

5 MULTISPECIFIC ANTI-ALLERGEN ANTIBODIES AND USES THEREOF

The present invention relates to multispecific antibodies binding to peanut allergens, in particular to Ara h 2, Ara h 3, and Ara h 6. The present invention also relates to compositions and kits comprising such multispecific antibodies. In addition, the present invention also
10 relates to the use of such antibodies, compositions and kits, e.g. for preventing or treating peanut allergy.

Allergies are conditions caused by hypersensitivity of the immune system. Allergen encounter results in the production of allergen-binding immunoglobulin E (IgE) antibodies, which are
15 pre-bound on FcεRI receptors on mast cells and basophils, where they trigger the release of inflammatory compounds, such as histamine, leukotriene and lipid mediators.

Peanut allergy is one of the most severe food allergies due to its prevalence, persistency, and potential severity of allergic reaction. Allergic reactions include clinical manifestations from
20 skin, respiratory and gastrointestinal symptoms up to severe and life-threatening reactions, such as systemic anaphylaxis. Peanut allergy is the most common cause of food-induced anaphylaxis.

Up to date, at least sixteen peanut proteins were identified as allergenic. Among these peanut
25 allergens, Ara h 1, Ara h 2, Ara h 3 and Ara h 6 are considered to be major allergens, which means that they trigger an immunological response in more than 50% of the allergic population. In particular, Ara h 2 was reported to be the dominant peanut allergen (Hemmings, Oliver et al. Ara h 2 is the dominant peanut allergen despite similarities with Ara h 6. The Journal of allergy and clinical immunology Vol. 146(3) (2020): 621-630.e5.
30 doi:10.1016/j.jaci.2020.03.026). In addition, Ara h 6 emerged as common and potent peanut

allergen (Blanc, F et al. (2009), Capacity of purified peanut allergens to induce degranulation in a functional in vitro assay: Ara h 2 and Ara h 6 are the most efficient elicitors. Clinical & Experimental Allergy, 39: 1277-1285.). In addition, Ara h 3, which makes up 19% of the total protein in peanut extracts, is classified as a major peanut allergen because it provokes sensitization of patients with this allergy.

Despite its prevalence, for long time there was no cure for peanut allergy other than strict avoidance of peanuts and peanut-containing foods. However, total avoidance can be complicated, in particular if no declaration of ingredients is available. In 2020 peanut oral immunotherapy was approved by the FDA, and so this represents the first potential disease-modifying treatment.

While allergen immunotherapy by repeated exposure to the allergen, also known as desensitization, attempts to reduce allergic sensitivity, it was recently found that it increases rather than decreases the risk of serious allergies (Chu DK, Wood RA, French S, et al. (April 2019). Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. The Lancet. 393 (10187): 2222–2232).

Recently, antibodies against peanut allergens emerged as promising options for treating peanut allergy. For example, WO 2018/234383 and WO 2019/222679 describe various human monoclonal antibodies against peanut allergens.

However, to efficiently target several peanut allergens, in particular the major allergens Ara h 1, Ara h 2, Ara h 3 and Ara h 6, at least two, or even three or four antibodies, each targeting a specific epitope of a peanut allergen, had to be administered in combination. In this respect, multispecific antibody formats would provide the ability to produce single molecules that simultaneously act on several peanut allergens, such as on at least some of the major peanut allergens, without the need to administer a mixture of several, e.g. three or four, distinct single antibodies

Various multispecific antibody formats and methods for obtaining multispecific antibodies are known in the art. For example, building blocks for bispecific and trispecific antibodies are described in Xiufeng Wu, Stephen J. Demarest, Building blocks for bispecific and trispecific

antibodies, *Methods*, Volume 154, 2019, Pages 3-9, ISSN 1046-2023, <https://doi.org/10.1016/j.ymeth.2018.08.010>. Methods for obtaining multispecific antibodies and further multispecific antibody formats are described in Amaral M, Hölper S, Lange C, Jung J, Sjuts H, Weil S, Fischer M, Radoevic K, Rao E. Engineered Technologies and
5 Bioanalysis of multispecific antibody formats. *J Appl Bioanal* 6(1), 26-51 (2020).

Coloma, M., Morrison, S. (Design and production of novel tetravalent bispecific antibodies. *Nat Biotechnol* 15, 159-163 (1997). <https://doi.org/10.1038/nbt0297-159>) describes
10 tetravalent, bispecific homodimer antibodies comprising a human IgG3 constant region having a C-terminal fusion of a single-chain variable fragment (scFv) (see also WO1995009917A1).

A major challenge in the construction of multispecific antibody formats is the stabilization of the fragments of which the multispecific antibody is composed, and, as for IgG4 antibodies,
15 the stabilization of the hinge region to prevent half-antibody formation.

WO2013158577A1 discloses a tetravalent, bispecific homodimer antibody comprising a human IgG4 constant region, including a S228P mutation for hinge stabilization, and a C-terminal genetic fusion of a disulfide stabilized (H44-L100) scFv.
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EP1297142A2 discloses a tetravalent, bispecific homodimer antibody having a dual variable domain (DVA)-IgG architecture (VH1-VH2-CH/VL1-VL2-CL).

EP3365366B1 discloses a trivalent, trispecific heterodimer antibody, wherein one half of the
25 heterodimer is composed of a "normal" IgG antibody, and the other half is a bispecific cross-over dual variable (CODV)-IgG. Ridgway JB, Presta LG, Carter P. ('Knobs-into-holes' engineering of antibody CH3 domains for heavy chain heterodimerization. *Protein Eng.* 1996 Jul; 9(7):617-21. doi: 10.1093/protein/9.7.617) discloses improvement of bispecific IgG heterodimerization by introducing "knob-into-hole" mutations into the antibody's heavy chains.
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In view of the above, it is the object of the present invention to provide potent and stable human-derived multispecific antibody formats against peanut allergens which recognize multiple allergen sites with high affinity. In particular, it is object of the present invention to

provide potent human-derived multispecific antibody formats binding to distinct, non-overlapping epitopes on the major peanut allergens Ara h 2, Ara h3, and Ara h 6. It is also an object of the present invention to provide a composition comprising one or more multispecific antibodies for (use in) treatment or prophylaxis of peanut allergy.

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This object is achieved by means of the subject-matter set out below and in the appended claims.

Although the present invention is described in detail below, it is to be understood that this invention is not limited to the particular methodologies, protocols and reagents described herein as these may vary. It is also to be understood that the terminology used herein is not intended to limit the scope of the present invention which will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art.

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In the following, the elements of the present invention will be described. These elements are listed with specific embodiments, however, it should be understood that they may be combined in any manner and in any number to create additional embodiments. The variously described examples and embodiments should not be construed to limit the present invention to only the explicitly described embodiments. This description should be understood to support and encompass embodiments which combine the explicitly described embodiments with any number of the disclosed elements. Furthermore, any permutations and combinations of all described elements in this application should be considered disclosed by the description of the present application unless the context indicates otherwise.

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Throughout this specification and the claims which follow, unless the context requires otherwise, the term "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated member, integer or step but not the exclusion of any other non-stated member, integer or step. The term "consist of" is a particular embodiment of the term "comprise", wherein any other non-stated member, integer or step is excluded. In the context of the present invention, the term "comprise" encompasses the term "consist of". The term "comprising" thus encompasses "including" as well as "consisting" e.g.,

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a composition "comprising" X may consist exclusively of X or may include something additional e.g., X + Y.

5 The terms "a" and "an" and "the" and similar reference used in the context of describing the invention (especially in the context of the claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were
10 individually recited herein. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the invention.

The word "substantially" does not exclude "completely" e.g., a composition which is "substantially free" from Y may be completely free from Y. Where necessary, the word
15 "substantially" may be omitted from the definition of the invention.

The term "about" in relation to a numerical value x means $x \pm 10\%$, for example, $x \pm 5\%$, or $x \pm 7\%$, or $x \pm 10\%$, or $x \pm 12\%$, or $x \pm 15\%$, or $x \pm 20\%$.

20 The term "disease" as used herein is intended to be generally synonymous, and is used interchangeably with, the terms "disorder" and "condition" (as in medical condition), in that all reflect an abnormal condition of the human or animal body or of one of its parts that impairs normal functioning, is typically manifested by distinguishing signs and symptoms, and causes the human or animal to have a reduced duration or quality of life.

25 As used herein, reference to "treatment" of a subject or patient is intended to include prevention, prophylaxis, attenuation, amelioration and therapy. The terms "subject" or "patient" are used interchangeably herein to mean all mammals including humans. Examples of subjects include humans, cows, dogs, cats, horses, goats, sheep, pigs, and rabbits. In some
30 embodiments, the subject or patient is a human.

Doses are often expressed in relation to the bodyweight. Thus, a dose which is expressed as [g, mg, or other unit]/kg (or g, mg etc.) usually refers to [g, mg, or other unit] “per kg (or g, mg etc.) bodyweight”, even if the term “bodyweight” is not explicitly mentioned.

- 5 The term “binding” and similar reference usually means “specifically binding”, which does not encompass non-specific sticking. In particular, specific binding of an antibody means that the antibody recognizes its target antigen and binds its target with greater affinity (or at lower antibody concentrations, e.g. EC₅₀) than it does to a structurally different antigen and/or to an antigen with a modified or mutated sequence. Thereby, a “greater” affinity may be at least
10 2fold, 3fold, 4fold, 5fold, 10fold, 15fold, 20fold, 25fold, 50fold, 75fold, 100fold 150fold, 200fold, 500fold, 750fold, 1,000fold, 1,500fold, 2,000fold, 5,000fold, 7,500fold, 10,000fold or even higher affinity as compared to the binding to a control antigen. In some instances, antibody-binding to the control antigen may be undetectable (below detection threshold), while antibody-binding to the specific antigen may be well detected/determined.

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- As used herein, the term “antibody” encompasses various forms of antibodies including, without being limited to, whole antibodies, antibody fragments (such as antigen binding fragments), human antibodies, chimeric antibodies, humanized antibodies, recombinant antibodies and genetically engineered antibodies (e.g., variant or mutant antibodies) as long
20 as the characteristic properties according to the invention are retained. In some embodiments, the antibody is a human antibody. In some embodiments, the antibody is a monoclonal antibody. For example, the antibody may be a human monoclonal antibody.

- As described above, the term “antibody” generally also includes antibody fragments.
25 Fragments of the antibodies may retain the antigen-binding activity of the antibodies. Such fragments are referred to as “antigen-binding fragments”. Antigen-binding fragments include, but are not limited to, single chain antibodies, Fab, Fab', F(ab')₂, Fv or scFv. Fragments of the antibodies can be obtained from the antibodies by methods that include digestion with enzymes, such as pepsin or papain, and/or by cleavage of disulfide bonds by chemical
30 reduction. Alternatively, fragments of the antibodies can be obtained by recombinant means, for example by cloning and expressing a part (fragment) of the sequences of the heavy and/or light chain. The invention also encompasses single-chain Fv fragments (scFv) derived from the variable regions of the heavy and light chains of an antibody of the invention. For

example, the invention includes a scFv comprising the CDRs from an antibody of the invention. Also included are heavy or light chain monomers and dimers, single domain heavy chain antibodies, single domain light chain antibodies, as well as single chain antibodies, e.g., single chain Fv in which the heavy and light chain variable domains are joined by a peptide linker. Antibody fragments of the invention may be contained in a variety of structures known to the person skilled in the art. Although the specification, including the claims, may, in some places, refer explicitly to antigen binding fragment(s), antibody fragment(s), variant(s) and/or derivative(s) of antibodies, it is understood that the term "antibody" includes all categories of antibodies, namely, antigen binding fragment(s), antibody fragment(s), variant(s) and derivative(s) of antibodies.

Human antibodies are well-known in the state of the art (van Dijk, M. A., and van de Winkel, J. G., *Curr. Opin. Chem. Biol.* 5 (2001) 368-374). Human antibodies can also be produced in transgenic animals (e.g., mice or chicken) that are capable, upon immunization, of producing a full repertoire or a selection of human antibodies in the absence of endogenous immunoglobulin production. Transfer of the human germ-line immunoglobulin gene array in such germ-line mutant mice will result in the production of human antibodies upon antigen challenge (see, e.g., Jakobovits, A., et al., *Proc. Natl. Acad. Sci. USA* 90 (1993) 2551-2555; Jakobovits, A., et al., *Nature* 362 (1993) 255-258; Bruggemann, M., et al., *Year Immunol.* 7 (1993) 3340). Human antibodies can also be produced in phage display libraries (Hoogenboom, H. R., and Winter, G., *J. Mol. Biol.* 227 (1992) 381-388; Marks, J. D., et al., *J. Mol. Biol.* 222 (1991) 581-597). The techniques of Cole et al. and Boerner et al. are also available for the preparation of human monoclonal antibodies (Cole et al., *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, p. 77 (1985); and Boerner, P., et al., *J. Immunol.* 147 (1991) 86-95). As used herein, the expression "human antibodies" includes non-naturally occurring sequence variants of human antibodies, which are usually obtained by introducing one or more mutations in the (naturally occurring) human antibodies. Such mutations include one or more mutations in a CDR or in a framework region, as well as Fc modifications (e.g., as known in the art for specific functionalities).

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As used herein, the term "variable region" (variable region of a light chain (V_L), variable region of a heavy chain (V_H)) denotes each of the pair of light and heavy chains which is involved directly in binding the antibody to the antigen.

Antibodies of the invention can be of any isotype (e.g., IgA, IgG, IgM i.e. an α , γ or μ heavy chain). Preferably, the antibody is of the IgG type or the IgA type. Within the IgG isotype, antibodies may be IgG1, IgG2, IgG3 or IgG4 subclass, preferably IgG1 or IgG4. Antibodies
5 of the invention may have a κ or a λ light chain.

Antibodies of the invention are "multispecific". As used herein, the term "multispecific" refers to the ability to bind to at least two different epitopes, e.g. on different antigens or on the same antigen. While conventional monospecific IgG-type antibodies usually have two
10 identical epitope binding sites (paratopes) and can, thus, only bind to identical epitopes (but not to different epitopes), a multispecific antibody, in contrast, has at least two different types of paratopes (antigen-binding sites) and can, thus, bind to at least two different epitopes. As used herein, "paratope" refers to an antigen-binding site (or epitope-binding site) of the antibody. Moreover, a single "specificity" may refer to one, two, three or more identical
15 paratopes in a single antibody (the actual number of paratopes in one single antibody molecule is referred to as "valency"). For example, a single native IgG antibody is monospecific and bivalent, since it has two identical paratopes. Accordingly, a multispecific antibody comprises at least two (different) paratopes. Thus, the term "multispecific antibodies" refers to antibodies having more than one paratope and the ability to bind to two
20 or more different epitopes.

As used herein, terms like "bispecific", "trispecific", "tetraspecific" etc. refer to the number of different epitopes to which the antibody can bind to. For example, a "bispecific" antibody has exactly two different specificities (two different antigen-binding sites, wherein each of the
25 two different antigen-binding sites may independently occur once or more than once, e.g. twice). For example, a "trispecific" antibody has exactly three different specificities (three different antigen-binding sites, wherein each of the three different antigen-binding sites may independently occur once or more than once, e.g. twice). For example, a "tetraspecific" antibody has exactly four different specificities (four different antigen-binding sites, wherein
30 each of the four different antigen-binding sites may independently occur once or more than once, e.g. twice).

For example, the multispecific antibody according to the present invention may be bispecific. As outlined above, a "bispecific" antibody has exactly two different specificities, i.e. two different antigen-binding sites, wherein each of the two different antigen-binding sites may independently occur more than once, e.g. twice.

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In another example, the multispecific antibody according to the present invention may be trispecific. As described above, a "trispecific" antibody has exactly three different specificities, i.e. three different antigen-binding sites, wherein each of the three different antigen-binding sites may independently occur once or more than once, e.g. twice.

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For example, the multispecific antibody of the invention may comprise three or more paratopes, wherein one or more paratopes may be identical so that all paratopes of the antibody belong to at least two different types of paratopes and, hence, the antibody has at least two specificities.

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In a particular embodiment, the multispecific antibody according to the present invention comprises four paratopes, wherein each two paratopes have the same specificity, and, thus, the antibody or fragment thereof is bispecific and tetravalent (two identical paratopes for each of the two specificities).

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In another embodiment, the multispecific antibody according to the present invention comprises four paratopes, wherein two paratopes have the same specificity, and the third and fourth paratopes each have specificities different from the two identical paratopes, and, thus, the antibody or fragment thereof is trispecific and tetravalent (four paratopes for three specificities).

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In another embodiment, the multispecific antibody according to the present invention comprises three paratopes, wherein each paratope has a different specificity, and, thus, the antibody or fragment thereof is trispecific and trivalent (three distinct paratopes for each of the three specificities).

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Multispecific antibodies according to the present invention may be provided in purified form. Typically, the antibody will be present in a composition that is substantially free of other

polypeptides e.g., where less than 90% (by weight), usually less than 60% and more usually less than 50% of the composition is made up of other polypeptides.

5 Multispecific antibodies according to the present invention may be immunogenic in human and/or in non-human (or heterologous) hosts e.g., in mice. For example, the antibodies may have an idiotope that is immunogenic in non-human hosts, but not in a human host. Multispecific antibodies of the invention for human use include those that cannot be easily isolated from hosts such as mice, goats, rabbits, rats, non-primate mammals, etc. and cannot generally be obtained by humanization or from xeno-mice.

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As used herein, the term "antigen" refers to any structural substance which serves as a target for the receptors of an adaptive immune response, in particular as a target for antibodies, T cell receptors, and/or B cell receptors. An "epitope", also known as "antigenic determinant", is the part (or fragment) of an antigen that is recognized by the immune system, in particular by antibodies, T cell receptors, and/or B cell receptors. Thus, one antigen has at least one epitope, i.e. a single antigen has one or more epitopes. An antigen may be (i) a peptide, a polypeptide, or a protein, (ii) a polysaccharide, (iii) a lipid, (iv) a lipoprotein or a lipopeptide, (v) a glycolipid, (vi) a nucleic acid, or (vii) a small molecule drug or a toxin. Thus, an antigen may be a peptide, a protein, a polysaccharide, a lipid, a combination thereof including lipoproteins and glycolipids, a nucleic acid (e.g. DNA, siRNA, shRNA, antisense oligonucleotides, decoy DNA, plasmid), or a small molecule drug (e.g. cyclosporine A, paclitaxel, doxorubicin, methotrexate, 5-aminolevulinic acid), or any combination thereof. Preferably, the antigen is selected from (i) a peptide, a polypeptide, or a protein, (ii) a polysaccharide, (iii) a lipid, (iv) a lipoprotein or a lipopeptide and (v) a glycolipid; more preferably, the antigen is a peptide, a polypeptide, or a protein.

As used herein, the term "mutation" relates to a change in the nucleic acid sequence and/or in the amino acid sequence in comparison to a reference sequence, e.g. a corresponding genomic sequence. A mutation, e.g. in comparison to a genomic sequence, may be, for example, a (naturally occurring) somatic mutation, a spontaneous mutation, an induced mutation, e.g. induced by enzymes, chemicals or radiation, or a mutation obtained by site-directed mutagenesis (molecular biology methods for making specific and intentional changes in the nucleic acid sequence and/or in the amino acid sequence). Thus, the terms

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“mutation” or “mutating” shall be understood to also include physically making a mutation, e.g. in a nucleic acid sequence or in an amino acid sequence. A mutation includes substitution, deletion and insertion of one or more nucleotides or amino acids as well as inversion of several successive nucleotides or amino acids. To achieve a mutation in an amino acid sequence, a mutation may be introduced into the nucleotide sequence encoding said amino acid sequence in order to express a (recombinant) mutated polypeptide. A mutation may be achieved e.g., by altering, e.g., by site-directed mutagenesis, a codon of a nucleic acid molecule encoding one amino acid to result in a codon encoding a different amino acid, or by synthesizing a sequence variant, e.g., by knowing the nucleotide sequence of a nucleic acid molecule encoding a polypeptide and by designing the synthesis of a nucleic acid molecule comprising a nucleotide sequence encoding a variant of the polypeptide without the need for mutating one or more nucleotides of a nucleic acid molecule.

As used herein (i.e. throughout the present specification), the term “sequence variant” refers to any alteration in comparison to a reference sequence. The term “sequence variant” includes nucleotide sequence variants and amino acid sequence variants. Preferably, a reference sequence is any of the sequences listed in the “Table of Sequences and SEQ ID Numbers” (Sequence listing), i.e. SEQ ID NO: 1 to SEQ ID NO: 79. In particular, a sequence variant shares (over the whole length of the sequence) at least 70% or at least 75%, preferably at least 80% or at least 85%, more preferably at least 90% or at least 93%, even more preferably at least 95% or at least 96%, still more preferably at least 97% or at least 98%, particularly preferably at least 99% sequence identity with its reference sequence. In some embodiments, the sequence variant shares at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity. Thereby, the higher the %-identity of a sequence variant, the more it is preferred. For example, a sequence variant having at least 84% sequence identity with a reference sequence is more preferred than a sequence variant having at least 75% sequence identity, but less than 84% sequence identity, with a reference sequence. In some embodiments, the sequence variant maintains the (biological) function of the reference sequence. For example, sequence variants relating to multispecific antibodies of the invention

preferably maintain the specific binding to the peanut allergen, in particular Ara h 2, Ara h 3 and Ara h 6.

Sequence identity may be calculated as described below. Usually a sequence variant may
5 preserve the specific function of the reference sequence. In some embodiments, an amino acid sequence variant has an altered sequence in which one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) of the amino acids in the reference sequence is deleted or substituted, or one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) amino acids are inserted into or added to the sequence of the reference amino acid sequence. As a result of the alterations, the amino
10 acid sequence variant has an amino acid sequence which is at least 70% or at least 75%, preferably at least 80% or at least 85%, more preferably at least 90% or at least 93%, even more preferably at least 95% or at least 96%, still more preferably at least 97% or at least 98%, particularly preferably at least 99% identical to the reference sequence. For example, variant sequences which are at least 90% identical have no more than 10 alterations, i.e., any
15 combination of deletions, insertions or substitutions, per 100 amino acids of the reference sequence. The same, of course, also applies similarly to nucleic acid sequences.

The "% identity" of the sequence variant is usually determined with respect to the reference sequence. It is usually calculated with regard to the full length of the reference sequence (i.e.
20 the sequence recited in the application). Percentage identity, as referred to herein, can be determined, for example, by methods known in the art, such as BLAST using the default parameters specified by the NCBI (the National Center for Biotechnology Information; <http://www.ncbi.nlm.nih.gov/>) [Blosum 62 matrix; gap open penalty=11 and gap extension penalty=1].

25 In general, while it is possible to have non-conservative amino acid substitutions, the substitutions are preferably conservative amino acid substitutions, wherein the substituted amino acid has similar structural or chemical properties with the corresponding amino acid in the reference sequence. By way of example, conservative amino acid substitutions involve
30 substitution of one aliphatic or hydrophobic amino acids, e.g. alanine, valine, leucine and isoleucine, with another; substitution of one hydroxyl-containing amino acid, e.g. serine and threonine, with another; substitution of one acidic residue, e.g. glutamic acid or aspartic acid, with another; replacement of one amide-containing residue, e.g. asparagine and glutamine,

with another; replacement of one aromatic residue, e.g. phenylalanine and tyrosine, with another; replacement of one basic residue, e.g. lysine, arginine and histidine, with another; and replacement of one small amino acid, e.g., alanine, serine, threonine, cysteine, and glycine, with another.

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Several documents are cited throughout the text of this specification. Each of the documents cited herein (including all patents, patent applications, scientific publications, manufacturer's specifications, instructions, etc.), whether supra or infra, are hereby incorporated by reference in their entirety. Nothing herein is to be construed as an admission that the invention is not
10 entitled to antedate such disclosure by virtue of prior invention.

It is to be understood that this invention is not limited to the particular methodology, protocols and reagents described herein as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is
15 not intended to limit the scope of the present invention which will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art.

Parental Anti-Peanut Antibodies

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In general, an antibody, or an antigen-binding fragment thereof, comprises (at least) three complementarity determining regions (CDRs) on a heavy chain and (at least) three CDRs on a light chain. In general, complementarity determining regions (CDRs) are the hypervariable regions present in heavy chain variable domains and light chain variable domains. Typically,
25 the CDRs of a heavy chain and the connected light chain of an antibody together form the antigen receptor. Usually, the three CDRs (CDR1, CDR2, and CDR3) are arranged non-consecutively in the variable domain. Since antigen receptors are typically composed of two variable domains (on two different polypeptide chains, i.e. heavy and light chain: heavy chain variable region (VH) and light chain variable region (VL)), there are typically six CDRs for
30 each antigen receptor (heavy chain: CDRH1, CDRH2, and CDRH3; light chain: CDRL1, CDRL2, and CDRL3). For example, a classical IgG antibody molecule usually has two antigen receptors and therefore contains twelve CDRs. The CDRs on the heavy and/or light chain may be separated by framework regions, whereby a framework region (FR) is a region in the

variable domain which is less “variable” than the CDR. For example, a variable region (or each variable region, respectively) may be composed of four framework regions, separated by three CDR’s.

- 5 The present inventors identified sequences of the heavy chains and light chains of distinct anti-peanut antibodies (17H9, 7G6, 15E3, and 2F8) each comprising three different CDRs on the heavy chain and three different CDRs on the light chain.

10 The “parental” antibodies, or the antigen-binding fragments thereof, comprise the combination of six CDR sequences shown in Table 1.

Antibody	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
17H9	1	2	3	4	5	6
7G6	7	8	9	10	11	12
15E3	13	14	15	16	17	18
2F8	19	20	21	22	23	24

Table 1: SEQ ID NOs for CDR sequences of antibodies 17H9, 7G6, 15E3, and 2F8

15 The amino acid sequences of the CDR1 of the heavy chain (CDRH1), the CDR2 of the heavy chain (CDRH2), the CDR3 of the heavy chain (CDRH3), the CDR1 of the light chain (CDRL1), the CDR2 of the light chain (CDRL2) and the CDR3 of the light chain (CDRL3) of parental antibodies 17H9, 15E3, 2F8 and 7G6 are shown in the “Table of Sequences” below (SEQ ID Nos: 1-24).

- 20 The parental antibodies, or an antigen-binding fragment thereof, specifically bind to the peanut allergen Ara h 2 (Arachis hypogaea allergen 2). Ara h 2 is a major peanut allergen, which is recognized by serum IgE from more than 90% of patients with peanut hypersensitivity. Ara h 2 is a 2S albumin storage protein of approximately 17.5 kDa. Two Ara h 2 isoforms are described, namely, Ara h 2.0101 (SEQ ID NO: 76) and Ara h 2.0201 (SEQ ID NO: 77) with Ara h 2.0201 containing twelve additional amino acids (Hales, Belinda et al. (2004). Isoforms of the Major Peanut Allergen Ara h 2: IgE Binding in Children with Peanut Allergy. International archives of allergy and immunology. 135. 101-7. 10.1159/000080652).
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The parental antibodies, or an antigen-binding fragment thereof, which specifically bind to Ara h 2, further binds specifically to Ara h 3 (Arachis hypogaea allergen 3; also referred to as "Ara h 3.0101"; SEQ ID NO: 78) or to Ara h 6 (Arachis hypogaea allergen 6; also referred to as "Ara h 6.0101"; SEQ ID NO: 79). Ara h 3 and Ara h 6 are further major peanut allergens.

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The peanut allergens, in particular Ara h 2, Ara h 3 and/or Ara h 6, may be of peanut origin, recombinantly expressed or a synthetic peanut peptide.

Multispecific antibodies of the present invention

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Starting from the CDRs identified for the "parental antibodies" (17H9, 7G6, 15E4, 2F8) described above, the present inventors developed new multispecific antibody formats which each (specifically) bind to several major peanut allergens, in particular to Ara h 2 (Arachis hypogaea allergen 2), Ara h 3 (Arachis hypogaea allergen 3), and Ara h 6 (Arachis hypogaea allergen 6).

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Accordingly, the multispecific antibody of the present invention binds in particular to a polypeptide or protein having an amino acid sequence according to SEQ ID NO: 76 and/or 77, and also binds to a polypeptide or protein having an amino acid sequence according to SEQ ID NO: 78, and further binds to a polypeptide or protein having an amino acid sequence according to SEQ ID NO: 79.

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Standard methods to assess binding of the antibody according to the present invention are known to those skilled in the art and include, for example, ELISA (enzyme-linked immunosorbent assay). Thereby, the relative affinities of antibody binding may be determined by measuring the concentration of the antibody (EC_{50}) required to achieve 50% maximal binding at saturation. A specific example of an ELISA, which may be used to assess binding of an antibody, is described in the example section of this specification.

25

In general, the multispecific antibody of the invention may be capable of reducing, inhibiting or neutralizing allergen-mediated biological activity. In particular, the multispecific antibodies may be capable of reducing or inhibiting the binding of an IgE antibody to a peanut allergen, in particular Ara h 2, Ara h 3 and Ara h 6, as described herein.

30

Thus, the multispecific antibodies according to the invention may decrease or inhibit the activation of the mast cells or basophils and therefore decrease or prevent the release of mediators (e.g. histamine, lipid mediators, leukotriene). Thereby, the multispecific antibodies described herein may inhibit allergy symptoms that would usually occur in the patient after contact with the allergen (e.g. contact with the eyes, nose or mouth or food uptake). Accordingly, the multispecific antibodies described herein may be capable of reducing, inhibiting or neutralizing allergen-mediated biological activity. In particular, the multispecific antibodies may be capable of reducing or inhibiting the binding of an IgE antibody to a peanut allergen, in particular Ara h 2, Ara h 3 and Ara h 6.

Therefore, in a first aspect, the present invention provides a multispecific antibody which binds specifically to distinct (non-overlapping) epitopes of Ara h 2, Ara h 3 and Ara h 6. The multispecific antibody of the present invention comprises two heavy chains and two light chains each comprising at least one constant domain and at least one variable domain (VL/VH). The multispecific antibody comprises at least three paratopes each comprising three heavy chain CDRs (CDRH1-3) and three light chain CDRs (CDRL1-3), wherein

- at least one paratope (a) is formed by the VH1 of a first heavy chain and by the VL1 of a first light chain,
- at least one paratope (b) is formed by the VH2 of a second heavy chain and by the VL2 of a second light chain, and
- at least one paratope (c) is formed by a single chain variable fragment (scFv), the scFv being covalently linked to the constant domain of the at least one heavy chain, and/or
- at least one paratope (d) is formed by variable domains VHx and/or VLx, the variable domains VHx and/or VLx being covalently linked to at least one of variable domains VH1/VL1 and/or VH2/VL2, thereby forming at least one dual variable domain (DVD).

Preferably, the "paratope-forming domain assembly Vx" is formed by a heavy chain variable domain VHx and a light chain variable domain VLx. VHx may be covalently linked to VH1 of the first heavy chain and/or VH2 of the second heavy chain; and VLx may be covalently linked to VL1 of the first light chain and/or VL2 of the second light chain.

In some embodiments, the multispecific antibody of the present invention comprising paratopes (a) and (b) additionally comprises both, at least one paratope (c) and at least one paratope (d). Thus, in a particular embodiment, the multispecific antibody of the present invention comprises at least one scFv as well as at least one DVD.

In some embodiments of the multispecific antibody according to the present invention, paratope (a) and paratope (b) have different specificities. In other embodiments of the multispecific antibody according to the present invention, paratope (a) and paratope (b) have the same specificity.

In some embodiments of the multispecific antibody of the present invention, the multispecific antibody comprises two paratopes (c1, c2), wherein a first scFv1 forming the paratope (c1) is covalently linked to the constant domain of the first heavy chain, and a second scFv 2 forming the paratope (c2) is covalently linked to the constant domain of the second heavy chain wherein the first paratope (c1), and the second paratope (c2) may have the same specificity or may have different specificities.

In some embodiments of the multispecific antibody according to the present invention, a paratope-forming domain assembly Vx1 forming a first paratope (d1) is covalently linked to the variable domain formed by VH1 and VL1, and a paratope-forming domain assembly Vx2 forming a second paratope (d2) is covalently linked to the variable domain formed by VH2 and VL2, wherein the first paratope (d1), and the second paratope (d2) may have the same specificity or may have different specificities.

In some embodiments of the multispecific antibody according to the present invention, a paratope-forming domain assembly Vx1 forming a first paratope (d1) is covalently linked to the variable domain formed by VH1 and VL1, or a paratope-forming domain assembly Vx2 forming a second paratope (d2) is covalently linked to the variable domain formed by VH2 and VL2, i.e. the multispecific antibody comprises only one dual variable domain.

Accordingly, the multispecific antibody of the present invention is an at least trivalent antibody having at least two specificities as defined above. That is, the multispecific antibody

according to the present invention can be a trivalent antibody having exact two specificities (i.e., a trivalent bispecific antibody); a trivalent antibody having exact three specificities (i.e., a trivalent trispecific antibody); a tetravalent antibody having exact two specificities (i.e., a tetravalent bispecific antibody); a tetravalent antibody having exact three specificities (i.e., a tetravalent trispecific antibody); a tetravalent antibody having exact four specificities (i.e., a tetravalent tetraspecific antibody); etc.

In a particular embodiment of the multispecific antibody according to the present invention, the at least three paratopes of the multispecific antibody are formed by at least three of the CDRH1-3/CDRL1-3 sequences selected from the group consisting of SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, or are formed by CDRH1-3/CDRL1-3 sequences having at least 70% identity, e.g., at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity, to SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, respectively. That is, in this specific embodiment, the multispecific antibody of the present invention is an at least trivalent antibody having at least three specificities as defined above. In this particular embodiment, it is preferred that the multispecific antibody according to the present invention is a trivalent antibody comprising exactly three specificities, i.e. the multispecific antibody is a trivalent, trispecific antibody.

In another particular embodiment, the multispecific antibody according to the present invention comprises at least four paratopes which are formed by at least two of the CDRH1-3/CDRL1-3 sequences selected from the group consisting of SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, or are formed by CDRH1-3/CDRL1-3 sequences having at least 70% identity, e.g. at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity, to SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-

24, respectively. Accordingly, in this specific embodiment, the multispecific antibody of the present invention is an at least tetravalent antibody having at least two specificities as defined above. In a specific embodiment, the multispecific antibody according to the present invention is a tetravalent antibody comprising exactly two specificities, i.e. a tetravalent, 5 bispecific antibody.

In a further particular embodiment, the multispecific antibody according to the present invention comprises at least four paratopes which are formed by at least three of the CDRH1-3/CDRL1-3 sequences selected from the group consisting of SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, or are formed by CDRH1-3/CDRL1-3 sequences having at least 70% identity, e.g. at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity, to SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, respectively. Accordingly, in this specific embodiment, the multispecific antibody of the present invention is an at least tetravalent antibody having at least three specificities as defined above. In a particular embodiment, the multispecific antibody according to the present invention is a tetravalent antibody comprising exactly three specificities, i.e. a tetravalent, trispecific antibody. 20

In a preferred embodiment of the multispecific antibody according to the present invention, the at least three paratopes ((a), (b), and (c) and/or (d), respectively) are formed by at least two 25 of the CDRH1-3/CDRL1-3 sequences selected from the group consisting of SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, or are formed by CDRH1-3/CDRL1-3 sequences having at least 70% identity, e.g., at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity, to SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, respectively. 30

Preferably, the CDRs or the variable regions of the multispecific antibody according to the present invention are human CDR or variable region sequences or are derived from human CDR or variable region sequences. The parental antibodies 2F8, 7G6, 17H9 and 15E3 (wild-type) are human antibodies, isolated from human patients. A "human-derived" CDR or VH/VL sequence includes engineered human antibody sequences, wherein mutations were introduced in the originally human CDR or VH/VL sequences. For example, a human-derived CDR may differ from the fully human (wild-type) CDR sequence in that it contains up to 5, i.e. 1, 2, 3, 4 or 5 mutations, preferably up to 4 mutations, more preferably up to 3 mutations. For example, a human-derived VH or VL sequence may differ from the fully human (wild-type) VH or VL sequence in that it contains up to 10, i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 mutations, preferably up to 7 mutations, more preferably up to 5 mutations (e.g., in the framework regions).

In some embodiments, the multispecific antibody is a human derived antibody. In some embodiments, the antibody is a monoclonal antibody. For example, the antibody may be a human derived monoclonal antibody.

Human derived antibodies are advantageous as compared to antibodies of non-human origin, because non-human antibodies, including chimeric and humanized antibodies, can trigger an adverse immune response, which can lead to nausea, diarrhoea and flu-like symptoms. In more severe cases, these side-effects can even be lethal. Non-human antibody segments often trigger immune responses in humans (anti-drug antibodies (ADA)), thereby not only eliciting undesired side effects, but also reducing the efficacy of the non-human antibody in humans. In contrast thereto, antibodies retrieved from humans have a higher safety profile, as the antibodies have proven tolerability in the human body, which is combined with the outstanding affinity maturation typical of the human immune system. As used herein, the term "human derived antibodies" not only includes antibodies comprising sequences originally found in humans, but also sequence variants thereof, wherein specific amino acid residues (but not entire antibody segments) are mutated. In contrast to non-human and humanized antibodies, which usually contain entire antibody segments (such as entire sets of CDR sequences) of non-human origin, sequence variants of human derived antibodies typically contain only selective/specific mutations within select antibody segments (e.g., within a CDR

or framework region and/or within a constant region; e.g. to modify the antibodies' affinity, functionality, half-life, etc.).

