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Zika Virus in the Americas - Yet Another Arbovirus Threat. *N Engl J Med*, 160113142101009 (2016); D. L. Heymann *et al.*, Zika virus and microcephaly: why is this situation a PHEIC? *Lancet*. 387, 719–721 (2016)). The main route of ZIKV infection is through bites by *Aedes* mosquitos, but the virus may also be sexually (D. Musso *et al.*, Potential sexual transmission of Zika virus. *Emerg Infect Dis*. 21, 359–361 (2015)) and vertically transmitted (J. Mlakar *et al.*, Zika Virus Associated with Microcephaly. *N Engl J Med*. 374, 951–958 (2016)). While most of the ZIKV infections are asymptomatic or cause only mild symptoms, there is evidence that ZIKV infection can lead to neurological complications, such as Guillain-Barré Syndrome in adults (V.-M. Cao-Lormeau *et al.*, Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. *Lancet*. 0 (2016), doi:10.1016/S0140-6736(16)00562-6) and congenital birth defects including microcephaly in the developing fetus (G. Calvet, R. S. Aguiar, A. Melo, S. A. Sampaio, Detection and sequencing of Zika virus from amniotic fluid of fetuses with microcephaly in Brazil: a case study. *Lancet Infect Dis* (2016), doi:10.1016/s1473-3099(16)00095-5; J. Mlakar *et al.*, Zika Virus Associated with Microcephaly. *N Engl J Med*. 374, 951–958 (2016); E. J. Rubin, M. F. Greene, L. R. Baden, Zika Virus and Microcephaly. *N Engl J Med* (2016), doi:10.1056/NEJMe1601862), likely through its ability to infect human neural progenitor cells (H. Tang *et al.*, Zika Virus Infects Human Cortical Neural Progenitors and Attenuates Their Growth. *Stem Cell*, 1–5 (2016)).

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ZIKV belongs to the genus flavivirus, which also includes the West Nile virus, dengue virus, tick-borne encephalitis virus, yellow fever virus, and several other viruses which may cause encephalitis. Flaviviruses are enveloped, with icosahedral and spherical geometries. The diameter is around 50 nm. Genomes are linear positive-sense RNA and non-segmented, around 10-11kb in length. The genome of flaviviruses encodes 3 structural proteins (Capsid, prM, and Envelope) and 8 non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5 and NS5B).

While flavivirus envelope (E) proteins mediate fusion and are the main target of neutralizing antibodies, the non-structural protein 1 (NS1) is secreted by infected cells and is involved in immune evasion and pathogenesis (D. A. Muller, P. R. Young, The flavivirus NS1 protein: molecular and structural biology, immunology, role in pathogenesis and application as a

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diagnostic biomarker. *Antiviral Res.* 98, 192–208 (2013)). Two recent structural studies showed a high level of structural similarity between the E protein of ZIKV and that of other flaviviruses, such as dengue virus (DENV), yellow fever virus (YFV) and West Nile virus (WNV) but also revealed unique features that may be related to the ZIKV neurotropism (L. Dai *et al.*, Structures of the Zika Virus Envelope Protein and Its Complex with a Flavivirus Broadly Protective Antibody. *Cell Host Microbe* (2016), doi:10.1016/j.chom.2016.04.013; D. Sirohi *et al.*, The 3.8 Å resolution cryo-EM structure of Zika virus. *Science*, aaf5316 (2016)). Similarly, the structural analysis of ZIKV NS1 revealed conserved features with NS1 of other flaviviruses although with different electrostatic characteristics (J. Kim *et al.*, Zika virus NS1 structure reveals diversity of electrostatic surfaces among flaviviruses, 1–6 (2016)).

A phenomenon that is characteristic of certain flaviviruses is the disease-enhancing activity of cross-reactive antibodies elicited by previous infection by heterologous viruses. In the case of Dengue virus (DENV), for which 4 serotypes are known, there is epidemiological evidence that a primary infection protects from reinfection with the same serotype, but represents a risk factor for the development of severe disease upon reinfection with a different serotype (S. B. Halstead, Dengue Antibody-Dependent Enhancement: Knowns and Unknowns. *Microbiol Spectr.* 2, 249–271 (2014)). The exacerbated disease is triggered by E and prM-specific antibodies that fail to neutralize the incoming virus but instead enhance its capture by Fc receptor-expressing (FcR⁺) cells, leading to enhanced viral replication and activation of cross-reactive memory T cells. The resulting cytokine storm is thought to be the basis of the most severe form of disease known as dengue hemorrhagic fever/dengue shock syndrome (S. B. Halstead, Neutralization and antibody-dependent enhancement of dengue viruses. *Adv Virus Res.* 60, 421–467 (2003); G. Screaton, J. Mongkolsapaya, S. Yacoub, C. Roberts, New insights into the immunopathology and control of dengue virus infection. *Nat Rev Immunol.* 15, 745–759 (2015). The role of antibodies in severe dengue is supported by studies showing that waning levels of maternal antibodies in infants represent a higher risk for development of severe dengue disease (S. B. Halstead, Neutralization and antibody-dependent enhancement of dengue viruses. *Adv Virus Res.* 60, 421–467 (2003); S. B. Halstead *et al.*, Dengue hemorrhagic fever in infants: research opportunities ignored. *Emerging Infect Dis.* 8, 1474–1479 (2002); T. H. Nguyen *et al.*, Dengue hemorrhagic fever in infants: a study of clinical

and cytokine profiles. *J Infect Dis.* 189, 221–232 (2004); A. L. Rothman, Dengue: defining protective versus pathologic immunity. *J Clin Invest.* 113, 946–951 (2004)).

5 Recently, it was shown that most antibodies that reacted to DENV envelope protein also bound to ZIKV, but those that recognize the major linear fusion-loop epitope (FLE) did not neutralize ZIKV and instead promoted antibody-dependent enhancement (ADE) of ZIKV infection (Dejnirattisai W, Supasa P, Wongwiwat W, Rouvinski A, Barba-Spaeth G, Duangchinda T, Sakuntabhai A, Cao-Lormeau VM, Malasit P, Rey FA, Mongkolsapaya J, Screaton GR: Dengue virus sero-cross-reactivity drives antibody-dependent enhancement of infection with zika virus. *Nat Immunol.* 2016 Jun 23. doi: 10.1038/ni.3515. [Epub ahead of print]).

15 Moreover, organisms with high rates of mutations, such as various viruses, for example Zika virus, often rely on so-called “mutational escape” as a mechanism to avoid destruction by host cells. Namely, a virus can defend itself from host immune responses by making mutations in its genotype and phenotype (referred to as “escape mutations”). Accordingly, the generation of escape mutants (i.e., viruses carrying escape mutations) can reduce the efficacy of antibody medications.

20 In view of the above, it is an object of the present invention to provide multispecific antibodies, which potentially neutralize Zika virus (ZIKV). Such antibodies do preferably not contribute to antibody-dependent enhancement (ADE) of Zika virus infection. It is also an object of the present invention to provide highly specific anti-ZIKV antibodies eliminating or minimizing generation of ZIKV escape mutants.

25 The object underlying the present invention is solved by the claimed subject matter.

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
30 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.

- 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 preferred 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 and/or preferred 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.
- 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.*, a composition "comprising" X may consist exclusively of X or may include something additional *e.g.*, X + Y.
- 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 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 "substantially" may be omitted from the definition of the invention.

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The term "about" in relation to a numerical value x means $x \pm 10\%$.

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
10 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.

As used herein, reference to "treatment" of a subject or patient is intended to include
15 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 one embodiment, the patient is a human.

20 As used herein, the terms "antigen binding fragment," "fragment," and "antibody fragment" are used interchangeably to refer to any fragment of an antibody of the invention that retains the antigen-binding activity of the antibody. Examples of antibody fragments include, but are not limited to, a single chain antibody, Fab, Fab', F(ab')₂, Fv or scFv. Further, the term "antibody" as used herein includes both antibodies and antigen binding fragments thereof.

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As used herein, the term "antibody" encompasses various forms of antibodies including, without being limited to, whole antibodies, antibody fragments, in particular antigen binding fragments, human antibodies, chimeric antibodies, humanized antibodies, recombinant antibodies and genetically engineered antibodies (variant or mutant antibodies) as long as the
30 characteristic properties according to the invention are retained. Monoclonal antibodies are preferred and especially preferred are monoclonal antibodies with human CDRs or human variable regions. In particular, antibodies, or antigen binding fragments thereof, according to

the present invention are preferably derived from human antibodies (i.e., they comprise CDRs and/or variable regions of human antibodies). More preferably, antibodies, or antigen binding fragments thereof, according to the present invention, also comprise constant regions of human antibodies. Most preferably, all constant and variable regions of the antibodies, or antigen binding fragments thereof, according to the present invention are of human origin, i.e. human constant and human variable regions, such as constant and variable regions of a human antibody.

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) 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). Preferably, human monoclonal antibodies are prepared by using improved EBV-B cell immortalization as described in Traggiai E, Becker S, Subbarao K, Kolesnikova L, Uematsu Y, Gismondo MR, Murphy BR, Rappuoli R, Lanzavecchia A. (2004): An efficient method to make human monoclonal antibodies from memory B cells: potent neutralization of SARS coronavirus. *Nat Med.* 10(8):871-5. The term "human antibody" as used herein also comprises such antibodies which are modified, e.g. in a variable region or in a constant region, to generate the properties according to the invention as described herein.

Antibodies of the invention can be of any isotype (e.g., IgA, IgG, IgM i.e. an α , γ or μ heavy chain), but will preferably be IgG. Within the IgG isotype, antibodies may be IgG1, IgG2,

IgG3 or IgG4 subclass, whereby IgG1 is preferred. Antibodies of the invention may have a κ or a λ light chain.

5 The antibody according to the present invention, or the antigen binding fragment thereof, may be a purified antibody or a single chain antibody, such as a bispecific single-chain Fv fragment (scFv).

10 The invention also provides fragments of the antibodies of the invention, particularly fragments that retain the antigen-binding activity of the antibodies. 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" or "antibody of the invention" includes all categories of antibodies, namely, antigen binding fragment(s), antibody fragment(s), variant(s) and derivative(s) of antibodies. Fragments of the antibodies of the invention can be obtained from the antibodies by methods
15 that include digestion with enzymes, such as pepsin or papain, and/or by cleavage of disulfide bonds by chemical reduction. Alternatively, fragments of the antibodies can be obtained by cloning and expression of part of the sequences of the heavy or light chains. For example, the invention includes a bispecific scFv comprising the CDRs from an antibody of the invention. Antibody fragments of the invention may impart monovalent or multivalent interactions and
20 be contained in a variety of structures. For instance, scFv molecules may be synthesized to create a trivalent "triabody" or a tetravalent "tetrabody." The scFv molecules may include a domain of the Fc region resulting in bivalent minibodies.

25 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.

30 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. 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.

As used herein, a "neutralizing antibody" is one that can neutralize, *i.e.*, prevent, inhibit, reduce, impede or interfere with, the ability of a pathogen to initiate and/or perpetuate an infection in a host. The terms "neutralizing antibody" and "an antibody that neutralizes" or "antibodies that neutralize" are used interchangeably herein. These antibodies can be used alone, or in combination, as prophylactic or therapeutic agents upon appropriate formulation, in association with active vaccination, as a diagnostic tool, or as a production tool as described herein.

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.

The term "specifically binding" and similar reference does not encompass non-specific sticking.

The term "vaccine" as used herein is typically understood to be a prophylactic or therapeutic material providing at least one antigen, preferably an immunogen. The antigen or immunogen may be derived from any material that is suitable for vaccination. For example, the antigen or immunogen may be derived from a pathogen, such as from bacteria or virus particles etc., or from a tumor or cancerous tissue. The antigen or immunogen stimulates the body's adaptive immune system to provide an adaptive immune response. In particular, an "antigen" or an "immunogen" refers typically to a substance which may be recognized by the immune system, preferably by the adaptive immune system, and which is capable of triggering an antigen-specific immune response, e.g. by formation of antibodies and/or antigen-specific T cells as part of an adaptive immune response. Typically, an antigen may be or may comprise a peptide or protein which may be presented by the MHC to T-cells.

As used herein, "sequence variant" (also referred to as "variant") refers to any alteration in a reference sequence, whereby a reference sequence is any of the sequences listed in the

“Tables of Sequences and SEQ ID Numbers” (sequence listing), i.e. SEQ ID NO: 1 to SEQ ID NO: 273. Thus, the term “sequence variant” includes nucleotide sequence variants and amino acid sequence variants. Of note, the sequence variants referred to herein are in particular functional sequence variants, i.e. sequence variants maintaining the biological function of, for example, the antibody. In the context of the present invention such a maintained biological function is preferably the neutralization of ZIKV infection and/or the binding of the antibody to the ZIKV E protein. Preferred sequence variants are thus functional sequence variants 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 to a reference sequence. The phrase *“functional 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”*, as used herein, means (i) that the sequence variant is functional as described herein and (ii) the higher the % sequence identity, the more preferred the sequence variant. In other words, the phrase *“functional 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”*, means in particular that the functional sequence variant has at least 70% sequence identity, preferably at least 75% sequence identity, preferably at least 80% sequence identity, more preferably at least 85% sequence identity, more preferably at least 88% sequence identity, even more preferably at least 90 % sequence identity, even more preferably at least 92% sequence identity, still more preferably at least 95% sequence identity, still more preferably at least 96% sequence identity, particularly preferably at least 97% sequence identity, particularly preferably at least 98% sequence identity and most preferably at least 99% sequence identity to the respective reference sequence.

The term “sequence variant” includes in particular such variants that comprise mutations and/or substitutions in comparison to the reference sequence. Exemplary variants of an Fc moiety sequence include, but are not limited to, those that have an L to A substitution at position CH2 4, CH2 5, or both.

Sequence identity is usually calculated with regard to the full length of the reference sequence (i.e. the sequence recited in the application). Percentage identity, as referred to herein, can be determined, for example, using BLAST using the default parameters specified by the NCBI (the National Center for Biotechnology Information; <http://www.ncbi.nlm.nih.gov/>) [Blosom 5 62 matrix; gap open penalty=11 and gap extension penalty=1].

As used herein, a "nucleotide sequence variant" has an altered sequence in which one or more of the nucleotides in the reference sequence is deleted, or substituted, or one or more nucleotides are inserted into the sequence of the reference nucleotide sequence. Nucleotides 10 are referred to herein by the standard one-letter designation (A, C, G, or T). Due to the degeneracy of the genetic code, a "nucleotide sequence variant" can either result in a change in the respective reference amino acid sequence, i.e. in an "amino acid sequence variant" or not. Preferred sequence variants are such nucleotide sequence variants, which do not result in amino acid sequence variants (silent mutations), but other non-silent mutations are within 15 the scope as well, in particular mutant nucleotide sequences, which result in an amino acid sequence, which is at least 80%, preferably at least 90 %, more preferably at least 95% sequence identical to the reference sequence.

An "amino acid sequence variant" has an altered sequence in which one or more of the 20 amino acids in the reference sequence is deleted or substituted, or one or more amino acids are inserted into the sequence of the reference amino acid sequence. As a result of the alterations, the amino acid sequence variant has an amino acid sequence which is at least 80% identical to the reference sequence, preferably, at least 90% identical, more preferably at least 95% identical, most preferably at least 99% identical to the reference sequence. 25 Variant sequences which are at least 90% identical have no more than 10 alterations, i.e. any combination of deletions, insertions or substitutions, per 100 amino acids of the reference sequence.

While it is possible to have non-conservative amino acid substitutions, it is preferred that the 30 substitutions be conservative amino acid substitutions, in which 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

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,
5 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, methionine, and glycine, with another.

10 Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include the fusion to the N- or C-terminus of an amino acid sequence to a reporter molecule or an enzyme.

15 Importantly, the alterations in the sequence variants do not abolish the functionality of the respective reference sequence, in the present case, e.g., the functionality of a sequence of an antibody, or antigen binding fragment thereof, to bind to the same epitope and/or to sufficiently neutralize infection of ZIKV. Guidance in determining which nucleotides and
20 amino acid residues, respectively, may be substituted, inserted or deleted without abolishing such functionality are found by using computer programs well known in the art.

As used herein, a nucleic acid sequence or an amino acid sequence "derived from" a designated nucleic acid, peptide, polypeptide or protein refers to the origin of the nucleic
25 acid, peptide, polypeptide or protein. Preferably, the nucleic acid sequence or amino acid sequence which is derived from a particular sequence has an amino acid sequence that is essentially identical to that sequence or a portion thereof, from which it is derived, whereby "essentially identical" includes sequence variants as defined above. Preferably, the nucleic acid sequence or amino acid sequence which is derived from a particular peptide or protein,
30 is derived from the corresponding domain in the particular peptide or protein. Thereby, "corresponding" refers in particular to the same functionality. For example, an "extracellular domain" corresponds to another "extracellular domain" (of another protein), or a

“transmembrane domain” corresponds to another “transmembrane domain” (of another protein). “Corresponding” parts of peptides, proteins and nucleic acids are thus easily identifiable to one of ordinary skill in the art. Likewise, sequences “derived from” other sequence are usually easily identifiable to one of ordinary skill in the art as having its origin
5 in the sequence.

Preferably, a nucleic acid sequence or an amino acid sequence derived from another nucleic acid, peptide, polypeptide or protein may be identical to the starting nucleic acid, peptide, polypeptide or protein (from which it is derived). However, a nucleic acid sequence or an
10 amino acid sequence derived from another nucleic acid, peptide, polypeptide or protein may also have one or more mutations relative to the starting nucleic acid, peptide, polypeptide or protein (from which it is derived), in particular a nucleic acid sequence or an amino acid sequence derived from another nucleic acid, peptide, polypeptide or protein may be a functional sequence variant as described above of the starting nucleic acid, peptide,
15 polypeptide or protein (from which it is derived). For example, in a peptide/protein one or more amino acid residues may be substituted with other amino acid residues or one or more amino acid residue insertions or deletions may occur.

As used herein, the term “mutation” relates to a change in the nucleic acid sequence and/or
20 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
25 changes in the nucleic acid sequence and/or in the amino acid sequence). Thus, the terms “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
30 acid sequence, preferably 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
5 without the need for mutating one or more nucleotides of a nucleic acid molecule.

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
10 in their entirety. Nothing herein is to be construed as an admission that the invention is not 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
15 terminology used herein is for the purpose of describing particular embodiments only, and 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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Multispecific antibodies binding to distinct Zika virus epitopes

The present invention is based, amongst other findings, on the discovery that multispecific antibodies, and antigen-binding fragments thereof, that bind specifically to distinct Zika virus
25 epitopes. Such antibodies minimize or eliminate the generation of Zika virus escape mutants. In particular, there is currently no prevention/treatment available for Zika virus infection. The antibodies according to the present invention are highly effective in preventing as well as treating or attenuating Zika virus infection. Moreover, due to the specificity of the antibodies for Zika virus, they do not elicit ADE, but rather block ADE.

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In a first aspect the present invention provides an isolated multispecific antibody, or an antigen binding fragment thereof, that specifically binds to distinct Zika virus epitopes. In

other words, the present invention provides an isolated multispecific antibody, or an antigen binding fragment thereof, that comprises at least two epitope binding sites, which specifically bind to distinct Zika virus epitopes.

- 5 Importantly, in contrast to conventional ("ordinary") antibodies exhibiting just one single specificity, multispecific antibodies are able to bind to at least two different epitopes. In the present case, the multispecific antibodies specifically bind to (at least two) distinct Zika virus epitopes.
- 10 Accordingly, as used herein, the term "multispecific" refers to the ability to bind to at least two different epitopes, e.g. on different antigens, such as different Zika virus (ZIKV) proteins or on the same antigen, e.g. the same ZIKV protein. Preferably, the multispecific antibodies, or the antigen binding fragments thereof, according to the present invention bind to at least two different epitopes on the same ZIKV protein, most preferably to at least two different
- 15 epitopes on Zika virus envelope (E) protein.

- Preferably, the antibody, or antigen binding fragment thereof, according to the present invention is bispecific, trispecific, tetraspecific or pentaspecific, more preferably the antibody, or the antigen binding fragment thereof, is bispecific, trispecific or tetraspecific, even more
- 20 preferably the antibody, or the antigen binding fragment thereof, is bispecific or trispecific, and most preferably the antibody, or the antigen binding fragment thereof, is bispecific.

- As used herein, terms like "bispecific", "trispecific", "tetraspecific" etc. refer to the number of different epitopes to which the antibody, or the antigen binding fragment thereof, can bind
- 25 to. For example, conventional monospecific IgG-type antibodies have two 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 epitope binding sites (paratopes) and can, thus, bind to at least two different epitopes. As used herein, the term "paratope" refers to an epitope-binding site of the antibody. Accordingly, the terms
- 30 "paratope" and "epitope binding site" are used herein interchangeably. Moreover, a single "specificity" may refer to one, two, three or more identical paratopes in a single antibody. The actual number of paratopes in one single antibody molecule is referred to as "valency".

Preferably, the antibody, or antigen binding fragment thereof, according to the present invention is bivalent, trivalent, tetravalent, hexavalent or octavalent, more preferably, the antibody, or the antigen binding fragment thereof, is bivalent or tetravalent, most preferably, the antibody, or the antigen binding fragment thereof, is tetravalent.

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Most preferably, the antibody, or antigen binding fragment thereof, according to the present invention is bispecific and tetravalent.

It is also preferred that the antibody, or antigen binding fragment thereof, according to the present invention comprises exactly two (identical) copies of each of the distinct epitope binding sites specifically binding to at least two distinct, Zika virus epitopes.

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For example, a single native IgG antibody is monospecific and bivalent, since it has two identical paratopes (two identical copies). However, a multispecific antibody comprises at least two (different) paratopes. Thus, the term "multispecific" refers to antibodies, and antigen binding fragments, having more than one paratope and the ability to bind to two or more different epitopes. The term "multispecific antibodies/antigen binding fragments" comprises in particular bispecific antibodies as defined above, but typically also protein, e.g. antibody, scaffolds, which bind in particular to three or more different epitopes, i.e. antibodies having three or more paratopes.

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In particular, the multispecific antibody, or the antigen binding fragment thereof, may comprise two or more paratopes, wherein some 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. For example, the multispecific antibody or antigen binding fragment thereof according to the present invention may comprise four paratopes, wherein each two paratopes are identical (i.e. have the same specificity) and, thus, the antibody or fragment thereof is bispecific and tetravalent (two identical paratopes for each of the two specificities). Thus, "one specificity" refers in particular to one or more paratopes exhibiting the same specificity (which typically means that such one or more paratopes are identical) and, thus, "two specificities" may be realized by two, three, four five, six or more paratopes as long as they refer to only two specificities. For example, a multispecific antibody

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may comprise one single paratope for each (of the at least two) specificity, i.e. the multispecific antibody comprises in total at least two paratopes. For example, a bispecific antibody comprises one single paratope for each of the two specificities, i.e. the antibody comprises in total two paratopes. Most preferably, the antibody comprises exactly two
5 (identical) paratopes for each of the two specificities, i.e. the antibody comprises in total four paratopes. Alternatively, the antibody may comprise three (identical) paratopes for each of the two specificities, i.e. the antibody comprises in total six paratopes.

As used herein, the term "antigen" refers to any structural substance which serves as a target
10 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
15 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,
20 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.

25 The antibody, or the antigen binding fragment thereof, according to the present invention, binds to at least two different Zika virus epitopes. The at least two different Zika virus epitopes may be located on different Zika virus antigens, such as different Zika virus (ZIKV) proteins, or on the same Zika virus antigen, e.g. on the same ZIKV protein. Preferred examples of ZIKV antigens/proteins include capsid, prM, envelope and the non-structural proteins NS1, NS2A,
30 NS2B, NS3, NS4A, NS4B, NS5 and NS5B. Most preferably, the antibody, or the antigen binding fragment thereof, according to the present invention, binds to (at least two) distinct epitopes on Zika virus envelope protein (ZIKV E protein). In other words, most preferably the

antibody, or the antigen binding fragment thereof, according to the present invention comprises at least two epitope binding sites, which specifically bind to distinct epitopes on Zika virus envelope protein (ZIKV E protein). ZIKV includes a nucleocapsid core, which comprising single-stranded RNA wrapped by core proteins. The nucleocapsid core is encapsulated by a lipid bilayer membrane with “membrane proteins” and “envelope proteins”. ZIKV envelope protein (E protein) is the dominant antigen. The structure and domains of ZIKV E protein is described, for example, in Dai L, Song J, Lu X, Deng YQ, Musyoki AM, Cheng H, Zhang Y, Yuan Y, Song H, Haywood J, Xiao H, Yan J, Shi Y, Qin CF, Qi J, Gao GF. Structures of the Zika Virus Envelope Protein and Its Complex with a Flavivirus Broadly Protective Antibody. *Cell Host Microbe*. 2016 May 11;19(5):696-704.

Preferably, the (at least two) distinct Zika virus epitopes, to which the antibody, or the antigen binding fragment thereof, according to the present invention, binds to, are non-overlapping epitopes. In particular, the amino acids forming the first Zika virus epitope, to which the antibody, or the antigen binding fragment thereof, according to the present invention, binds to, are distinct from the amino acids forming the second Zika virus epitope, to which the antibody, or the antigen binding fragment thereof, according to the present invention, binds to.

The antibody, or the antigen binding fragment thereof, according to the present invention may be of any antibody format. In particular, multispecific antibodies preferably encompass “whole” antibodies, such as whole IgG- or IgG-like molecules, while antigen binding fragments in the context of the present invention preferably refer to small recombinant formats, such as a format based on bispecific T-cell engagers (BiTE®s; except that in the context of the present invention both specificities target Zika virus, accordingly, the T-cell specificity of BiTE®s may be replaced by a (second) ZIKV specificity), tandem single chain variable fragment molecules (taFvs), diabodies (Dbs), single chain diabodies (scDbs) and various other derivatives of these (cf. bispecific antibody formats as described by Byrne H. et al. (2013) *Trends Biotech*, 31 (11): 621-632 with Figure 2 showing various bispecific antibody formats; Weidle U.H. et al. (2013) *Cancer Genomics and Proteomics* 10: 1-18, in particular Fig. 1 showing various bispecific antibody formats; and Chan, A.C. and Carter, P.J. (2010) *Nat Rev Immu* 10: 301-316 with Fig. 3 showing various bispecific antibody formats).

Examples of bispecific antibody formats include, but are not limited to, Fabs-in-tandem-Ig, DVD-Ig, quadroma, chemically coupled Fab (fragment antigen binding), and BiTE® (bispecific T cell engager). In one embodiment of the present invention the antibody is preferably a Fabs-in-tandem-Ig (FIT-Ig) or a DVD-Ig.

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Thus, the antibody, or the antigen binding fragment thereof, according to the present invention may be selected from the group comprising Fabs-in-tandem-Ig (FIT-Ig); DVD-Ig; hybrid hybridoma (quadroma); Multispecific anticalin platform (Pieris); Diabodies; Single chain diabodies; Tandem single chain Fv fragments; TandAbs, Trispecific Abs (Affimed) (105-
 10 110 kDa); Darts (dual affinity retargeting; MacroGenics); Bispecific Xmabs (Xencor); Bispecific T cell engagers (Bites; Amgen; 55kDa); Triplebodies; Tribody = Fab-scFv Fusion Protein (Creative Biolabs) multifunctional recombinant antibody derivatives (110 kDa); Duobody platform (Genmab); Dock and lock platform; Knob into hole (KIH) platform; Humanized bispecific IgG antibody (REGN1979) (Regeneron); Mab² bispecific antibodies (F-Star); DVD-Ig = dual variable domain immunoglobulin (Abbott); kappa-lambda bodies; TBTI = tetravalent
 15 bispecific tandem Ig; and CrossMab.

The antibody, or the antigen binding fragment thereof, according to the present invention may be selected from bispecific IgG-like antibodies (BsIgG) comprising CrossMab; DAF (two-
 20 in-one); DAF (four-in-one); DutaMab; DT-IgG; Knobs-in-holes common LC; Knobs-in-holes assembly; Charge pair; Fab-arm exchange; SEEDbody; Triomab; LUZ-Y; Fcab; κλ-body; and Orthogonal Fab. These bispecific antibody formats are shown and described for example in Spiess C., Zhai Q. and Carter P.J. (2015) Molecular Immunology 67: 95-106, in particular Fig. 1 and corresponding description, e.g. p. 95 – 101.

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Preferably, the antibody, or the antigen binding fragment thereof, according to the present invention may be selected from bispecific antibody fragments comprising Nanobody; Nanobody-HAS; BiTE; Diabody; DART; TandAb; scDiabody; sc-Diabody-CH3; Diabody-CH3; Triple Body; Miniantibody; Minibody; TriBi minibody; scFv-CH3 KIH; Fab-scFv; scFv-CH-CL-scFv; F(ab')₂; F(ab')₂-scFv₂; scFv-KIH; Fab-scFv-Fc; Tetravalent HCAB; scDiabody-Fc; Diabody-Fc; Tandem scFv-Fc; and Intrabody. These bispecific antibody formats are shown
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and described for example in Spiess C., Zhai Q. and Carter P.J. (2015) *Molecular Immunology* 67: 95-106, in particular Fig. 1 and corresponding description, e.g. p. 95 – 101.

- More preferably, the antibody, or the antigen binding fragment thereof, according to the present invention may be selected from IgG-appended antibodies with an additional antigen-binding moiety comprising DVD-IgG; IgG(H)-scFv; scFv-(H)IgG; IgG(L)-scFv; scFv-(L)IgG; IgG(L,H)-Fv; IgG(H)-V; V(H)-IgG; IgG(L)-V; V(L)-IgG; KIH IgG-scFab; 2scFv-IgG; IgG-2scFv; scFv4-Ig; scFv4-Ig; Zyboby; and DVI-IgG (four-in-one). These bispecific antibody formats are shown and described for example in Spiess C., Zhai Q. and Carter P.J. (2015) *Molecular Immunology* 67: 95-106, in particular Fig. 1 and corresponding description, e.g. p. 95 – 101. Of those antibody formats DVD-Ig (dual variable domain immunoglobulin (Abbott)) is even more preferred. This antibody format is described in detail, for example, in Wu C, Ying H, Grinnell C, Bryant S, Miller R, Clabbers A, Bose S, McCarthy D, Zhu RR, Santora L, Davis-Taber R, Kunes Y, Fung E, Schwartz A, Sakorafas P, Gu J, Tarcsa E, Murtaza A, Ghayur T. Simultaneous targeting of multiple disease mediators by a dual-variable-domain immunoglobulin. *Nat Biotechnol.* 2007 Nov;25(11):1290-7; or in DiGiammarino E, Ghayur T, Liu J. Design and generation of DVD-IgTM molecules for dual-specific targeting. *Methods Mol Biol.* 2012;899:145-56.
- Most preferably, the antibody, or the antigen binding fragment thereof, according to the present invention is an IgG-appended antibody of the Fabs-in-tandem-Ig (FIT-Ig) format. In others words, the antibody, or the antigen binding fragment thereof, according to the present invention is most preferably of the Fabs-in-tandem-Ig (FIT-Ig) format. The Fabs-in-tandem-Ig (FIT-Ig) format is described in detail, for example, in WO 2015/103072 A1, which is incorporated by reference herein in its entirety, or in Gong S, Ren F, Wu D, Wu X, Wu C: Fabs-in-tandem immunoglobulin is a novel and versatile bispecific design for engaging multiple therapeutic targets. *MAbs* 2017. Similar to DVD-Ig, also FIT-Ig is a bispecific tetravalent symmetric format. FIT-Ig may be produced using three polypeptides: Polypeptide 1 usually comprises the light chain of the outer Fab fused, preferably without linkers, to the N-terminal region of the inner Fab heavy chain. Polypeptide 2 usually comprises the heavy chain variable and CH1 regions of the outer Fab, and polypeptide 3 usually comprises by the

light chain of the inner Fab. Accordingly, an antibody of the FIT-Ig format usually comprises an "inner Fab" and an "outer Fab".

5 Preferably, the antibody according to the present invention, or the antigen-binding fragment thereof, neutralizes Zika virus infection. In other words, the antibody, or the antigen binding fragment thereof, according to the present invention, reduces preferably viral infectivity of Zika virus.

10 To study and quantitate virus infectivity (or "neutralization") in the laboratory the person skilled in the art knows various standard "neutralization assays". For a neutralization assay animal viruses are typically propagated in cells and/or cell lines. In the context of the present invention a neutralization assay is preferred, wherein cultured cells are incubated with a fixed amount of Zika virus (ZIKV) in the presence (or absence) of the antibody to be tested. As a readout for example flow cytometry may be used. Alternatively, also other readouts are
15 conceivable, such as determining the amount of ZIKV non-structural proteins (such as ZIKV NS1) secreted into culture supernatant. For example, a ZIKV nonstructural protein 1 (NS1) antigen capture enzyme-linked immunosorbent assay (ELISA)-based tissue culture infectious dose-50 (TCID50) test (TCID50-ELISA) may be used as an alternative to the standard plaque assay for titrating Zika virus – in a similar manner as described for dengue virus (DENV) by Li
20 J, Hu D-M, Ding X-X, Chen Y, Pan Y-X, Qiu L-W, Che X-Y: Enzyme-linked immunosorbent assay-format tissue culture infectious dose-50 test for titrating dengue virus. PLoS ONE 2011, 6:e22553. In such an assay for example the ZIKV NS1-binding antibodies as described in the present application may be advantageously used.

25 In a preferred embodiment of a ZIKV neutralization assay, cultured cells, for example Vero cells, are incubated with a fixed amount of ZIKV in the presence or absence of the antibody to be tested, for example for about four days. After incubation, cells may be washed and further cultivated. To measure virus infectivity, flow cytometry may be used. To this end, cells may be fixed, e.g. with 2% formaldehyde, permeabilizes, e.g. in PBS (phosphate buffered
30 saline) 1% FCS (fetal calf serum) 0.5% saponin, and stained, e.g. with mouse antibody 4G2. Cells may then be incubated with a goat anti-mouse IgG conjugated to a dye, such as Alexa Fluor488 and analyzed by flow cytometry. Alternatively, viable cells may be detected by flow

cytometry using for example the WST-1 reagent (Roche). A preferred ZIKV strain to be used in such a neutralization assay is ZIKV H/PF/2013.

The antibody and antigen binding fragment of the invention have high neutralizing potency.

5 The concentration of the antibody required for 50% neutralization of Zika virus (IC_{50}) as compared to no-antibody controls, is, for example, up to about 3 $\mu\text{g/ml}$ or up to about 1 $\mu\text{g/ml}$. Preferably, the concentration of the antibody of the invention required for 50% neutralization of ZIKV (IC_{50}) is up to about 500 ng/ml, more preferably the concentration of the antibody of the invention required for 50% neutralization of ZIKV (IC_{50}) is up to about

10 250 ng/ml, even more preferably the concentration of the antibody of the invention required for 50% neutralization of ZIKV (IC_{50}) is up to about 150 ng/ml. Most preferably, the concentration of the antibody of the invention required for 50% neutralization of ZIKV (IC_{50}) is about 100 ng/ml or less, e.g. about 90 ng/ml or less, about 80 ng/ml or less, about 70 ng/ml or less, about 60 ng/ml or less, about 50 ng/ml or less, about 45 ng/ml or less, about 40 ng/ml or less, about 35 ng/ml or less, about 30 ng/ml or less, about 25 ng/ml or less, about 20 ng/ml or less or, particularly preferably, about 15 ng/ml or less. In particular, the concentration of the antibody of the invention required for 50% neutralization of ZIKV (IC_{50}) is preferably about 50 ng/ml or less. This means that only low concentrations of the antibody are required for 50% neutralization of ZIKV. The concentration of the antibody of the invention required for

15 50% neutralization of ZIKV (IC_{50}) can be measured using standard neutralization assays as known to one of skill in the art or, in particular, as described above.

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In general, binding of an antibody may be assessed by use of a standard ELISA (enzyme-linked immunosorbent assay), which is well-known to the skilled person. An exemplary standard

25 ELISA may be performed as follows: ELISA plates may be coated (e.g., overnight at 4°C) with a sufficient amount (e.g., 1 $\mu\text{g/ml}$) of the protein/complex/particle to which binding of the antibody is to be tested (for example, for DENV binding as outlined below, DENV E proteins and/or DENV VLPs are used), e.g. in PBS. Plates may then be blocked, e.g. with a 1% w/v solution of Bovine Serum Albumin (BSA) in PBS, and incubated with the antibody to be tested

30 (e.g. for about 1.5 hours at room temperature). After washing, antibody binding can be revealed, e.g. using goat anti-human IgG coupled to alkaline phosphatase. Plates may then be washed, the required substrate (e.g., p-NPP) may be added and plates may be read, e.g. at

405 nm. The relative affinities of antibody binding may be determined by measuring the concentration of mAb (EC_{50}) required to achieve 50% maximal binding at saturation. The EC_{50} values may be calculated by interpolation of binding curves fitted with a four-parameter nonlinear regression with a variable slope.

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Preferably, the antibody, or an antigen binding fragment thereof, according to the present invention does essentially not bind to Dengue virus-like particles and/or to Dengue envelope protein. More preferably, the antibody, or an antigen binding fragment thereof, according to the present invention does essentially not bind to Dengue virus-like particles and/or to
10 Dengue envelope protein of any of the four DENV serotypes DENV1, DENV2, DENV3 and DENV4. Thereby "essentially not binding" means that for the antibody, or an antigen binding fragment thereof, no EC_{50} -value up to 10^2 ng/ml, preferably up to 10^3 ng/ml, more preferably up to $5 \cdot 10^3$ ng/ml, even more preferably up to $8 \cdot 10^3$ ng/ml, and most preferably up to 10^4 ng/ml can be determined in a standard ELISA to Dengue virus-like particles (DENV VLP)
15 and/or to Dengue envelope protein (DENV E protein). In other words, the concentration of the antibody, or an antigen binding fragment thereof, required to achieve 50% maximal binding at saturation (EC_{50}) to Dengue virus-like particles (DENV VLP) and/or to Dengue envelope protein (DENV E protein) in a standard ELISA is typically more than 10^2 ng/ml, preferably more than 10^3 ng/ml, more preferably more than $5 \cdot 10^3$ ng/ml, even more
20 preferably more than $8 \cdot 10^3$ ng/ml, and most preferably more than 10^4 ng/ml.

