

poorly controlled amounts of IgG1 aggregates, and is comprised primarily of inactive fractions for treating complement-mediated diseases. What is more, IVIG treatment also often leads to an unwanted proinflammatory response by binding to low affinity Fc receptors (Andresen et. al. Product equivalence study comparing various human immunoglobulin-G formulations. J Clin Pharmacol 2000;40:722-730 and Ghielmetti et. al. Gene expression profiling of the effects of intravenous immunoglobulin in human whole blood. Mol Immunol 43 (2006) 939–949). There is a need for novel, consistent, recombinantly-produced therapies that mimic the natural process of aggregated soluble IgG1 Fc acting as a complement sink by avidly binding C1q, while at the same time avoiding unwanted pro-inflammatory responses by preferentially binding to complement components over other natural ligands including low affinity Fc receptors.

SUMMARY

[0013] The present disclosure relates to biologically active fusion protein biomimetic molecules comprising one or more human immunoglobulin Fc domains and one or more multimerization domains, wherein the Fc domain portion of the fusion protein comprises one or more point mutations. In one example, the biomimetic molecules preferentially bind one or more complement components relative to a normal non-aggregated human immunoglobulin Fc. In some examples, preferential binding to one or more complement components is achieved by the Fc domain of the biomimetic having reduced binding to canonical Fc Receptors relative to normal non-aggregated immunoglobulin Fc or alternatively normal aggregated immunoglobulin Fc. In some examples, the biologically active fusion protein biomimetic molecules comprise stradomer units. Compositions comprising the biologically active fusion protein biomimetics and methods for using the same are provided.

[0014] In one example, the present disclosure provides a stradomer unit comprising at least one IgG1 Fc domain having one or more point mutations corresponding to at least one of positions 267, 268, and/or 324 of the IgG1 Fc domain. In some examples, the stradomer unit further comprises at least one multimerization domain. In some examples, the amino acid at position 267 is mutated from serine (Ser; S) to any other amino acid. In further examples,

the amino acid at position 267 is mutated to glutamic acid (Glu; E). In some examples, the amino acid at position 268 is mutated from histidine (His; H) to any other amino acid. In further examples, the amino acid at position 268 is mutated to phenylalanine (Phe; F). In some examples, the amino acid at position 324 is mutated from serine to any other amino acid. In further examples, the amino acid at position 324 is mutated to threonine (Thr; T). In some examples, the Fc domain of the stradomer unit comprises point mutations at positions 267, 268, and 324. In further examples, the Fc domain comprises the point mutations S267E, H268F, and S324T.

[0015] In some examples, the stradomer unit comprises an IgG1 Fc domain having an amino acid sequence comprising point mutations at positions 267, 268, and/or 324 and further comprising at least one point mutation at position 233 and/or 234 and/or 235 and/or 236 and/or 238 and/or 265 and/or 297 and/or 299 and/or 328. In one example, the amino acid at position 297 is mutated from asparagine (Asn; N) to any other amino acid. In a further example, the amino acid at position 297 is mutated to alanine (Ala; A). In one example, the amino acid at position 299 is mutated from threonine (T) to any other amino acid other than serine or cysteine. In a further example, the amino acid at position 299 is mutated to alanine (Ala; A). In one example, the amino acid at position 238 is mutated from proline (Pro; P) to any other amino acid. In a further example, the amino acid at position 238 is mutated to aspartic acid (Asp; D). In one example, the amino acid at position 233 is mutated from glutamic acid (Glu; E) to any other amino acid. In a further example, the amino acid at position 233 is mutated to proline (Pro; P). In another example, the amino acid at position 236 is mutated from glycine (Gly; G) to any other amino acid. In a further example, the amino acid at position 236 is mutated to arginine (Arg; R). In one example, the amino acid at position 236 is deleted. In one example, the amino acid at position 234 is mutated from leucine (Leu; L) to any other amino acid. In a further example, the amino acid at position 234 is mutated to valine (Val; V) or alanine (Ala; A). In another example, the amino acid at position 235 is mutated from leucine (Leu; L) to any other amino acid. In a further example, the amino acid at position 235 is mutated to alanine (Ala; A). In one example, the amino acid