- For example, a human derived multispecific antibody according to the present invention may
- 5 comprise only a limited number of mutations per CDR (e.g. no more than 6, preferably no more than 5, more preferably no more than 4, even more preferably no more than 3, still more preferably no more than 2 and particularly preferably only a single mutation per CDR), as compared to the sequences shown in Table 1. In case of more than two mutations they may not occur in a consecutive manner (to avoid creating a non-human sequence segment).
- 10 The same applies to the framework regions (or the entire VH/VL sequences) as well to the constant regions.

- The CDRs, in particular the three different CDRs on the heavy chain (CDRH1, CDRH2 and CDRH3) and three different CDRs on the light chain (CDRL1, CDRL2 and CDRL3), as
- 15 identified by the present inventors, may be grafted on any variable framework region, in particular any variable human framework region, without abrogating their specificity.

The human variable framework regions of the heavy chain (VH) may be retrieved from the website:

- 20 "<https://www.imgt.org/genedb/resultPage.action;jsessionid=49EB34C22C79EAC51862C76108963216?gene.id.species=Homo+sapiens&molComponent=IG&geneTypeLike=variable&allele.fcode=functional&cloneName=&locusLike=IGH&mainLocusLike=IGH+locus&cosLocusLike=any&groupLike=any&subgroup=-1&geneLike=&selection=any>", the contents of which is incorporated herein by reference. Thus, the VH chain may be selected from the
- 25 group consisting of the amino acid sequences encoded by the genes IGHV1-18, IGHV1-2, IGHV1-24, IGHV1-3, IGHV1-45, IGHV1-46, IGHV1-58, IGHV1-69, IGHV1-69-2, IGHV1-69D, IGHV1-8, IGHV2-26, IGHV2-5, IGHV2-70, IGHV2-70D, IGHV3-11, IGHV3-13, IGHV3-15, IGHV3-20, IGHV3-21, IGHV3-23, IGHV3-23D, IGHV3-30, IGHV3-30-3, IGHV3-30-5, IGHV3-33, IGHV3-35, IGHV3-43, IGHV3-43D, IGHV3-48, IGHV3-49,
- 30 IGHV3-53, IGHV3-62, IGHV3-64, IGHV3-64D, IGHV3-66, IGHV3-7, IGHV3-72, IGHV3-73, IGHV3-74, IGHV3-9, IGHV3-NL1, IGHV4-28, IGHV4-30-1, IGHV4-30-2, IGHV4-30-4, IGHV4-31, IGHV4-34, and IGHV4-38-2.

The human variable framework regions of the light chain (VK, kappa) may be retrieved from the website:

“<https://www.imgt.org/genedb/resultPage.action;jsessionid=49EB34C22C79EAC51862C76108963216?gene.id.species=Homo+sapiens&molComponent=IG&geneTypeLike=variable&allele.fcode=functional&cloneName=&locusLike=IGK&mainLocusLike=IGK+locus&cosLocusLike=any&groupLike=any&subgroup=-1&geneLike=&selection=any>”, the contents of which is incorporated herein by reference. Thus, the VK (kappa) chain may be selected from the group consisting of the amino acid sequences encoded by the genes IGKV1-12, IGKV1-13, IGKV1-16, IGKV1-17, IGKV1-27, IGKV1-33, IGKV1-39, IGKV1-5, IGKV1-6, IGKV1-8, IGKV1-9, IGKV1-NL1, IGKV1D-12, IGKV1D-13, IGKV1D-16, IGKV1D-17, IGKV1D-33, IGKV1D-39, IGKV1D-43, IGKV1D-8, IGKV2-24, IGKV2-28, IGKV2-29, IGKV2-30, IGKV2-40, IGKV2D-26, IGKV2D-28, IGKV2D-29, IGKV2D-30, IGKV2D-40, IGKV3-11, IGKV3-15, IGKV3-20, IGKV3D-11, IGKV3D-15, IGKV3D-20, IGKV3D-7, IGKV4-1, IGKV5-2, IGKV6-21, and IGKV6D-21.

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The human variable framework regions of the light chain (VL, lambda) may be retrieved from the website:

„<https://www.imgt.org/genedb/resultPage.action;jsessionid=49EB34C22C79EAC51862C76108963216?gene.id.species=Homo+sapiens&molComponent=IG&geneTypeLike=variable&allele.fcode=functional&cloneName=&locusLike=IGL&mainLocusLike=IGL+locus&cosLocusLike=any&groupLike=any&subgroup=-1&geneLike=&selection=any>”, the contents of which incorporated herein by reference. Thus, the VL (lambda) chain may be selected from the group consisting of the amino acid sequences encoded by the genes IGLV1-36, IGLV1-40, IGLV1-44, IGLV1-47, IGLV1-51, IGLV10-54, IGLV2-11, IGLV2-14, IGLV2-18, IGLV2-23, IGLV2-8, IGLV3-1, IGLV3-10, IGLV3-12, IGLV3-16, IGLV3-19, IGLV3-21, IGLV3-22, IGLV3-25, IGLV3-27, IGLV3-9, IGLV4-3, IGLV4-60, IGLV4-69, IGLV5-37, IGLV5-39, IGLV5-45, IGLV5-52, IGLV6-57, IGLV7-43, IGLV7-46, IGLV8-61, and IGLV9-49.

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The human variable framework region of the heavy and the light chain may also contain the respective human HJ (heavy chain), and light chain KJ (kappa) or LJ (lambda) sequences.

30

The HJ sequences may be retrieved from the website:

“<https://www.imgt.org/genedb/resultPage.action?gene.id.species=Homo+sapiens&molComponent=IG&geneTypeLike=any&allele.fcode=functional&cloneName=&locusLike=IGH&mainLocusLike=IGH+locus&cosLocusLike=any&groupLike=IGHJ&subgroup=-1&geneLike=&selection=any>”, the contents of which is incorporated herein by reference. In particular, the HJ sequence may be selected from amino acid sequences encoded by the genes consisting of the group: IGHJ1, IGHJ2, IGHJ3, IGHJ4, IGHJ5, and IGHJ6.

The KJ sequences may be retrieved from the website:
“<https://www.imgt.org/genedb/resultPage.action?gene.id.species=Homo+sapiens&molComponent=IG&geneTypeLike=any&allele.fcode=functional&cloneName=&locusLike=IGK&mainLocusLike=IGK+locus&cosLocusLike=any&groupLike=IGKJ&subgroup=-1&geneLike=&selection=any>”, the contents of which is incorporated herein by reference. In particular, the KJ sequence may be selected from amino acid sequences encoded by the genes consisting of the group IGKJ1, IGKJ2, IGKJ3, IGKJ4, and IGKJ5.

The LJ sequences may be retrieved from the website:
“<https://www.imgt.org/genedb/resultPage.action?gene.id.species=Homo+sapiens&molComponent=IG&geneTypeLike=any&allele.fcode=functional&cloneName=&locusLike=IGL&mainLocusLike=IGL+locus&cosLocusLike=any&groupLike=IGLJ&subgroup=-1&geneLike=&selection=any>”, the contents of which is incorporated herein by reference. In particular, the LJ sequence may be selected from amino acid sequences encoded by the genes consisting of the group: IGLJ1, IGLJ2, IGLJ3, IGLJ6, and IGLJ7.

The heavy chain CDR sequences (CDRH1, CDRH2 and CDRH3) may be comprised by a human heavy chain variable framework sequence as defined by a human VH sequence as described herein in combination with a human HJ sequence as described herein. Analogously, the light chain CDR sequences (CDRL1, CDRL2 and CDRL3) may be comprised by a human light chain variable framework sequence as defined by a human VL or VK sequence as described herein in combination with a human LJ or KJ sequence as described herein.

The combination of (i) a human VH sequence (comprising an CDRH1, an CDRH2 and an CDRH3 sequence, respectively) and of a human VL sequence (comprising an CDRL1, an

CDRL2 and an CDRL3 sequence, respectively) or of (ii) a human VH sequence (comprising an CDRH1, an CDRH2 and an CDRH3 sequence, respectively) and of a human VK sequence (comprising an CDRL1, an CDRL2 and an CDRL3 sequence, respectively) may thus characterize the variable framework region of an antibody and its binding region. Also, the
5 variable framework region may be characterized (i) by a human VH sequence and a human HJ sequence in combination with a human VL and a human LJ sequence or (ii) by a human VH sequence and a human HJ sequence in combination with a human VK and a human KJ sequence, thereby forming the variable framework region of an antibody and its binding region.

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The numbering of the residues in the variable regions was done according to the IMGT numbering system (IMGT: <http://www.imgt.org/>; cf. Lefranc, M.-P. et al. (2009) *Nucleic Acids Res.* 37, D1006-D1012). To define the CDR regions, the Kabat CDR definition was applied (Tai Te Wu, Elvin A. Kabat; An analysis of the sequences of the variable regions of Bence
15 Jones proteins and myeloma light chains and their implications for antibody complementarity. *J Exp Med* 1 August 1970; 132 (2): 211–250; George Johnson, Tai Te Wu, Kabat Database and its applications: 30 years after the first variability plot, *Nucleic Acids Research*, Volume 28, Issue 1, 1 January 2000, Pages 214–218).

20 The constant regions may carry, for example, specific modifications known in the art to modify the antibody's (Fc-related) functionality, as described herein below.

Multispecific antibodies of the invention can be of any isotype (e.g., IgA, IgG, IgM i.e. an α , γ or μ heavy chain). Preferably, the multispecific antibody is an IgG or IgA antibody. IgG and
25 IgA usually compete with IgE for binding sites on the allergen and thereby prevent recognition of allergens by IgE bound to Fcε receptors on the surface of mast cells and basophils. This may include direct competition by binding to the same epitope or competition through steric hindrance. Furthermore, IgG antibodies bound to the allergen can lead to cross-linking of Fcs and inhibitory FcγRIIB receptors, resulting in the decrease of effector cell activity. Thereby
30 the IgG and IgA antibodies or binding fragments thereof according to the invention can be used for the effective prevention or treatment of allergies. In some embodiments, the variable regions or the CDRs of the antibody as defined herein are derived from a (human) IgE antibody and grafted in a scaffold of an IgG or IgA antibody. Preferably, the scaffold is of a human IgG

or IgA. Accordingly, the variable regions, portions thereof or the CDRs may be human and grafted in an antibody framework, which is preferably of human origin, but a distinct antibody type, such as IgG or IgA instead of IgE. Typically, the human-derived portions of the variable regions that are grafted into the antibody framework comprise the CDRs. Among IgG, IgG1
5 and IgG4 are preferred, and IgG4 is particularly preferred.

Accordingly, the multispecific antibody according to the present invention may comprise an Fc moiety. The Fc moiety may be derived from human origin, e.g. from human IgA or IgG, such as IgG1, IgG2, IgG3, and/or IgG4, e.g. human IgG4.

10

As used herein, the term "Fc moiety" refers to a sequence derived from the portion of an immunoglobulin heavy chain beginning in the hinge region just upstream of the papain cleavage site (e.g., residue 216 in native IgG, taking the first residue of heavy chain constant region to be 114) and ending at the C-terminus of the immunoglobulin heavy chain.
15 Accordingly, an Fc moiety may be a complete Fc moiety or a portion (e.g., a domain) thereof. A complete Fc moiety comprises at least a hinge domain, a CH2 domain, and a CH3 domain (e.g., EU amino acid positions 216-446). An additional lysine residue (K) is sometimes present at the extreme C-terminus of the Fc moiety, but is often cleaved from a mature antibody.

20 In the context of the present invention an Fc moiety comprises at least one of: a hinge (e.g., upper, middle, and/or lower hinge region) domain, a CH2 domain, a CH3 domain, or a variant, portion, or fragment thereof. An Fc moiety may comprise at least a hinge domain, a CH2 domain or a CH3 domain. The Fc moiety may be a complete Fc region. The Fc moiety may also comprises one or more amino acid insertions, deletions, or substitutions relative to
25 a naturally-occurring Fc moiety. For example, at least one of a hinge domain, CH2 domain or CH3 domain (or portion thereof) may be deleted.

As used herein, the term "Fc region" refers to the portion of an immunoglobulin formed by two or more Fc moieties of antibody heavy chains. For example, the Fc region may be
30 monomeric or "single-chain" Fc region (i.e., a scFc region). Single chain Fc regions are comprised of Fc moieties linked within a single polypeptide chain (e.g., encoded in a single contiguous nucleic acid sequence). Exemplary scFc regions are disclosed in WO 2008/143954 A2. The Fc region may be dimeric. A "dimeric Fc region" or "dcFc" refers to

the dimer formed by the Fc moieties of two separate immunoglobulin heavy chains. The dimeric Fc region may be a homodimer of two identical Fc moieties (e.g., an Fc region of a naturally occurring immunoglobulin) or a heterodimer of two non-identical Fc moieties.

5 It will be understood by one of ordinary skill in the art that the Fc moiety/Fc region may be modified such that it varies in amino acid sequence from the complete Fc moiety/Fc region of a naturally occurring immunoglobulin molecule, while retaining at least one desirable function conferred by the naturally-occurring Fc moiety/Fc region. Such functions include Fc
10 receptor (FcR) binding, antibody half-life modulation, ADCC function, protein A binding, protein G binding, and complement binding. The portions of naturally occurring Fc moieties/Fc regions, which are responsible and/or essential for such functions, are well known by those skilled in the art. In some embodiments, the multispecific antibody according to the present invention comprises a (complete) Fc moiety/Fc region, wherein the interaction/binding with the Fc receptor is not compromised.

15

In general, binding of the antibody to an Fc receptor may be assessed by various methods known to the skilled person, such as ELISA (Hessell AJ, Hangartner L, Hunter M, Havenith CEG, Beurskens FJ, Bakker JM, Lanigan CMS, Landucci G, Forthal DN, Parren PWHI, et al.: Fc receptor but not complement binding is important in antibody protection against HIV.
20 Nature 2007, 449:101–104; Grevys A, Bern M, Foss S, Bratlie DB, Moen A, Gunnarsen KS, Aase A, Michaelsen TE, Sandlie I, Andersen JT: Fc Engineering of Human IgG1 for Altered Binding to the Neonatal Fc Receptor Affects Fc Effector Functions. 2015, 194:5497–5508) or flow-cytometry (Perez LG, Costa MR, Todd CA, Haynes BF, Montefiori DC: Utilization of immunoglobulin G Fc receptors by human immunodeficiency virus type 1: a specific role for
25 antibodies against the membrane-proximal external region of gp41. J Virol 2009, 83:7397–7410; Piccoli L, Campo I, Fregni CS, Rodriguez BMF, Minola A, Sallusto F, Luisetti M, Corti D, Lanzavecchia A: Neutralization and clearance of GM-CSF by autoantibodies in pulmonary alveolar proteinosis. Nat Commun 2015, 6:1–9).

30 In some embodiments, the Fc moiety, or the Fc region, comprises or consists of an amino acid sequence derived from a human immunoglobulin sequence (e.g., from an Fc region or Fc moiety from a human IgG molecule). However, the Fc moiety, or the Fc region, may comprise one or more amino acids from another mammalian species. For example, a primate

Fc moiety or a primate binding site may be included in the multispecific antibody. Alternatively, one or more murine amino acids may be present in the Fc moiety or in the Fc region.

- 5 The Fc moieties of the Fc region may be of the same or different class and/or subclass. For example, the Fc moieties may be derived from an immunoglobulin G (e.g., a human immunoglobulin G). Within the IgG isotype, antibodies may be IgG1, IgG2, IgG3 or IgG4 subclass, preferably IgG1 or IgG4. Exemplified sequences for IgG4 constant regions (HC), which may be useful in the multispecific antibody as described herein, are provided in SEQ
- 10 ID NOs: 50-51, 53, 55-56, and 59-60. Accordingly, the multispecific antibody of the invention may comprise amino acid sequences selected from sequences according SEQ ID NOs: 50-51, 53, 55-56, and 59-60, or sequence variants thereof as described herein. Preferably, the human IgG4 constant region comprises the stable hinge mutation S228P (S. Angal, D.J. King, M.W. Bodmer, A. Turner, A.D.G. Lawson, G. Roberts, B. Pedley, J.R. Adair,
- 15 A single amino acid substitution abolishes the heterogeneity of chimeric mouse/human (IgG4) antibody, *Molecular Immunology*, Volume 30, Issue 1, 1993, Pages 105-108, ISSN 0161-5890, [https://doi.org/10.1016/0161-5890\(93\)90432-B](https://doi.org/10.1016/0161-5890(93)90432-B)).

- Antibodies of the invention may comprise a κ or a λ light chain. An exemplified sequence for
- 20 κ light chain constant region, which may be useful in the antibody as described herein, is provided in SEQ ID NOs: 52, 54, 57, and 61. Accordingly, the multispecific antibody of the invention may comprise an amino acid sequence according to any one of sequences SEQ ID NOs: 52, 54, 57, and 61, or a sequence variant thereof as described herein. An exemplified
- 25 sequence for λ light chain constant region, which may be useful in the antibody as described herein, is provided in SEQ ID NOs: 58 and 62. Accordingly, the multispecific antibody of the invention may comprise an amino acid sequence according to any one of sequences SEQ ID NOs: 58 and 62, or a sequence variant thereof as described herein.

- The (human) IgG4 constant region of the multispecific antibody according to the present
- 30 invention preferably comprises a "knob-into-hole conformation" to improve dimerization of the C-terminal heavy chain (CH2 and CH3) domains. Preferably, the "knob-into-hole conformation" further comprises a stabilizing disulfide bridge, as described e.g. by Merchant A.M. et al. (An efficient route to human bispecific IgG. *Nature Biotechnology* 16, 677-681

(1998)). Thus, in a preferred embodiment, the multispecific antibody of the present invention comprises a T366W mutation in the CH3 domain of the "knob chain", and T366S, L368A, Y407V mutations in the CH3 domain of the "hole chain". In a more preferred embodiment, an additional interchain disulfide bridge between the CH3 domains is used, e.g. by introducing a S354C mutation or a E356C mutation into the CH3 domain of the "knob chain", and a Y349C mutation into the CH3 domain of the "hole chain". Thus, in a more preferred embodiment, the multispecific antibody of the present invention comprises S354C, T366W mutations in one of the two CH3 domains ("knob chain"), and Y349C, T366S, L368A, Y407V mutations in the other of the two CH3 domains ("hole chain"); alternatively, the multispecific antibody according to the present invention comprises E356C, T366W mutations in one of the two CH3 domains ("knob chain"), and Y349C, T366S, L368A, Y407V mutations in the other of the two CH3 domains ("hole chain") (the additional Y349C mutation in one CH3 domain and the additional E356C or S354C mutation in the other CH3 domain forming a interchain disulfide bridge (numbering always according to EU index of Kabat).

But also other knobs-in-holes technologies as described by EP 1 870 459A1, can be used alternatively or additionally. For example, the multispecific antibody of the present invention may comprise R409D, K370E mutations in the CH3 domain of the "knob chain" and D399K, E357K mutations in the CH3 domain of the "hole chain" (numbering always according to EU index of Kabat).

In another embodiment the multispecific antibody comprises a T366W mutation in the CH3 domain of the "knob chain", and T366S, L368A, Y407V mutations in the CH3 domain of the "hole chain", and additionally R409D, K370E mutations in the CH3 domain of the "knob chain" and D399K, E357K mutations in the CH3 domain of the "hole chain".

In still another embodiment the multispecific antibody comprises Y349C, T366W mutations in one of the two CH3 domains and S354C, T366S, L368A, Y407V mutations in the other of the two CH3 domains, or the multispecific antibody comprises Y349C, T366W mutations in one of the two CH3 domains and S354C, T366S, L368A, Y407V mutations in the other of the two CH3 domains and additionally R409D, K370E mutations in the CH3 domain of the "knob chain" and D399K, E357K mutations in the CH3 domain of the "hole chain".

The multispecific antibody according to the present invention preferably comprises a human IgG4 constant region having a hinge stabilizing S228P mutation. This single residue substitution, changing the serine at 228 to proline, leads to the production of a homogeneous antibody (see Angal S. et al., A single amino acid substitution abolishes the heterogeneity of chimeric mouse/human (IgG4) antibody. *Molecular Immunology*, Vol. 30 (1), January 1993, pp. 105.108). Angal S. et al. further showed that the variant IgG4 has significantly extended serum half-life and shows an improved tissue distribution.

Moreover, the multispecific antibody according to the present invention preferably comprises a R409K mutation in the (human) IgG4 constant region for conferring stability at low pH conditions which are present e.g. during purification of the multispecific antibody. As shown by Namisaki H. et al., (PLOS ONE 15(3): e0229027. <https://doi.org/10.1371/journal.pone.0229027>), R409K mutation prevents acid-induced aggregation of human IgG4. Preferably, the multispecific antibody of the present invention comprises a S228P mutation and a R409K mutation in the constant chain region. More preferably, the multispecific antibody of the present invention comprises a S228P mutation and a R409K mutation in combination with a knob-into hole conformation, preferably including a stabilizing disulphide bridge, preferably as described above.

Preferably, the multispecific antibody according to the present invention comprises a L445P mutation in the (human) IgG4 constant region for the prevention of clipping of the C-terminus and reduction of binding of pre-existing anti-drug antibodies (PE-ADA). C-terminal lysine clipping is a common phenomenon occurring during the bioproduction of mAbs and leads to variable amounts of final process-related charge variants. By introducing a proline instead of a lysine at position 445, this phenomenon can be avoided (Xu et al., L44P mutation on heavy chain stabilizes IgG4 under acidic conditions. *MAbs* 2019 Oct.; 11(7): 1289-1299). Preferably, the multispecific antibody according to the present invention comprises a L445P mutation in combination with a S228P hinge stabilizing mutation and/or a R409K mutation. More preferably, the multispecific antibody according to the present invention comprises a L445P mutation, a S228P hinge stabilizing mutation and a R409K mutation. Even more preferably, the multispecific antibody comprises, in addition to the L445P, R409K and/or S228P mutation, a knob-into hole conformation as described above. Most preferably, the

multispecific antibody comprises a L445P mutation, a S228P hinge stabilizing mutation and a R409K mutation in combination with a knob-into-hole conformation as described above.

In a further preferred embodiment, the Fc region of the multispecific antibody according to the present invention comprises a mutation which increases the *in vivo* half-life of the antibody. Such mutations are described in WO 2009/086320 A. Thus, the Fc region of the multispecific antibody may comprise, for example, an M428L/N434S or a V308F/M428L/N434S mutation, wherein a M428L/N434S mutation is preferred.

- 5 As described above, in a preferred embodiment, the multispecific antibodies according to the present invention comprise at least three paratopes which may be formed by at least two of the CDRH1-3/CDRL1-3 sequences selected from the group consisting of SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, or are formed by CDRH1-3/CDRL1-3 sequences having at least 70% identity, i.e. at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity, to SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, respectively.

In the following, specific multispecific IgG-scFv antibodies and IgG:DVD antibodies according to the present invention are described in detail. The design of exemplary multispecific IgG-scFv and IgG:DVD antibodies according to the present invention is schematically shown in Figure 1.

Multispecific (IgG-)scFv (single chain variable fragment) antibodies

- A multispecific (IgG-)scFv (single chain variable fragment) antibody according to the present invention comprises at least three paratopes, wherein at least one paratope (a) is formed by the VH1 of a first heavy chain and a VL1 of a first light chain, at least one paratope (b) is formed by a VH2 of a second heavy chain and a VL2 of a second light chain, and at least one

paratope (c) is formed by a single chain variable fragment (scFv) covalently linked to the constant domain of the (first and/or second) heavy chain.

In this respect, "covalently linked to the constant domain" means that the single chain variable fragment (scFv) is linked by a covalent bond to the constant domain. Preferably, the single chain variable fragment (scFv) may be covalently linked to the C-terminus of the constant domain. Preferably, the amino group of the N-terminal amino acid of the scFv may be covalently linked to the carboxy group of the last amino acid of the constant domain, preferably via a peptide (amide) bond. Alternatively, the N-terminal amino acid of the single chain variable fragment (scFv) may also be covalently linked to a side chain of any amino acid (e.g. threonine, serine, glutamate, aspartate) located in the constant domain, preferably in the C-terminal region of the constant domain. For example, the N-terminal amino acid of the single chain variable fragment (scFv) may be covalently linked to a side chain of any one of the 10 amino acids upstream to the C-terminus of the constant domain, e.g. to the last, next-to-last, third from last, forth from last, etc. amino acid upstream to the C-terminus of the constant domain), e.g. by a -C-N-, -C-C-, or -C-O- bond. In another alternative, a side chain of an amino acid located in the scFv (preferably in the N-terminal region of the scFv) may be covalently linked either to the C-terminal amino acid of the constant domain or to another side chain of any amino acid of the constant chain, which is preferably located in the C-terminal region, as described above, and more preferably not involved in paratope formation of the scFv. In a further alternative, the C-terminal carboxy group of the single chain variable fragment (scFv) may be covalently linked to a side chain of the constant domain having an amino function (e.g. arginine or lysine), preferably a sidechain not involved in paratope formation.

The VH of the first and second heavy chains (VH1/VH2) comprises CDR (complementarity determining region) sequences CDRH1-3; the VL of the first and second light chains (VL1/VL2) comprises CDR (complementarity determining region) sequences CDRL1-3; and the scFv covalently linked to the constant domain of the (first and/or second) heavy chain preferably comprises at least two scFv domains (scFv1/scFv2) comprising CDRH1-3 and CDRL1-3 sequences, respectively.

In a preferred embodiment, a multispecific (IgG-)scFv antibody according to the present invention comprises at least three paratopes which are formed by at least two of the CDRH1-3/CDRL1-3 sequences selected from the group consisting of SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, or are formed by CDRH1-3/CDRL1-3 sequences having at least 70% identity, i.e. at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity, to SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, respectively.

In some embodiments, the paratopes (a) and (b) of the multispecific (IgG-)scFv antibody may have different specificities, i.e., the CDRH1-3/CDRL1-3 sequences forming the paratope (a), and the CDRH1-3/CDRL1-3 sequences forming the paratope (b) may be selected from (two) different CDRH1-3/CDRL1-3 sequences selected from the group consisting of SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, or CDRH1-3/CDRL1-3 sequences having at least 70%, i.e. at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99%, identity to SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, respectively.

In preferred embodiments, the paratopes (a) and (b) of the multispecific (IgG-)scFv antibody according to the present invention have the same specificity, i.e., paratopes (a) and (b) comprise the same CDRH1-3/CDRL1-3 sequences which are selected from the group consisting of SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, or are formed by CDRH1-3/CDRL1-3 sequences having at least 70% identity, i.e. at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at

least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity, to SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, respectively.

- 5 The multispecific (IgG-)scFv antibody according to the present invention comprises at least one scFv (forming the paratope (c)) linked to the constant domain of at least one heavy chain as a single chain variable fragment (scFv). The scFv may comprise at least two scFv domains forming the paratope. In a preferred embodiment, a first scFv1 is linked to the constant domain of the first heavy chain forming a first (C-terminal) paratope (c1), and a second scFv2
10 is linked to the constant domain of the second heavy chain forming a second (C-terminal) paratope (c2), so that a tetravalent multispecific antibody according to the present invention is obtained.

- In a particular embodiment of the tetravalent (IgG-)scFv antibody according to the present
15 invention, the first (C-terminal) paratope (c1) which is formed by a (first) scFv1 being covalently linked to the constant domain of the first heavy chain, and the second C-terminal paratope (c2) which is formed by a (second) scFv2 being covalently linked to the constant domain of the second heavy chain may have the same specificity. The tetravalent IgG-scFv antibody may be a trispecific antibody (in case that the N-terminal paratopes (a) and (b) have
20 different specificities), or may be a bispecific antibody (in case that the N-terminal paratopes (a) and (b) have the same specificity).

- In a further particular embodiment of the tetravalent (IgG-)scFv antibody according to the present invention, the first C-terminal paratope (c1) formed by a scFv1 linked to the constant
25 domain of the first heavy chain, and the second C-terminal paratope (c2) formed by a scFv2 linked to the constant domain of the second heavy chain may have different specificities. The tetravalent IgG-scFv antibody may be a tetraspecific antibody (in case that the N-terminal paratopes (a) and (b) have different specificities), or may be a trispecific antibody (in case that the N-terminal paratopes (a) and (b) have the same specificity).

- 30 The first C-terminal paratope (c1) formed by a scFv covalently linked to the constant domain of the first heavy chain, and the second C-terminal paratope formed by a scFv covalently linked to the constant domain of the second heavy chain may be formed by one or two of the

CDRH1-3/CDRL1-3 sequences selected from the group consisting of SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, or are formed by CDRH1-3/CDRL1-3 sequences having at least 70%, i.e. at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%,
5 at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99%, identity to SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, respectively, wherein the CDRH1-3/CDRL1-3 sequences forming the C-terminal
10 paratope(s) (c1, c2) are preferably different from the CDRH1-3/CDRL1-3 sequences forming the N-terminal paratope(s).

In a preferred embodiment of the multispecific (IgG-)scFv antibody according to the present invention, paratopes (a) and (b) have the same specificity. That is, the tetravalent antibody is
15 a bispecific antibody (in case that the paratopes (c1, c2) have the same specificity), or is a trispecific antibody (in case that the paratopes (c1, c2) have different specificities).

Thus, in a particular embodiment of the multispecific (IgG-)scFv antibody according to the present invention, the paratopes (a) and (b) may comprise CDRH1-3/CDRL1-3 sequences
20 according to SEQ ID NOs: 7-12 or CDRH1-3/CDRL1-3 sequences having at least 70%, i.e. at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%,
25 at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99%, identity to SEQ ID NOs: 7-12, and the paratopes (c1, c2) comprise CDRH1-3/CDRL1-3 sequences selected from one (in case of a bispecific antibody) or two (in the case of a trispecific antibody) of the group consisting of SEQ ID NOs: 1-6, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, or of CDRH1-3/CDRL1-3
30 sequences having at least 70%, i.e. at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at

least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99%, identity to SEQ ID NOs: 1-6, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, respectively.

In another particular embodiment of the multispecific (IgG-)scFv antibody according to the present invention, the paratopes (a) and (b) comprise CDRH1-3/CDRL1-3 sequences according to SEQ ID NOs: 13-18 or CDRH1-3/CDRL1-3 sequences having at least 70%, i.e. at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99%, identity to SEQ ID NOs: 13-18, and the paratopes (c1, c2) comprise CDRH1-3/CDRL1-3 sequences selected from one (in case of a bispecific antibody) or two (in the case of a trispecific antibody) of the group consisting of SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, and SEQ ID NOs: 19-24, or of CDRH1-3/CDRL1-3 sequences having at least 70%, i.e. at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99%, identity to SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, and SEQ ID NOs: 19-24, respectively.

In yet another particular embodiment of the multispecific (IgG-)scFv antibody according to the present invention, the paratopes (a) and (b) comprise CDRH1-3/CDRL1-3 sequences according to SEQ ID NOs: 19-24 or CDRH1-3/CDRL1-3 sequences having at least 70%, i.e. at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99%, identity to SEQ ID NOs: 19-24, and the paratopes (c1, c2) comprise CDRH1-3/CDRL1-3 sequences selected from one (in case of a bispecific antibody) or two (in the case of a trispecific antibody) of the group consisting of SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, and SEQ ID NOs: 13-18, or of CDRH1-3/CDRL1-3 sequences having at least 70%, i.e. at least 70%, at least 71%, at least 72%, at least 73%, at

least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99%, identity to SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, and SEQ ID NOs: 13-18, respectively.

In a preferred embodiment, the multispecific (IgG)-scFv antibody according to the present invention, the paratopes (a) and (b) comprise CDRH1-3/CDRL1-3 sequences according to SEQ ID NOs: 1-6 or CDRH1-3/CDRL1-3 sequences having at least 70%, i.e. at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99%, identity to SEQ ID NOs: 1-6, and the paratopes (c1, c2) comprise CDRH1-3/CDRL1-3 sequences selected from one (in case of a bispecific antibody) or two (in the case of a trispecific antibody) of the group consisting of SEQ ID NOs: 7-12, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, or of CDRH1-3/CDRL1-3 sequences having at least 70%, i.e. at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99%, identity to SEQ ID NOs: 7-12, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, respectively.

Thus, in a preferred embodiment, as shown in Figure 1 (A and B), the multispecific IgG-scFv antibody format comprises a Fab portion, which is derived from the parental antibody 17H9. The single chain variable fragments (scFv) covalently linked to the constant domains of the heavy chains may be derived from a single parenteral antibody (e.g. 7G6) yielding a bispecific antibody (i.e. IgG-scFv), or may be derived from two distinct parenteral antibodies (e.g. 7G6, and 15E3) yielding an asymmetric and tri-specific antibody format (i.e. IgG-scFv2).

In a preferred embodiment, the N-terminal paratopes of the multispecific (IgG)-scFv and (IgG)-scFv2 antibodies comprise the VH and VL domains derived from the parental antibody

17H9. Thus, the VH and VL domains of the paratopes (a) and (b) of the multispecific IgG-scFv and IgG-scFv2 antibody formats comprise CDRs (heavy chain CDRs: CDRH1, CDRH2, CDRH3; light chain CDRs: CDRL1, CDRL2, CDRL3) according to SED ID NOs: 1-6, or CDRs having at least 70% identity, i.e. at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity, to SED ID NOs: 1-6 .

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In a preferred embodiment, as shown in Figure 1B, the scFvs of the bispecific IgG-scFv antibody comprise VH and VL domains derived from the parental antibody 7G6. Accordingly, the bispecific (IgG-)scFv antibody according to the present invention comprises two scFvs (covalently linked to the constant domain of a first heavy chain and a second heavy chain, respectively) comprising heavy chain CDRs (CDRH1-3) according to SEQ ID NOs: 7-9, or CDRHs1-3 having at least 70% identity, i.e. at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity, to SEQ ID NOs: 7-9, respectively, and light chain CDRs (CDRL1-3) according to SEQ ID NOs: 10-12, or CDRLs1-3 having at least 70% identity, i.e. at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity, to SEQ ID NOs: 10-12, respectively.

In another preferred embodiment, as shown in Figure 1A, one of the (C-terminal) scFvs of the trispecific IgG-scFv2 antibody comprises VH and VL domains derived from the parental antibody 7G6, and the other (C-terminal) scFv of the trispecific IgG-scFv2 antibody comprises VH and VL domains derived from the parental antibody 15E3. Accordingly, the trispecific (IgG-)scFv2 antibody according to the present invention preferably comprises a scFv

(covalently linked to the constant domain of a first heavy chain) comprising heavy chain CDRs (CDRH1-3) according to SEQ ID NOs: 7-9, or CDRH1-3 having at least 70% identity, i.e. at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity to SEQ ID NOs: 7-9, respectively, and light chain CDRs (CDRL1-3) according to SEQ ID NOs: 10-12, or CDRL1-3 having at least 70% identity, i.e. at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity, to SEQ ID NOs: 10-12, respectively, and further comprises a scFv (covalently linked to the constant domain of a second heavy chain) comprising heavy chain CDRs (CDRH1-3) according to SEQ ID NOs: 13-15, or CDRH1-3 having at least 70% identity, i.e. at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity, to SEQ ID NOs: 13-15, respectively, and light chain CDRs (CDRL1-3) according to SEQ ID NOs: 16-18, or CDRL1-3 having at least 70% identity, i.e. at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity, to SEQ ID NOs: 16-18, respectively.

In each scFv covalently linked to the constant domain of a first or second heavy chain of the (IgG-)scFv antibody according to the present invention, the heavy chain CDRs (e.g. SEQ ID NOs: 7-9, SEQ ID NOs: 13-15) may be included in a (VH) scFv domain, and the light chain CDRs (e.g. SEQ ID NOs: 10-12, SEQ ID NOs: 16-18) are included in a (VL) scFv domain.

In a particular embodiment of the bispecific or trispecific (IgG-)scFv antibody, the scFv may be covalently linked to the constant domain in such a way that the CDRs are arranged in a VH-VL (i.e. CDRH1-3 – CDRL1-3) orientation. In this configuration, the scFv domain comprising the heavy chain CDRs (CDRH1-3) is covalently linked to the constant domain of the heavy chain.

In another embodiment of the bispecific or trispecific (IgG-)scFv antibody according to the present invention, the scFv is covalently linked to the constant domain in such a way that the CDRs are arranged in a VL-VH (i.e. CDRL1-3 – CDRH1-3) orientation. In this configuration, the scFv domain comprising the heavy chain CDRs (CDRH1-3) is covalently linked to the constant domain of the heavy chain.