Preferably, the antibody, or an antigen binding fragment thereof, according to the present invention does not contribute to antibody-dependent enhancement (ADE) of Zika virus infection. More preferably, the antibody, or an antigen binding fragment thereof, according
25 to the present invention blocks antibody-dependent enhancement (ADE) of Zika virus infection.

ADE may be assessed by a flow-cytometry based assay using, for example cultured cells or cell lines, such as K562 cells. For example, the antibodies to be tested and ZIKV may be
30 mixed for 1 hour at 37°C and added to 5000 K562 cells/well. After four days, cells may be fixed, permeabilized, and stained with m4G2, e.g. as described above for neutralization

assays. The number of infected cells was determined by flow cytometry, as described above for neutralization assays.

Preferably, the antibody according to the present invention, or the antigen-binding fragment thereof, eliminates generation of ZIKV escape mutants. Elimination of generation of escape mutants can easily be assessed by the person skilled in the art. For example, to identify the propensity of an antibody or antibody fragment to generate escape mutants, ZIKV is repeatedly passaged in the presence of sub-neutralizing concentrations of the antibody or antigen binding fragment thereof of interest. As shown in examples 10 and 11 of the present application, ZIKV escape mutants ("MARMS") typically appear after the third or fourth passage of ZIKV. Accordingly, an antibody can be considered to eliminate the generation of ZIKV escape mutants, if even after five passages of the virus (ZIKV) in presence of sub-neutralizing concentrations of that antibody or antigen binding fragment thereof, no ZIKV escape mutants can be identified. More preferably, no ZIKV escape mutants can be identified after six passages of the virus (ZIKV) in presence of sub-neutralizing concentrations of the antibody, or antigen binding fragment thereof, according to the present invention. Even more preferably, no ZIKV escape mutants can be identified after seven passages of the virus (ZIKV) in presence of sub-neutralizing concentrations of the antibody, or antigen binding fragment thereof, according to the present invention. Most preferably, no ZIKV escape mutants can be identified after eight passages of the virus (ZIKV) in presence of sub-neutralizing concentrations of the antibody, or antigen binding fragment thereof, according to the present invention.

For example, to assess the propensity of an antibody or antibody fragment to generate escape mutants, ZIKV, for example strain H/PF/2013, is incubated with various sub-neutralizing concentrations of the antibody/antigen binding fragment of interest, e.g., for at least 30 min, for example, at about 37°C (body temperature). Thereafter, (living) cells, for example Vero cells, are added, followed by incubation, e.g. for at least one day, preferably 3 – 4 days, for example, at about 37°C (body temperature) to allow virus propagation to occur. Then, supernatants from three conditions may be selected: the lowest concentration of the antibody/antigen binding fragment of interest at which full protection of the monolayer was observed, one concentration at which a partial CPE effect on the cell monolayer was observed and one concentration at which 100% of the cell monolayer was destroyed by the ZIKV CPE.

One part of the selected supernatant can be used for micro-neutralization assays and subsequent sequencing of the virus (to identify escape mutants), while another part of the (same) selected supernatant can be used for the next selection step (passage). Namely, for the next passage, (a part of the) selected supernatant can be mixed with the various sub-neutralizing concentrations of the antibody/antigen binding fragment of interest and incubated, as described above, followed by addition of (living) cells and incubation as described above, to finally again select supernatants. This selection and propagation process is repeated to arrive at least at five passages, preferably at least six passages, more preferably at least seven passages, and most preferably at least eight passages.

Preferably, each CDR or each variable region of at least one epitope binding site of the antibody, or an antigen binding fragment thereof, according to the present invention is a human CDR or a human variable region, respectively. More preferably, each CDR or each variable region comprised in the antibody, or an antigen binding fragment thereof, according to the present invention is a human CDR or a human variable region, respectively. Most preferably, all constant regions and variable regions comprised in the antibody, or an antigen binding fragment thereof, according to the present invention are a human constant regions and human variable regions.

It is also preferred that the antibody, or an antigen binding fragment thereof, according to the present invention is a monoclonal antibody, preferably a monoclonal antibody wherein each CDR or each variable region comprised in the antibody, or an antigen binding fragment thereof, according to the present invention is a human CDR or a human variable region, respectively.

Preferably, the antibody, or the antigen binding fragment thereof, according to the present invention is of the IgG type, such as IgG1 type, IgG2 type, IgG3 type, or IgG4 type, more preferably of the IgG1 type. More preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises (i) a heavy chain constant region of the IgG1 CH1-CH2-CH3 type, wherein "CH1" refers to the constant domain 1 of the heavy chain, "CH2" refers to the constant domain 2 of the heavy chain, and "CH3" refers to the constant domain 3 of the heavy chain; and (ii) a light chain constant region of the IgG CL type, wherein

“CL” refers to the constant domain of the light chain. Even more preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain constant region of the IgG1 CH1-CH2-CH3 type comprising or consisting of an amino acid sequence according to SEQ ID NO: 91 or 92, or a functional sequence variant thereof,
5 and a light chain constant region of the IgG CL type comprising or consisting of an amino acid sequence according to SEQ ID NO: 93 or 94, or a functional sequence variant thereof.

Accordingly, it is preferred that the antibody according to the present invention, or an antigen binding fragment thereof, comprises an Fc moiety. More preferably, the Fc moiety is derived
10 from human origin, e.g. from human IgG1, IgG2, IgG3, and/or IgG4, whereby human IgG1 is particularly preferred. Various multispecific antibody formats comprising an Fc moiety are known in the art. Preferred antibody formats comprising an Fc moiety are the IgG-appended antibody formats described above. Typically, an antibody comprising an Fc moiety is more effective and displays a longer half-life than antibodies or antibody fragments without Fc
15 moiety.

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
20 region to be 114) and ending at the C-terminus of the immunoglobulin heavy chain. 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. Each
25 of the amino acid positions within an Fc moiety have been numbered according to the art-recognized EU numbering system of Kabat, see e.g., by Kabat et al., in “Sequences of Proteins of Immunological Interest”, U.S. Dept. Health and Human Services, 1983 and 1987.

Preferably, in the context of the present invention an Fc moiety comprises at least one of: a
30 hinge (e.g., upper, middle, and/or lower hinge region) domain, a CH2 domain, a CH3 domain, or a variant, portion, or fragment thereof. In preferred embodiments, an Fc moiety comprises at least a hinge domain, a CH2 domain or a CH3 domain. More preferably, the Fc

moiety is a complete Fc moiety. The Fc moiety may also comprises one or more amino acid insertions, deletions, or substitutions relative to 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. For example, an Fc moiety may comprise or consist of: (i) hinge domain (or portion thereof) fused to a CH2 domain (or portion thereof), (ii) a hinge domain (or portion thereof) fused to a CH3 domain (or portion thereof), (iii) a CH2 domain (or portion thereof) fused to a CH3 domain (or portion thereof), (iv) a hinge domain (or portion thereof), (v) a CH2 domain (or portion thereof), or (vi) a CH3 domain or portion thereof.

- 10 It will be understood by one of ordinary skill in the art that the Fc moiety may be modified such that it varies in amino acid sequence from the complete Fc moiety of a naturally occurring immunoglobulin molecule, while retaining at least one desirable function conferred by the naturally-occurring Fc moiety. Such functions include Fc 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, which are responsible and/or essential for such functions are well known by those skilled in the art.

- For example, to activate the complement cascade C1q binds to at least two molecules of IgG1 or one molecule of IgM, attached to the antigenic target (Ward, E. S., and Ghetie, V., *Ther. Immunol.* 2 (1995) 77-94). Burton, D. R., described (*Mol. Immunol.* 22 (1985) 161-206) that the heavy chain region comprising amino acid residues 318 to 337 is involved in complement fixation. Duncan, A. R., and Winter, G. (*Nature* 332 (1988) 738-740), using site directed mutagenesis, reported that Glu318, Lys320 and Lys322 form the binding site to C1q. The role of Glu318, Lys320 and Lys 322 residues in the binding of C1q was confirmed by the ability of a short synthetic peptide containing these residues to inhibit complement mediated lysis.

- For example, FcR binding can be mediated by the interaction of the Fc moiety (of an antibody) with Fc receptors (FcRs), which are specialized cell surface receptors on hematopoietic cells. Fc receptors belong to the immunoglobulin superfamily, and were shown to mediate both the removal of antibody-coated pathogens by phagocytosis of immune complexes, and the lysis of erythrocytes and various other cellular targets (e.g. tumor cells) coated with the corresponding antibody, via antibody dependent cell mediated cytotoxicity (ADCC; Van de

Winkel, J. G., and Anderson, C. L., *J. Leukoc. Biol.* 49 (1991) 511-524). FcRs are defined by their specificity for immunoglobulin classes; Fc receptors for IgG antibodies are referred to as FcγR, for IgE as FcεR, for IgA as FcαR and so on and neonatal Fc receptors are referred to as FcRn. Fc receptor binding is described for example in Ravetch, J. V., and Kinet, J. P., *Annu. Rev. Immunol.* 9 (1991) 457-492; Capel, P. J., et al., *Immunomethods* 4 (1994) 25-34; de Haas, M., et al., *J Lab. Clin. Med.* 126 (1995) 330-341; and Gessner, J. E., et al., *Ann. Hematol.* 76 (1998) 231-248.

Cross-linking of receptors by the Fc domain of native IgG antibodies (FcγR) triggers a wide variety of effector functions including phagocytosis, antibody-dependent cellular cytotoxicity, and release of inflammatory mediators, as well as immune complex clearance and regulation of antibody production. Therefore, Fc moieties providing cross-linking of receptors (FcγR) are preferred. In humans, three classes of FcγR have been characterized, which are: (i) FcγRI (CD64), which binds monomeric IgG with high affinity and is expressed on macrophages, monocytes, neutrophils and eosinophils; (ii) FcγRII (CD32), which binds complexed IgG with medium to low affinity, is widely expressed, in particular on leukocytes, is known to be a central player in antibody-mediated immunity, and which can be divided into FcγRIIA, FcγRIIB and FcγRIIC, which perform different functions in the immune system, but bind with similar low affinity to the IgG-Fc, and the ectodomains of these receptors are highly homologous; and (iii) FcγRIII (CD16), which binds IgG with medium to low affinity and exists as two types: FcγRIIIA found on NK cells, macrophages, eosinophils and some monocytes and T cells and mediating ADCC and FcγRIIIB, which is highly expressed on neutrophils. FcγRIIA is found on many cells involved in killing (e.g. macrophages, monocytes, neutrophils) and seems able to activate the killing process. FcγRIIB seems to play a role in inhibitory processes and is found on B-cells, macrophages and on mast cells and eosinophils. Importantly, 75% of all FcγRIIB is found in the liver (Ganesan, L. P. et al., 2012: FcγRIIb on liver sinusoidal endothelium clears small immune complexes. *Journal of Immunology* 189: 4981–4988). FcγRIIB is abundantly expressed on Liver Sinusoidal Endothelium, called LSEC, and in Kupffer cells in the liver and LSEC are the major site of small immune complexes clearance (Ganesan, L. P. et al., 2012: FcγRIIb on liver sinusoidal endothelium clears small immune complexes. *Journal of Immunology* 189: 4981–4988).

Accordingly, in the present invention such antibodies, and antigen binding fragments thereof, are preferred, which are able to bind to FcγRIIb, for example antibodies comprising an Fc moiety for binding to FcγRIIb, in particular an Fc region, such as, for example IgG-type antibodies. Moreover, it is possible to engineer the Fc moiety to enhance FcγRIIb binding by introducing the mutations S267E and L328F as described by Chu, S. Y. et al., 2008: Inhibition of B cell receptor-mediated activation of primary human B cells by coengagement of CD19 and FcγRIIb with Fc-engineered antibodies. *Molecular Immunology* 45, 3926–3933. Thereby, the clearance of immune complexes can be enhanced (Chu, S., et al., 2014: Accelerated Clearance of IgE In Chimpanzees Is Mediated By Xmab7195, An Fc-Engineered Antibody With Enhanced Affinity For Inhibitory Receptor FcγRIIb. *Am J Respir Crit, American Thoracic Society International Conference Abstracts*). Accordingly, in the context of the present invention such antibodies, or antigen binding fragments thereof, are preferred, which comprise an engineered Fc moiety with the mutations S267E and L328F, in particular as described by Chu, S. Y. et al., 2008: Inhibition of B cell receptor-mediated activation of primary human B cells by coengagement of CD19 and FcγRIIb with Fc-engineered antibodies. *Molecular Immunology* 45, 3926–3933.

On B-cells it seems to function to suppress further immunoglobulin production and isotype switching to say for example the IgE class. On macrophages, FcγRIIb acts to inhibit phagocytosis as mediated through FcγRIIA. On eosinophils and mast cells the b form may help to suppress activation of these cells through IgE binding to its separate receptor.

Regarding FcγRI binding, modification in native IgG of at least one of E233-G236, P238, D265, N297, A327 and P329 reduces binding to FcγRI. IgG2 residues at positions 233-236, substituted into IgG1 and IgG4, reduces binding to FcγRI by 10³-fold and eliminated the human monocyte response to antibody-sensitized red blood cells (Armour, K. L., et al. *Eur. J. Immunol.* 29 (1999) 2613-2624). Regarding FcγRII binding, reduced binding for FcγRIIA is found e.g. for IgG mutation of at least one of E233-G236, P238, D265, N297, A327, P329, D270, Q295, A327, R292 and K414. Regarding FcγRIII binding, reduced binding to FcγRIIIA is found e.g. for mutation of at least one of E233-G236, P238, D265, N297, A327, P329, D270, Q295, A327, S239, E269, E293, Y296, V303, A327, K338 and D376. Mapping of the

binding sites on human IgG1 for Fc receptors, the above mentioned mutation sites and methods for measuring binding to FcγRI and FcγRIIA are described in Shields, R. L., et al., *J. Biol. Chem.* 276 (2001) 6591-6604.

- 5 Regarding binding to the crucial FcγRII, two regions of native IgG Fc appear to be critical for interactions of FcγRIIs and IgGs, namely (i) the lower hinge site of IgG Fc, in particular amino acid residues L, L, G, G (234 – 237, EU numbering), and (ii) the adjacent region of the CH2 domain of IgG Fc, in particular a loop and strands in the upper CH2 domain adjacent to the lower hinge region, e.g. in a region of P331 (Wines, B.D., et al., *J. Immunol.* 2000; 164: 5313
10 – 5318). Moreover, FcγRI appears to bind to the same site on IgG Fc, whereas FcRn and Protein A bind to a different site on IgG Fc, which appears to be at the CH2-CH3 interface (Wines, B.D., et al., *J. Immunol.* 2000; 164: 5313 – 5318).

- For example, the Fc moiety may comprise or consist of at least the portion of an Fc moiety
15 that is known in the art to be required for FcRn binding or extended half-life. Alternatively or additionally, the Fc moiety of the antibody of the invention comprises at least the portion of known in the art to be required for Protein A binding and/or the Fc moiety of the antibody of the invention comprises at least the portion of an Fc molecule known in the art to be required for protein G binding. Preferably, the retained function is the neutralization of Zika virus
20 infection, which is assumed to be mediated by FcγR binding. Accordingly, a preferred Fc moiety comprises at least the portion known in the art to be required for FcγR binding. As outlined above, a preferred Fc moiety may thus at least comprise (i) the lower hinge site of native IgG Fc, in particular amino acid residues L, L, G, G (234 – 237, EU numbering), and (ii) the adjacent region of the CH2 domain of native IgG Fc, in particular a loop and strands
25 in the upper CH2 domain adjacent to the lower hinge region, e.g. in a region of P331, for example a region of at least 3, 4, 5, 6, 7, 8, 9, or 10 consecutive amino acids in the upper CH2 domain of native IgG Fc around P331, e.g. between amino acids 320 and 340 (EU numbering) of native IgG Fc.

- 30 Preferably, the antibody, or antigen binding fragment thereof, according to the present invention comprises an Fc region. 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 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. Preferably, the Fc region is a dimeric Fc region. 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.

- 10 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 (e.g., a human immunoglobulin) of an IgG1, IgG2, IgG3 or IgG4 subclass. Preferably, the Fc moieties of Fc region are of the same class and subclass. However, the Fc region (or one or more Fc moieties of an Fc region) may also be chimeric, whereby a chimeric Fc region may comprise Fc
- 15 moieties derived from different immunoglobulin classes and/or subclasses. For example, at least two of the Fc moieties of a dimeric or single-chain Fc region may be from different immunoglobulin classes and/or subclasses. Additionally or alternatively, the chimeric Fc regions may comprise one or more chimeric Fc moieties. For example, the chimeric Fc region or moiety may comprise one or more portions derived from an immunoglobulin of a first
- 20 subclass (e.g., an IgG1, IgG2, or IgG3 subclass) while the remainder of the Fc region or moiety is of a different subclass. For example, an Fc region or moiety of an Fc polypeptide may comprise a CH2 and/or CH3 domain derived from an immunoglobulin of a first subclass (e.g., an IgG1, IgG2 or IgG4 subclass) and a hinge region from an immunoglobulin of a second subclass (e.g., an IgG3 subclass). For example, the Fc region or moiety may comprise a hinge
- 25 and/or CH2 domain derived from an immunoglobulin of a first subclass (e.g., an IgG4 subclass) and a CH3 domain from an immunoglobulin of a second subclass (e.g., an IgG1, IgG2, or IgG3 subclass). For example, the chimeric Fc region may comprise an Fc moiety (e.g., a complete Fc moiety) from an immunoglobulin for a first subclass (e.g., an IgG4 subclass) and an Fc moiety from an immunoglobulin of a second subclass (e.g., an IgG1, IgG2
- 30 or IgG3 subclass). For example, the Fc region or moiety may comprise a CH2 domain from an IgG4 immunoglobulin and a CH3 domain from an IgG1 immunoglobulin. For example, the Fc region or moiety may comprise a CH1 domain and a CH2 domain from an IgG4

molecule and a CH3 domain from an IgG1 molecule. For example, the Fc region or moiety may comprise a portion of a CH2 domain from a particular subclass of antibody, e.g., EU positions 292-340 of a CH2 domain. For example, an Fc region or moiety may comprise amino acids at positions 292-340 of CH2 derived from an IgG4 moiety and the remainder of
5 CH2 derived from an IgG1 moiety (alternatively, 292-340 of CH2 may be derived from an IgG1 moiety and the remainder of CH2 derived from an IgG4 moiety).

Moreover, an Fc region or Fc moiety may (additionally or alternatively) for example comprise a chimeric hinge region. For example, the chimeric hinge may be derived, e.g. in part, from
10 an IgG1, IgG2, or IgG4 molecule (e.g., an upper and lower middle hinge sequence) and, in part, from an IgG3 molecule (e.g., an middle hinge sequence). In another example, an Fc region or moiety may comprise a chimeric hinge derived, in part, from an IgG1 molecule and, in part, from an IgG4 molecule. In another example, the chimeric hinge may comprise upper and lower hinge domains from an IgG4 molecule and a middle hinge domain from an
15 IgG1 molecule. Such a chimeric hinge may be made, for example, by introducing a proline substitution (Ser228Pro) at EU position 228 in the middle hinge domain of an IgG4 hinge region. In another embodiment, the chimeric hinge can comprise amino acids at EU positions 233-236 are from an IgG2 antibody and/or the Ser228Pro mutation, wherein the remaining amino acids of the hinge are from an IgG4 antibody (e.g., a chimeric hinge of the sequence
20 ESKYGPPCPPCPAPPVAGP). Further chimeric hinges, which may be used in the Fc moiety of the antibody according to the present invention are described in US 2005/0163783 A1.

In the present invention it is preferred that the Fc moiety, or the Fc region, comprises or consists of an amino acid sequence derived from a human immunoglobulin sequence (e.g.,
25 from an Fc region or Fc moiety from a human IgG molecule). However, polypeptides 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 subject polypeptides. Alternatively, one or more murine amino acids may be present in the Fc moiety or in the Fc region.

30 Preferably, the antibody according to the present invention comprises, in particular in addition to an Fc moiety as described above, other parts derived from a constant region, in particular from a constant region of IgG, preferably from a constant region of IgG1, more

preferably from a constant region of human IgG1. More preferably, the antibody according to the present invention comprises, in particular in addition to an Fc moiety as described above, all other parts of the constant regions, in particular all other parts of the constant regions of IgG, preferably all other parts of the constant regions of IgG1, more preferably all other parts of the constant regions of human IgG1.

Particularly preferred sequences of constant regions are the amino acid sequences according to SEQ ID NOs: 91 – 94 (encoded, for example, by nucleic acid sequences according to SEQ ID NOs: 95 – 98, respectively). Preferably, the amino acid sequence of IgG1 CH1-CH2-CH3 is according to SEQ ID NO: 91 or a functional sequence variant thereof, as described herein. Even more preferably, the amino acid sequence of IgG1 CH1-CH2-CH3 is according to SEQ ID NO: 92 or a functional sequence variant thereof, as described herein, wherein the “LALA” mutation is maintained.

As outlined above, a particularly preferred antibody according to the present invention comprises a (complete) Fc region derived from human IgG1. More preferably, the antibody according to the present invention comprises, in particular in addition to a (complete) Fc region derived from human IgG1 also all other parts of the constant regions of IgG, preferably all other parts of the constant regions of IgG1, more preferably all other parts of the constant regions of human IgG1.

Without being bound to any theory, it is believed that antibody-dependent enhancement (ADE) of Zika virus infection is brought about by the binding of the Fc moiety of the antibody, in particular, the Fc moiety of the heavy chain of an IgG molecule, to an Fc receptor, e.g., an Fcγ receptor on a host cell. It is thus preferred that the antibody according to the present invention, or an antigen binding fragment thereof, comprises one or more mutations in the Fc moiety. The mutation(s) may be any mutation that reduces binding of the antibody to an Fc receptor (FcR), in particular reduces binding of the antibody to an Fcγ receptor (FcγR). On the other hand, it is preferred that the antibody according to the present invention comprises a (complete) Fc moiety/Fc region, wherein the interaction/binding with FcRn is not compromised. Accordingly, it is particularly preferred that the antibody according to the present invention, or an antigen binding fragment thereof, comprises one or more mutations

in the Fc moiety, which (i) reduce(s) binding of the antibody to an Fcγ receptor, but do(es) not compromise interaction with FcRn. One example of such a mutation is the “LALA” mutation described below.

- 5 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. 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 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).
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In general, the antibody according to the present invention may be glycosylated. N-linked glycans attached to the CH2 domain of a heavy chain, for instance, can influence C1q and FcR binding, with aglycosylated antibodies having lower affinity for these receptors. Accordingly, the CH2 domain of the Fc moiety of the antibody according to the present invention may comprise one or more mutations, in which a glycosylated residue is substituted by a non-glycosylated residue. The glycan structure can also affect activity e.g. differences in complement-mediated cell death may be seen depending on the number of galactose sugars (0, 1 or 2) at the terminus of a glycan's biantennary chain. Preferably, the antibody's glycans do not lead to a human immunogenic response after administration.

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Furthermore, the antibody according to the present invention can be modified by introducing random amino acid mutations into particular region of the CH2 or CH3 domain of the heavy chain in order to alter their binding affinity for FcR and/or their serum half-life in comparison to unmodified antibodies. Examples of such modifications include, but are not limited to,

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substitutions of at least one amino acid from the heavy chain constant region selected from the group consisting of amino acid residues 250, 314, and 428.

Particularly preferably, the Fc moiety of an antibody of the invention comprises a substitution
5 at positions CH2 4, CH2 5, or both. In general, the amino acid at positions 4 and 5 of CH2 of the wild-type IgG1 and IgG3 is a leucine ("L"). Preferably, the antibody according to the present invention comprises an amino acid at position CH2 4, CH2 5, or both, that is not an L. More preferably, antibody according to the present invention comprises an alanine ("A") at position CH2 4, or CH2 5, or both. Most preferably, the antibody according to the present
10 invention comprises both, a CH2 L4A and a CH2 L5A substitution. Such antibodies are referred to herein as a "LALA" variant. Interestingly, such a "LALA" mutation in the Fc moiety does not only result in a lack of contribution of the respective antibody in antibody-dependent enhancement (ADE) of Zika virus infection, but also blocks antibody-dependent enhancement (ADE) of Zika virus infection. An exemplary amino acid sequence of IgG1 CH1-CH2-CH3
15 comprising the "LALA" mutation is according to SEQ ID NO: 92. Accordingly, the amino acid sequence of IgG1 CH1-CH2-CH3 is preferably according to SEQ ID NO: 92 or a functional sequence variant thereof, as described herein, wherein the "LALA" mutation is maintained. Most preferably, the antibody is of the FIT-Ig format described above comprising a "LALA" mutation in the Fc moiety as described herein.

20 Preferably, the antibody, or antigen binding fragment thereof, according to the present invention does not comprise a binding site for an Fc receptor. More preferably, the antibody, or antigen binding fragment thereof, does not comprise an Fc region, even more preferably, the antibody, or antigen binding fragment thereof, does not comprise an Fc moiety. Various
25 multispecific antibody formats without Fc moiety are known in the art and described above.

As described above, the antibody, or the antigen binding fragment thereof, according to the present invention preferably binds specifically to (at least two) distinct epitopes on Zika virus envelope protein (ZIKV E protein). More preferably, the antibody, or antigen binding fragment
30 thereof, binds to domain III of Zika virus envelope protein (EDIII, also referred to as "DIII"). In other words, it is preferred that the antibody, or antigen binding fragment thereof, according to the present invention binds to an epitope of Zika virus envelope protein, which includes

one or more amino acid residues of domain III of Zika virus envelope protein (EDIII). ZIKV includes a nucleocapsid core, which comprising single-stranded RNA wrapped by core proteins. The nucleocapsid core is encapsulated by a lipid bilayer membrane with “membrane proteins” and “envelope proteins”. ZIKV envelope protein (E protein) is the dominant antigen. The ectodomain of the envelope protein comprises three distinct domains: E protein domain I (EDI), E protein domain II (EDII), and E protein domain III (EDIII). EDIII is highly conserved among different ZIKV strains (see Figure 8 for an alignment of amino acid sequences of EDIII of different ZIKV strains). Antibodies binding to domain III of Zika virus envelope protein (EDIII) show (i) increased neutralization of ZIKV and (ii) decreased cross-reactivity with DENV (in particular essentially no cross-reactivity with DENV) as compared to antibodies binding to domain I/II of Zika virus envelope protein (EDI/II).

Accordingly, the antibody, or antigen binding fragment thereof, more preferably binds to domain III of Zika virus envelope protein (EDIII) with EDIII having the following amino acid sequence (SEQ ID NO: 263):

TAAFTFTKXPAEXXHGTVTVEXQYXGXDGPCKXPXQMAVDXQTLTPVGRLITANPVITEXTENS
KMMLELDPPFGDSYIVIGXGXKKITHHWHR

wherein X may be any (naturally occurring) amino acid. In other words, it is preferred that the , the antibody, or antigen binding fragment thereof, according to the present invention binds to an epitope of Zika virus envelope protein, which includes one or more amino acid residues of SEQ ID NO: 263.

It is also preferred that the antibody, or antigen binding fragment thereof, according to the present invention binds to domain III of Zika virus envelope protein (EDIII) with EDIII having the following amino acid sequence (SEQ ID NO: 265):

X₁GX₂X₃YSLCTAAFTFTKX₄PAEX₅X₆HGTVTVEX₇QYX₈GX₉DGPCKX₁₀PX₁₁QMAVDX₁₂QTLTP
VGRLITANPVITEX₁₃TX₁₄NSKMMLELDPPFGDSYIVIGX₁₅GX₁₆X₁₇KITHHWHRSG

wherein X₁ may be any (naturally occurring) amino acid, preferably K, A, or E;

- X2 may be any (naturally occurring) amino acid, preferably V, F, or L;
 X3 may be any (naturally occurring) amino acid, preferably S or F;
 X4 may be any (naturally occurring) amino acid, preferably I or V;
 X5 may be any (naturally occurring) amino acid, preferably T or V;
 5 X6 may be any (naturally occurring) amino acid, preferably L or D;
 X7 may be any (naturally occurring) amino acid, preferably V or G;
 X8 may be any (naturally occurring) amino acid, preferably A or G;
 X9 may be any (naturally occurring) amino acid except R, preferably T or A;
 X10 may be any (naturally occurring) amino acid, preferably V or I;
 10 X11 may be any (naturally occurring) amino acid, preferably A or V;
 X12 may be any (naturally occurring) amino acid, preferably M or T;
 X13 may be any (naturally occurring) amino acid, preferably S or G;
 X14 may be any (naturally occurring) amino acid, preferably E or K;
 X15 may be any (naturally occurring) amino acid, preferably V or I;
 15 X16 may be any (naturally occurring) amino acid, preferably E, A, K, or D; and
 X17 may be any (naturally occurring) amino acid, preferably E, A, or K, more preferably K or A.

In other words, it is preferred that the , the antibody, or antigen binding fragment thereof,
 20 according to the present invention binds to an epitope of Zika virus envelope protein, which includes one or more amino acid residues of SEQ ID NO: 265.

For example, EDIII stretches from amino acid 309 to amino acid 403 of ZIKV E protein of the
 ZIKV H/PF/2013 strain (Genbank accession number KJ776791). Accordingly, the antibody,
 25 or antigen binding fragment thereof, most preferably binds to domain III of Zika virus envelope protein (EDIII) with EDIII having the following amino acid sequence (SEQ ID NO: 264):

TAAFTFTKIPAETLHGTVTVEVQYAGTDGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENS
 30 KMMLELDPPFGDSYIVIGVGEKKITHHWHS.

In other words, it is preferred that the antibody, or antigen binding fragment thereof, according to the present invention binds to an epitope of Zika virus envelope protein, which includes one or more amino acid residues of SEQ ID NO: 264.

- 5 More preferably, the antibody, or antigen binding fragment thereof, according to the present invention binds to an epitope of Zika virus envelope protein, which includes one or more amino acid residues of the lateral ridge (LR) of EDIII and/or one or more amino acid residues of the EDI-EDIII hinge region. The EDIII lateral ridge and EDI-EDIII hinge region are known to the skilled person and described, for example, in Zhao, H., Fernandez, E., Dowd, K.A.,
10 Speer, S.D., Platt, D.J., Gorman, M.J., Govero, J., Nelson, C.A., Pierson, T.C., Diamond, M.S., et al. (2016). Structural Basis of Zika Virus-Specific Antibody Protection. *Cell* 166(4):1016-27 and in Kostyuchenko VA, Lim EX, Zhang S, Fibriansah G, Ng TS, Ooi JS, Shi J, Lok SM. Structure of the thermally stable Zika virus. *Nature*. 2016 May 19;533(7603):425-8. Without being bound to any theory, it is assumed that (i) binding to the LR may inhibit fusion by
15 trapping a fusion transitional state of the virus and (ii) binding to the EDI-EDIII hinge and EDIII may hinder the movement of EDIII to form the trimeric post-fusion structure, thereby halting membrane fusion.

- Accordingly, it is preferred that the antibody, or antigen binding fragment thereof, according to the present invention (is able to) inhibit(s) a post-attachment step of ZIKV. "Post-attachment" typically refers to any step of ZIKV infection after attachment of ZIKV to the cell membrane (of the cell targeted by ZIKV). For example, the antibody, or antigen binding fragment thereof, according to the present invention preferably (is able to) prevent(s) membrane fusion. Furthermore, it is also preferred that the antibody, or antigen binding
25 fragment thereof, according to the present invention (is able to) cause(s) aggregation of ZIKV (particles). Most preferably, the antibody, or antigen binding fragment thereof, according to the present invention (is able to) (i) inhibit(s) a post-attachment step of ZIKV and (ii) cause(s) aggregation of ZIKV (particles).

- 30 Particularly preferably, the antibody, or antigen binding fragment thereof, according to the present invention comprises at least one CDR, preferably all six CDRs, more preferably a variable region, even more preferably both variable regions (i.e., an epitope binding site), in

particular a specificity, of the exemplified human antibody ZKA190, which binds to ZIKV EDIII (cf. Example 1, Figure 1). Amino acid sequences of CDRs and variable regions of ZKA190, which are preferably comprised in the antibody, or antigen binding fragment thereof, according to the present invention, are described in Tables 1 and 2 below.

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It is also preferred that the antibody, or antigen binding fragment thereof, binds to a quaternary epitope displayed on a ZIKV infectious virion. Despite considerable neutralizing activity, such antibodies show typically no detectable binding to recombinant ZIKV E protein or to ZIKV EDIII in a standard ELISA (as described above), i.e. if tested *in vitro*, in particular in purified form (i.e. ZIKV E protein “outside/without” a virion, a virus-like particle or the like). Thereby, “no detectable binding” typically means that no EC₅₀ up to 10000 ng/ml was detected in a standard ELISA. In other words, if the EC₅₀ detectable in a standard ELISA is above 10000 ng/ml, it is referred to as “no detectable binding”.

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Therefore, such antibodies are also referred to herein as “neutralizing-non-E-binding” (NNB) antibodies. The quaternary epitope displayed on a ZIKV infectious virion is typically a conformational epitope. For example, the quaternary epitope displayed on a ZIKV infectious virion may be formed at the interface of two envelope protein monomers making up a dimer (“envelope dimer epitope”; EDE) or it may be formed across neighbouring dimers (“herring-bone epitope”).

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Particularly preferably, the antibody, or antigen binding fragment thereof, according to the present invention comprises at least one CDR, preferably all six CDRs, more preferably a variable region, even more preferably both variable regions (i.e., an epitope binding site), in particular a specificity, of the exemplified human antibody ZKA230, which binds to a quaternary epitope displayed on a ZIKV infectious virion (cf. Example 1, Figure 1). Amino acid sequences of CDRs and variable regions of ZKA230, which are preferably comprised in the antibody, or antigen binding fragment thereof, according to the present invention, are described in Tables 1 and 2 below.

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It is also preferred that the antibody, or antigen binding fragment thereof, binds to domain II of Zika virus envelope protein (EDII). EDII is an elongated finger-like domain containing a

conserved fusion loop that interacts with the host cell endosomal membrane extending approx. from amino acid position 52 to amino acid position 132 and approx. from amino acid position 193 to amino acid position 280 of ZIKV E protein (Dai L, Song J, Lu X, Deng YQ, Musyoki AM, Cheng H, Zhang Y, Yuan Y, Song H, Haywood J, Xiao H, Yan J, Shi Y, Qin CF, Qi J, Gao GF. Structures of the Zika Virus Envelope Protein and Its Complex with a
5 Flavivirus Broadly Protective Antibody. Cell Host Microbe. 2016 May 11;19(5):696-704).

Particularly preferably, the antibody, or antigen binding fragment thereof, according to the present invention comprises at least one CDR, preferably all six CDRs, more preferably a
10 variable region, even more preferably both variable regions (i.e., an epitope binding site), in particular a specificity, of the exemplified human antibody ZKA185, which binds to ZIKV EDII. Amino acid sequences of CDRs and variable regions of ZKA185, which are preferably comprised in the antibody, or antigen binding fragment thereof, according to the present invention, are described in Tables 1 and 2 below.

15 Preferably, the antibody, or antigen binding fragment thereof, according to the present invention (i) binds to domain III of Zika virus envelope protein (EDIII) and (ii) binds to domain II of Zika virus envelope protein (EDII). In other words, it is preferred that antibody, or antigen binding fragment thereof, according to the present invention comprises (i) an epitope binding
20 site, which specifically binds to domain III of Zika virus envelope protein (EDIII), and (ii) an epitope binding site, which specifically binds to domain II of Zika virus envelope protein (EDII). As described above, it is preferred that domain III of Zika virus envelope protein comprises or consists of an amino acid sequence as set forth in SEQ ID NO: 263 or 265, in particular as set forth in SEQ ID NO: 264. Moreover, as described above, it is also preferred
25 that the antibody, or antigen binding fragment thereof, binds to an epitope of Zika virus envelope protein, which includes one or more amino acid residues of the lateral ridge (LR) of EDIII and/or one or more amino acid residues of the EDI-EDIII hinge region. In other words, the epitope binding site targeting EDIII preferably binds to one or more amino acid residues of the lateral ridge (LR) of EDIII and/or one or more amino acid residues of the EDI-EDIII
30 hinge region.

It is also preferred that the antibody, or antigen binding fragment thereof, according to the present invention (i) binds to domain III of Zika virus envelope protein (EDIII) and (ii) binds to a quaternary epitope displayed on a ZIKV infectious virion. In other words, it is preferred that antibody, or antigen binding fragment thereof, according to the present invention

5 comprises (i) an epitope binding site, which specifically binds to domain III of Zika virus envelope protein (EDIII), and (ii) an epitope binding site, which specifically binds to a quaternary epitope displayed on a ZIKV infectious virion. As described above, it is preferred that domain III of Zika virus envelope protein comprises or consists of an amino acid sequence as set forth in SEQ ID NO: 263 or 265, in particular as set forth in SEQ ID NO: 264.

10 Moreover, as described above, it is also preferred that the antibody, or antigen binding fragment thereof, binds to an epitope of Zika virus envelope protein, which includes one or more amino acid residues of the lateral ridge (LR) of EDIII and/or one or more amino acid residues of the EDI-EDIII hinge region. In other words, the epitope binding site targeting EDIII preferably binds to one or more amino acid residues of the lateral ridge (LR) of EDIII and/or

15 one or more amino acid residues of the EDI-EDIII hinge region.

In general, a single epitope binding site (also referred to as "paratope" or "antigen receptor") of the antibody according to the present invention, or the antigen binding fragment thereof, preferably comprises three complementarity determining regions (CDRs) on a heavy chain

20 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, the CDRs of a heavy chain and the connected light chain of an antibody together form the antigen receptor (epitope binding site). Usually, the three CDRs (CDR1, CDR2, and CDR3) are arranged non-consecutively in the variable domain. Since

25 epitope binding sites are typically composed of two variable domains (for example, on two different polypeptide chains, i.e. heavy and light chain), there are six CDRs for each epitope binding site (heavy chain: CDRH1, CDRH2, and CDRH3; light chain: CDRL1, CDRL2, and CDRL3). 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"

30 than the CDR. For example, a chain (or each chain, respectively) may be composed of four framework regions, separated by three CDR's.

