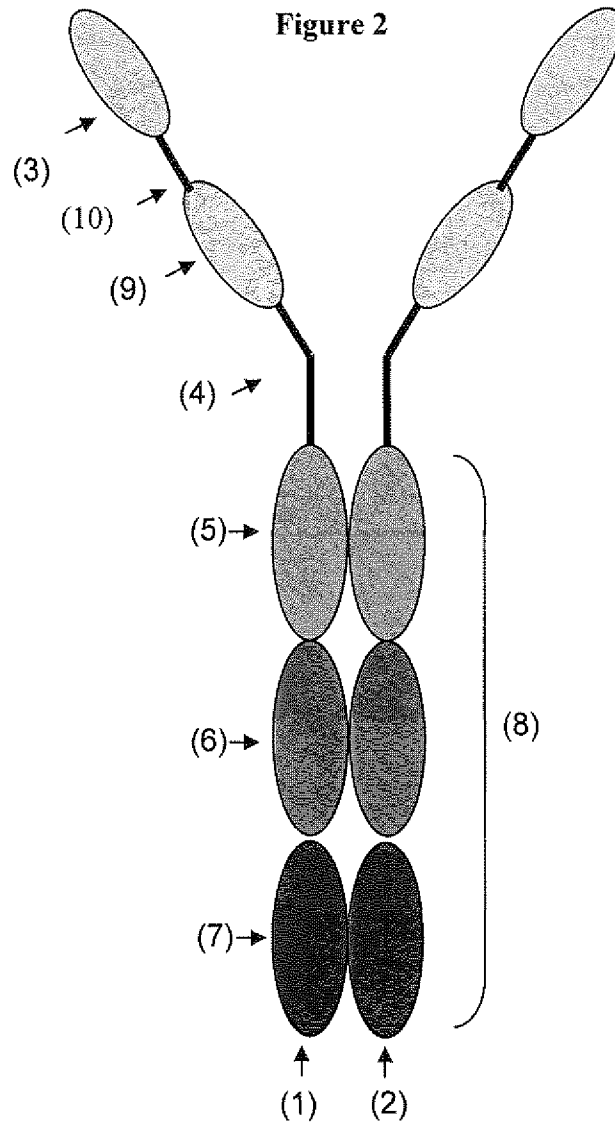


Figure 3

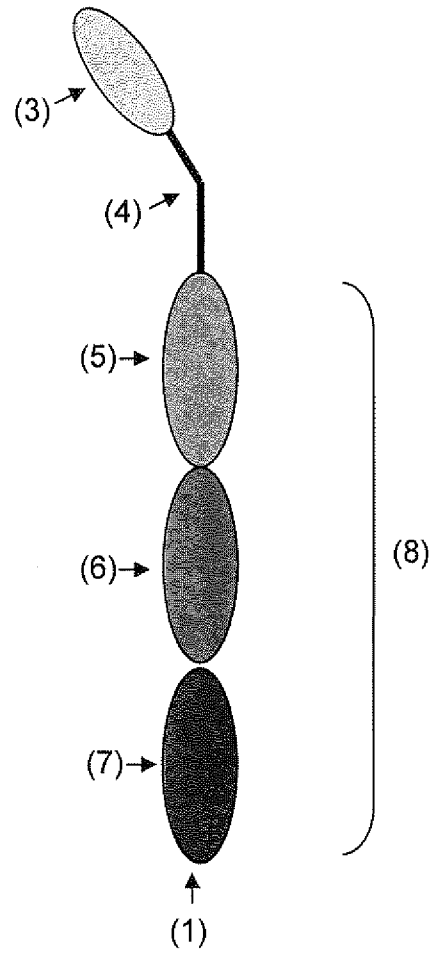


Figure 4

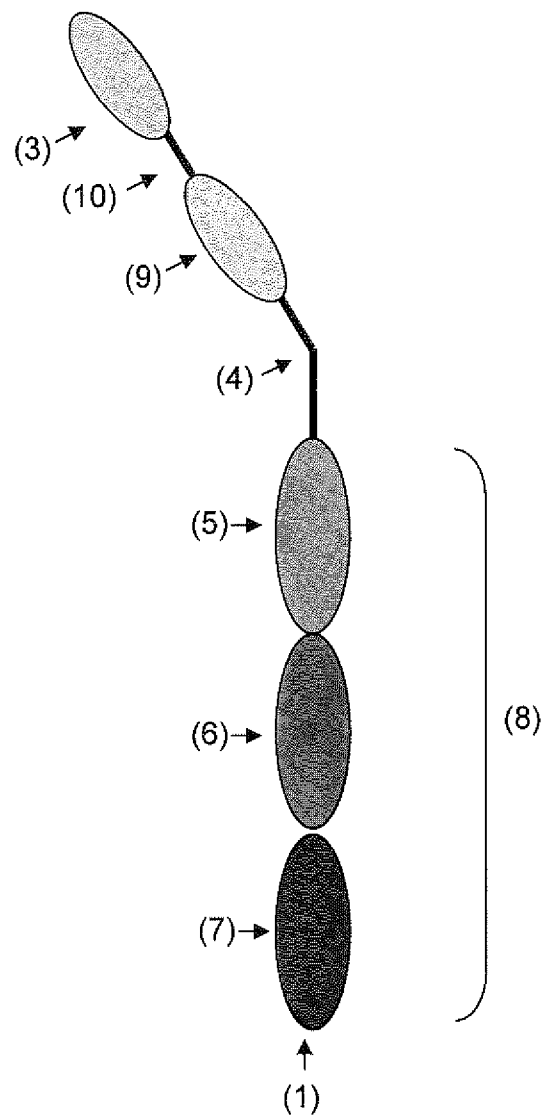


Figure 5A

>CEA1_Hu-C1-C2-C3-C4 IgE
EVQLLESGGGLVQPGGSLRLSCAASGFTFSKYDMSWVRQAPGKGLEWVSRISSGGGSTYYADSVKGRFTISRDNK
NTLYLQMNSLRAEDTAVVYCAKPTYSSDYRGLPPGQGTQVTVSSTQSPSVFPLTRCKNIPSNATSVTLGCLATGYF
PEPVMVTCDTGSLNGTTMTLPATTLTSLGHYATISLLTVSGAWAKQMFTCRVAHTPSSTDWVDNKTFSVCSRDFTP
PTVKILQSSCDGGGHFPPTIQLLCLVSGYTPGTINITWLEDGQVMDVDLSTASTTQEGELASTQSELTLSQKHWSR
TYTCQVTYQGHTFEDSTKKCADSNPRGV SAYLSRPSFFDLFIRKSPTITCLVVDLAPSKGTVNL TWSRASGKPVNHS
TRKEEKQRNGTLTVTSTLPVGTRDWIEGETYQCRVTHPHLPRALMRSTTKTSGPRAAPEVYAFA TPWPGRDKRT
LACLIQNFMPEDISVQWLHNEVQLPDARHSTTQPRKTKGSGFFVFSRLEVTRAWEQKDEFICRAVHEAASPSQTVQ
RAVSVNPGK