Accordingly, in a preferred embodiment, a bispecific (IgG-)scFv antibody according to the present invention comprises:

- 15 (i) a first heavy chain comprising, preferably from the N-terminus to the C-terminus,
 - a VH1 domain comprising a CDRH1 having at least 70% identity to SEQ ID NO: 1, a CDRH2 having at least 70% identity to SEQ ID NO: 2, and a CDRH3 having at least 70% identity to SEQ ID NO: 3;
 - 20 - a first scFv domain comprising a CDRL1 having at least 70% identity to SEQ ID NO: 10, a CDRL2 having at least 70% identity to SEQ ID NO: 11, and a CDRL3 having at least 70% identity to SEQ ID NO: 12; and
 - a second scFv domain comprising a CDRH1 having at least 70% identity to SEQ ID NO: 7, a CDRH2 having at least 70% identity to SEQ ID NO: 8, and a CDRH3 having at least 70% identity to SEQ ID NO: 9; wherein the order of the first and second scFv domains may be reversed;
 - 25
- (ii) a second heavy chain comprising a VH2 domain as defined for the VH1 domain in (i);
- (iii) a first light chain comprising
 - 30 - a VL1 domain comprising a CDRL1 having at least 70% identity to SEQ ID NO: 4, a CDRL2 having at least 70% identity to SEQ ID NO: 5, and a CDRL3 having at least 70% identity to SEQ ID NO: 6; and

- (iv) a second light chain comprising a VL2 domain as defined for the VL1 domain in (iii);

wherein "at least 70% identity" means, in each case, "at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity".

In a further preferred embodiment, a trispecific (IgG-)scFv antibody according to the present invention comprises:

- (i) a first heavy chain comprising, preferably from the N-terminus to the C-terminus,
- a VH1 domain comprising a CDRH1 having at least 70% identity to SEQ ID NO: 1, a CDRH2 having at least 70% identity to SEQ ID NO: 2, and a CDRH3 having at least 70% identity to SEQ ID NO: 3;
 - a first scFv domain comprising a CDRL1 having at least 70% identity to SEQ ID NO: 10, a CDRL2 having at least 70% identity to SEQ ID NO: 11, and a CDRL3 having at least 70% identity to SEQ ID NO: 12; and
 - a second scFv domain comprising a CDRH1 having at least 70% identity to SEQ ID NO: 7, a CDRH2 having at least 70% identity to SEQ ID NO: 8, and a CDRH3 having at least 70% identity to SEQ ID NO: 9; wherein the order of the first and second scFv domains may be reversed;
- (ii) a second heavy chain comprising, preferably from the N-terminus to the C-terminus
- a VH2 domain comprising a CDRH1 having at least 70% identity to SEQ ID NO: 1, a CDRH2 having at least 70% identity to SEQ ID NO: 2, and a CDRH3 having at least 70% identity to SEQ ID NO: 3;
 - a first scFv domain comprising a CDRL1 having at least 70% identity to SEQ ID NO: 16, a CDRL2 having at least 70% identity to SEQ ID NO: 17, and a CDRL3 having at least 70% identity to SEQ ID NO: 18; and
 - a second scFv domain comprising a CDRH1 having at least 70% identity to SEQ ID NO: 13, a CDRH2 having at least 70% identity to SEQ ID NO: 14, a CDRH3 having at least 70% identity to SEQ ID NO: 15; wherein the order of the first and second scFv domains may be reversed;
- (iii) a first light chain comprising

- a VL1 domain comprising a CDRL1 having at least 70% identity to SEQ ID NO: 4, a CDRL2 having at least 70% identity to SEQ ID NO: 5, and a CDRL3 having at least 70% identity to SEQ ID NO: 6; and
- (iv) a second light chain comprising a VL2 domain as defined for the VL1 domain in (iii);

wherein "at least 70% identity" means, in each case, "at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity".

In a more preferred embodiment, a bispecific (IgG-)scFv antibody according to the present invention comprises:

- (i) a first heavy chain comprising, preferably from the N-terminus to the C-terminus
 - a VH1 domain comprising a CDRH1 according to SEQ ID NO: 1, a CDRH2 according to SEQ ID NO: 2, and a CDRH3 according to SEQ ID NO: 3; and
 - a first scFv domain comprising a CDRL1 according to SEQ ID NO: 10, a CDRL2 according to SEQ ID NO: 11, and a CDRL3 according to SEQ ID NO: 12; and
 - a second scFv domain comprising a CDRH1 according to SEQ ID NO: 7, a CDRH2 according to SEQ ID NO: 8, a CDRH3 according to SEQ ID NO: 9;wherein the order of the first and second scFv domains may be reversed;
- (ii) a second heavy chain comprising a VH2 domain as defined for the VH1 domain in (i);
- (iii) a first light chain comprising
 - a VL1 domain comprising a CDRL1 according to SEQ ID NO: 4, a CDRL2 according to SEQ ID NO: 5, and a CDRL3 according to SEQ ID NO: 6; and
- (iv) a second light chain comprising a VL2 domain as defined for the VL1 domain in (iii).

In a further preferred embodiment, a trispecific (IgG-)scFv antibody according to the present invention comprises:

- (i) a first heavy chain comprising, preferably from the N-terminus to the C-terminus

- a VH1 domain comprising a CDRH1 according to SEQ ID NO: 1, a CDRH2 according to SEQ ID NO: 2, and a CDRH3 according to SEQ ID NO: 3; and
- a first scFv domain comprising a CDRL1 according to SEQ ID NO: 10, a CDRL2 according to SEQ ID NO: 11, and a CDRL3 according to SEQ ID NO: 12; and
- 5 - a second scFv domain comprising a CDRH1 according to SEQ ID NO: 7, a CDRH2 according to SEQ ID NO: 8, a CDRH3 according to SEQ ID NO: 9;
- (ii) a second heavy chain comprising, preferably from the N-terminus to the C-terminus
- a VH2 domain comprising a CDRH1 according to SEQ ID NO: 1, a CDRH2 according to SEQ ID NO: 2, and a CDRH3 according to SEQ ID NO: 3;
- 10 - a first scFv domain comprising a CDRL1 according to SEQ ID NO: 16, a CDRL2 according to SEQ ID NO: 17, and a CDRL3 according to SEQ ID NO: 18, and
- a second scFv domain comprising a CDRH1 according to SEQ ID NO: 13, a CDRH2 according to SEQ ID NO: 14, and a CDRH3 according to SEQ ID NO: 15;
- 15 15; wherein the order of the first and second scFv domains may be reversed;
- (iii) a first light chain comprising
- a VL1 domain comprising a CDRL1 according to SEQ ID NO: 4, a CDRL2 according to SEQ ID NO: 5, and a CDRL3 according to SEQ ID NO: 6; and
- (iv) a second light chain comprising a VL2 domain as defined for the VL1 domain
- 20 in (iii).

In a preferred embodiment of the multispecific, preferably bispecific or trispecific, (IgG-)scFv antibody according to the present invention, the scFv domains (VL and VH domains) of the scFv are linked to each other using a flexible linker, such as e.g. a (GGGGS)_n-linker, preferably a four repeat GGGGS-linker.

25

In a preferred embodiment of the multispecific, preferably bispecific or trispecific, (IgG-)scFv antibody according to the present invention the first and second scFv domains are disulfide stabilized, as e.g. described by Reiter et al. (Stabilization of the Fv fragments in recombinant immunotoxins by disulfide bonds engineered into conserved framework regions. Biochemistry 1994, 33, 5451-5459). In a preferred embodiment, the scFv of the multispecific, preferably bispecific or trispecific, antibody according to the present invention contains an interdomain disulfide bond between the residues H44 and L100 as e.g. described by Zhao et

30

al. (Stabilization of the Single-Chain Fragment Variable by an Interdomain Disulfide Bond and Its Effect on Antibody Affinity. *Int J Mol Sci.* 2011; 12(1): 1–11).

Accordingly, in a preferred embodiment, a bispecific (IgG-)scFv antibody according to the present invention comprises:

- 5 (i) a first heavy chain comprising, preferably from the N-terminus to the C-terminus
 - 10 - a VH1 having at least 70% identity (e.g., at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity) to SEQ ID NO: 25; and
 - 15 - a scFv having at least 70% identity (e.g., at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity) to SEQ ID NO: 26;
- 20 (ii) a second heavy chain as defined in (i);
- (iii) a first light chain comprising
 - 25 - a VL1 having at least 70% identity (e.g., at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity) to SEQ ID NO: 28; and
 - 30 (iv) a second light chain comprising
 - a VL2 having at least 70% identity (e.g., at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%,

at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%,
at least 97%, at least 98% or at least 99% identity) to SEQ ID NO: 28.

Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3
sequences as set forth in SEQ ID NOs: 1-3, 7-9 and 13-15, respectively; and light chain CDR1,
5 CDR2, and CDR3 sequences as set forth in SEQ ID NOs: 4-6, 10-12 and 16-18, respectively)
are preferably maintained.

Accordingly, in a preferred embodiment, a trispecific (IgG)-scFv antibody according to the
present invention comprises:

- 10 (i) a first heavy chain comprising, preferably from the N-terminus to the C-terminus
- a VH1 having at least 70% identity (e.g., at least 70%, at least 71%, at least 72%,
at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%,
at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%,
15 at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%,
at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%,
at least 97%, at least 98% or at least 99% identity) to SEQ ID NO: 25; and
 - a scFv having at least 70% identity (e.g., at least 70%, at least 71%, at least 72%,
at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%,
20 at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%,
at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%,
at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%,
at least 97%, at least 98% or at least 99% identity) to SEQ ID NO: 26;
- 25 (ii) a second heavy chain comprising, preferably from the N-terminus to the C-terminus
- a VH2 having at least 70% identity (e.g., at least 70%, at least 71%, at least 72%,
at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%,
at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%,
at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%,
30 at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%,
at least 97%, at least 98% or at least 99% identity) to SEQ ID NO: 25; and
 - a scFv having at least 70% identity (e.g., at least 70%, at least 71%, at least 72%,
at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%,

at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%,
at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%,
at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%,
at least 97%, at least 98% or at least 99% identity) to SEQ ID NO: 27;

- 5 (iii) a first light chain comprising
- a VL1 having at least 70% identity (e.g., at least 70%, at least 71%, at least 72%,
at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%,
at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%,
at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%,
10 at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%,
at least 97%, at least 98% or at least 99% identity) to SEQ ID NO: 28; and
- (iv) a second light chain comprising
- a VL2 having at least 70% identity (e.g., at least 70%, at least 71%, at least 72%,
at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%,
15 at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%,
at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%,
at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%,
at least 97%, at least 98% or at least 99% identity) to SEQ ID NO: 28.

Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3
20 sequences as set forth in SEQ ID NOs: 1-3, 7-9 and 13-15, respectively; and light chain CDR1,
CDR2, and CDR3 sequences as set forth in SEQ ID NOs: 4-6, 10-12 and 16-18, respectively)
are preferably maintained.

In a preferred embodiment, a bispecific (IgG-)scFv antibody according to the present
25 invention comprises:

- (i) a first heavy chain comprising, preferably from the N-terminus to the C-terminus
 - a VH1 according to SEQ ID NO: 25; and
 - a scFv according to SEQ ID NO: 26;
- 30 (ii) a second heavy chain comprising a VH2 as defined for the VH1 in (i);
- (iii) a first light chain comprising
 - a VL1 according to SEQ ID NO: 28, and
- (iv) a second light chain comprising

- a VL2 according to SEQ ID NO: 28.

In a preferred embodiment, a trispecific (IgG-)scFv2 antibody according to the present invention comprises:

- 5 (i) a first heavy chain comprising, preferably from the N-terminus to the C-terminus
 - a VH1 according to SEQ ID NO: 25; and
 - a scFv according to SEQ ID NO: 26;
- 10 (ii) a second heavy chain comprising, preferably from the N-terminus to the C-terminus,
 - a VH2 according to SEQ ID NO: 25; and
 - a scFv according to SEQ ID NO: 27;
- (iii) a first light chain comprising
 - a VL1 according to SEQ ID NO: 28, and
- 15 (iv) a second light chain comprising
 - a VL2 according to SEQ ID NO: 28.

In a preferred embodiment of the multispecific, preferably bispecific or trispecific, (IgG-)scFv antibody according to the present invention, a scFv (comprising at least two scFv domains) is
20 fused to the C-terminus of the (first and second) heavy chain via a peptide linker, preferably via a flexible (GGGGS)_n-linker, e.g. via a flexible (GGGGS)_n-linker comprising three repeats of GGGGS.

Preferably, the multispecific, e.g. bispecific or trispecific, (IgG-)scFv antibody according to
25 the present invention comprises a C-terminal deletion of at least one amino acid residue that eliminates the interaction of a pre-existing antibody with the multispecific (IgG-)scFv antibody of the present invention without interfering with the binding of the (IgG-)scFv antibody of the present invention with its target. Preferably, the (IgG-)scFv antibody according to the present invention comprises a C-terminal deletion of a serine residue (S) to reduce the binding of
30 pre-existing anti-drug antibodies (PE-ADA) (see US20140161796A1).

Accordingly, in a preferred embodiment, a bispecific IgG-scFv antibody according to the present invention comprises:

- 5 (i) a first heavy chain having at least 70% identity (e.g., at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity) to SEQ ID NO: 40;
- 10 (ii) a second heavy chain having at least 70% identity (e.g., at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity) to SEQ ID NO: 40;
- 15 (iii) a first light chain having at least 70% identity (e.g., at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity) to SEQ ID NO: 41; and
- 20 (iv) a second light chain having at least 70% identity (e.g., at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity) to SEQ ID NO: 41.
- 25

30 Thereby, the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NOs: 1-3, 7-9 and 13-15, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NOs: 4-6, 10-12 and 16-18, respectively) are preferably maintained.

Accordingly, in a preferred embodiment, a trispecific IgG-scFv2 antibody according to the present invention comprises:

- 5 (i) a first heavy chain having at least 70% identity (e.g., at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity) to SEQ ID NO: 37;
- 10 (ii) a second heavy chain having at least 70% identity (e.g., at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity) to SEQ ID NO: 38;
- 15 (iii) a first light chain having at least 70% identity (e.g., at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity) to SEQ ID NO: 39;
- 20 (iv) a second light chain having at least 70% identity (e.g., at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity) to SEQ ID NO: 39.
- 25
- 30

In a more preferred embodiment, a bispecific IgG-scFv antibody according to the present invention comprises:

- (i) a first heavy chain according to SEQ ID NO: 40;
- (ii) a second heavy chain according to SEQ ID NO: 40;
- (iii) a first light chain according to SEQ ID NO: 41; and
- (iv) a second light chain according to SEQ ID NO: 41.

5

In another more preferred embodiment, a trispecific IgG-scFv2 antibody according to the present invention comprises:

- (i) a first heavy chain according to SEQ ID NO: 37;
- (ii) a second heavy chain according to SEQ ID NO: 38;
- 10 (iii) a first light chain according to SEQ ID NO: 39; and
- (iv) a second light chain according to SEQ ID NO: 39.

As shown in the appended examples, such bispecific IgG-scFv and trispecific IgG-scFv2 antibodies bind specifically to Ara h 2, Ara h3, and Ara h 6, and show superior properties in
15 in terms of inhibition of patients' IgE binding to peanut allergens, inhibition of mast cell degranulation, and inhibition of basophil degranulation, respectively, compared to antibody cocktails containing various monospecific (parental) antibodies, as well as prior art antibody cocktails.

20 Multispecific IgG-DVD (dual variable domain) antibodies

The multispecific IgG-DVD antibody according to the present invention comprises at least one paratope (a) formed by a VH1 of a first heavy chain and a VL1 of a first light chain, at least one paratope (b) formed by a VH2 of a second heavy chain and a VL2 of a second light
25 chain, and at least one (additional) paratope (d1, d2) formed by a paratope-forming domain assembly Vx which is covalently linked to at least one variable domain formed e.g. by VH1/VL1 and/or VH2/VL2, thereby forming at least one dual variable domain. Thus, the multispecific IgG-DVD antibody according to the present invention may comprise at least one dual variable domain which comprises a first VH domain (VHx) and a second VH domain
30 (VH; VH1 or VH2), and a first VL domain (VLx), and a second VL domain (VL; VL1 or VL2), respectively.

In this respect, "covalently linked to the variable domain" means that at least one of the variable domains VHx and VLx is/are linked by a covalent bond to the variable domain VH1 or VH2 or VL1 or VL2. Preferably, the at least one paratope-forming domain assembly Vx forming the paratope (d1, d2) may be covalently linked to the N-terminus of VH1, VH2, VL1 or VL2 or, more preferably, to at least one of VH1/VL1 or VH2/VL2 forming the paratopes (a) and (b). Preferably, the carboxy group of the (last) amino acid of VHx1/VLx1 or VHx2/VLx2 forming the paratope (d1, d2) may be linked to the amino group of the first amino acid of VH1/VL1 or VH2/VL2 forming the paratope(s) (a) and/or (b), preferably via a peptide (amide) bond. Alternatively, the carboxy group of the (last) amino acid of VHx1/VLx1 or VHx2/VLx2 forming the paratope (d1, d2) may also be covalently linked to a side chain of any amino acid located in VH1/VL1 or VH2/VL2 forming the paratopes (a) and/or (b); for example in the N-terminal region of VH1/VL1 or VH2/VL2 forming the paratopes (a) and/or (b), preferably to a side chain of an amino acid which is not involved in paratope formation (e.g. to a side chain of any one of the 10 amino acids downstream to the N-terminus, e.g. to the last, next-to-last, third from last, forth from last, etc., amino acid downstream from the N-terminus VH1/VL1 or VH2/VL2 forming the of paratopes (a) and (b)); preferably by a -C-N-, -C-C-, or -C-O- bond. E.g. the side chain for linking the carboxy group of the terminus may be arginine or lysine with an amino function. In another alternative, a side chain of an amino acid located in VxH1/VxL1 or VxH2/VxL2 forming the paratope (d1, d2), e.g. with a carboxy function, e.g. glutamate or aspartate) (preferably in the C-terminal region) may be covalently linked either to the N-terminal amino acid of VH1/VL1 or VH2/VL2 forming the paratopes (a) and/or (b) or to another side chain of any amino acid of VH1/VL1 or VH2/VL2 forming the paratopes (a) and/or (b) (preferably located in the N-terminal region), as described above, and preferably not involved in paratope formation).

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In a preferred embodiment, the VHx is covalently linked to VH1 or VH2, and VLx is covalently linked to VL1 or VL2. In one embodiment, VHx is covalently linked to VH1, and VLx is covalently linked to the VL1. In another embodiment, VHx is covalently linked to the VH2, and VLx is covalently linked to the VL2. In still another embodiment, VHx is covalently linked to the VL1, and VLx is covalently linked to the VH1. In still another embodiment, VHx is covalently linked to the VL2, and VLx is covalently linked to the VH2. In still another embodiment, two distinct or identical paratope-forming domain assemblies Vx may be linked

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to the IgG format, i.e. VHx1/VLx1 and VHx2/VLx2. They may be covalently linked as described above to VH1/VL1 and VH2/VL2.

Preferably, the multispecific IgG-DVD antibody according to the present invention is a human
5 derived antibody. More preferably, the multispecific IgG-DVD antibody according to the present invention is a human derived monoclonal antibody.

Preferably, the multispecific IgG-DVD antibody according to the present invention is of the
IgG1 or IgG4 type. More preferably, the multispecific IgG-DVD antibody according to the
10 present invention comprises a human IgG4 constant region having a S228P mutation for hinge
stabilization as described above.

According to a preferred embodiment, the multispecific IgG-DVD antibody of the present
invention comprises a knob-into-hole conformation which preferably comprises a stabilizing
15 disulphide bridge, as described above. Preferably, the knob-into-hole conformation
comprises the mutations S354C:T366W/Y349 C:T366 S:L368 A:Y407 V, as described above.

In a preferred embodiment of the multispecific IgG-DVD antibody according to the present
invention, the constant region comprises a R409K mutation for conferring stability at low pH,
20 as described above.

In a preferred embodiment of the multispecific IgG-DVD antibody according to the present
invention, the constant region comprises a L445P mutation for prevention of clipping of the
C-terminus and reduction of binding of pre-existing anti-drug antibodies (PE-ADA), as
25 described above.

Preferably, the multispecific IgG-DVD antibody according to the present invention is a human
derived monoclonal IgG4 antibody comprising: (i) a constant region having a S228P mutation
for hinge stabilization, (ii) a knob-into-hole conformation which preferably comprises the
30 mutations S354C, T366W on one Fc half (knob), and Y349C, T366S, L368A, and Y407V on
the other Fc half (hole), (iii) a constant region comprising a R409K mutation for conferring
stability at low pH, and (iv) a constant region L445P mutation for prevention of clipping of
the C-terminus and reduction of binding of pre-existing anti-drug antibodies (PE-ADA).

In a further preferred embodiment, the Fc region of the multispecific DVA antibody according to the present invention comprises (preferably in combination with at least one of the above mutations (i) to (iv)), a mutation which increases the *in vivo* half-life of the antibody. Such mutations are described in WO 2009/086320 A. Thus, the Fc region of the multispecific antibody may comprise, for example, an M428L/N434S or a V308F/M428L/N434S mutation, wherein a M428L/N434S mutation is preferred.

In preferred embodiments of the multispecific DVD antibody according to the present invention, the at least three paratopes ((a), (b), (d1) and/or (d2)) may be formed by at least
5 three of the CDRH1-3/CDRL1-3 sequences selected from the group consisting of SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, or are formed by CDRH1-3/CDRL1-3 sequences having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID
10 NOs: 1-6, SEQ ID NOs: 7-12, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, respectively.

Accordingly, in a particular embodiment of the multispecific DVD antibody according to the present invention, paratopes (a) and (b) are formed by CDRH1-3/CDRL1-3 sequences according to SEQ ID NOs: 1-6, and SEQ ID NOs: 7-12, respectively, or are formed by
15 CDRH1-3/CDRL1-3 sequences having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NOs: 1-6, and SEQ ID NOs: 7-12, respectively; and the at least one paratope (d1, d2) is formed by at least one of CDRH1-3/CDRL1-3 sequences selected from the group consisting
20 of SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, or is formed by at least one of CDRH1-3/CDRL1-3 sequences having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, respectively.

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In another particular embodiment of the multispecific DVD antibody according to the present invention, paratopes (a) and (b) are formed by CDRH1-3/CDRL1-3 sequences according to

SEQ ID NOs: 1-6, and SEQ ID NOs: 19-24, respectively, or are formed by CDRH1-3/CDRL1-3 sequences having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NOs: 1-6, and SEQ ID NOs: 19-24, respectively; and the at least one paratope (d1, d2) is formed by at least one of CDRH1-3/CDRL1-3 sequences selected from the group consisting of SEQ ID NOs: 7-12, and SEQ ID NOs: 13-18, or is formed by at least one of CDRH1-3/CDRL1-3 sequences having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NOs: 7-12, and SEQ ID NOs: 13-18, respectively.

In another particular embodiment of the multispecific DVD antibody according to the present invention, paratopes (a) and (b) are formed by CDRH1-3/CDRL1-3 sequences according to SEQ ID NOs: 7-12, and SEQ ID NOs: 19-24, respectively, or are formed by CDRH1-3/CDRL1-3 sequences having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NOs: 7-12, and SEQ ID NOs: 19-24, respectively; and the at least one paratope (d1, d2) is formed by at least one of CDRH1-3/CDRL1-3 sequences selected from the group consisting of SEQ ID NOs: 1-6, and SEQ ID NOs: 13-18, or is formed by at least one of CDRH1-3/CDRL1-3 sequences having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NOs: 1-6, and SEQ ID NOs: 13-18, respectively.

In another particular embodiment of the multispecific DVD antibody according to the present invention, paratopes (a) and (b) are formed by CDRH1-3/CDRL1-3 sequences according to SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, respectively, or are formed by CDRH1-3/CDRL1-3 sequences having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, respectively; and the at least one paratope (d1, d2) is formed by at

least one of CDRH1-3/CDRL1-3 sequences selected from the group consisting of SEQ ID NOs: 1-6, and SEQ ID NOs: 7-12, or is formed by at least one of CDRH1-3/CDRL1-3 sequences having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NOs: 1-6, and SEQ ID NOs: 7-12, respectively.

In another particular embodiment of the multispecific DVD antibody according to the present invention, paratopes (a) and (b) are formed by CDRH1-3/CDRL1-3 sequences according to SEQ ID NOs: 1-6, and SEQ ID NOs: 13-18, respectively, or are formed by CDRH1-3/CDRL1-3 sequences having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NOs: 1-6, and SEQ ID NOs: 13-18, respectively; and the at least one paratope (d1, d2) is formed by at least one of CDRH1-3/CDRL1-3 sequences selected from the group consisting of SEQ ID NOs: 7-12, and SEQ ID NOs: 19-24, or is formed by at least one of CDRH1-3/CDRL1-3 sequences having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NOs: 7-12, and SEQ ID NOs: 19-24, respectively.

In another particular embodiment of the multispecific DVD antibody according to the present invention, paratopes (a) and (b) are formed by CDRH1-3/CDRL1-3 sequences according to SEQ ID NOs: 7-12, and SEQ ID NOs: 13-18, respectively, or are formed by CDRH1-3/CDRL1-3 sequences having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NOs: 7-12, and SEQ ID NOs: 13-18, respectively; and the at least one paratope (d1, d2) is formed by at least one of CDRH1-3/CDRL1-3 sequences selected from the group consisting of SEQ ID NOs: 1-6, and SEQ ID NOs: 19-24, or is formed by at least one of CDRH1-3/CDRL1-3 sequences having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%,

92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NOs: 1-6, and SEQ ID NOs: 19-24, respectively.

5 In a preferred embodiment, the multispecific DVD antibody according to the present invention comprises only one paratope (d) forming a trispecific DVD antibody comprising a single (N-terminal) dual variable domain. Exemplary multispecific DVA antibodies are shown in Figure 1 C and D.

10 A preferred multispecific DVD antibody, as exemplified in Figure 1C, comprises a paratope (a) (formed by the VH1 of a first heavy chain and the VL1 of a first light chain) which is derived from the parental antibody 17H9, and a dual variable domain (formed by a dual VH2/VHx of a second heavy chain and a dual VL2/VLx of a second light chain) comprising two paratopes which are derived from the parental antibodies 15E3 and 7G6.

15 Another preferred multispecific DVD antibody, as exemplified in Figure 1D, comprises a paratope (a) (formed by the VH1 of a first heavy chain and the VL1 of a first light chain) which is derived from the parental antibody 7G6, and a dual variable domain (formed by a dual VH2/VHx of a second heavy chain and a dual VL2/VLx of a second light chain) comprising two paratopes which are derived from the parental antibodies 15E3 and 17H9.

20

Accordingly, in a preferred embodiment, the multispecific, in particular trispecific, DVD antibody according to the present invention comprises:

- (i) a first heavy chain comprising
 - 25 - a VH1 domain comprising a CDRH1 having at least 70% identity to SEQ ID NO: 1, a CDRH2 having at least 70% identity to SEQ ID NO: 2, and a CDRH3 having at least 70% identity to SEQ ID NO: 3;
- (ii) a second heavy chain comprising, preferably from the N-terminus to the C-terminus
 - 30 - a first VH domain (VHx) comprising a CDRH1 having at least 70% identity to SEQ ID NO: 7, a CDRH2 having at least 70% identity to SEQ ID NO: 8, and a CDRH3 having at least 70% identity to SEQ ID NO: 9; and

- a second VH domain (VH2) comprising a CDRH1 having at least 70% identity to SEQ ID NO: 13, a CDRH2 having at least 70% identity to SEQ ID NO: 14, and a CDRH3 having at least 70% identity to SEQ ID NO: 15;
 - (iii) a first light chain comprising
 - 5 - a VL1 domain CDRL1 having at least 70% identity to SEQ ID NO: 4, a CDRL2 having at least 70% identity to SEQ ID NO: 5, and a CDRL3 having at least 70% identity to SEQ ID NO: 6; and
 - (iv) a second light chain comprising, preferably from the N-terminus to the C-terminus
 - 10 - a first VL domain (VLx) comprising a CDRL1 having at least 70% identity to SEQ ID NO: 10, a CDRL2 having at least 70% identity to SEQ ID NO: 11, and a CDRL3 having at least 70% identity to SEQ ID NO: 12; and
 - a second VL domain (VL2) comprising a CDRL1 having at least 70% identity to SEQ ID NO: 16, a CDRL2 having at least 70% identity to SEQ ID NO: 17, and a
 - 15 CDRL3 having at least 70% identity to SEQ ID NO: 18,
- wherein "at least 70% identity" means, in each case, "at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity".
- 20 In another preferred embodiment, the multispecific, in particular trispecific, DVD antibody according to the present invention comprises:
- (i) a first heavy chain comprising
 - a VH1 domain comprising a CDRH1 having at least 70% identity to SEQ ID NO: 7, a CDRH2 having at least 70% identity to SEQ ID NO: 8, and a CDRH3 having
 - 25 at least 70% identity to SEQ ID NO: 9;
 - (ii) a second heavy chain comprising, preferably from the N-terminus to the C-terminus
 - a first VH domain (VHx) comprising a CDRH1 having at least 70% identity to SEQ ID NO: 1, a CDRH2 having at least 70% identity to SEQ ID NO: 2, and a CDRH3
 - 30 having at least 70% identity to SEQ ID NO: 3; and

- a second VH domain (VH2) comprising a CDRH1 having at least 70% identity to SEQ ID NO: 13, a CDRH2 having at least 70% identity to SEQ ID NO: 14, and a CDRH3 having at least 70% identity to SEQ ID NO: 15;
 - (iii) a first light chain comprising
 - 5 - a VL1 domain comprising a CDRL1 having at least 70% identity to SEQ ID NO: 10, a CDRL2 having at least 70% identity to SEQ ID NO: 11, and a CDRL3 having at least 70% identity to SEQ ID NO: 12; and
 - (iv) a second light chain comprising, preferably from the N-terminus to the C-terminus
 - 10 - a first VL domain (VLx) comprising a CDRL1 having at least 70% identity to SEQ ID NO: 4, a CDRL2 having at least 70% identity to SEQ ID NO: 5, and a CDRL3 having at least 70% identity to SEQ ID NO: 6; and
 - a second VL domain (VL2) comprising a CDRL1 having at least 70% identity to SEQ ID NO: 16, a CDRL2 having at least 70% identity to SEQ ID NO: 17, and a
 - 15 CDRL3 having at least 70% identity to SEQ ID NO: 18,
- wherein "at least 70% identity" means, in each case, "at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity".
- 20 In a more preferred embodiment, the multispecific, in particular trispecific, DVD antibody according to the present invention comprises:
- (i) a first heavy chain comprising
 - a VH1 domain comprising a CDRH1 according to SEQ ID NO: 1, a CDRH2 according to SEQ ID NO: 2, and a CDRH3 according to SEQ ID NO: 3;
 - 25 (ii) a second heavy chain comprising preferably from the N-terminus to the C-terminus
 - a first VH domain (VHx) comprising a CDRH1 according to SEQ ID NO: 7, a CDRH2 according to SEQ ID NO: 8, and a CDRH3 according to SEQ ID NO: 9; and
 - 30 - a second VH domain (VH2) comprising a CDRH1 according to SEQ ID NO: 13, a CDRH2 according to SEQ ID NO: 14, and a CDRH3 according to SEQ ID NO: 15;
 - (iii) a first light chain comprising

- a VL1 domain comprising a CDRL1 according to SEQ ID NO: 4, a CDRL2 according to SEQ ID NO: 5, and a CDRL3 according to SEQ ID NO: 6; and
- (iv) a second light chain comprising, preferably from the N-terminus to the C-terminus,
- 5 - a first VL domain (VLx) comprising a CDRL1 according to SEQ ID NO: 10, a CDRL2 according to SEQ ID NO: 11, and a CDRL3 according to SEQ ID NO: 12; and
- a second VL domain (VL2) comprising a CDRL1 according to SEQ ID NO: 16, a CDRL2 according to SEQ ID NO: 17, and a CDRL3 according to SEQ ID NO: 18.

10

In another more preferred embodiment, the multispecific, in particular trispecific, DVD antibody according to the present invention comprises:

- (i) a first heavy chain comprising
 - a VH1 domain comprising a CDRH1 according to SEQ ID NO: 7, a CDRH2 according to SEQ ID NO: 8, and a CDRH3 according to SEQ ID NO: 9;
 - 15 (ii) a second heavy chain comprising, preferably from the N-terminus to the C-terminus
 - a first VH domain (VHx) comprising a CDRH1 according to SEQ ID NO: 1, a CDRH2 according to SEQ ID NO: 2, and a CDRH3 according to SEQ ID NO: 3;
 - 20 and
 - a second VH domain (VH2) comprising a CDRH1 according to SEQ ID NO: 13, a CDRH2 according to SEQ ID NO: 14, and a CDRH3 according to SEQ ID NO: 15;
 - (iii) a first light chain comprising
 - 25 - a VL1 domain comprising a CDRL1 according to SEQ ID NO: 10, a CDRL2 according to SEQ ID NO: 11, and a CDRL3 according to SEQ ID NO: 12; and
 - (iv) a second light chain comprising, preferably from the N-terminus to the C-terminus
 - a first VL domain (VLx) comprising a CDRL1 according to SEQ ID NO: 4, a CDRL2 according to SEQ ID NO: 5, and a CDRL3 according to SEQ ID NO: 6; and
 - 30 - a second VL domain (VL2) comprising a CDRL1 according to SEQ ID NO: 16, a CDRL2 according to SEQ ID NO: 17, and a CDRL3 according to SEQ ID NO: 18.

In a preferred embodiment of the multispecific, in particular trispecific, DVD antibody according to the present invention, the first and second VH domains of the dual variable domain are linked via a peptide linker. Preferably, the peptide linker linking the first and second VH domains of the dual variable domain has the amino acid sequence ASTKGP.

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In a further preferred embodiment of the multispecific, in particular trispecific, DVD antibody according to the present invention, the first and second VL domains of the dual variable domain are linked via a peptide linker. Preferably, the peptide linker linking the first and second VL domains has the amino acid sequence RTVAAPSVFIPP.

10

In a preferred embodiment of the multispecific, in particular trispecific, DVD antibody according to the present invention, the peptide linker linking the first and second VH domains of the dual variable domain has the amino acid sequence ASTKGP, and the peptide linker linking the first and second VL domains has the amino acid sequence RTVAAPSVFIPP.

15

Accordingly, in a particular preferred embodiment, the multispecific, in particular trispecific, DVD antibody according to the present invention comprises:

(i) a first heavy chain comprising

- a VH1 having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NO: 29);

20

(ii) a second heavy chain comprising

- a dual variable domain having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NO: 30;

25

(iii) a first light chain comprising

- a VL having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NO: 31; and

30

(iv) a second light chain comprising

- a dual variable domain having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NO: 32;
- 5 wherein the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NOs: 1-3, 7-9 and 13-15, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NOs: 4-6, 10-12 and 16-18, respectively) are preferably maintained.
- 10 In another particular preferred embodiment, the multispecific, in particular trispecific, DVD antibody according to the present invention comprises:
- (i) a first heavy chain comprising
 - a VH having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NO: 33;
 - (ii) a second heavy chain comprising
 - a dual variable domain having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NO: 34;
 - (iii) a first light chain comprising
 - a VL having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NO: 35;
 - (iv) a second light chain comprising
 - a dual variable domain having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NO: 36,
- wherein the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NOs: 1-3, 7-9 and 13-15, respectively; and light chain CDR1,

CDR2, and CDR3 sequences as set forth in SEQ ID NOs: 4-6, 10-12 and 16-18, respectively) are preferably maintained.

- In a more preferred embodiment, the multispecific, in particular trispecific, DVD antibody according to the present invention comprises:
- 5 (i) a first heavy chain comprising
 - a VH according to SEQ ID NO: 29;
 - (ii) a second heavy chain comprising
 - a dual variable domain according to SEQ ID NO: 30;
 - 10 (iii) a first light chain comprising
 - a VL according to SEQ ID NO: 31; and
 - (iv) a second light chain comprising
 - a dual variable domain according to SEQ ID NO: 32.

- 15 In another more preferred embodiment, the multispecific, in particular trispecific, DVD antibody according to the present invention comprises:
- (i) a first heavy chain comprising
 - a VH according to SEQ ID NO: 33;
 - (ii) a second heavy chain comprising
 - a dual variable domain according to SEQ ID NO: 34;
 - 20 (iii) a first light chain comprising
 - a VL according to SEQ ID NO: 35;
 - (iv) a second light chain comprising
 - a dual variable domain according to SEQ ID NO: 36.

- 25 In a particularly preferred embodiment, the multispecific, in particular trispecific, DVD antibody according to the present invention comprises a first heavy chain constant domain according to SEQ ID NO: 55 or 59, a second heavy chain constant domain according to SEQ ID NO: 56 or 60, a first light chain constant domain according SEQ ID NO: 57 or 61, and a
- 30 second light chain constant domain according SEQ ID NO: 58 or 62.