The sequences of the heavy chains and light chains of various exemplified human anti ZIKV E protein antibodies, comprising three different CDRs on the heavy chain and three different CDRs on the light chain were determined (cf. Tables 1 and 2 below). The position of the CDR amino acids are defined according to the IMGT numbering system (IMGT: <http://www.imgt.org/>; cf. Lefranc, M.-P. et al. (2009) Nucleic Acids Res. 37, D1006-D1012). Preferably, the antibody, or antigen binding fragment thereof, according to the present invention comprises at least one CDR of the following exemplified antibodies. More preferably, the antibody, or antigen binding fragment thereof, according to the present invention comprises all six CDRs (of an epitope binding site) of the following exemplified antibodies. Even more preferably, the antibody, or antigen binding fragment thereof, according to the present invention comprises the heavy chain variable region (VH) and the light chain variable region (VL) of the following exemplified antibodies.

Table 1 shows the SEQ ID NO's of the amino acid sequences of the heavy chain CDR's (CDRH1, CDRH2, and CDRH3) and of the heavy chain variable region (referred to as "VH") of exemplary antibodies:

Antibody name	CDRH1	CDRH2	CDRH3	VH
ZKA190	1	2	3	8
ZKA185	19	20	21	26
ZKA230	37	38	39	44
ZKA78	55	56	57	62
ZKA64	73	74	75	80
ZKA3	99	100	101	102
ZKA4	103	104	105	106
ZKA5	107	108	109	110
ZKA6	111	112	113	114
ZKA7	115	116	117	118
ZKA8	119	120	121	122
ZKA76	123	124	125	126
ZKA117	127	128	129	130

Antibody name	CDRH1	CDRH2	CDRH3	VH
ZKB27	131	132	133	134
ZKB29	135	136	137	138
ZKB34	139	140	141	142
ZKB39	143	144	145	146
ZKB46	147	148	149	150
ZKB53	151	152	153	154
ZKC26	155	156	157	158
ZKD5	159	160	161	162
ZKD7	163	164	165	166
ZKD8	167	168	169	170
ZKD15	171	172	173	174
ZKD16	175	176	177	178
ZKD17	179	180	181	182
ZKD20	183	184	185	186
ZKA134	187	188	189	190
ZKA246	191	192	193	194
ZKA256	195	196	197	198
ZKB42	199	200	201	202
ZKB85	203	204	205	206
ZKB47	207	208	209	210
ZKC6	211	212	213	214
ZKA160	215	216	217	218
ZKA172	219	220	221	222
ZKA174	223	224	225	226
ZKA189	227	228	229	230
ZKA195	231	232	233	234
ZKA215	235	236	237	238
ZKA218	239	240	241	242
ZKB75	243	244	245	246
ZKB83	247	248	249	250

Antibody name	CDRH1	CDRH2	CDRH3	VH
ZKC3	251	252	253	254
ZKC18	255	256	257	258
ZKD1	259	260	261	262

Table 2 below shows the SEQ ID NO's of the amino acid sequences of the light chain CDR's (CDRL1, CDRL2, and CDRL3) and of the light chain variable region (referred to as "VL") of exemplary antibodies:

Antibody name	CDRL1	CDRL2	CDRL2 long	CDRL3	VL
ZKA190	4	5	6	7	9
ZKA185	22	23	24	25	27
ZKA230	40	41	42	43	45
ZKA78	58	59	60	61	63
ZKA64	76	77	78	79	81

It is thus preferred that the antibody, or the antigen binding fragment thereof, according to the present invention comprises amino acid sequences 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% identity to at least one of the CDR sequences, the VH sequence and/or the VL sequence shown in Table 1 and/or in Table 2.

It is preferred that the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein at least one CDR, preferably the at least one heavy chain CDRH3, comprises or consists of an amino acid sequence according to any of SEQ ID NOs: 3, 75, 39, 21, 57, 101, 105, 109, 113, 117, 121, 125, 129, 133, 137, 141, 145, 149, 153, 157, 161, 165, 169, 173, 177, 181, 185, 189, 193, 197, 201, 205, 209, 213, 217,

221, 225, 229, 233, 237, 241, 245, 249, 253, 257, and 261, or a functional 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.

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More preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein at least one CDR, preferably the at least one heavy chain CDRH3, comprises or consists of an amino acid sequence according to any of SEQ ID NOs: 3, 21, and 39, 57 and 75 or a functional 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. More preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein at least one CDR, preferably the at least one heavy chain CDRH3, comprises or consists of an amino acid sequence according to any of SEQ ID NOs: 3, 21, and 39 or a functional 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.

It is also preferred that the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein at least one CDR, preferably the at least one heavy chain CDRH3, comprises or consists of an amino acid sequence according to SEQ ID NO: 21 or according to SEQ ID NO: 39; or a functional 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.

- Most preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein at least one CDR, preferably the at least one heavy chain CDRH3, comprises or consists of an amino acid sequence according to SEQ ID NO: 3 or a functional 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.
- 10 More preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein
- 15 (i) the at least one heavy chain CDRH1 comprises an amino acid sequence according to any of SEQ ID NOs: 1, 19, 37, 55, 73, 99, 103, 107, 111, 115, 119, 123, 127, 131, 135, 139, 143, 147, 151, 155, 159, 163, 167, 171, 175, 179, 183, 187, 191, 195, 199, 203, 207, 211, 215, 219, 223, 227, 231, 235, 239, 243, 247, 251, 255, and 259, or a functional 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;
- 20 (ii) the at least one CDRH2 comprises an amino acid sequence according to any of SEQ ID NOs: 2, 20, 38, 56, 74, 100, 104, 108, 112, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200, 204, 208, 212, 216, 220, 224, 228, 232, 236, 240, 244, 248, 252, 256, and 260, or a functional 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; and/or
- 25 (iii) the at least one heavy chain CDRH3 comprises an amino acid sequence according to any of SEQ ID NOs: 3, 21, 39, 57, 75, 101, 105, 109, 113, 117, 121, 125, 129, 133, 137, 141, 145, 149, 153, 157, 161, 165, 169, 173, 177, 181, 185, 189, 193, 197, 201, 205, 209, 213, 217, 221, 225, 229, 233, 237, 241, 245, 249, 253, 257, and 261, or a functional sequence variant thereof having at least 70%, at least 75%, at least
- 30

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.

5 Still more preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein

- 10 (i) the at least one heavy chain CDRH1 comprises an amino acid sequence according to any of SEQ ID NOs: 1, 19, 37, 55 and 73 or a functional 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;
- 15 (ii) the at least one CDRH2 comprises an amino acid sequence according to any of SEQ ID NOs: 2, 20, 38, 56 and 74 or a functional 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; and/or
- 20 (iii) the at least one heavy chain CDRH3 comprises an amino acid sequence according to any of SEQ ID NOs: 3, 21, 39, 57 and 75 or a functional 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.

Even more preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein

- 25 (i) the at least one heavy chain CDRH1 comprises an amino acid sequence according to any of SEQ ID NOs: 1, 19, and 37 or a functional 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;
- 30

- (ii) the at least one CDRH2 comprises an amino acid sequence according to any of SEQ ID NOs: 2, 20, and 38 or a functional 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; and/or
- (iii) the at least one heavy chain CDRH3 comprises an amino acid sequence according to any of SEQ ID NOs: 3, 21, and 39 or a functional 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.
- Still more preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein
- (i) the at least one heavy chain CDRH1 comprises an amino acid sequence according to SEQ ID NO: 1 or according to SEQ ID NO: 73; or a functional 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;
- (ii) the at least one CDRH2 comprises an amino acid sequence according to SEQ ID NO: 2 or according to SEQ ID NO: 74; or a functional 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; and/or
- (iii) the at least one heavy chain CDRH3 comprises an amino acid sequence according to SEQ ID NO: 3 or according to SEQ ID NO: 75; or a functional 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.
- It is also preferred that the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one

CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein

- (i) the at least one heavy chain CDRH1 comprises an amino acid sequence according to SEQ ID NO: 19 or according to SEQ ID NO: 37; or a functional 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;
- (ii) the at least one CDRH2 comprises an amino acid sequence according to SEQ ID NO: 20 or according to SEQ ID NO: 38; or a functional 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; and/or
- (iii) the at least one heavy chain CDRH3 comprises an amino acid sequence according to SEQ ID NO: 21 or according to SEQ ID NO: 39; or a functional 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.

Most preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein

- (i) the at least one heavy chain CDRH1 comprises an amino acid sequence according to SEQ ID NO: 1 or a functional 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;
- (ii) the at least one CDRH2 comprises an amino acid sequence according to SEQ ID NO: 2 or a functional 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; and/or
- (iii) the at least one heavy chain CDRH3 comprises an amino acid sequence according to SEQ ID NO: 3 or a functional 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.

It is also preferred that the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein

- (i) the at least one CDRL1 comprises an amino acid sequence according to any of SEQ ID NOs: 4, 22, 40, 58 and 76 or a functional 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;
- (ii) the at least one CDRL2 comprises an amino acid sequence according to any of SEQ ID NOs: 5, 6, 23, 24, 41, 42, 59, 60, 77 and 78 or a functional 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; and/or
- (iii) the at least one CDRL3 amino comprises an amino acid sequence according to any of SEQ ID NOs: 7, 25, 43, 61 and 79 or a functional 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.

More preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein

- (i) the at least one CDRL1 comprises an amino acid sequence according to any of SEQ ID NOs: 4, 22, and 40 or a functional 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;
- (ii) the at least one CDRL2 comprises an amino acid sequence according to any of SEQ ID NOs: 5, 6, 23, 24, 41, and 42, or a functional 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; and/or

- (iii) the at least one CDRL3 amino comprises an amino acid sequence according to any of SEQ ID NOs: 7, 25, and 43 or a functional 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.

Even more preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein

- (i) the at least one CDRL1 comprises an amino acid sequence according to SEQ ID NO: 4 or according to SEQ ID NO: 76; or a functional 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;

- (ii) the at least one CDRL2 comprises an amino acid sequence according to any of SEQ ID NOs: 5, 6, 77 and 78 or a functional 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; and/or

- (iii) the at least one CDRL3 amino comprises an amino acid sequence according to SEQ ID NO: 7 or according to SEQ ID NO: 79; or a functional 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.

It is also preferred that the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein

- (i) the at least one CDRL1 comprises an amino acid sequence according to SEQ ID NO: 22 or according to SEQ ID NO: 40; or a functional 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;

- 5 (ii) the at least one CDRL2 comprises an amino acid sequence according to any of SEQ ID NOs: 23, 24, 41 and 42 or a functional 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; and/or
- 10 (iii) the at least one CDRL3 amino comprises an amino acid sequence according to SEQ ID NO: 25 or according to SEQ ID NO: 43; or a functional 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.

Most preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein

- 15 (i) the at least one CDRL1 comprises an amino acid sequence according to SEQ ID NO: 4 or a functional 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;
- 20 (ii) the at least one CDRL2 comprises an amino acid sequence according to SEQ ID NO: 5 or 6, or a functional 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; and/or
- 25 (iii) the at least one CDRL3 amino comprises an amino acid sequence according to SEQ ID NO: 7 or a functional 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.

30 Preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises CDRH1, CDRH2, and CDRH3 amino acid sequences (i) according to SEQ ID NOs: 1 - 3; or functional sequence variants 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; (ii) according to SEQ ID NOs: 19 - 21; or functional sequence variants 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%,
5 at least 97%, at least 98% or at least 99% sequence identity; (iii) according to SEQ ID NOs: 37 - 39; or functional sequence variants 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; (iv) according to SEQ ID NOs: 55 - 57; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%,
10 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; (v) according to SEQ ID NOs: 73 - 75; or functional sequence variants 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; (vi) according to SEQ ID NOs: 99 - 101; or
15 functional sequence variants 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; (vii) according to SEQ ID NOs: 103 - 105; or functional sequence variants 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
20 least 98% or at least 99% sequence identity; (viii) according to SEQ ID NOs: 107 - 109; or functional sequence variants 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; (ix) according to SEQ ID NOs: 111 - 113; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least
25 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; (x) according to SEQ ID NOs: 115 - 117; or functional sequence variants 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; (xi) according to SEQ ID NOs: 119 - 121; or
30 functional sequence variants 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; (xii) according to SEQ ID NOs: 123 - 125; or

functional sequence variants 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; (xiii) according to SEQ ID NOs: 127 – 129; or functional sequence variants 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; (xiv) according to SEQ ID NOs: 131 – 133; or functional sequence variants 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; (xv) according to SEQ ID NOs: 135 - 137; or functional sequence variants 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; (xvi) according to SEQ ID NOs: 139 - 141; or functional sequence variants 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; (xvii) according to SEQ ID NOs: 143 - 145; or functional sequence variants 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; (xviii) according to SEQ ID NOs: 147 – 149; or functional sequence variants 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; (xix) according to SEQ ID NOs: 151 – 153; or functional sequence variants 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; (xx) according to SEQ ID NOs: 155 - 157; or functional sequence variants 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; (xxi) according to SEQ ID NOs: 159 - 161; or functional sequence variants 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; (xxii) according to SEQ ID NOs: 163 - 165; or functional sequence variants 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; (xxiii) according to SEQ ID NOs: 167 – 169; or functional sequence variants 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; (xxiv) according to SEQ ID NOs: 171 – 173; or
5 functional sequence variants 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; (xxv) according to SEQ ID NOs: 175 – 177; or functional sequence variants 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
10 least 98% or at least 99% sequence identity; (xxvi) according to SEQ ID NOs: 179 – 181; or functional sequence variants 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; (xxvii) according to SEQ ID NOs: 183 – 185; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least
15 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; (xxviii) according to SEQ ID NOs: 187 – 189; or functional sequence variants 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; (xxix) according to SEQ ID NOs: 191 – 193; or
20 functional sequence variants 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; (xxx) according to SEQ ID NOs: 195 – 197; or functional sequence variants 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
25 least 98% or at least 99% sequence identity; (xxxi) according to SEQ ID NOs: 199 – 201; or functional sequence variants 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; (xxxii) according to SEQ ID NOs: 203 – 205; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least
30 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; (xxxiii) according to SEQ ID NOs: 207 – 209; or functional sequence variants 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; (xxxiv) according to SEQ ID NOs: 211 – 213; or functional sequence variants 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; (xxxv) according to SEQ ID NOs: 215 – 217; or functional sequence variants 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; (xxxvi) according to SEQ ID NOs: 219 – 221; or functional sequence variants 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; (xxxvii) according to SEQ ID NOs: 223 – 225; or functional sequence variants 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; (xxxviii) according to SEQ ID NOs: 227 – 229; or functional sequence variants 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; (xxxix) according to SEQ ID NOs: 231 – 233; or functional sequence variants 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; (xli) according to SEQ ID NOs: 239 – 241; or functional sequence variants 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; (xlii) according to SEQ ID NOs: 243 – 245; or functional sequence variants 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; (xliii) according to SEQ ID NOs: 247 – 249; or functional sequence variants 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; (xliv) according to SEQ ID NOs: 251 – 253; or

functional sequence variants 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; (xlv) according to SEQ ID NOs: 255 – 257; or functional sequence variants 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; or (xlvi) according to SEQ ID NOs: 259 – 261; or functional sequence variants 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.

Accordingly, it is also preferred that the antibody, or the antigen binding fragment thereof, according to the present invention comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 1 - 5 and 7; or functional sequence variants 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; (ii) according to SEQ ID NOs: 1 – 4 and 6 – 7; or functional sequence variants 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; (iii) according to SEQ ID NOs: 19 – 23 and 25; or functional sequence variants 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; (iv) according to SEQ ID NOs: 19 – 22 and 24 – 25; or functional sequence variants 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; (v) according to SEQ ID NOs: 37 – 41 and 43; or functional sequence variants 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; (vi) according to SEQ ID NOs: 37 – 40 and 42 – 43; or functional sequence variants 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; (vii) according to SEQ ID NOs: 55 – 59 and 61; or functional sequence variants 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; (viii) according to SEQ ID NOs: 55 – 58 and 60 – 61; or functional sequence variants 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; (ix) according to SEQ ID NOs: 73 – 77 and 79; or functional sequence variants 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; or (x) according to SEQ ID NOs: 73 – 76 and 78 – 79; or functional sequence variants 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.

More preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 1 - 5 and 7; or functional sequence variants 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; (ii) according to SEQ ID NOs: 1 – 4 and 6 – 7; or functional sequence variants 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; (iii) according to SEQ ID NOs: 19 – 23 and 25; or functional sequence variants 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; (iv) according to SEQ ID NOs: 19 – 22 and 24 – 25; or functional sequence variants 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; (v) according to SEQ ID NOs: 37 – 41 and 43; or functional sequence variants 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; (vi) according to SEQ ID NOs: 37 – 40 and 42 – 43; or functional sequence variants 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;(vii) according to SEQ ID NOs: 73 – 77 and 79; or functional sequence variants 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; or (viii) according to SEQ ID NOs: 73 – 76 and 78 – 79; or functional sequence variants 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.

10 Even more preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 1 - 5 and 7; or functional sequence variants 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%,
15 at least 98% or at least 99% sequence identity; (ii) according to SEQ ID NOs: 1 – 4 and 6 – 7; or functional sequence variants 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; (iii) according to SEQ ID NOs: 73 – 77 and 79; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%,
20 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; or (iv) according to SEQ ID NOs: 73 – 76 and 78 – 79; or functional sequence variants 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.

25 It is also preferred that preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 19 – 23 and 25; or functional sequence variants 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; (ii) according to SEQ ID NOs: 19 – 22 and 24 – 25; or functional sequence variants 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; (iii) according to SEQ ID NOs: 37 – 41 and 43; or functional sequence variants 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%,
5 at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (vi) according to SEQ ID NOs: 37 – 40 and 42 – 43; or functional sequence variants 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.
- 10 Still more preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 1 - 5 and 7; or functional sequence variants 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%,
15 at least 98% or at least 99% sequence identity; or (ii) according to SEQ ID NOs: 1 – 4 and 6 – 7; or functional sequence variants 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.
- 20 It is also preferred that the antibody, or the antigen binding fragment thereof, according to the present invention as described above comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 19 – 23 and 25; or functional sequence variants 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
25 least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (ii) according to SEQ ID NOs: 19 – 22 and 24 – 25; or functional sequence variants 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.
- 30 Most preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises

- 5 (a) a first epitope binding site comprising CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 1 - 5 and 7; or functional sequence variants 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; or (ii) according to SEQ ID NOs: 1 - 4 and 6 - 7; or functional sequence variants 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; and
- 10 (b) a second epitope binding site comprising CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 19 - 23 and 25; or functional sequence variants 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;
- 15 or (ii) according to SEQ ID NOs: 19 - 22 and 24 - 25; or functional sequence variants 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.
- 20 It is also preferred that the antibody, or the antigen binding fragment thereof, according to the present invention as described above comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 37 - 41 and 43; or functional sequence variants 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
- 25 least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (ii) according to SEQ ID NOs: 37 - 40 and 42 - 43; or functional sequence variants 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.
- 30 More preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises

- (a) a first epitope binding site comprising CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 1 - 5 and 7; or functional sequence variants 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; or (ii) according to SEQ ID NOs: 1 - 4 and 6 - 7; or functional sequence variants 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; and
- (b) a second epitope binding site comprising CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 37 - 41 and 43; or functional sequence variants 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; or (ii) according to SEQ ID NOs: 37 - 40 and 42 - 43; or functional sequence variants 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.
- In addition, it is also preferred that the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain variable region (VH) and, optionally, a light chain variable region (VL), wherein the heavy chain variable region (VH) comprises or consists of an amino acid sequence according to any of SEQ ID NOs: 8, 26, 44, 62, 80, 102, 106, 110, 114, 118, 122, 126, 130, 134, 138, 142, 146, 150, 154, 158, 162, 166, 170, 174, 178, 182, 186, 190, 194, 198, 202, 206, 210, 214, 218, 222, 226, 230, 234, 238, 242, 246, 250, 254, 258, and 262; or a functional 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.
- Moreover, it is also preferred that the antibody, or the antigen binding fragment thereof, according to the present invention comprises (i) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 8 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 9 or a functional 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; (ii) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 26 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 27 or a functional 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; (iii) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 44 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 45 or a functional 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; (iv) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 62 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 63 or a functional 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; or (v) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 80 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 81 or a functional 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.

More preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises (i) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 8 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 9 or a functional 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; (ii) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 26 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 27 or a functional 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; (iii) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 44 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 45 or a functional 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; or (iv) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 80 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 81 or a functional 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.

Even more preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises (i) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 8 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 9 or a functional 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; or (ii) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 80 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 81 or a functional 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.

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It is also preferred that the antibody, or the antigen binding fragment thereof, according to the present invention comprises (i) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 26 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 27 or a functional 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; or (ii) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 44 or a functional 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 and/or a light chain

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variable region (VL) amino acid sequence according to SEQ ID NO: 45 or a functional 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.

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Still more preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 8 or a functional 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%,
10 at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 9 or a functional 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.

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It is also preferred that the antibody, or the antigen binding fragment thereof, according to the present invention as described above comprises a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 26 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least
20 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 27 or a functional 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.

25

Most preferably, the antibody, or the antigen binding fragment thereof, according to the present invention as described above comprises

- (a) a first epitope binding site comprising a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 8 or a functional sequence variant thereof having
30 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 and/or a light chain variable region (VL) amino acid sequence

according to SEQ ID NO: 9 or a functional 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; and

- 5 (b) a second epitope binding site comprising a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 26 or a functional 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 and/or a light chain variable region (VL) amino acid sequence
10 according to SEQ ID NO: 27 or a functional 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.

- It is also preferred that the antibody, or the antigen binding fragment thereof, according to the
15 present invention as described above comprises a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 44 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 45
20 or a functional 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.

- More preferably, the antibody, or the antigen binding fragment thereof, according to the
25 present invention as described above comprises

- (a) a first epitope binding site comprising a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 8 or a functional 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 and/or a light chain variable region (VL) amino acid sequence
30 according to SEQ ID NO: 9 or a functional 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;
and
- (b) a second epitope binding site comprising a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 44 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 45 or a functional 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.

Particularly preferably, the antibody, or the antigen binding fragment thereof, according to the present invention is in the Fabs-in-tandem-Ig (FIT-Ig) format and the outer Fab of the FIT-Ig format comprises an epitope binding site comprising CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 1 - 5 and 7; or functional sequence variants 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; or (ii) according to SEQ ID NOs: 1 - 4 and 6 - 7; or functional sequence variants 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. More preferably, the outer Fab of the FIT-Ig format comprises an epitope binding site comprising a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 8 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 9 or a functional 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. Even more preferably, the inner Fab of the FIT-Ig format comprises an epitope binding site comprising CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 19 - 23 and 25; or functional sequence variants

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; or (ii) according to SEQ ID NOs: 19 – 22 and 24 – 25; or functional sequence variants 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. Still more preferably, the inner Fab of the FIT-Ig format comprises an epitope binding site comprising a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 26 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 27 or a functional 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.

Preferably, the antibody, or an antigen binding fragment thereof, according to the present invention is for use as a medicament. In other words, the antibody, or an antigen binding fragment thereof, according to the present invention may be used in the preparation of a medicament. More preferably, the antibody, or an antigen binding fragment thereof, according to the present invention is for use in the prevention and/or treatment of Zika virus infection. In other words, the antibody, or an antigen binding fragment thereof, according to the present invention may be used in the preparation of a medicament or use in the prevention and/or treatment of Zika virus infection. This aspect is described in more detail below.

25

Nucleic acid molecules

In another aspect, the invention also provides a nucleic acid molecule comprising at least one polynucleotide encoding the antibody, or the antigen binding fragment thereof, according to the present invention as described above or a fragment thereof, wherein the fragment comprises at least one CDR of the antibody, or the antigen binding fragment thereof.

30

A nucleic acid molecule is a molecule comprising, preferably consisting of nucleic acid components. The term nucleic acid molecule preferably refers to DNA or RNA molecules. In particular, it is used synonymous with the term "polynucleotide". Preferably, a nucleic acid molecule is a polymer comprising or consisting of nucleotide monomers which are covalently
5 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 the nucleic acid molecule according to the present invention, the encoded fragment of the
10 antibody or antigen binding fragment thereof according to the present invention comprises at least one CDR of the antibody, or the antigen binding fragment thereof. Tables 1 and 2 provide the SEQ ID numbers for the amino acid sequences of the CDRs and VH and VL of exemplary antibodies according to the present invention. Accordingly, the nucleic acid molecule according to the present invention preferably comprises a polynucleotide encoding one or
15 more of the amino acid sequences shown in Tables 1 and 2. Preferably, the encoded fragment of the antibody or antigen binding fragment thereof according to the present invention comprises three CDRs, more preferably all three heavy chain CDRs of an epitope binding site (CDRH1, CDRH2, CDRH3) and/or all three light chain CDRs of an epitope binding site (CDRL1, CDRL2, CDRL3). Accordingly, it is preferred that the encoded fragment of the
20 antibody or antigen binding fragment thereof comprises (exactly) three or six CDRs. Accordingly, the nucleic acid molecule according to the present invention preferably comprises a polynucleotide encoding three or six of the CDR amino acid sequences shown in Tables 1 and 2, in particular corresponding CDRH1, CDRH2, and CDRH3 sequences, and/or CDRL1, CDRL2, and CDRL3 sequences. More preferably, the encoded fragment of the
25 antibody or antigen binding fragment thereof comprises a variable region, for example a heavy chain variable region (VH) and/or a light chain variable region (VL). Accordingly, it is preferred that the encoded fragment of the antibody or antigen binding fragment thereof comprises (exactly) one or two variable regions. Accordingly, the nucleic acid molecule according to the present invention preferably comprises a polynucleotide encoding one or
30 two of the variable region amino acid sequences shown in Tables 1 and 2. Most preferably, the encoded fragment of the antibody or antigen binding fragment thereof comprises a (complete) polypeptide chain of the antibody or antigen binding fragment thereof according

to the present invention. Such a (complete) polypeptide chain may be, for example, a (complete) heavy chain or a (complete) light chain. However, such a (complete) polypeptide chain may also comprise both, heavy and light chain elements, which is known in the art for many multispecific antibody formats (e.g., polypeptide chains comprising heavy chain
5 constant regions, but also, e.g. in addition to one or more heavy chain variable region(s), a light chain variable region).

The nucleic acid molecule may be mono-, bi-, or multicistronic, such as tricistronic. A bicistronic or multicistronic nucleic acid molecule is typically a nucleic acid molecule that
10 typically may have two (bicistronic) or more (multicistronic) open reading frames (ORFs). An open reading frame in this context is a sequence of codons that is translatable into a peptide or protein. More generally, the nucleic acid molecule of the present invention contains at least one polynucleotide coding for at least one antibody, or antigen binding fragment thereof, according to the present invention. If more the nucleic acid molecule according to the present
15 invention comprises more than one coding polynucleotide, the second, third etc. coding polynucleotide may code for other peptides/proteins and/or may code for antibodies, e.g. according to the present invention, or fragments thereof as well, which may be the same or distinct from the first antibody coding region. In a preferred embodiment, the inventive nucleic acid molecule contains at least two coding polynucleotides, for example (exactly)
20 two or three coding polynucleotides, all of them coding for identical or distinct antibodies or fragments or variants thereof. For example, distinct fragments of an antibody, or an antigen binding fragment thereof, according to the present invention may be encoded by different polynucleotides on the same nucleic acid molecule. In still another embodiment of the present invention, an inventive nucleic acid molecule may code for more than one antibody
25 or a fragment of an antibody within the same coding region. In summary, the inventive nucleic acid molecule may be mono-, bi- or multicistronic.

For example, in one preferred embodiment, the antibody, or the antigen binding fragment thereof, according to the present invention may be a single chain antibody. In this case, it is
30 preferred that the complete single chain of the antibody or the antigen binding fragment thereof is encoded by one single polynucleotide. Accordingly, it is preferred that the nucleic acid molecule according to the present invention is monocistronic, in particular it may

comprise one (single) polynucleotide encoding the antibody, or the antigen binding fragment thereof, according to the present invention.

It is also preferred that the antibody, or the antigen binding fragment thereof, according to the present invention comprises (exactly) two distinct polypeptide chains, such as, for example, a heavy chain and a light chain. This may be illustrated by a classical native IgG molecule, which comprises two identical heavy chains and two identical light chains and, thus, two distinct polypeptide chains (even though the antibody finally comprises four polypeptide chains, they may be encoded by two (distinct) polynucleotides). Preferably, such two distinct polypeptide chains (e.g., a heavy chain and a light chain) of the antibody, or the antigen binding fragment thereof, according to the present invention may be encoded by two distinct polynucleotides, which may be located on the same nucleic acid molecule, e.g. in a bicistronic nucleic acid molecule, or on (exactly two) distinct nucleic acid molecules (e.g., each nucleic acid molecule may be monocistronic). Accordingly, it is preferred that the nucleic acid molecule according to the present invention is bicistronic, in particular it may comprise (exactly) two polynucleotides encoding (together) the antibody, or the antigen binding fragment thereof, according to the present invention. It is also preferred that the nucleic acid molecule according to the present invention comprises (at least or exactly) one polynucleotide encoding a fragment of the antibody, or the antigen binding fragment thereof, according to the present invention, as described above (e.g., a (complete) polypeptide chain). Accordingly, it is preferred that the nucleic acid molecule according to the present invention is monocistronic. Moreover, the antibody, or the antigen binding fragment thereof, according to the present invention may be encoded by a plurality of (e.g., monocistronic) nucleic acid molecules. For example, an antibody comprising two distinct polypeptide chains may be encoded by two polynucleotides located on two distinct nucleic acid molecules.

It is also preferred that the antibody, or the antigen binding fragment thereof, according to the present invention comprises (exactly) three distinct polypeptide chains. Accordingly, it is preferred that the nucleic acid molecule is tricistronic (e.g., encoding all three polypeptide chains comprised in such an antibody, or the antigen binding fragment thereof, according to the present invention). However, it is also preferred that the nucleic acid molecule is mono- or bicistronic, for example encoding one single or two polypeptide chains comprised in such

an antibody, or the antigen binding fragment thereof, according to the present invention. For example, a plurality of nucleic acid molecules, such as two or three nucleic acid molecules, may encode (together) the antibody, or the antigen binding fragment thereof, according to the present invention.

5

For example, the antibody, or the antigen binding fragment thereof, according to the present invention is particularly preferably in the Fabs-in-tandem-Ig (FIT-Ig) format, which usually comprises the following three polypeptide chains:

- 10 — Polypeptide 1 comprising or consisting of the light chain of the outer Fab and the heavy chain of the inner Fab including the constant domains CH1-CH2-CH3, preferably with the "LALA" mutation as described above, wherein preferably the light chain of the outer Fab is fused, preferably without linkers, to the N-terminus of the heavy chain of the inner Fab;
- 15 — Polypeptide 2 comprising or consisting of the heavy chain of the outer Fab (VH and CH1 of the outer Fab); and
- Polypeptide 3 comprising or consisting of the light chain of the inner Fab.

Accordingly, such a FIT-Ig may preferably be encoded by one (e.g., tricistronic) nucleic acid molecule, by three (e.g., monocistronic) nucleic acid molecule, or by two (e.g., one monocistronic, one bicistronic) nucleic acid molecules.

20

Accordingly, it is preferred that the nucleic acid molecule according to the present invention comprises a polynucleotide encoding polypeptide 1 of a FIT-Ig antibody according to the present invention. More preferably, the nucleic acid molecule does not comprise polynucleotides encoding polypeptide 2 or polypeptide 3 of the FIT-Ig antibody according to the present invention. Such a nucleic acid molecule is preferably monocistronic.

25

It is also preferred that the nucleic acid molecule according to the present invention comprises a polynucleotide encoding polypeptide 2 of a FIT-Ig antibody according to the present invention. More preferably, the nucleic acid molecule does not comprise polynucleotides encoding polypeptide 1 or polypeptide 3 of the FIT-Ig antibody according to the present invention. Such a nucleic acid molecule is preferably monocistronic.

30

It is also preferred that the nucleic acid molecule according to the present invention comprises a polynucleotide encoding polypeptide 3 of a FIT-Ig antibody according to the present invention. More preferably, the nucleic acid molecule does not comprise polynucleotides encoding polypeptide 1 or polypeptide 2 of the FIT-Ig antibody according to the present invention. Such a nucleic acid molecule is preferably monocistronic.

It is also preferred that the nucleic acid molecule according to the present invention comprises a polynucleotide encoding polypeptide 1 and a polynucleotide encoding polypeptide 2 of a FIT-Ig antibody according to the present invention. More preferably, the nucleic acid molecule does not comprise a polynucleotide encoding polypeptide 3 of the FIT-Ig antibody according to the present invention. Such a nucleic acid molecule is preferably bicistronic.

It is also preferred that the nucleic acid molecule according to the present invention comprises a polynucleotide encoding polypeptide 1 and a polynucleotide encoding polypeptide 3 of a FIT-Ig antibody according to the present invention. More preferably, the nucleic acid molecule does not comprise a polynucleotide encoding polypeptide 2 of the FIT-Ig antibody according to the present invention. Such a nucleic acid molecule is preferably bicistronic.

It is also preferred that the nucleic acid molecule according to the present invention comprises a polynucleotide encoding polypeptide 2 and a polynucleotide encoding polypeptide 3 of a FIT-Ig antibody according to the present invention. More preferably, the nucleic acid molecule does not comprise a polynucleotide encoding polypeptide 1 of the FIT-Ig antibody according to the present invention. Such a nucleic acid molecule is preferably bicistronic.

Particularly preferably, the nucleic acid molecule according to the present invention comprises a polynucleotide encoding polypeptide 1, a polynucleotide encoding polypeptide 2 and a polynucleotide encoding polypeptide 3 of a FIT-Ig antibody according to the present invention. Such a nucleic acid molecule is preferably tricistronic.

In general, the nucleic acid molecule may be a DNA molecule or an RNA molecule. Examples of nucleic acid molecules and/or polynucleotides include, e.g., a recombinant polynucleotide, a vector, an oligonucleotide, an RNA molecule such as an rRNA, an mRNA,

an miRNA, an siRNA, or a tRNA, or a DNA molecule such as a cDNA. Preferably, the nucleic acid molecule is a DNA plasmid or an mRNA molecule. A DNA plasmid is a circular, preferably double-stranded, DNA molecule.

- 5 Table 3 below provides the SEQ ID numbers for exemplary nucleic acid sequences encoding the CDRs and VH and VL of exemplary antibodies according to the present invention. Due to the redundancy of the genetic code, the present invention also comprises sequence variants of these nucleic acid sequences and in particular such sequence variants, which encode the same amino acid sequences.