at position 265 is mutated from aspartic acid (Asp; D) to any other amino acid. In a further example, the amino acid at position 265 is mutated to alanine (Ala; A). In another example, the amino acid at position 265 is mutated to tryptophan (Trp; W). In one example, the amino acid at position 297 is mutated from asparagine (Asn; N) to any other amino acid. In one example, the amino acid at position 297 is mutated to alanine (Ala; A). In one example, the amino acid at position 297 is mutated to glutamine (Gln; Q). In one example, the amino acid at position 299 is mutated from threonine (Thr; T) to any other amino acid, other than serine (Ser; S) or cysteine (Cys; C). In one example, the amino acid at position 299 is mutated to alanine. In one example, the amino acid at position 298 is mutated to any amino acid other than proline. In one example, the amino acid at position 328 is mutated from leucine (Leu; L) to any other amino acid. In a further example, the amino acid at position 328 is mutated to phenylalanine (Phe; F).

[0016] In some examples, the Fc domain of the stradomer unit comprises point mutations at positions 267, 268, 297, and 324. In further examples, the Fc domain comprises the point mutations S267E, H268F, N297A, and S324T.

[0016a] In one aspect, the present disclosure refers to a peptide homodimer comprising:

(a) at least one IgG1 Fc domain comprising the point mutation S267E, H268F, and S324T and further comprising:

(i) the point mutation N297A;

(ii) the point mutation G236R; or

(iii) the point mutation G236R and E233P; and

(b) at least one multimerization domain capable of multimerizing the peptide homodimer; wherein the peptide homodimer exhibits preferential binding to complement relative to FcγRI, FcγRIIa, FcγRIIb and/or FcγRIII.

[0017] In some examples, the Fc domain of the stradomer unit comprises point mutations at positions 234, 235, 267, 268, and 324. In further examples, the Fc domain comprises the point mutations L234V, L235A, S267E, H268F, and S324T.

[0018] In some examples, the Fc domain of the stradomer unit comprises point mutations at positions 234, 235, 267, 268, 297, and 324. In further examples, the Fc domain comprises the point mutations L234V, L235A, S267E, H268F, N297A, and S324T.

[0019] In some examples, the Fc domain of the stradomer unit comprises point mutations at of positions 233, 234, 235, 267, 268, and 324, and deletion of the amino acid at position 236. In further examples, the Fc domain comprises the point mutations E233P, L234A, L235A, S267E, H268F, and S324T, and deletion of the amino acid at position 236.

[0020] In some examples, the Fc domain of the stradomer unit comprises point mutations at of positions 233, 234, 235, 267, 268, 297, and 324. In further examples, the Fc

domain comprises the point mutations E233P, L234A, L235A, S267E, H268F, N297A, and S324T.

[0021] In some examples, the Fc domain of the stradomer unit comprises a point mutation at positions 265, 267, 268, and 324. In further examples, the Fc domain comprises the point mutations D265A, S267E, H268F, and S324T.

[0022] In some examples, the Fc domain of the stradomer unit comprises a point mutation at positions 238, 267, 268, and 324. In further examples, the Fc domain comprises the point mutations P238D, S267E, H268F, and S324T.

[0023] In some examples, the Fc domain of the stradomer unit comprises a point mutation at positions 238, 267, 268, 297, and 324. In further examples, the Fc domain comprises the point mutations P238D, S267E, H268F, N297A, and S324T.

[0024] In some examples, the Fc domain of the stradomer unit comprises a point mutation at positions 236, 267, 268, and 324. In further examples, the Fc domain comprises the point mutations G236R, S267E, H268F, and S324T.

[0025] In some examples, the Fc domain of the stradomer unit comprises a point mutation at positions 233, 236, 267, 268, and 324. In further examples, the Fc domain comprises the point mutations E233P, G236R, S267E, H268F, and S324T.

[0026] In some examples, the Fc domain of the stradomer unit comprises a point mutation at positions 233, 236, 267, 268, 324, and 328. In further examples, the Fc domain comprises the point mutations E233P, G236R, S267E, H268F, S324T, and L328F.

[0027] In some examples, the Fc domain of the stradomer unit comprises a point mutation at positions 238, 265, 267, 268, and 324. In further examples, the Fc domain comprises the point mutations P238D, D265G, S267E, H268F, and S324T. In other examples, the Fc domain comprises the point mutations P238D, D265W, S267E, H268F, and S324T.

[0028] In some examples, the Fc domain of the stradomer unit comprises a point mutation at positions 267, 268, 324, and 328. In further examples, the Fc domain comprises the point mutations S267E, H268F, S324T, and L328F.