Accordingly, in a particularly preferred embodiment, the multispecific, in particular trispecific, DVD antibody according to the present invention comprises:

- (i) a first heavy chain having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NO: 42;
- 5 (ii) a second heavy chain having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NO: 43;
- 10 (iii) a first light chain having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NO: 44; and
- (iv) a second heavy chain having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NO: 45,
- 15

wherein the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NOs: 1-3, 7-9 and 13-15, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NOs: 4-6, 10-12 and 16-18, respectively) are preferably maintained.

20

In another particularly preferred embodiment, the multispecific, in particular trispecific, DVD antibody according to the present invention comprises:

- 25 (i) a first heavy chain having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NO: 46;
- (ii) a second heavy chain having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NO: 47;
- 30 (iii) a first light chain having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%,

86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NO: 48; and

- 5 (iv) a second heavy chain having at least 70% identity (i.e. at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity) to SEQ ID NO: 49,

wherein the CDR sequences as defined above (heavy chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NOs: 1-3, 7-9 and 13-15, respectively; and light chain CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NOs: 4-6, 10-12 and 16-18, respectively)
10 are preferably maintained.

In a particular preferred embodiment, the multispecific, in particular trispecific, DVD antibody according to the present invention comprises:

- 15 (i) a first heavy chain according to SEQ ID NO: 42;
(ii) a second heavy chain according to SEQ ID NO: 43;
(iii) a first light chain according to SEQ ID NO: 44; and
(iv) a second heavy chain according to SEQ ID NO: 45.

In another particular preferred embodiment, the multispecific, in particular trispecific, DVD antibody according to the present invention comprises:

- 20 (i) a first heavy chain according to SEQ ID NO: 46;
(ii) a second heavy chain according to SEQ ID NO: 47;
(iii) a first light chain according to SEQ ID NO: 48; and
(iv) a second heavy chain according to SEQ ID NO: 49.

25

As shown in the appended examples, such trispecific IgG-DVD antibodies bind specifically to Ara h 2, Ara h 3, and Ara h 6.

Variant multispecific antibodies are also included within the scope of the invention. Thus,
30 variants of the sequences recited in the application are also included within the scope of the invention. Such variants include natural variants generated by somatic mutation *in vivo* during the immune response or *in vitro* upon culture of immortalized B cell clones.

Alternatively, variants may arise due to the degeneracy of the genetic code or may be produced due to errors in transcription or translation.

5 Multispecific antibodies of the invention may be provided in purified form. Typically, the multispecific antibody will be present in a composition that is substantially free of other polypeptides *e.g.*, where less than 90% (by weight), usually less than 60% and more usually less than 50% of the composition is made up of other polypeptides.

Nucleic Acids

10

In another aspect, the invention also provides a nucleic acid molecule comprising a polynucleotide encoding the multispecific antibody according to the present invention, as described above.

15 Examples of nucleic acid molecules and/or polynucleotides include, *e.g.*, a recombinant polynucleotide, a vector, an oligonucleotide, an RNA molecule such as an mRNA, or a DNA molecule such as a cDNA. Nucleic acids may encode the light chain and/or the heavy chain of a multispecific antibody. In other words, the light chains and the heavy chains of the multispecific antibodies may be encoded by the same nucleic acid molecule (*e.g.*, for single
20 chain antibodies or for antibodies with separate heavy and light chains in bicistronic manner or an expression cassette containing more than one ribosome entry site such as IRES). Alternatively, the light chains and the heavy chains of the multispecific antibodies may be encoded by distinct nucleic acid molecules.

25 Due to the redundancy of the genetic code, the present invention also comprises sequence variants of nucleic acid sequences, which encode the same amino acid sequences. The polynucleotide encoding the antibody (or the complete nucleic acid molecule) may be optimized for expression of the antibody. For example, codon optimization of the nucleotide sequence may be used to improve the efficiency of translation in expression systems for the
30 production of the antibody. Moreover, the nucleic acid molecule may comprise heterologous elements (*i.e.*, elements, which in nature do not occur on the same nucleic acid molecule as the coding sequence for the (heavy or light chain of) an antibody. For example, a nucleic acid molecule may comprise a heterologous promotor, a heterologous enhancer, heterologous

UTR (e.g., for optimal translation/expression), a heterologous poly-A-tail, heterologous DNA insulator elements and the like.

- A nucleic acid molecule is a molecule comprising nucleic acid components. The term nucleic acid molecule usually refers to DNA or RNA molecules. It may be used synonymous with the term "polynucleotide", i.e. the nucleic acid molecule may consist of a polynucleotide encoding the multispecific antibody. Alternatively, the nucleic acid molecule may also comprise further elements in addition to the polynucleotide encoding the multispecific antibody. Typically, a nucleic acid molecule is a polymer comprising or consisting of nucleotide monomers which are covalently linked to each other by phosphodiester-bonds of a sugar/phosphate-backbone. The term "nucleic acid molecule" also encompasses modified nucleic acid molecules, such as base-modified, sugar-modified or backbone-modified etc. DNA or RNA molecules.
- In general, the nucleic acid molecule may be manipulated to insert, delete or alter certain nucleic acid sequences. Changes from such manipulation include, but are not limited to, changes to introduce restriction sites, to amend codon usage, to add or optimize transcription and/or translation regulatory sequences, etc. It is also possible to change the nucleic acid to alter the encoded amino acids. For example, it may be useful to introduce one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, etc.) amino acid substitutions, deletions and/or insertions into the antibody's amino acid sequence. Such point mutations can modify effector functions, antigen-binding affinity, post-translational modifications, immunogenicity, etc., can introduce amino acids for the attachment of covalent groups (e.g., labels) or can introduce tags (e.g., for purification purposes). Alternatively, a mutation in a nucleic acid sequence may be "silent", i.e. not reflected in the amino acid sequence due to the redundancy of the genetic code. In general, mutations can be introduced in specific sites or can be introduced at random, followed by selection (e.g., molecular evolution). For instance, one or more nucleic acids encoding any of the light or heavy chains of an (exemplary) multispecific antibody can be randomly or directionally mutated to introduce different properties in the encoded amino acids. Such changes can be the result of an iterative process wherein initial changes are retained and new changes at other nucleotide positions are introduced. Further, changes achieved in independent steps may be combined.

In some embodiments, the polynucleotide(s) (or the (complete) nucleic acid molecule(s)) encoding the multispecific antibody may be codon-optimized. The skilled artisan is aware of various tools for codon optimization, such as those described in: Ju Xin Chin, Bevan Kai-Sheng Chung, Dong-Yup Lee, Codon Optimization OnLine (COOL): a web-based multi-objective optimization platform for synthetic gene design, *Bioinformatics*, Volume 30, Issue 15, 1 August 2014, Pages 2210–2212; or in: Grote A, Hiller K, Scheer M, Munch R, Nortemann B, Hempel DC, Jahn D, JCat: a novel tool to adapt codon usage of a target gene to its potential expression host. *Nucleic Acids Res.* 2005 Jul 1; 33(Web Server issue):W526-31; or, for example, Genscript's OptimumGene™ algorithm (as described in US 2011/0081708 A1).

For example, the nucleic acid molecule(s) of the invention may comprise a nucleic acid sequence as set forth in any one of SEQ ID NOs 63-75; or a sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity. Thereby, the nucleic acid molecule may encode any one of the exemplified antibodies IgG-scFv-2, IgG-scFv, IgG:DVD#1, and IgG:DVD#2 (by combining the sequences as shown in Table 2 below), or a sequence variant thereof as described herein.

The present invention also provides a plurality of nucleic acid molecules encoding the multispecific antibody, as described herein, wherein each of the nucleic acid molecules (of the plurality of nucleic acid molecules) comprises a polynucleotide encoding an immunoglobulin chain of the multispecific antibody. Thereby, the plurality of nucleic acid molecules, taken together, encodes (all of the immunoglobulin chains of) the multispecific antibody, as described herein. In some embodiments (e.g. in case of the exemplary multispecific antibody IgG-scFv according to the present invention), the plurality of nucleic acid molecules encoding the multispecific antibody, as described herein, may be a combination of a first and a second nucleic acid molecule, wherein the first nucleic acid molecule comprises a polynucleotide encoding the heavy chains of the multispecific antibody, and the second nucleic acid molecule comprises a polynucleotide encoding the corresponding light chains of the same multispecific antibody.

- In some embodiments (e.g. in case of the exemplary multispecific antibody IgG-scFv2 according to the present invention), the plurality of nucleic acid molecules encoding the multispecific antibody, as described herein, may be a combination of a first, a second, and a third nucleic acid molecule, wherein the first nucleic acid molecule comprises a polynucleotide encoding the first heavy chain of the multispecific antibody, the second nucleic acid molecule comprises a polynucleotide encoding the second heavy chain of the multispecific antibody, and the third nucleic acid molecule comprises a polynucleotide encoding the corresponding (first and second) light chains of the same antibody.
- 10 In some embodiments (e.g. in case of the exemplary multispecific antibodies IgG:DVD#1 and IgG:DVD#2 according to the present invention), the plurality of nucleic acid molecules encoding the multispecific antibody, as described herein, may be a combination of a first, a second, a third and a fourth nucleic acid molecule, wherein the first nucleic acid molecule comprises a polynucleotide encoding the first heavy chain of the multispecific antibody, the second nucleic acid molecule comprises a polynucleotide encoding the second heavy chain of the multispecific antibody, the third nucleic acid molecule comprises a polynucleotide encoding the first light chain of the same antibody, and the fourth nucleic acid molecule comprises a polynucleotide encoding the second light chain of the same antibody.
- 20 In general, the above description regarding the (general) features of the nucleic acid molecule of the invention applies accordingly to the nucleic acid molecules of the plurality of nucleic acid molecules. Accordingly, one or more of the polynucleotides encoding the immunoglobulin chains of the antibody may be codon-optimized. For example, the plurality may comprise a nucleic acid sequence as set forth in any one of SEQ ID NOs 63-75; or a sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity. Thereby, the plurality of nucleic acid molecules may encode any one of the exemplified multispecific antibodies IgG-scFv-2, IgG-scFv, IgG:DVD#1, IgG:DVD#2 (by combining the sequences as shown in Table 2), or a sequence variant thereof as described herein.
- 30

Vectors

Further included within the scope of the invention are vectors, for example, expression vectors, comprising a nucleic acid molecule according to the present invention or the plurality of nucleic acid molecules according to the present invention. Usually, a vector comprises a nucleic acid molecule as described above.

5

The present invention also provides a plurality of vectors comprising the plurality of nucleic acid molecules according to invention as described above. Thereby, each vector of the plurality of vectors may contain one or more nucleic acid molecules of the plurality of nucleic acid molecules according to invention as described above. In some embodiments, the plurality of vectors may be a combination of a first and a second vector, wherein the first vector comprises a first nucleic acid molecule as described above (for the combination of nucleic acid molecules) and the second vector comprises a second nucleic acid molecule as described above (for the combination of nucleic acid molecules). In some embodiments, the plurality of vectors may be a combination of a first, a second and a third vector, wherein the first vector comprises a first nucleic acid molecule as described above (for the combination of nucleic acid molecules), the second vector comprises a second nucleic acid molecule as described above (for the combination of nucleic acid molecules), and the third vector comprises a third nucleic acid molecule as described above (for the combination of nucleic acid molecules). In some embodiments, the plurality of vectors may be a combination of a first, a second, a third and a fourth vector, wherein the first vector comprises a first nucleic acid molecule as described above (for the combination of nucleic acid molecules), the second vector comprises a second nucleic acid molecule as described above (for the combination of nucleic acid molecules), the third vector comprises a third nucleic acid molecule as described above (for the combination of nucleic acid molecules), and the fourth vector comprises a fourth nucleic acid molecule as described above (for the combination of nucleic acid molecules).

A vector is usually a recombinant nucleic acid molecule, i.e. a nucleic acid molecule which does not occur in nature. Accordingly, the vector may comprise heterologous elements (i.e., sequence elements of different origin in nature). For example, the vector may comprise a multiple cloning site, a heterologous promotor, a heterologous enhancer, a heterologous selection marker (to identify cells comprising said vector in comparison to cells not comprising said vector), heterologous origin of replications, heterologous DNA insulator

30

- elements and the like. A vector in the context of the present invention is suitable for incorporating or harboring a desired nucleic acid sequence. Such vectors may be storage vectors, expression vectors, cloning vectors, transfer vectors etc. A storage vector is a vector which allows the convenient storage of a nucleic acid molecule. Thus, the vector may
- 5 comprise a sequence corresponding, e.g., to a (heavy and/or light chain of a) desired multispecific antibody according to the present invention. An expression vector may be used for production of expression products such as RNA, e.g. mRNA, or peptides, polypeptides or proteins. For example, an expression vector may comprise sequences needed for transcription of a sequence stretch of the vector, such as a (heterologous) promoter sequence. A cloning
- 10 vector is typically a vector that contains a cloning site, which may be used to incorporate nucleic acid sequences into the vector. A cloning vector may be, e.g., a plasmid vector or a bacteriophage vector. A transfer vector may be a vector which is suitable for transferring nucleic acid molecules into cells or organisms, for example, viral vectors. A vector in the context of the present invention may be, e.g., an RNA vector or a DNA vector. For example,
- 15 a vector in the sense of the present application comprises a cloning site, a selection marker, such as an antibiotic resistance factor, and a sequence suitable for multiplication of the vector, such as an origin of replication. A vector in the context of the present application may be a plasmid vector.
- 20 As used herein, the term "vector" may also refer to a delivery vector, e.g. for viral or non-viral delivery of a nucleic acid of the invention. Alternatively, it may be referred to viral or non-viral delivery systems. Accordingly, the present invention also provides a delivery vector/system comprising the nucleic acid molecule as described above (or comprising an expression vector as described above). The delivery vector/system may be viral or non-viral.
- 25 Various examples of viral and non-viral delivery vectors/systems are known in the art and described, for example, in Nayerossadat N, Maedeh T, Ali PA. Viral and nonviral delivery systems for gene delivery. *Adv Biomed Res.* 2012;1:27. doi:10.4103/2277-9175.98152, which is incorporated herein by reference. Non-limiting examples of viral delivery vectors/systems include retroviral vectors; adenoviral vectors; adeno-associated viral (AAV)
- 30 vectors, including helper-dependent adenoviral vectors and hybrid adenoviral vectors; herpes simplex virus vectors; lentivirus vectors; poxvirus vectors and Epstein-Barr virus vectors. Among the viral vectors, adenoviral vectors and adeno-associated viral (AAV) vectors are preferred. Non-limiting examples of non-viral delivery vectors/systems include chemical and

non-chemical methods. Non-chemical delivery includes physical methods, such as electroporation and other methods for transient penetration of the cell membrane by mechanical, electrical, ultrasonic, hydrodynamic, or laser-based energy; naked DNA or RNA delivery; gene gun; hydrodynamic delivery; ultrasound delivery and magnetofection.

- 5 Chemical non-viral delivery systems include cationic particles, in particular cationic lipids/liposomes, cationic polymers and lipid/polymer systems. Among non-viral vectors/systems, cationic liposomes are preferred.

Cells

10

In a further aspect, the present invention also provides a (host) cell expressing the antibody according to the present invention; and/or comprising the vector (or the plurality of vectors) according to the present invention. The (host) cell may be an isolated cell, which is not part of a human or animal body, e.g. a cell line or an engineered cell. The cell may express the

15 nucleic acid(s) or vector(s) of the invention in a recombinant manner, e.g. in a heterologous manner (i.e., the cell/cell type does not express the antibody or an antigen-binding fragment thereof in nature).

20

Examples of such cells include, but are not limited to, eukaryotic cells, e.g., yeast cells, animal cells or plant cells. Other examples of such cells include, but are not limited to, prokaryotic cells, e.g. *E. coli*. In some embodiments, the cells are mammalian cells, such as a mammalian cell line. Examples include human cells, CHO cells, HEK293 cells, PER.C6 cells, NS0 cells, human liver cells, myeloma cells or hybridoma cells.

25

The cell may be transfected with a vector according to the present invention, for example with an expression vector. The term "transfection" refers to the introduction of nucleic acid molecules, such as DNA or RNA (e.g. mRNA) molecules, into cells, e.g. into eukaryotic or prokaryotic cells. In the context of the present invention, the term "transfection" encompasses any method known to the skilled person for introducing nucleic acid molecules into cells,

30 such as into mammalian cells. Such methods encompass, for example, electroporation, lipofection, e.g. based on cationic lipids and/or liposomes, calcium phosphate precipitation, nanoparticle based transfection, virus based transfection, or transfection based on cationic

polymers, such as DEAE-dextran or polyethylenimine etc. In some embodiments, the introduction is non-viral.

Moreover, the cells of the present invention may be transfected stably or transiently with the vector or plurality of vectors according to the present invention, e.g. for expressing the multispecific antibody according to the present invention. In some embodiments, the cells are stably transfected with the vector(s) according to the present invention encoding the multispecific antibody according to the present invention. In other embodiments, the cells are transiently transfected with the vector(s) according to the present invention encoding the multispecific antibody according to the present invention.

Accordingly, the present invention also provides a recombinant host cell, which heterologously expresses the multispecific antibody of the invention. For example, the cell may be of another species than the antibody (e.g., CHO cells expressing human antibodies). In some embodiments, the cell type of the cell does not express (such) antibodies in nature. Moreover, the host cell may impart a post-translational modification (PTM; e.g., glycosylation) on the antibody that is not present in their native state. Such a PTM may result in a functional difference (e.g., decreased immunogenicity). Accordingly, the multispecific antibody of the invention may have a post-translational modification, which is distinct from the naturally produced antibody (e.g., an antibody of an immune response in a human).

Production of Antibodies

Multispecific antibodies according to the invention can be made by any method known in the art. For example, the general methodology for making monoclonal antibodies using hybridoma technology is well known (Kohler, G. and Milstein, C., 1975; Kozbar et al. 1983).

Standard techniques of molecular biology may be used to prepare DNA sequences encoding the multispecific antibodies of the present invention. Desired DNA sequences may be synthesized completely or in part, e.g., using oligonucleotide synthesis techniques. Site-directed mutagenesis and polymerase chain reaction (PCR) techniques may be used as appropriate.

Any suitable host cell/vector system may be used for expression of the DNA sequences encoding the antibody molecules of the present invention. Eukaryotic, *e.g.*, mammalian, host cell expression systems may be used for production of antibody molecules, such as antibody light and heavy chain molecules. Suitable mammalian host cells include, but are not limited to, CHO, HEK293, PER.C6, NS0, myeloma or hybridoma cells. Also, prokaryotic, *e.g.* bacterial host cell expression systems may be used for the production of antibody molecules, such as antibody light and heavy chain molecules. Suitable bacterial host cells include, but are not limited to, *E. coli* cells.

- 10 Accordingly, the present invention provides a method for preparing the multispecific antibody, or an immunoglobulin chain(s) thereof, according to the present invention, said method comprising
- (i) culturing the host cell as described above; and
 - (ii) isolating the antibody or immunoglobulin chain(s) thereof from the culture.

15 In other words, the present invention also provides a process for the production of an antibody molecule according to the present invention comprising culturing a (heterologous) host cell comprising (a) vector(s) encoding (a) nucleic acid(s) of the present invention, in particular under conditions suitable for expression of protein from DNA encoding the antibody molecule(s) of the present invention, and isolating the antibody molecule(s).

20

For production of the multispecific antibody comprising both heavy and both light chains, a host cell, such as a cell line, may be transfected with two vectors, a first vector encoding a light chain polypeptide and a second vector encoding a heavy chain polypeptide, *e.g.* as described above. In a particular embodiment, the host cell, such as a cell line, may be transfected with three vectors, a first vector encoding a light chain polypeptide, a second vector encoding a first heavy chain polypeptide, and a third vector encoding a second heavy chain polypeptide *e.g.* as described above. In a further particular embodiment, the host cell, such as a cell line, may be transfected with four vectors, a first vector encoding a first light chain polypeptide, a second vector encoding a second light chain polypeptide, a third vector encoding a first heavy chain polypeptide, and a fourth vector encoding a second heavy chain polypeptide *e.g.* as described above. Alternatively, a single vector may be used, the vector including sequences encoding light chain and heavy chain polypeptides.

25

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Thus, the invention also provides a method for preparing a recombinant cell, comprising the steps of: (i) providing one or more nucleic acids that encode(s) the multispecific antibody of the invention; (ii) inserting the nucleic acid(s) into (an) expression vector(s) and (iii) 5 transfecting the vector(s) into a (heterologous) host cell in order to permit expression of the multispecific antibody of interest in that host cell. The nucleic acid of step (i) may, but need not, be manipulated to introduce restriction sites, to change codon usage, and/or to optimize transcription and/or translation regulatory sequences.

10 Furthermore, the invention also provides a method of preparing a transfected host cell, comprising the step of transfecting a host cell with one or more nucleic acids that encode a multispecific antibody of interest. Thus the procedures for first preparing the nucleic acid(s) and then using it to transfect a host cell can be performed at different times by different people in different places (e.g., in different countries).

15

These recombinant cells of the invention can then be used for expression and culture purposes. They are particularly useful for expression of antibodies for large-scale pharmaceutical production. They can also be used as the active ingredient of a pharmaceutical composition. Any suitable culture technique can be used, including but not 20 limited to static culture, roller bottle culture, ascites fluid, hollow-fiber type bioreactor cartridge, modular minifermenter, stirred tank, microcarrier culture, ceramic core perfusion, etc.

The transfected host cell may be a eukaryotic cell, including yeast and animal cells, 25 particularly mammalian cells (e.g., CHO cells, NS0 cells, human cells such as PER.C6, HEK293 or HKB-11 cells, myeloma cells, or a human liver cell), as well as plant cells. In some embodiments, the transfected host cell is a mammalian cell, such as a human cell. In some embodiments, expression hosts can glycosylate the antibody of the invention, particularly with carbohydrate structures that are not themselves immunogenic in humans. In some 30 embodiments the transfected host cell may be able to grow in serum-free media. In further embodiments the transfected host cell may be able to grow in culture without the presence of animal-derived products. The transfected host cell may also be cultured to give a cell line.

The invention also provides a method of preparing the antibody of interest comprising the steps of: culturing or sub-culturing a transfected host cell population, e.g. a stably transfected host cell population, under conditions where the antibody of interest is expressed and, optionally, purifying the antibody of interest. The transfected host cell population may be prepared by (i) providing nucleic acid(s) encoding a selected multispecific antibody of interest, (ii) inserting the nucleic acid(s) into an expression vector, (iii) transfecting the vector in a host cell that can express the antibody of interest, and (iv) culturing or sub-culturing the transfected host cell comprising the inserted nucleic acids to produce the multispecific antibody of interest.

10

In some embodiments, multispecific antibodies according to the invention may be produced by (i) expressing (a) nucleic acid sequence(s) according to the invention in a host cell, e.g. by use of a vector (or host cell) according to the present invention, and (ii) isolating the expressed antibody product. Additionally, the method may include (iii) purifying the isolated multispecific antibody.

15

Accordingly, after production, the antibodies may be further purified, if desired, using filtration, centrifugation and various chromatographic methods such as HPLC or affinity chromatography. Techniques for purification of antibodies, e.g., monoclonal antibodies, including techniques for producing pharmaceutical-grade antibodies, are well known in the art.

20

Compositions and kits

25 The present invention also provides a composition comprising one or more of:

- (i) the multispecific antibody of the present invention;
- (ii) the nucleic acid or the plurality of nucleic acids of the present invention;
- (iii) the vector or the plurality of vectors of the present invention; or
- (iv) the cell expressing the multispecific antibody according to the present invention or comprising the vector according to the present invention.

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The composition may be used for treatment or diagnostic purposes. Accordingly, the composition may be a pharmaceutical composition or a diagnostic composition. The composition may comprise a (pharmaceutically acceptable) excipient, diluent or carrier.

- 5 Accordingly, the present invention also provides a pharmaceutical composition comprising the multispecific antibody according to the present invention, the nucleic acid or the plurality of nucleic acids of the present invention, the vector or the plurality of vectors of the present invention, and/or the cell according to the present invention.
- 10 The pharmaceutical composition may optionally also contain a pharmaceutically acceptable carrier, diluent and/or excipient. Although the carrier or excipient may facilitate administration, it should not itself induce the production of antibodies harmful to the individual receiving the composition. Nor should it be toxic. Suitable carriers may be large, slowly metabolized macromolecules such as proteins, polypeptides, liposomes,
- 15 polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers and inactive virus particles. In some embodiments, the pharmaceutically acceptable carrier, diluent and/or excipient in the pharmaceutical composition is not an active component in respect to peanut allergy.
- 20 Pharmaceutically acceptable salts can be used, for example mineral acid salts, such as hydrochlorides, hydrobromides, phosphates and sulphates, or salts of organic acids, such as acetates, propionates, malonates and benzoates.

- Pharmaceutically acceptable carriers in a pharmaceutical composition may additionally
- 25 contain liquids such as water, saline, glycerol and ethanol. Additionally, auxiliary substances, such as wetting or emulsifying agents or pH buffering substances, may be present in such compositions. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries and suspensions, for ingestion by the subject.

- 30 Pharmaceutical compositions may be prepared in various forms. For example, the compositions may be prepared as injectables, either as liquid solutions or suspensions. Solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection can also be

prepared (e.g., a lyophilized composition, similar to Synagis™ and Herceptin®, for reconstitution with sterile water containing a preservative). The composition may be prepared for topical administration e.g., as an ointment, cream or powder. The composition may be prepared for oral administration e.g., as a tablet or capsule, as a spray, or as a syrup (optionally
5 flavored). The composition may be prepared for pulmonary administration e.g., as an inhaler, using a fine powder or a spray. The composition may be prepared as a suppository or pessary. The composition may be prepared for nasal, aural or ocular administration e.g., as drops. The composition may be in kit form, designed such that a combined composition is reconstituted just prior to administration to a subject. For example, a lyophilized antibody may be provided
10 in kit form with sterile water or a sterile buffer.

In some embodiments, the (only) active ingredient in the composition is the multispecific antibody as described herein. As such, it may be susceptible to degradation in the gastrointestinal tract. Thus, if the composition is to be administered by a route using the
15 gastrointestinal tract, the composition may contain agents which protect the antibody from degradation but which release the antibody once it has been absorbed from the gastrointestinal tract.

A thorough discussion of pharmaceutically acceptable carriers is available in Gennaro (2000)
20 Remington: The Science and Practice of Pharmacy, 20th edition, ISBN: 0683306472.

The present invention also provides a method of preparing a pharmaceutical composition comprising the steps of: (i) preparing a multispecific antibody of the invention; and (ii) admixing the purified multispecific antibody with one or more pharmaceutically acceptable
25 excipients, diluents or carriers.

In other embodiments, a method of preparing a pharmaceutical composition comprises the step of: admixing a multispecific antibody with one or more pharmaceutically-acceptable carriers, wherein the multispecific antibody is a monoclonal antibody.
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Pharmaceutical compositions may generally have a pH between 5.5 and 8.5, in some embodiments this may be between 6 and 8, for example about 7. The pH may be maintained by the use of a buffer. The composition may be sterile and/or pyrogen free. The composition

may be isotonic with respect to humans. In some embodiments pharmaceutical compositions are supplied in hermetically-sealed containers.

Within the scope of the invention are compositions present in several forms of administration; the forms include, but are not limited to, those forms suitable for parenteral administration, e.g., by injection or infusion, for example by bolus injection or continuous infusion. Where the product is for injection or infusion, it may take the form of a suspension, solution or emulsion in an oily or aqueous vehicle and it may contain formulatory agents, such as suspending, preservative, stabilizing and/or dispersing agents. Alternatively, the antibody may be in dry form, for reconstitution before use with an appropriate sterile liquid.

A vehicle is typically understood to be a material that is suitable for storing, transporting, and/or administering a compound, such as a pharmaceutically active compound, in particular the multispecific antibodies as described herein. For example, the vehicle may be a physiologically acceptable liquid, which is suitable for storing, transporting, and/or administering a pharmaceutically active compound, in particular the multispecific antibodies as described herein. Once formulated, the compositions can be administered directly to the subject. In some embodiments the compositions are adapted for administration to mammalian, e.g., human subjects.

Pharmaceutical compositions may include an antimicrobial, particularly if packaged in a multiple dose format. They may comprise detergent e.g., a Tween (polysorbate), such as Tween 80. Detergents are generally present at low levels e.g., less than 0.01%. Compositions may also include sodium salts (e.g., sodium chloride) to give tonicity. For example, a concentration of 10 ± 2 mg/ml NaCl is typical.

Further, pharmaceutical compositions may comprise a sugar alcohol (e.g., mannitol) or a disaccharide (e.g., sucrose or trehalose) e.g., at around 15-30 mg/ml (e.g., 25 mg/ml), particularly if they are to be lyophilized or if they include material which has been reconstituted from lyophilized material. The pH of a composition for lyophilization may be adjusted to between 5 and 8, or between 5.5 and 7, or around 6.1 prior to lyophilization.

The pharmaceutical compositions may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intraperitoneal, intrathecal, intraventricular, transdermal, transcutaneous, topical, subcutaneous, intranasal, enteral, sublingual, intravaginal or rectal routes. Optionally, the pharmaceutical composition may be prepared for oral administration, e.g. as tablets, capsules and the like, for topical administration, or as injectable, e.g. as liquid solutions or suspensions. In some embodiments, the pharmaceutical composition is an injectable. Solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection are also encompassed, for example the pharmaceutical composition may be in lyophilized form.

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For injection, e.g. intravenous, cutaneous or subcutaneous injection, or injection at the site of affliction, the active ingredient may be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles such as Sodium Chloride Injection, Ringer's Injection, Lactated Ringer's Injection. Preservatives, stabilizers, buffers, antioxidants and/or other additives may be included, as required. Whether it is an antibody, a peptide, a nucleic acid molecule, or another pharmaceutically useful compound that is to be given to an individual, administration is usually in an "effective amount", e.g. in a "prophylactically effective amount" or a "therapeutically effective amount" (as the case may be), this being sufficient to show benefit to the individual. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of what is being treated, in particular the nature and severity of a peanut allergy. For injection, the pharmaceutical composition may be provided for example in a pre-filled syringe.

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The pharmaceutical composition may also be administered orally in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient, i.e. the antibody as defined above, is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

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The pharmaceutical composition may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, e.g. including accessible epithelial tissue. Suitable topical formulations are readily prepared for each of these areas or organs. For topical applications, the pharmaceutical composition may be formulated in a suitable ointment, containing the pharmaceutical composition, particularly its components as defined above, suspended or dissolved in one or more carriers. Carriers for topical administration include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated in a suitable lotion or cream. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

Dosage treatment may be a single dose schedule or a multiple dose schedule. For a single dose, e.g. a daily, weekly or monthly dose, the amount of the antibody in the pharmaceutical composition, may not exceed 1 g or 500 mg. In some embodiments, for a single dose, the amount of the antibody in the pharmaceutical composition, may not exceed 200 mg, or 100 mg. For example, for a single dose, the amount of the antibody in the pharmaceutical composition, may not exceed 50 mg.

In some embodiments, the composition may include multispecific antibodies of the invention, wherein the antibodies may make up at least 50% by weight (e.g., 60%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more) of the total protein in the composition. In the composition, the multispecific antibodies may be in purified form.

As an alternative to delivering multispecific antibodies for therapeutic purposes, it is possible to deliver nucleic acid (typically DNA) that encodes the monoclonal multispecific antibody of interest to a subject, such that the nucleic acid can be expressed in the subject *in situ* to provide a desired therapeutic effect. Suitable gene therapy and nucleic acid delivery vectors are known in the art.

Pharmaceutical compositions typically include an "effective" amount of one or more multispecific antibodies as described herein, i.e. an amount that is sufficient to treat, ameliorate, attenuate, decrease or prevent a desired disease or condition, or to exhibit a detectable therapeutic effect. Therapeutic effects also include reduction or attenuation in pathogenic potency or physical symptoms. The precise effective amount for any particular subject will depend upon their size, weight, and health, the nature and extent of the condition, and the therapeutics or combination of therapeutics selected for administration. The effective amount for a given situation is determined by routine experimentation and is within the judgment of a clinician. An effective dose may generally be from about 0.005 to about 100 mg/kg, for example from about 0.0075 to about 50 mg/kg or from about 0.01 to about 10 mg/kg. In some embodiments, the effective dose will be from about 0.02 to about 5 mg/kg, of the antibody (e.g. amount of the antibody in the pharmaceutical composition) in relation to the bodyweight (e.g., in kg) of the individual to which it is administered.

Moreover, the pharmaceutical composition may also comprise an additional active component, which may be a further antibody or a component, which is not an antibody. In other embodiments, the pharmaceutical composition may not comprise an additional active component (in addition to the multispecific antibody of the invention or respective nucleic acids, vectors or cells as described above).

Accordingly, the pharmaceutical composition may comprise one or more of the additional active components. The multispecific antibody of the invention can be present either in the same pharmaceutical composition as the additional active component or, alternatively, the multispecific antibody may be comprised by a first pharmaceutical composition and the additional active component may be comprised by a second pharmaceutical composition different from the first pharmaceutical composition. Accordingly, if more than one additional active component is envisaged, each additional active component and the multispecific antibody may be comprised in a different pharmaceutical composition. Such different pharmaceutical compositions may be administered either combined/simultaneously or at separate times or at separate locations (e.g. separate parts of the body), optionally by different routes of administration.

The multispecific antibody and the additional active component may provide an additive therapeutic effect, such as a synergistic therapeutic effect. The term “synergy” is used to describe a combined effect of two or more active agents that is greater than the sum of the individual effects of each respective active agent. Thus, where the combined effect of two or more agents results in “synergistic inhibition” of an activity or process, it is intended that the inhibition of the activity or process is greater than the sum of the inhibitory effects of each respective active agent. The term “synergistic therapeutic effect” refers to a therapeutic effect observed with a combination of two or more therapies wherein the therapeutic effect (as measured by any of a number of parameters) is greater than the sum of the individual therapeutic effects observed with the respective individual therapies.

Preferably, the composition comprises at least one multispecific antibody according to the present invention. However, in a particular embodiment, the composition may also comprise two, three or more different multispecific antibodies according to the present invention which may be selected from the four different antibodies IgG-scFv-2, IgG-scFv, IgG:DVD#1, IgG:DVD#2, or the variants thereof, as described above. As shown in the appended examples, each of IgG-scFv-2, IgG-scFv, IgG:DVD#1, IgG:DVD#2 bind to distinct, non-overlapping epitopes of Ara h 2, Ara h 3 and Ara h 6.

Alternatively or additionally, the composition may further comprise at least one additional agent useful for treating peanut allergy. The additional agent useful for treating peanut allergy may be selected from the group comprising: a β -adrenergic agonist (e.g. epinephrine), antihistamine, a corticosteroid, an anti-IgE antibody, an anti-IgE antibody binding fragment, a peptide vaccine and further antibodies capable of binding to a peanut allergen, such as for example one or more of the parental antibodies 17H9, 7G6, 15E3 and 2F8 from which the multispecific antibodies according to the present invention are derived. In some embodiments, the composition comprises a β -adrenergic agonist, such as epinephrine.

In some embodiments, the composition comprises a peanut allergen. The peanut allergen may be untreated or treated peanut, such as peanut powder, roasted peanut or peanut butter. In some embodiments, the peanut allergen may be a commercially available product, such as Palforzia (defatted powder of peanuts). The peanut allergen may be a peanut protein, such as Ara h 1, Ara h 2, Ara h 3, Ara h 4, Ara h 5, Ara h 6/7, Ara h 8, Ara h 9 and Ara h 10/11. In

a specific embodiment the peanut protein may be in particular selected from Ara h 2, Ara h 3 and Ara h 6, or a combination thereof. The peanut allergen may be of peanut origin, recombinantly expressed or is a synthetic peanut peptide. In some embodiments, the anti-peanut allergen antibodies, as described herein, may be pre-incubated with the peanut allergen and may be administered as a mixture to a subject.

Combining a peanut allergen, preferably selected from the group consisting of Ara h 1, Ara h 2, Ara h 3, Ara h 4, Ara h 5, Ara h 6/7, Ara h 8, Ara h 9 and Ara h 10/11 or a mixture thereof, or more preferably selected from the group consisting of Ara h2, Ara h3 and Ara h6 or a mixture thereof, with the multispecific antibodies of the invention increases the safety of administering the allergen (e.g. in desensitization). Furthermore, without being bound to any theory, the present inventors assume that the combination of multispecific antibodies with the respective allergens (targeted by the antibodies), i.e. the combination of passive (antibodies) and active (allergen) immunization, has a synergistic effect. The components, i.e. the allergen component and the multispecific antibody component, may be administered simultaneously or in a timely staggered manner, e.g. by administering the components separately from one another, e.g. within 15, 30, 60 or 90 min.

The present invention also provides a diagnostic composition comprising a multispecific antibody according to the present invention, (a) nucleic acid(s) according to the present invention, (a) vector(s) according to the present invention, and/or a cell according to the present invention. The diagnostic composition may optionally comprise suitable means for detection, such as reagents conventionally used in immuno- or nucleic acid based diagnostic methods.