10

Table 3 shows exemplary nucleic acid sequences of the CDR's and the heavy chain variable region (VH) and the light chain variable region (VL) of five exemplary antibodies ("ZKA190", "ZKA64", "ZKA230", "ZKA185", "ZKA78"):

ZKA190	SEQ ID NO.	Nucleic acid sequence
CDRH1	10	ggattcaccttcagtaaatatggc
CDRH2	11	atatcatatgaggggaagtaataaa
CDRH3	12	gcgaaatcggggacccaatactatgatactactggttatg agtataggggtttggaatacttttggtac
CDRL1	13	cagagtgttagtagcagttac
CDRL2	14	gatgcatcc
CDRL2 long	15	ctcatctat gatgcatcc agcagggcc
CDRL3	16	cagcagtatggtaggtcaaggtggaca
VH	17	caggtgcagctggtggagtctgggggaggcgtggtccagc ctgggaggtccctgagactctcctgtgcagcctct ggatt caccttcagtaaatatggc atgcactgggtccgccaggct ccaggcaaggggctggagtgggtggcagtt atatcatatg agggaagtaataaa tattatgcagactccgtgaagggccg attcaccatctccagagacaattccaagaacacgctgtat ctgcaaatgaacagcctgagagctgaggacacggcagtg attactgt gcgaaatcggggacccaatactatgatactac

		tggttatgagtataggggtttggaatactttggctactgg ggccagggaaccctgggtcaccgtctcctcag
VL	18	gaaattgtgttgacgcagtcctccaggcacccctgtctttgt ctccaggggaaagagccaccctctcctgcaggggcagtc ca gagtgttagtagcagttac ttagcctggtagccagcagaaa cgtggccaggctcccaggctcctcatctat gatgcattcca gcaggggccactggcatcccagacaggttcagtggcagtg gtctgggacagacttcactctcaccatcagcagactggag cctgaagattttgcagtgtattactgt cagcagtatggta ggtcaagggtggaca ttcggccaagggaaccaagggtgaaat caaac
ZKA185	SEQ ID NO.	Nucleic acid sequence
CDRH1	28	ggatatagttttaccagttactgg
CDRH2	29	tttgatcctagtgactctcaaacc
CDRH3	30	gcgagaagatattgtagtagtagtagttgttatgtggaca at
CDRL1	31	gcattgccaataaaattt
CDRL2	32	gaggacaac
CDRL2 long	33	gtcatctat gaggacaac aaacgaccc
CDRL3	34	tactcaacagacagcagtttctaatacccctgggagta
VH	35	gaagtgcagctgggtgcagtcgggagcagaggtgaaaaagc ccggggagtccttgaggatctcctgtaagggttct ggata tagttttaccagttactgg atcacctgggtgcgccagatg cccgggaaaggcctggagtggatggcgaag tttgatccta gtgactctcaaacca aactacagccgtccttccaaggcca cgtcaccatctcagttgacaagtccatcagcactgcctac ttgcagtggagcagcctgaaggcctcggaacccgcatgt attactgt gcgagaagatattgtagtagtagtagttgtta

		tgtggacaatt ggggccaggggaaccctgggtcaccatcttc tcag
VL	36	tcctatgagctgacacagccaccctcggtgtcagtggtccc caggacaaacggccaggatcacctgctctggagat gcatt gccaataaaattt gcttattgggtaccggcagaagtcaggc caggccctgttctgggtcatctat gaggacaacaaacgac cctccgggatccctgagagattctctgggtccagctcagg gacaatggccaccttgactatcagtggggcccagggtggag gatgaagctgactaccactgt tactcaacagacagcagtt ctaataccctgggagta ttcggcggagggaaccaagctgac cgtcctag
ZKA230	SEQ ID NO.	Nucleic acid sequence
CDRH1	46	ggtggctccatcagtagtgactac
CDRH2	47	atctattacagtgaggagcacc
CDRH3	48	gcgaggaggaggaagtatgattccctttgggggagttttg cttttgataatc
CDRL1	49	agctccaacatcggaggtaattat
CDRL2	50	attaatgat
CDRL2 long	51	ctcatctgt attaatgat caccggccc
CDRL3	52	gcaacatgggatgacagccctgggtggccttgta
VH	53	cagggtgcagctgcaggagtcgggcccaggcctgggtgaagc cttcggagaccctgtccctcacctgcgcagtcctct ggtgg ctccatcagtagtgactact ggagctggatccggcagccc ccagggaagggactggagtggattgggtat atctattaca gtgggagcacca actacaacccctccctcaagagtcgagt caccatatcagtagacacgtccaagaaccacttctccctg aagctgaactctgtgaccgctgaggacacggccgtgtatt actgt gcgaggaggaggaagtatgattccctttgggggag ttttgcttttgata tctggggccaagggaacaatggtcacc gtctcttcag
VL	54	cagtctgtgctgactcagccaccctcagcgtctgggaccc ccgggcagaggggtcaccatctcttgttctggaag cagctc caacatcggaggtaattat gtatactggtaccagcagctc ccagggaacggcccccaactcctcatctgt attaatgatc

		accggccctcaggggtccctgaccgattctctggetccaa gtctggcacctcagcctccctggccatcagtggggtccag tccgaggatgaggctgattattactgt gcaacatgggatg acagcctgggtggccttgta ttcggcggagggaccaagct gaccgtcctag
ZKA78	SEQ ID NO.	Nucleic acid sequence
CDRH1	64	ggcttcacttttagtaactatgca
CDRH2	65	atcgggcgcaacgggactctatc
CDRH3	66	gtgaaagatctggccatccccgagtcctacagaattgaag ctgattat
CDRL1	67	cagtcogtgctgtaccgctctaacaacaagaattac
CDRL2	68	tgggcttca
CDRL2 long	69	ctgatctat tgggcttca accgggaa
CDRL3	70	cagcagtactattctagtcctcgaact
VH	71	gaggtgcagctggcagaatcaggcgggggactgggtccagc ctggcggcagcctgacactgtcttgacagtggatcag ggctt cacttttagtaactatgca atgggtgtgggcaaggcaggct cctgggaagggactggagtatgtctctggc atcggggcgca acggggactctatc tactatactgatagtgtgaagggccg gttcaccatcagcagagacaatagcaaattccatgggtgtac ctgcagatgagctccctgcgaaccgaagacacagcagtg actattgc gtgaaagatctggccatccccgagtcctacag aattgaagctgattat tggggacagggcaccctgggtcatc gtgagcgccg
VL	72	gacatcgtgatgacacagtctccagatagtctggcagtca gtctgggggagagggccactattaactgcaagagctcc ca gtccgtgctgtaccgctctaacaacaagaattac ctgtct tggtatcagcagaagcccgacagccccctaaactgtga tctat tgggcttca accgggaaagcggcgtcccagacag attctcaggcagcgggtccggaacagacttcaccctgaca attagccccctgcaggcagaggacgtggctgtctactatt gt cagcagtactattctagtcctcgaact ttcggccaggg gaccaaggtggaaatcaaac
ZKA64	SEQ ID NO.	Nucleic acid sequence

CDRH1	82	ggctacaccttcacagggatcac
CDRH2	83	attaaccctaattctggcgggacc
CDRH3	84	gctcggatgagctcctctatcttggggcttcgatcat
CDRL1	85	cagtctgtgctgattaac
CDRL2	86	ggagcatcc
CDRL2 long	87	ctgatctat ggagcatcct ccagggct
CDRL3	88	cagcagtacaatgattggccccctatcaca
VH	89	caggtgcagctgggtccagagcggagcagaggtgaagaaac ccggcgccctcagtgaaggtcagctgcaaagcttcc ggcta caccttcacagggatcac atcgactgggtgaggcaggca agaggacagggactggaatggatgggacgg attaacccta attctggcgggacca actacgccagaagtttcagggccg agtgactatgaccagagacaccagcatctccacagcttat atgcagctgtcccggctgagatctgacgatagtgcggtct actattgt gctcggatgagctcctctatcttggggcttcga tcat tgggggacaggggaactgggtgactgtcagttcag
VL	90	gagatcgtgatgactcagtctccagccaccctgtcagtc gcccaggagaacgggcaaccctgtcttgagagcctcc ca gtctgtgctgattaac ctggcttgggtaccagcagaagcca ggccaggcaccgccgactgctgatctat ggagcatcctcca gggctaccggcattcctgcacgcttcagtggatcaggaag cggaacagagtttacccctgacaatctctagtctgcagtc gaagacttcgctgtctactattgt cagcagtacaatgatt ggccccctatcaca tttggccaggggactagactggagat caagc

Preferably, the sequence of the nucleic acid molecule according to the present invention comprises or consists of a nucleic acid sequence according to any one of SEQ ID NOs: 10 – 18, 28 – 36, 46 – 54, 64 – 72, and 82 – 90; or a functional sequence variant thereof.

It is also preferred that nucleic acid sequences according to the invention include nucleic acid sequences 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%

identity to the nucleic acid encoding a CDR, a VH sequence and/or a VL sequence shown in Tables 1 and 2, for example to the sequences shown in Table 3.

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). 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 CDR regions, a VH sequence and/or a VL sequence of an (exemplary) antibody of the invention 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. Different properties introduced into the encoded amino acids may include, but are not limited to, enhanced affinity.

In a further aspect, the present invention also provides a plurality of nucleic acid molecules as described above, wherein each nucleic acid molecule comprises at least one polynucleotide encoding a fragment of the antibody, or of the antigen binding fragment thereof, according to the present invention, as described above. Preferably, the plurality of fragments encoded by the plurality of nucleic acid molecules forms an antibody, or an antigen binding fragment thereof, according to the present invention. In other words, it is preferred that the plurality of nucleic acid molecules according to the present invention encodes the (complete) antibody, or the (complete) antigen binding fragment thereof, according to the present invention. This means that, in particular, no further nucleic acid molecules (in addition to the plurality of nucleic acid molecules according to the present invention) are

required to encode/produce the (complete) antibody, or the (complete) antigen binding fragment thereof, according to the present invention. For example, the plurality of nucleic acid molecules according to the present invention, encodes all polypeptide chains of an antibody, or of an antigen binding fragment thereof, according to the present invention.

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A preferred example of the plurality of nucleic acid molecules according to the present invention are (exactly) two nucleic acid molecules, wherein each of the nucleic acid molecules comprises one single or more than one (e.g., two or three) polynucleotides, each polynucleotide encoding a (distinct) polypeptide chain of the antibody, or of the antigen binding fragment thereof, according to the present invention. Accordingly, the nucleic acid molecules of such a plurality of nucleic acid molecules are preferably mono- or bicistronic. An example thereof are two nucleic acid molecules encoding together a FIT-Ig antibody according to the present invention as described above (e.g., one bicistronic nucleic acid molecule combined with the corresponding monocistronic nucleic acid molecule, such that polypeptides 1, 2 and 3 of the FIT-Ig are encoded by the two nucleic acid molecules; as described above).

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In another preferred example, the present invention provides (exactly) three nucleic acid molecules, wherein each of the nucleic acid molecules comprises one (single) polynucleotide encoding a (distinct) polypeptide chain of the antibody, or of the antigen binding fragment thereof, according to the present invention. Accordingly, the nucleic acid molecules of such a plurality of nucleic acid molecules are preferably monocistronic. An examples thereof are three nucleic acid molecules encoding together a FIT-Ig antibody according to the present invention as described above (e.g., three (e.g., monocistronic) nucleic acid molecules, one encoding polypeptide 1 of the FIT-Ig, another encoding polypeptide 2 of the FIT-Ig, and the third encoding polypeptide 3 of the FIT-Ig; as described above).

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Vector

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

The term "vector" refers to a nucleic acid molecule, preferably to a recombinant nucleic acid molecule, i.e. a nucleic acid molecule which does not occur in nature. A vector in the context of the present invention is suitable for incorporating or harboring a desired nucleic acid
10 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 comprise a sequence corresponding, e.g., to a desired antibody or antibody fragment thereof according to the present invention. An expression vector may be used for production of expression products such as RNA, e.g. mRNA, or
15 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 promoter sequence. A cloning 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
20 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. Preferably, a vector is a DNA molecule, such as a DNA plasmid. For example, 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
25 an origin of replication. Preferably, a vector in the context of the present application is a plasmid vector.

In a further aspect, the present invention also provides a plurality of vectors according to the present invention, preferably encoding the antibody, or the antigen binding fragment thereof,
30 according to the present invention. Accordingly, preferred embodiments and examples of the plurality of nucleic acid molecules according to the present invention as described above also apply for the plurality of vectors according to the present invention.

Cells

In a further aspect, the present invention also provides cell expressing the antibody, or the antigen binding fragment thereof, according to the present invention; and/or comprising the vector according to the present invention or the plurality of vectors according to the present invention.

Examples of such cells include but are not limited to, eukaryotic cells, e.g., yeast cells, animal cells or plant cells. Preferably, the cells are mammalian cells, more preferably a mammalian cell line. Preferred examples include human cells, CHO cells, HEK293T cells, PER.C6 cells, NS0 cells, human liver cells, myeloma cells or hybridoma cells.

In particular, the cell may be transfected with the vector according to the present invention or with the plurality of vectors according to the present invention, preferably with an expression vector or a plurality thereof. The term "transfection" refers to the introduction of nucleic acid molecules, such as DNA or RNA (e.g. mRNA) molecules, into cells, preferably into eukaryotic 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, preferably into eukaryotic cells, 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. Preferably, the introduction is non-viral.

Moreover, the cells of the present invention may be transfected stably or transiently with the vector according to the present invention or with the plurality of vectors according to the present invention, e.g. for expressing the antibody, or the antigen binding fragment thereof, according to the present invention. Preferably, the cells are stably transfected with the vector according to the present invention or with the plurality of vectors according to the present invention encoding the antibody, or the antigen binding fragment thereof, according to the present invention. Alternatively, it is also preferred that the cells are transiently transfected with the vector according to the present invention or with the plurality of vectors according

to the present invention encoding the antibody, or the antigen binding fragment thereof, according to the present invention.

5 *Optional additional features of the antibodies*

Antibodies of the invention may be coupled, for example, to a drug for delivery to a treatment site or coupled to a detectable label to facilitate imaging of a site comprising cells of interest. Methods for coupling antibodies to drugs and detectable labels are well known in the art, as
10 are methods for imaging using detectable labels. Labeled antibodies may be employed in a wide variety of assays, employing a wide variety of labels. Detection of the formation of an antibody-antigen complex between an antibody of the invention and an epitope of interest can be facilitated by attaching a detectable substance to the antibody. Suitable detection means include the use of labels such as radionuclides, enzymes, coenzymes, fluorescers,
15 chemiluminescers, chromogens, enzyme substrates or co-factors, enzyme inhibitors, prosthetic group complexes, free radicals, particles, dyes, and the like. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β -galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include
20 umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material is luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{35}S , or ^3H . Such labeled reagents may be used in a variety of well-known assays, such as radioimmunoassays, enzyme
25 immunoassays, e.g., ELISA, fluorescent immunoassays, and the like. Labeled antibodies according to the present invention may be thus be used in such assays for example as described in US 3,766,162; US 3,791,932; US 3,817,837; and US 4,233,402.

An antibody according to the invention may be conjugated to a therapeutic moiety such as a
30 cytotoxin, a therapeutic agent, or a radioactive metal ion or radioisotope. Examples of radioisotopes include, but are not limited to, ^{131}I , ^{125}I , ^{90}Y , ^{188}Re , ^{186}Re , ^{211}At , ^{67}Cu , ^{212}Bi , ^{213}Bi , ^{109}Pd , ^{99}Tc , ^{111}In , and the like. Such antibody conjugates

can be used for modifying a given biological response; the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin.

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Techniques for conjugating such therapeutic moiety to antibodies are well known. See, for example, Arnon et al. (1985) "Monoclonal Antibodies for Immunotargeting of Drugs in Cancer Therapy," in *Monoclonal Antibodies and Cancer Therapy*, ed. Reisfeld et al. (Alan R. Liss, Inc.), pp. 243-256; ed. Hellstrom et al. (1987) "Antibodies for Drug Delivery," in *Controlled Drug Delivery*, ed. Robinson et al. (2d ed; Marcel Dekker, Inc.), pp. 623-653; Thorpe (1985) "Antibody Carriers of Cytotoxic Agents in Cancer Therapy: A Review," in *Monoclonal Antibodies '84: Biological and Clinical Applications*, ed. Pinchera et al. pp. 475-506 (Editrice Kurtis, Milano, Italy, 1985); "Analysis, Results, and Future Prospective of the Therapeutic Use of Radiolabeled Antibody in Cancer Therapy," in *Monoclonal Antibodies for Cancer Detection and Therapy*, ed. Baldwin et al. (Academic Press, New York, 1985), pp. 303-316; and Thorpe et al. (1982) *Immunol. Rev.* 62:119-158.

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Alternatively, an antibody, or antibody fragment thereof, can be conjugated to a second antibody, or antibody fragment thereof, to form an antibody heteroconjugate as described in US 4,676,980. In addition, linkers may be used between the labels and the antibodies of the invention, *e.g.*, as described in US 4,831,175. Antibodies or, antigen-binding fragments thereof may be directly labeled with radioactive iodine, indium, yttrium, or other radioactive particle known in the art, *e.g.*, as described in US 5,595,721. Treatment may consist of a combination of treatment with conjugated and non-conjugated antibodies administered simultaneously or subsequently *e.g.*, as described in WO00/52031; WO00/52473.

25

Antibodies of the invention may also be attached to a solid support. Additionally, antibodies of the invention, or functional antibody fragments thereof, can be chemically modified by covalent conjugation to a polymer to, for example, increase their circulating half-life. Examples of polymers, and methods to attach them to peptides, are shown in US 4,766,106; US 4,179,337; US 4,495,285 and US 4,609,546. In some embodiments the polymers may be selected from polyoxyethylated polyols and polyethylene glycol (PEG). PEG is soluble in

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water at room temperature and has the general formula: $R(O-CH_2-CH_2)_nO-R$, wherein R can be hydrogen, or a protective group such as an alkyl or alkanol group. Preferably, the protective group may have between 1 and 8 carbons. For example, the protective group is methyl. The symbol n is a positive integer. In one embodiment n is between 1 and 1,000. In
5 another embodiment n is between 2 and 500. Preferably, the PEG has an average molecular weight between 1,000 and 40,000, more preferably the PEG has a molecular weight between 2,000 and 20,000, even more preferably the PEG has a molecular weight between 3,000 and 12,000. Furthermore, PEG may have at least one hydroxy group, for example the PEG may have a terminal hydroxy group. For example, it is the terminal hydroxy group which is
10 activated to react with a free amino group on the inhibitor. However, it will be understood that the type and amount of the reactive groups may be varied to achieve a covalently conjugated PEG/antibody of the present invention.

Water-soluble polyoxyethylated polyols are also useful in the present invention. They include
15 polyoxyethylated sorbitol, polyoxyethylated glucose, polyoxyethylated glycerol (POG), and the like. In one embodiment, POG is used. Without being bound by any theory, because the glycerol backbone of polyoxyethylated glycerol is the same backbone occurring naturally in, for example, animals and humans in mono-, di-, triglycerides, this branching would not necessarily be seen as a foreign agent in the body. POG may have a molecular weight in the
20 same range as PEG. Another drug delivery system that can be used for increasing circulatory half-life is the liposome. Methods of preparing liposome delivery systems are known to one of skill in the art. Other drug delivery systems are known in the art and are described in, for example, referenced in Poznansky et al. (1980) and Poznansky (1984).

25 Antibodies of the 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.

30 Antibodies of the invention may be immunogenic in non-human (or heterologous) hosts *e.g.*, in mice. In particular, the antibodies may have an idiotope that is immunogenic in non-human hosts, but not in a human host. In particular, 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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Pharmaceutical Composition

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

- 10 (i) the antibody, or the antibody fragment thereof, according to the present invention;
- (ii) the nucleic acid molecule or the plurality of nucleic acid molecules according to the present invention;
- (iii) the vector or the plurality of vectors according to the present invention; and/or
- (iv) the cell according to the present invention.

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In other words, the present invention also provides a pharmaceutical composition comprising the antibody, or the antigen binding fragment thereof, according to the present invention, the nucleic acid molecule according to the present invention, the plurality of nucleic acid molecules according to the present invention, the vector according to the present invention,
20 the plurality of vectors according to the present invention and/or the cell according to the present invention.

The pharmaceutical composition may preferably also contain a pharmaceutically acceptable carrier, diluent and/or excipient. Although the carrier or excipient may facilitate
25 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, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers and inactive virus particles. In general, pharmaceutically acceptable carriers in a
30 pharmaceutical composition according to the present invention may be active components or inactive components. Preferably, the pharmaceutically acceptable carrier in a

pharmaceutical composition according to the present invention is not an active component in respect to Zika virus infection.

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 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.

Pharmaceutical compositions of the invention 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 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 in kit form with sterile water or a sterile buffer.

It is preferred that the active ingredient in the composition is an antibody molecule, an antibody fragment or variants and derivatives thereof, in particular the active ingredient in the composition is an antibody, an antibody fragment or variants and derivatives thereof, according to the present invention. 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 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.

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

Pharmaceutical compositions of the invention generally have a pH between 5.5 and 8.5, in
10 some embodiments this may be between 6 and 8, and in other embodiments 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 one embodiment pharmaceutical compositions of the invention are supplied in hermetically-sealed containers.

15 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
20 suspending, preservative, stabilizing and/or dispersing agents. Alternatively, the antibody molecule 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 antibodies according to the present invention. For example, the vehicle may be a
25 physiologically acceptable liquid, which is suitable for storing, transporting, and/or administering a pharmaceutically active compound, in particular the antibodies according to the present invention. Once formulated, the compositions of the invention can be administered directly to the subject. In one embodiment the compositions are adapted for administration to mammalian, e.g., human subjects.

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The pharmaceutical compositions of this invention 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. Hyposprays may also be used to administer the pharmaceutical compositions of the invention. Preferably, the pharmaceutical composition may be prepared for oral
5 administration, e.g. as tablets, capsules and the like, for topical administration, or as injectable, e.g. as liquid solutions or suspensions, whereby it is particularly preferred that the pharmaceutical composition is an injectable. Solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection are also preferred, e.g. that the pharmaceutical composition is in lyophilized form.

10 For injection, e.g. intravenous, cutaneous or subcutaneous injection, or injection at the site of affliction, the active ingredient will preferably 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,
15 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 a polypeptide, peptide, or nucleic acid molecule, other pharmaceutically useful compound according to the present invention that is to be given to an individual, administration is preferably in a "prophylactically effective amount" or a
20 "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. For injection, the pharmaceutical composition according to the present invention may be provided for example in a pre-filled syringe.

25 The inventive pharmaceutical composition as defined above 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
30 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 inventive transporter cargo conjugate molecule as defined above, is combined with

emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

The inventive pharmaceutical composition may also be administered topically, especially
5 when the target of treatment includes areas or organs readily accessible by topical application, e.g. including diseases of the skin or of any other accessible epithelial tissue. Suitable topical formulations are readily prepared for each of these areas or organs. For topical applications, the inventive pharmaceutical composition may be formulated in a suitable ointment, containing the inventive pharmaceutical composition, particularly its components
10 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 inventive pharmaceutical composition can be formulated in a suitable lotion or cream. In the context of the present invention, suitable carriers include,
15 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. In particular, the pharmaceutical composition may be provided as single-dose product. Preferably, the
20 amount of the antibody in the pharmaceutical composition – in particular if provided as single-dose product – does not exceed 200 mg, more preferably does not exceed 100 mg, and even more preferably does not exceed 50 mg.

For example, the pharmaceutical composition according to the present invention may be
25 administered daily, e.g. once or several times per day, e.g. once, twice, three times or four times per day, preferably once or twice per day, more preferable once per day, for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 or more days, e.g. daily for 1, 2, 3, 4, 5, 6 months. Preferably, the pharmaceutical composition according to the present invention may be administered weekly, e.g. once or twice per week, for 1, 2, 3, 4, 5, 6, 7, 8,
30 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 or more weeks, e.g. weekly for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months or weekly for 2, 3, 4, or 5 years. Moreover, the pharmaceutical composition according to the present invention may be preferably

administered monthly, e.g. once per month or, more preferably, every second month for 1, 2, 3, 4, or 5 or more years. It is also preferred that the administration continues for the lifetime. In addition, also one single administration only is also envisaged, in particular in respect to certain indications, e.g. for prevention of Zika virus infection in case of accidental exposure, 5 e.g. in non-immunised subjects. However, the most preferred treatment schedule is post-exposure prophylaxis (PEP), wherein one or more single doses are administered as soon as possible after Zika infection. A prophylactic setting, wherein one or more single doses are administered to prevent Zika infection (i.e. before Zika infection, in particular in non-Zika-immunised subjects) is also preferred.

10

In particular, it is preferred that for a single dose, e.g. a daily, weekly or monthly dose, preferably for a weekly dose, the amount of the antibody, or the antigen binding fragment thereof, in the pharmaceutical composition according to the present invention, does not exceed 1 g, preferably does not exceed 500 mg, more preferably does not exceed 200 mg, 15 even more preferably does not exceed 100 mg, and particularly preferably does not exceed 50 mg.

Pharmaceutical compositions typically include an "effective" amount of one or more antibodies of the invention, i.e. an amount that is sufficient to treat, ameliorate, attenuate or 20 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 25 situation is determined by routine experimentation and is within the judgment of a clinician. For purposes of the present invention, an effective dose will generally be from about 0.005 to about 100 mg/kg, preferably from about 0.0075 to about 50 mg/kg, more preferably from about 0.01 to about 10 mg/kg, and even more preferably from about 0.02 to about 5 mg/kg, of the antibody of the present invention (e.g. amount of the antibody in the pharmaceutical 30 composition) in relation to the bodyweight (e.g., in kg) of the individual to which it is administered.

Moreover, the pharmaceutical composition according to the present invention may also comprise an additional active component, which may be a further antibody or a component, which is not an antibody. The additional active component is preferably a checkpoint inhibitor. It is also preferred that a ZIKV neutralizing antibody, or an antigen binding fragment thereof, as described herein is combined with a ZIKV NS1-binding antibody, or an antigen binding fragment thereof, as described herein as additional active component (co-agent). Thereby, the pathogenic role of NS1 may be blocked in addition to neutralization of ZIKV. The pharmaceutical composition according to the present invention may comprise one or more of the additional active components, e.g. as described as co-agents below in the context of a combination therapy.

The antibody, or the antigen binding fragment, according to the present invention can be present either in the same pharmaceutical composition as the additional active component or, preferably, the antibody, or the antigen binding fragment, according to the present invention is comprised by a first pharmaceutical composition and the additional active component is 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 antibody, or the antigen binding fragment, according to the present invention is preferably comprised by 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).

Preferably, antibody, or the antigen binding fragment, according to the present invention and the additional active component provide an additive therapeutic effect or, preferably, 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.

5 A pharmaceutical composition comprising the antibody according to gZKA190, gZKA64, gZKA230, gZKA185, gZKA78 or an antigen binding fragment thereof, and a pharmaceutically acceptable carrier is preferred.

10 In one embodiment, a composition of the invention may include 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 such a composition, the antibodies are preferably in purified form.

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

20 In another embodiment, a method of preparing a pharmaceutical composition comprises the step of: admixing an antibody with one or more pharmaceutically-acceptable carriers, wherein the antibody is a monoclonal antibody that was obtained from a transformed B cell or a cultured plasma cell of the invention.

25 As an alternative to delivering antibodies or B cells for therapeutic purposes, it is possible to deliver nucleic acid (typically DNA) that encodes the monoclonal antibody (or active fragment thereof) of interest derived from the B cell or the cultured plasma cells 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.

30 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
5 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.

10 The compositions of the invention may also comprise one or more immunoregulatory agents.
In one embodiment, one or more of the immunoregulatory agents include(s) an adjuvant.

Medical Treatments, Kits and Uses

15

Medical treatments

In a further aspect, the present invention provides the use of the antibody, or an antigen
binding fragment thereof, according to the present invention, the nucleic acid molecule
20 according to the present invention, the vector according to the present invention, the plurality
of nucleic acid molecules according to the present invention, 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 in (i) prevention and/or
treatment of Zika virus infection; or in (ii) diagnosis of Zika virus infection. Thereby, use of
25 the antibody, or an antigen binding fragment thereof, according to the present invention (and
in particular its preferred embodiments as described above) or of the (plurality of) nucleic
acid molecule(s) according to the present invention encoding the antibody, or an antigen
binding fragment thereof, according to the present invention is preferred in (i) prevention
and/or treatment of Zika virus infection as described herein; or in (ii) diagnosis of Zika virus
30 infection as described herein.

Methods of diagnosis may include contacting an antibody or an antibody fragment with a sample. Such samples may be isolated from a subject, for example an isolated tissue sample taken from, for example, nasal passages, sinus cavities, salivary glands, lung, liver, pancreas, kidney, ear, eye, placenta, alimentary tract, heart, ovaries, pituitary, adrenals, thyroid, brain,
5 skin or blood, preferably 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 or an antibody fragment with a sample. Such a detection step is typically performed at the bench, i.e. without any contact to the human or animal body. Examples of detection methods are well-known to the person skilled in the art and include, e.g., ELISA (enzyme-linked immunosorbent assay).
10

Prevention of Zika virus infection refers in particular to prophylactic settings, wherein the subject was not diagnosed with Zika virus infection (either no diagnosis was performed or diagnosis results were negative) and/or the subject does not show symptoms of Zika virus
15 infection. Accordingly, prevention of Zika virus infection includes "post-exposure prophylaxis" (PEP), i.e. preventive treatment after a possible Zika virus infection, for example after a mosquito bite in a Zika virus affected area. Prevention of Zika virus infection is in particular useful in high-risk subjects, such as in pregnant subjects and/or in subjects staying in Zika virus affected areas (such as subjects living in Zika virus affected areas or travelling to
20 Zika virus affected areas).

In therapeutic settings, in contrast, the subject is typically infected by Zika virus, diagnosed with Zika virus infection and/or showing symptoms of Zika virus infection. Of note, the terms "treatment" and "therapy"/"therapeutic" of ZIKV infection include (complete) cure as well as
25 attenuation of ZIKV infection.

Accordingly, the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid molecule according to the present invention, the vector according to the present invention, the plurality of nucleic acid molecules according to the present
30 invention, 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 is

preferably used for treatment of Zika virus infection in subjects diagnosed with Zika virus infection or in subjects showing symptoms of Zika infection.

5 It is also preferred that the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid molecule according to the present invention, the vector according to the present invention, the plurality of nucleic acid molecules according to the present invention, 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 is used for prevention and/or treatment of Zika virus infection in
10 asymptomatic subjects. Those subjects may be diagnosed or not diagnosed with Zika virus infection.

Preferably, the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid molecule according to the present invention, the vector according to the present invention, the plurality of nucleic acid molecules according to the present
15 invention, 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 is used for prevention and/or treatment of Zika virus infection in pregnant subjects, in particular to prevent congenital infection. For example, this may be performed in a similar manner as
20 for the prevention of HCMV congenital infection as described in Nigro G, Adler SP, La Torre R, Best AM, Congenital Cytomegalovirus Collaborating Group: Passive immunization during pregnancy for congenital cytomegalovirus infection; N Engl J Med 2005, 353:1350–1362.

Without being bound to any theory, it is assumed that the antibody, or the antigen-binding
25 fragment thereof, according to the present invention can pass the placenta through the interaction with FcRn, for example if administered to a pregnant subject, e.g. by (i.v.) injection or any other route of administration as described herein. Importantly, the interaction of “LALA” variants of antibodies as described herein with FcRn is not compromised. It is believed that FcRn is already expressed in the first trimester in the placenta.

30

Alternatively, the antibody, or the antigen-binding fragment thereof, or the (plurality of) nucleic acid molecule(s) according to the present invention may also be administered to the extra-amniotic space.

- 5 Preferably, the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid molecule according to the present invention, the vector according to the present invention, the plurality of nucleic acid molecules according to the present invention, 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 is
- 10 used for prevention and/or treatment of Zika virus infection, wherein the antibody, or the antigen binding fragment thereof, the nucleic acid, the vector, the plurality of nucleic acids, the plurality of vectors, the cell, or the pharmaceutical composition is administered up to seven days after (a possible) Zika virus infection, preferably up to five days after (a possible) Zika virus infection, more preferably up to four days after (a possible) Zika virus infection,
- 15 even more preferably up to three days after (a possible) Zika virus infection, and most preferably up to one day or two days after (a possible) Zika virus infection. Such a treatment schedule may be useful in therapeutic settings as well as in prophylactic settings, in particular in post-exposure prophylaxis (PEP).
- 20 In PEP typically the first administration of the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid molecule according to the present invention, the vector according to the present invention, the plurality of nucleic acid molecules according to the present invention, the plurality of vectors according to the present invention, the cell according to the present invention or the pharmaceutical composition
- 25 according to the present invention is as soon as possible after a possible ZIKV infection, e.g. after a mosquito bite in a ZIKV affected area. Accordingly, in PEP the first administration of the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid molecule according to the present invention, the vector according to the present invention, the plurality of nucleic acid molecules according to the present invention, 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 is typically
- 30 up to one or more days after (a possible) ZIKV infection, as described above.

It is also preferred that the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid molecule according to the present invention, the vector according to the present invention, the plurality of nucleic acid molecules according to the present invention, 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 is used for prevention and/or treatment of Zika virus infection, wherein the antibody, or the antigen binding fragment thereof, the nucleic acid, the vector, the plurality of nucleic acids, the plurality of vectors, the cell, or the pharmaceutical composition is administered up to three months before (a possible) Zika virus infection, preferably up to one month before (a possible) Zika virus infection, more preferably up to two weeks before (a possible) Zika virus infection, even more preferably up to one week before (a possible) Zika virus infection, and most preferably up to one day before (a possible) Zika virus infection. Such a treatment schedule refers in particular to a prophylactic setting.

In general – and in particular in PEP – after the first administration of the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid molecule according to the present invention, the vector according to the present invention, the plurality of nucleic acid molecules according to the present invention, 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, one or more subsequent administrations may follow, preferably a single dose per day or per every second day for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 days. It is also preferred that after the first administration of the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid molecule according to the present invention, the vector according to the present invention, the plurality of nucleic acid molecules according to the present invention, 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, one or more subsequent administrations may follow, preferably a single dose once or twice per week for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 weeks. It is also preferred that after the first administration of the antibody, or an antigen binding fragment thereof, according to the present invention, the

nucleic acid molecule according to the present invention, the vector according to the present invention, the plurality of nucleic acid molecules according to the present invention, 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, one or more
5 subsequent administrations may follow, preferably a single dose every 2 or 4 weeks for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 1, 15, 16, 17, 18, 19, 20, or 21 weeks. It is also preferred that after the first administration of the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid molecule according to the present invention, the vector according to the present invention, the plurality of nucleic acid
10 molecules according to the present invention, 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, one or more subsequent administrations may follow, preferably a single dose every two or four months for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 1, 15, 16, 17, 18, 19, 20, or 21 months. It is also preferred that after the first administration
15 of the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid molecule according to the present invention, the vector according to the present invention, the plurality of nucleic acid molecules according to the present invention, 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, one or more
20 subsequent administrations may follow, preferably a single dose once or twice per year for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 years.

Preferably, the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid molecule according to the present invention, the vector according
25 to the present invention, the plurality of nucleic acid molecules according to the present invention, 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 is administered at a (single) dose of 0.005 to 100 mg/kg bodyweight, preferably at a (single) dose of 0.0075 to 50 mg/kg bodyweight, more preferably at a (single) dose of 0.01 to 10
30 mg/kg bodyweight, even more preferably at a (single) dose of 0.05 to 5 mg/kg bodyweight, and particularly preferably at a (single) dose of 0.1 to 1 mg/kg bodyweight.

The antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid molecule according to the present invention, the vector according to the present invention, the plurality of nucleic acid molecules according to the present invention, 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 administered by any number of routes such as oral, intravenous, intramuscular, intra-arterial, intramedullary, intraperitoneal, intrathecal, intraventricular, transdermal, transcutaneous, topical, subcutaneous, intranasal, enteral, sublingual, intravaginal or rectal routes. Intravenous administration, or subcutaneous administration or intramuscular administration are preferred and intravenous administration or subcutaneous administration are more preferred.

In pregnant subjects the antibody, or an antigen binding fragment thereof, or the (plurality of) nucleic acid molecule(s) according to the present invention may also be administered intra- or extra-amniotic, e.g. by injection.

Accordingly, the present invention also provides a method of preventing and/or treating Zika virus infection in a subject, wherein the method comprises administering to a subject in need thereof the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid molecule according to the present invention, the vector according to the present invention, the plurality of nucleic acid molecules according to the present invention, 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. Preferred embodiments of this method correspond to preferred embodiments of the medical use as described above (and below, regarding combination therapy). For example, a preferred subject in this method is a subject diagnosed with Zika virus infection or showing symptoms of Zika virus infection. Another preferred subject in this method is a pregnant subject.

Combination therapy

The administration of the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid molecule according to the present invention, the vector

according to the present invention, the plurality of nucleic acid molecules according to the present invention, 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 in the methods and uses according to the invention can be carried out alone
5 or in combination with a co-agent (also referred to as “additional active component” herein), which is in particular useful for preventing and/or treating ZIKV infection.

The invention encompasses the administration of the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid molecule according to
10 the present invention, the vector according to the present invention, the plurality of nucleic acid molecules according to the present invention, 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, wherein it is administered to a subject prior to, simultaneously or sequentially with other therapeutic regimens or co-agents useful for
15 treating and/or preventing ZIKV infection. Said antibody, nucleic acid, vector, cell or pharmaceutical composition, that is administered simultaneously with said co-agents can be administered in the same or different composition(s) and by the same or different route(s) of administration.

20 Said other therapeutic regimens or co-agents may be, for example, a checkpoint inhibitor.

Thus, in another aspect of the present invention the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid molecule according to the present invention, the vector according to the present invention, the plurality of nucleic acid
25 molecules according to the present invention, 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 is administered in combination with a checkpoint inhibitor for the (medical) uses as described herein.

30 Preferred checkpoint inhibitors are directed to a blockade of PD-1/PD-L1 and/or of CTLA4 and, thus, include anti-PD-1 antibodies, anti-PD-L1 antibodies and anti-CTLA4 antibodies.

Thus, the pharmaceutical composition according to the present invention may comprise one or more of the additional active components.

It is also preferred that a ZIKV neutralizing antibody, or an antigen binding fragment thereof, as described herein is combined with a ZIKV NS1-binding antibody, or an antigen binding fragment thereof, as additional active component (co-agent). Thereby, the pathogenic role of NS1 may be blocked in addition to neutralization of ZIKV. Accordingly, a ZIKV NS1-binding antibody, or an antigen binding fragment thereof, for example as described in PCT/EP2017/067581, which is incorporated herein in its entirety, is a preferred additional active component (co-agent).

The antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid molecule according to the present invention, the vector according to the present invention, the plurality of nucleic acid molecules according to the present invention, the plurality of vectors according to the present invention, or the cell according to the present invention can be present either in the same pharmaceutical composition as the additional active component (co-agent) or, preferably, the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid molecule according to the present invention, the vector according to the present invention, the plurality of nucleic acid molecules according to the present invention, the plurality of vectors according to the present invention, or the cell according to the present invention is comprised by a first pharmaceutical composition and the additional active component (co-agent) is comprised by a second pharmaceutical composition different from the first pharmaceutical composition. Accordingly, if more than one additional active component (co-agent) is envisaged, each additional active component (co-agent) is preferably comprised by 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).

Preferably, the antibody, or the antigen binding fragment, according to the present invention and the additional active component (co-agent) provide an additive therapeutic effect or, preferably, 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.

10 Further Use and Kits

In a further aspect, the present invention also provides the use of the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid molecule according to the present invention, the vector according to the present invention, the plurality of nucleic acid molecules according to the present invention, 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 for monitoring the quality of an anti-Zika vaccine by checking that the antigen of said vaccine contains the specific epitope in the correct conformation. Preferred antigens comprised by such an anti-Zika vaccine to be checked include ZIKV envelope protein or any other molecule/complex comprising or consisting of (i) domain III of ZIKV E protein (EDIII) as described above or (ii) a quaternary ZIKV epitope as described above.

Moreover, the present invention also provides the use of the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid molecule according to the present invention, the vector according to the present invention, the plurality of nucleic acid molecules according to the present invention, 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 in (*in vitro*) diagnosis of Zika virus infection.

In addition also the use of the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid molecule according to the present invention, the

vector according to the present invention, the plurality of nucleic acid molecules according to the present invention, 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 in determining whether an isolated blood sample (e.g., whole blood, serum and/or plasma) is infected with Zika virus is provided.

As described above, methods of diagnosis may include contacting an antibody or an antibody fragment with a sample. Such samples may be isolated from a subject, for example an isolated tissue sample taken from, for example, nasal passages, sinus cavities, salivary glands, lung, liver, pancreas, kidney, ear, eye, placenta, alimentary tract, heart, ovaries, pituitary, adrenals, thyroid, brain, skin or blood, preferably serum or plasma. The methods of diagnosis may also include the detection of an antigen/antibody complex, in particular following the contacting of an antibody or an antibody fragment with a sample. Such a detection step is typically performed at the bench, i.e. without any contact to the human or animal body. Examples of detection methods are well-known to the person skilled in the art and include, e.g., ELISA (enzyme-linked immunosorbent assay).