[0029] In some examples, the Fc domain of the stradomer unit comprises a point mutation at positions 233, 234, 235, 267, 268, 297, 324, and 328, and deletion of the amino acid at position 236. In further examples, the Fc domain comprises the point mutations E233P, L234V, L235A, S267E, H268F, N297A, S324T, and L328F, and deletion of the amino acid at position 236.

[0030] In some examples, the Fc domain of the stradomer unit comprises a point mutation at positions 233, 268, and 324. In further examples, the Fc domain comprises the point mutations E233P, H268F, and S324T.

[0031] In some examples, the Fc domain of the stradomer unit comprises a point mutation at positions 233, 268, 297, and 324. In further examples, the Fc domain comprises the point mutations E233P, H268F, S324T and a point mutation at position 297 other than N297A or N297Q.

[0032] In some examples, the Fc domain of the stradomer unit comprises a point mutation at positions 233, 268, 299, and 324. In further examples, the Fc domain comprises the point mutations E233P, H268F, S324T and a point mutation at position 299 other than T299S and T299C. In some examples, the Fc domain of the stradomer unit comprises the point mutations E233P, H268F, S324T, and T299A.

[0033] In some examples, the Fc domain of the stradomer unit comprises point mutations at positions 233, 268, 324, and 267. In some examples, the Fc domain of the stradomer unit comprises the point mutations E233P, H268F, S324T, and a point mutation at position 267 other than the point mutation S267E.

[0034] In some examples, the Fc domain of the stradomer unit comprises point mutations at positions 233, 268, 324, 267, and 297. In further examples, the Fc domain of the stradomer unit comprises the point mutations E233P, H268F, S324T, a point mutation at position 267 other than the point mutation S267E, and a point mutation at position 297 other than the point mutation N297A and N297Q. In further examples, the Fc domain of the stradomer unit comprises mutations at positions 233, 268, 324, 267, and 297. In further examples, the Fc domain of the stradomer unit comprises the point mutations E233P, H268F, S324T, a point

mutation at position 267 other than the point mutation S267E, a point mutation at position 297 other than the point mutation N297A and N297Q, and a point mutation at position 299 other than the point mutations T299S and T299C. In further examples, the mutation at position 299 is T299A.

[0035] In some examples, the Fc domain of the stradomer unit comprises point mutations at positions 233, 268, 324, 267, and 236. In some examples, the Fc domain of the stradomer unit comprises the point mutations E233P, H268F, S324T, a point mutation at position 267 other than S267E, and a point mutation at position 236 other than G236R.

[0036] In some examples, the Fc domain of the stradomer unit comprises point mutations at positions 233, 268, 324, 267, 236, and 297. In some examples, the Fc domain of the stradomer unit comprises the point mutations E233P, H268F, S324T, a point mutation at position 267 other than S267E, a point mutation at position 236 other than G236R, and a point mutation at position 297 other than N297A and N297Q.

[0037] In some examples, the Fc domain of the stradomer unit comprises point mutations at positions 233, 268, 324, 267, 236, and 299, wherein the point mutation at position 299 is a point mutation other than T299S and T299C. In some examples, the Fc domain of the stradomer unit comprises the point mutations E233P, H268F, S324T, a point mutation at position 267 other than S267E, a point mutation at position 236 other than G236R, and T299A.

[0038] In some examples, the Fc domain of the stradomer unit comprises point mutations at at least one of positions 267, 268, and/or 324 and further comprises a point mutation at three or more of positions 233, 235, 236, 267, 268, 297, 299, and/or 324. In some examples, the Fc domain of the stradomer unit comprises point mutations at at least one of positions 267, 268, and/or 324 and further comprises a point mutation at three or more of positions 233, 235 other than L235H, 236 other than 236R, 267 other than S267E, 268, 297 other than N297A, or alternatively 299, and/or 324.

[0039] In one example, the stradomer comprises a multimerization domain, wherein the multimerization domain is selected from the group consisting of an IgG2 hinge, an isoleucine zipper and a GPP domain and is capable of multimerizing said stradomer units. In

some examples, the multimerization domain creates multimers of said stradomer units. In further examples, the multimers of said stradomer units are high order multimers.