The multispecific antibodies described herein are, for example, suited for diagnostic purposes. Accordingly, they may be used in immunoassays, in which they can be utilized in liquid phase or bound to a solid phase carrier. Such immunoassays may be competitive or non-competitive immunoassays; in either a direct or in an indirect format. Examples of such immunoassays include, but are not limited to, radioimmunoassay (RIA), enzyme-linked immunoassay (ELISA), sandwich (immunometric assay), immunohistochemistry, flow cytometry and Western blot assay. To this end, the multispecific antibody may be labelled, e.g. as described above.

In a further aspect the present invention also provides a kit comprising one or more of

- (i) the multispecific antibody according to the present invention, as described above,
- (ii) the nucleic acid molecule (or the plurality of nucleic acid molecules) according to the present invention as described above,
- (iii) the vector (or the plurality of vectors) according to the present invention as described above,
- (iv) the cell according to the present invention as described above, and/or
- (v) the composition according to the present invention as described above.

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In addition, the kit may comprise means for administration of the multispecific antibody according to the present invention, the nucleic acid according to the present invention, the vector according to the present invention, the cell according to the present invention or the pharmaceutical composition according to the present invention, such as a syringe or a vessel, a leaflet, and/or a co-agent to be administered as described herein. For example, the kit may contain a leaflet, e.g. comprising instructions for use. In addition or alternatively, the kit may comprise one or more reagents, e.g. for use in appropriate diagnostic assays. In some instances, the kit may contain a reference agent or control. In some embodiments, the composition of the invention may be provided in kit form, e.g., designed such that a combined composition is reconstituted just prior to administration to a subject. For example, a lyophilized multispecific antibody may be provided in kit form with sterile water or a sterile buffer (e.g., in a separate container).

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In some embodiments, the kit may comprise two, three or more multispecific antibodies (or nucleic acids encoding such antibodies or compositions comprising such antibodies), wherein the distinct antibodies may be provided in distinct containers. In some embodiments, the kit may comprise one, two, three or more multispecific antibodies (or nucleic acids encoding such antibodies or compositions comprising such antibodies) according to the present invention, and one, two or more further antibodies (or nucleic acids encoding such antibodies or compositions comprising such antibodies) capable of binding to a peanut allergen, which may be e.g. selected from the parental antibodies 17H9, 7G6, 15E3 and 2F8, or antigen-binding fragments thereof, wherein the distinct antibodies (or nucleic acids

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encoding such antibodies or compositions comprising such antibodies) may be provided in distinct containers

Alternatively or additionally, the kit may further comprise at least one additional agent useful for treating peanut allergy, which may be provided in a separate container. The additional agent useful for treating peanut allergy may be selected from the group comprising: a β -adrenergic agonist (e.g. epinephrine), antihistamine, a corticosteroid, an anti-IgE antibody, an anti-IgE antibody binding fragment, a peptide vaccine and further antibodies capable of binding to a peanut allergen. In some embodiments, the kit comprises a β -adrenergic agonist, such as epinephrine.

In some embodiments, the kit comprises a peanut allergen. The peanut allergen may be untreated or treated peanut, such as peanut powder, roasted peanut or peanut butter. In some embodiments, the peanut allergen may be a commercially available product, such as Palforzia (defatted powder of peanuts). The peanut allergen may be a peanut protein, such as Ara h 1, Ara h 2, Ara h 3, Ara h 4, Ara h 5, Ara h 6/7, Ara h 8, Ara h 9 and Ara h 10/11. In a specific embodiment the peanut protein may be in particular selected from Ara h 2, Ara h 3 and Ara h 6, or a combination thereof. The peanut allergen may be of peanut origin, recombinantly expressed or is a synthetic peanut peptide. In some embodiments, the anti-peanut allergen antibodies, as described herein, may be provided (in a separate container) with instructions for pre-incubation with the peanut allergen before it is administered as a mixture to a subject. In other embodiments, the anti-peanut allergen antibodies, as described herein, may be provided (in a separate container) with instructions for separate administration with the peanut allergen in a combined treatment schedule.

Medical treatments and other uses

In a further aspect, the present invention provides the use of the multispecific antibody according to the present invention, the nucleic acid molecule (or the plurality of nucleic acid molecules) according to the present invention, the vector (or the plurality of vectors) according to the present invention, the cell according to the present invention or the (pharmaceutical) composition according to the present invention as a medicament. In particular, the multispecific antibody according to the present invention, the nucleic acid molecule (or the plurality of nucleic acid molecules) according to the present invention, the

vector (or the plurality of vectors) according to the present invention, the cell according to the present invention or the (pharmaceutical) composition according to the present invention may be used in prophylaxis and/or treatment of a peanut allergy or of a symptom of a peanut allergy, such as an anaphylactic reaction due to a peanut allergy.

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Accordingly, the present invention also provides a method of treating, ameliorating or reducing a peanut allergy or a symptom of a peanut allergy, such as an anaphylactic reaction due to a peanut allergy, or lowering the risk of (occurrence of) a peanut allergy or a symptom of a peanut allergy, such as an anaphylactic reaction due to a peanut allergy, comprising:
10 administering to a subject (in need thereof), (a therapeutically effective amount of) a multispecific antibody according to the present invention, a nucleic acid molecule (or the plurality of nucleic acid molecules) according to the present invention, a vector (or the plurality of vectors) according to the present invention, a cell according to the present invention or a (pharmaceutical) composition according to the present invention. Moreover,
15 the present invention also provides the use of a multispecific antibody according to the present invention, a nucleic acid molecule (or the plurality of nucleic acid molecules) according to the present invention, a vector (or the plurality of vectors) according to the present invention, a cell according to the present invention, or a pharmaceutical composition according to the present invention in the manufacture of a medicament for prophylaxis,
20 treatment or attenuation of a peanut allergy or of a symptom of a peanut allergy, such as an anaphylactic reaction due to a peanut allergy.

As used herein, the terms "treat" or "treatment" include therapeutic treatment and prophylactic or preventative measures. Prophylaxis of a peanut allergy refers in particular to prophylactic
25 settings, wherein the subject was either not diagnosed with a peanut allergy (either no diagnosis was performed or diagnosis results were negative) and/or the subject does not show symptoms of a peanut allergy. Prophylaxis of a symptom of a peanut allergy, such as an anaphylactic reaction due to a peanut allergy, refers in particular to prophylactic settings, wherein the subject is not currently experiencing a symptom of a peanut allergy, such as an
30 anaphylactic reaction due to a peanut allergy, but may possibly expect to experience a symptom of a peanut allergy, such as an anaphylactic reaction due to a peanut allergy, in the (near) future, e.g. due to the contact with substances (e.g., food intake) of unknown components or known to contain peanut (components). In therapeutic settings, in contrast,

the subject is typically diagnosed with a peanut allergy and/or showing symptoms of a peanut allergy. Of note, the terms "treatment" and "therapy"/"therapeutic" include (complete) cure as well as attenuation/reduction of a peanut allergy and/or related symptoms.

- 5 In general, the object of the "treatment" may be to decrease, ameliorate, inhibit, prevent or slow down (lessen or delay) an undesired physiological change or disorder, such as the peanut allergy or a symptom of a peanut allergy, such as an anaphylactic reaction due to a peanut allergy. Beneficial or desired clinical results of a treatment include, but are not limited to, alleviation of symptoms, diminishment of the extent of a disease, stabilized (i.e., not
10 worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival, e.g. as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the condition or disorder as well as those prone to have the condition or disorder or those in
15 which the manifestation of the condition or disorder or the risk thereof is to be decreased, delayed or prevented.

In some embodiments the subject may be a human. The human may be selected from the group of a human suffering from peanut allergy, a peanut-sensitized human without clinical
20 relevant allergy, a human suffering from peanut allergy that underwent immunotherapy, a human at risk of developing a peanut allergy and a human of unknown clinical history for peanut allergy.

Symptoms of peanut allergy may include one or more of skin rash, itching skin, itching or
25 tingling sensation in or around the mouth or throat, headache, sneezing, swelling, nausea, diarrhea or anaphylaxis. Whether or not a subject suffers from peanut allergy may be determined by correlation of allergic symptoms to contact with (e.g. intake of) peanuts or products containing components of peanuts. Accordingly, diagnosis may include a food diary and/or an elimination diet. Additionally or alternatively, an allergen skin test and/or a blood
30 test (for peanut-allergy IgE) may be performed.

One way of checking efficacy of therapeutic treatment involves monitoring disease symptoms after administration of the antibody or of the composition. Treatment can be a single dose

schedule or a multiple dose schedule. In some embodiments, an antibody, antibody fragment, nucleic acid, vector, cell, or composition as described herein may be administered to a subject in need of such treatment. Such a subject includes, but is not limited to, one who is particularly at risk of, or susceptible to, a peanut allergy or a symptom of a peanut allergy,
5 such as an anaphylactic reaction due to a peanut allergy.

The multispecific antibody according to the present invention, the nucleic acid molecule (or the plurality of nucleic acid molecules) according to the present invention, the vector (or the plurality of vectors) according to the present invention, the cell according to the present
10 invention, or the pharmaceutical composition according to the present invention may be administered by any route of administration including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intraperitoneal, transdermal, transcutaneous, topical, subcutaneous, intranasal, enteral, sublingual or rectal routes. In addition, any gene therapy approaches may be used, e.g. the multispecific antibody according to the present invention
15 may be administered as nucleic acid or vector encoding said antibody, e.g. using viral or non-viral vectors as described above. In some embodiments, the multispecific antibody according to the present invention, the nucleic acid molecule (or the plurality of nucleic acid molecules) according to the present invention, the vector (or the plurality of vectors) according to the present invention, the cell according to the present invention or the pharmaceutical
20 composition according to the present invention may be administered systemically, for example by intravenous or subcutaneous administration.

Combination treatments

25 In some embodiments, co-administration or sequential administration of (i) a multispecific antibody according to the present invention, a nucleic acid molecule (or the plurality of nucleic acid molecules) according to the present invention, a vector (or the plurality of vectors) according to the present invention, a cell according to the present invention or the pharmaceutical composition according to the present invention and (ii) a co-agent may be
30 desirable. In some instances, the co-agent may be comprised in the pharmaceutical composition.

- Alternatively, or additionally, at least one additional agent useful for treating peanut allergy may be administered (in combination) with the multispecific antibodies, as described herein. The additional agent useful for treating peanut allergy may be selected from the group comprising: a β -adrenergic agonist (e.g. epinephrine), antihistamine, a corticosteroid, an anti-
5 IgE antibody, an anti-IgE antibody binding fragment, a peptide vaccine and further antibodies capable of binding to a peanut allergen, such as, for example, one or more of the (monospecific) parental antibodies 17H9, 7G6, 15E3, 2F8 . In some embodiments, the additional agent is a β -adrenergic agonist, such as epinephrine.
- 10 In some embodiments, a peanut allergen may be administered (in combination) with the multispecific antibodies, as described herein. The peanut allergen may be untreated or treated peanut, such as peanut powder, roasted peanut or peanut butter. In some embodiments, the peanut allergen may be a commercially available product, such as Palforzia (defatted powder of peanuts). The peanut allergen may be a peanut protein, such as Ara h 1, Ara h 2, Ara h 3,
15 Ara h 4, Ara h 5, Ara h 6/7, Ara h 8, Ara h 9 and Ara h 10/11. In a specific embodiment the peanut protein may be in particular selected from Ara h 2, Ara h 3 and Ara h 6, or a combination thereof. The peanut allergen may be of peanut origin, recombinantly expressed or is a synthetic peanut peptide.
- 20 In some embodiments, the anti-peanut allergen antibodies, as described herein, may be pre-incubated with the peanut allergen and may be administered as a mixture to a subject. In other embodiments, the multispecific antibody or the composition comprising said antibody is administered before or during a desensitization procedure with a peanut allergen.
- 25 Combining administration of a peanut allergen with the multispecific antibodies of the invention increases the safety of administering the allergen (e.g. in desensitization). Furthermore, without being bound to any theory, the present inventors assume that the combination of antibodies with the respective allergen (targeted by the antibodies), i.e. the combination of passive (antibodies) and active (allergen) immunization, has a synergistic
30 effect.

Further uses

Multispecific antibodies and fragments thereof as described herein may also be used for the (*in-vitro*) diagnosis of a peanut allergy. Methods of diagnosis may include contacting an antibody with a sample. Such samples may be isolated from a subject, for example an isolated blood sample, such as whole blood, plasma or serum. The methods of diagnosis may also include the detection of an antigen/antibody complex, in particular following the contacting of an antibody with a sample. Furthermore, it may be tested, whether the sample contains antibodies competing with the antibodies as described herein, e.g. for allergen binding. This is typically performed *in vitro*, i.e. without any contact to the human or animal body. Examples of analytical methods are well-known to the person skilled in the art and include immunoassays such as flow cytometry, dot or slot blots, Western blots, ELISA (enzyme-linked immunosorbent assay), e.g. for cross-competition, immunohistochemistry and immunoprecipitation followed by SDS-PAGE immunocytochemistry. Accordingly, the diagnosis may be performed *in vitro*, for example by using an isolated sample as described above (and an *in vitro* analysis step as described above).

The present invention also provides a method of detecting whether a sample comprises a peanut allergen, in particular Ara h 2, Ara h 3 and/or Ara h 6. Such a method may comprise the following steps:

- a. contacting the sample with the multispecific antibody described herein under conditions permissive to produce an antibody/antigen complex; and
- b. detecting the presence of the antibody/antigen complex.

Thereby, the presence of detectable antibody/antigen complex may be indicative that the sample may contain a peanut allergen, in particular Ara h 2, Ara h 3 and/or Ara h 6.

In some embodiments, in step (b) the amount of the antigen/antibody complex may be determined (e.g., measured) in the test sample. Thereafter, said amount may be compared to a control.

Accordingly, the multispecific antibody of the present invention may be used in an (*in vitro*) method for detecting a peanut allergen, in particular Ara h 2, Ara h 3 and/or Ara h 6. Likewise, the multispecific antibody of the present invention may be used in an (*in vitro*) method for binding a peanut allergen, in particular Ara h 2, Ara h 3 and/or Ara h 6. For detecting a peanut allergen, in particular Ara h 2, Ara h 3 and/or Ara h 6, the multispecific antibody may be

brought in contact with a (isolated) sample (i.e., a sample to be tested for the presence of the antigen). By the specific binding of the multispecific antibody to its antigen(s) (peanut allergen(s), in particular Ara h 2, Ara h 3 and/or Ara h 6), an antibody/antigen complex is formed, which can be easily detected by methods known in the art.

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Such a detection method may be used for testing samples (e.g., production/manufacture), such as food, cosmetics or medication samples. Accordingly, multispecific antibodies, antibody fragments, or variants thereof, as described in the present invention may also be used in a non-therapeutic/non-diagnostic context, e.g. in development or manufacture of various products.

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Furthermore, the detection method may be used for testing vaccine samples (e.g. for use in desensitization), whether they contain the major peanut allergens Ara h 2, Ara h 3 and/or Ara h 6. This may be useful in the development and/or manufacture of such vaccines.

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Accordingly, the present invention therefore also provides the use of the multispecific antibodies as described herein for testing immunogenic compositions/vaccines, in particular of an immunogenic composition/vaccine comprising a peanut allergen. To this end, the multispecific antibody may be brought in contact with the immunogenic composition/vaccine, e.g. to test for antibody/antigen complexes. Accordingly, the present invention also provides a method for testing immunogenic compositions (vaccines) based on peanut allergens, wherein the immunogenic composition/vaccine is contacted with the multispecific antibody, and, optionally, the presence of antibody/antigen complexes is determined. Furthermore, the present invention also encompasses the use of the multispecific antibody of the present invention for monitoring the quality of immunogenic compositions/vaccines based on peanut allergens by checking whether the immunogenic composition/vaccine contains the desired antigen, e.g. Ara h 2, Ara h 3 and/or Ara h 6.

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BRIEF DESCRIPTION OF THE FIGURES

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In the following a brief description of the appended figures will be given. The figures are intended to illustrate the present invention in more detail. However, they are not intended to limit the subject matter of the invention in any way.

Fig. 1 shows the design of the exemplary multispecific antibodies IgG-scFv2, IgG-scFv, IgG:DVD#1, and IgG:DVD#2 derived from the parental antibodies 17H9, 7G6, and 15E3.

5 A: IgG-scFv2 comprises two (identical) N-terminal paratopes derived from the parental antibody 17H9, and comprises two different C-terminal scFv paratopes, which are derived from the parental antibodies 7G6 and 15E3, respectively, thereby forming a tetravalent trispecific antibody format.

10 B: IgG-scFv comprises two (identical) N-terminal paratopes derived from the parental antibody 17H9, and comprises two (identical) C-terminal scFv paratopes derived from the parental antibody 7G6, thereby forming a tetravalent bispecific antibody format.

15 C: IgG:DVD#1 comprises two different N-terminal paratopes derived from the parental antibodies 17H9 and 15E3, respectively, and comprises a further N-terminal paratope linked to the N-terminal 15E3 paratope (forming a DVD domain) which is derived from the parental antibody 7G6, thereby forming a trivalent trispecific antibody format.

20 D: IgG:DVD#2 comprises two different N-terminal paratopes derived from the parental antibodies 7G6 and 15E3, respectively, and comprises a further N-terminal paratope linked to the N-terminal 15E3 paratope (forming a DVD domain) which is derived from the parental antibody 17H9, thereby forming a trivalent trispecific antibody format.

25 Fig. 2 shows for Example 1 epitope blocking ELISA data with the 4x antibody cocktail (comprising the parental antibodies 17H9, 7G6, 15E3 and 2F8) (A) in comparison to the 3x antibody cocktail (comprising the parental antibodies 17H9, 7G6, and 15E3) (B).

30 Fig. 3A-D show for Example 3 an allergen-specificity ELISA, an epitope blocking ELISA, an IgG competition ELISA and a mast cell activation test for the tetravalent trispecific antibody IgG-scFv2.

- Fig. 4A-D show for Example 3 an allergen-specificity ELISA, an epitope blocking ELISA, an IgG competition ELISA and a mast cell activation test for the tetravalent trispecific antibody IgG-scFv.
- 5 Fig. 5A-D show for Example 3 an allergen-specificity ELISA, an epitope blocking ELISA, an IgG competition ELISA and a mast cell activation test for the trivalent trispecific antibody IgG-DVD#1.
- 10 Fig. 6A-D show for Example 3 an allergen-specificity ELISA, an epitope blocking ELISA, an IgG competition ELISA and a mast cell activation test for the trivalent trispecific antibody IgG-DVD#2.
- 15 Fig. 7 shows for Example 4 the *in vivo* efficacy (Fig. 7B) of the multispecific antibodies IgG-scFv2, IgG:DVD#1, and IgG-scFv in comparison to a MY006-3 cocktail (comprising the parental antibodies 17H9, 7G6 and 15E3) and isotype control in a NOG-EXL mouse model (shown in Fig. 7A).
- 20 Fig. 8 shows, for Example 5, the surface plasmon resonance (SPR) sensorgram of the trispecific antibody IgG-scFv2.
- 25 Fig. 9 shows, for Example 5, % IgE binding inhibition on peanut extract in an IgE competition ELISA with single plasma for the trispecific antibody IgG-scFv2 in comparison to MY006-4 cocktail (comprising the parental antibodies 17H9, 7G6, 15E3 and 2F8) and isotype control.
- 30 Fig. 10 shows, for Example 5, % inhibition in an IgE competition ELISA with plasma pool for the trispecific antibody IgG-scFv2 in comparison to prior art antibody cocktail IGX001 (comprising a 1:1 mixture of IGX-107-bispecific and IGX-109-IgG4) and isotype control.
- Fig. 11 shows, for Example 6, % inhibition in a mast cell activation test (MAT) with plasma pool for the trispecific antibody IgG-scFv2 in comparison to the

MY006-4 cocktail (comprising the parental antibodies 17H9, 7G6, 15E3 and 2F8) and isotype control.

5 Fig. 12 shows, for Example 6, % change from baseline EC50 in a mast cell activation test (MAT) with single plasma for the trispecific antibody IgG-scFv2 in comparison to the MY006-4 cocktail (comprising the parental antibodies 17H9, 7G6, 15E3 and 2F8) and isotype control.

10 Fig. 13 shows, for Example 6, % change from baseline EC50 in a mast cell activation test (MAT) with plasma pool (Fig. 13A) and single plasma (Fig. 13B) for the trispecific antibody IgG-scFv2 in comparison to prior art antibody cocktail IGX001 (comprising a 1:1 mixture of IGX-107-bispecific and IGX-109-IgG4) and isotype control.

15 Fig. 14 shows, for Example 6, % inhibition of mast cell degranulation in a mast cell activation test (MAT) with plasma pool derived from 5 patients for the trispecific antibody IgG-scFv2 in comparison to prior art antibody cocktail IGX001 (comprising a 1:1 mixture of IGX-107-bispecific and IGX-109-IgG4) and isotype control.

20 Fig. 15 shows, for Example 7, % inhibition of basophil degranulation in a leukotriene release assay with plasma pool (91 patients) for the trispecific antibody IgG-scFv2 in comparison to the MY006-4 cocktail (comprising the parental antibodies 17H9, 7G6, 15E3 and 2F8) and isotype control.

25

EXAMPLES

30 In the following, particular examples illustrating various embodiments and aspects of the invention are presented. However, the present invention shall not be limited in scope by the specific embodiments described herein. The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. The present invention, however, is not limited in scope by the exemplified

embodiments, which are intended as illustrations of single aspects of the invention only, and methods which are functionally equivalent are within the scope of the invention. Indeed, various modifications of the invention in addition to those described herein will become readily apparent to those skilled in the art from the foregoing description, accompanying
5 figures and the examples below. All such modifications fall within the scope of the appended claims.

Example 1: Epitope Blocking efficacy of parental antibody cocktails

10 Fully human parental antibodies 2F8 and 7G6 were previously described in WO 2018/234383 A1. Fully human antibodies 17H9 and 15E3 were isolated and cloned in a similar manner, i.e. by the method as described in detail in WO 2018/234383 A1. Briefly, as starting material for the cloning of fully human antibodies, human lymphocytes were obtained from peripheral blood of voluntary allergic patients. Antibodies specific to major peanut
15 allergens were isolated by molecular cloning of immunoglobulin genes obtained from single-cell sorted cells derived from short term oligoclonal cultures of activated memory B cells producing the antibodies of interest. Molecular cloning of human antibodies specific to peanut allergens was carried out according to Huang J, Doria-Rose NA, Longo NS, Laub L, Lin CL, Turk E, Kang BH, Migueles SA, Bailer RT, Mascola JR, Connors M. Isolation of human
20 monoclonal antibodies from peripheral blood B cells. Nat Protoc. 2013 Oct;8(10):1907-15. doi: 10.1038/nprot.2013.117, as described in detail in WO 2018/234383 A1.

Antibody cocktails were prepared containing the parental antibodies 15E3, 17H9 and 7G6 (MY006-3 cocktail) or 15E3, 17H9, 7G6 and 2F8 (MY006-4 cocktail). The antibody cocktails
25 were compared in respect of their epitope blocking capacity using an epitope blocking ELISA.

ELISA plates were coated with mAbs (MY006-7G6, MY006-17H9, MY006-15E3, MY006-2F8) or the MY006 cocktails (MY006-4 comprising the parental antibodies 17H9, 7G6, 15E3 and 2F8; MY006-3 comprising the parental antibodies 17H9, 7G6, and 15E3) overnight at 4°C.
30 Biotinylated Ara h 2 (3 nM) was pre-incubated with the MY006-4 or MY006-3 cocktails (titrated 0-70 nM) for 1h at RT. Allergen binding to mAbs in presence of antibodies was measured by Streptavidin-HRP (0.5 ug/ml).

The results are shown in Figure 2. These data show that the cocktail MY006-3 of parental antibodies 17H9, 7G6, and 15E3 also does not specifically block the 2F8 epitope.

Example 2: Design, expression and purification of multispecific antibodies

5

Design of IgG-scFv2

The IgG-scFv2 tri-specific is an asymmetric antibody format, wherein the Fab portion of each half antibody is the same, but the single chain variable fragments (scFv), fused at the C-terminus of the HC, have different specificities. The scFvs were genetically fused to the C-terminus of the heavy chain via a flexible linker comprising three repeats of GGGGS. Additionally, scFvs were stabilized by including a VH-VL disulfide bridge. The scFv domains were configured in the VL-VH orientation, which were fused using a four-repeat GGGGS linker. Additionally, mutations in the IgG4-Fc region were incorporated to ensure product stability at low pH during manufacturing (R409K and L445P), and a S228P mutation was incorporated into the IgG4-Fc region for hinge stabilization. Finally, for efficient heterodimerization, the knob-into-hole technology, stabilized by disulfide bonds, was applied as a heterodimerization domain, ensuring the proper assembly and functionality of the IgG-scFv2 tri-specific antibody.

20

Design of IgG-scFv

The IgG-scFv bi-specific is an symmetric antibody format, wherein the Fab portion of each half antibody is the same, and the single chain variable fragments (scFv), fused at the C-terminus of the HC, have the same specificities. The scFvs were genetically fused to the C-terminus of the heavy chain via a flexible linker comprising three repeats of GGGGS. Additionally, scFvs were stabilized by including a VH-VL disulfide bridge. The scFv domains were configured in the VL-VH orientation, which were fused using a four-repeat GGGGS linker. Additionally, mutations in the IgG4-Fc region were incorporated to ensure product stability at low pH during manufacturing (R409K and L445P), and a S228P mutation was incorporated into the IgG4-Fc region for hinge stabilization.

30

Design of IgG:DVD

The IgG:DVD format is an asymmetric molecule, in which one half of the antibody molecule is comprised of a standard IgG/Fab, whereas the other half is comprised of an dual variable

domain (DVD) IgG/Fab. The DVD features a VH1-VH2 linker composed of the amino acid sequence ASTKGP, providing a short yet robust linkage based on the first six amino acids of the CH1 domain. For the VL1-VL2 linker, a longer and robust sequence RTVAAPSVFIFPP is employed, derived from the first 13 amino acids of the CK region. This extended linker
5 contributed to the stability and proper orientation of the variable light chain domains. To ensure efficient heterodimerization, the IgG:DVD format incorporated the knob-into-hole technology, further reinforced by the inclusion of disulfide bonds. Additionally, mutations in the IgG4-Fc region were incorporated to ensure product stability at low pH during manufacturing (R409K and L445P), and a S228P mutation was incorporated for hinge
10 stabilization.

Expression of multispecific molecules

ExpiCHO cells (Gibco) were used to express the different multi-specific antibody molecules. To express antibodies in ExpiCHO cells, cells were maintained in a growth medium at 37°C
15 with 8% CO₂. When they reached the desired density, cells were transfected with plasmids encoding for multispecific antibodies and an ExpiCHO-optimized transfection reagent. After transfection, incubation was continued to allow antibody expression. The culture was harvested after reaching desired levels, usually 5-7 days post-transfection, and the antibodies were further purified through protein A affinity chromatography and a second purification
20 step, consisting of either HIC or IEX (see below for detailed protocols).

Purification of IgG-scFv(2)

To purify IgG-scFv(2) molecules, a 5ml HiTrap MabSelect PrismA column (Cytiva 10329882) for the affinity purification step was used. The column was equilibrated with Buffer A, which
25 was PBS, and elution was carried out using 100% Buffer B containing 100 mM Sodium Acetate at pH 3.6. Subsequently, ion exchange chromatography (IEX) was employed with a 4.7 ml HiScreen CaptoS ImpAct column (Cytiva, 17371747). For IEX, Buffer A consisted of 15mM CAPSO, 14 mM TABS, 11 mM MOPS, and 13 mM MES at pH 6.0, while Buffer B was composed of 15mM CAPSO, 14 mM TABS, 11 mM MOPS, and 13 mM MES at pH 10.5.
30 Elution and separation of the target molecule from aggregates and other impurities was achieved using a gradient of 30-60% Buffer B over 30 column volumes (CV) at a pH range from 7.3 to 8.7.

Purification of IgG:DVD

To purify the IgG:DVD format, a 5ml HiTrap MabSelect Prisma column (Cytiva 10329882) for the affinity purification step was used. The resin was initially equilibrated with PBS, and elution was achieved using 100% Buffer B containing 100 mM Sodium Acetate at pH 3.6. Subsequently, a second purification, Hydrophobic Interaction Chromatography (HIC), was performed. Therefore, a 4.7 ml HiScreen Butyl HP column (Cytiva 28978242) was employed. Buffer A, which facilitates HIC, was prepared with 50 mM Na2PO4 and 1M Ammonium sulfate at pH 7, while Buffer B consisted of 50 mM Na2PO4 at pH 7. Loading of the molecules on the column was performed in Buffer A. Subsequently, elution and separation of the target molecules from aggregates and other impurities was accomplished using a gradient from 45% to 100% of Buffer B over 25 column volumes (CV), corresponding to a change in Ammonium sulfate concentration from 0.55 M to 0 M.

The nucleic acid sequences encoding the heavy chain and light chain sequences of multispecific antibodies as used herein are summarized in Table 2 below.

Antibody	IgG4 (knob)- HC	IgG4 (hole)- HC	IgG4-HC	LC	DVD-LC
IgG-scFv-2	63	64	-	65	-
IgG-scFv	-	-	66	67	-
IgG:DVD#1	68	69	-	70	71
IgG:DVD#2	72	73	-	74	75

Table 2: SEQ ID NOs for polynucleotide sequences encoding the heavy chain and light chain sequences of multispecific antibodies IgG-scFv-2, IgG-scFv, IgG:DVD#1, IgG:DVD#2

The amino acid sequences of the heavy chains and light chains of multispecific antibodies as used herein are summarized in Table 3 below.

Antibody	IgG4 (knob)- HC	IgG4 (hole)- HC	IgG4-HC	LC	DVD-LC
IgG-scFv-2	37	38	-	39	-
IgG-scFv	-	-	40	41	-

IgG:DVD#1	42	43	-	44	45
IgG:DVD#2	46	47	-	48	49

Table 3: SEQ ID NOs for amino acid sequences of the heavy chains and light chains of multispecific antibodies IgG-scFv-2, IgG-scFv, IgG:DVD#1, IgG:DVD#2

5 Example 3: Functional characterization of multispecific antibodies IgG-scFv2, IgG-scFv,
IgG:DVD#1 and IgG:DVD#2

1. Allergen specificity ELISA

10 Multispecific monoclonal antibodies IgG-scFv2, IgG-scFv, IgG:DVD#1 and IgG:DVD#2 were tested for their specificity against the major peanut allergens Ara h 1, 2, 3, and 6 by ELISA (enzyme linked immunosorbent assay).

ELISA plates were coated with respective Ara h proteins (Arah1: 0.1 ug/ml, Arah2: 0.01 ug/ml, Arah3: 0.1 ug/ml, Arah6: 0.05 ug/ml, Peanut Extract (PE): 0.05 ug/ml) overnight at 4°C. Afterwards, plates were blocked with BSA (2% in PBS) for 1 hour at room temperature. Antibody titration series starting from 3ug/ml was prepared, added to the single ELISA plate wells and incubated for 2h at room temperature. The read-out was performed by adding anti-hu-IgG-HRP (anti-human-IgG horseradish peroxidase; Jackson ImmunoResearch, West Grove, PA, USA) for 1h at room temperature. Tetramethylbenzidine substrate solution (TMB, Sigma-Aldrich Chemie GmbH, Buchs, Switzerland) was added, then after 5 minutes of hydrolysis time, the reaction was stopped by the addition of 1 M H₂SO₄ and the absorbances were read at 450 nm.

The results are shown in Figure 3A (for IgG-scFv2), Figure 4A (for IgG-scFv), Figure 5A (for
25 IgG:DVD#1) and Figure 6A (for IgG:DVD#2). These data show that all tested multispecific
antibodies IgG-scFv2, IgG-scFv, IgG:DVD#1 and IgG:DVD#2 bind specifically to Ara h 2,
Ara h3, and Ara h 6.

The EC50 (nM) of the multispecific antibodies IgG-scFv2, IgG-scFv, IgG:DVD#1 and IgG:DVD#2 in respect of the Ara h proteins are summarized in Table 4 below:

EC50 (nM)	nat Ara h 1	Ara h 2	Ara h 3	Ara h 6	PE	BSA
IgG-scFv2	not binding	0.105	0.402	0.233	0.112	not binding
IgG-DVD#1	not binding	0.051	6.094	0.088	0.058	not binding
IgG-scFv	not binding	0.109	0.337	0.158	0.088	not binding
IgG-DVD#2	not binding	0.070	2.937	0.075	0.052	not binding

Table 4: EC50 (nM) of allergen specific ELISA

2. Epitope blocking ELISA

Multispecific monoclonal antibodies IgG-scFv2, IgG-scFv, IgG:DVD#1 and IgG:DVD#2 were tested for their capacity of blocking the epitopes of major peanut allergen Ara h 2.

ELISA plates were coated with mAbs (MY006-7G6, MY006-17H9, MY006-15E3, MY006-2F8) or the multispecific construct (0.2 ug/ml), overnight at 4°C. Biotinylated Ara h 2 (3 nM) was pre-incubated with the multispecific construct (titrated 0-70 nM) for 1 h at RT. Allergen binding to mAbs in presence of antibodies was measured by Streptavidin-HRP (0.5 ug/ml).

The results are shown in Figures 3B (for IgG-scFv2), Figure 4B (for IgG-scFv), Figure 5B (for IgG:DVD#1) and Figure 6B (for IgG:DVD#2). These data show that all the tested trispecific antibodies IgG-scFv2, IgG:DVD#1 and IgG:DVD#2 completely block binding of the competing monoclonal antibodies MY006-7G6, MY006-17H9, MY006-15E3, and additionally MY006-2F8 to Ara h 2. The bispecific IgG-scFv completely blocks binding of the competing monoclonal antibodies MY006-7G6 and MY006-17H9, and additionally MY006-2F8 to Ara h 2.

3. IgE competition ELISA

The multispecific antibodies IgG-scFv2, IgG-scFv, IgG:DVD#1 and IgG:DVD#2 were further tested for their efficacy in inhibiting binding of IgEs derived from a plasma pool of peanut allergic patients to peanut extract.

ELISA plates were coated with anti-IgE (10 ug/ml), overnight at 4°C, and IgE from a plasma pool of peanut allergic patients were captured (2h incubation at room temperature). At the same time, biotinylated allergen (1.12 nM peanut extract) was pre-incubated with Mabylon’s anti-peanut antibodies or isotype control (titrated 0-80 nM). Allergen binding to IgE in presence of antibodies was measured. % IgE binding inhibition was calculated as: % inhibition = 100-(OD450_{Ab}/ OD450_{w/o Ab} *100) and normalized to assay internal control.

The results are shown in Figure 3C (for IgG-scFv2), Figure 4C (for IgG-scFv), Figure 5C (for IgG:DVD#1) and Figure 6C (for IgG:DVD#2). These data confirm that the multispecific antibodies IgG-scFv2, IgG-scFv, IgG:DVD#1 and IgG:DVD#2 inhibit patients’ IgE binding to peanut allergens to the same extent as the MY006-4 cocktail of monoclonal antibodies.

The IC50 (nM) of the multispecific antibodies IgG-scFv2, IgG-scFv, IgG:DVD#1 and IgG:DVD#2 in a IgE competition ELISA are summarized in Table 5 below:

IC50 (nM)	IgG-scFv2	IgG-DVD#1	IgG-scFv	IgG-DVD#2	MY006-4-cocktail	Isotype control
	0.8851	2.284	1.889	1.811	3.024	not inhibiting

Table 5: IC50 (ng/ml) of IgE competition ELISA

4. Mast cell activation test

Further, it was investigated whether the multispecific antibodies IgG-scFv2, IgG-scFv, IgGDVD#1 and IgGDVD#2 can inhibit allergen-mediated activation of bone marrow derived mast cells isolated from transgenic mice.

Bone marrow derived mast cells isolated from transgenic mice expressing the human FcER1a are sensitized with plasma pool from peanut allergic patients. Activation of mast cells is quantified in terms of %CD107a positive. Cells are sensitized with plasma pool overnight at 37°C and then stimulated for 35 minutes, at 37°C, with titrated peanut extract alone or previously pre-incubated with antibodies (80 nM).

The results are shown in Figure 3D (for IgG-scFv2), Figure 4D (for IgG-scFv), Figure 5D (for IgG:DVD#1) and Figure 6D (for IgG:DVD#2). The data show that multispecific antibodies

IgG-scFv2, IgGDVD#1 and IgG-scFv inhibit allergen-mediated activation of bone marrow derived mast cells to a similar extent as the MY006-4 cocktail (including the parental antibodies 15E3, 17H9, 7G6 and 2F8), which was tested in parallel.