Figure 5B

>CEA1_Hu-C1-C2-C3-C4 IgE
gaggtgcagctgctcgagctctgggggaggtcttggtgcagcctgggggtctctgagactctcctgtgcagcctctggattcac
attcagtaaaatacgacatgagctgggtccgccaaggtccagggaaggggctcgagtggtctcagctattagtagtggtggtg
gtagcacatactatgcagactccgtgaagggccgattcaccatctccagagacaacagtaagaacacgctgtatctgcaaatg
aacagtttgcgggccgaggacactgcctgtgtattactgcgccaaagccaacctacagtagcgactatcgaggcctcccccg
ccaggggacccaggtcacctgtctctcaacacagagcccatccgtcttcccttgaccgctgctgcaaaaaacattccctcca
atgccacctccgtgactctgggtgcctggccacgggctacttcccgagccggtgatggtgacctgcgacacaggtccctc
aacgggacaactatgaccttaccagccaccaccctcacgctctctggtcactatgccaccatcagcttgctgacctctcggg
tgctggtggccaagcagatgttcacctgcctgtgtggcacacactccatcgccacagactgggtcgacaacaaaaccttcagcg
tctgtctcagggacttcacccccccacccgtgaagatettacagtcgtcctgcgacggcgccggcaettccccccgaccatc
cagctcctgtgcctcgtctctgggtacacccccaggactatcaacatccctggctggaggacgggcaggtcatggacgtgga
cttgctccaccgctctaccacgcaggaggggtgagctggcctccacacaaaagcgagctcacctcagccagaagcactggctgt
cagaccgcacctacacctgccaggtcacctatcaagggtcacaccttgaggacagcaccagaagtgtgcagattccaacccg
agaggggtgagcgctacctaagccggcccgccggttcgacctgttcacccgcaagtcgcccacgatccctgtctgggtggt
ggacctggcaccagcaaggggacccgtgaacctgacctgggtcccgggccagtgagggaagcctgtgaacctccaccagaaag
aggagaagcagcgcaatggcacgttaacctgcagtcacacctgcgggtgggcacccgagactggatcgagggggagacctac
cagtgacgggtgacccacccccacctgcccaggccctcatgcggtccacgaccaagaaccagcgcccggtgtgccccgga
agtctatgcgtttgcgacgcccagtggtggccggggagccgggacaagcgacccctcgctgcctgatccagaacttcagcctg
aggacatctcgggtgcagtggtgcacaacgaggtgcagctcccggaagcccgccacagcagcagcagcccgcaagaccaag
ggctccggcttctctcgtcttcagccgctggaggtgaccagggccgaatgggagcagaaagatgagttcatctgcctgtcag
ccatgaggcagcgagccctcacagaccgtccagcgagcggtgtctgtaaattcccggtaaatga

>EGFR 7H10-G/S-C2-3-4 IgE
QVQLVESGGGLVQAGGSLRLSCAASGRTFTSTYMAWFRQAPGKEREFVQGISRSDGGTYDADSVKGRFTISRDNK
NTVYLMNSLKPEDTAVYFCAAASVKLVYVNPNNRYSYWGQGTQVTVSSGGGSGGGSGGGSVDNKTFVCSRDF
PPTVKILQSSCDGGGHFPPTIQLLCLVSGYTPGTINITWLEDGQVMDVDLSTASTTQEGELASTQSELTLSQKHWLSD
RTYTCQVTYQGHTFEDSTKKCADSNPRGVSA YLSRPSFDFLRKSPITITCLVVDLAPSKGTVNLTWSRASGKPVNH
STRKEEKQRNGTLTVTSTLPVGTRDWIEGETYQCRVTHPHLPRALMRSTTKTSGPRAAPEVYAFATPEWPGSRDKR
TLACLIQNFMPEDISVQWLHNEVQLPDARHSTTQPRKTKGSGFFVFSRLEVTRAWEQKDEFICRAVHEAASPSQTV
QRAVSVNPGK

Figure 6B

[illegible]

Figure 7A

>Her2 47D5-G/S-C2-3-4 IgE
KVQLVESGGGLVQPGGSLRLSCAASGSIQGFNDMAWYRQAPGKQRELVALISRVGVTSSADSVKGRFTISRVA
TVYLQMNSLPEDTAVYYCYMDQRLDGLAYWGQGTQVTVSSGGGSGGGSGGGSVDNKTFVCSRDFTPTVKI
LQSSCDGGGHFPPTIQLLCLVSGYTPGTINITWLEDGQVMDVDLSTASTTQEGELASTQSELTSQKHWSDRYTC
QVTYQGHTFEDSTKKCADSNPRGV SAYLSRSPFDLFIRKSPITITCLVVDLAPSKGTVNLTWSRASGKPVNHSTRKE
EKQRNGTLTVTSTLPVGTTRDWIEGETYQCRVTHPLPRALMRSTTKTSGPRAAPEVYAFATPEWPGRDKRTLACLI
QNFMPEDISVQWLHNEVQLPDARHSTTQPRKTKGSGFFVFSRLEVTRAWEQKDEFICRAVHEAASPSQTVQRAVS
VNPGK