[0040] In some examples, the stradomer comprises, from amino to carboxy terminus, a leader sequence; an Fc domain comprising an IgG1 hinge, IgG1 CH2, and IgG1 CH3; and an IgG2 hinge, wherein the stradomer comprises one or more point mutations as provided herein. In a further example, the leader sequence is cleaved upon expression. Therefore, in another example, there is provided a stradomer comprising, from amino to carboxy terminus, an Fc domain comprising an IgG1 hinge, IgG1 CH2, and IgG1 CH3; and an IgG2 hinge, wherein the stradomer comprises one or more point mutations as provided herein. In one example, the stradomer comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 10-16, 18-63, and 65-77, or a functional variant thereof.

[0041] In some examples, the stradomer comprises, from amino to carboxy terminus, a leader sequence; an IgG2 hinge; and an Fc domain comprising an IgG1 hinge, IgG1 CH2, and IgG1 CH3, wherein the stradomer comprises one or more point mutations provided herein. In a further example, the leader sequence is cleaved upon expression. Therefore, in another example, there is provided a stradomer comprising, from amino to carboxy terminus, an IgG2 hinge; and an Fc domain comprising an IgG1 hinge, IgG1 CH2, and IgG1 CH3, wherein the stradomer comprises one or more point mutations provided herein. In one example, the stradomer comprises an amino acid sequence selected from SEQ ID NO: 17 and SEQ ID NO: 64, or a functional variant thereof.

[0042] In some examples, the stradomer comprises, from amino to carboxy terminus, a leader sequence; an IgG2 hinge; and an Fc domain comprising an IgG1 CH2 and IgG1 CH3, wherein the stradomer comprises one or more point mutations provided herein. In a further example, the leader sequence is cleaved upon expression. Therefore, in another example, there is provided a stradomer comprising, from amino to carboxy terminus, an IgG2 hinge; and an Fc domain comprising an IgG1 CH2 and IgG1 CH3, wherein the stradomer comprises one or more point mutations provided herein.

[0043] In one example, the stradomer unit further comprises one or more amino acid linker sequence. In a further example, the linker is cleavable. In a further example, the linker is protease sensitive. In one example, the linker is cleaved by a protease that is predominantly intracellular. In a further example, the linker is cleaved by a protease that is predominantly present in the Golgi and the Endoplasmic Reticulum. In one example, the linker is cleaved by furin. In another example, the linker is cleaved by a protease that is predominantly an organ-specific protease such as, for example, the brain-related protease neuropsin. In another example, the linker is cleaved by a protease that is predominantly a tumor-specific protease, such as, for example, metalloproteinase 9 and urokinase plasminogen activator.

[0044] In some examples, the stradomer unit exhibits preferential binding to complement relative to FcγRI, FcγRII including FcγRIIa and/or FcγRIIb, and/or FcγRIII. In certain examples, the stradomer unit exhibits reduced binding to a low affinity Fcγ Receptor. In other examples, the stradomer unit exhibits reduced binding to FcγRI, FcγRII including FcγRIIa and/or FcγRIIb, and/or FcγRIII relative to a stradomer of the same structure that does not comprise a point mutation at one or more of positions 267, 268 and/or 324.

[0045] In certain examples, the stradomer unit comprises a mutation at 297, 298, or 299 and retains binding to C1q, inhibits CDC, and retains binding to FcγRI or to a low affinity Fcγ Receptor including FcγRIIa, FcγRIIb and/or FcγRIII.

[0046] In one example, the present disclosure provides a cluster stradomer comprising two or more stradomer units as disclosed herein. For example, in some examples, the present disclosure provides a cluster stradomer comprising two or more stradomer units comprising an IgG1 Fc domain having an amino acid sequence comprising point mutations at positions 267, 268, and/or 324. In further examples, the two or more stradomer units further comprise at least one point mutation at position 233 and/or 234 and/or 235 and/or 236 and/or 238 and/or 265 and/or 297 and/or 299 and/or 328. In some examples, the two or more stradomer units comprise a deletion of the amino acid at position 236.

[0046a] In another aspect, the present disclosure refers to a molecule comprising two or more homodimers as disclosed herein.

[0047] In some examples, the stradomers provided herein are used to treat or prevent diseases and disorders including but not limited to complement-mediated diseases, autoimmune diseases, inflammatory diseases, allergies, B-cell mediated diseases, antibody-mediated diseases, renal disorders, and blood disorders.

[0047a] In another aspect, the present disclosure refers to use of a homodimer as disclosed herein in the manufacture of a medicament for treating or preventing a complement-mediated disease, an antibody-mediated disease, an autoimmune disease, an inflammatory disease, an allergy, or a blood disorder.