5 Example 4: *In vivo* efficacy of multispecific antibodies in NOG-EXL mice

Further, the multispecific antibodies IgG-scFv2, IgGDVD#1 and IgG-scFv were tested in a humanized mouse model (NOG-EXL mice). NOG-EXL (NOD.Cg-*Prkdc^{scid} Il2rg^{tm1Sug}* Tg(SV40/HTLV-IL3,CSF2)10-7Jic/JicTac) is an immunodeficient mouse,
10 expressing human GM-CSF and IL-3 cytokines (hGM-CSF/hIL-3 NOG), supporting the differentiation of human myeloid cell lineages. Mice are humanized by engraftment with hematopoietic stem cells (CD34+ from cord blood donors). Engrafted NOG-EXL mice were passively sensitized with plasma from peanut allergic patients (200 µl, i.v.), which resulted in anaphylaxis upon oral gavage of peanut butter (data not shown).

15

To test efficacy of multispecific antibodies, NOG-EXL mice were administered subcutaneously with multispecific antibodies IgG-scFv2, IgGDVD#1, IgG-scFv or cocktail of parental antibodies 7G6, 17H9 and 15E3 or isotype control. Three days later, mice were sensitized intravenously (i.v.) with 200 µl of plasma derived from peanut allergic patients. 24
20 hours after i.v. sensitization, mice were challenged with peanut butter by oral gavage (1 mg peanut protein). The schedule is shown in Figure 7A.

Body temperature and signs of allergic reactions were measured over 60 minutes upon gavage.

25

Results are shown in Figure 7B. Figure 7B shows a pronounced decrease in body temperature of sensitized mice treated with isotype control in comparison to mice treated with the multispecific antibodies or antibody cocktail, indicating an anaphylactic reaction of the control mice, but not in mice treated with the multispecific antibodies or antibody cocktail.

30

These data demonstrate that multispecific antibodies IgG-scFv2, IgGDVD#1 and IgG-scFv prevent anaphylaxis in a humanized mouse model of peanut allergy.

Example 5: Further characterization of the multispecific construct IgG-scFv2 – SPR measurement and IgE competition ELISA

1. SPR measurement of IgG-scFv2

5 To further characterize the tetravalent trispecific antibody format IgG-scFv2, surface plasmon resonance (SPR) analysis was performed using a Biacore T200 device and the Biotin CAPture Kit (Cytiva). Biotinylated nArah 2 (Inbio, BI-NAH2-4) was employed as ligand, while IgGscFv2 served as analyte. The CAP immobilization levels ranged from 2700 to 2873 response units
10 (RU), achieved using a 1:6 dilution of the CAP reagent. Capture levels for nArah 2 were maintained between 55 and 66 RU. The measurement temperature was set at 37°C, with the sample compartment maintained at 25°C. Biotin CAPture reagent was applied with a contact time of 300 seconds at a flow rate of 2 µL/min. Ligand capturing was performed under similar conditions. Single-cycle kinetic runs were performed using 12.5 nM, 25 nM and 50 nM of
15 analyte with an association phase of 180 seconds, followed by a dissociation phase of 1200 seconds, at a flow rate of 30 µL/min. To ensure reproducibility and reliability, the measurements were conducted in three independent runs. Data fitting was performed using a bivalent model to analyze the binding kinetics and affinity of the interactions.

20 The SPR sensorgram is shown in Figure 8. The average apparent dissociation constant 1 (K_D1) of the trispecific format IgG-scFv2 was determined to be 257 pM, with a standard deviation of 53.4 pM.

The results of SPR measurements are summarized in Table 6 below.

25

Measure-ment	K_D1 (M)	k_a1 ($M^{-1}s^{-1}$)	k_d1 (s^{-1})	k_a2 (RUs-1)	k_d2 (s-1)	Rmax (RU)	Chi^2 (RU^2)
#1	2.57E-10	1.03E+05	2.64E-05	9.23E-04	3.97E-02	441.2	5
#2	3.11E-10	9.15E+04	2.85E-05	5.82E-04	2.97E-02	411.9	5.02
#3	2.04E-10	9.38E+04	1.92E-05	7.59E-04	3.78E-02	421	4.55
Average	2.57E-10	9.60E+04	2.47E-05	7.55E-04	3.57E-02	424.70	4.86
SD	5.33866E-11	5.96E+03	4.89052E-06	1.71E-04	5.33E-03	15.00	0.27

Table 6: SPR measurement of IgG-scFv2

2. IgE competition ELISA with single plasma in comparison to MY006-4 cocktail

Further, IgG-scFv2 was tested for its efficacy in inhibiting binding of IgEs derived from 42 single patients' plasma samples in comparison to a cocktail comprising the parent antibodies 15E3, 17H9, 7G6 and 2F8 (MY006-4 cocktail).

5 ELISA plates were coated with anti-IgE (10 ug/ml), overnight at 4°C, and IgE from single plasma of peanut allergic patients were captured (2h incubation at room temperature). At the same time, biotinylated allergen (0.05 µg/mL peanut extract) was pre-incubated with Mabylon's anti-peanut antibodies or isotype control. MY006-IgG-scFv2, MY006-4 cocktail
10 are tested at 80 nM. Allergen binding to IgE in presence of antibodies was measured. % IgE binding inhibition was calculated as: % inhibition = 100-(OD450_{Ab} / OD450_{w/o Ab} *100) and normalized to assay internal control.

The results are shown in Figure 9. These data confirm that the multispecific antibody IgG-scFv2 inhibits patients' IgE binding to peanut allergens to an even greater extent than the
15 MY006-4 cocktail of monoclonal antibodies.

The % inhibition of IgE binding to peanut extract of IgG-scFv2, MY006-4 cocktail and isotype control in an IgE competition ELISA are summarized in Table 7 below:

20

% inhibition of IgE binding to PE			
	IgG-scFv2	MY006-4 cocktail	isotype control
mean	70.4	66.0	-1.3
SD	14.8	14.9	6.0

Table 7: % inhibition of IgE binding to plasma extract (PE)

3. IgE competition ELISA with plasma pool in comparison to prior art antibody cocktail
IGNX001

25 IgG-scFv2 was tested for its efficacy in inhibiting binding of IgEs derived from a plasma pool of peanut allergic patients in comparison to a cocktail (IGNX001) comprising the prior art antibodies IGX-107-bispecific (aka Molecule-1a) and IGX-109-IgG4 (Molecule-2c).

The sequences for IGNX001 were obtained from WO2024/102700 A2, subsequently reverse-translated, and the corresponding DNA was synthesized by Twist Bioscience. These synthesized sequences were then cloned into Mabyon expression plasmids and expressed in ExpiCHO cells (Gibco), following previously the manufacturer’s protocols. The recombinant antibodies underwent a two-step purification process, initially utilizing Protein A affinity chromatography, followed by preparative size exclusion chromatography (prepSEC) using the AKTA pure system from Cytiva. To accurately replicate the IGNX001 cocktail, an equimolar mixture of IGX0107 and IGX0109 was prepared, ensuring a precise representation of the prior art product for the comparative analysis.

ELISA plates were coated with anti-IgE (10 ug/ml), overnight at 4°C, and IgE from single plasma of peanut allergic patients were captured (2h incubation at room temperature). At the same time, biotinylated allergen (0.05 µg/mL peanut extract) was pre-incubated with MY006-IgG-scFv2, IGNX001 or isotype control. Antibodies are titrated from 15.94 ug/ml to 0. Allergen binding to IgE in presence of antibodies was measured. % IgE binding inhibition was calculated as: % inhibition = 100-(OD450_{Ab} / OD450_{w/o Ab} *100) and normalized to assay internal control.

The results are shown in Figure 10. These data confirm that the multispecific antibody IgG-scFv2 inhibits patients’ IgE binding to peanut allergens to a significantly greater extent than the prior art IGNX001 antibody cocktail (IGNX001: IGX-107-bispecific + IGX-109-IgG4 mixed at 1:1 ratio).

The IC50 (nM) and % inhibition of IgE binding to peanut extract of IgG-scFv2, IGNX001 cocktail and isotype control in an IgE competition ELISA are summarized in Table 8 below:

	MY006-IgG-scFv2	IGNX001	Isotype control
IC50 nM	0.8461	4.88	-
% inhibition*	73.82	58.42	0

**calculated at the highest antibody concentration*

Table 8: IC50 (nM) and % inhibition of IgE competition ELISA

Example 6: Further characterization of the multispecific construct IgG-scFv2 – Mast cell activation test (MAT)

5 IgG-scFv2 was further characterized in terms of its ability to inhibit mast cell degranulation in various experimental approaches.

Bone marrow derived mast cells isolated from transgenic mice expressing the human FcεRIα are sensitized with single plasma or plasma pool from peanut allergic patients. Activation of mast cells is quantified in terms of %CD107a positive. To evaluate the efficacy of the antibodies, cells are sensitized with plasma samples overnight at 37°C and then stimulated for 35 minutes, at 37 °C, with titrated peanut extract alone or in the presence of antibodies. Efficacy is then evaluated in terms of percent of change from baseline EC50, with baseline being the dose response curve of peanut extract without treatment: %change from baseline EC50 = ((EC50(with Ab)/EC50(w/o Ab))-1)*100. The potency of the antibodies (IC50 and IC90) was evaluated stimulating the cells with titrated antibodies previously pre-incubated with fixed concentration of peanut extract (EC50 of the of the peanut only-dose response curve).

1. Potency of MY006-IgG-scFv2 in inhibition of mast cell degranulation with plasma pool in comparison to MY006-4 cocktail

20 Potency of MY006-IgG-scFv2 is evaluated by mast cell activation test with a pool of patients' plasma (n= 5 patients' plasma from US) in comparison to MY006-4 cocktail and isotype control. Antibody Titration: MY006-IgG-scFv2 titrated (80 nM- 0nM) and fixed doses of peanut based on EC50 determined via allergen titration (PE: 1.7 ng/ml).

25 The results are shown in Figure 11. The data show that multispecific antibody IgG-scFv2 inhibits allergen-mediated activation of bone marrow derived mast cells to an even greater extent than the MY006-4 cocktail (including the parental antibodies 15E3, 17H9, 7G6 and 2F8), which was tested in parallel.

30 The IC 50 (pM) and % inhibition at the highest concentration of IgG-scFv2 and MY006-4 cocktail are summarized in Table 9 below:

	MY006-IgG-scFv2	MY006-4 cocktail
IC50 pM	8.1	67.1
% inhibition	76.3	70.1

Table 9: IC50 (pM) and % inhibition in MAT with plasma pool

2. Efficacy of MY006-IgG-scFv2 in inhibition of mast cell degranulation with single plasma in comparison to MY006-4 cocktail

5

Efficacy of MY006-IgG-scFv2 is evaluated by mast cell activation test in 20 single patients' plasma samples in comparison to MY006-4 cocktail and isotype control.

10

Allergen titration set-up: cells are pre-incubated with fixed concentration of antibodies (80 nM) for 30 minutes, at 37 °C and then stimulated with titrated peanut extract (1000 ng/ml to 0 ng/mL). Efficacy is evaluated by calculating the percentage change from baseline EC₅₀:
%change from baseline EC₅₀ = ((EC₅₀(with Ab)/EC₅₀(w/o Ab))-1)*100.

15

The results are shown in Figure 12. The data show that MY006-IgG-scFv2 shows efficacy in increasing mast cell tolerance to peanut extract in all 20 single patient samples tested.

The % change from baseline EC50 are summarized in Table 10 below:

	% change from baseline EC50		
	MY006-IgG-scFv2	MY006-4 cocktail	isotype control
mean	1757.0	1521.0	7.0
SEM	294.8	270.2	6.9

Table 10: % change from baseline EC50 in MAT with single plasma

20

3. Efficacy of MY006-IgG-scFv2 in inhibiting mast cell degranulation in comparison to IGNX001

25

Efficacy of MY006-IgG-scFv2 is evaluated by mast cell activation test in comparison to IGNX001 cocktail (IGX-107-bispecific + IGX-109-IgG4 mixed at 1:1 ratio) and isotype control. Sensitization of the cells was done with plasma pool or single plasma.

Allergen titration set-up: cells are pre-incubated with fixed concentration of antibodies (15.94 ug/ml) for 30 minutes, at 37 °C and then stimulated with titrated peanut extract (600 ng/ml to 0 ng/ml). Efficacy is evaluated by calculating the percentage change from baseline EC₅₀: %change from baseline EC₅₀ = ((EC₅₀(with Ab)/EC₅₀(w/o Ab))-1)*100.

5

The results are shown in Figure 13A (for plasma pool) and 13 B (for single plasma). The data show that, compared to IGNX001, MY006-IgG-scFv2 shows superior efficacy in MAT assays.

The % change from baseline EC₅₀ are summarized in Table 11 below:

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	% change from baseline EC50		
	MY006-IgG-scFv2	IGNX001	isotype control
Mean	1580.8	915.3	4.6
SEM	341.4	132.8	8.3

Table 11: Table 10: % change from baseline EC₅₀ in MAT with single plasma

4. Potency of MY006-IgG-scFv2 in inhibition of mast cell degranulation in comparison to IGNX001

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Potency of MY006-IgG-scFv2 is evaluated by mast cell activation test in comparison to IGNX001 cocktail (IGX-107-bispecific + IGX-109-IgG4 mixed at 1:1 ratio) and isotype control. Sensitization of the cells was done with plasma pool or single plasma.

20

Antibody Titration: MY006-IgG-scFv2, IGNX001 and isotype control are titrated (15.94 ug/ml – 0 ug/ml) and fixed doses of peanut based on EC₅₀ determined via allergen titration. The potency of the antibodies is evaluated by calculating of IC₅₀s and IC₉₀s of the curves. The results for plasma pool are shown in Figure 14. The data show that MY006-IgG-scFv2 is significantly more potent than IGNX001.

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The IC₅₀ and IC₉₀ values of MY006-IgG-scFv2 and IGNX001 are summarized in Table 12 below:

	Potency		
	MY006-IgG-scFv2	IGNX001	isotype control

IC50 (pM)	20.7	56.63	-
IC90 (pM)	119	465	-

Table 12: IC50 and IC90 values of MY006-IgG-scFv2 and IGNX001

Similar experiments were performed with plasma samples derived from 12 single peanut allergic patients.

5

The IC50 and IC90 values of MY006-IgG-scFv2 and IGNX001 are summarized in Tables 13 and 14 below:

	IC50 (pM)	
	MY006-IgG-scFv2	IGNX001
plasma 1	12.09	40.23
plasma 2	70.49	229.7
plasma 3	10.86	29.69
plasma 4	24.76	46.76
plasma 5	38.24	60.71
plasma 6	26.75	48.74
plasma 7	66.01	130.5
plasma 8	32.22	63.01
plasma 9	43.68	130.5
plasma 10	34.06	69.13
plasma 11	63.36	109.5
plasma 12	108.8	214.5

Table 13: IC50 of MY006-IgG-scFv2 and IGNX001 in single plasma samples

	IC90 (pM)	
	MY006-IgG-scFv2	IGNX001
plasma 1	99.03	236.6
plasma 2	253.1	1057
plasma 3	32.97	69.39
plasma 4	92.53	491.6
plasma 5	167.3	519.4
plasma 6	226.4	545.7
plasma 7	182	561.4

plasma 8	179.6	515.5
plasma 9	548.3	2785
plasma 10	169.9	566.5
plasma 11	241.1	786.6
plasma 12	317.3	1894

Table 14: IC90 of MY006-IgG-scFv2 and IGNX001 in single plasma samples

The above results show that MY006-IgG-scFv2 has greater potency than IGNX001 in MAT. In particular: The IC50 of MY006-IgG-scFv2 is, on average, 2.3 times lower than that of
5 IGNX001. The IC90 of MY006-IgG-scFv2 is, on average, 3.6 times lower than that of IGNX001. This indicates that MY006-IgG-scFv2 needs only about one-third the concentration to achieve 90% inhibition compared to IGNX001.

These results show that MY006-IgG-scFv2 is significantly more potent than prior art IGNX001,
10 as it can achieve the same level of inhibition at much lower concentrations in the MAT.

Example 7: Further characterization of the multispecific construct IgG-scFv2 – Inhibition of basophil degranulation

15 1. Leukotriene release assay (LTRA)

Potency of MY006-IgG-scFv2 is further evaluated by a leukotriene release assay with a plasma pool of 91 patients’ plasma in comparison to MY006-4 cocktail and isotype control.

20 Leukocytes from healthy blood donors are isolated and surface IgEs are removed by incubation with lactic acid. Leukocytes are then sensitized with IgE by incubation with a pool containing plasma derived from 91 peanut allergic patients for 1h at 37°C. Sensitized leukocytes are stimulated for 40 minutes at 37 °C with titrated antibodies previously pre-incubated with fixed concentration of peanut extract (PE, 0.5 nM) in the presence of IgG-
25 scFv2 or MY006-4 cocktail. Cell activation is measured by quantifying the release of sulfidoleukotrienes (sLTs) by ELISA (Bühlmann EK CAST ®).

Antibody Titration: MY006-IgG-scFv2 titrated (80 nM- 0nM) and fixed doses of peanut based on EC50 determined via allergen titration (plasma pool: peanut extract = 0.01 ng/ml).

The results are shown in Figure 15. The LTRA data confirm that the multispecific MY006-IgG-scFv2 is more potent than the MY006-4 cocktail containing 4 distinct (parental) antibodies.

5 The IC50 values of MY006-IgG-scFv2 and MY006-4 cocktail are summarized in Table 15 below:

	MY006-IgG-scFv2	MY006-4	isotype
IC50 pM	5.959	74.29	-
% inhibition	100.09	97.00	-

Table 15: IC50 of MY006-IgG-scFv2 and MY006-4 cocktail plasma pool

10

TABLE OF SEQUENCES AND SEQ ID NUMBERS (SEQUENCE LISTING):

SEQ ID NO	Sequence	Remarks
Antibody CDR sequences		
17H9		
SEQ ID NO: 1	TYGMH	CDRH1
SEQ ID NO: 2	IISPDGGHQDYADPVRG	CDRH2
SEQ ID NO: 3	TLCARTDCTWVRSDS	CDRH3
SEQ ID NO: 4	RASQRVSGDYLA	CDRL1
SEQ ID NO: 5	GASSRAT	CDRL2
SEQ ID NO: 6	QHYNPPVT	CDRL3
7G6		
SEQ ID NO: 7	DYTMH	CDRH1
SEQ ID NO: 8	AISYGGTNKYYADSVKG	CDRH2
SEQ ID NO: 9	DSGYRSLH	CDRH3
SEQ ID NO: 10	RSSQSLVHRNGYNYLD	CDRL1
SEQ ID NO: 11	MASKRAS	CDRL2
SEQ ID NO: 12	MQALQWT	CDRL3
15E3		
SEQ ID NO: 13	TFYMT	CDRH1
SEQ ID NO: 14	NIKQDGSEKDYLDSVRG	CDRH2

SEQ ID NO: 15	NGLQDSYSGDFFDH	CDRH3
SEQ ID NO: 16	SGTGSNIGHNYVS	CDRL1
SEQ ID NO: 17	DNTKRPS	CDRL2
SEQ ID NO: 18	ATWDADLSAVL	CDRL3
2F8		
SEQ ID NO: 19	DYNMN	CDRH1
SEQ ID NO: 20	SITRSSRTIYYADSVKG	CDRH2
SEQ ID NO: 21	EDFDVSTGPYYMDV	CDRH3
SEQ ID NO: 22	RASQSVSNMFLV	CDRL1
SEQ ID NO: 23	GASTRAT	CDRL2
SEQ ID NO: 24	QQNGNSPYT	CDRL3
Antibody VH, VL, scFv and DVD sequences		
IgG-scFv2/IgG-scFv		
SEQ ID NO: 25	QVQLVESGGGVVQPGRSLRLSCAASGSLGT YGMH WVRQAPGKGLEWVAII SPDGGH QDYADPVRGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCATTLCARTDC TWVRS DS WGQGT LV TVSS	17H9 VH
SEQ ID NO: 26	EIVLTQSP LSLP VTGPGEPA ISCRSSQSLV HRNGYNYLD WYLQKPGQSPQLLIY MASKRAS GVPDRFSGSGSGTD FTLKISRVEAEDVGVYYCMQALQ TWTF GC GT KVEIK GGGGSGGGSGGGSGGGG QVQLVESGGGVV QPGRSLRLSCAASGIAFNDYTMHWVRQAPGKCLEW VAISYGGTNKYYADSVKGRFTISRDN SKNTLYLQM NSLRAEDTAVYYCARD SGYRSL LHWGQGT LV TVS	7G6 scFv (VL- VH)
SEQ ID NO: 27	QSVLTQPPSVSAAPGQKVTISCSGTGSNIGHNYVSW YQQLPGTAPKLLIFD N TKRPSGIPDRFSGSKSGSATL GITGLQTGDEADYFCATWDADLSAVLFGCGTKLTVL GGGGSGGGSGGGSGGGG EVQLVESGGGLVQ PGGSLRLSCAASGFKFSTFYMTWVRQAPGKCLEWVA NIKQDGSEKDYLDSVRGRFTISRDN AKNSLYLQMNSL RAEDTAVYYCTR NGLQDSYSGDFFDH WGQGT LV TVS	15E3 scFv (VL- VH)
SEQ ID NO: 28	AIVLTQSPGTLSLSPGERATLSCRASQ RVSGDYL AWY QQKPGQAPRLLIY GASSRAT GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCQHYNGPPVTFGQGT KLEIK	17H9 VL
IgGDVD#1		

SEQ ID NO: 29	QVQLVESGGGVVQPGRSLRLSCAASGSLGT Y GMH WVRQAPGKGLEWVAIISPDGGHQDYADPVRGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCATTLCARTDC TWVRSDSWGQGLTVTVSS	17H9 VH
SEQ ID NO: 30	QVQLVESGGGVVQPGRSLRLSCAASGIAFNDYTMH WVRQAPGKGLEWVAIISYGGTNKYYADSVKGRFTIS RDNSKNTLYLQMNSLRAEDTAVYYCARD S GYRSLH WGQGLTVTVSSA5TKGFEVQLVESGGGLVQPGGSL RLSCAASGFKFSTFYMTWVRQAPGKGLEWVANIKQ DGSEKDYLDSVRGRFTISRDNANKNSLYLQMNSLRAE DTAVYYCTRNGLQDSYSGDFFDHWGQGLTVTVSS	7G6-15E3-DVD (VH)
SEQ ID NO: 31	AIVLTQSPGTLSPGERATLSCRASQRVSGDYLA W Y QQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCQHYN G PPVTFGQGTKLEIK	17H9 VL
SEQ ID NO: 32	EIVLTQSPSLPVTTPGEPASISCRSSQSLVHRNGYNYLD WYLQKPGQSPQLLIYMASKRASGV P DRFSGSGSGTD FTLKISRVEAEDVGVYYCMQALQ T WTFGQGTKVEIK RTVAAPSVFIFPPQSVLTQPPSVSAAPGQKVTISCSGT GSNIGHNYVSWYQQLPGTAPKLLIFD N TKRPSGIPDR FSGSKSGSSATLGITGLQTGDEADYFCATWDADLSA VLFGGGTKLTVL	7G6-15E3-DVD (VL)
IgG:DVD#2		
SEQ ID NO: 33	QVQLVESGGGVVQPGRSLRLSCAASGIAFNDYTMH WVRQAPGKGLEWVAIISYGGTNKYYADSVKGRFTIS RDNSKNTLYLQMNSLRAEDTAVYYCARD S GYRSLH WGQGLTVTVSS	7G6 VH
SEQ ID NO: 34	QVQLVESGGGVVQPGRSLRLSCAASGSLGT Y GMH WVRQAPGKGLEWVAIISPDGGHQDYADPVRGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCATTLCARTDC TWVRSDSWGQGLTVTVSSA5TKGFEVQLVESGGGL VQPGGSLRLSCAASGFKFSTFYMTWVRQAPGKGLE WVANIKQDGSEKDYLDSVRGRFTISRDNANKNSLYLQ MNSLRAEDTAVYYCTRNGLQDSYSGDFFDHWGQG TLTVTVSS	17H9-15E3- DVD (VH)
SEQ ID NO: 35	EIVLTQSPSLPVTTPGEPASISCRSSQSLVHRNGYNYLD WYLQKPGQSPQLLIYMASKRASGV P DRFSGSGSGTD FTLKISRVEAEDVGVYYCMQALQ T WTFGQGTKVEIK	7G6 VL

SEQ ID NO: 36	AIVLTQSPGTLSPGERATLSCRASQRVSGDYLA WYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSDFTL TISRLEPEDFAVYYCQHYNGPPVTFGQGTKLEIKRTVA APSVFIFPPQSVLTQPPSVSAAPGQKVTISCSGTGSNIG HNYVSWYQQLPGTAPKLLIFDNTKRPSGIPDRFSGSK SGSSATLGITGLQTGDEADYFCATWDADLSAVLFGQ GTKLTVL	17H9-15E3- DVD (VL)
Antibody heavy chain and light chain amino acid sequences		
IgG-scFv2		
SEQ ID NO: 37	QVQLVESGGGVVQPGRSRLSCAASGSLGT YGMHWVRQAPGKGLEWVAIISPDGGHQDYADPVRGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCATLTCARTDC TWVRSDSWGQGTLVTVSSASTKGPSVFPLAPCSRSTS ESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSVVTVPSSSLGKTYTCNVDHKPSNTKV DKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLM SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAK TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKGLPSSIEKTISKAKGQPREPQVYTLPPCQEEMTKNQ VSLWCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL DSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHN HYTQKSLSLSPGGGGSGGGSGGGSGEIVLTQSPL SLPVTGPGEASISCRSSQSLVHRNGYNYLDWYLQKPG QSPQLLIYMASKRASGVPDRFSGSGSDFTLKISRVE AEDVGVYYCMQALQWTWTFGCGTKVEIKGGGSGG GGSGGGSGGGGQVQLVESGGGVVQPGRSRLS CAASGIAFNDYTMHWVRQAPGKCLEWVAISYGGT NKYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTA VYYCARDSGYRSLHGWGQGTLVTVS	17H9-IgG4 (knob)-7G6scFv HC

SEQ ID NO: 38	QVQLVESGGGVVQPGRSLRLSCAASGSTLGTYGMH WVRQAPGKGLEWVAIIISPDGGHQDYADPVRGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCATTLCARTDC TWVRS DS WGQGT LV TVSSA 57KG PS VFPLAPCSRSTS ESTAALGCLVKDYFPEPVT SV WNSGALTSGVHTFPAV LQSSGLYSLSSV TV PSSSLG TK TYTCNV DH KPSNTKV DKR VE SKYGP PC PPC PA PEFLGGPSV FL FPPKPKDTLMI SRTPEVTCV V VDVSQEDPEVQFNWYVDGVEVHNAK TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKGLPSSI E KTISKAKGQPREPQVCTLP PS QEEMTKNQ VSLCAVKG F YPSDIAVEWESNGQPENNYK TT PPVLD SDGSFFLVSKLTVDKSRWQEGNVFSCSV M HEALHNH YTQKSLSLSPG GGGGSGGGSGGGG S SVLTQPPS VSAAPGQKV T ISCSGTGSNIGHN YV SWYQQLPGTAP KLLIFD NT KR PS GIPDRFSGSKSGSSATLGITGLQTGDE ADYFCATWDADLSAVLFGCGTKLTVL GGGGSGGG SGGGGGSGGGG S EVQLVESGGGLVQPGGSLRLSCA ASGFKFSTFYMTWVRQAPGKCLEWVANIKQDGSEK DYLD SV RGRFTISRDN AK NSLYLQMNSLRAEDTAVYY CTRNGLQDSYSGDFFDHWGQGT LV TVS	17H9-Ig4 (hole)- 15E3scFv HC
SEQ ID NO: 39	AIVLTQSPGTL SL SPGERATLSCRASQ RV SGDYLAWY QQKPGQAPRLLIY G ASSRATGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCQHYNGPPVTFGQGT K EIKRTVA APSVFIFP S DEQLKSGTASV V CLLN N FYPREAKVQW KVDNALQSGNSQESVTEQDSK D STYLSSTL TL SKAD YE HK VYACEVTHQGLSSPVT K SFNRGEC	17H9 LC
IgG-scFv		
SEQ ID NO: 40	QVQLVESGGGVVQPGRSLRLSCAASGSTLGTYGMH WVRQAPGKGLEWVAIIISPDGGHQDYADPVRGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCATTLCARTDC TWVRS DS WGQGT LV TVSSASTKGPSVFPLAPCSRSTS ESTAALGCLVKDYFPEPVT SV WNSGALTSGVHTFPAV LQSSGLYSLSSV TV PSSSLG TK TYTCNV DH KPSNTKV DKR VE SKYGP PC PPC PA PEFLGGPSV FL FPPKPKDTLMI SRTPEVTCV V VDVSQEDPEVQFNWYVDGVEVHNAK TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKGLPSSI E KTISKAKGQPREPQV Y TLPPSQEEMTKNQ VSLTCLVKG F YPSDIAVEWESNGQPENNYK TT PPVLD SDGSFFLYSKLTVDKSRWQEGNVFSCSV M HEALHNH YTQKSLSLSPG GGGGSGGGSGGGG S EVLTQSP SL PVT P GE P ASISCRSSQSLVHRNGYNYLDWYLQKPGQ SPQLLIY M ASKRASGV P DRFSGSGSGTDFTLKISRVEAE DVG V YYCMQALQ T WTFGCGTKVEIK GGGGSGGG SGGGGGSGGGG S QVQLVESGGGVVQPGRSLRLSC AASGIAFN D YTMHWVRQAPGKCLEWVA AI SYGGTN KYYADSVKGRFTISRDN SK NTLYLQMNSLRAEDTAVY YCARD S GYRSL L HWGQGT LV TVS	17H9-IgG4- 7G6scFv HC

SEQ ID NO: 41	AIVLTQSPGTLSPGERATLSCRASQRVSGDYLA WYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCQHYNQPPVTFGQGTKEIKRTVA APSVFIFPPSDEQLKSGTASVCLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKAD YEKHKVYACEVTHQGLSPVTKSFNRGEC	17H9 LC
IgG:DVD#1		
SEQ ID NO: 42	QVQLVESGGGVVQPGRSLRLSCAASGSLGT YGMHWVRQAPGKGLEWVAIISPDGGHQDYADPVRGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCATTLCARTDC TWVRSDSWGQGTLLTVSSASTKGPSVFPLAPCSRSTS ESTAALGCLVKDYFPEPVTWSNSGALTSGVHTFPAV LQSSGLYSLSSVTVPSSSLGTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPCQEEEMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQEGNVFSCSVSMHEALHNHYTQKSLSLSPGK	17H9-IgG4 (knob) HC
SEQ ID NO: 43	QVQLVESGGGVVQPGRSLRLSCAASGIAFN DYMHWVRQAPGKGLEWVAIISYGGTNKYADSVKGRFTIS RDNSKNTLYLQMNSLRAEDTAVYYCARDSGYRSLH WGQGTLLTVSSASTKGPEVQLVESGGGLVQPGGSL RLSCAASGFKFSTEYMTWVRQAPGKGLEWVANIKQ DGSEKDYLDSVRGRFTISRDNANKNSLYLQMNSLRAE DTAVYYCTRNLQDSYSGDFFDHWGQGTLLTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT WSNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS SSLGTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVCTLPSSQEEEMTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLVSKLTVDKSRWQEGNVFSCSVSMHEALHNHYTQKSLSLSPGK	7G6-15E3-DVD- IgG4(hole) HC
SEQ ID NO: 44	AIVLTQSPGTLSPGERATLSCRASQRVSGDYLA WYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCQHYNQPPVTFGQGTKEIKRTVA APSVFIFPPSDEQLKSGTASVCLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKAD YEKHKVYACEVTHQGLSPVTKSFNRGEC	17H9 LC

SEQ ID NO: 45	EIVLTQSP LS LPVTPGEPASISCRSSQSLVHRNGYNYLD WYLQKPGQSPQ LLIY MASKRASGV PDR FSGSGSGTD FTLKISRVEAEDVGVYYC MQALQ TWTFGQGTKVEIK <i>RTVAAPSVFIFPPQSVLTQPPSVSAAPGQKVTISCSGT</i> <i>G</i> <u>SNIGHN</u> YVSWYQQLPGTAPKLLIFDNTKRP <u>SGIPDR</u> FSGSKSGSATLGITGLQTGDEADYFCATWDADLSA <u>VL</u> FGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATL VCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRYSYSCQVTHEGSTVEKTV APTECS	7G6-15E3-DVD LC
IgG:DVD#2		
SEQ ID NO: 46	QVQLVESGGGVVQPGRSLRLSCAASGIAFN DY TMH WVRQAPGKGLEWVA AI SYGGTNKYYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCARD <u>SGYRSL</u> <u>H</u> WGQGT LV TVSSASTKGPSVFPLAPCSRSTSESTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVTVPSSSLGKTYTCNV DH KPSNTKVDKRVE SKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPE VTCVVDVSQEDPEVQFNWYVDGVEVHNAKTKPR EEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGL PSSIEKTISKAKGQPREPQVYTLPPCQEEMTKNQVSL WCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDS GSFFLYSKLTVDKSRWQEGNVFSCSV M HEALHNHYT QKSLSLSPGK	7G6-IgG4(knob) HC
SEQ ID NO: 47	QVQLVESGGGVVQPGRSLRLSCAASGSTLGTYGMH WVRQAPGKGLEWVA II SPDGGHQDYADPVGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCATL <u>CARTDC</u> <u>TW</u> VRSDSWGQGT LV TVSSA <u>57KG</u> F EV QLVESGGGL VQPGGSLRLSCAASGFKFSTFYMTWVRQAPGKGLE WVANIKQDGSEKDYLDSVRGRFTISRDN AK NSLYLQ MNSLRAEDTAVYYCTR <u>NGLQ</u> DSYSGDFFDHWGQG TLTVSSA <u>57KG</u> F SV FPLAPCSRSTSESTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV TVPSSSLGKTYTCNV DH KPSNTKVDKRVESKYGPPC PPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVCTLPPSQEEMTKNQVSLSCAVKGF YPSDIAVEWESNGQPENNYKTTTPVLDSGFFLVSK LTVDKSRWQEGNVFSCSV M HEALHNHYTQKSLSLSP GK	17H9-15E3- DVD-IgG4(hole) HC
SEQ ID NO: 48	EIVLTQSP LS LPVTPGEPASISCRSSQSLVHRNGYNYLD WYLQKPGQSPQ LLIY MASKRASGV PDR FSGSGSGTD FTLKISRVEAEDVGVYYC MQALQ TWTFGQGTKVEIK RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDYSLSSLTTL SKADYEEKHKVYACEVTHQGLSPVTKSFNRGEC	7G6 LC

SEQ ID NO: 49	AIVLTQSPGTLSPGERATLSCRASQRVSGDYLA WYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSDFTL TISRLEPEDFAVYYCQHYNGPPVTFGQGTKLEIKR7V AAPSVFIFPPQSVLTQPPSVSAAPGQKVTISCSGTGSN IGHNYVSWYQQLPGTAPKLLIFDNTKRPSGIPDRFSG SKSGSSATLGITGLQTGDEADYFCATWDADLSAVLF GQGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVC LISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNN KYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTV PTECS	17H9-15E3- DVD LC
Antibody constant regions		
IgG-scFv2		
SEQ ID NO: 50	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSL GTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAP EFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQED PEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQ PREPQVYTLPPCQEEMTKNQVSLWCLVKGFYPSDIA VEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKS RWQEGNVFSCSVMHREALHNHYTQKSLSLSPG	HC (knob)
SEQ ID NO: 51	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSL GTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAP EFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQED PEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQ PREPQVCTLPQSQEEMTKNQVSLCAVKGFYPSDIAV EWESNGQPENNYKTTTPVLDSGDSFFLVSKLTVDKSR WQEGNVFSCSVMHREALHNHYTQKSLSLSPG	HC (hole)
SEQ ID NO: 52	RTVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLT LTKADYEEKHKVYACEVTHQGLSPVTKSFNRGEC	LC (kappa)
IgG-scFv		
SEQ ID NO: 53	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSL GTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAP EFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQED PEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQ PREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSR WQEGNVFSCSVMHREALHNHYTQKSLSLSPG	HC

SEQ ID NO: 54	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKSTYLSSTLT SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	LC (kappa)
IgG:DVD#1		
SEQ ID NO: 55	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS GTKYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAP EFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQED PEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQ PREPQVYTLPPCQEEMTKNQVSLWCLVKGFYPSDIA VEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKS RWQEGNVFSCSVMHLEAHNHYTQKSLSLSPGK	HC (knob)
SEQ ID NO: 56	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS GTKYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAP EFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQED PEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQ PREPQVCTLPSSQEEMTKNQVSLSCAVKGFYPSDIAV EWESNGQPENNYKTTTPVLDSDGSFFLVSKLTVDKSR WQEGNVFSCSVMHLEAHNHYTQKSLSLSPGK	HC (hole)
SEQ ID NO: 57	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKSTYLSSTLT SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	LC (kappa)
SEQ ID NO: 58	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAV TVAWKADSSPVKAGVETTPSKQSNNKYAASSYLSLT PEQWKS SYSCQVTHEGSTVEKTVAPTECS	LC DVD (lambda)
IgG:DVD#2		
SEQ ID NO: 59	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS GTKYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAP EFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQED PEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQ PREPQVYTLPPCQEEMTKNQVSLWCLVKGFYPSDIA VEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKS RWQEGNVFSCSVMHLEAHNHYTQKSLSLSPGK	HC (knob)