Figure 7B

>Her2 47D5-G/S-C2-3-4 IgE
AAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTGCAGCCTGGGGGGTCTCTGAGACTCTCCTGTGCAGCCTCTGGAAGCAT
CTTCGGTTTCAATGACATGGCCTGGTACCGCCAGGCTCCAGGGAAGCAGCGCGAGTTGGTCGCACTAATTAGTAGGGTTGGTG
TCACAAGTTCTGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGTCAACGCCAAGGACACGGTGTATCTGCAATGAAC
AGCCTGAAACCTGAGGATACGGCCGTCTATTATTGTTATATGGATCAGCGACTCGACGGTAGTACTTTAGCGTACTGGGGCCA
GGGGACCCAGGTCACCGTATCGAGTGGCGGGCGGCAGCGGGCGGCAGCGGGCGGCAGCGTcgacaacaaaaaccttcagcg
tctgctccagggaacttcaccccgccacccgtgaagatcttacagtcgtcctgcgacggcgggcggaacttcccccgaccatc
cagctcctgtgcctcgtctctgggtacaccccgaggactatcaacatcacctggctggaggacgggcaggtcatggacgtgga
cttgctccaccgcctctaccacgcaggaggggtgagctggcctccacacaaaagcgagctcacctcagccagaagcactggctgt
cagacccgcacctacacctgccaggtcacctatcaagggtcacacctttgaggacagcaccagaagtggtgcagattccaacccg
agaggggtgagcgctacctaagccggccagcccggttcgacctgttcacccgcaagtcgcccacgatcacctgtctgggtgt
ggacctggcaccacgaaggggacccgtgaacctgacctgggtcccgggccagtggaagcctgtgaacctccaccagaaagg
aggagaagcagcgcaatggcacgttaacctgcagtcacccctgcccgggtgggaccccgagactggatcgagggggagacctac
cagtgccaggtgacccacccccacctgcccaggccctcatgcggtccacgaccaagaccagcgcccgcgctgctgccccgga
agtctatgcgtttgacgacgcccggagtgccggggagccgggacaaagcgacccctcgccctgctgatccagaacttcagcctg
aggacatctcgggtgcagtggtgtcacaaagaggtgcagctcccggaagcccgccacagcacgacgcagccccgcaagaccaag
ggctccggcttcttcgtcttcagccgctggaggtgaccagggccgaatgggagcagaaagatgagttcatctgcccgtgcag
ccatgaggcagcgagccctcacagaccgtccagcgagcggtgtctgtaaatcccggtaaatga

Figure 8A

>Her2 2D3-G/S-C2-3-4 IgE
EVQLVESGGSLVQPGGSLRLSCAASGFTFDDYAMSWVRQVPGKGLEWVSSINWSGTHTDYADSVKGRFTISRNNANNTLYLQM
NSLKSEDTAVYYCAKNWRDAGTTWFEKSGSAGQGTQVTVSSGGGSGGGSGGGSVDNKTFVCSRDFTPPTVKILQSSCDGGGH
FPPTIQLLCLVSGYTPGTINITWLEDGQVMDVDLSTASTTQEGELASTQSELTLSQKHWLSDRTYTCQVITYQGHTFEDSTKRC
ADSNPRGVSAYLSRPSFDFLIRKSPITITCLVVDLAPSKGTVNLTWSRASGKPVNHSTRKEEKQRNGTLTVTSTLPVGTDRDWI
EGETYQCRVTHPHLPRALMRSTTKTSGPRAAPEVYAFATPEWPGSRDKRTLACLIQNFMPEDISVQWLHNEVQLPDRHSTTQ
PRKTKSGSFFVFSRLEVTRAWEQKDEFICRAVHEAASPSQTVQRAVSVNPGK