In a further aspect, the present invention also provides a kit of parts comprising at least one antibody, or antigen binding fragment thereof, according to the present invention, at least one nucleic acid according to the present invention, the plurality of nucleic acids according to the present invention, at least one vector according to the present invention, the plurality of vectors according to the present invention, at least one cell according to the present invention, and/or at least one pharmaceutical composition according to the present invention. In addition, the kit may comprise means for administration of of the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid molecule according to the present invention, the vector according to the present invention, the plurality of nucleic acid molecules according to the present invention, 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, such as a syringe or a vessel, a leaflet, and/or a co-agent to be administered as described above.

DESCRIPTION OF FIGURES

- Figure 1 shows the reactivity (ELISA) and ZIKV and DENV1 neutralizing activity of antibodies derived from four ZIKV immune donors (ZKA, ZKB, ZKC and ZKD) to E protein of ZIKV and DENV1-4 and to EDIII-domain of ZIKV E protein; NNB – neutralizing, non-E-protein binding antibodies.
- Figure 2 shows the binding of ZKA190, ZKA78 and ZKA64 antibodies to ZIKV and DENV1 E and to ZIKV EDIII proteins as measured by ELISA.
- Figure 3 shows the binding of ZKA185 and ZKA190 antibodies to ZIKV E, DENV1 VLP and to ZIKV EDIII proteins as measured by ELISA.
- Figure 4 shows for Example 3 the neutralizing activity of ZKA190, ZKA64, ZKA64-LALA, ZKA230 and ZKA78 antibodies against ZIKV (H/PF/2013 strain) and DENV1 on Vero cells as measured by flow-cytometry (% of infected cells).
- Figure 5 shows for Example 3 the neutralizing activity of ZKA190, ZKA64, ZKA185, ZKA230 and ZKA78 antibodies against ZIKV (H/PF/2013 strain) on Vero cells as measured with a cell viability readout (wst-1, Roche).
- Figure 6 shows for Example 4 the infection enhancing activity (ADE, antibody-dependent enhancement) of ZKA190, ZKA64, ZKA64-LALA, ZKA185, ZKA230 and ZKA78 antibodies for ZIKV (H/PF/2013 strain) on non-permissive K562 cells as measured by flow-cytometry (% of infected cells).
- Figure 7 shows for Example 4 that four ZIKV-immune plasma and one DENV-immune plasma showed similar capacity to enhance ZIKV infection of K562 cells (upper panel). This ADE effect was completely blocked in all five immune plasma by the EDIII-specific ZKA64-LALA antibody (lower panel).

- Figure 8 shows the amino acid alignment of the EDIII region of 39 ZIKV strains from the Asian lineage since 2013 (including the prototypic strain MR766 of the African lineage isolated in 1947).
- 5 Figure 9 shows for Example 3 the neutralizing activity of ZKA190 and ZKA190-LALA antibody against three strains of ZIKV (H/PF/2013, MR766 and MRS_OPY_Martinique_PaRi_2015) on Vero cells as measured by flow-cytometry (% of infected cells).
- 10 Figure 10 shows for Example 5 neutralization of ZKA190 and C8 mAbs tested against a panel of four strains of ZIKV, as determined by the percentage of infected Vero cells in the presence of increasing amounts of the mAbs (A). Shown are also the IC50 values (B) and statistics (C). Data are representative of at least two independent experiments.
- 15 Figure 11 shows for Example 6 the neutralization and enhancement of ZIKV infection by antibody ZKA190. (A) Neutralization of ZIKV PRVABC59 strain infection of hNPCs by ZKA190, ZKA190-LALA and a control mAb as determined by plaque assay on Vero cells (left panel) and indirect immunofluorescence of infected hNPCs using fluorophore-labelled anti-E antibody (right panel). (B) ADE of ZIKV infection of non-permissive K562 cells by ZKA190 and ZKA190-LALA. (C) ADE induced in K562 cells when ZIKV is pre-incubated with serial dilutions of plasma serum from different ZIKV-positive patients (left panel). When ZKA190 LALA is added to the ZIKV-serum complexes, ADE is inhibited (right panel). (D) ADE induced in K562 cells when ZIKV is pre-incubated with serial dilutions of a prM cross-reactive mAb (DV62) derived from a DENV-immune donor. ZKA190-LALA inhibits ADE of ZIKV when complexed with prM-reactive antibody DV62. (E) Effect on ADE induced by peak enhancing dilution of a DENV2 plasma (left panel) or anti-prM DV62 mAb (right panel)
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- 25
- 30 by serial dilutions of indicated mAbs.

Figure 12 shows for Example 7 the identification of ZKA190 epitope and analysis of its conservation in ZIKV strains. (A) Overlay of ^{15}N , ^1H -HSQC spectra of ^{15}N -labeled ZIKV EDIII in absence (black) or presence (red) of unlabelled ZKA190 Fab. Differences identify EDIII residues affected by antibody binding. (B) NMR epitope mapping of ZKA190 Fab in complex with ZKV EDIII. The chemical shift perturbation (CSP, y-axis) is plotted against the EDIII residue number. Residues affected by antibody binding are in red. (C) Residues in FG loop identified by NMR epitope mapping is partially hidden in E protein mol A but largely exposed in mols B and C. EDIII of E protein was coloured in blue. Residues identified by NMR epitope mapping are coloured in magenta except those in the FG loop are coloured in green. Adjacent E proteins are shown as grey surface. (D) Level of amino acid residue conservation in ZKA190 epitope as calculated by the analysis of sequences from 217 ZIKV strains found in ZIKV Resources (NCBI) databases as of November 24th 2016. (E) Open-book representation showing charge complementarity between the epitope and paratope of the docking result. Boundaries of the epitope and paratope are circled in green. The borders between heavy and light chains of Fab and its corresponding footprint on EDIII are shown as yellow dashed lines.

Figure 13 shows for Example 7 the ZKA190 epitope identified by NMR and Docking. (A) Cartoon representation of the 12 lowest energy NMR structures of ZIKV EDIII, with residues affected by ZKA190 binding in red. Flexibility in the N-terminus of the construct is apparent. (B) Model of the ZKA190:EDIII complex derived by computational docking and molecular simulation validated by NMR results. The NMR identified epitope on EDIII (grey) is in red. The ZKA190 heavy and light chain are colored in dark and light green, respectively. EDIII residues that affect or not antibody binding when mutated are shown as orange and blue sticks, respectively. (C) NMR identified ZKA190 epitope (red) is accessible on the virus surface (white).

- Figure 14 shows for Examples 7 and 10 the binding of wt or mutated EDIII to ZKA190 IgG. SPR data and binding kinetics are shown. EDIII mutants that affect (red highlights) or do not affect binding are shown as indicated in the figure.
- 5 Figure 15 shows for Example 8 the results of the confocal microscopy experiments. ZIKV incubated with a concentration exceeding 10'000-fold the IC50 value of either ZKA190 Fab or full IgG were added to Vero cells. The ZIKV:antibody complex is detected inside the cells (green) and co-localizes with endosomes (red, yellow overlay). Endosomes and acidic organelles are marked by LysoTracker red; Alexa-488 conjugated ZKA190 is in green. Nuclei are stained with DAPI (blue).
- 10
- Figure 16 shows for Example 9 prophylactic and therapeutic efficacy of ZKA190. (A) ZKA190 is strongly protective against ZIKV infection when administered prophylactically to mice (A129 in (A) and AG129 in (B)) challenged with a lethal dose of ZIKV strain MP17451. Experiments used N=4-8 mice per group. Kaplan-Meier survival curves are shown (A). Significance was determined by using the Mantel-Cox log-rank test. Panel A, top left: ZKA190 at 5, 1 and 0.2 mg/kg versus Ctr mAb, P = 0.0031; ZKA190 at 0.04 mg/kg versus Ctr mAb, P = 0.0116; ZKA190-LALA at 5, 1, 0.2 and 0.04 mg/kg versus Ctr mAb, P = 0.0031. Panel A, top right: Morbidity score of mice monitored over a 14-15 day period (two different scoring methods were used; see (Dowall, S.D., Graham, V.A., Rayner, E., Atkinson, B., Hall, G., Watson, R.J., Bosworth, A., Bonney, L.C., Kitchen, S., and Hewson, R. (2016). A Susceptible Mouse Model for Zika Virus Infection. PLoS Negl Trop Dis 10, e0004658–13). Panel A, lower panels: body weight of mice. Panels B: ZKA190 or ZKA190-LALA were administered at 15 mg/kg at different time-points after ZIKV infection. Panel B, top left: A Kaplan-Meier survival curve is shown. Experiments used N=5 mice per group. Significance was determined by using the Mantel-Cox log-rank test. ZKA190 and ZKA190-LALA given either on day 1, 2, 3 or 4 versus Ctr., P = 0.0016. Panel B, top right: Morbidity score of mice monitored over a 14-day according to (Dowall et al., 2016). Mice were monitored over a 14 day period
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- 20
- 25
- 30

for body weight loss (Panel B, lower panels). Control antibody is MPE8 specific for RSV F protein (Corti, D., et al. Cross-neutralization of four paramyxoviruses by a human monoclonal antibody. *Nature* 501, 439-443 (2013)).

5 Figure 17 shows for Example 9 the prophylactic efficacy of the anti-ZIKV EDIII-specific
mAb ZKA190 against ZIKV strains MP1741. (A) Shown is the viremia
measured as PFU/ml on day 5 in blood of all animals. (B) Viral load was
measured as genomic copies/ml by qPCR on day 5 in blood of all animals and
in blood and indicated tissues when animals were culled at the end of the
10 study or when the humane end points were met. (C) Mice were monitored
over a 14 day period for body weight loss (D) Human serum IgG concentration
in day 5 blood samples. Significance was determined compared to control
antibody treatment by nonparametric unpaired Mann-Whitney U test. *p <
0.05; **p < 0.01; ***p < 0.001.

Figure 18 shows for Example 9 the therapeutic efficacy of the anti-ZIKV EDIII-specific mAb ZKA190. (A) Viral loads were measured as PFUs on day 5 in blood of all animals. (B) Viral loads were measured as genomic copies by qPCR on day 5 in blood of all animals and in blood and indicated tissues when animals were culled at the end of the study or when the human end points were met. Significance was determined compared to control antibody treatment by nonparametric unpaired Mann-Whitney U test. * $p < 0.05$; ** $p < 0.01$. (C) Human serum IgG concentration in day 5 blood samples.

25 Figure 19 shows for Example 11 and 12 the engineering of ZKA190 into the bispecific
FIT-1 mAb and its *in vitro* characterization. (A) ZKA185 and ZKA230 mAbs
were tested for neutralization of four strains of ZIKV, as determined by the
percentage of infected Vero cells in the presence of increasing amounts of
mAbs. Data are representative of at least two independent experiments. (B)
30 Binding of ZKA185 and ZKA230 IgG and Fab to recombinant ZIKV VLP, E and
DIII antigens as assessed by ELISA. (C) ZKA190, ZKA185 and ZKA230 were
tested for neutralization of H/PF/2013 (wt) and MARMs 1-4. (D) Surface

representation of two E protein dimers bound by ZKA190 (green); the ZKA190 NMR derived epitope is in red; positions mutated in MARMs are indicated in yellow (E370), blue (T335), orange (D67) and magenta (K84). (E) Model of FIT-1. The natural linkers between inner and outer Fabs allow a flexible movement of Fabs in the FIT-1 antibody. The variable regions of ZKA185 and ZKA190 are highlighted in blue and green, respectively. (F) Binding of FIT-1 IgG and Fab to recombinant ZIKV VLP, E and DIII antigens as assessed by ELISA. (G) ZKA190, ZKA185 and FIT-1 mAbs were tested for neutralization of four strains (IC50 values, G) and four MARMs (H) of ZIKV. (I) Neutralization of ZIKV H/PF/2013 strain by ZKA185, ZKA230 and FIT-1 IgG and Fab determined as in (A). (J) Confocal microscopy experiments as shown in Figure 3G. (K) Effect on ADE induced by peak enhancing dilution of anti-prM DV62 mAb or DENV2 plasma by serial dilutions of FIT-1 IgG and Fab.

15 Figure 20 shows the therapeutic efficacy of FIT-1. FIT-1 is strongly effective against ZIKV infection when administered therapeutically at different time-points to mice (A129) challenged with a lethal dose of ZIKV strain MP17451. Experiments used N=5-6 mice per group. (A) Kaplan-Meier survival curves are shown. Significance was determined by using the Mantel-Cox log-rank test. FIT-1 at 15, 5 and 1 mg/kg given either on day 1, 2 versus Ctr mAb, $P = 0.0012$; ZKA190 at 15 and 5 mg/kg given on day 3 versus Ctr mAb, $P = 0.0012$; ZKA190 at 1 mg/kg given on day 3 versus Ctr mAb, $P = 0.0170$. (B) Morbidity score of mice monitored over a 21 day period (Dowall et al., 2016). (C) Viral loads were measured as PFUs on day 5 in blood of all animals. (D) Mice were monitored over a 21 day period for body weight loss. Control mAb in panel A is MPE8 mAb (specific for RSV F protein (Corti, D., et al. Cross-neutralization of four paramyxoviruses by a human monoclonal antibody. *Nature* 501, 439-443 (2013)). (E) Viral loads were measured as genomic copies by qPCR on day 5 in blood of all animals and in blood and indicated tissues when animals were culled at the end of the study or when the human end points were met. Significance was determined compared to control antibody treatment by nonparametric unpaired Mann-Whitney U test. * $p < 0.05$; ** $p < 0.01$.

- Figure 21 shows for Example 14 that female AG129 mice treated with FIT-1 after challenge with Malaysian ZIKV were protected from mortality as compared with placebo-treated mice.
- 5
- Figure 22 shows for Example 14 intrauterine growth restriction (IUGR) in pups born to females treated with FIT-1 and challenged with ZIKV.
- Figure 23 shows for Example 14 average weight of pups on the date of birth born to females treated with FIT-1 and infected with ZIKV.
- 10
- Figure 24 shows for Example 14 the weight of placenta collected 11 dpi from females treated with FIT-1.
- Figure 25 shows for Example 14 quantification of viral RNA in (A) fetus, (B) placenta, (C) maternal spleen and (D) maternal brain (**P<0.001, *P<0.01, as compared with MPE8 treatment).
- 15
- Figure 26 shows for Example 15 the survival of male AG129 mice infected with ZIKV and treated with FIT-1 24 or 72 h after virus challenge (*P<0.05, as compared with MPE8 negative control treatment).
- 20
- Figure 27 shows for Example 15 mean percent weight change of AG129 mice treated with FIT-1 at various times after challenge with ZIKV.
- 25
- Figure 28 shows for Example 15 the disease score of the A) testicle or B) epididymis of male AG129 mice treated with FIT-1 24 or 72 h after challenge with ZIKV. Treatment with reactive Ab results in reduction in disease of the testicle and the epididymis.
- 30
- Figure 29 shows for Example 16 the viral load in serum of the 3 groups tested. The horizontal line indicates the LLOQ of 860 GC/mL.

EXAMPLES

Exemplary embodiments of the present invention are provided in the following examples. The following examples are presented only by way of illustration and to assist one of ordinary skill in using the invention. The examples are not intended in any way to otherwise limit the scope of the invention.

Example 1: Isolation of ZIKV-specific antibodies and production of monoclonal antibodies

IgG+ memory B cells were isolated from cryopreserved peripheral blood mononuclear cells (PBMCs) of four ZIKV-infected donors (ZKA, ZKB, ZKC and ZKD) using CD22 microbeads (Miltenyi Biotec), followed by depletion of cells carrying IgM, IgD and IgA by cell sorting. Memory B cells from the ZIKV-infected donors were then immortalized with EBV (Epstein Barr Virus) and CpG (CpG oligodeoxynucleotide 2006) in multiple replicate wells as previously described (Traggiai, E. et al., Nat. Med. 10, 871–875, 2004) and culture supernatants were then tested in a primary screening using in parallel a 384-well based micro-neutralization assay and a binding assay (ELISA) to test their binding to ZIKV NS1 protein or to ZIKV E protein. Results of the binding assay (binding to ZIKV E protein) are shown in Fig. 1.

Neutralization assays were undertaken on Vero cells. In a 384-well plate, ZIKV H/PF/2013 that resulted in an infection rate (m.o.i, multiplicity of infection) of 0.35 was incubated with supernatants for 1 h at 37% (5% CO₂) before the addition to pre-seeded 5'000 Vero cells. These were incubated for a further 5 days, after which supernatant was removed and WST-1 reagent (Roche) was added. Positive cultures were collected and expanded. From positive cultures the VH and VL sequences were retrieved by RT-PCR. Antibodies were cloned into human IgG1 and Ig kappa or Ig lambda expression vectors (kindly provided by Michel Nussenzweig, Rockefeller University, New York, US) essentially as described (Tiller T, Meffre E, Yurasov S, Tsuiji M, Nussenzweig MC, Wardemann H (2008) Efficient generation of monoclonal antibodies from single human B cells by single cell RT-PCR and expression vector cloning. J Immunol Methods 329: 112-124). Monoclonal antibodies were produced from

EBV-immortalized B cells or by transient transfection of 293 Freestyle cells (Invitrogen). Supernatants from B cells or transfected cells were collected and IgG were affinity purified by Protein A or Protein G chromatography (GE Healthcare) and desalted against PBS.

5 Figure 1 provides an overview over selected ZIKV neutralizing antibodies (cf. Tables 1 and 2 for the amino acid sequences of their CDRs and heavy/light chain variable regions). The last two columns of Figure 1 provide the neutralization activities (IC_{50}) of ZIKV and DENV1 (if tested). The other columns provide binding activities (EC_{50}) of the antibodies to ZIKV E protein (ZIKV E), DENV1 E protein (DENV1 E), DENV2 E protein (DENV2 E), DENV3 E protein
 10 (DENV3 E), DENV4 E protein (DENV4 E), DENV1 virus-like particle (DENV1 VLP), DENV2 virus-like particle (DENV2 VLP), DENV3 virus-like particle (DENV3 VLP), DENV4 virus-like particle (DENV4 VLP), and to EDIII-domain of ZIKV E protein (DIII ZKA).

15 Example 2: Characterization of antibodies ZKA190, ZKA185, ZKA230, ZKA64 and ZKA78

In Example 1, a large number of ZIKV-neutralizing antibodies were identified and characterized for their specificity to ZIKV, in particular ZIKV E protein and ZIKV EDIII as well as for their cross-reactivity towards DENV. Antibodies ZKA190 (SEQ ID NOs: 1 – 18), ZKA185
 20 (SEQ ID NOs: 19 – 36), ZKA230 (SEQ ID NOs: 37 – 54), ZKA64 (SEQ ID NOs: 73 – 90) and ZKA 78 (SEQ ID NOs: 55 – 72) described in Example 1 were then selected and further tested against ZIKV E protein ("ZIKV"), ZIKV EDIII ("DIII ZI") and also tested against the E protein of dengue virus (DENV, serotype number 1) by ELISA. To this end, a standard ELISA was used. Briefly, ELISA plates were coated with ZIKV E protein at 1 or 3 $\mu\text{g/ml}$, blocked with 10% FCS
 25 in PBS, incubated with sera or human antibodies and washed. Bound antibodies were detected by incubation with AP-conjugated goat anti-human IgG (Southern Biotech). Plates were then washed, substrate (p-NPP, Sigma) was added and plates were read at 405 nm. The relative affinities of monoclonal antibody binding were determined by measuring the concentration of antibody (EC_{50}) required to achieve 50% maximal binding at saturation.

30 Results are shown in Figures 3 and 4. Of note, ZKA64 and ZKA190 bound to ZIKV E and ZIKV EDIII ("DIII ZI") with low EC_{50} values, thereby indicating that ZKA64 and ZKA190 are

binding to domain III of ZIKV E protein (EDIII). ZKA78 bound to ZIKV E, but not to ZIKV EDIII, indicating that ZKA78 is binding to ZIKV E, but not targeting the EDIII region. Despite their considerable ZIKV neutralizing activity (cf. Fig. 1), antibodies ZKA185 and ZKA230 did not show any detectable binding to ZIKV E and ZIKV EDIII (Fig. 3). Accordingly, ZKA185 and ZKA230 were referred to as “neutralizing-non-E-binding” (NNB) antibodies. Those NNB antibodies are assumed to recognize quaternary epitopes that are displayed on the ZIKV infectious virions but not on soluble proteins.

Moreover, none of ZKA190, ZKA185, ZKA230, and ZKA64 showed any detectable binding to DENV E proteins (Figure 1, DENV1-4 serotypes, and Figures 3 and 4), indicating that ZKA190, ZKA185, ZKA230, and ZKA64 are specific for ZIKV and not cross-reactive to dengue virus. ZKA78, in contrast, which is assumed to bind to ZIKV EDI/II, but not to ZIKV EDIII (cf. Fig. 2), bound to DENV E proteins (Figures 1 and 3), indicating that ZKA78 is a cross-reactive antibody binding to both, ZIKV and DENV.

To further confirm those results, the ZIKV E protein binding antibodies ZKA190, ZKA64 and ZKA78 were additionally tested against E protein of dengue virus (DENV, serotypes number 1 – 4). ZKA64 and ZKA190 did not bind to DENV1-4 E protein, thereby confirming that ZKA64 and ZKA190 are specific for ZIKV. ZKA78, in contrast, bound to DENV1-4 E, confirming that ZKA78 is a cross-reactive antibody binding to the E protein of both ZIKV and DENV (cf. Fig. 1).

Example 3: The isolated antibodies potentially neutralize ZIKV infection

The isolated antibodies ZKA190, ZKA185, ZKA230, ZKA64 and ZKA78 were tested for their ability to neutralize ZIKV and DENV1 infection *in vitro*.

Neutralization of DENV and ZIKV infection by antibodies was measured using a micro-neutralization flow cytometry-based assay. Different dilutions of antibodies were mixed with ZIKV (MOI of 0.35) or attenuated DENV1 (all at MOI of 0.04) for 1 hour at 37°C and added to 5000 Vero cells/well in 96-well flat-bottom plates. After four days for ZIKV and five days

for DENV, the cells were fixed with 2% formaldehyde, permeabilized in PBS 1% FCS 0.5% saponin, and stained with the mouse mAb 4G2. The cells were incubated with a goat anti-mouse IgG conjugated to Alexa Fluor488 (Jackson Immuno- Research, 115485164) and analyzed by flow cytometry. In other cases the ZIKV neutralization data are also determined
5 measuring cell viability using the WST-1 reagent (Roche). The neutralization titer (50% inhibitory concentration [IC₅₀]) was expressed as the antibody concentration that reduced the infection by 50% compared to cell-only control wells.

Results are shown in Figures 4, 5 and 9. The EDIII-specific mAbs ZKA64 and ZKA190 and the
10 NNB mAb ZKA230 were highly potent in ZIKV neutralization (strain H/PH/2013), with IC₅₀ values of 93, 9 and 10 ng/ml, respectively (Figure 4, upper panel). In contrast, the cross-reactive antibody ZKA78 only partially neutralized ZIKV infectivity and cross-neutralized DENV1 infectivity (Figure 4, lower panels). Similar data were obtained by measuring the ZIKV-induced cytopathic effect as measured with the WST-1 reagent (Figure 5). In this second
15 assay, NNB antibody ZKA185 was also included in the panel of tested antibodies and showed an IC₅₀ similar to the most potent antibodies ZKA190 (EDIII-specific) and ZKA230 (NNB).

It is important to note that the ultra-potent ZKA64 and ZKA190 antibodies in addition to their ability to neutralize the ZIKV H/PH/2013 strain (present example), also bound to the E protein
20 and EDIII derived from the ZIKV strains MR766 and SPH2015, respectively (Figure 1 and Figure 2). ZKA190 and ZKA190-LALA was also confirmed to effectively neutralize two additional ZIKV strains (MR766 and MRS_OPY_Martinique_PaRi_2015) (Fig. 9). Taken together the results indicate that the ultra-potent ZKA64 and ZKA190 antibodies cross-react with multiple strains of ZIKV belonging to different genotypes and origins (East African and
25 Asian from Uganda, French Polynesia, Martinique and Brazil).

Example 4: The "LALA" mutation inhibits antibody-dependent enhancement of ZIKV infection by serum antibodies

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Neutralizing antibodies were also tested for their ability to enhance the infection of ZIKV in the non-permissive K562 cells (antibody-dependent enhancement assay, ADE assay). ADE

was measured by a flow based assay using K562 cells. Antibodies and ZIKV H/PF/2013 (MOI 0.175) were mixed for 1 hour at 37°C and added to 5000 K562 cells/well. After four days, cells were fixed, permeabilized, and stained with m4G2. The number of infected cells was determined by flow cytometry.

5

Results are shown in Figure 6. All antibodies enhanced infection of ZIKV in the non-permissive K562 cells at a broad range of concentrations, including those that fully neutralized ZIKV infection on Vero cells (Figure 6). Of note, while EDIII-specific antibodies ZKA64 and ZKA190 fully neutralized ZIKV infections of K562 cells above 1 µg/ml, the NNB antibody ZKA230 failed to do so, a result that might be due to the different mechanisms of neutralization of free viruses versus Fc-gamma-receptor-internalized viruses. In contrast, the cross-reactive ZKA78 that only partially neutralized ZIKV infectivity, effectively enhanced ZIKV infection of K562 cells. These results show that cross-reactive antibodies elicited by either ZIKV or DENV infection can mediate heterologous ADE.

10

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In view thereof it was investigated whether ADE could be also induced by immune sera and whether this could be blocked by neutralizing antibodies delivered as a "LALA variant". To obtain the LALA variant, each of the heavy chains was mutated at amino acids 4 and 5 of CH2 domain by substituting an alanine in place of the natural leucine using site-directed mutagenesis. As described above, LALA variants (of human IgG1 antibodies) do not bind to Fc-gamma-receptors and complement.

20

To investigate the effect of ZKA64-LALA antibody in ZIKV ADE, an inhibition of ADE assay was used. Since ADE of ZIKV is observed using ZIKV- or DENV-immune plasma, ZIKV (MOI 0.175) was mixed with plasma from primary ZIKV- or DENV-infected donors for 30 minutes at 37°C. ZKA64-LALA antibody was added at 50 µg/ml, mixed with 5000 K562 cells/well and incubated for three days. Cells were then stained with 4G2 and analyzed by flow cytometry.

25

Results are shown in Figure 7. In a homologous setting, four ZIKV-immune plasma collected from convalescent patients and one DENV-immune plasma showed similar capacity to enhance ZIKV infection of K562 cells (Figure 7, upper panel), and this ADE effect was completely blocked by the EDIII-specific ZKA64-LALA antibody (Figure 7, lower panel).

30

Of note, the ADE effect of ZIKV- and DENV-immune plasma was completely blocked by the EDIII-specific ZKA64-LALA antibody. The ADE blocking ability of a single EDIII-specific LALA antibody could be related not only to its capacity to out-compete serum enhancing antibodies but also to neutralize virus once internalized into endosomes.

These results indicate that a potentially neutralizing antibody, such as ZKA190, ZKA230, ZKA185 or ZKA64, developed in the "LALA" form, have a strong potential to be used in prophylactic or therapeutic settings to prevent congenital ZIKV infection, e.g. in pregnant women and/or in people living in high risk areas. The use of the LALA form avoids the risk of ZIKV ADE and, as shown above, could also block ADE of pre-existing cross-reactive antibodies, such as in the case of patients already immune to DENV.

Example 5: ZKA190 neutralizes ZIKV more potently than prior art antibody EDE1 mAb C8

To compare the isolated neutralizing antibodies with highly neutralizing anti-ZIKV antibodies of the prior art, neutralization performance of ZKA190 was compared to that of prior art highly neutralizing mAb EDE1 C8 (Barba-Spaeth G, Dejnirattisai W, Rouvinski A, Vaney MC, Medits I, Sharma A, Simon-Lorière E, Sakuntabhai A, Cao-Lormeau VM, Haouz A, England P, Stiasny K, Mongkolsapaya J, Heinz FX, Screaton GR, Rey FA. Structural basis of potent Zika-dengue virus antibody cross-neutralization. Nature. 2016 Aug 4;536(7614):48-53). Neutralization of both antibodies was tested against a panel of four distinct ZIKV strains (H/PF/2013; MR766, MRS-OPY and PV10552).

Briefly, neutralization of ZIKV infection by mAbs was measured using a micro-neutralization flow cytometry-based assay. Different dilutions of mAbs were mixed with ZIKV (MOI of 0.35) for 1 hour at 37°C and added to 5000 Vero cells/well in 96-well flat-bottom plates. After four days for ZIKV, the cells were fixed with 2% formaldehyde, permeabilized in PBS containing 1% fetal calf serum (Hyclone) and 0.5% saponin, and stained with the mouse mAb 4G2. The cells were incubated with a goat anti-mouse IgG conjugated to Alexa Fluor488 (Jackson Immuno- Research, 115485164) and analyzed by flow cytometry. The neutralization titer

(50% inhibitory concentration [IC₅₀]) is expressed as the antibody concentration that reduced the infection by 50% compared to virus-only control wells.

Results are shown in Figure 10. ZKA190 mAb potently neutralized African, Asian and American strains with an IC₅₀ ranging from 0.6 to 8 ng/ml. In comparison, prior art antibody C8 was about 24-fold less potent.

Example 6: Further characterization of antibody ZKA190

The potency of antibody ZKA190 was further investigated *in vitro* and *in vivo*. To this end, the mAb was synthesized in IgG1 wild-type (wt) format and in an IgG1 Fc-LALA format. Briefly, the VH and VL sequences were cloned into human Igγ1, Igκ and Igλ expression vectors (kindly provided by Michel Nussenzweig, Rockefeller University, New York, NY, USA), essentially as described (Tiller T, Meffre E, Yurasov S, Tsuiji M, Nussenzweig MC, Wardemann H: Efficient generation of monoclonal antibodies from single human B cells by single cell RT-PCR and expression vector cloning. J Immunol Methods 2008, 329:112–124). Recombinant mAbs were produced by transient transfection of EXPI293 cells (Invitrogen), purified by Protein A chromatography (GE Healthcare) and desalted against PBS. To obtain the LALA variant, each of the heavy chains was mutated at amino acids 4 and 5 of CH2 domain by substituting an alanine in place of the natural leucine using site-directed mutagenesis. As described above, LALA variants (of human IgG1 antibodies) do not bind to Fc-gamma-receptors and complement.

As shown in Figure 10A and described in Example 5, ZKA190 was tested against a panel of four ZIKV strains. ZKA190 mAb potently neutralized African, Asian and American strains with an IC₅₀ ranging from 0.004 to 0.05 nM (Figure 10A; 0.6 to 8 ng/ml).

Since ZIKV has been shown to infect human neural progenitor cells (hNPC) leading to heightened cell toxicity, dysregulation of cell-cycle and reduced cell growth, ZKA190 and ZKA190-LALA were tested in hNPCs. To this end, adult male fibroblasts obtained from the Movement Disorders Bio-Bank (Neurogenetics Unit of the Neurological Institute 'Carlo

Besta', Milan) were reprogrammed using the CytoTune-iPS 2.0 Sendai kit (Life Technologies). hiPSCs were maintained in feeder-free conditions in mTeSR1 (Stem Cell Technologies). To generate embryoid bodies (EBs), dissociated hiPSCs were plated into low adhesion plates in mTeSR1 supplemented with N2 (0.5x) (ThermoFisher Scientific), human Noggin (0.5 mg/ml, R&D System), SB431542 (5 μ M, Sigma), Y27632 (10 μ M, Miltenyi Biotec) and penicillin/streptomycin (1%, Sigma) (as described in Marchetto MCN, Carromeu C, Acab A, Yu D, Yeo GW, Mu Y, Chen G, Gage FH, Muotri AR: A model for neural development and treatment of Rett syndrome using human induced pluripotent stem cells. *Cell* 2010, 143:527–539). To obtain rosettes, EBs were plated after 10 days onto matrigel-coated plates (1:100, matrigel growth factor reduced, Corning) in DMEM/F12 (Sigma) with N2 (1:100), non-essential amino acids (1%, ThermoFisher Scientific) and penicillin/streptomycin. After 10 days, cells were passaged with Accutase (Sigma) and seeded onto matrigel coated-flasks in NPC media containing DMEM/F12, N2 (0.25%), B27 (0.5%, ThermoFisher Scientific), penicillin/streptomycin and FGF2 (20 ng/ml, ThermoFisher Scientific). hNPCs (3x10⁴) were plated on coverslips in 24-well plates 3 days prior to infection with PRVABC59 strain. Virus stock was incubated with the mAbs 1h prior to addition to hNPCs to obtain an MOI of 0.5. After 4h of virus adsorption, culture supernatant was removed and fresh medium containing the mAbs was re-added. Supernatant was collected 96h post-infection to measure virus titers by plaque assay on Vero cells. Cells were fixed in 4% paraformaldehyde (PFA, Sigma) solution in phosphate-buffered saline (PBS, Euroclone) for 30 min for indirect immunofluorescence. Fixed cells were permeabilized for 30 minutes (min) in blocking solution, containing 0.2% Triton X-100 (Sigma) and 10% donkey serum (Sigma), and incubated overnight at 4°C with the primary antibodies in blocking solution. The following antibody was used for detection: anti-envelope (1:200, Millipore, MAB10216). Then, cells were washed with PBS and incubated for 1h with Hoechst and anti-mouse Alexa Fluor-488 secondary antibodies (1:1,000 in blocking solution, ThermoFisher Scientific). After PBS washes, cells were washed again and mounted. Results are shown in Fig. 11A. Both, ZKA190 and ZKA190-LALA, fully abolished infection and replication of ZIKV in hNPCs.

Next, the ability of ZKA190 and ZKA190-LALA to cause ADE was tested in the K562 cell line as described in Example 4. Briefly, ADE was measured by a flow based assay using K562 cells. Briefly, for ZKA190, ZKA190 and ZIKV H/PF/2013 (MOI 0.175) were mixed for 1 hour

at 37°C and added to 5000 K562 cells/well. After four days, cells were fixed, permeabilized, and stained with mAb m4G2. The number of infected cells was determined by flow cytometry. For ZKA190-LALA, ZIKV (MOI 0.175) was mixed with plasma from primary ZIKV-infected donors for 30 minutes at 37°C. ZKA190-LALA was added at 50 µg/ml, mixed with
5 5000 K562 cells/well and incubated for three days. Cells were then stained with 4G2 and analyzed by flow cytometry. Results are shown in Figure 11B. ZKA190 supports ADE from 0.0001 to 1 nM; as expected, ZKA190-LALA did not show any ADE activity. The ability of ZKA190-LALA to inhibit ADE induced by plasma from four ZIKV-immune donors in K562 cells was also tested. Results are shown in Figure 11C. It was found that ZKA190-LALA
10 completely inhibited the ADE induced by plasma antibodies (Figure 11C).

Anti-prM antibodies form part of the predominant antibodies elicited during the human immune response against flaviviruses and have been shown to enhance virus infection *in vitro* (Dejnirattisai, W., Jumnainsong, A., Onsirakul, N., Fitton, P., Vasanawathana, S., Limpitikul, W., Puttikhunt, C., Edwards, C., Duangchinda, T., Supasa, S., et al. (2010). Cross-reacting
15 antibodies enhance dengue virus infection in humans. *Science* 328, 745–748). K562 cells were pre-incubated with serial dilutions of prM cross-reactive antibody DV62 (Beltramello, M., Williams, K.L., Simmons, C.P., Macagno, A., Simonelli, L., Quyen, N.T.H., Sukupolvi-Petty, S., Navarro-Sanchez, E., Young, P.R., de Silva, A.M., et al. (2010). The human immune
20 response to Dengue virus is dominated by highly cross-reactive antibodies endowed with neutralizing and enhancing activity. *Cell Host Microbe* 8, 271–283) derived from a DENV immune donor. Results are shown in Figure 11D. DV62 cross-reacted with ZIKV prM protein and caused ADE at a broad range of concentrations (Figure 11D). ZKA190-LALA can fully block anti-prM DV62 mAb-induced ADE of immature or partially immature ZIKV particles
25 (Figure 11D).

Finally, the ability of different concentrations of ZKA190, ZKA190-LALA and ZKA190 Fab to cause or block ADE of ZIKV in the presence of enhancing concentrations of human anti-DENV2 plasma or DV62 was tested. Results are shown in Figure 11E. ZKA190 at low
30 concentrations increased the prM DV62-mediated ADE of ZIKV infection, consistent with its ability to promote the entry of both immature and mature virions, while at concentrations above 1.3 nM (i.e., 200 ng/ml) ZKA190 blocked ADE induced by both DENV plasma and

mAb DV62. ZKA190-LALA, as well as its Fab fragment, reduced ADE at concentrations above 0.06 nM, indicating that both inhibited virus infection at a post-attachment step, such as fusion.

5

Example 7: ZKA190 binds to a conserved and highly accessible region of EDIII

To determine the ZKA190 epitope at the residue level, solution NMR spectroscopy was used as described in Bardelli, M., Livoti, E., Simonelli, L., Pedotti, M., Moraes, A., Valente, A.P.,
10 and Varani, L. (2015). Epitope mapping by solution NMR spectroscopy. J. Mol. Recognit. 28, 393–400; Simonelli, L., Beltramello, M., Yudina, Z., Macagno, A., Calzolari, L., and Varani, L. (2010). Rapid structural characterization of human antibody-antigen complexes through experimentally validated computational docking. J Mol Biol 396, 1491–1507; and Simonelli,
15 Varani, L. (2013). Rational Engineering of a Human Anti-Dengue Antibody through Experimentally Validated Computational Docking. PLoS ONE 8, e55561.