SEQ ID NO: 60	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSL GTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAP EFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQED PEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQ PREPQVCTLPSSQEEMTKNQVSLSCAVKGFYPSDIAV EWESNGQPENNYKTTTPVLDSGSEFLVSKLTVDKSR WQEGNVFSCSVMEALHNHYTQKSLSLSPGK	HC (hole)
SEQ ID NO: 61	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSYSTLSSTLTL SKADYEEKHKVYACEVTHQGLSPVTKSFNRGEC	LC (kappa)
SEQ ID NO: 62	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAV TVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLT PEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	LC DVD (lambda)
Antibody nucleic acid sequences		
IgG-scFv2		

SEQ ID NO: 63	CAGGTGCAACTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCC TGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATCCAC CTTGGGTACCTATGGCATGCACTGGGTCCGTCAAGGCTCCAGG CAAGGGGGCTGGAGTGGGTGGCAATTATATCACCTGATGGAG GTCACCAAGACTATGCAGACCCCGTGAGGGGCCGATTACCA TCTCCAGAGACAATTCCAAGAATACCCTTTATCTGCAAATGAAC AGCCTGAGAGCTGAGGACACGGCTGTTTATTATTGTGCGACC ACGTTGTGTGCTAGGACCGACTGTACATGGGTGAGGTCTGAC TCCTGGGGTCAGGGAACCCCTGGTCACCGTCTCCTCAGCTAGC ACCAAAGGACCCAGTGTGTTTCTCTGGCCCCCTGCTCCAGGA GCACTTCTGAAAGCACAGCTGCTCTGGGCTGCCTGGTGAAGG ACTACTTCCCCGAGCCTGTGACAGTGTCTGGAACAGTGGGG CCCTGACCAGCGGCGTGACACCTTCCCTGCTGTCTGCAGA GCAGTGGCCTCTACAGCCTTTCTTCAGTGGTCAACCGTGCCCTC CAGCAGCCTGGGGACCAAGACATATACCTGCAATGTTGACCA CAAGCCATCCAACACAAAAGTGGACAAGAGGGTGGAGAGCA AATATGGCCCCCATGCCCCCTTGCCCAGCCCCAGAATTTCT TGGCGGCCCTTCTGTCTTCTCTTCCCACCCAAGCCCAAAGAC ACCCTGATGATCAGCAGGACCCCTGAAGTGACTTGTGTGGTT GTTGATGTGAGCCAGGAAGATCCTGAGGTGCAGTTTAACTGG TACGTGGATGGAGTGGAAGTCCACAATGCCAAAACAAAGCCT CGGAGGGAGCAGTTCAACAGCACCTACCGCGTGGTGTCTGTG CTCACTGTCTCCACCAGGACTGGCTGAATGGGAAGGAGTAC AAGTGCAAGGTGAGCAACAAGGGGCTGCCCTCTTCCATCGAG AAGACCATCTCCAAGGCCAAGGGCCAGCCCAGGGAGCCCCA GGTGTACACACTGCCTCCCTGCCAAGAAGAGATGACCAAGAA CCAGGTCTCCCTCTGGTGTGTTGGTGAAAGGCTTCTACCCAAGT GACATTGCTGTGGAGTGGGAGTCCAATGGACAGCCAGAGAA CAACTACAAAACCAACCCACCAGTGCTGGACAGTGATGGCAG CTTCTTCTGTACTCCAAGCTGACTGTGGACAAAAGCCGTGG CAGGAGGGCAATGTGTTCACTGCTGACGCGTATGCACGAGGC CCTGCACAACCACTACACCCAGAAGTCTCTGTCTTAAGCCCG GGCGGGGGAGGAGTAGTGGTGGTGGTGGTAGCGGCGGTG GTGGGTCAAGATTGTGTTGACTCAGTCTCCACTCTCCTGCC CGTACCCCTGGTGAGCCGGCCTCCATCTCCTGCAGGTCGAG TCAGAGCCTCGTGCATAGAAATGGATACAACTATTTAGATTGG TACCTGCAGAAGCCAGGGCAGTCTCCACAGTCTCCTGATCTATA TGGCTTCTAAACGGGCCTCCGGGGTCCCTGACAGGTTCACTG GCAGTGGGTCAAGCACAGATTTTACACTGAAAATCAGCAGAG TGGAGGCTGAGGATGTTGGAGTTTATTACTGCATGCAAGCTCT ACAAACTTGGACGTTCCGGCTGCGGGACCAAGGTGGAAATCAA AGGCGGTGGTGGAAAGTGGGGGAGGTGGATCCGGAGGGGGT GGATCCGGCGGAGGCGGCTCTCAGGTGCAGCTGGTGGAGTC TGGGGGAGGCGTGGTGCAGCCTGGGAGGTCCCTGAGACTCT CATGTGCAGCCTCTGGCATCGCCTTCAATGACTACACTATGCA CTGGGTCCGCCAGGCTCCAGGCAAGTGCCTGGAGTGGGTGG CAGCTATATCATATGGTGGGACTAATAAATACTACGCAGATTC CGTGAAGGGCCGATTACCATCTCCAGAGACAATTCCAAGAA CACCTGTATCTGCAGATGAACAGCCTGAGAGCTGAGGACAC GGCTGTGTATTACTGTGCGAGAGATTCTGGTTATCGGAGTCTT TGCCTGAGGGCCAGGGAACCCCTGGTCACCGTCTCCTGA	17H9- IgG4(knob) -7G6scFv HC
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SEQ ID NO: 64	CAGGTGCAACTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCC TGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATCCAC CTTGGGTACCTATGGCATGCACTGGGTCCGTCAGGCTCCAGG CAAGGGGCTGGAGTGGGTGGCAATTATATCACCTGATGGAG GTCACCAAGACTATGCAGACCCCGTGAGGGGCCGATTACCA TCTCCAGAGACAATTCCAAGAATACCCTTTATCTGCAAATGAAC AGCCTGAGAGCTGAGGACACGGCTGTTATTATTGTGCGACC ACGTTGTGTGCTAGGACCGACTGTACATGGGTGAGGTCTGAC TCCTGGGGTCAGGGAACCCTGGTCACCGTCTCCTCAGCTAGC ACCAAAGGACCCAGTGTGTTTCCTCTGGCCCCCTGCTCCAGGA GCACTTCTGAAAGCACAGCTGCTCTGGGCTGCCTGGTGAAGG ACTACTCCCCGAGCCTGTGACAGTGTCTTGGAACAGTGGGG CCCTGACCAGCGCGGTGCACACCTTCCCTGCTGTCTGCAGA GCAGTGGCCTCTACAGCCTTTCTTCAGTGGTCACCGTGCCCTC CAGCAGCCTGGGGACCAAGACATATACCTGCAATGTTGACCA CAAGCCATCCAACACAAAAGTGGACAAGAGGGTGGAGAGCA AATATGGCCCCCATGCCCCCTTGCCCAGCCCCAGAATTTCT TGGCGGCCCTTCTGTCTTCTCTTCCCACCCAAGCCCAAAGAC ACCCTGATGATCAGCAGGACCCCTGAAGTGACTTGTGTGGTT GTTGATGTGAGCCAGGAAGATCCTGAGGTGCAGTTTAACTGG TACGTGGATGGAGTGGAAGTCCACAATGCCAAAACAAAGCCT CGGGAGGAGCAGTTCAACAGCACCTACCGCGTGGTGTCTGTG CTCACTGTCTCCACCAGGACTGGCTGAATGGGAAGGAGTAC AAGTGCAAGGTGAGCAACAAGGGGCTGCCCTCTTCCATCGAG AAGACCATCTCCAAGGCCAAGGGCCAGCCCAGGGAGCCCCA GGTGTGCACACTGCCTCCCAGCCAAGAAGAGATGACCAAGAA CCAGGTCTCCCTCAGCTGTGCCGTGAAAGGCTTCTACCCAAGT GACATTGCTGTGGAGTGGGAGTCCAATGGACAGCCAGAGAA CAACTACAAAACCACCCACCAAGTGCTGGACAGTGATGGCAG CTTCTTCTGGTGTCCAAGCTGACTGTGGACAAAAGCCGCTGG CAGGAGGGCAATGTGTTCACTGCAGCGTGATGCACGAGGC CCTGCACAACCACTACACCCAGAAGTCTGTCTTAAAGCCCG GGCGGGGGAGGAGTAGTGGTGGTGGTGGTAGCGGCGGTG GTGGGTCAAGTCTGTGCTGACTCAGCCGCCCTCAGTGTCTG CGGCCCCAGGACAGAAGGTCAACATCTCCTGCTCTGGAACCG GCTCCAACATTGGACATAATTATGTCTCCTGGTACCAACAACCTC CCAGGAACAGCCCCCAAACTCCTCATTTTTGACAATACTAAGC GACCCTCAGGCATTCTGACCGATTCTCTGGCTCTAAGTCTGG CTCGTCAGCCACCCTGGGCATCACCGGACTCCAGACTGGGGA CGAGGCCGATTATTTCTGCGCAACGTGGGATGCCGACCTGAG TGCTGTGCTTTTCGGCTGCGGGACCAAGCTGACCGTCCCTGGG CGGTGGTGGAAAGTGGGGGAGGTGGATCCGGAGGGGGTGGGA TCCGGCGGAGGCGGCTCTGAAGTGCAACTGGTGGAGTCGGG GGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTGTCT GTGCAGCCTCTGGATTCAAATTTAGCACTTTTATATGACGTGG GTCCGCCAGGCTCCAGGGAAGTGCCTGGAGTGGGTGGCCAA TATAAAGCAGGACGGAAGTGAGAAAGACTATCTGGACTCTGT GCGGGGCCGTTTCACCATCTCCAGAGACAACGCCAAGAACCTC ACTGTATCTGCAGATGAACAGCCTGAGAGCCGAGGACACGGC TGTCTACTATTGTACGAGAAATGGTCTCCAAGATTCTTACAGTG GTGACTTTTTTGACCACTGGGGCCAGGGAACCTGGTCAACG TCTCCTGA	17H9- IgG4(hole) -15E3scFv HC
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SEQ ID NO: 65	GCAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTC CAGGGGAAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGA GTCAGTGGCGACTACTTAGCCTGGTACCAGCAGAAGCCTGGC CAGGCTCCCAAGGCTCCTCATCTATGGTGCATCCAGCAGGGCC ACTGGCATCCCAGACAGGTTCACTGGCAGTGGGTCTGGGAC GGACTTCACTCTCACCATCAGCAGACTGGAGCCTGAAGATTTT GCAGTGTATTACTGTCAACACTATAATGGTCCACCCGTCACTTT TGGCCAGGGGACCAAGCTGGAGATCAAACGTACGGTGGCTG CACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAA TCTGGAAGTCTAGCGTTGTGTGCCTGCTGAATAACTTCTATCC CAGAGAGGCCAAAGTACAGTGGAAAGGTGGATAACGCCCTCC AATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGC AAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAGC AAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTC ACCCATCAGGGCCTGAGTTCGCCCCGTACAAAGAGCTTCAAC AGGGGAGAGTGTTAG	17H9 LC
IgG-scFv		

SEQ ID NO: 66	CAGGTGCAACTGGTGGAGTCTGGGGGAGGCGTGGTCCAGC CTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATCC ACCTTGGGTACCTATGGCATGCACTGGGTCCGTCAGGCTCC AGGCAAGGGGCTGGAGTGGGTGGCAATTATATCACCTGAT GGAGGTCACCAAGACTATGCAGACCCCGTGAGGGGCCGAT TCACCATCTCCAGAGACAATTCCAAGAATACCCTTTATCTGCA AATGAACAGCCTGAGAGCTGAGGACACGGCTGTTTATTATT GTGCGACCACGTTGTGTGCTAGGACCGACTGTACATGGGTG AGGTCTGACTCCTGGGGTCAGGGAACCCCTGGTCACCGTCTC CTCAGCTAGCACCAAAGGACCCAGTGTGTTTCCTCTGGCCCC CTGCTCCAGGAGCACTTCTGAAAGCACAGCTGCTCTGGGCT GCCTGGTGAAGGACTACTTCCCCGAGCCTGTGACAGTGTCC TGGAACAGTGGGGCCCTGACCAGCGGCGTGACACCTTCC CTGCTGTCCTGCAGAGCAGTGGCCTCTACAGCCTTCTTCAG TGGTCACCGTGCCCTCCAGCAGCCTGGGGACCAAGACATAT ACCTGCAATGTTGACCACAAGCCATCCAACACAAAAAGTGGA CAAGAGGGTGGAGAGCAAATATGGCCCCCATGCCCCCTT GCCCAGCCCCAGAATTTCTTGGCGGCCCTTCTGTCTTCTCTT CCCACCCAAGCCCAAGACACCCTGATGATCAGCAGGACCC CTGAAGTGACTTGTGTGGTTGTTGATGTGAGCCAGGAAGAT CCTGAGGTGCAGTTTAACTGGTACGTGGATGGAGTGGAAAGT CCACAATGCCAAAACAAAGCCTCGGGAGGAGCAGTTCAACA GCACCTACCGCGTGGTGTCTGTGCTCACTGTCTCCACCAG GACTGGCTGAATGGGAAGGAGTACAAGTGCAAGGTGAGCA ACAAGGGGGCTGCCCTCTTCCATCGAGAAGACCATCTCCAAG GCCAAGGGCCAGCCAGGGAGCCCCAGGTGTACACACTGC CTCCCAGCCAAGAAGAGATGACCAAGAACCAGGTCTCCCTC ACCTGTTTGGTGAAAGGCTTCTACCCAAGTGACATTGCTGTG GAGTGGGAGTCCAATGGACAGCCAGAGAACAACACTACAAAA CCACCCCAACAGTGCTGGACAGTGATGGCAGCTTCTTCCCTG ACTCCAAGCTGACTGTGGACAAAAGCCGCTGGCAGGAGGG CAATGTGTTTCACTGCAGCGTGATGCACGAGGCCCTGCACA ACCACTACACCCAGAAGTCTCTGTCTTAAGCCCGGGCGGG GGAGGAGGTAGTGGTGGTGGTGGTAGCGGCGGTGGTGGG TCAGAGATTGTGTGACTCAGTCTCCACTCTCCTTGCCCGTCA CCCCTGGTGAGCCGGCCTCCATCTCCTGCAGGTGAGTCAAG AGCCTCGTGCATAGAAATGGATACAACTATTTAGATTGGTAC CTGCAGAAGCCAGGGCAGTCTCCACAGCTCCTGATCTATAT GGCTTCTAAACGGGCCTCCGGGGTCCCTGACAGGTTCAGTG GCAGTGGGTGAGGCACAGATTTTAACTGAAAATCAGCAGA GTGGAGGCTGAGGATGTTGGAGTTTATTACTGCATGCAAGC TCTACAAACTTGGACGTTCCGGCTGCGGGACCAAGGTGGAAA TCAAAGGCGGTGGTGGAAAGTGGGGGAGGTGGATCCGGAG GGGGTGGATCCGGCGGAGGCGGCTCTCAGGTGCAGTCTG TGGAGTCTGGGGGAGGCGTGGTGCAGCCTGGGAGGTCCCT GAGACTCTCATGTGCAGCCTCTGGCATCGCCTTCAATGACTA CACTATGCACTGGGTCCGCCAGGCTCCAGGCAAGTGCTGG AGTGGGTGGCAGCTATATCATATGGTGGGACTAATAAAATACT ACGCAGATTCCGTGAAGGGCCGATTACCATCTCCAGAGAC AATCCAAGAACACCCTGTATCTGCAGATGAACAGCCTGAGA GCTGAGGACACGGCTGTGTATTACTGTGCGAGAGATTCTGG TTATCGGAGTCTTTTGCAGTGGGGCCAGGGAACCCCTGGTCA CCGTCTCTGA	17H9-IgG4- 7G6scFv HC
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SEQ ID NO: 67	GCAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCT CCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGA GAGTCAGTGGCGACTACTTAGCCTGGTACCAGCAGAAGCCT GGCCAGGCTCCCAGGCTCCTCATCTATGGTGCATCCAGCAG GGCCACTGGCATCCCAGACAGGTTCACTGGCAGTGGGTCT GGGACGGACTTCACTCTCACCATCAGCAGACTGGAGCCTGA AGATTTTGCAGTGTATTACTGTCAACACTATAATGGTCCACCC GTCACTTTTGGCCAGGGGACCAAGCTGGAGATCAAACGTAC GGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGA GCAGTTGAAATCTGGAAGTCTAGCGTTGTGTGCCTGCTGA ATAACTTCTATCCCAGAGAGGGCCAAAGTACAGTGGAAGGTG GATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTAC AGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGC ACCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGT CTACGCCTGCGAAGTCACCCATCAGGGCCTGAGTTCGCCCG TCACAAAGAGCTTCAACAGGGGAGAGTGTTAG	17H9 LC
IgG:DVD#1		
SEQ ID NO: 68	CAGGTGCAACTGGTGGAGTCTGGGGGAGGCGTGGTCCAGC CTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATCCA CCTGGGTACCTATGGCATGCACTGGGTCCGTCAAGGCTCCA GGCAAGGGGCTGGAGTGGGTGGCAATTATACCTGATGG AGGTCACCAAGACTATGCAGACCCCGTGAGGGGGCCGATTCA CCATCTCCAGAGACAATTCCAAGAATACCCTTTATCTGCAAT GAACAGCCTGAGAGCTGAGGACACGGCTGTTTATTATTGTGC GACCACGTTGTGTGCTAGGACCGACTGTACATGGGTGAGGT CTGACTCCTGGGGTCAGGGAACCCTGGTCACCGTCTCCTCA GCTAGCACCAAAGGACCCAGTGTGTTTCCTCTGGCCCCCTGC TCCAGGAGCACTTCTGAAAGCACAGCTGCTCTGGGCTGCCT GGTGAAGGACTACTTCCCCGAGCCTGTGACAGTGTCTGGA ACAGTGGGGCCCTGACCAGCGCGTGCACACCTTCCCTGCT GTCCTGCAGAGCAGTGGCCTCTACAGCCTTTCTTCACTGGTC ACCGTGCCCTCCAGCAGCCTGGGGACCAAGACATATACCTG CAATGTTGACCACAAGCCATCCAACACAAAAGTGGACAAGA GGGTGGAGAGCAAATATGGCCCCCATGCCCCCTTGCCCA GCCCCAGAATTTCTTGGCGGCCCTTCTGTCTTCTCTTCCAC CCAAGCCCCAAAGACACCCTGATGATCAGCAGGACCCCTGAA GTGACTTGTGTGGTTGTTGATGTGAGCCAGGAAGATCCTGA GGTGCAGTTTAACTGGTACGTGGATGGAGTGGAAGTCCACA ATGCCAAAACAAAGCCTCGGGAGGAGCAGTTCAACAGCACC TACCGCGTGGTGTCTGTGCTCACTGTCTCCACCAGGACTGG CTGAATGGGAAGGAGTACAAGTGCAAGGTGAGCAACAAGG GGCTGCCCTCTTCCATCGAGAAGACCATCTCCAAGGCCAAG GGCCAGCCCAGGGAGCCCCAGGTGTACACACTGCCTCCCTG CCAAGAAGAGATGACCAAGAACCAGGTCTCCCTCTGGTGTT GGTGAAAGGCTTCTACCCAAGTGACATTGCTGTGGAGTGGG AGTCCAATGGACAGCCAGAGAACAATAACAAACCACCCCA CCAGTGCTGGACAGTGATGGCAGCTTCTTCTGTACTCCAAG CTGACTGTGGACAAAAGCCGCTGGCAGGAGGGCAATGTGTT CAGCTGCAGCGTGATGCACGAGGCCCTGCACAACCACTACA CCCAGAAGTCTCTGTCTTAAGCCCCGGGCTAAAAG	17H9- IgG4(knob) HC

SEQ ID NO: 69	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTGCAGC CTGGGAGGTCCCTGAGACTCTCATGTGCAGCCTCTGGCATC GCCTTCAATGACTACACTATGCACTGGGTCCGCCAGGCTCCA GGCAAGGGCCTGGAGTGGGTGCCAGCTATATCATATGGTG GGACTAATAAATACTACGCAGATTCCGTGAAGGGCCGATTCA CCATCTCCAGAGACAATTCCAAGAACACCCTGTATCTGCAGA TGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGT GCGAGAGATTCTGGTTATCGGAGTCTTTTGCAGTGGGGCCA GGGAACCCTGGTCACCGTCTCGAGTGGTTCGACGAAGGGG CCGGAGGTGCAGCTGGTGGAGTGGGGGGAGGCTTGGTCC AGCCGGGGGGGTCCCTGAGACTGTCTGTGCAGCCTCTGGA TTCAAATTTAGCACTTTTATATGACGTGGGTCCGCCAGGCTC CAGGGAAGGGCCTGGAGTGGGTGGCCAATATAAAGCAGGA CGGAAGTGAGAAAGACTATCTGGACTCTGTGCGGGGCCGTT TCACCATCTCCAGAGACAACGCCAAGAACTCACTGTATCTGC AGATGAACAGCCTGAGAGCCGAGGACACGGCTGTCTACTAT TGTACGAGAAATGGTCTCCAAGATTCTTACAGTGGTGACTTTT TTGACCACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA GCTAGCACCAAAGGACCCAGTGTGTTTCCTCTGGCCCCCTGC TCCAGGAGCACTTCTGAAAGCACAGCTGCTCTGGGCTGCCT GGTGAAGGACTACTTCCCCGAGCCTGTGACAGTGCCTGGA ACAGTGGGGCCCTGACCAGCGGCGTGCACACCTTCCCTGCT GTCCTGCAGAGCAGTGGCCTCTACAGCCTTTCTTCAGTGGTC ACCGTGCCCTCCAGCAGCCTGGGGACCAAGACATATACCTG CAATGTTGACCACAAGCCATCCAACACAAAAGTGGACAAGA GGGTGGAGAGCAAATATGGCCCCCATGCCCCCCTTGCCCA GCCCCAGAATTTCTTGGCGGCCCTTCTGTCTTCTCTTCCCAC CCAAGCCCCAAGACACCCTGATGATCAGCAGGACCCCTGAA GTGACTTGTGTGGTTGTTGATGTGAGCCAGGAAGATCCTGA GGTGCAGTTTAACTGGTACGTGGATGGAGTGGAAAGTCCACA ATGCCAAAACAAAGCCTCGGGAGGAGCAGTTCAACAGCACC TACCGCGTGGTGTCTGTGCTCACTGTCTCCACCAGGACTGG CTGAATGGGAAGGAGTACAAGTGCAAGGTGAGCAACAAGG GGCTGCCCTCTTCCATCGAGAAGACCATCTCCAAGGCCAAG GGCCAGCCCAGGGAGCCCCAGGTGTGCACACTGCCTCCCA GCCAAGAAGAGATGACCAAGAACCAGGTCTCCCTCAGCTGT GCCGTGAAAGGCTTCTACCCAAGTGACATTGCTGTGGAGTG GGAGTCCAATGGACAGCCAGAGAACAATAACAAAACCAACC CACCAGTGCTGGACAGTGATGGCAGCTTCTTCTGGTGTCCA AGCTGACTGTGGACAAAAGCCGCTGGCAGGAGGGCAATGT GTTCACTGCAGCGTATGCACGAGGCCCTGCACAACCACT ACACCCAGAAGTCTCTGTCTTAAGCCCGGGCTAAAAG	7G6-15E3- DVD- IgG4(hole) HC
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SEQ ID NO: 70	GCAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCT CCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGA GAGTCAGTGGCGACTACTTAGCCTGGTACCAGCAGAAGCCT GGCCAGGCTCCCAGGCTCCTCATCTATGGTGCATCCAGCAG GGCCACTGGCATCCCAGACAGGTTCAGTGGCAGTGGGTCT GGGACGGACTTCACTCTCACCATCAGCAGACTGGAGCCTGA AGATTTTGCAGTGTATTACTGTCAACACTATAATGGTCCACCC GTCACTTTTGGCCAGGGGACCAAGCTGGAGATCAAACGTAC GGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGA GCAGTTGAAATCTGGAAGTCTAGCGTTGTGTGCCTGCTGA ATAACTTCTATCCCAGAGAGGGCAAAGTACAGTGGAAAGGTG GATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTAC AGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGC ACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGT CTACGCCTGCGAAGTCACCCATCAGGGCCTGAGTTCGCCCG TCACAAAGAGCTTCAACAGGGGAGAGTGTTAG	17H9 LC
SEQ ID NO: 71	GAGATTGTGTTGACTCAGTCTCCACTCTCCTTGCCCGTCACC CCTGGTGAGCCGGCCTCCATCTCCTGCAGGTGAGTCAGAG CCTCGTGATAGAAATGGATACAATATTTAGATTGGTACCT GCAGAAGCCAGGGCAGTCTCCACAGCTCCTGATCTATATGG CTTCTAAACGGGCCTCCGGGGTCCCTGACAGGTTCAGTGGC AGTGGGTCAGGCACAGATTTTACACTGAAAATCAGCAGAGT GGAGGCTGAGGATGTTGGAGTTTATTACTGCATGCAAGCTC TACAACTTGGACGTTCCGGCCAAGGGACCAAGGTCGAGATC AAAAGGACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCA CAGTCTGTGCTGACTCAGCCGCCCTCAGTGTCTGCGGCCCC AGGACAGAAGGTCACCATCTCCTGCTCTGGAACCGGATCCA ACATTGGACATAATTATGTCTCCTGGTACCAACAACCTCCCAG GAACAGCCCCCAAACCTCCTATTTTGAACAATAAGCGAC CCTCAGGCATTCTGACCGATTCTCTGGCTCTAAGTCTGGCT CGTCAGCCACCCTGGGCATCACCGGACTCCAGACTGGGGA CGAGGCCGATTATTTCTGCGCAACGTGGGATGCCGACCTGA GTGCTGTGCTTTTCGGCGGCGGGACCAAGCTGACCGTCCTG GGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCACC CTCGAGTGAGGAACTCCAAGCGAATAAAGCCACTCTGGTTT GTCTTATTTAGATTTCTATCCAGGGGCAGTCACGGTTGCCT GGAAAGCGGATAGTTCACCAAGTAAAAGCCGGTGTGAGAC TACGACCCCTAGTAAGCAGAGCAATAATAAATACGCTGCTTC CTCCTATTTGTCACTTACGCCCCGAGCAATGGAAATCCCACCG GAGTTACTCATGCCAGGTCACTCACGAGGGGTCAACAGTGG AGAAGACAGTTGCACCTACAGAATGCTCCTAG	7G6-15E3- DVD LC
IgG:DVD#2		

SEQ ID NO: 72	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTGCAGC CTGGGAGGTCCCTGAGACTCTCATGTGCAGCCTCTGGCATC GCCTTCAATGACTACACTATGCACTGGGTCCGCCAGGCTCCA GGCAAGGGCCTGGAGTGGGTGGCAGCTATATCATATGGTG GGACTAATAAATACTACGCAGATTCCGTGAAGGGCCGATTCA CCATCTCCAGAGACAATTCCAAGAACACCCTGTATCTGCAGA TGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGT GCGAGAGATTCTGGTTATCGGAGTCTTTTGCAGTGGGGCCA GGGAACCCTGGTCACCGTCTCCTCAGCTAGCACCAAAGGAC CCAGTGTGTTTCCTCTGGCCCCCTGCTCCAGGAGCACTTCTG AAAGCACAGCTGCTCTGGGCTGCCTGGTGAAGGACTACTTC CCCGAGCCTGTGACAGTGTCTGGAACAGTGGGGCCCTGAC CAGCGGCGTGCACACCTTCCCTGCTGTCTGCAGAGCAGTG GCCTCTACAGCCTTCTTCAGTGGTCACCGTGCCCTCCAGCA GCCTGGGGACCAAGACATATACCTGCAATGTTGACCACAAG CCATCCAACACAAAAGTGGACAAGAGGGTGGAGAGCAAATA TGGCCCCCATGCCCCCTTGCCCAGCCCCAGAATTTCTTGG CGGCCCTTCTGTCTTCTCTTCCCAAGCCCAAAGACACC CTGATGATCAGCAGGACCCCTGAAGTGACTTGTGTGGTTGTT GATGTGAGCCAGGAAGATCCTGAGGTGCAGTTTAACTGGTA CGTGGATGGAGTGGAAGTCCACAATGCCAAAACAAAGCCTC GGGAGGAGCAGTTCAACAGCACCTACCGCGTGGTGTCTGTG CTCACTGTCTCCACCAGGACTGGCTGAATGGGAAGGAGTA CAAGTGCAAGGTGAGCAACAAGGGGCTGCCCTCTTCCATCG AGAAGACCATCTCCAAGGCCAAGGGCCAGCCCAGGGAGCC CCAGGTGTACACACTGCCTCCCTGCCAAGAAGAGATGACCA AGAACCAGGTCTCCCTCTGGTGTGTTGGTGAAAGGCTTCTACC CAAGTGACATTGCTGTGGAGTGGGAGTCCAATGGACAGCCA GAGAACAATAACAAAACCAACCCACCAAGTGTGGACAGTGA TGGCAGCTTCTTCTGTACTCCAAGCTGACTGTGGACAAAAG CCGCTGGCAGGAGGGCAATGTGTTGAGCTGCAGCGTGATGC ACGAGGCCCTGCACAACCACTACACCCAGAAGTCTCTGTCTT TAAGCCCGGGCTAAAAG	7G6-IgG4 (knob) HC
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SEQ ID NO: 73	CAGGTCCAACCTCGTCGAAAGTGGCGGCGGAGTAGTGCAACC AGGAAGAAAGTCTCAGGTTAAGTTGCGCCGCTAGTGGTTCTAC ACTTGGGACTTACGGAATGCATTGGGTACGCCAAGCCCCCG GGAAAGGCTTGGAAATGGGTAGCTATAATCAGCCCGGACGGC GGACATCAGGATTACGCCGATCCAGTCAGAGGTCTGTTTTACA ATTTCTAGGGATAACAGTAAGAACACACTGTACCTTCAGATG AATTCCCTGCGGGCGGAAGATACAGCCGTCTACTACTGCGC CACGACACTTTGCGCACGCACTGATTGCACTTGGGTTCGGTC AGATAGCTGGGGTCAAGGTACCCTGGTCACCGTCTCGAGTG CGTCGACGAAGGGGCGGAGGTGCAGCTGGTGGAGTCGG GGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTGTC CTGTGCAGCCTCTGGATTCAAATTTAGCACTTTTATATGACG TGGGTCCGCCAGGCTCCAGGGAAGGGCCTGGAGTGGGTGG CCAATATAAAGCAGGACGGAAGTGAGAAAGACTATCTGGAC TCTGTGCGGGGCGTTTCACCATCTCCAGAGACAACGCCAA GAACTCACTGTATCTGCAGATGAACAGCCTGAGAGCCGAGG ACACGGCTGTCTACTATTGTACGAGAAATGGTCTCCAAGATT CTTACAGTGGTGACTTTTTTGACCACTGGGGCCAGGGAACCC TGGTCACCGTCTCCTCAGCTAGCACCAAAGGACCCAGTGCT TTCCTCTGGCCCCCTGCTCCAGGAGCACTTCTGAAAGCACAG CTGCTCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCT GTGACAGTGCTCTGGAACAGTGGGGCCTGACCAGCGCG TGACACCTTCCCTGCTGCTCTGCAGAGCAGTGGCCTCTACA GCCTTTCTTCAGTGGTCACCGTGCCCTCCAGCAGCCTGGGGA CCAAGACATATACCTGCAATGTTGACCACAAGCCATCCAACA CAAAAGTGGAACAAGAGGGTGGAGAGCAAATATGGCCCCC ATGCCCCCCTTGCCAGCCCCAGAATTTCTTGGCGGCCCTTC TGCTTCTCTTCCCACCCAAGCCCAAAGACACCCTGATGATC AGCAGGACCCCTGAAGTGACTTGTGTGGTTGTTGATGTGAG CCAGGAAGATCCTGAGGTGCAGTTTAACTGGTACGTGGATG GAGTGGAAGTCCACAATGCCAAAACAAAGCCTCGGGAGGA GCAGTTCAACAGCACCTACCGCGTGGTGTCTGTGCTCACTGT CCTCCACCAGGACTGGCTGAATGGGAAGGAGTACAAGTGCA AGGTGAGCAACAAGGGGCTGCCCTCTCCATCGAGAAGACC ATCTCCAAGGCCAAGGGCCAGCCCAGGGAGCCCCAGGTGT GCACACTGCCTCCCAGCCAAGAAGAGATGACCAAGAACCAG GTCTCCCTCAGCTGTGCCGTGAAAGGCTTCTACCCAAGTGAC ATTGCTGTGGAGTGGGAGTCCAATGGACAGCCAGAGAACAA CTACAAAACCACCCACCAAGTGCTGGACAGTGATGGCAGCTT CTTCTGGTGTCCAAGCTGACTGTGGACAAAAGCCGCTGGC AGGAGGGCAATGTGTTGAGCTGCAGCGTGATGCACGAGGC CCTGCACAACCACTACCCAGAAAGTCTCTGTCTTAAGCCC GGGCTAAAAG	17H9-15E3- DVD- IgG4(hole) HC
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SEQ ID NO: 74	GAGATTGTGTTGACTCAGTCTCCACTCTCCTTGCCCCGTACCCCTGGTGAGCCGGCCTCCATCTCCTGCAGGTCGAGTCAGAGCCTCGTGCATAGAAATGGATACAACCTATTTAGATTGGTACCTGCTAAACGGGCCTCCGGGGTCCCTGACAGGTTCACTGGCAGTGGGTCAGGCACAGATTTTACACTGAAAATCAGCAGAGTGGAAGCTGAGGATGTTGGAGTTTATTACTGCATGCAAGCTCTACAACCTGGACGTTCCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAAGTCTAGCGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTACCCATCAGGGCCTGAGTTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG	7G6 LC
SEQ ID NO: 75	GCAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCAGGGGAAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGAGTCAGTGGCGACTACTTAGCCTGGTACCAGCAGAAGCCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGCATCCAGCAGGCCACTGGCATCCCAGACAGGTTCACTGGCAGTGGGTCTGGGACGGACTTCACTCTCACCATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAACACTATAATGGTCCACCCGTCACTTTTGGCCAGGGGACCAAGCTCGAGATCAAAGGACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCACAGTCTGTGCTGACTCAGCCGCCCTCAGTGTCTGCGGCCCCAGGACAGAAGGTCACCATCTCTGCTCTGGAACCGGATCCAACATTGGACATAATTATGTCTCCTGGTACCAACAACCTCCCAGGAACAGCCCCCAACTCCTCATTTTTGACAATACTAAGCGACCCTCAGGCATTCTGACCGATTCTGGCTCTAAGTCTGGCTCGTCAGCCACCCTGGGCATCACCGGACTCCAGACTGGGGACGAGGCCGATTATTCTGCGCAACGTGGGATGCCGACCTGAGTGCTGTGCTTTTCGGCGGCGGGACCAAGCTGACCGTCTGGGTGAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCACCCCTCGAGTGAGGAACCCAAGCGAATAAAGCCACTCTGGTTTGTCTTATTTGAGATTTCTATCCAGGGGCAGTCACGGTTGCCTGGAAAGCGGATAGTTCACCAAGTAAAAGCCGGTGTGAGACTACGACCCCTAGTAAGCAGAGCAATAATAAATACGCTGCTTCTCCTATTTGTCACTTACGCCGAGCAATGAAATCCCACCGGAGTTACTCATGCCAGGTCACTCACGAGGGGTCAACAGTGGAGAAGACAGTTGCACCTACAGAATGCTCCTAGTAA	17H9-15E3-DVD LC
Allergens		
SEQ ID NO: 76	RQQWELQGDRRCSQSLERANLRPCEQHLMQKIQRDEDSYGRDPYSPSQDPYSPYDRRGAGSSQHQRCCNELNEFENNQRCEALQQIMENQSDRLQGRQQEQQFKRELRLNPQQCGLRAPQRCDLEVESGGRDRY	Ara h 2.0101

SEQ ID NO: 77	RQQWELQGD RRCQSQLERA NLRPCEQHLM QKIQRDEDSY GRDPYSPSQD PYSPSQDPDR RDPYSPSPYD RRGAGSSQHQ ERCCNELNEF ENNQRCMCEA LQQIMENQSD RLQGRQQEQQ FKRELRNLPQ QCGLRAPQRC DLEVESGGRD RY	Ara h 2.0201
SEQ ID NO: 78	RQQPEENACQ FQRLNAQRPD NRIESEGGYI ETWNPNNQEF ECAGVALSRL VLRRNALRRP FYSNAPQEIF IQQGRGYFGL IFPGCPRHYE EPHTQGRRSQ SQRPPRRLQG EDQSQQQRDS HQKVHRFDEG DLIAVPTGVA FWLYNDHDTD VVAVSLTDTN NNDNQLDQFP RRFNLAGNTE QEFLRYQQQS RQSRRRSLPY SPYSPQSQPR QEEREFSPRG QHSRRERAGQ EEENEGGNIF SGFTPEFLEQ AFQVDDRQIV QNLRGETESE EEGAIVTVRG GLRILSPDRK RRADEEEYD EDEYEDDEED RRRGRGSRGR GNGIETICT ASAKKNIGRN RSPDIYNPQA GSLKTANDLN LLILRWLGPS AEYGNLYRNA LFVAHYNTNA HSIIYRLRGR AHVQVVDNSG NRVYDEELQE GHVLVVPQNF AVAGKSQSEN FEYVAFKTD S RPSIANLAGE NSVIDNLPEE VVANSYGLQR EQARQLKNNN PFKFFVPPSQ QSPRAVA	Ara h 3.0101
SEQ ID NO: 79	MRRERGRQGDSSSCERQVDRVNLKPCEQHIMQRIMGEQE QYDSYDIRSTRSSDQQQRCCDELNEMENTQRCMCEALQQ IMENQCDRLQDRQM VQQFKRELMNLPQQCNFRAPQRC DLDVSGGRC	Ara h 6.0101

CLAIMS

1. A multispecific antibody which binds specifically to distinct (non-overlapping) epitopes of Ara h 2, Ara h 3 and Ara h 6,
wherein the antibody comprises two heavy chains and two light chains each comprising at least one constant domain and at least one variable domain (VH/VL),
wherein the multispecific antibody comprises at least three paratopes each comprising three heavy chain CDRs (CDRH1-3) and three light chain CDRs (CDRL1-3),
wherein
 - at least one paratope (a) is formed by the VH1 of a first heavy chain and by the VL1 of a first light chain,
 - at least one paratope (b) is formed by the VH2 of a second heavy chain and by the VL2 of a second light chain, and
 - at least one paratope (c) is formed by a single chain variable fragment (scFv), the scFv being covalently linked to the constant domain of the at least one heavy chain, and/or
 - at least one paratope (d) is formed by variable domains VHx and/or VLx, the variable domains VHx and/or VLx being covalently linked to at least one of variable domains VH1/VL1 and/or VH2/VL2, thereby forming at least one dual variable domain (DVD).
2. The multispecific antibody according to claim 1, wherein paratope (a) and paratope (b) have different specificities.
3. The multispecific antibody according to claim 1, wherein paratope (a) and paratope (b) have the same specificity.
4. The multispecific antibody according to any one of the previous claims, wherein the multispecific antibody comprises at least two paratopes (c1, c2), wherein a first scFv1 forming the paratope (c1) is covalently linked to the at least one constant domain of the first heavy chain, and a second scFv1 forming the paratope (c2) is covalently linked to the at least one constant domain of the second heavy chain.