Figure 8B

>Her2 2D3-G/S-C2-3-4 IgE
gaagtgcagtttagtcgagtcaggggtagccttggtgcagccgggggtagcctgcgcctgagctgcgcgcgagcggccttcac
cttcgacgattatgcgatgtcatgggtcagacaggtccctggttaagggccttgatgggtttcctcaataaactggagcggca
cccatacggattatgcggatagcgtgaaaggacgttttaccattagccgcaataacgctaataacactctgtacctacaaatg
aactcgtctaaaatctgaagatactgctgtctactattgtgccaaagaattggcgtgacgcagggaccacatgggtttgagaaatc
cggtagcgcggggccaaggcactcaggtgacagtgagcagcGGCGGCGGCAGCGGCGGCGGCAGCGGCGGCGGCAGCgtcgaca
acaaaaaccttcagcgtctgtctccagggacttcaccccgccaccgtgaagatcttacagtcgtcctgcgacggcggcgggcac
ttcccccgaccatccagctcctgtgcctcgtctctgggtacaccccgaggactatcaacatcacctggctggaggacgggca
ggtcatggacgtggacttgctccaccgcctctaccacgcaggagggtgagctggcctccacacaaagcgagctcacctcagcc
agaagcactggctgtcagaccgcacctacacctgccagggtcacctatcaaggtcacacctttgaggacagcaccagaagtg
gcagattccaacccgagaggggtgagcgcctacctaagccggcccagccggttcgacctgttcacccgaagtcgcccacgat
cacctgtctggtggtagcctggcaccagcaagggaacgtgaacctgacctggtcccgggccagtggggaagcctgtgaacc
actccaccagaaaaggaggagaagcagcgcgaatggcacgttaaccgtcacgtccacctgccggtgggcaaccgagactggatc
gagggggagacctaccagtgccagggtagcccaacccccacctgccagggccctcatgcggtccacgaccaagaccagcggccc
gcgtgctgccccggaagtctatgcgtttgogacgcggagtgccggggagccgggacaagcgcacccctgcctgctgatcc
agaacttcatgcctgaggacatctcgtgtagtggtgcacaacgaggtgcagctcccgagcggccggcacagcagcagcag
ccccgcaagaccaagggtccggctctctcgtcttcagccgcttgaggtgaccagggccgaatgggagcagaaagatgagtt
catctgcggtgcagtcacatgaggcagcagccctccacagaccgtccagcagcgggtgtctgtaaatcccggtaaatga

Figure 9A

>Her2 47D5-G/S-2D3-G/S-C2-3-4 IgE
KVQLVESGGGLVQPGGSLRLSCAASGSIQGFNDMAWYRQAPGKQRELVALISRVGVTSSADSVKGRFTISRVAKD
TVYLLQMNSLKPEDTAVYYCYMDQRLDGSTLAYWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGG
GGGGSEVQLVESGGSLVQPGGSLRLSCAASGFTFDDYAMSWVRQVPGKGLEWVSSINWSGTHTDYADSVKGRFTI
SRNNANNTLYLQMNSLKSIEDTAVYYCAKNWRDAGTTWFEKSGSAGQGTQVTVSSGGGSGGGGSGGGSVDNKTFVS
CSRDFTPPTVKILQSSCDGGGHFPPTIQLLCLVSGYTPGTINITWLEDGQVMDVDLSTASTQEGLASTQSELTLSQK
HWLSDRTYTCQVTYQGHTFEDSTKKCADSNPRGVSAYLSPSPFDLFIRKSPITITCLVVDLAPSKGTNLTWSRASG
KPVNHSTRKEEKQRNGTLTVTSTLPVGTDRDIEGETYQCRVTHPHLPRALMRSTTKTSGPRAAPEVYAFATPEWPG
SRDKRTLACLIQNFMPEDISVQWLHNEVQLPDARHSTTQPRKTKGSGFFVFSRLEVTRAWEQKDEFICRAVHEAAS
PSQTVQRAVSVNPGK