Briefly, spectra were recorded on a Bruker Avance 700 MHz NMR spectrometer at 300 K. For assignments of backbone resonances standard triple resonance experiments (HNCO,
20 HN(CA)CO, HN(CO)CACB, HNCACB were used, while sidechains were annotated using HCCH-TOCSY and HBHA(CO)NH experiments. All NMR experiments were processed using Topspin 2.1 (Bruker Biospin) and analysed with CARA. NOESY cross peaks were automatically assigned using the CYANA “noeassign” macro based on the manually assigned chemical shifts. Upper-distance restraints used for the structure calculations in CYANA using
25 the standard simulated annealing protocol were derived from 70 ms ¹⁵N- and ¹³C-resolved NOESY spectra. Backbone dynamics of ZIKV EDIII were derived from ¹⁵N relaxation measurements recorded on 600 and 700 MHz spectrometers. Proton-detected versions of the CPMG (R2), inversion-recovery (R1) and ¹⁵N{¹H}-steady-state NOE were utilized. Delay settings for the T2 series were in the range of 0 to 0.25 sec and for the T1 series between 0.02
30 to 2 sec. The ¹⁵N{¹H}-NOE experiment used a relaxation delay of 5 s. The R1 and R2 relaxation rates were derived from least-squares fits of corresponding exponential functions to the measured data using home-written scripts. The relaxation data were analyzed in a

model-free approach using the software package DYNAMICS. The program ROTDIF was used to calculate the overall correlation time from the relaxation data (8.5 ns). NMR epitope mapping was performed as previously described (Bardelli et al., 2015; Simonelli et al., 2010; 2013). Briefly, overlay of ^{15}N HSQC spectra of labelled EDIII free or bound to ZKA190 Fab
5 allowed identification of EDIII residues whose NMR signal changed upon complex formation, indicating that they were affected by ZKA190 binding. Changes were identified by manual inspection and by the Chemical Shift Perturbation (CSP), $\text{CSP} = ((\Delta\delta_{\text{H}})^2 + (\Delta\delta_{\text{N}}/10)^2)^{1/2}$. NMR samples were typically 800 μM of [^{15}N , ^{13}C]-labeled EDIII in 20 mM sodium phosphate, 50 mM NaCl, pH 6.0. Perdeuterated (nominally 70%) ^2H , ^{15}N EDIII samples were used for NMR
10 epitope mapping with a EDIII:ZKA190 Fab ratio of 1:1.1; EDIII concentration was typically 0.4 mM.

Since the NMR signal is strongly dependent on the local chemical environment, changes upon complex formation identify antigen residues that are affected by antibody binding, either
15 directly or through allosteric effects. By comparing the NMR spectra of free and bound EDIII (Figure 12A), residues affected by ZKA190 were mapped to the LR of EDIII, in particular to the BC, DE and FG loops, as well as to part of the EDI-EDIII hinge (Figure 13A). These residues are nearly identical among 217 known ZIKV strains, with the exception of substitutions at V341I and E393D in the Uganda 1947 isolate (Figure 12D). These mutations are also present
20 in the MR766 strain that was efficiently neutralized by ZKA190 (Figure 10A). Analysis of the ZKA190 epitope on the uncomplexed ZIKV structure showed that the epitope is highly accessible, except for the FG loop in the 5-fold vertex (Figure 13B and 12C, molecule A).

Computational docking followed by molecular dynamics simulation, guided and validated
25 by NMR-derived epitope information as well as EDIII mutagenesis, showed that ZKA190 binds through an interface characterized by shape and charge complementarity (Figure 13B and 12E). Docking indicates that there are no direct contacts between ZKA190 and the FG loop on EDIII, suggesting that changes in its NMR signals upon antibody binding derive from allosteric effects. This notion is supported by the fact that mutations of FG loop residues in
30 recombinant EDIII, but not in other epitope regions, did not affect the binding affinity of ZKA190 for EDIII (Figure 13B and 14).

Example 8: Mechanisms of ZKA190 neutralization

The ability of ZKA190 to efficiently neutralize the virus may involve inhibition of either cell attachment or membrane fusion. A further mechanism might involve virus inactivation
5 through cross-linking of viral particles.

ZKA190 Fab can neutralize ZIKV, albeit less efficiently than the corresponding IgG. By binding to the EDI-EDIII linker, ZKA190 (both Fab and IgG) might inhibit the ~70 degree rotation of DIII required for viral fusion to the host cell membrane (Bressanelli, S., Stiasny, K., Allison, S.L., Stura, E.A., Duquerroy, S., Lescar, J., Heinz, F.X., and Rey, F.A. (2004). Structure
10 of a flavivirus envelope glycoprotein in its low-pH-induced membrane fusion conformation. *Embo J* 23, 728–738; Modis, Y., Ogata, S., Clements, D., and Harrison, S.C. (2004). Structure of the dengue virus envelope protein after membrane fusion. *Nature* 427, 313–319). Alternatively, ZKA190 might prevent the attachment of ZIKV to target cells.

15 The ability of ZKA190 to inhibit membrane fusion is supported by confocal microscopy analysis. To this end, Vero cells were plated at 7,500 cells/well on 12 mm-diameter coverslips in 24-well plates and incubated overnight. Cells were infected with ZIKV H/PF/2013 (MOI of 100) in the presence or absence of neutralizing concentrations of Alexa-488 conjugated mAbs (0.7 μ M) at 37°C for 3 h, washed with PBS, and fixed with 2% paraformaldehyde in PBS for
20 30 min at room temperature. Acidified endosome were identified with Lysotracker red (Invitrogen) by adding the dye (50 nM) to the cells for the last 30 min of the incubation prior to fixation. Fixation was followed by extensive washes in PBS and 50 mM glycine and finally the coverslips were prepared for microscopy analysis using Vectashield mounting medium
25 for fluorescence with DAPI (Vector Laboratories). Samples were analyzed by confocal microscopy using a Leica TCS SP5 microscope with a 63 $\times$ /1.4 N.A. objective. Image analysis and processing was performed with FIJI software.

Results are shown in Figure 15. Confocal microscopy analysis shows that ZKA190 (Fab or
30 IgG) can enter Vero cells only when complexed with ZIKV, at neutralizing concentrations exceeding the IC50 by 10,000-fold (Figure 15).

Example 9: *In vivo* characterization of the EDIII-specific mAb ZKA190

To evaluate their prophylactic and therapeutic properties, ZKA190 and ZKA190-LALA were tested in A129 mice challenged with a lethal dose of ZIKV strain MP1751 (African lineage).

- 5 To test their prophylactic potencies, ZKA190 and ZKA190-LALA were administered one day before virus challenge.

Female A129 mice (IFN- α /beta receptor $-/-$) and wild-type 129Sv/Ev mice aged 5-8 weeks were administered mAbs (ZKA190, ZKA190-LALA and control antibody MPE8 (Corti, D., et
10 al. Cross-neutralization of four paramyxoviruses by a human monoclonal antibody. Nature 501, 439-443 (2013)) diluted in PBS at different doses via the intraperitoneal (i.p.) route in a volume of 500 μ l. MAbs were administered either 1 day before or 1, 2, 3 or 4 days after virus challenge. Animals were challenged subcutaneously with 102 pfu ZIKV (strain MP1751) and followed for 14 days. Weights and temperatures were monitored daily and clinical
15 observations were recorded at least twice per day. On day 5 post-challenge, 50 μ l of blood was collected from each animal into a RNeasy Protect tube (Qiagen, UK) and frozen at -80°C . At the end of the study (14 days post-challenge) or when animals met human endpoints, necropsies were undertaken, and blood and sections of brain, spleen, liver, kidney and ovary were collected for virological analysis.

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Tissue samples from A129 mice were weighed and homogenized into PBS using ceramic beads and an automated homogenizer (Precellys, UK) using six 5 second cycles of 6500 rpm with a 30 second gap. Two hundred μ l of tissue homogenate or blood solution was transferred into 600 μ l RLT buffer (Qiagen, UK) for RNA extraction using the RNeasy Mini extraction kit
25 (Qiagen, UK); samples were passed through a QIAshredder (Qiagen, UK) as an initial step. A ZIKV specific realtime RT-PCR assay was utilized for the detection of viral RNA from subject animals. The primer and probe sequences were adopted from Quick et al., 2017 (Quick, J, Grubaugh ND, Pullan ST, Claro IM, Smith AD, Gangavarapu K, Oliveira G, Robles-Sikisaka R, Rogers TF, Beutler NA, et al.: Multiplex PCR method for MinION and Illumina sequencing
30 of Zika and other virus genomes directly from clinical samples. Nat Protoc 2017, 12:1261–1276) with in-house optimization and validation performed to provide optimal mastermix and cycling conditions. Real-time RT-PCR was performed using the SuperScript III Platinum

One-step qRT-PCR kit (Life Technologies, UK). The final mastermix (15 µl) was comprised of 10 µl of 2x Reaction Mix, 1.2 µl of PCR-grade water, 0.2 µl of 50 mM MgSO₄, 1 µl of each primer (ZIKV 1086 and ZIKV 1162c both at 18 µM working concentration), 0.8 µl of probe (ZIKV 1107-FAM at 25 µM working concentration) and 0.8 µl of SSIII enzyme mix. Five µl of
5 template RNA was added to the mastermix, yielding a final reaction volume of 20 µl. The cycling conditions used were 50°C for 10 minutes, 95°C for 2 minutes, followed by 45 cycles of 95°C for 10 seconds and 60°C for 40 seconds, plus a final cooling step of 40°C for 30 seconds. Quantification analysis using fluorescence was performed at the end of each 60°C step. Reactions were run and analyzed on the 7500 Fast platform (Life Technologies, UK)
10 using 7500 software version 2.0.6. Quantification of viral load in samples was performed using a dilution series of quantified RNA oligonucleotide (Integrated DNA Technologies). The oligonucleotide comprised the 77 bases of ZIKV RNA targeted by the assay, based on GenBank accession AY632535.2 and was synthesized to a scale of 250 nmol with HPLC purification.

15 Results are shown in Figures 16, 17 and 18. ZKA190 and ZKA190-LALA were shown to protect mice from mortality and morbidity at concentrations of 5, 1 or 0.2 mg/kg (Figure 16A-B). ZKA190-LALA, and to a lesser extent ZKA190, delayed morbidity and mortality as compared to the control group at 0.04 mg/kg. Viral titers in blood and organs were reduced
20 significantly compared to control antibody-treated animals, even in the presence of serum antibody levels below 1 µg/ml (Figure 17A-D).

To evaluate the therapeutic potential of ZKA190, we administered ZKA190 and ZKA190-LALA at different time-points following ZIKV infection. At a dose of 15 mg/kg, survival rates
25 of 80%-100% were achieved, and the morbidity was greatly reduced even when treatment was given four days post-infection (Figure 16E-G). ZKA190 and ZKA190-LALA treatment at all post-infection time-points resulted in significantly reduced viral titers, compared to animals treated with control antibody, with a clear trend for greater reduction with earlier treatment (Figure 18A-16C). Of note, ZKA190-LALA showed a significantly reduced antiviral
30 activity in the blood day 5 sample as compared to ZKA190 when mAbs were given four days post-infection, a result that might be related to the impaired ability of the LALA variant to facilitate rapid clearance of coated virions.

Of the 16 treated mice, one *in vivo* escape mutant (Monoclonal Antibody Resistant Mutant 1, MARM1), containing an amino acid substitution in DIII (T335R, in the center of the epitope) was isolated, while viruses from the other treated mice did not contain any E mutations. Introduction of the T335R mutation into recombinant DIII showed that it abrogated ZKA190 binding, as determined by SPR (Figure 14; cf. Example 7 for experimental methods).

Example 10: *In vitro* selection of ZIKV escape mutants

Use of antibody therapeutics may result in the selection of escape mutants. To assess the ability of ZKA190 to select for resistant mutants (MARMs) *in vitro*, ZIKV (H/PF/2013) was passaged in the presence of sub-neutralizing concentrations of ZKA190.

Briefly, two-thousands TCID₅₀ of H/PF/2013 ZIKV in 500 µl were incubated with 250 µl containing varying concentrations of mAb (8 different concentrations, starting with a final concentration of 200 µg/ml and performing serial 1:4 dilutions). The mixture was incubated for 45 minutes at 37°C, followed by the addition of 250 µl of a Vero cells suspension (3.2 x10⁶ cells) and an incubation in a 24 well plate for three-four days at 37°C to allow virus propagation to occur. After each step of selection, 500 µl of supernatants from three conditions were selected: the lowest concentration of mAb at which full protection of the monolayer was observed, one concentration at which a partial CPE effect on the cell monolayer was observed and one concentration at which 100% of the cell monolayer was destroyed by the ZIKV CPE. The tube was spun down for 5 minutes at 1000 x g, aliquoted and stored at -80°C. Half of the volume was again pre-mixed with varying concentrations of mAb to repeat the selection and propagation process. The remaining supernatant was used for micro-neutralization assays and subsequent sequencing of the virus.

To identify the escape mutations of the selected MARMs virus, a genomic RNA extraction was done followed by a one-step-PCR to amplify and sequence the ZIKV E protein amplicon. Cell supernatant (140 µl) from the MARMs selection was used for RNA extraction with the QIAamp Viral RNA mini kit (Qiagen). cDNA synthesis and PCR amplification were performed together using the SuperScript III One-Step RT-PCR with Platinum Taq (Invitrogen). For one

reaction 25 µl reaction mix, 8 µl sterile water, 2 µM of each primer, 1 µl RNase out (Life Technologies), 2 µl Superscript III RT/Platinum TaqMix and 12 µl RNA were used giving a final reaction volume of 50 µl. For the E protein N-terminal part, the primer pair Zika-E-F1 5'-TGCAAACGCGGTGCGCAAACCTGGTTG-3' (SEQ ID NO: 266) and ZIKV-E-R1 5'-CGTGCCAAGGTAATGGAATGTCGTG-3' (SEQ ID NO: 267) and for the C-terminal part the primer pair ZIKV-Ef1530 5'-AGCCTAGGACTTGATTGTGAACCGA-3' (SEQ ID NO: 268) and ZIKV-E-R2769 5'-TTACAGATCCCACAACGACCGTCAG-3' (SEQ ID NO: 269) were used. The cycling conditions were 54°C for 40 minutes, 94°C for 2 min followed by 45 cycles of 94°C for 45 seconds, 50°C for 45 seconds and 68°C for 1.5 minutes with a final elongation step at 68°C for 5 minutes and a final cooling step at 4°C. The PCR products were analyzed and extracted from a 1.5 % agarose gel and further purified with the GFX PCR DNA and Gel Band Purification kit (GE Healthcare). For the sequencing reaction 8 µl of purified PCR product was mixed with 2 µM primer in a final volume of 10 µl and sent for sequencing (Microsynth). E protein N-terminal products were sequenced with ZIKV-E-F2 5'-ACTTGGTCATGATACTGCTGATTGC-3' (SEQ ID NO: 270) and ZIKV-E-R2 5'-TCGGTTCACAATCAAGTCCTAGGCT-3' (SEQ ID NO: 271), C-terminal PCR products with ZIKV-E-f2058 5'-GCTAACCCCGTAATCACTGAAAGCA-3' (SEQ ID NO: 272) and ZIKV-E-r2248 5'-AAGACTGCCATTCTCTTGGCACCTC-3' (SEQ ID NO: 273). Sequences were assembled and analyzed using CLC Main Workbench software (CLC Bio, version 5).

Resistant mutant MARM2 was isolated after three rounds of selection, and its E protein showed a E370K mutation in DIII. The mutation abolished neutralization by ZKA190, although the antibody can bind to the mutated DIII (Figure 14). The mutations in the *in vivo* (T335R) and *in vitro* (E370K) MARMS are located on the BC and DE loops of DIII, respectively, and are consistent with the epitope identified by NMR.

Example 11: Development of bispecific antibodies according to the present invention

Viral escape mutants can greatly hinder the efficacy of therapeutic antibodies. To overcome this problem, the present inventors hypothesized that the possibility of virus escaping would be greatly reduced when combining two highly neutralizing antibodies. In view thereof, a

series of bispecific antibodies combining ZKA190 with other potentially neutralizing mAbs directed towards distinct sites on the E protein was generated. Thereby, it was focused on two mAbs, ZKA185 and ZKA230, that are highly neutralizing and do not compete with ZKA190.

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Firstly, their ability to cross-neutralize four ZIKV strains was analyzed as described above. ZKA185, and to a lesser extent ZKA230, potentially neutralized African, Asian and American strains with an IC₅₀ ranging from 0.02 to 0.62 nM (Figure 19A). ZKA185 binds with high affinity to recombinant ZIKV E protein and to Zika virus-like particles (VLP) but not to the isolated DIII (Figure 19B). Conversely, ZKA230 bound to ZIKV VLPs, but not to recombinant E or DIII, suggesting that it recognizes a quaternary epitope displayed only on the viral surface (Figure 19B). ZKA185 IgG and Fab were shown to bind to E and VLP antigens with similar high affinity by ELISA.

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To identify the ZKA185 and ZKA230 epitopes and also their propensity to generate escape mutants, MARMs against ZKA185 (MARM3) and ZKA230 (MARM4) were isolated by passaging virus in the presence of sub-neutralizing antibody concentrations as described above. MARM3 contained substitutions at K84E and D67H, which are both located on DII (Figure 19D). MARM4 showed a mixture of different amino acid substitutions at position 84 (from K to G, E or R), confirmed in multiple sequencing experiments. Finally, MARMs 1 to 4 were tested against ZKA190, ZKA185 and ZKA230. ZKA190 neutralized ZKA185 and ZKA230 MARMs as well as the parental virus (Figure 19C). ZKA185 neutralized both ZKA190 and ZKA230 MARMs. ZKA230 neutralized only ZKA190 MARM2 and did not neutralize either ZKA190 MARM1 or ZKA185 MARM3.

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To gain insight into the development of MARMs capable of escaping from the pressure of multiple antibodies, ZKA190 MARM2 (E370K) were serially passaged in the presence of ZKA185 or ZKA230. Thereby, it was found that double MARMs emerged after 3 to 4 passages. ZKA230 introduced an extra K84E mutation while ZKA185, selected for a D76G mutation. These findings indicate that ZIKV can escape the neutralization by multiple antibodies targeting distinct sites when the selection is performed in a stepwise fashion, and confirmed a high plasticity of the ZIKV E protein.

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In conclusion, ZKA185 was selected to be used together with ZKA190 for the development of a bispecific antibody since it potentially cross-neutralizes ZIKV strains, binds to an alternative site, and does not compete with ZKA190. The bispecific antibody was produced in a tetravalent symmetric format called Fabs-in-tandem-Ig (FIT-Ig). FIT-Igs are described in detail, for example, in WO 2015/103072 A1 and in Gong S, Ren F, Wu D, Wu X, Wu C: Fabs-in-tandem immunoglobulin is a novel and versatile bispecific design for engaging multiple therapeutic targets. MAbs 2017.

FIT-Ig may be produced using three polypeptides. Polypeptide 1 usually comprises the light chain of the outer Fab fused, preferably without linkers, to the N-terminal region of the inner Fab heavy chain. Polypeptide 2 usually comprises the heavy chain variable and CH1 regions of the outer Fab, and polypeptide 3 usually comprises by the light chain of the inner Fab. Accordingly, an antibody of the FIT-Ig format usually comprises an "inner Fab" and an "outer Fab". Two types of FIT-Igs were generated with ZKA190 Fab either in the outer or inner position. Briefly, the three genes encoding for FIT-Ig were codon optimized, synthesized by Genscript and cloned as follows: i) the VL of the outer Fab, followed by the full constant region (lambda or kappa), is fused with the VH of the inner and cloned into the Igγ1 expression vector (modified to encode for the LALA mutation). The resulting polypeptide 1 is formed by VL and CL of the outer Fab, VH of the inner Fab fused to IgG1 CH1-hinge-CH2-CH3 domains; ii) the VH gene of the outer Fab (encoding for polypeptide 2 formed by VH and CH1 of the outer Fab) was cloned into the Fab expression vector (Igγ1 expression vector in which a stop codon is introduced after the codon encoding for the CH1 cysteine residue 220); iii) the VL gene of the inner Fab is cloned into the Igκ or Igλ expression vectors (encoding for polypeptide 3 formed by VL and CL of the inner Fab). Recombinant FIT-Ig mAbs were produced by transient transfection of EXPI293 cells (Invitrogen) using a molar ratio of 1:3:3 of the three constructs described above (as described in WO 2015/103072 A1), purified by Protein A chromatography (GE Healthcare) and desalted against PBS. The proteins were analyzed by SDS-PAGE in both reduced and non-reduced conditions and their concentrations determined by BCA (Pierce, Rockford, IL). In non-reduced conditions, FIT-Ig migrated as a major single band of approximately 250 KDa. In reducing conditions, each of the FIT-Ig proteins yielded two bands, one higher MW band is polypeptide 1 of approximately 75 KDa, and one lower MW band corresponds to both polypeptide 2 and 3 overlapped at

approximately 25 kDa. To further study the physical properties of FIT-Ig in solution, size exclusion chromatography (SEC) was used to analyze each protein. Purified FIT-Ig, in PBS, was applied on a Superdex 200 Increase 5/150 GL. All proteins were determined using UV detection at 280 nm and 214 nm. FIT-Ig proteins exhibited a single major peak, demonstrating physical homogeneity as monomeric proteins.

Example 12: *In vitro* characterization of an antibody according to the present invention (FIT-1)

The FIT-Ig bispecific antibody (here designated FIT-1) with ZKA190 in the outer and ZKA185 in the inner Fab positions (Figure 19E) was selected and further characterized. ELISA showed FIT-1 to bind DIII, E and VLP (Figure 19F). FIT-1 retained high neutralizing potency against ZIKV strains, with IC₅₀ values largely similar to those of the parental ZKA190 and ZKA185 antibodies (Figure 19G). FIT-1 was produced using the backbone IgG1 antibody in the LALA format, thereby eliminating any possibility of causing ADE. Several lines of evidence suggest that the ZKA190 and ZKA185 moieties in the FIT-1 format are both active. Firstly, FIT-1 bound to E protein with higher affinity than either the parental ZKA190 and ZKA185 antibodies (KD values: ZKA185 1.8 nM, ZKA190 9.3 nM and FIT-1 KD <1 pM due to slower dissociation rate, presumably through avidity effects). Secondly, FIT-1 effectively neutralized all the ZKA190, ZKA185 and ZKA230 MARMs (Figure 19H) in contrast to the individual mAbs. The neutralizing activity of the Fab fragment of FIT-1 (each comprising one ZKA190 and one ZKA185) was reduced only by about 6-fold (Figure 19I, right panel).

Next, the ability of FIT-1 to select MARMs was tested (as described above). However, despite eight rounds of serial passages, no MARMs could be isolated. By contrast, MARMs appeared after 3 to 4 passages when individual mAbs were used. These results suggest that the use of FIT-1 as a therapeutic is safer, since simultaneous mutations in both DIII and DII are less likely to occur.

Confocal microscopy studies using Vero cells also showed that FIT-1, as ZKA190, likely inhibits virus infection at a post-attachment step, likely fusion (Fig. 19J).

Finally, FIT-1, as well as its Fab fragment, blocked ADE of human anti-DENV2 plasma or DV62 at concentrations above 0.1 nM and 10 nM, respectively (Figure 19K), demonstrating that FIT-1 did not cause ADE and could block ADE of monocytic cells by poorly neutralizing cross-reactive antibodies.

Example 13: In vivo therapeutic potential of FIT-1

To evaluate the therapeutic potential of FIT-1, three different doses (15, 5 and 1 mg/kg) were administered at three different time-points to female A129 mice following ZIKV infection. Briefly, female A129 mice were assigned to 10 distinct groups (control and three different doses with three different administration time points for each dose). All animals were challenged subcutaneously with 102 pfu ZIKV (strain MP1751) and followed for 14 days. Mice of the nine treatment groups were administered with bispecific antibody FIT-1 diluted in PBS at 15, 5 or 1 mg/kg via the intraperitoneal (i.p.) route in a volume of 500 µl on day 1, day 2, or day 3 after ZIKV virus challenge. Weights and temperatures of all animals were monitored daily and clinical observations were recorded at least twice per day. On day 5 post-challenge, 50 µl of blood was collected from each animal into a RNAprotect tube (Qiagen,UK) and frozen at -80°C. At the end of the study (14 days post-challenge) or when animals met human endpoints, necropsies were undertaken, and blood and sections of brain and ovary were collected for virological analysis.

Results are shown in Figure 20. The data show that at a dose of 15 mg/kg, survival rates were 100% without signs of morbidity even when treatment was given three days post-infection (Figure 20A); viral titers were abrogated and no escape mutants were detected, indicating high *in vivo* efficacy. Administration of 5 mg/kg resulted in survival rates of 70-100%, also no escape mutants were detected on day 5 after infection. The lowest dose tested (i.e., 1 mg/kg) protected when administered on day 1 or 2, but not day 3, after infection.

Example 14: Effect of FIT-1 on disease in a congenital infection model in AG129 mice

The effect of treatment of infected dams with FIT-1 on the pups born to the infected and treated dams was assessed in a mouse model of congenital infection with ZIKV, which results in live offspring after congenital exposure with ZIKV. In this model, AG129 mice, deficient in IFN receptors, are used, which results in viral replication in the placenta, transmission of virus to the fetus, and potential long-term implications such as intrauterine growth restriction and hearing deficits.

The effect of FIT-1 treatment on various parameters in the context of intrauterine infection was tested. To this end, mice were infected with ZIKV 7 days post-coitus (dpc) and treated with FIT-1 1 or 3 days after virus challenge (cf. Example 13). Various outcomes of disease, such as virus titer in the fetus and placenta and intrauterine growth restriction, were assessed to determine the effect of FIT-1 treatment.

Materials and Methods:

Animals: 42 female AG129 mice were used. Groups of animals were randomly assigned to experimental groups and individually marked with ear tags. Hormonal treatment was used to induce estrous in females. Females were individually placed with males and examined for a vaginal plug 0.5 days post-coitus (dpc).

Virus: Zika virus Malaysia (P6-740) was used. A suitable challenge dose was administered via s.c. injection in a volume of 0.1 ml.

Test agent: FIT-1 was administered at a dose of 45 mg/kg. The non-specific control antibody MPE8-LALA Ctr IgG1 was used as an isotype control placebo treatment.

Quantification of virus: The virus titer of various tissues was quantified using a quantitative RT-PCR assay. Total RNA was extracted from tissue samples using TRIzol (ThermoFisher Scientific, Cat#15596018). A volume of 2 µl of the RNA preparation was used for amplification. Serial dilutions of synthetic RNA spanning the amplification region were used

to make a positive control; undiluted synthetic ZIKV RNA had $10^{8.0}$ copies/ μ l. Samples were subjected to 40 cycles of 15 seconds at 95°C and 60 seconds at 60°C following an initial single cycle of 30 min at 50°C and 10 min at 95°C. Samples of unknown quantity were quantified by extrapolation of C(t) values using a curve generated from serial dilutions of synthetic ZIKV RNA.

Experiment Design: Dams were challenged 7 days-post coitus (dpc), and were treated with FIT-1 24 or 72 hours post virus challenge. 2 dams per group were necropsied 11 days after virus challenge. The placenta, fetal tissues, brain tissue, and spleen tissue were collected for determination of virus titer by QRT-PCR. 2 females per group were followed through parturition. Occipito-frontal diameter (OF) of the head and crown rump length (CRL) of pups was recorded with a digital caliper and intrauterine growth restriction was determined by determining the pup size by the formula: CRL X OF. Weights of pups and dams were measured at various times.

Statistical analysis: Survival data were analyzed using the Wilcoxon log-rank survival analysis (Prism 5, GraphPad Software, Inc).

Results and Discussion:

Treatment with FIT-1 was evaluated in a mouse model of congenital infection and disease associated with ZIKV infection. Treatment with FIT-1 was protective to pregnant females with the large majority of treated females being protected from mortality, regardless of when treatment was administered (Figure 21). Females treated with a non-specific negative control antibody had a mortality rate that was similar to that observed in previous studies.

A trend towards improved measurements in average pup size. The average size of pups from dams treated with FIT-1 were higher than those treated the control MPE8 and were similar to sham-infected animals (Figure 22). This difference was less pronounced in regard to fetal weight, where all groups had similar averages (Figure 23). There was a trend towards higher placenta weight in dams treated with FIT-1 (Figure 24).

The virus titer of various tissues is shown in Figure 25. Significant reduction in viral RNA in the fetus and placenta of dams treated with FIT-1 were observed (Figure 25A and 25B, respectively). The reduction was especially evident in placental tissues with an approximate 5-log₁₀ reduction in ZIKV RNA levels. Maternal spleen and brain also had significantly reduced viral RNA in FIT-1-treated animals as compared with MPE8, with several log₁₀ reductions in levels (Figure 25C and 25D, respectively).

Conclusions:

Overall, these data support a protective role of FIT-1 in preventing or treating disease in fetuses congenitally exposed to ZIKV. A trend towards improvement in fetal and placental size parameters was observed, with a highly significant reduction in virus titer in various maternal and fetal tissues.

Example 15: Effect of FIT-1 on disease in a testis infection model in AG129 mice

Sexual transmission and persistent infection of the male reproductive tract has been documented in men infected with ZIKV (D'Ortenzio E, Matheron S, Yazdanpanah Y, et al. Evidence of Sexual Transmission of Zika Virus. N Engl J Med 2016; 374:2195-8). In the AG129 mouse strain, severe disease is usually observed around 2 weeks after virus challenge, including significant replication of the virus in the testes of mice (Julander JG, Siddharthan V, Evans J, et al. Efficacy of the broad-spectrum antiviral compound BCX4430 against Zika virus in cell culture and in a mouse model. Antiviral Res 2016; 137:14-22). Key sites of virus replication in the reproductive tract of male AG129 mice include the epididymis and testicle, as well as various accessory sex glands.

In the present study, the effect of FIT-1 on ZIKV infected male mice is assessed in the testis infection model. To this end, male AG129 mice were infected with ZIKV and the pathology in the male reproductive tract after ZIKV infection and treatment with FIT-1 is assessed.

Materials and Methods:

Animals: Male AG129 mice were used. Groups of animals were randomly assigned to experimental groups and individually marked with ear tags.

5

Virus: Zika virus (Puerto Rican strain, PRVABC-59). A challenge dose of 10^2 CCID₅₀ was administered via s.c. injection in the inguinal fold in a volume of 0.1 ml. This challenge dose is typically lethal in untreated AG129 mice with mortality occurring around 2 weeks after challenge.

10

Test agent: FIT-1 was administered at a dose of 15 mg/kg. The non-specific control antibody MPE8-LALA Ctr IgG1 was used as an isotype control placebo treatment.

Histopathology: Tissues were collected and incubated for 24 hours in neutral buffered formalin. Following appropriate fixation, all collected tissues were trimmed and held in 70% ethanol until routine processing, paraffin embedding and sectioning were performed. All tissues were blindly analyzed independently by a veterinary anatomic pathology resident and a board certified veterinary anatomic pathologist. A scoring system was developed to grade the severity of inflammation in the reproductive tract.

20

Experiment Design: Mice were infected with ZIKV and were monitored for 28 days post-virus challenge for survival and weight change. Treatment with 15 mg/kg of FIT-1 was performed 24 or 72 h after virus challenge. A single treatment was administered i.p. in a volume of 0.1 ml. An isotype matched control Ab, MPE8-LALA Crt IgG1, was administered as described above with treatment occurring 24 h after virus challenge. A group of mock-infected, FIT-1-treated mice were included as toxicity controls and a group of normal controls was included. Individual weights were taken on 0, and every other day from 7-21 dpi. Mice were observed daily for signs of disease including conjunctivitis, hunching, and limb weakness or paralysis and initial onset of disease signs was recorded. A cohort of 3 animals was necropsied on 6 dpi and tissue samples were collected for histopathologic analysis.

30

Statistical analysis: Survival data were analyzed using the Wilcoxon log-rank survival analysis (Prism 5, GraphPad Software, Inc).

Results and Discussion:

5 Zika virus (ZIKV) can persist in male reproductive tissues for extended periods up to six months, representing a clear target for antiviral treatment. To determine the efficacy of a bispecific anti-ZIKV Ab in preventing or reducing pathology to the male reproductive tract, groups of mice were treated 24 or 72 h after virus challenge with a Puerto Rican isolate of
10 ZIKV. Survival, weight change, and histopathology were used to determine the efficacy of mAb treatment. An isotype control mAb, MPE8-LALA Ctr IgG1, was used as a placebo treatment.

A significant ($P < 0.05$) improvement in survival was observed as compared with placebo mAb
15 treatment (Figure 26). Complete survival was observed in mice treated 24 h post-challenge with FIT-1, while mice treated at 72 h post-virus inoculation resulted in one animal that succumbed to virus infection. This single animal was euthanized 24 days after virus challenge, which was much later than animals treated with placebo (Figure 26). Since infection of AG129 mice with ZIKV results in lethality, which is much more severe than a
20 typical natural infection with this virus, high levels of protection that are seen with FIT-1 are very promising.

Mean weight change of mice treated with FIT-1 was similar to that of sham-infected treatment controls, while mean weight of mice treated with MPE8 declined rapidly after 7 dpi, which
25 further demonstrates potent protection of the mice from disease (Figure 27).

Since the primary purpose of this study was to evaluate the effects of treatment on the male reproductive tract, and in previous studies the testes and epididymides were the most severely impacted after infection, specific attention was paid to the histopathology of these tissues. No
30 disease was observed in the testicle or epididymis of mice treated with FIT-1, aside from a single animal in the 24 h treatment group (Figure 28), further demonstrating the efficacy of FIT-1 treatment. FIT-1 also protected mice from disease when treatment was initiated 72 h

after virus challenge and none of the mice treated at this time had observable disease in the testicle or epididymis (Figure 28). The majority of mice in the placebo treatment group had inflammation in the testicle (2/3) and epididymis (3/3) (Figure 28), although disease severity in this study was fairly mild.

5

Conclusions:

Treatment with FIT-1 was effective in reducing all evaluated disease parameters. Therapeutic treatment up to 72 h after virus challenge was highly efficacious.

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Example 16: Prophylactic and therapeutic efficacy of FIT-1 in rhesus macaques challenged with ZIKV

15 This study evaluated the prophylactic and therapeutic efficacy of a bi-specific antibody targeting Zika virus (ZIKV) in Indian Rhesus Macaques (IRM) challenged with ZIKV strain PRVABC59. Sixteen (16) IRMs were randomized into three treatment groups. One group received FIT-1 one day prior to challenge (5mg/kg) and a second received the treatment one day following challenge (15 mg/kg). A third group was treated with an isotype control (FIT-3, 20 5 mg/kg) one day prior to challenge. On Day 0, all IRMs were challenged with 1×10^5 PFU of ZIKV strain PRVABC59 delivered by subcutaneous (SC) injection. Sera, urine, and saliva were collected at predetermined time points and tested for ZIKV load as measured by quantitative RT-PCR.

25 Methods:

Prior to Study Day 0, sixteen (16) IRMs were randomized into respective groups according to gender/weight using Provantis Software. On Days -1 or 1, animals received either FIT-1 or isotype control FIT-3 delivered intravenously at the dose listed in Table 4 below. On Day 0, 30 all macaques were anesthetized and challenged with 0.5 mL of wild type ZIKV strain PRVABC59 with a target challenge dose of 1.0×10^5 PFU per animal by subcutaneous

injection. Blood, urine, and saliva samples were collected at predetermined time points as indicated in Table 5 for an assessment of viral load by RT-qPCR.

Table 4: Animal Groupings

Group	Treatment	Treatment Day	Route, Dosage	Challenge ¹
1 (3M/3F)	FIT-1	Day -1	i.v., 5 mg/kg	PRVABC59 (1×10 ⁵ PFU)
2 (3M/3F)	FIT-1	Day +1	i.v., 15 mg/kg	PRVABC59 (1×10 ⁵ PFU)
3 (2M/2F)	FIT-3	Day -1	i.v., 5 mg/kg	PRVABC59 (1×10 ⁵ PFU)

5 ¹Subcutaneously challenged on Day 0 with 0.5 mL of wild type ZIKV.

Table 5: Key Activities

Study Day:	-1	0	1	5	10	15	20	25	30
Treatment	✓		✓						
ZIKV challenge (s.c.)		✓							
Daily Observations		All animals were observed two times daily							
Body Weight		Daily				✓	✓	✓	✓
Body Temperature		Daily				✓	✓	✓	✓
Blood Collections ¹		Daily				✓	✓	✓	✓
Urine/Saliva Collections		✓		✓	✓	✓	✓	✓	✓
Viral Load: RT-qPCR		Daily				✓	✓	✓	✓
Blood Volume (mL)		2				2	2	2	20
Euthanasia									✓

¹Day 0 and 1 blood was collected prior to challenge and treatment

- 10 On Study Days -1 (Groups 1 and 3) and 1 (Group 2) anesthetized animals were administered either FIT-1 (stock concentration: 3.67 mg/mL) or FIT-3 (stock concentration: 3.79 mg/mL) via intravenous injection into the right saphenous or cephalic veins.

- 15 ZIKV strain PRVABC59; Human/2015/Puerto Rico (American Isolate) was the challenge material used in this study. Preparation of the virus inoculum was performed in a Class II Biological Safety Cabinet under BSL-2 conditions. The virus stock was thawed in a 37 ± 1 °C

water bath, vortexed, and diluted with VP-SFM to yield an inoculum of the appropriate concentration of 2×10^5 PFU/mL. Each syringe was filled with 0.5 mL of virus inoculum and kept on ice until transferred to the animal facility for dosing. On Study Day 0, all animals were anesthetized, the injection site clipped, wiped with alcohol and marked with an indelible marker. Animals were inoculated SC on the anterior surface of the left forearm with 0.5 mL of the ZIKV isolate and dose indicated in Table 4.

All macaques were observed twice daily throughout the quarantine and study periods for signs of morbidity and mortality. Animals were observed twice daily (at no less than 8 hour intervals) for responsiveness and clinical signs including rash, erythema, conjunctivitis, ocular discharge and swelling. For all animals, blood was collected at the time points indicated in Table 5 for *in vitro* testing via RT-qPCR viral load. During the terminal bleed on Day 30, a volume not exceeding 20 mL per animal was collected. For all animals, urine was collected at the time points indicated in Table 5 for *in vitro* testing via RT-qPCR for monitoring of virus shedding. Animals were individually housed during the urine collection periods of the study. Urine was collected directly from the cage pans, placed on wet ice following collection, separated into aliquots and stored at -70°C or below until ready for assay testing. Saliva (drool) was collected from anesthetized animals directly into tubes (up to approximately 0.5 mL). Samples were kept on wet ice following collection and stored at -70°C or below until ready for assay testing.