5. The multispecific antibody according to claim 4, wherein the first paratope (c1), and the second paratope (c2) have the same specificity.
6. The multispecific antibody according to claim 4, wherein the first paratope (c1), and the second paratope (c2) have different specificities.
7. The multispecific antibody according to any one of the previous claims, wherein the multispecific antibody comprises at least two paratopes (d1, d2), wherein the variable domains VHx1 and VLx1 forming a first paratope (d1) is covalently linked to the variable domain formed by VH1 and VL1, and a variable domain VHx2 and VLx2 forming a second paratope (d2) is covalently linked to the variable domain formed by VH2 and VL2.
8. The multispecific antibody according to claim 7, wherein the first paratope (d1), and the second paratope (d2) have the same specificity.
9. The multispecific antibody according to claim 7, wherein the first paratope (d1), and the second paratope (d2) have different specificities.
10. The multispecific antibody according to any one of the previous claims 1 to 6, wherein a variable domain VHx1 and VLx1 forming the first paratope (d1) is covalently linked to the variable domain formed by VH1 and VL1, or a variable domain VHx2 and VLx2 forming a second paratope (d2) is covalently linked to the variable domain formed by VH2 and VL2.
11. The multispecific antibody according to any one of the previous claims which is a human derived antibody.
12. The multispecific antibody according to any one of the previous claims, which is a monoclonal antibody.

13. The multispecific antibody according to any one of the previous claims, which comprises an Fc moiety, which preferably comprises at least one CH3 domain, wherein the at least one paratope (c) is preferably covalently linked to the at least one CH3 domain.
14. The multispecific antibody according to any one of the previous claims, which is of the IgG or IgA type.
15. The multispecific antibody according to any one of the previous claims, which is of the IgG1 or IgG4 type.
16. The multispecific antibody according to claim 14, which comprises a constant region comprising a knob-into-hole conformation, preferably a knob-into-hole conformation with a stabilizing disulphide bridge, preferably a human IgG4 constant region comprising the mutations S354C, T366W on one Fc half (knob), and Y349 C, T366 S, L368 A and Y407 V on the other Fc half (hole).
17. The multispecific antibody according according to any one of claims 15 or 16, which comprises a human IgG4 constant region having a hinge stabilizing mutation, preferably a S228P mutation.
18. The multispecific antibody according to any one of claims 15 to 17, which comprises a human IgG4 constant region having a mutation which confers stability at low pH, preferably an R409K mutation.
19. The multispecific antibody according to any one of claims 15 to 18, which comprises a human IgG4 constant region having a mutation which prevents clipping of the C-terminus and reduces binding of pre-existing anti-drug-antibodies, preferably an L445P mutation.
20. The multispecific antibody according to any one claims 15 to 19, which comprises a deletion of a C-terminal serine residue (S).

21. The multispecific antibody according to any one claims 15 to 20, which comprises a mutation which increases the *in vivo* half-life of the antibody, preferably an M428L/N434S mutation.
22. The multispecific antibody according to any one of the previous claims, wherein the at least three paratopes are formed by at least two of the CDRH1-3/CDRL1-3 sequences selected from the group consisting of (i) SEQ ID NOs: 1-6, (ii) SEQ ID NOs: 7-12, (iii) SEQ ID NOs: 13-18, and (iv) SEQ ID NOs: 19-24, or are formed by CDRH1-3/CDRL1-3 sequences having at least 70% identity to (i) SEQ ID NOs: 1-6, (ii) SEQ ID NOs: 7-12, (iii) SEQ ID NOs: 13-18, and (iv) SEQ ID NOs: 19-24, respectively.
23. The multispecific antibody according to any one of the previous claims, wherein the at least three paratopes are formed by at least three of the CDRH1-3/CDRL1-3 sequences selected from the group consisting of (i) SEQ ID NOs: 1-6, (ii) SEQ ID NOs: 7-12, (iii) SEQ ID NOs: 13-18, and (iv) SEQ ID NOs: 19-24, or are formed by CDRH1-3/CDRL1-3 sequences having at least 70% identity to (i) SEQ ID NOs: 1-6, (ii) SEQ ID NOs: 7-12, (iii) SEQ ID NOs: 13-18, and (iv) SEQ ID NOs: 19-24, respectively.
24. The multispecific antibody according to any one of the previous claims, comprising at least four paratopes which are formed by at least two of the CDRH1-3/CDRL1-3 sequences selected from the group consisting of (i) SEQ ID NOs: 1-6, (ii) SEQ ID NOs: 7-12, (iii) SEQ ID NOs: 13-18, and (iv) SEQ ID NOs: 19-24, or are formed by CDRH1-3/CDRL1-3 sequences having at least 70% identity to (i) SEQ ID NOs: 1-6, (ii) SEQ ID NOs: 7-12, (iii) SEQ ID NOs: 13-18, and (iv) SEQ ID NOs: 19-24, respectively.
25. The multispecific antibody according to claim 24, wherein the at least four paratopes are formed by at least three of the CDRH1-3/CDRL1-3 sequences selected from the group consisting of (i) SEQ ID NOs: 1-6, (ii) SEQ ID NOs: 7-12, (iii) SEQ ID NOs: 13-18, and (iv) SEQ ID NOs: 19-24, or are formed by CDRH1-3/CDRL1-3 sequences having at least 70% identity to (i) SEQ ID NOs: 1-6, (ii) SEQ ID NOs: 7-12, (iii) SEQ ID NOs: 13-18, and (iv) SEQ ID NOs: 19-24, respectively.

26. The multispecific antibody according to any one of claims 22 to 25, wherein the paratopes (a) and (b) comprise CDRH1-3/CDRL1-3 sequences according to SEQ ID NOs: 7-12 or CDRH1-3/CDRL1-3 sequences having at least 70% identity to SEQ ID NOs: 7-12, and the paratope(s) (c1) and/or (c2) comprise CDRH1-3/CDRL1-3 sequences selected from at least one of the group consisting of SEQ ID NOs: 1-6, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, or of CDRH1-3/CDRL1-3 sequences having at least 70% identity to SEQ ID NOs: 1-6, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, respectively.
27. The multispecific antibody according to any one of claims 22 to 25, wherein the paratopes (a) and (b) comprise CDRH1-3/CDRL1-3 sequences according to SEQ ID NOs: 13-18 or CDRH1-3/CDRL1-3 sequences having at least 70% identity to SEQ ID NOs: 13-18, and the paratope(s) (c1) and/or (c2) comprise CDRH1-3/CDRL1-3 sequences selected from at least one of the group consisting of SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, and SEQ ID NOs: 19-24, or of CDRH1-3/CDRL1-3 sequences having at least 70% identity to SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, and SEQ ID NOs: 19-24, respectively.
28. The multispecific antibody according to any one of claims 22 to 25, wherein the paratopes (a) and (b) comprise CDRH1-3/CDRL1-3 sequences according to SEQ ID NOs: 19-24 or CDRH1-3/CDRL1-3 sequences having at least 70% identity to SEQ ID NOs: 19-24, and the paratope(s) (c1) and/or (c2) comprise CDRH1-3/CDRL1-3 sequences selected from at least one of the group consisting of SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, and SEQ ID NOs: 13-18, or of CDRH1-3/CDRL1-3 sequences having at least 70% identity to SEQ ID NOs: 1-6, SEQ ID NOs: 7-12, and SEQ ID NOs: 13-18, respectively.
29. The multispecific antibody according to any one of claims 22 to 25, wherein the paratopes (a) and (b) comprise CDRH1-3/CDRL1-3 sequences according to SEQ ID NOs: 1-6 or CDRH1-3/CDRL1-3 sequences having at least 70% identity to SEQ ID NOs: 1-6, and the paratope(s) (c1) and/or (c2) comprise CDRH1-3/CDRL1-3 sequences selected from at least one of the group consisting of SEQ ID NOs: 7-12, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, or of CDRH1-3/CDRL1-3 sequences having at least

70% identity to SEQ ID NOs: 7-12, SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, respectively.

30. The multispecific antibody according to claim 29, which comprises:
- (i) a first heavy chain comprising
 - a VH1 domain comprising a CDRH1 having at least 70% identity to SEQ ID NO: 1, a CDRH2 having at least 70% identity to SEQ ID NO: 2, and a CDRH3 having at least 70% identity to SEQ ID NO: 3;
 - a first scFv domain comprising a CDRL1 having at least 70% identity to SEQ ID NO: 10, a CDRL2 having at least 70% identity to SEQ ID NO: 11, and a CDRL3 having at least 70% identity to SEQ ID NO: 12; and
 - a second scFv domain comprising a CDRH1 having at least 70% identity to SEQ ID NO: 7, a CDRH2 having at least 70% identity to SEQ ID NO: 8, and a CDRH3 having at least 70% identity to SEQ ID NO: 9;
 - (ii) a second heavy chain comprising
 - a VH2 domain comprising a CDRH1 having at least 70% identity to SEQ ID NO: 1, a CDRH2 having at least 70% identity to SEQ ID NO: 2, and a CDRH3 having at least 70% identity to SEQ ID NO: 3;
 - a first scFv domain comprising a CDRL1 having at least 70% identity to SEQ ID NO: 16, a CDRL2 having at least 70% identity to SEQ ID NO: 17, and a CDRL3 having at least 70% identity to SEQ ID NO: 18; and
 - a second scFv domain comprising a CDRH1 having at least 70% identity to SEQ ID NO: 13, a CDRH2 having at least 70% identity to SEQ ID NO: 14, a CDRH3 having at least 70% identity to SEQ ID NO: 15; wherein the order of the first and second scFv domains may be reversed;or a second heavy chain as defined in (i);
 - (iii) a first light chain comprising
 - a VL1 domain comprising a CDRL1 having at least 70% identity to SEQ ID NO: 4, a CDRL2 having at least 70% identity to SEQ ID NO: 5, and a CDRL3 having at least 70% identity to SEQ ID NO: 6; and
 - (iv) a second light chain comprising

a VL2 domain comprising a CDRL1 having at least 70% identity to SEQ ID NO: 4, a CDRL2 having at least 70% identity to SEQ ID NO: 5, and a CDRL3 having at least 70% identity to SEQ ID NO: 6

31. The multispecific antibody according to claim 30, which comprises:
- (i) a first heavy chain comprising,
 - a VH1 domain comprising a CDRH1 according to SEQ ID NO: 1, a CDRH2 according to SEQ ID NO: 2, and a CDRH3 according to SEQ ID NO: 3; and
 - a first scFv domain comprising a CDRL1 according to SEQ ID NO: 10, a CDRL2 according to SEQ ID NO: 11, and a CDRL3 according to SEQ ID NO: 12; and
 - a second scFv domain comprising a CDRH1 according to SEQ ID NO: 7, a CDRH2 according to SEQ ID NO: 8, a CDRH3 according to SEQ ID NO: 9;
 - (ii) a second heavy chain comprising a VH2 domain comprising a CDRH1 according to SEQ ID NO: 1, a CDRH2 according to SEQ ID NO: 2, and a CDRH3 according to SEQ ID NO: 3;
 - a first scFv domain comprising a CDRL1 according to SEQ ID NO: 16, a CDRL2 according to SEQ ID NO: 17, and a CDRL3 according to SEQ ID NO: 18, and
 - a second scFv domain comprising a CDRH1 according to SEQ ID NO: 13, a CDRH2 according to SEQ ID NO: 14, and a CDRH3 according to SEQ ID NO: 15;or a second heavy chain as defined in (i);
 - (iii) a first light chain comprising
 - a VL1 domain comprising a CDRL1 according to SEQ ID NO: 4, a CDRL2 according to SEQ ID NO: 5, and a CDRL3 according to SEQ ID NO: 6; and
 - (iv) a second light chain comprising
 - a VL2 domain comprising a CDRL1 according to SEQ ID NO: 4, a CDRL2 according to SEQ ID NO: 5, and a CDRL3 according to SEQ ID NO: 6
32. The multispecific antibody according to any one of the previous claims, wherein the first and second scFv domains are linked via a peptide linker, preferably via a flexible (GGGGS)_n-linker, preferably comprising four repeats of GGGGS.

33. The multispecific antibody according to any one of the previous claims, wherein the first and second scFv domains are disulfide stabilized, preferably by an interdomain disulfide bond between H44 and L100.
34. The multispecific antibody according to any one of claims 32 to 33, which comprises:
- (i) a first heavy chain comprising,
 - a VH1 having at least 70% identity to SEQ ID NO: 25; and
 - a scFv having at least 70% identity to SEQ ID NO: 26;
 - (ii) a second heavy chain comprising,
 - a VH2 having at least 70% identity to SEQ ID NO: 25; and
 - a scFv having at least 70% identity to SEQ ID NO: 27;or a second heavy chain as defined in (i);
 - (iii) a first light chain comprising
 - a VL1 having at least 70% identity to SEQ ID NO: 28; and
 - (iv) a second light chain comprising
 - a VL2 having at least 70% identity to SEQ ID NO: 28.
35. The multispecific antibody according to claim 34, which comprises:
- (i) a first heavy chain comprising,
 - a VH1 according to SEQ ID NO: 25; and
 - a scFv according to SEQ ID NO: 26;
 - (ii) a second heavy chain comprising,
 - a VH2 according to SEQ ID NO: 25; and
 - a scFv according to SEQ ID NO: 27;or a second heavy chain according to (i);
 - (iii) a first light chain comprising
 - a VL1 according to SEQ ID NO: 28, and
 - (iv) a second light chain comprising
 - a VL2 according to SEQ ID NO: 28.
36. The multispecific antibody according to any one of the previous claims, wherein the first or second scFv domain is covalently linked to the constant domain of the first and

second heavy chains via a peptide linker, preferably via a flexible (GGGGS)_n-linker, preferably comprising three repeats of GGGGS.

37. The multispecific antibody according to claim 36, which comprises:

- (i) a first heavy chain having at least 70% identity to SEQ ID NO: 37;
 - (ii) a second heavy chain having at least 70% identity to SEQ ID NO: 38;
 - (iii) a first light chain having at least 70% identity to SEQ ID NO: 39;
 - (iv) a second light chain having at least 70% identity to SEQ ID NO: 39;
- or
- (i) a first heavy chain having at least 70% identity to SEQ ID NO: 40;
 - (ii) a second heavy chain having at least 70% identity to SEQ ID NO: 40;
 - (iii) a first light chain having at least 70% identity to SEQ ID NO: 41; and
 - (iv) a second light chain having at least 70% identity to SEQ ID NO: 41.

38. The multispecific antibody according to claim 37, which comprises:

- (i) a first heavy chain according to SEQ ID NO: 37;
 - (ii) a second heavy chain according to SEQ ID NO: 38;
 - (iii) a first light chain according to SEQ ID NO: 39; and
 - (iv) a second light chain according to SEQ ID NO: 39;
- or
- (i) a first heavy chain according to SEQ ID NO: 40;
 - (v) a second heavy chain according to SEQ ID NO: 40;
 - (vi) a first light chain according to SEQ ID NO: 41; and
 - (vii) a second light chain according to SEQ ID NO: 41.

39. The multispecific antibody according to any one of claims 1 to 25, wherein the paratopes (a) and (b) comprise CDRH1-3/CDRL1-3 sequences according to SEQ ID NOs: 1-6, and SEQ ID NOs: 7-12, respectively, or CDRH1-3/CDRL1-3 sequences having at least 70% identity to SEQ ID NOs: 1-6, and SEQ ID NOs: 7-12, respectively; and the paratope(s) (d1) and/or (d2) comprise CDRH1-3/CDRL1-3 sequences selected from the group consisting of SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, or CDRH1-3/CDRL1-3 sequences having at least 70% identity to SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, respectively.

40. The multispecific antibody according to any one of claims 1 to 25, wherein the paratopes (a) and (b) comprise CDRH1-3/CDRL1-3 sequences according to SEQ ID NOs: 1-6, and SEQ ID NOs: 19-24, respectively, or CDRH1-3/CDRL1-3 sequences having at least 70% identity to SEQ ID NOs: 1-6, and SEQ ID NOs: 19-24, respectively; and the paratope(s) (d1) and/or (d2) comprise CDRH1-3/CDRL1-3 sequences selected from the group consisting of SEQ ID NOs: 7-12, and SEQ ID NOs: 13-18, or CDRH1-3/CDRL1-3 sequences having at least 70% identity to SEQ ID NOs: 7-12, and SEQ ID NOs: 13-18, respectively.
41. The multispecific antibody according to any one of claims 1 to 25, wherein the paratopes (a) and (b) comprise CDRH1-3/CDRL1-3 sequences according to SEQ ID NOs: 7-12, and SEQ ID NOs: 19-24, respectively, or CDRH1-3/CDRL1-3 sequences having at least 70% identity to SEQ ID NOs: 7-12, and SEQ ID NOs: 19-24, respectively; and the paratope(s) (d1) and/or (d2) comprise CDRH1-3/CDRL1-3 sequences selected from the group consisting of SEQ ID NOs: 1-6, and SEQ ID NOs: 13-18, or CDRH1-3/CDRL1-3 sequences having at least 70% identity to SEQ ID NOs: 1-6, and SEQ ID NOs: 13-18, respectively.
42. The multispecific antibody according to any one of claims 1 to 25, wherein the paratopes (a) and (b) comprise CDRH1-3/CDRL1-3 sequences according to SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, respectively, or CDRH1-3/CDRL1-3 sequences having at least 70% identity to SEQ ID NOs: 13-18, and SEQ ID NOs: 19-24, respectively; and the paratope(s) (d1) and/or (d2) comprise CDRH1-3/CDRL1-3 sequences selected from the group consisting of SEQ ID NOs: 1-6, and SEQ ID NOs: 7-12, or CDRH1-3/CDRL1-3 sequences having at least 70% identity to SEQ ID NOs: 1-6, and SEQ ID NOs: 7-12, respectively.
43. The multispecific antibody according to any one of claims 1 to 25, wherein the paratopes (a) and (b) comprise CDRH1-3/CDRL1-3 sequences according to SEQ ID NOs: 1-6, and SEQ ID NOs: 13-18, respectively, or CDRH1-3/CDRL1-3 sequences having at least 70% identity to SEQ ID NOs: 1-6, and SEQ ID NOs: 13-18, respectively; and the paratope(s) (d1) and/or (d2) comprise CDRH1-3/CDRL1-3 sequences selected

from the group consisting of SEQ ID NOs: 7-12, and SEQ ID NOs: 19-24, or CDRH1-3/CDRL1-3 sequences having at least 70% identity to SEQ ID NOs: 7-12, and SEQ ID NOs: 19-24, respectively.

44. The multispecific antibody according to any one of claims 1 to 25, wherein the paratopes (a) and (b) comprise CDRH1-3/CDRL1-3 sequences according to SEQ ID NOs: 7-12, and SEQ ID NOs: 13-18, respectively, or CDRH1-3/CDRL1-3 sequences having at least 70% identity to SEQ ID NOs: 7-12, and SEQ ID NOs: 13-18, respectively; and the paratope(s) (d1) and/or (d2) comprise CDRH1-3/CDRL1-3 sequences selected from the group consisting of SEQ ID NOs: 1-6, and SEQ ID NOs: 19-24, or CDRH1-3/CDRL1-3 sequences having at least 70% identity to SEQ ID NOs: 1-6, and SEQ ID NOs: 19-24, respectively.
45. The multispecific antibody according claim 44, which comprises:
- (i) a first heavy chain comprising
 - a VH1 domain comprising a CDRH1 having at least 70% identity to SEQ ID NO: 1, a CDRH2 having at least 70% identity to SEQ ID NO: 2, and a CDRH3 having at least 70% identity to SEQ ID NO: 3;
 - (ii) a second heavy chain comprising,
 - a first VH domain (VHx) comprising a CDRH1 having at least 70% identity to SEQ ID NO: 7, a CDRH2 having at least 70% identity to SEQ ID NO: 8, and a CDRH3 having at least 70% identity to SEQ ID NO: 9; and
 - a second VH domain (VH2) comprising a CDRH1 having at least 70% identity to SEQ ID NO: 13, a CDRH2 having at least 70% identity to SEQ ID NO: 14, and a CDRH3 having at least 70% identity to SEQ ID NO: 15;
 - (iii) a first light chain comprising
 - a VL1 domain CDRL1 having at least 70% identity to SEQ ID NO: 4, a CDRL2 having at least 70% identity to SEQ ID NO: 5, and a CDRL3 having at least 70% identity to SEQ ID NO: 6; and
 - (iv) a second light chain comprising,
 - a first VL domain (VLx) comprising a CDRL1 having at least 70% identity to SEQ ID NO: 10, a CDRL2 having at least 70% identity to SEQ ID NO: 11, and a CDRL3 having at least 70% identity to SEQ ID NO: 12; and

- a second VL domain (VL2) comprising a CDRL1 having at least 70% identity to SEQ ID NO: 16, a CDRL2 having at least 70% identity to SEQ ID NO: 17, and a CDRL3 having at least 70% identity to SEQ ID NO: 18;
or
 - (i) a first heavy chain comprising
 - a VH1 domain comprising a CDRH1 having at least 70% identity to SEQ ID NO: 7, a CDRH2 having at least 70% identity to SEQ ID NO: 8, and a CDRH3 having at least 70% identity to SEQ ID NO: 9;
 - (ii) a second heavy chain comprising,
 - a first VH domain (VHx) comprising a CDRH1 having at least 70% identity to SEQ ID NO: 1, a CDRH2 having at least 70% identity to SEQ ID NO: 2, and a CDRH3 having at least 70% identity to SEQ ID NO: 3; and
 - a second VH domain (VH2) comprising a CDRH1 having at least 70% identity to SEQ ID NO: 13, a CDRH2 having at least 70% identity to SEQ ID NO: 14, and a CDRH3 having at least 70% identity to SEQ ID NO: 15;
 - (iii) a first light chain comprising
 - a VL1 domain comprising a CDRL1 having at least 70% identity to SEQ ID NO: 10, a CDRL2 having at least 70% identity to SEQ ID NO: 11, and a CDRL3 having at least 70% identity to SEQ ID NO: 12; and
 - (iv) a second light chain comprising,
 - a first VL domain (VLx) comprising a CDRL1 having at least 70% identity to SEQ ID NO: 4, a CDRL2 having at least 70% identity to SEQ ID NO: 5, and a CDRL3 having at least 70% identity to SEQ ID NO: 6; and
 - a second VL domain (VL2) comprising a CDRL1 having at least 70% identity to SEQ ID NO: 16, a CDRL2 having at least 70% identity to SEQ ID NO: 17, and a CDRL3 having at least 70% identity to SEQ ID NO: 18.
46. The multispecific antibody according to claim 45, which comprises:
- (i) a first heavy chain comprising
 - a VH1 domain comprising a CDRH1 according to SEQ ID NO: 1, a CDRH2 according to SEQ ID NO: 2, and a CDRH3 according to SEQ ID NO: 3;
 - (ii) a second heavy chain comprising

- a first VH domain (VHx) comprising a CDRH1 according to SEQ ID NO: 7, a CDRH2 according to SEQ ID NO: 8, and a CDRH3 according to SEQ ID NO: 9; and
- a second VH domain (VH2) comprising a CDRH1 according to SEQ ID NO: 13, a CDRH2 according to SEQ ID NO: 14, and a CDRH3 according to SEQ ID NO: 15;
- (iii) a first light chain comprising
 - a VL1 domain comprising a CDRL1 according to SEQ ID NO: 4, a CDRL2 according to SEQ ID NO: 5, and a CDRL3 according to SEQ ID NO: 6; and
- (iv) a second light chain comprising
 - a first VL domain (VLx) comprising a CDRL1 according to SEQ ID NO: 10, a CDRL2 according to SEQ ID NO: 11, and a CDRL3 according to SEQ ID NO: 12; and
 - a second VL domain (VL2) comprising a CDRL1 according to SEQ ID NO: 16, a CDRL2 according to SEQ ID NO: 17, and a CDRL3 according to SEQ ID NO: 18;
- or
- (i) a first heavy chain comprising
 - a VH1 domain comprising a CDRH1 according to SEQ ID NO: 7, a CDRH2 according to SEQ ID NO: 8, and a CDRH3 according to SEQ ID NO: 9;
- (ii) a second heavy chain comprising,
 - a first VH domain (VHx) comprising a CDRH1 according to SEQ ID NO: 1, a CDRH2 according to SEQ ID NO: 2, and a CDRH3 according to SEQ ID NO: 3; and
 - a second VH domain (VH2) comprising a CDRH1 according to SEQ ID NO: 13, a CDRH2 according to SEQ ID NO: 14, and a CDRH3 according to SEQ ID NO: 15;
- (iii) a first light chain comprising
 - a VL1 domain comprising a CDRL1 according to SEQ ID NO: 10, a CDRL2 according to SEQ ID NO: 11, and a CDRL3 according to SEQ ID NO: 12; and
- (iv) a second light chain comprising
 - a first VL domain (VLx) comprising a CDRL1 according to SEQ ID NO: 4, a CDRL2 according to SEQ ID NO: 5, and a CDRL3 according to SEQ ID NO: 6; and

- a second VL domain (VL2) comprising a CDRL1 according to SEQ ID NO: 16, a CDRL2 according to SEQ ID NO: 17, and a CDRL3 according to SEQ ID NO: 18.
47. The multispecific antibody according to any one of claims 45 to 46, wherein the first and second VH domains are linked via a peptide linker, which preferably has the amino acid sequence ASTKGP.
48. The multispecific antibody according to any one of claims 45 to 47, wherein the first and second VL domains are linked via a peptide linker, which preferably has the amino acid sequence RTVAAPSVFIPP.
49. The multispecific antibody according to any one of claims 45 to 48, which comprises:
- (i) a first heavy chain comprising
 - a VH1 having at least 70% identity to SEQ ID NO: 29;
 - (ii) a second heavy chain comprising
 - a dual variable domain having at least 70% identity to SEQ ID NO: 30;
 - (iii) a first light chain comprising
 - a VL1 having at least 70% identity to SEQ ID NO: 31; and
 - (iv) a second light chain comprising
 - a dual variable domain having at least 70% identity to SEQ ID NO: 32;
- or
- (i) a first heavy chain comprising
 - a VH1 having at least 70% identity to SEQ ID NO: 33;
 - (ii) a second heavy chain comprising
 - a dual variable domain having at least 70% identity to SEQ ID NO: 34;
 - (iii) a first light chain comprising
 - a VL1 having at least 70% identity to SEQ ID NO: 35;
 - (iv) a second light chain comprising
 - a dual variable domain having at least 70% identity to SEQ ID NO: 36.
50. The multispecific antibody according to claim 49, which comprises:
- (i) a first heavy chain comprising
 - a VH1 according to SEQ ID NO: 29;

- (ii) a second heavy chain comprising
 - a dual variable domain according to SEQ ID NO: 30;
 - (iii) a first light chain comprising
 - a VL1 according to SEQ ID NO: 31; and
 - (iv) a second light chain comprising
 - a dual variable domain according to SEQ ID NO: 32;
 - or
 - (i) a first heavy chain comprising
 - a VH1 according to SEQ ID NO: 33;
 - (ii) a second heavy chain comprising
 - a dual variable domain according to SEQ ID NO: 34;
 - (iii) a first light chain comprising
 - a VL1 according to SEQ ID NO: 35;
 - (iv) a second light chain comprising
 - a dual variable domain according to SEQ ID NO: 36.
51. The multispecific antibody according to any one of claims 45 to 50, which comprises:
- (i) a first heavy chain having at least 70% identity to SEQ ID NO: 42;
 - (ii) a second heavy chain having at least 70% identity to SEQ ID NO: 43;
 - (iii) a first light chain having at least 70% identity to SEQ ID NO: 44; and
 - (iv) a second heavy chain having at least 70% identity to SEQ ID NO: 45;
- or
- (i) a first heavy chain having at least 70% identity to SEQ ID NO: 46;
 - (ii) a second heavy chain having at least 70% identity to SEQ ID NO: 47;
 - (iii) a first light chain having at least 70% identity to SEQ ID NO: 48; and
 - (iv) a second heavy chain having at least 70% identity to SEQ ID NO: 49.
52. The multispecific antibody according to claim 51, which comprises:
- (i) a first heavy chain according to SEQ ID NO: 42;
 - (ii) a second heavy chain according to SEQ ID NO: 43;
 - (iii) a first light chain according to SEQ ID NO: 44; and
 - (iv) a second heavy chain according to SEQ ID NO: 45;
- or

- (i) a first heavy chain according to SEQ ID NO: 46;
 - (ii) a second heavy chain according to SEQ ID NO: 47;
 - (iii) a first light chain according to SEQ ID NO: 48; and
 - (iv) a second heavy chain according to SEQ ID NO: 49.
53. The multispecific antibody according to any one of the previous claims, wherein the antibody is purified.
54. The multispecific antibody according to any one of the previous claims for use as a medicament.
55. The multispecific antibody for use according to claim 54 in prophylaxis or treatment of peanut allergy.
56. A nucleic acid molecule comprising a polynucleotide encoding the multispecific antibody according to any one of claims 1 to 53.
57. The nucleic acid molecule according to claim 56, comprising a nucleic acid sequence as set forth in any one of SEQ ID Nos: 63 to 75, or a sequence variant thereof having at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.
58. A plurality of nucleic acid molecules encoding the multispecific antibody according to any one of claims 1 to 53, wherein each of the nucleic acid molecules comprises a polynucleotide encoding an immunoglobulin chain of the antibody.
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59. The plurality of nucleic acid molecules according to claim 58, comprising a nucleic acid sequence as set forth in any one of SEQ ID NOs 63 to 75, or a sequence variant thereof having at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

60. A vector comprising the nucleic acid molecule according to claim 56 or 57 or the plurality of nucleic acid molecules according to claim 58 or 59.
61. A plurality of vectors comprising the plurality of nucleic acid molecules according to claim 58 or 59.
62. A host cell expressing the multispecific antibody according to any one of claims 1 to 53, or comprising the vector according to claim 60 or the combination of vectors according to claim 61.
63. A method for preparing the multispecific antibody according any one of claims 1 to 53, or immunoglobulin chain(s) thereof, said method comprising
 - (i) culturing the host cell according to claim 62; and
 - (ii) isolating the multispecific antibody or immunoglobulin chain(s) thereof from the culture.
64. A composition comprising the multispecific antibody according to any one of claims 1 to 53, the nucleic acid or the plurality of nucleic acids according to any one of claims 56 to 59, the vector or the plurality of vectors according to any one of claims 60 and 61, or the cell according to claim 62.
65. The composition according to claim 64, further comprising a pharmaceutically acceptable excipient, diluent or carrier.
66. The composition according to claim 64 or 65, wherein the composition comprises at least two distinct multispecific antibodies.

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67. The composition according to any one of claims 64 to 66, wherein the composition further comprises at least one additional agent useful for treating peanut allergy.
68. The composition according to claim 67, wherein the additional agent useful for treating peanut allergy is selected from the group consisting of: β -adrenergic agonists, epinephrine, antihistamine, corticosteroid, anti-IgE antibody, anti-IgE antibody binding

fragment, peptide vaccine and further antibodies capable of binding to a peanut allergen.

69. The composition according to any one of claims 64 to 68, wherein the composition further comprises a peanut allergen, preferably selected from the group consisting of Ara h1, Ara h2, Ara h3 and Ara h6 or a mixture thereof.
70. A kit comprising one or more of
- (i) the multispecific antibody according to any one of claims 1 to 53;
 - (ii) the nucleic acid molecule(s) according to any one of claims 56 to 59;
 - (iii) the vector(s) according to claim 60 or 61;
 - (iv) the cell according to claim 62; and/or
 - (v) the composition according to any one of claims 64 to 69.
71. The kit according to claim 70, wherein the kit further comprises at least one additional agent useful for treating peanut allergy.
72. The kit according to any one of claims 70 to 71, wherein the kit further comprises a peanut allergen.
73. The multispecific antibody according to any one of claims 1 to 53, the nucleic acid or the plurality of nucleic acids according to any one of claims 56 to 59, the vector or the plurality of vectors according to claim 60 or 61, the cell according to claim 62, the composition according to any one of claims 64 to 69, or the kit according to any one of claims 70 to 72 for use as a medicament.
74. The multispecific antibody according to any one of claims 1 to 53, the nucleic acid or the plurality of nucleic acids according to any one of claims 56 to 59, the vector or the plurality of vectors according to claim 60 or 61, the cell according to claim 62, the composition according to any one of claims 64 to 69, or the kit according to any one of claims 70 to 72 for use in the prophylaxis or treatment of a peanut allergy.

75. The multispecific antibody, the nucleic acid or the plurality of nucleic acids, the vector or the plurality of vectors, the cell, or the composition for use according to claim 73 or 74, wherein the administration of the multispecific antibody, the nucleic acid or the plurality of nucleic acids, the vector or the plurality of vectors, the cell, or the composition is combined with the administration of a peanut allergen, preferably selected from the group consisting of Ara h1, Ara h2, Ara h3 and Ara h6 or a mixture thereof.
76. The multispecific antibody, or the composition for use according to claim 75, wherein the multispecific antibody or the composition is administered before or during a desensitization procedure with a peanut allergen.
77. Use of the multispecific antibody according to any one of claims 1 to 53, the composition according to any one of claims 64 to 69, or the kit according to any one of claims 70 to 72 in (*in-vitro*) diagnosis of a peanut allergy.
78. Use of the multispecific antibody according to any one of claims 1 to 53, the composition according to any one of claims 64 to 69, or the kit according to any one of claims 70 to 72 in a method for detecting a peanut allergen.
79. Use of the multispecific antibody according to any one of claims 1 to 53, the nucleic acid or the plurality of nucleic acids according to any one of claims 56 to 59, the vector or the plurality of vectors according to claim 60 or 61, the cell according to claim 62, the composition according to any one of claims 64 to 69, or the kit according to any one of claims 70 to 72 in the manufacture of a medicament for prophylaxis, treatment or attenuation of a peanut allergy.
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80. A method of treating, ameliorating or reducing a peanut allergy, or lowering the risk of a peanut allergic or anaphylactic reaction, comprising: administering to a subject in need thereof, a therapeutically effective amount of the multispecific antibody according to any one of claims 1 to 53, the nucleic acid or the plurality of nucleic acids according to any one of claims 56 to 59, the vector or the plurality of vectors according to claim

60 or 61, the cell according to claim 62, the composition according to any one of claims 64 to 69, or the kit according to any one of claims 70 to 72.