[0048] In some examples, the antibody-mediated disease is selected from the group consisting of Goodpasture's disease; solid organ transplantation rejection; Neuromyelitis Optica; neuromyotonia; limbic encephalitis; Morvan's fibrillary chorea syndrome; Myasthenia gravis; Lambert Eaton myasthenic syndrome; autonomic neuropathy; Alzheimer's Disease; atherosclerosis; Parkinson's Disease; stiff person syndrome or hyperekplexia; recurrent spontaneous abortion; Hughes syndrome; Systemic Lupus Erythematosus; autoimmune cerebellar ataxia; Connective Tissue Diseases including scleroderma, Sjogren's syndrome; Polymyositis; rheumatoid arthritis; Polyarteritis Nodosa; CREST syndrome; endocarditis; Hashimoto's thyroiditis; Mixed Connective Tissue Disease; channelopathies; Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS); clinical conditions associated with antibodies against *N*-methyl-D-aspartate receptors especially NR1, contactin-associated protein 2, AMPAR, GluR1/GluR2, glutamic acid decarboxylase, GlyR alpha 1a, acetylcholine receptor, VGCC P/Q-type, VGKC, MuSK, GABA(B)R; aquaporin-4; and pemphigus. In some examples, the autoimmune disease is arthritis.

[0049] In some examples, the complement-mediated disease is selected from the group consisting of myasthenia gravis, hemolytic uremic syndrome (HUS), atypical hemolytic uremic syndrome (aHUS), paroxysmal nocturnal hemoglobinuria (PNH), neuromyelitis optica, antibody-mediated rejection of allografts, nephropathy including membranous nephropathy, and nephritis including membranoproliferative glomerulonephritis (MPGN) and lupus nephritis.

[0050] In some examples, the blood disorder is an anemia, such as sickle cell diseases, including Hemoglobin SS, Hemoglobin SC, Hemoglobin S β^0 thalassemia, Hemoglobin S β^+ thalassemia, Hemoglobin SD, and Hemoglobin SE. In some examples, the inflammatory disorder is Age-Related Macular Degeneration, Alzheimer's Disease, Amyotrophic Lateral Sclerosis, or Parkinson's Disease.

[0051] In some examples, the stradomers provided herein are administered to a subject in need thereof. In further examples, the stradomers provided herein are administered intravenously, subcutaneously, orally, intraperitoneally, sublingually, buccally, transdermally, by subdermal implant, or intramuscularly.

[0052] In some examples, the present disclosure provides stradomers useful in treating or preventing autoimmune-related vision loss or hearing loss, such as noise-induced or age-related hearing loss. In another example, the provided stradomers are useful in reducing inflammation or autoimmune responses related to device implantation, such as implantation of cochlear or other hearing devices.

BRIEF DESCRIPTION OF THE FIGURES

[0053] Figure 1 shows the binding of stradomer GL-2045 to FcγRI, FcγRIIb, FcγRIIIa, FcγRIIa, or FcRn, as measured by biolayer interferometry (ForteBio Octet).

[0054] Figure 2 is a radar graph of the maximum Response Units (RU_{max}) for each Fc receptor, C1q ELISA, and CDC inhibition data for G045c and complement-preferential stradomer G997. Each radar graph in these descriptions has been generated from a visual reading of the binding curves resulting from the output of the Octet biolayer interferometry.

[0055] Figure 3 shows the binding of stradomer G997 to FcγRI, FcγRIIb, FcγRIIIa, FcγRIIa, and FcRn, as measured by biolayer interferometry.

[0056] Figure 4A provides a radar graph of the RU_{max} for each Fc receptor, C1q ELISA, and CDC inhibition data for G045c and complement-preferential stradomer G998. Figure 4B provides a radar graph of the RU at 300 seconds (RU_{300s}) for each Fc receptor for G045c and complement-preferential stradomers G997 and G998.

[0057] Figure 5 shows the binding of stradomer G998 to FcγRI, FcγRIIb, FcγRIIIa, FcγRIIa, and FcRn, as measured by biolayer interferometry.

[0058] Figure 6A provides a radar graph of the RU_{max} for each Fc receptor, C1q ELISA, and CDC inhibition data for G045c and complement-preferential stradomers G1022 and

Claims:

1. A peptide homodimer comprising:

(a) at least one IgG1 Fc domain comprising the point mutation S267E, H268F, and S324T and further comprising

(i) the point mutation N297A;

(ii) the point mutation G236R; or

(iii) the point mutation G236R and E233P; and

(b) at least one multimerization domain capable of multimerizing the peptide homodimer;

wherein the peptide homodimer exhibits preferential binding to complement relative to FcγRI, FcγRIIa, FcγRIIb and/or FcγRIII.