Viral loads were measured using a RT-qPCR method for detection of ZIKV genomes in the serum, urine, and saliva samples collected at the time points indicated in Table 5. Samples recovered from virus inoculated animals were tested using primers and probes designed for the detection of ZIKV strain PRVABC59. A description of the PCR methods, including primer and probe sequences, has been published (Goebel et. al., 2016, A Sensitive virus yield assay for evaluation of antivirals against Zika virus. J. Virol. Methods). Viral RNA was isolated from biological fluids using the QIAmp Viral RNA mini kit (Qiagen, 52906). The viral RNA was eluted with sterile RNase and DNase free H_2O and stored at -70°C or below. The lower limit of quantitation (LLOQ) of this assay was determined to be 10 copies per reaction.

An aliquot of the challenge virus inocula was back-titrated by standard plaque assay on Vero cells to confirm the actual delivered dose. Ten-fold serial dilutions of the challenge inocula were used to infect confluent monolayers of Vero cells in 6-well plates that were plated the day before. Plates were incubated at 37°C and 5% CO₂ for 1 hour before the addition of overlay media containing 0.5% agarose. Plates were incubated for 3 days until discernable plaques form after which they were fixed, stained with crystal violet and counted.

Results:

10 Macaques were monitored twice daily for signs of mortality and morbidity for the duration of the study. All animals survived to the scheduled termination. Body weights and temperatures of all animals were measured at the time points indicated in Table 5. There was no significant body weight loss during the course of the study. All animals maintained a normal range of body temperatures throughout the study. Clinical observations were limited to mild redness
15 at the challenge site in a few animals.

Viral loads were measured using a RT-qPCR method for detection of ZIKV genomes in serum, urine, and saliva samples collected at the time points indicated in Table 5. Viral load in the serum is presented in Figure 29.

20 Animals in Group 3, treated with the isotype control, had detectable viral load in the serum the day following challenge. Viral load in three of the four animals peaked above 1×10^5 genome copies/mL (GC/mL) on either Day 2 or 3. The average serum viral load peaked in this group on Day 3 at 1.15×10^5 GC/mL. Viral loads decreased below the LLOQ of the assay (860
25 GC/mL) by Day 4 in one animal and by Day 5 in the remaining three.

Group 2 animals, treated with 15 mg/kg of FIT-1 the day after challenge, had an average viral load of 3.99×10^3 GC/mL prior to treatment. On Day 2, average serum viral load decreased to only 96.5 GC/mL. While low levels of viral RNA were sporadically detected after Day 1, at
30 no point following treatment were viral loads detected in Group 2 animals at or above the LLOQ of the RT-qPCR assay.

Pretreatment with 5 mg/kg of FIT-1 decreased Day 1 average serum viral loads by greater than 50-fold compared to Group 3. At no time point after challenge were viral loads detected at or above the LLOQ of the assay, and by Day 2 no viral RNA was detected in the serum of any of the Group 1 animals.

5

Only sporadic, low levels of ZIKV RNA were detected in the urine or saliva from any of the animals. At no point were viral loads detected at or above the LLOQ of the assay in urine or saliva from any animal.

- 10 An aliquot of the challenge virus inocula was back-titrated by standard plaque assay on Vero cells to confirm the actual delivered dose. The plaque assay yielded a titer of 1.7×10^5 PFU/mL.

Summary and Conclusions:

- 15 This study evaluated the prophylactic and therapeutic efficacy of FIT-1 in IRMs challenged with ZIKV. There was no mortality throughout the course of the study and clinical observations were limited to mild redness at the challenge site in a few animals. Viral load as detected by RT-qPCR in serum collected following challenge was the primary end point of the study. Viral RNA was readily detected in the serum of all animals treated with the isotype control, with viral loads peaking on Days 2 or 3 and sustaining at levels above the LLOQ of 860 GC/mL until Days 4 or 5. Average peak load was 1.15×10^5 GC/mL on Day 3. In contrast, prophylactic treatment with 5 mg/kg of FIT-1 effectively reduced peak viral loads and time to viral clearance in ZIKV challenged IRMs. Low levels of viral RNA were detected in all six animals from this group on Day 1 but by Day 2, no viral RNA was detected in any animal. At no point was ZIKV RNA detected above the LLOQ of 860 GC/mL in the serum of any animal from this group. Similarly, therapeutic treatment with 15 mg/kg of FIT-1 the day following challenge reduced both peak viral loads and time to viral clearance from the serum compared to animals treated with the isotype control. Group 2 macaques had a mean peak viral load of 3.99×10^3 GC/mL on Day 1 but after treatment on Day 1, average viral loads in the serum of this group decreased to only 96.5 GC/mL by Day 2. No animals in this group had viral loads above the LLOQ of 860 GC/mL for the remainder of the observation period.
- 20
- 25
- 30

Tables of Sequences and SEQ ID Numbers

ZKA190	SEQ ID NO.	Amino acid sequence
CDRH1	1	GFTFSKYG
CDRH2	2	ISYEGSNK
CDRH3	3	AKSGTQYYDTTGYEYRGLEYFGY
CDRL1	4	QSVSSSY
CDRL2	5	DAS
CDRL2 long	6	LIYDASSRA
CDRL3	7	QQYGRSRWT
VH	8	QVQLVESGGGVVQPGRSLRLSCAAS GFTFSKYGMHWVRQAPGKGLE WVAV ISYEGSNK YYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA VYYC AKSGTQYYDTTGYEYRGLEYFGY WGQGT LVTVSS
VL	9	EIVLTQSPGTL SLSPGERATLSCRAS QSVSSSY LAWYQQKRGQAPR LLIY DASSRAT GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC QQY GRSRWTF GQGTKVEIK

ZKA190	SEQ ID NO.	Nucleic acid sequence
CDRH1	10	ggattcaccttcagtaaatatggc
CDRH2	11	atatcatatgaggggaagtaataaa
CDRH3	12	gcgaaatcggggacccaatactatgatactactgggttatg agtataggggtttggaatactttggctac
CDRL1	13	cagagtgttagtagcagttac
CDRL2	14	gatgcatcc
CDRL2 long	15	ctcatctat gatgcatcc agcagggcc

CDRL3	16	cagcagtatggttaggtcaaggtggaca
VH	17	caggtgcagctgggtggagtctgggggagggcgtggtccagc ctgggaggtccctgagactctcctgtgcagcctct ggatt caccttcagtaaatatggcatgcactgggtccgccaggct ccaggcaaggggctggagtgggtggcagtt atatcatatg agggaagtaataaa tattatgcagactccgtgaagggccg attcaccatctccagagacaattccaagaacacgctgtat ctgcaaataaacagcctgagagctgaggacacggcagtg attactgt gcgaaatcggggacccaatactatgatactac tggttatgagtataggggtttggaatactttggctactgg ggccaggggaaccctggtcaccgtctcctcag
VL	18	gaaattgtgttgacgcagctctccaggcaccctgtctttgt ctccaggggaaagagccaccctctcctgcagggccagt ca gagtgttagtagcagttact tagcctggtaccagcagaaa cgtggccagggtcccagggtcctcatctat gatgcaccca gcagggccactggcatcccagacaggttcagtggcagtg gtctgggacagacttcactctcaccatcagcagactggag cctgaagattttgcagtgattactgt cagcagtatggtta ggtcaaggtggaca attcgccaagggaaggtggaat caaac

ZKA185	SEQ ID NO.	Amino acid sequence
CDRH1	19	GYSFTSYW
CDRH2	20	FDPSDSQT
CDRH3	21	ARRYCSSSSCYVDN
CDRL1	22	ALPNKF
CDRL2	23	EDN
CDRL2 long	24	VIY EDN KRP
CDRL3	25	YSTDSSSNPLGV
VH	26	EVQLVQSGAEVKKPGESLRISCKGSG GYSFTSYW ITWVRQMPGKGLE WMAK FDPSDSQT NYSPSFQGHVTISVDKSISTAYLQWSSLKASDTA MYYC ARRYCSSSSCYVDN WGQGLVTIFS

VL	27	SYELTQPPSVSVSPGQTARITCSGD ALPNKF AYWYRQKSGQAPVLV IY EDN KRPSGIPERFSGSSSGTMATLTISGAQVEDEADYHC YSTDS SSNPLGV FGGGTKLTVL
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ZKA185	SEQ ID NO.	Nucleic acid sequence
CDRH1	28	ggatatagttttaccagttactgg
CDRH2	29	tttgatcctagtgactctcaaacc
CDRH3	30	gcgagaagataattgtagtagtagtagttgttatgtggacaa t
CDRL1	31	gcattgccaaataaattt
CDRL2	32	gaggacaac
CDRL2 long	33	gtcatctat gaggacaac aaacgaccc
CDRL3	34	tactcaacagacagcagttctaatcccctgggagta
VH	35	gaagtgcagctggtgcagtcgggagcagaggtgaaaaagcc cggggagtccttgaggatctcctgtaagggttct ggatata gttttaccagttactgg atcacctgggtgcgccagatgcc gggaaaggcctggagtggatggcgaag tttgatcctagtga ctctcaaacc aactacagcccgctccttccaaggccacgtca ccatctcagttgacaagtccatcagcactgcctacttgtag tggagcagcctgaaggcctcggacaccgccatgtattactg tgcgagaagataattgtagtagtagtagttgttatgtggaca attggggccaggggaaccctggtcaccatcttctcag
VL	36	tcctatgagctgacacagccaccctcggtgtcagtggtccc aggacaaacggccaggatcacctgctctggagat gcattgc caataaattt gcttattggtaccggcagaagtcaggccag gcccctgttctggtcatctat gaggacaac aaacgaccctc cgggatccctgagagattctctggctccagctcagggacaa tggccaccttgactatcagtggggcccaggtggaggatgaa gctgactaccactgt tactcaacagacagcagttctaatcc cctgggagta ttcggcgaggaggaccaagctgaccgtcctag

ZKA230	SEQ ID NO.	Amino acid sequence
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CDRH1	37	GGSISSDY
CDRH2	38	IYYSGST
CDRH3	39	ARRRKYDSLWGSFAFDI
CDRL1	40	SSNIGGNY
CDRL2	41	IND
CDRL2 long	42	LIC IND HRP
CDRL3	43	ATWDDSLGGLV
VH	44	QVQLQESGPGGLVKPSETLSLTCAVSG GGSISSDY WSWIRQPPGKGLE WIGY IYYSGST NYNPSLKSRTISVDTSKNHFSKLNSVTAADTAV YYC ARRRKYDSLWGSFAFDI WGQGTMTVSS
VL	45	QSVLTQPPSASGTPGQRTISCSGSS SSNIGGNY VYWYQQLPGTAPK LLIC IND HRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYC CATW DDSLGGLV FGGGTKLTVL

ZKA230	SEQ ID NO.	Nucleic acid sequence
CDRH1	46	ggtgggtccatcagtagtgactac
CDRH2	47	atctattacagtgggagcacc
CDRH3	48	gcgaggaggaggaagtatgattccctttgggggagttttgc ttttgatatc
CDRL1	49	agctccaacatcggaggtaattat
CDRL2	50	attaatgat
CDRL2 long	51	ctcatctgt attaatgat caccggccc
CDRL3	52	gcaacatgggatgacagcctgggtggccttgta

VH	53	caggtgcagctgcaggagtcgggcccaggcctggtgaagcc ttcggagaccctgtccctcacctgcgcagtcctct ggtggct ccatcagtagtgactact ggagctggatccggcagccccc gggaagggaactggagtggaattgggtat atctattacagtgg gagcacca aactacaacccctccctcaagagtcgagtcacca tatcagtagacacgtccaagaaccacttctccctgaagctg aactctgtgaccgctgcggaacggccgtgtattactgt gc gaggaggaggaagtatgattccctttgggggagttttgctt ttgatata ctggggccaagggaacaatggtcacctctcttca g
VL	54	cagtctgtgctgactcagccaccctcagcgtctgggacccc cgggcagaggggtcaccatctcttgttctggaagc agotcca acatcggaggttaattat gtatactggtaccagcagctccca ggaacggcccccaactcctcatctgt attaatgat caccg gccctcaggggtccctgaccgattctctggctccaagtctg gcacctcagcctccctggccatcagtgggctccagtcagag gatgaggctgattattactgt gcaacatgggatgacagcct gggtggccttgta ttcggcggagggaaccaagctgaccgtcc tag

ZKA78	SEQ ID NO.	Amino acid sequence
CDRH1	55	GFTFSNYA
CDRH2	56	IGRNGDSI
CDRH3	57	VKDLAIPESYRIEADY
CDRL1	58	QSVLYRSNNKNY
CDRL2	59	WAS
CDRL2 long	60	LIY WAS TRE
CDRL3	61	QQYYSSPRT
VH	62	EVQLAESGGGLVQPGGSLTLSCSGS GFTFSNYA MVWARQAPGKGLE YVSG IGRNGDSI YYTDSVKGRFTISRDNKSMVYLQMSSLRTEDTA VYYC VKDLAIPESYRIEADY WGQGTLVIVSA
VL	63	DIVMTQSPDSLAVSLGERATINCKSS QSVLYRSNNKNY LSWYQQKP GQPPKLLIY WAS TRESGPVDRFSGSGGTDFTLTISPLQAEDVAVY YC QQYYSSPRT FGQGTKVEIK

ZKA78	SEQ ID NO.	Nucleic acid sequence
CDRH1	64	ggcttcacttttagtaactatgca
CDRH2	65	atcgggcgcaacggggactctatc
CDRH3	66	gtgaaagatctggccatccccgagtcctacagaattgaagctgattat
CDRL1	67	cagtcctgtctgtaccgctctaacaacaagaattac
CDRL2	68	tgggcttca
CDRL2 long	69	ctgatctatt tgggcttca acccgggaa
CDRL3	70	cagcagtactattctagtcctcgaact
VH	71	gaggtgcagctggcagaatcaggcgggggactgggtccagc ctggcggcagcctgacactgtcttgagtggtgatc aggctt cacttttagtaactatgca atgggtgtgggcaaggcaggct cctgggaagggaactggagtatgtctctggc atcgggcgca acggggactctatc tactatactgatagtgtgaagggccg gttcaccatcagcagagacaatagcaaatccatgggtgtac ctgcagatgagctccctgcgaaccgaagacacagcagtg actattgc gtgaaagatctggccatccccgagtcctacag aattgaagctgattat tggggacagggcaccctggtcac gtgagcgccg
VL	72	gacatcgtgatgacacagtcctccagatagtctggcagtc gtctgggggagagggccactattaactgcaagagctcc ca gtccgtgctgtaccgctctaacaacaagaattac ctgtct tggatcagcagaagcccgacagccccctaaactgctga tctatt tgggcttca acccgggaaagcggcgtcccagacag attctcaggcagcgggtccggaacagacttcaccctgaca attagccccctgcaggcagaggacgtggctgtctactatt gt cagcagtactattctagtcctcgaact ttcggccaggg gaccaaggtggaatcaaac

ZKA64	SEQ ID NO.	Amino acid sequence
CDRH1	73	GYTFTGYH
CDRH2	74	INPNSGGT

CDRH3	75	ARMSSSIWGF DH
CDRL1	76	QSV LIN
CDRL2	77	GAS
CDRL2 long	78	LIY GAS SRA
CDRL3	79	QQYNDWPPIT
VH	80	QVQLVQSGAEVKKPGASVKVSCKAS GYTFTGYH IDWVRQARGQGLE WMGR INPNSGGT NYAQKFQGRVTMTRDTSISTAYMQLSRLRSDDSA VYYC ARMSSSIWGF DH WGQGLVTVSS
VL	81	EIVMTQSPATLSVSPGERATLSCRAS QSV LIN LAWYQQKPGQAPRL LIY GAS SRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYC QQYN DWPPIT FGQGRLEIK

ZKA64	SEQ ID NO.	Nucleic acid sequence
CDRH1	82	ggctacaccttcacagggtatcac
CDRH2	83	attaaccctaattctggcgggacc
CDRH3	84	gctcggatgagctcctctatattggggcttcgatcat
CDRL1	85	cagtctgtgctgattaac
CDRL2	86	ggagcatcc
CDRL2 long	87	ctgatctat ggagcatcc tcagggt
CDRL3	88	cagcagtacaatgattggccccctatcaca
VH	89	caggtgcagctggtccagagcggagcagaggtgaagaaacc cggcgccctcagtgaaggtcagctgcaaagcttc ggctaca ccttcacagggtatcac atcgactgggtgaggcaggcaaga ggacagggactggaatggatgggacgg attaaccctaattc tggcgggacca aactacgcccagaagtttcagggccgagtga ctatgaccagagacaccagcatctccacagcttatatgcag ctgtcccggctgagatctgacgatagtgccgtctactattg tgctcggatgagctcctctatattggggcttcgatcat tggg ggcaggggaacactgggtgactgtcagttcag

VL	90	gagatcgtgatgactcagtcctccagccaccctgtcagtcag cccaggagaaacgggcaaccctgtcttgagagcctcc agt ctgtgctgattaac ctggcttggtaccagcagaagccaggc caggcaccgccgactgctgatctat ggagcatcct ccagggc taccggcattcctgcacgcttcagtggtatcaggaagcggaa cagagtttaccctgacaatctctagtctgcagtcggaagac ttcgtgtctactattgt cagcaggtacaatgattggccccc tatcaca tttgccagggggactagactggagatcaagc
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Constant regions	SEQ ID NO.	Sequence
IgG1 CH1-CH2-CH3 aa	91	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT YICNVNHKPSNTKVDKRVKPKSCDKHTHTCPPCPAPELLG GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEAL HNHYTQKSLSLSPGK
IgG1 CH1-CH2-CH3 LALA aa	92	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT YICNVNHKPSNTKVDKRVKPKSCDKHTHTCPPCPAPEAAAG GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEAL HNHYTQKSLSLSPGK
IgG CK aa	93	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADY EKHKVYACEVTHQGLSSPVTKSFNRGEC
IgG CL aa	94	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVA WKADSSPVKAGVETTPSKQSNNKYAASSYLSLTPEQWK SHRSYSQCVTHEGSTVEKTVAPTECS
IgG1 CH1-CH2-CH3 nucl	95	gcgtcgaccaaggcccatcggtcttcccctggcaccctcctcaagagcac ctctgggggcacagcgccctgggtgcctgggtcaaggactactccccgaac ctgtgacggtctcgtggaactcaggcgccctgaccagcggtgcacacctcc cggctgtctacagtctcaggactctactccctcagcagcggtgaccgtgc cctccagcagctgggcacccagacctacatctgcaacgtgaatcacaagccc agcaacaccaaggtggacaagagagttgagcccaaatctgtgacaaaactca cacatgccaccgtgccagcacctgaactcctggggggaccgtcagttctct cttcccccaaaacccaaggacacctcatgatctccggaccctgaggtca catgctggtggtggacgtgagccacgaAgaCctgaggtcaagttcaactgg tacgtggacggcggtggaggtgcataatgccaagacaagccgaggaggagc agtacaacagcacgtaccgtggtgcagctcctcaccgtcctgcaccaggact

		ggctgaatggcaaggagtacaagtgaagggtccaacaaagccctcccagc ccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccac aggtgtacaccctgccccatcccgggaggagatgaccaagaaccaggtcag cctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggga gagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctgga ctccgacggctccttctctatagcaagctaccgtggacaagagcaggtg gcagcaggggaacgtcttctatgctccgtgatgcatgaggctctgcacaacca ctacacgcagaagagcctctccctgtccccgggtaaa
IgG1 CH1-CH2- CH3 LALA nucl	96	gcgtcgaccaagggcccatcggtcttccccctggcaccctcctccaagagcac ctctgggggacagcggccctgggctgcctggtcaaggactacttccccgaac ctgtgacgggtcctggaactcaggcgccctgaccagcggcgtgcacacttcc cggctgtctacagtctcaggacttactccctcagcagcgtggtagcgtgc cctccagcagcttgggcacccagacctatctgcaacgtgaatcacaagccc agcaacaccaaggtggacaagagagttgagcccaaatctgtgacaaaactca cacatgcccaccgtgcccagcacctgaaGCCGCGgggggaccgtcagtc ttctcttcccccaaaaccaaggacacctcatgatctccggaccctgag gtcacatgcgtggtggtagcgtgagccacgaagccctgaggtcaagtcaac tggtagcgtggacggcgtggagggtgcataatgccaagacaaagcgcgggagg agcagtacaacagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccag gactggctgaatggcaaggagtacaagtgaagggtctccaacaaagccctccc agccccatcgagaaaaccatctccaaagccaaagggcagccccgagaac cacagggtgacacctgccccatcccgggaggagatgaccaagaaccaggt cagcctgacctgcctgtcaaaggcttctatcccagcgacatcgccgtggagt ggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgct ggactccgacggctccttctctatagcaagctaccgtggacaagagcag gtggcagcaggggaacgtcttctatgctccgtgatgcatgaggctctgcaca ccactacgcagaagagcctctccctgtccccgggtaaa
IgG CK nucl	97	cGTacGgtggctgaccatctgtcttcatcttcccgccatctgatgagcagttga aatctggaactgcctctgtgtgtgcctgctgaataacttctatcccagagaggcc aaagtacagtggaaagggtgataacgcctccaatcgggtaactcccaggagag tgtcacagagcaggacagcaaggacagcacctacagcctcagcagcacct gacgtgagcaaaagcagactacgagaaacacaaagtctacgctgcaagtc acccatcagggcctgagctcgccgtcacaagagcttaacaggggagagt gt
IgG CL nucl	98	ggtcagcccaaggctgccccctcggtcactctgttcccgccctccttgaggag cttcaagccaacaaggccacactggtgtgtctcataagtacttaccggga gccgtgacagtggcttgaaagcagatagcagccccgtcaaggcgggagtg agaccaccacacctccaaacaaagcaacaagaacgacgagccagcagc tatctgagcctgacgcctgagcagtggaagtcacacagaagctacagctcca ggtcacgcatgaaggagcaccgtggagaagacagtggtccctacagaatgtt ca

ZKA3	SEQ ID NO.	Amino acid sequence
CDRH1	99	GFIFSNYA
CDRH2	100	IGGKGDSI

CDRH3	101	VKDLAVLESDRLEVDQ
VH	102	EVQLAESGGGLVQPGGSLRLSCSGS GFIFSNY AMVWARQAP GKGLEYVSG IGGKDSI YHIDSVKGRFTISRDN SKRTVYLQ MSRLRTEDTAVYYC VKDLAVLESDRLEVDQ WGQGTLVIVSA
ZKA4	SEQ ID NO.	Amino acid sequence
CDRH1	103	GFTFSSYV
CDRH2	104	TSYDGSNK
CDRH3	105	ARGPVPYWSGESYSGAYFDF
VH	106	QVQLVESGGGVVQPGRSLRLSCAAS GFTFSSYV MHWVRQAP GKGLEWVTV TSYDGSNK YYADSVKGRFTISRDN AKNTLYLQ MNSLRGEDTAIYYC ARGPVPYWSGESYSGAYFDF WGQGILV TVSS
ZKA5	SEQ ID NO.	Amino acid sequence
CDRH1	107	GFTFSNYY
CDRH2	108	MSSSETIK
CDRH3	109	ARSGIETVAGSIDYYGMDV
VH	110	QVQLVESGGGLVKPGGSLRLSCAGS GFTFSNYY MTWIRQAP GKGLELVSY MSSSETIK YYADSVKGRFTISRDN AKNSLYLQ MNSLRADDTARYYC ARSGIETVAGSIDYYGMDV WGHGTPVT VSS
ZKA6	SEQ ID NO.	Amino acid sequence
CDRH1	111	DFTVSNYA
CDRH2	112	VSYDGSNK
CDRH3	113	ATGVTMFQGAQTNAEYLHY
VH	114	QVHLVESGGGVVQPGRSLRLSCEAS DFTVSNYA MHWVRQAP GKGLEWVAV VSYDGSNK YYADSVKGRFTISRDN SKNTLYLQ MNSLRAEDTALYYC ATGVTMFQGAQTNAEYLHY WGQGSLVT ISS
ZKA7	SEQ ID NO.	Amino acid sequence
CDRH1	115	GFTFSRYG
CDRH2	116	VSGDGSST
CDRH3	117	VKDFWSGDQSLESDF

VH	118	EVQLVESGGGLVQPGGSLRLSCSAS GFTFSRY GMVWARQAP GKGLLEYLSG VSGDGSST YYANSVKGRFTISRDN SKNTLYLH MSRLRDEDTAMY YCVKDFWSGDQSLESDF WGQ GALVTVSS
ZKA8	SEQ ID NO.	Amino acid sequence
CDRH1	119	GFTFSAHA
CDRH2	120	ISRNEDYT
CDRH3	121	VKDFGTSPQTDF
VH	122	DERLVESGGGLVQPGGSLRLVCSAS GFTFSAHA MHWVRQPP GKGLLEYVST ISRNEDYT YYADSVKGRFTISRDN SKNSLYLQ MRRLRPEDTAI YYCVKDFGTSPQTDF WGQ GTLVAVSS
ZKA76	SEQ ID NO.	Amino acid sequence
CDRH1	123	GFTFSTYF
CDRH2	124	ISSTGSYK
CDRH3	125	ARPFHSEYTYGLDAFDI
VH	126	EVQLVESGGGLVKPGGSLRLSCAAS GFTFSTYF MHWVRQAP GKGLEWVAS ISSTGSYK FYADSVKGRFTISRDN TKNSLFLQ MNSLRAEDTAVFY CARPFHSEYTYGLDAFDI WGQ GTMLTVS S
ZKA117	SEQ ID NO.	Amino acid sequence
CDRH1	127	GGSIIRRTNSY
CDRH2	128	ISYSGST
CDRH3	129	ARLNDGSTVTTSSYFDY
VH	130	QLQLQESGPGLVKPSETLSLTCTVSG GGSIIRRTNSY WGWIRO TTGKGLQWIGS ISYSGST FYNPSLKSRVTISLDTSKDHFSL ELSSVTAADTAI YYCARLNDGSTVTTSSYFDY WGQ GTLTV SS
ZKB27	SEQ ID NO.	Amino acid sequence
CDRH1	131	GYSFTSSW
CDRH2	132	IDPSDSYT
CDRH3	133	ARHDYSVSENGMDV
VH	134	EVQLVQSGAEVKKPGESLRISCKAS GYSFTSSW INWVRQMP GKGLEWMGR IDPSDSYT TYNPSFQGHVTISVDK SIGTAYLQ WNSLRASDTAMY YCARHDYSVSENGMDV WGQ GTTVTVSS

ZKB29	SEQ ID NO.	Amino acid sequence
CDRH1	135	GFTFSSYT
CDRH2	136	ISYDGSHK
CDRH3	137	ARRSYSISCFDY
VH	138	QVQLVESGGGVVQPGRSLRLSCAAS GFTFSSYTMHWVRQAP GKGLEWVAV ISYDGSHK FYADSVKGRFTISRDN SKDTLYLQ MNSLR AEDTALYYC ARRSYSISCFDY WGQGT LVTISS
ZKB34	SEQ ID NO.	Amino acid sequence
CDRH1	139	GFTFSRSG
CDRH2	140	VSYDGSNK
CDRH3	141	AKDLTMVRGVHYYYVMDV
VH	142	QVQLVESGGGVVQPGRSLRLSCAAS GFTFSRSGMHWVRQAP GKGLEWVAV VSYDGSNK YYSDSVKGRFTISRDN SKNTLYLQ MNSLRVEDTAVYYC AKDLTMVRGVHYYYVMDV WGQGT TTVT VSS
ZKB39	SEQ ID NO.	Amino acid sequence
CDRH1	143	GYTFDDYY
CDRH2	144	INPHRGGT
CDRH3	145	VRDQYCDGGNCYGIHQPHYGMDV
VH	146	QVQLVQSGAEVKKPGASLKVSCKAS GYTFDDYY IHWVRQAP GQGLEWLGR INPHRGGT NYAQKFQGRVIMTL DMSISTTYME LRRITSDDAVYYC VRDQYCDGGNCYGIHQPHYGMDV WGQG TTVT VSS
ZKB46	SEQ ID NO.	Amino acid sequence
CDRH1	147	GYSFTSYW
CDRH2	148	IDPSDSYT
CDRH3	149	ARREYSSSSGQEDWFDP
VH	150	EVQLVQSGAEVKKPGESLRISCKGSG GYSFTSYW ISWVRQMP GKGLEWMGR IDPSDSYT NYSPSFQGHVTISADKSISTAYLQ WSSLKASDTAMY C ARREYSSSSGQEDWFDP WGQGT LVTVS S
ZKB53	SEQ ID NO.	Amino acid sequence

CDRH1	151	GFTFSSYA
CDRH2	152	ISYDGSNR
CDRH3	153	ARHVEQLPSSGYFQH
VH	154	QVQLVESGGGVVQPGRSLRLSCAAS GFTFSSYA MHWVRQTP GKGLEWVTV ISYDGSNR YYADSVKGRFTISRDN SKNTLYLQ MNSLRSEDTAVYYC ARHVEQLPSSGYFQH HWGQGLTVTVSS
ZKC26	SEQ ID NO.	Amino acid sequence
CDRH1	155	GFIFSDFY
CDRH2	156	IGHDGSYI
CDRH3	157	ARAHGGFRH
VH	158	QVQVVESGGGLVKPGGSLRLSCAAS GFIFSDFY MSWMRQAP GKGLEWVAY IGHDGSYI LYADSVKGRFTISRDN AKNSLFLR MNSLRVEDTAVYYC ARAHGGFRH WGQGT VVAVSP
ZKD5	SEQ ID NO.	Amino acid sequence
CDRH1	159	GFTFTSYG
CDRH2	160	ISYDGSNK
CDRH3	161	ARDRDHYDLWNAYTFDY
VH	162	QVQLVESGGGVVQPGRSLRLSCAAS GFTFTSYG MHWVRQTP GKGLDWVAV ISYDGSNK YYADSVKGRFTISRDN SKDTLYLQ MNSLRAADTALYYC ARDRDHYDLWNAYTFDY WGQGLTVTVS S
ZKD7	SEQ ID NO.	Amino acid sequence
CDRH1	163	GFTFSNYA
CDRH2	164	ISYDVSDK
CDRH3	165	AGGPLGVVVIKPSNAEHFHH
VH	166	QVQLVESGGGVVQPGRSLRLSCAAS GFTFSNYA MHWVRQAP GKGLEWVAV ISYDVSDK YYADSVKGRFTISRDN SKNTLFLQ MNSLRAEDTAAYYC AGGPLGVVVIKPSNAEHFHH WGQGLTV TVSS
ZKD8	SEQ ID NO.	Amino acid sequence
CDRH1	167	GFTFINYA

CDRH2	168	ISYDGSNK
CDRH3	169	ATDADAYGDSGANFHY
VH	170	QVQLVESGGGVVQPGKSLRLSCAAS GFTTFINYA IHWVRQAP GKGLEWVAV ISYDGSNK FYTDSVKGRFTISRDN SKNTLYLQ MNSLRADDTAVYYC ATDADAYGDSGANFHY WGQGT LVT VSS
ZKD15	SEQ ID NO.	Amino acid sequence
CDRH1	171	DASISSGGFS
CDRH2	172	IYSSGDT
CDRH3	173	ARAHTPTSKFYYYAMDV
VH	174	QLQLQESGGLVKPSQTL SLTCTVSD DASISSGGFS WSWIRQ PLGKGLEWLG IYSSGDT FYNPSLQGRVTMSVDIFRSQFSL KLTSVTAADTAMYYC ARAHTPTSKFYYYAMDV WGQGT T VSS
ZKD16	SEQ ID NO.	Amino acid sequence
CDRH1	175	GFTFSDHF
CDRH2	176	SRNKPN SYTT
CDRH3	177	AKVGGCYGGDCHVENDY
VH	178	EVQLVESGGDLVQPGGSLRLSCVAS GFTFSDHF MDWVRQAP GKGLEWVGR SRNKPN SYTT EYAASVKGRFSISRDDSKKALY LQMNSLQTEDTAVYYC AKVGGCYGGDCHVENDY WGQGT L VSS
ZKD17	SEQ ID NO.	Amino acid sequence
CDRH1	179	GFIFSDYA
CDRH2	180	ISYDGSSR
CDRH3	181	ARGYC SSGTCFSTNAEYFHP
VH	182	QVQMVESGGGVVQPGTSLRLSCATSG GFIFSDYA MHWVRQAP GKGLEWVAV ISYDGSSR LYADSVKGRFTVSRDN SKNTLYLQ MHS LRAGDTAVYYC ARGYC SSGTCFSTNAEYFHP WGQGT L TISS
ZKD20	SEQ ID NO.	Amino acid sequence
CDRH1	183	GFTFSDHF
CDRH2	184	SRNKPN SYTT

CDRH3	185	ARVGGCNGGDCHVENDY
VH	186	EVQLVESGGGLVQPGGSLRLSCVAS GGTFSDHF MDWVRQAP GKGLEWVGR SRNKPNSYTT EYAASVKGRFTISRDDSKNSLY LQMNSLQTEDTAVYYC ARVGGCNGGDCHVENDY WGQGLVT VSS
ZKA134	SEQ ID NO.	Amino acid sequence
CDRH1	187	GGTFSAYA
CDRH2	188	IIPFFGTA
CDRH3	189	ARSDIVSTTRGYHHYGMDV
VH	190	QVHLVQSGAEVKKPGSSVNVSCKAS GGTFSAYA ISWVRQAP GQGLEWMGG IIPFFGTAYYAQ KFKGRVTVTADKSTSTVYME MTSLRSED TAVYYC ARSDIVSTTRGYHHYGMDV WGQGT T V T VSS
ZKA246	SEQ ID NO.	Amino acid sequence
CDRH1	191	GYTFSDYY
CDRH2	192	INPYSGGT
CDRH3	193	ARGFTMISDREFDP
VH	194	QVQLVQSGAEVKRPGASVKVSCKAS GYTFSDYY MHWVRQAP GQGLEWMGR INPYSGGTNYAQ KFHGRVTVTTRDTSISTVYME LRGLRSDDTAVYYC ARGFTMISDREFDP WGQGLVT V S S
ZKA256	SEQ ID NO.	Amino acid sequence
CDRH1	195	GFTFSTYW
CDRH2	196	IKQDGSEK
CDRH3	197	ARDPGYDDFWSGSYSGSFDI
VH	198	EVQLVESGGGLVQPGGSLRLSCAAS GFTFSTYWM TWVRQAP GKGLEWVAN IKQDGSEKYYV DSVKGRFTISRDN TKNSLYLQ VNSLRAEDTAIYYC ARDPGYDDFWSGSYSGSFDI WGQGT M V TVSS
ZKB42	SEQ ID NO.	Amino acid sequence
CDRH1	199	GFTFNNG
CDRH2	200	ISYDGNKK
CDRH3	201	VKYGERINGYSDPFDH

VH	202	QVQVVESGGGVVQPGRSLRLFCAAS GYTFNNY MHWVRQAP GKGLEWVAL ISYDGNKKYY ADSVKGRFSISRDN SKNTLYLQ MNRRLRSGDTAVYHC VKYGERINGYSDPFDH WGQGLTVTVSS
ZKB85	SEQ ID NO.	Amino acid sequence
CDRH1	203	GYTFTTYA
CDRH2	204	INTNTGNP
CDRH3	205	ARVIVPYAFDI
VH	206	QVQLVQSGSELKKPGASVKVSCKAS GYTFTTYA MNWVRQAP GQGPEWVGW INTNTGNP TYAQGFGRFVLSLDTSVSTAFLO ISLKAEDTAVYYC ARVIVPYAFDI WGQGTMTVTVSS
ZKB47	SEQ ID NO.	Amino acid sequence
CDRH1	207	GYTFTNYY
CDRH2	208	INPSGGPT
CDRH3	209	ARDQYGGYARYGMDV
VH	210	QVQLVQSGAEVKKPGASVKVSCQAS GYTFTNYY MHWVRQAP GQGLEWMGI INPSGGPT SYAQKFQGRVTMTTDTSTSTVYME LSSLRSED TAVYYC ARDQYGGYARYGMDV WGQGTMTVTVSS
ZKC6	SEQ ID NO.	Amino acid sequence
CDRH1	211	GYTFTGYI
CDRH2	212	INPNSGGT
CDRH3	213	ARVSDWGFADF
VH	214	QVQLVQSGTEVKKPGASVKVSCKAS GYTFTGYI MHWVRQAP GQGLEWMGR INPNSGGT NYAQKFQGRVTMTTRDTSISTAYME LSGLRSDDTAVYYC ARVSDWGFADF WGQGTMTVTVSS
ZKA160	SEQ ID NO.	Amino acid sequence
CDRH1	215	GGSTITSY
CDRH2	216	IFYSGST
CDRH3	217	ARDQTMPVWVGMDV
VH	218	QVQLQESGPGLVKPSSETLSLTCTVSG GGSTITSY SWSWIRQPP GKGLEWIGY IFYSGST DYNPSLKSRVTISVDTSKQFSLRL RSVTAADTAVYYC ARDQTMPVWVGMDV WGQGTMTVTVSS
ZKA172	SEQ ID NO.	Amino acid sequence

CDRH1	219	GYIFTRYW
CDRH2	220	IDPSDSYT
CDRH3	221	ARQETAREDGMAV
VH	222	EVQLVQSGAEVKKPGKSLRISCKGSG GYIFTRYW ISWVRQMP GKGLEWMGR IDPSDSYT NYSPSFQGHVTISADKSISTAYLQ WSSLKASDTAMY YCARQETAREDGMAV WGQGTITVTVSS
ZKA174	SEQ ID NO.	Amino acid sequence
CDRH1	223	GGSMSNSYYH
CDRH2	224	IYYSGST
CDRH3	225	ARNPVFNPLTLTHDAFDI
VH	226	QLQLQESGPGLVKPSSETLSLTCTVSG GGSMSNSYYH WGWIRQ PPGKGLEWIGS IYYSGST YYNPSLKSRTISVDTSKNQFSL KLNSVTAADTAVYY CARNPVFNPLTLTHDAFDI WGQGTMTV VSS
ZKA189	SEQ ID NO.	Amino acid sequence
CDRH1	227	GFTFSSYA
CDRH2	228	ISGSGDNT
CDRH3	229	AKWPYYDFWSGSESFYDP
VH	230	GVQLLESGGALVQPGKSLRLSCAAS GFTFSSYA LTWVRQAP GKGLQWVSA ISGSGDNT YYADSVKGRFTISRDNSTLYLQ MNSLR AEDTAVYY CAKWPYYDFWSGSESFYDP WGQGTITVTV SS
ZKA195	SEQ ID NO.	Amino acid sequence
CDRH1	231	GYNFPSYW
CDRH2	232	IDPSDSYT
CDRH3	233	ARADCRSTSCYLVFE
VH	234	EVQLVQSGAEVKKPGESLRISCKDS GYNFPSYW IHWVRQMP GKGLEWMGT IDPSDSYT NYSPSFQGHVTISADKSISTAYLQ WSSLKASDTAMY YCARADCRSTSCYLVFE GQGTITVTVSS
ZKA215	SEQ ID NO.	Amino acid sequence
CDRH1	235	GYTFTSYW