Figure 9B

>Her2 47D5-G/S-2D3-G/S-C2-3-4 IgE
aaggtgcagctgggtgagctctgggggaggccttggtgcagcctggggggtctctgagactctcctgtgcagcctctggaagcat
cttcgggtttcaatgacatggcctggtaaccgccaggctccagggaagcagcgagtggtgcgactaattagtagggttggtg
tcacaagttctgcagactccgtgaaggccgattcaccatctccagagtcaacgccaaaggacacgggtgtatctgcaaatgaac
agcctgaaacctgaggatacggccgtctattattgttatatggatcagcgactcgacggtagtagtacttttagcgtactggggcca
ggggacccagggtcaccgtatcgagtgggggcgggggaagtggcgaggtgggtccgggtggcgaggcagcgggtggaggaggtg
gtggcggtggcggttagtgggcggtggcggcagtgaggcgaggatccgaagtgcagttagtcgagtcagggggttagcttggtg
cagccggggggttagcctgcgcctgagctgcgcgcgagcggtctcacttcgacgattatgcgatgtcatgggtcagacaggt
ccctggtaaaaggccttgatgggtttcctcaataaaactggagcggcaccatacggattatgcggatagcgtgaaaggacgtt
ttaccattagccgcaataacgctaataaactctgtacctacaaatgaactcgtcacaatctgaagatactgctgtctactat
tgtgccaagaattggcgtgacgcagggaccacatgggttgagaaatccggtagcgcgggccaaggcactcaggtgacagttag
cagcGGCGGCGGCAGCGGCGGCGGCAGCGGCGGCGGCAGCGtcgacacaaaaccttcagcgtctgtccagggtactcacc
cgccacccgtgaagatttacagtcgtcctgcgacggcgggcgggcacttcccccgaccatccagctcctgtgcctcgtctct
gggtacaccccagggaactatcaacatcacctggctggaggacgggcaggtcatggacgtggacttgctccaccgctctaccac
gcaggaggggtgagctggcctccacacaaaagcgagctcacctcagccagaagcactggctgtcagaccgcaacctacacctgcc
aggtcacctatcaagggtcacacctttgaggacagcaccaagaagtgtgcagattccaacccgagaggggtgagcgctaccta
agccggccagcccggttcgacctgttcacccgaagtgcgccacgatcacctgtctggtgggtggacctggcaccacagcaagg
gacctggaacctgacctgggtcccgggccagtgaggaaagcctgtgaaccactccaccagaaaggaggagaagcagcgcaatggca
cgttaacccgtcacgtccacacctgccggtgggcacccgagactggatcgagggggagacctaccagtcaggggtgacccacccc
cacctgccagggccctcatgcggtccacgaccaagaccagcgggcccgctgctgccccggaagtctatgcgtttgcgacgcc
ggagtggccggggagccgggacaaagcgacccctgcctgctgatccagaacttcacgctgaggacatctcgggtgcagtggtg
tgcaaacgaggtgcagctcccgacgcccggcacagcacgacgagccccgcaagaccaagggtccggctctctcgtctctc
agccgcctggaggtgaccagggccgaatgggagcagaaagatgagttcatctgcctgcagtcctagggcagcgagccctc
acagaccgtccagcgagcggtgtctgtaaatcccggtaaatga

Figure 10A

>Her2 2D3-G/S-47D5-G/S-C2-3-4 IgE
EVQLVESGGSLVQPGGSLRLSCAASGFTFDDYAMSWVRQVPGKGLEWVSSINWSGTHTDYADSVKGRFTISRNNANNTLYLQM
NSLKSEDTAVYYCAKNWRDAGTTWFEKSGSAGQGTQVTVSSGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVES
GGGLVQPGGSLRLSCAASGSIFGFNDMAWYRQAPGKQRELVALISRVGVTSSADSVKGRFTISRNVAKDTVYLQMNSLKPEDT
AVYYCYMDQRLDGSTLAYWQGTQVTVSSGGGSGGGGSGGGGSDNKTFSVCSRDFTPPTVKILQSSCDGGGHFPPTIQLLCLVS
GYTPGTINITWLEDGQVMDVDLSTASTTQEGELASTQSELTLSQKHWLSDRTYTCQVTVYQGHTFEDSTKKCADSNPRGV SAYL
SRPSPFDLFIRKSPITITCLVVDLAPSKGTVNLTWSRASGKPVNHSTRKEEKQRNGTLTVTSTLPVGRDWDIEGETYQCRVTHP
HLPRALMRSTTKTSGPRAAPEVYAFATPEWPGSRDKRTLACLIQNFMPEDISVQWLHNEVQLPDARHSTTQPRKTRGSGFFVF
SRLEVTRAWEQKDEFICRAVHEAASPSQTVQRAVSVNPGK