2. The homodimer of claim 1, wherein the Fc domain comprises either the EEM or DEL polymorphism of IgG1.

3. The homodimer of claim 1 wherein the multimerization domain is selected from the group consisting of an IgG2 hinge, an isoleucine zipper, and a GPP domain.

4. The homodimer of claim 1, wherein the multimerization domain creates multimers of said homodimers.

5. The homodimer of claim 4, wherein the multimers of said homodimers are high order multimers.

6. The homodimer of claim 1, wherein the homodimer exhibits reduced binding to a low affinity Fcγ Receptor.

7. The homodimer of claim 1, wherein the homodimer further comprises a mutation at 298, or 299 and binds C1q, inhibits CDC, and retains binding to FcγRI, FcγRIIa, FcγRIIb and/or FcγRIII.
8. The homodimer of claim 1, wherein the homodimer exhibits reduced binding to FcγRI, FcγRII, and/or FcγRIII relative to a homodimer of the same structure that does not comprise a point mutation at one or more of positions 267, 268 and/or 324.
9. The homodimer of claim 1, wherein the homodimer comprises, from amino to carboxy terminus, a leader sequence; an Fc domain comprising an IgG1 hinge, IgG1CH2, and IgG1 CH3; and an IgG2 hinge.
10. The homodimer of claim 9, wherein the homodimer comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 11, 12, 13, 14, and 15.
11. The homodimer of claim 1, wherein the homodimer comprises, from amino to carboxy terminus, a leader sequence, an IgG2 hinge, an IgG1 hinge, and an Fc domain comprising an IgG1 CH2 and an IgG1 CH3.
12. The homodimer of claim 11, wherein the homodimer comprises an amino acid sequence selected from the group according to SEQ ID NOs: 17 and 64.
13. A molecule comprising two or more homodimers according to any one of claims 1 to 12.
14. Use of a homodimer according to claim 1 in the manufacture of a medicament for treating or preventing a complement-mediated disease, an antibody-mediated disease, an autoimmune disease, an inflammatory disease, an allergy, or a blood disorder.

15. The use according to claim 14, wherein:

(a) the antibody-mediated disease is selected from the group consisting of Goodpasture's disease; solid organ transplantation rejection; Neuromyelitis Optica; neuromyotonia; limbic encephalitis; Morvan's syndrome; Myasthenia gravis; Lambert Eaton myasthenic syndrome; autonomic neuropathy; Alzheimer's Disease; atherosclerosis; Parkinson's Disease; stiff person syndrome or hyperekplexia; recurrent spontaneous abortion; Hughes syndrome; Systemic Lupus Erythematosus; autoimmune cerebellar ataxia;

Connective Tissue Diseases including scleroderma, Sjogren's syndrome; Polymyositis; rheumatoid arthritis; Polyarteritis Nodosa; CREST syndrome; endocarditis; Hashimoto's thyroiditis; Mixed Connective Tissue Disease; channelopathies; Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS); clinical conditions associated with antibodies against N-methyl-D-aspartate receptors especially NR1, contactin-associated protein 2, AMPAR, GluR1/GluR2, glutamic acid decarboxylase, GlyR alpha 1a, acetylcholine receptor, VGCC P/Q-type, VGKC, MuSK, GABA(B)R, aquaporin-4; and pemphigus;

(b) the autoimmune disease is selected from the group consisting of rheumatoid arthritis, autoimmune-related vision loss, and autoimmune-related hearing loss;

(c) the complement-mediated disease is selected from the group consisting of myasthenia gravis, hemolytic uremic syndrome (HUS), atypical hemolytic uremic syndrome (aHUS), paroxysmal nocturnal hemoglobinuria (PNH), neuromyelitis optica, antibody-mediated rejection of allografts, nephropathic disease including membranous nephropathy, and nephritic diseases including membranoproliferative glomerulonephritis (MPGN) and lupus nephritis

(d) the blood disorder is sickle cell disease.

16. The use according to claim 14, wherein the homodimer is to be administered intravenously, subcutaneously, orally, intraperitoneally, sublingually, buccally, transdermally, by subdermal implant, or intramuscularly.