CDRH2	236	IDPSDSHT
CDRH3	237	ARHALPNYFDS
VH	238	EVQLVQSGAEVKKPGESLRISCKGSG YTF TSYWISWVRQMP GKGLEWMGR IDPSDSHT DYSPSFQGHVTISADKSISAAYLQ WSSLKASDTAMY YCARHALPNYFDS WGQGLTVTVSS
ZKA218	SEQ ID NO.	Amino acid sequence
CDRH1	239	GFPFSSYW
CDRH2	240	INSDGRNT
CDRH3	241	ARGGYDYDSSGCFDY
VH	242	EVQLVESGGGLVQPGGSLRLSCAAS GFPFSSY WMHWVRQAP GKGLVWVSR INSDGRNT NYADSVKGRFTISRDN AENTVYLQ MNSLRAEDTAV YYCARGGYDYDSSGCFDY WGQGLTVTVSS
ZKB75	SEQ ID NO.	Amino acid sequence
CDRH1	243	GFTFSNYA
CDRH2	244	ISGTGGST
CDRH3	245	AKDSASRGGYC SGGVCYLNP GHHDY
VH	246	EVQVLESGGGLLQPGGSLRLSCAAS GFTFSNYA MSWVRQAP GKGLEWVST ISGTGGST YYADSVKGRFTISRDN SKNTLYLQ MNSLRAEDTAV YYCAKDSASRGGYC SGGVCYLNP GHHDY WG QGLTVTVSS
ZKB83	SEQ ID NO.	Amino acid sequence
CDRH1	247	GYSFTNYW
CDRH2	248	IDPSDSYT
CDRH3	249	ARLRGSLYC SGGRCYVP GETPNW FDP
VH	250	EVQLVQSGAEVKKPGESLRISCKGSG YSF TNYWITWVRQMP GKGLEWMGS IDPSDSYT NYSPSFQGHVTISADWSINTAYLQ WSSLKASDTAK YYCARLRGSLYC SGGRCYVP GETPNW FDP WGQGLTVTVSS
ZKC3	SEQ ID NO.	Amino acid sequence
CDRH1	251	GGSITSYY
CDRH2	252	IYYSGST

CDRH3	253	ARVGGAPYYYYGMDV
VH	254	QVQLQESGPGGLVKPSETLSLTCTVSGGSITSYYWSWIRQPP GKGLEWIGY IYYSGST NYNPSLKSRTISVDTSKNQFSLKL SSVTAADTAVYYC ARVGGAPYYYYGMDV WGQGTITVTVSS
ZKC18	SEQ ID NO.	Amino acid sequence
CDRH1	255	GFTFGDYA
CDRH2	256	IRSKAYGGTT
CDRH3	257	SRDHTGTTTAFDI
VH	258	EVQLVESGGGLVQPGRSLRLSCTAS GFTFGDYA MSWFRQAP GKGLEWVG IRSKAYGGTT EYAASVKGRFTISRDDSKSIAY LQMNSLKTEDTAVYYC SRDHTGTTTAFDI WGQGTMTVTVSQ
ZKD1	SEQ ID NO.	Amino acid sequence
CDRH1	259	GFTFSSYG
CDRH2	260	IWYDGSNK
CDRH3	261	ARDRRGYGDYVGYYYGMDV
VH	262	QVQLVESGGGVVQPGRSLRLSCAAS GFTFSSYG MHWVRQAP GKGLEWVAV IWYDGSNK YYADSVKGRFTISRDNKNTLYLQ MNSLRAEDTAVYYC ARDRRGYGDYVGYYYGMDV WGQGTITV VSS

Name	SEQ ID NO.	Amino acid sequence
ZIKV EDIII generic	263	TAAFTFTKXPAEXXHGTVTVEVQYXGXDGPCCKXPXQMAV DXQTLTPVGRITANPVITEXTENSKMMLELDPPFGDSYIVI GXGKKITHHWHRS
ZIKV H/PF/2013 EDIII	264	TAAFTFTKIPAETLHGTVTVEVQYAGTDGPCKVPAQMAVD MQTLTPVGRITANPVITESTENSKMMLELDPPFGDSYIVIG VGEKKITHHWHRS
ZIKV EDIII generic	265	X ₁ GX ₂ X ₃ YSLCTAAFTFTKX ₄ PAEX ₅ X ₆ HGTVTVEVQYX ₈ GX ₉ D GPCCKX ₁₀ PX ₁₁ QMAVDX ₁₂ QTLTPVGRITANPVITEX ₁₃ TX ₁₄ N SKMMLELDPPFGDSYIVIGX ₁₅ GX ₁₆ X ₁₇ KITHHWHRSC wherein X1 may be any (naturally occurring) amino acid, preferably K, A, or E; X2 may be any (naturally occurring) amino acid, preferably V, F, or L;

		<p>X3 may be any (naturally occurring) amino acid, preferably S or F; X4 may be any (naturally occurring) amino acid, preferably I or V; X5 may be any (naturally occurring) amino acid, preferably T or V; X6 may be any (naturally occurring) amino acid, preferably L or D; X7 may be any (naturally occurring) amino acid, preferably V or G; X8 may be any (naturally occurring) amino acid, preferably A or G; X9 may be any (naturally occurring) amino acid except R, preferably T or A; X10 may be any (naturally occurring) amino acid, preferably V or I; X11 may be any (naturally occurring) amino acid, preferably A or V; X12 may be any (naturally occurring) amino acid, preferably M or T; X13 may be any (naturally occurring) amino acid, preferably S or G; X14 may be any (naturally occurring) amino acid, preferably E or K; X15 may be any (naturally occurring) amino acid, preferably V or I; X16 may be any (naturally occurring) amino acid, preferably E, A, K, or D; and X17 may be any (naturally occurring) amino acid, preferably E, A, or K, more preferably K or A</p>
Zika-E-F1 primer	266	TGCAAACGCGGTCGCAAACCTGGTTG
ZIKV-E-R1 primer	267	CGTGCCAAGGTAATGGAATGTCGTG
ZIKV-Ef1530 primer	268	AGCCTAGGACTTGATTGTGAACCGA
ZIKV-E-R2769 primer	269	TTACAGATCCCACAACGACCGTCAG
ZIKV-E-F2	270	ACTTGGTCATGATACTGCTGATTGC
ZIKV-E-R2	271	TCGGTTCACAATCAAGTCCTAGGCT
ZIKV-E-f2058	272	GCTAACCCCGTAATCACTGAAAGCA
ZIKV-E-r2248	273	AAGACTGCCATTCTCTGGCACCTC

* the sequences highlighted in bold are CDR regions (nucleotide or aa) and the underlined residues are mutated residues as compared to the "germline" sequence.

CLAIMS

1. An isolated multispecific antibody, or an antigen binding fragment thereof, specifically binding to distinct Zika virus epitopes.
2. The antibody, or the antigen binding fragment thereof, according to claim 1, wherein the antibody, or the antigen binding fragment thereof, neutralizes Zika virus infection.
3. The antibody, or the antigen binding fragment thereof, according to claim 1 or 2, wherein the antibody, or the antigen binding fragment thereof, eliminates generation of Zika virus escape mutants.
4. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 3, characterized in that the antibody, or antigen binding fragment thereof, does not contribute to antibody-dependent enhancement of Zika virus infection.
5. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 4, characterized in that each CDR or each variable region comprised in the antibody, or the antigen binding fragment thereof, is a human CDR or human variable region, respectively, most preferably all constant and variable regions comprised in the antibody, or the antigen binding fragment thereof, are human constant regions and human variable regions.
6. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 5, characterized in that the antibody, or antigen binding fragment thereof, is a monoclonal antibody.
7. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 6, characterized in that the antibody, or antigen binding fragment thereof, is bispecific, trispecific, tetraspecific or pentaspecific, preferably the antibody, or the antigen binding fragment thereof, is bispecific, trispecific or tetraspecific, more preferably the

antibody, or the antigen binding fragment thereof, is bispecific or trispecific, even more preferably the antibody, or the antigen binding fragment thereof, is bispecific.

8. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 7, characterized in that the antibody, or antigen binding fragment thereof, is bivalent, trivalent, tetravalent, hexavalent or octavalent, more preferably, the antibody, or the antigen binding fragment thereof, is bivalent or tetravalent, most preferably, the antibody, or the antigen binding fragment thereof, is tetravalent.
9. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 8, characterized in that the antibody, or antigen binding fragment thereof, is bispecific and tetravalent.
10. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 9, characterized in that the antibody molecule comprises exactly two copies of each of the distinct epitope binding sites specifically binding to at least two distinct, Zika virus epitopes.
11. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 10, characterized in that the antibody, or antigen binding fragment thereof, is of the IgG type, preferably of the IgG1 type, more preferably comprising a heavy chain constant region of the IgG1 CH1-CH2-CH3 type and a light chain constant region of the IgG CL type, even more preferably comprising a heavy chain constant region of the IgG1 CH1-CH2-CH3 type comprising or consisting of an amino acid sequence according to SEQ ID NO: 91 or 92, or a functional sequence variant thereof, and a light chain constant region of the IgG CL type comprising or consisting of an amino acid sequence according to SEQ ID NO: 93 or 94, or a functional sequence variant thereof.
12. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 11, characterized in that the antibody, or antigen binding fragment thereof, comprises an Fc moiety.

13. The antibody, or the antigen binding fragment thereof, according to claim 12, characterized in that the antibody, or antigen binding fragment thereof, comprises a mutation in the Fc moiety, said mutation reducing binding of the antibody to an Fc receptor.
14. The antibody, or the antigen binding fragment thereof, according to claim 11 or 13, characterized in that the antibody, or antigen binding fragment thereof, comprises a CH2 L4A mutation, a CH2 L5A mutation, or both.
15. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 14, characterized in that the antibody, or antigen binding fragment thereof, is of the Fabs-in-tandem-Ig antibody format.
16. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 14, characterized in that the antibody, or antigen binding fragment thereof, is of the of the DVD-Ig antibody format.
17. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 9, characterized in that the antibody, or antigen binding fragment thereof, does not comprise a binding site for an Fc receptor, preferably, the antibody, or antigen binding fragment thereof, does not comprise an Fc region, more preferably, the antibody, or antigen binding fragment thereof, does not comprise an Fc moiety.
18. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 17, characterized in that the antibody, or antigen binding fragment thereof, binds specifically to (at least two) distinct epitopes on Zika virus envelope protein (ZIKV E protein).
19. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 18, characterized in that the antibody, or antigen binding fragment thereof, binds to domain III of Zika virus envelope protein (EDIII).

20. The antibody, or the antigen binding fragment thereof, according to claim 19, wherein domain III of Zika virus envelope protein comprises or consists of an amino acid sequence as set forth in SEQ ID NO: 263 or 265.
21. The antibody, or the antigen binding fragment thereof, according to claim 20, wherein domain III of Zika virus envelope protein comprises or consists of an amino acid sequence as set forth in SEQ ID NO: 264.
22. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 21, characterized in that the antibody, or antigen binding fragment thereof, binds to an epitope of Zika virus envelope protein, which includes one or more amino acid residues of the lateral ridge (LR) of EDIII and/or one or more amino acid residues of the EDI-EDIII hinge region.
23. The antibody, or the antigen binding fragment thereof, according to claim 22, characterized in that the epitope of Zika virus envelope protein includes one or more amino acid residues of the lateral ridge (LR) of EDIII and one or more amino acid residues of the EDI-EDIII hinge region.
24. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 23, characterized in that the antibody, or antigen binding fragment thereof, binds to a quaternary epitope displayed on a ZIKV infectious virion.
25. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 24, characterized in that the antibody, or antigen binding fragment thereof, binds to domain II of Zika virus envelope protein (EDII).
26. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 25, characterized in that the antibody, or antigen binding fragment thereof, (i) binds to domain III of Zika virus envelope protein (EDIII) and (ii) binds to domain II of Zika virus envelope protein (EDII).

27. The antibody, or the antigen binding fragment thereof, according to claim 26, characterized in that domain III of Zika virus envelope protein comprises or consists of an amino acid sequence as set forth in SEQ ID NO: 263 or 265, in particular as set forth in SEQ ID NO: 264.
28. The antibody, or the antigen binding fragment thereof, according to claim 26 or 27, characterized in that the antibody, or antigen binding fragment thereof, binds to an epitope of Zika virus envelope protein, which includes one or more amino acid residues of the lateral ridge (LR) of EDIII and/or one or more amino acid residues of the EDI-EDIII hinge region.
29. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 25, characterized in that the antibody, or antigen binding fragment thereof, (i) binds to domain III of Zika virus envelope protein (EDIII) and (ii) binds to a quaternary epitope displayed on a ZIKV infectious virion.
30. The antibody, or the antigen binding fragment thereof, according to claim 29, characterized in that domain III of Zika virus envelope protein comprises or consists of an amino acid sequence as set forth in SEQ ID NO: 263 or 265, in particular as set forth in SEQ ID NO: 264.
31. The antibody, or the antigen binding fragment thereof, according to claim 29 or 30, characterized in that the antibody, or antigen binding fragment thereof, binds to an epitope of Zika virus envelope protein, which includes one or more amino acid residues of the lateral ridge (LR) of EDIII and/or one or more amino acid residues of the EDI-EDIII hinge region.
32. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 31, characterized in that the antibody, or antigen binding fragment thereof, can inhibit a post-attachment step of ZIKV.

33. The antibody, or the antigen binding fragment thereof, according to claim 32, characterized in that the antibody, or antigen binding fragment thereof, can prevent membrane fusion.
34. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 33, characterized in that the antibody, or antigen binding fragment thereof, can cause aggregation of ZIKV (particles).
35. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 34, characterized in that the antibody or antigen binding fragment thereof, comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein at least one CDR, preferably the at least one heavy chain CDRH3, comprises or consists of an amino acid sequence according to any of SEQ ID NOs: 3, 75, 39, 21, 57, 101, 105, 109, 113, 117, 121, 125, 129, 133, 137, 141, 145, 149, 153, 157, 161, 165, 169, 173, 177, 181, 185, 189, 193, 197, 201, 205, 209, 213, 217, 221, 225, 229, 233, 237, 241, 245, 249, 253, 257, and 261, or a functional 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.
36. The antibody, or the antigen binding fragment thereof, according to claim 35, characterized in that the antibody or antigen binding fragment thereof, comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein at least one CDR, preferably the at least one heavy chain CDRH3, comprises or consists of an amino acid sequence according to any of SEQ ID NOs: 3, 39, and 21, or a functional 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.

37. The antibody, or the antigen binding fragment thereof, according to claim 36, characterized in that the antibody or antigen binding fragment thereof, comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein at least one CDR, preferably the at least one heavy chain CDRH3, comprises or consists of an amino acid sequence according to any of SEQ ID NOs: 3 or a functional 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.
38. The antibody, or the antigen binding fragment thereof, according to claim 37, characterized in that the antibody or antigen binding fragment thereof, comprises a further CDRH1, CDRH2 and CDRH3 and a further CDRL1, CDRL2 and CDRL3, wherein at least one CDR, preferably the further heavy chain CDRH3, comprises or consists of an amino acid sequence according to any of SEQ ID NOs: 21, or a functional 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.
39. The antibody, or the antigen binding fragment thereof, according to claim 37, characterized in that the antibody or antigen binding fragment thereof, comprises a further CDRH1, CDRH2 and CDRH3 and a further CDRL1, CDRL2 and CDRL3, wherein at least one CDR, preferably the further heavy chain CDRH3, comprises or consists of an amino acid sequence according to any of SEQ ID NOs: 39, or a functional 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.
40. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 39, characterized in that the antibody or antigen binding fragment thereof, comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one

CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein

- (i) the at least one heavy chain CDRH1 comprises an amino acid sequence according to any of SEQ ID NOs: 1, 19, 37, 55, 73, 99, 103, 107, 111, 115, 119, 123, 127, 131, 135, 139, 143, 147, 151, 155, 159, 163, 167, 171, 175, 179, 183, 187, 191, 195, 199, 203, 207, 211, 215, 219, 223, 227, 231, 235, 239, 243, 247, 251, 255, and 259, or a functional 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;
- (ii) the at least one CDRH2 comprises an amino acid sequence according to any of SEQ ID NOs: 2, 20, 38, 56, 74, 100, 104, 108, 112, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200, 204, 208, 212, 216, 220, 224, 228, 232, 236, 240, 244, 248, 252, 256, and 260, or a functional 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; and/or
- (iii) the at least one heavy chain CDRH3 comprises an amino acid sequence according to any of SEQ ID NOs: 3, 21, 39, 57, 75, 101, 105, 109, 113, 117, 121, 125, 129, 133, 137, 141, 145, 149, 153, 157, 161, 165, 169, 173, 177, 181, 185, 189, 193, 197, 201, 205, 209, 213, 217, 221, 225, 229, 233, 237, 241, 245, 249, 253, 257, and 261, or a functional 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.

41. The antibody, or the antigen binding fragment thereof, according to claim 40, characterized in that the antibody or antigen binding fragment thereof, comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein

- (i) the at least one heavy chain CDRH1 comprises an amino acid sequence according to any of SEQ ID NOs: 1, 19, and 37, or a functional 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;
 - (ii) the at least one CDRH2 comprises an amino acid sequence according to any of SEQ ID NOs: 2, 20, and 38, or a functional 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; and/or
 - (iii) the at least one heavy chain CDRH3 comprises an amino acid sequence according to any of SEQ ID NOs: 3, 21, and 39, or a functional 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.
42. The antibody, or the antigen binding fragment thereof, according to claim 41, characterized in that the antibody or antigen binding fragment thereof, comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein
- (i) the at least one heavy chain CDRH1 comprises an amino acid sequence according to SEQ ID NO: 1 or a functional 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;
 - (ii) the at least one CDRH2 comprises an amino acid sequence according to SEQ ID NO: 2 or a functional 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; and/or

- (iii) the at least one heavy chain CDRH3 comprises an amino acid sequence according to SEQ ID NO: 3 or a functional 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.
43. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 42, characterized in that the antibody, or the antigen binding fragment thereof, comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein
- (i) the at least one CDRL1 comprises an amino acid sequence according to any of SEQ ID NOs: 4, 22, and 40, or a functional 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;
 - (ii) the at least one CDRL2 comprises an amino acid sequence according to any of SEQ ID NOs: 5, 6, 23, 24, 41, and 42, or a functional 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; and/or
 - (iii) the at least one CDRL3 amino comprises an amino acid sequence according to any of SEQ ID NOs: 7, 25, and 43, or a functional 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.
44. The antibody, or the antigen binding fragment thereof, according to claim 43, characterized in that the antibody, or the antigen binding fragment thereof, comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein

- (i) the at least one CDRL1 comprises an amino acid sequence according to SEQ ID NO: 4 or a functional 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;
 - (ii) the at least one CDRL2 comprises an amino acid sequence according to SEQ ID NO: 5 or 6, or a functional 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; and/or
 - (iii) the at least one CDRL3 amino comprises an amino acid sequence according to SEQ ID NO: 7 or a functional 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.
45. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 44, characterized in that the antibody, or the antigen binding fragment thereof, comprises CDRH1, CDRH2, and CDRH3 amino acid sequences (i) according to SEQ ID NOs: 1 - 3; or functional sequence variants 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; (ii) according to SEQ ID NOs: 19 - 21; or functional sequence variants 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; (iii) according to SEQ ID NOs: 37 - 39; or functional sequence variants 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; (iv) according to SEQ ID NOs: 55 - 57; or functional sequence variants 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; (v) according to SEQ ID NOs: 73 - 75; or functional

sequence variants 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; (vi) according to SEQ ID NOs: 99 - 101; or functional sequence variants 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; (vii) according to SEQ ID NOs: 103 - 105; or functional sequence variants 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; (viii) according to SEQ ID NOs: 107 - 109; or functional sequence variants 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; (ix) according to SEQ ID NOs: 111 - 113; or functional sequence variants 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; (x) according to SEQ ID NOs: 115 - 117; or functional sequence variants 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; (xi) according to SEQ ID NOs: 119 - 121; or functional sequence variants 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; (xii) according to SEQ ID NOs: 123 - 125; or functional sequence variants 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; (xiii) according to SEQ ID NOs: 127 - 129; or functional sequence variants 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; (xiv) according to SEQ ID NOs: 131 - 133; or functional sequence variants 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; (xv) according to SEQ ID NOs: 135 - 137; or functional sequence

variants 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; (xvi) according to SEQ ID NOs: 139 - 141; or functional sequence variants 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; (xvii) according to SEQ ID NOs: 143 - 145; or functional sequence variants 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; (xviii) according to SEQ ID NOs: 147 - 149; or functional sequence variants 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; (xix) according to SEQ ID NOs: 151 - 153; or functional sequence variants 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; (xx) according to SEQ ID NOs: 155 - 157; or functional sequence variants 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; (xxi) according to SEQ ID NOs: 159 - 161; or functional sequence variants 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; (xxii) according to SEQ ID NOs: 163 - 165; or functional sequence variants 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; (xxiii) according to SEQ ID NOs: 167 - 169; or functional sequence variants 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; (xxiv) according to SEQ ID NOs: 171 - 173; or functional sequence variants 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; (xxv) according to SEQ ID NOs: 175 - 177; or functional sequence

variants 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; (xxvi) according to SEQ ID NOs: 179 – 181; or functional sequence variants 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; (xxvii) according to SEQ ID NOs: 183 – 185; or functional sequence variants 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; (xxviii) according to SEQ ID NOs: 187 – 189; or functional sequence variants 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; (xxix) according to SEQ ID NOs: 191 – 193; or functional sequence variants 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; (xxx) according to SEQ ID NOs: 195 – 197; or functional sequence variants 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; (xxxi) according to SEQ ID NOs: 199 – 201; or functional sequence variants 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; (xxxii) according to SEQ ID NOs: 203 – 205; or functional sequence variants 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; (xxxiii) according to SEQ ID NOs: 207 – 209; or functional sequence variants 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; (xxxiv) according to SEQ ID NOs: 211 – 213; or functional sequence variants 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; (xxxv) according to SEQ ID NOs:

215 – 217; or functional sequence variants 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; (xxxvi) according to SEQ ID NOs: 219 – 221; or functional sequence variants 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; (xxxvii) according to SEQ ID NOs: 223 - 225; or functional sequence variants 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; (xxxviii) according to SEQ ID NOs: 227 – 229; or functional sequence variants 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; (xxxix) according to SEQ ID NOs: 231 – 233; or functional sequence variants 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; (xl) according to SEQ ID NOs: 235 – 237; or functional sequence variants 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; (xli) according to SEQ ID NOs: 239 – 241; or functional sequence variants 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; (xlii) according to SEQ ID NOs: 243 – 245; or functional sequence variants 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; (xliii) according to SEQ ID NOs: 247 – 249; or functional sequence variants 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; (xliv) according to SEQ ID NOs: 251 - 253; or functional sequence variants 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; (xlv) according to

SEQ ID NOs: 255 – 257; or functional sequence variants 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; or (xlvii) according to SEQ ID NOs: 259 – 261; or functional sequence variants 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.

46. The antibody, or the antigen binding fragment thereof, according to claim 45, characterized in that the antibody, or the antigen binding fragment thereof, comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 1 – 5 and 7; or functional sequence variants 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; (ii) according to SEQ ID NOs: 1 – 4 and 6 – 7; or functional sequence variants 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; (iii) according to SEQ ID NOs: 19 – 23 and 25; or functional sequence variants 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; (iv) according to SEQ ID NOs: 19 – 22 and 24 – 25; or functional sequence variants 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; (v) according to SEQ ID NOs: 37 – 41 and 43; or functional sequence variants 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; (vi) according to SEQ ID NOs: 37 – 40 and 42 – 43; or functional sequence variants 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; (vii) according to SEQ ID NOs: 55 – 59 and 61; or functional sequence variants 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; (viii) according to SEQ ID NOs: 55 – 58 and 60 – 61; or functional sequence variants 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; (ix) according to SEQ ID NOs: 73 – 77 and 79; or functional sequence variants 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; or (x) according to SEQ ID NOs: 73 – 76 and 78 – 79; or functional sequence variants 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.

47. The antibody, or the antigen binding fragment thereof, according to claim 46, characterized in that the antibody, or the antigen binding fragment thereof, comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 1 - 5 and 7; or functional sequence variants 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; or (ii) according to SEQ ID NOs: 1 – 4 and 6 – 7; or functional sequence variants 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.
48. The antibody, or the antigen binding fragment thereof, according to claim 46 or 47, characterized in that the antibody, or the antigen binding fragment thereof, comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 19 – 23 and 25; or functional sequence variants 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; or (ii) according to SEQ ID NOs: 19 – 22 and 24 – 25; or functional sequence variants 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.

49. The antibody, or the antigen binding fragment thereof, according to claim 48, characterized in that the antibody, or the antigen binding fragment thereof, comprises
- (a) a first epitope binding site comprising CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 1 - 5 and 7; or functional sequence variants 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; or (ii) according to SEQ ID NOs: 1 - 4 and 6 - 7; or functional sequence variants 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; and
 - (b) a second epitope binding site comprising CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 19 - 23 and 25; or functional sequence variants 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; or (ii) according to SEQ ID NOs: 19 - 22 and 24 - 25; or functional sequence variants 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.
50. The antibody, or the antigen binding fragment thereof, according to any one of claims 46 - 49, characterized in that the antibody, or the antigen binding fragment thereof, comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 37 - 41 and 43; or functional sequence variants 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; or (ii) according to SEQ ID NOs: 37 – 40 and 42 – 43; or functional sequence variants 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.

51. The antibody, or the antigen binding fragment thereof, according to claim 50, characterized in that the antibody, or the antigen binding fragment thereof, comprises
- (a) a first epitope binding site comprising CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 1 - 5 and 7; or functional sequence variants 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; or (ii) according to SEQ ID NOs: 1 – 4 and 6 – 7; or functional sequence variants 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; and
 - (b) a second epitope binding site comprising CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 37 – 41 and 43; or functional sequence variants 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; or (ii) according to SEQ ID NOs: 37 – 40 and 42 – 43; or functional sequence variants 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.
52. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 51, characterized in that the antibody, or the antigen binding fragment thereof, comprises a heavy chain variable region (VH) and, optionally, a light chain variable region (VL), wherein the heavy chain variable region (VH) comprises or consists of an

amino acid sequence according to any of SEQ ID NOs: 8, 26, 44, 62, 80, 102, 106, 110, 114, 118, 122, 126, 130, 134, 138, 142, 146, 150, 154, 158, 162, 166, 170, 174, 178, 182, 186, 190, 194, 198, 202, 206, 210, 214, 218, 222, 226, 230, 234, 238, 242, 246, 250, 254, 258, and 262; or a functional 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.

53. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 52, characterized in that the antibody, or the antigen binding fragment thereof, comprises (i) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 8 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 9 or a functional 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; (ii) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 26 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 27 or a functional 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; (iii) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 44 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 45 or a functional 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; (iv) a heavy chain variable

region (VH) amino acid sequence according to SEQ ID NO: 62 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 63 or a functional 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; or (v) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 80 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 81 or a functional 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.

54. The antibody, or the antigen binding fragment thereof, according to claim 53, characterized in that the antibody, or the antigen binding fragment thereof, comprises a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 8 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 9 or a functional 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.
55. The antibody, or the antigen binding fragment thereof, according to claim 53 or 54, characterized in that the antibody, or the antigen binding fragment thereof, comprises a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 26 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 27 or a functional 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.

56. The antibody, or the antigen binding fragment thereof, according to claim 48, characterized in that the antibody, or the antigen binding fragment thereof, comprises
- (a) a first epitope binding site comprising a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 8 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 9 or a functional 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; and
 - (b) a second epitope binding site comprising a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 26 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 27 or a functional 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.
57. The antibody, or the antigen binding fragment thereof, according to any one of claims 53 – 56, characterized in that the antibody, or the antigen binding fragment thereof, comprises a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 44 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 45 or a functional 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.

58. The antibody, or the antigen binding fragment thereof, according to claim 57, characterized in that the antibody, or the antigen binding fragment thereof, comprises
- (a) a first epitope binding site comprising a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 8 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 9 or a functional 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; and
 - (b) a second epitope binding site comprising a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 44 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 45 or a functional 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.
59. The antibody, or the antigen binding fragment thereof, according to any one of claims 1 – 58, characterized in that the antibody, or the antigen binding fragment thereof, is in the Fabs-in-tandem-Ig (FIT-Ig) format and the outer Fab of the FIT-Ig format comprises an epitope binding site comprising CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ

ID NOs: 1 - 5 and 7; or functional sequence variants 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; or (ii) according to SEQ ID NOs: 1 - 4 and 6 - 7; or functional sequence variants 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.

60. The antibody, or the antigen binding fragment thereof, according to claim 59, characterized in that the outer Fab of the FIT-Ig format comprises an epitope binding site comprising a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 8 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 9 or a functional 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.
61. The antibody, or the antigen binding fragment thereof, according to claim 59 or 60, characterized in that the inner Fab of the FIT-Ig format comprises an epitope binding site comprising CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 19 - 23 and 25; or functional sequence variants 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; or (ii) according to SEQ ID NOs: 19 - 22 and 24 - 25; or functional sequence variants 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.
62. The antibody, or the antigen binding fragment thereof, according to claim 61, characterized in that the inner Fab of the FIT-Ig format comprises an epitope binding

site comprising a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 26 or a functional 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 and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 27 or a functional 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.

63. The antibody, or the antigen binding fragment thereof, according to any one of the previous claims, characterized in that the antibody, or the antigen binding fragment thereof, is a purified antibody or a single chain antibody, such as an scFv.
64. The antibody, or the antigen binding fragment thereof, according to any one of the previous claims, for use as a medicament.
65. The antibody, or the antigen binding fragment thereof, according to any one of the previous claims, for use in prevention and/or treatment of Zika virus infection.
66. A nucleic acid molecule comprising at least one polynucleotide encoding the antibody, or the antigen binding fragment thereof, according to any one of claims 1 – 63, or a fragment thereof, wherein the fragment comprises at least one CDR of the antibody, or the antigen binding fragment thereof.
67. The nucleic acid molecule according to claim 66, wherein the encoded fragment of the antibody or antigen binding fragment thereof comprises three CDRs, preferably all three heavy chain CDRs of an epitope binding site (CDRH1, CDRH2, CDRH3) and/or all three light chain CDRs of an epitope binding site (CDRL1, CDRL2, CDRL3).
68. The nucleic acid molecule according to claim 66 or 67, wherein the nucleic acid molecule is mono-, bi-, or multicistronic.

69. The nucleic acid molecule according to any one of claims 66 – 68, wherein the nucleic acid molecule is DNA or RNA.
70. The nucleic acid molecule according to claim 69, wherein the nucleic acid molecule is a DNA plasmid or mRNA.
71. The nucleic acid molecule according to any one of claims 66 – 70, wherein the polynucleotide sequence comprises or consists of a nucleic acid sequence according to any one of SEQ ID NOs: 10 – 18, 28 – 36, 46 – 54, 64 – 72, and 82 – 90; or a functional 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.
72. A vector comprising the nucleic acid molecule according to any one of claims 66 – 71.
73. A plurality of nucleic acid molecules according to any one of claims 66 – 71, each nucleic acid molecule comprising at least one polynucleotide encoding a fragment of the antibody, or of the antigen binding fragment thereof, according to any one of claims 1 – 63.
74. The plurality of nucleic acids according to claim 73 encoding the antibody, or the antigen binding fragment thereof, according to any one of claims 1 – 63.
75. A plurality of vectors according to claim 72, preferably encoding the antibody, or the antigen binding fragment thereof, according to any one of claims 1 – 63.
76. A cell expressing the antibody, or the antigen binding fragment thereof, according to any of claims 1 to 63; or comprising the vector according to claim 40 or the plurality of vectors according to claim 75.
77. A pharmaceutical composition comprising the antibody, or the antigen binding fragment thereof, according to any one of claims 1 to 63, the nucleic acid molecule

according to any one of claims 66 – 71, the vector according to claim 72, the plurality of nucleic acid molecules according to claim 73 or 74, the plurality of vectors according to claim 75 and/or the cell according to claim 76.

78. The pharmaceutical composition according to claim 77 further comprising a pharmaceutically acceptable excipient, diluent or carrier.
79. The pharmaceutical composition according to claim 77 or 78, which is provided as a single-dose product.
80. The pharmaceutical composition according to any of claims 77 – 79, wherein the amount of the antibody, or the antigen binding fragment thereof, as defined in any of claims 1 to 63, does not exceed 500 mg, preferably does not exceed 200 mg, more preferably does not exceed 100 mg, and even more preferably does not exceed 50 mg.
81. The antibody, or the antigen binding fragment thereof, according to any one of claims 1 to 63, the nucleic acid molecule according to any one of claims 66 – 71, the vector according to claim 72, the plurality of nucleic acid molecules according to claim 73 or 74, the plurality of vectors according to claim 75, the cell according to claim 76, or the pharmaceutical composition according to any of claims 77 – 80 for use in prevention or treatment of Zika virus infection.
82. The antibody, or the antigen binding fragment thereof, the nucleic acid molecule, the vector, the plurality of nucleic acid molecules, the plurality of vectors, the cell, or the pharmaceutical composition for use according to claim 81 in prevention or treatment of Zika virus infection in subjects diagnosed with Zika virus infection or in subjects showing symptoms of Zika infection.
83. The antibody, or the antigen binding fragment thereof, the nucleic acid molecule, the vector, the plurality of nucleic acid molecules, the plurality of vectors, the cell, or the pharmaceutical composition for use according to claim 81 in asymptomatic subjects.

84. The antibody, or the antigen binding fragment thereof, the nucleic acid molecule, the vector, the plurality of nucleic acid molecules, the plurality of vectors, the cell, or the pharmaceutical composition for use according to any one of claims 81 – 83 in pregnant subjects.
85. The antibody, or the antigen binding fragment thereof, the nucleic acid molecule, the vector, the plurality of nucleic acid molecules, the plurality of vectors, the cell, or the pharmaceutical composition for use according to any one of claims 81 – 84, wherein the antibody, or the antigen binding fragment thereof, the nucleic acid, the vector, the plurality of nucleic acid molecules, the plurality of vectors, the cell, or the pharmaceutical composition is administered up to seven days after (a possible) Zika virus infection, preferably up to five days after (a possible) Zika virus infection, more preferably up to four days after (a possible) Zika virus infection, even more preferably up to three days after (a possible) Zika virus infection, and most preferably up to one day or two days after (a possible) Zika virus infection.
86. The antibody, or the antigen binding fragment thereof, the nucleic acid molecule, the vector, the plurality of nucleic acid molecules, the plurality of vectors, the cell, or the pharmaceutical composition for use according to any one of claims 81 – 85, wherein the antibody, or the antigen binding fragment thereof, the nucleic acid, the vector, the plurality of nucleic acid molecules, the plurality of vectors, the cell, or the pharmaceutical composition is administered in combination with a checkpoint inhibitor.
87. The antibody, or the antigen binding fragment thereof, the nucleic acid molecule, the vector, the plurality of nucleic acid molecules, the plurality of vectors, the cell, or the pharmaceutical composition for use according to any one of claims 81 – 86, wherein the antibody, or the antigen binding fragment thereof, the nucleic acid, the plurality of nucleic acid molecules, the plurality of vectors, the vector, the cell, or the pharmaceutical composition is administered at a (single) dose of 0.005 to 100 mg/kg, preferably at a (single) dose of 0.0075 to 50 mg/kg, more preferably at a (single) dose

of 0.01 to 10 mg/kg, even more preferably at a (single) dose of 0.05 to 5 mg/kg, and particularly preferably at a (single) dose of 0.1 to 1 mg/kg.

88. Use of the antibody, or the antigen binding fragment thereof, according to any of claims 1 to 63, the nucleic acid molecule according to any of claims 66 – 71, the vector according to claim 72, the plurality of nucleic acid molecules according to claim 73 or 74, the plurality of vectors according to claim 75, the cell according to claim 76, or the pharmaceutical composition according to any of claims 77 – 80 for monitoring the quality of an anti-Zika vaccine by checking that the antigen of said vaccine contains the specific epitope in the correct conformation.
89. Use of the antibody, or the antigen binding fragment thereof, according to any of claims 1 to 63, the nucleic acid molecule according to any of claims 66 – 71, the vector according to claim 72, the plurality of nucleic acid molecules according to claim 73 or 74, the plurality of vectors according to claim 75, the cell according to claim 76, or the pharmaceutical composition according to any of claims 77 – 80 in (*in vitro*) diagnosis of Zika virus infection.
90. A kit of parts comprising at least one antibody, or the antigen binding fragment thereof, according to any of claims 1 to 63, at least one nucleic acid according to any of claims 66 – 71, at least one vector according to claim 72, the plurality of nucleic acid molecules according to claim 73 or 74, the plurality of vectors according to claim 75, at least one cell according to claim 76, or at least one pharmaceutical composition according to any of claims 77 – 80.
91. Method of preventing and/or treating Zika virus infection in a subject, wherein the method comprises administering to a subject in need thereof the antibody, or the antigen binding fragment thereof, according to any of claims 1 to 63, the nucleic acid molecule according to any of claims 66 – 71, the vector according to claim 72, the plurality of nucleic acid molecules according to claim 73 or 74, the plurality of vectors according to claim 75, the cell according to claim 76, or the pharmaceutical composition according to any of claims 77 – 80.

92. Method according to claim 91, wherein the subject was diagnosed with Zika virus infection or shows symptoms of Zika virus infection.
93. Method according to claim 91 or 92, wherein the subject is pregnant.