Figure 10B

>Her2 2D3-G/S-47D5-G/S-C2-3-4 IgE
gaggtgcagctggtgaggtctgggggtccttgggtgcagcctgggggtctctgagactctcctgtgcagcctctggcttcac
ttttgatgattatgccatgagctgggtccgacaggttcagggaagggttgagtggttttcattctattaattggtctggta
ctcacacagactatgcagactccgtgaagggccgattcaccatctccagaaacaacgccaataaacacgctgtatctacaaatg
aacagctctgaaatctgaggacacggcctgtattactgtgcaaaaaactggagagacgcaggtactacctgggttcgaaaagtc
cggctccgcgggccaggggacccaggtcaccgtatcagagtggggcgggggaagtggcggaggtgggtccgggtggcggaggca
gcggtggaggaggtagtggtgggtggcggtagtggtggcggtggcgaggtggaggtccgaggtgcagctggtggaggtct
gggggaggcttggtgcagcctgggggtctctgagactctcctgtgcagcctctggaagcatcttcgggtttcaatgacatggc
ctggtaccgcccaggctccagggaagcagcgcgagttggtgcgactaattagtagggttggtgtcacaagttctgcagactccg
tgaagggccgattcaccatctccagagtcaacgccaaggacacgggtgtatctgcaaatgaacagcctgaaacctgaggatagc
gccgtctattattgttatatggatcagcgactcgacggtagtacttttagcgtactggggccaggggacccaggtcaccgtctc
ctcaGGGGCGGGCAGCGGGCGGGCAGCGGGCGGGCAGCGctcgacaacaaaaccttcagcgtctgctccagggtaccc
cgccacccgtgaagatcttacagtcgtcctgcgacggcgggcgggcacttccccccgaccatccagctcctgtgcctcgtctc
gggtacaccccagggtactatcaacatcacctggctggaggacgggcaggtcatggcgtggacttgccacccgctctacac
gcaggaggggtgagctggcctccacacaaaagcagctcaacctcagccagaagcactggctgtcagacccgacctacacctgcc
agggtcacctatcaagggtcacacctttgaggacagcaccaagaagtgtgcagattccaacccgagaggggtgagcgctaccta
agccggcccagcccggttcgacctgttcacccgaagtcgcccacgatcacctgtctggtgggtggacctggcaccagcaagg
gacctggaacctgacctgggtcccgggccagtggaagcctgtgaaccactccaccagaaaggaggagaagcagcgcaatggca
cgttaacctgcagctccacctgcccgtgggcaccccgagactggatcgagggggagacctaccagtgagggtgacccacccc
cacctgcccaggggccctcatgctggtccacgaccaagaccagcgggcccgctgctgccccggaagtctatgcgtttgagcgcgc
ggagtggccggggagccgggacaaagcgacccctcgctgctgatccagaacttcagctgaggaacatctcggtgcagtggc
tgcacaacgaggtgcagctcccggaacgcccggcacagcacgacgcagccccgcaagaccaagggtccgggtctctcgtcttc
agccgcctggaggtgaccagggccgaatgggagcagaaagatgagttcatctgccgtgcagtcctgagggcagcgagccctc
acagaccgtccagcgagcggtgtctgtaaatcccggtaaatga

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/066366

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07K16/32

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/008548 A (UNIV ERASMUS MEDICAL CT [NL]; KINGDON CRAIG R [GB]; GROSVELD FRANKLIN) 26 January 2006 (2006-01-26) pages 7-8, 30-35 figures 1, 2 claim 7	1-49
X	WO 2007/118670 A (ABLYNX NV [BE]; KOLKMAN JOOST ALEXANDER [BE]) 25 October 2007 (2007-10-25) pages 54,56-58	1-49
X	WO 2006/040153 A (ABLYNX NV [BE]; LAUWEREYS MARC [BE]; VAN LEUVEN FRED [BE]; VAN DER AUW) 20 April 2006 (2006-04-20) pages 117-120	1-49
	----- -/--	



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

2 April 2009

Date of mailing of the international search report

14/04/2009

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Bernhardt, Wiebke

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2008/066366

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KARAGIANNIS SOPHIA N ET AL: "IgE-antibody-dependent immunotherapy of solid tumors: cytotoxic and phagocytic mechanisms of eradication of ovarian cancer cells" JOURNAL OF IMMUNOLOGY, AMERICAN ASSOCIATION OF IMMUNOLOGISTS, US, vol. 179, no. 5, 1 September 2007 (2007-09-01), pages 2832-2843, XP009113408 ISSN: 0022-1767 abstract page 2832, column 2833 -----	1-8, 10-13, 15-17, 19, 23-26, 28-30, 32, 36-44, 46-49
A	GOULD HANNAH J ET AL: "Comparison of IgE and IgG antibody-dependent cytotoxicity in vitro and in a SCID mouse xenograft model of ovarian carcinoma" EUROPEAN JOURNAL OF IMMUNOLOGY, vol. 29, no. 11, November 1999 (1999-11), pages 3527-3537, XP009113415 ISSN: 0014-2980 page 3533, column 3534 -----	1-8, 10-13, 15-17, 19, 23-26, 28-30, 32, 36-44, 46-49
A	RIEMER ANGELIKA B ET AL: "Active induction of tumor-specific IgE antibodies by oral mimotope vaccination" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD.; US, vol. 67, no. 7, 1 April 2007 (2007-04-01), pages 3406-3411, XP009113409 ISSN: 0008-5472 the whole document in particular pg. 3406; references 17-21 -----	1-49
A	ELS CONRATH K ET AL: "Camel single-domain antibodies as modular building units in bispecific and bivalent antibody constructs" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BIRMINGHAM,; US, vol. 276, no. 10, 9 March 2001 (2001-03-09), pages 7346-7350, XP002248402 ISSN: 0021-9258 abstract; figure 1 -----	15-18, 28-31
	----- -/--	

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2008/066366

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WARD E S ET AL: "BINDING ACTIVITIES OF A REPERTOIRE OF SINGLE IMMUNOGLOBULIN VARIABLE DOMAINS SECRETED FROM ESCHERICHIA COLI" NATURE, NATURE PUBLISHING GROUP, LONDON, UK, vol. 341, no. 6242, 12 October 1989 (1989-10-12), pages 544-546, XP000086104 ISSN: 0028-0836 abstract -----	1-49
A	MUYLDERMANS S: "SINGLE DOMAIN CAMEL ANTIBODIES: CURRENT STATUS" JOURNAL OF BIOTECHNOLOGY, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 74, no. 4, 1 January 2001 (2001-01-01), pages 277-302, XP008019929 ISSN: 0168-1656 the whole document -----	1-49
A	EP 1 498 427 A (UNIV BRUXELLES [BE]) 19 January 2005 (2005-01-19) pages 2-6 -----	1-49
A	HOLT L J ET AL: "Domain antibodies: proteins for therapy" TRENDS IN BIOTECHNOLOGY, ELSEVIER PUBLICATIONS, CAMBRIDGE, GB, vol. 21, no. 11, 1 November 2003 (2003-11-01), pages 484-490, XP004467495 ISSN: 0167-7799 page 485 -----	21,34

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2008/066366

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2006008548	A	26-01-2006	AU 2005263994 A1	26-01-2006
			BR PI0513577 A	06-05-2008
			CA 2580336 A1	26-01-2006
			EP 1776383 A2	25-04-2007
			EP 1978032 A2	08-10-2008
			JP 2008512987 T	01-05-2008
			KR 20070050927 A	16-05-2007
WO 2007118670	A	25-10-2007	AU 2007237501 A1	25-10-2007
			CA 2649009 A1	25-10-2007
			EP 2010568 A1	07-01-2009
WO 2006040153	A	20-04-2006	AU 2005293752 A1	20-04-2006
			CA 2583017 A1	20-04-2006
			EP 1814917 A2	08-08-2007
			JP 2008515446 T	15-05-2008
			KR 20070084170 A	24-08-2007
			US 2008107601 A1	08-05-2008
EP 1498427	A	19-01-2005	EP 1589107 A1	26-10-2005
			EP 1621554 A1	01-02-2006