CLAIMS

1. A dimeric protein comprising a first and a second polypeptide, each polypeptide comprising at least C_H2 and C_H3 regions of ~~an immunoglobulin heavy chain, wherein in said first and/or second polypeptide~~a human IgG1, IgG2, IgG3 or IgG4 heavy chain, wherein at least one of the polypeptides comprises a binding region that specifically binds to a target, wherein in said first and second polypeptide the amino acids in the positions corresponding to E345, E430 and S440 in a human IgG1 heavy chain are R, G and Y, respectively; or alternatively K, G and Y, respectively; or alternatively R, S and Y, respectively; or alternatively R, G and W, respectively, which is predominantly in oligomeric form, in a phosphate buffer at a pH of about 6.8, which is predominantly in monomeric form at a pH of less than 6.0, wherein the amino acids are numbered according to the Eu numbering as set forth in Kabat.

~~the amino acids in the positions corresponding to E345 and E430 in a human IgG1 heavy chain are not E, and~~

~~the amino acid in at least one position selected from the group consisting of S440, Y436, D/E356, T359, E382, N434, Q438, I253 and S254 is Y, K, R or W; not Y; not D or E; not T; not E; not N; not Q; not I; and not S, for each position, respectively.~~

~~2. The dimeric protein of claim 1, wherein, for one or both polypeptides, the amino acid at the position corresponding to E345 is selected from the group consisting of R, K, Q, N, Y, A, C, D, F, G, H, I, L, M, P, S, T, V and W, such as from the group consisting of R, K, Q, N, and Y.~~

~~3. The dimeric protein of any one of the preceding claims, wherein, for one or both polypeptides, the amino acid at the position corresponding to E430 is selected from the group consisting of G, S, T, F, H, A, C, D, I, K, L, M, N, P, Q, R, V, W and Y, such as from the group consisting of G, S, T, F and H.~~

~~4. The dimeric protein of any one of the preceding claims, wherein, for one or both polypeptides the amino acid in at least one position selected from the group consisting of S440, Y436, D/E356, T359, E382, N434, Q438, I253 and S254 is Y or W; not Y; not D or E; not T; not E; not N; not Q; not I; and not S, for each position, respectively, in particular the amino acid in the position corresponding to S440 is Y or W.~~

~~5. The dimeric protein of any one of the preceding claims wherein, the amino acid in a position selected from the group consisting of Y436, D/E356, T359, E382, N434, Q438, I253 and S254 is, in one or both polypeptides,~~

~~(a) I, N, Q, S, T, R, A, E, F, H, K, L, M or V, such as I, N, Q, or S;~~

~~(b) R, G, T, I, L, M, K, H, S, V, Y, Q, N, W, F, A, or C;~~

~~(c) R;~~

~~(d) V, L, M, D, Q, K, R, N, H, S, T, W or Y, such as V, L or M;~~

~~(e) W, H, K, Q, R, D, E, S, T, or Y, such as W, H, K, Q or R;~~

~~(f) N, S, T, A, E, G, H, K, Q, R, W or Y, such as N, S or T;~~
~~(g) V, L, N, Q, E, S or T, such as V, L, N or Q;~~
~~(h) L, G, I or V;~~
~~for each position, respectively.~~

~~6. The dimeric protein of any one of the preceding claims, wherein in one or both polypeptides, the amino acids in the positions corresponding to E345, E430 and S440 are R, G and Y, respectively; or alternatively K, G and Y, respectively; or alternatively R, S and Y, respectively; or alternatively R, G and W, respectively; or alternatively R, G, and K, respectively; or alternatively the amino acids in the positions corresponding to E345, E430 and Y436 are R, G and I, respectively.~~

~~7. The dimeric protein of any one of the preceding claims, wherein said first and/or second polypeptide further comprises a region capable of covalent binding between said first and second polypeptide.~~

~~8. The dimeric protein of any one of the preceding claims, wherein said first and/or said second polypeptide further comprises a hinge region of an immunoglobulin heavy chain.~~

~~9. The dimeric protein of any one of claims 7 or 8, wherein said first and second polypeptides are interconnected via hinge region disulphide bonds.~~

~~10. The dimeric protein of any one of the preceding claims, wherein the isotype of the immunoglobulin heavy chain is selected from the group consisting of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE and IgM.~~

~~11. The dimeric protein of any one of the preceding claims, wherein the immunoglobulin heavy chain is of primate or murine origin, such as human.~~

2. ~~12.~~ The dimeric protein of any one of the preceding claims, wherein at least one of the polypeptides comprises a binding region that specifically binds to a target, the target is a molecule present on a cell, bacterium or virion.

~~13. The dimeric protein of claim 12, wherein each polypeptide comprises a binding region specifically binding to a target, optionally the same target.~~

~~14. The dimeric protein of claim 13, wherein the target is a molecule present on a cell, bacterium or virion.~~

~~15. The dimeric protein of any one of the preceding claims, wherein at least one of the polypeptides comprises an immunoglobulin heavy chain variable region.~~

3. ~~16.~~ The dimeric protein of any one of the preceding claims, which is an antibody.

~~17. The dimeric protein of claim 16, wherein each of the first and second polypeptides comprises immunoglobulin heavy and light chain variable regions to form a first and a second antigen-binding region, optionally binding the same antigen.~~

4. ~~18. The dimeric protein of claim 16~~The dimeric protein of claim 3, wherein each of the first and second polypeptides comprises an immunoglobulin heavy-chain variable region associated with an immunoglobulin light chain sequence comprising light chain variable and constant regions to form a first and a second antigen-binding region, optionally binding the same antigen.

~~19. The dimeric protein of any one of claims 16 to 18, wherein one or both polypeptides comprise a full-length heavy chain constant region, such as a full-length human IgG1 heavy chain constant region.~~

~~20.~~ The dimeric protein of any one of the preceding claims, wherein in said first and~~/or~~ second polypeptide the amino acid in the position corresponding to K439 is not K~~.~~

5. ~~21. The dimeric protein of claim 20, wherein the amino acid in the position corresponding to K439 is~~ e.g. E or D~~, such as E~~.

6. ~~22.~~ The dimeric protein according to claim ~~21~~5, wherein in ~~one or~~ both polypeptides, e.g. each polypeptide, the amino acids in the positions corresponding to E345, E430, K439 and S440 are R, G, E and Y~~, respectively~~.

~~23~~7. The dimeric protein ~~according to~~of any one of the preceding claims, wherein in said first and~~/or second polypeptide the amino acid in the position corresponding to S440 is K or R.~~

~~24. The dimeric protein according to claim 23, wherein in one or both polypeptides, e.g. each polypeptide, the amino acids in the positions corresponding to E345, E430 and S440 are R, G, and K, respectively.~~

~~25. The dimeric protein of any one of the preceding claims, wherein in said first and/or second polypeptide at least one amino acid in a position selected from the group consisting of Y436,~~

~~E356, T359, E382, N434, Q438, I253 and S254 is not Y; not D or E; not T; not E; not N; not Q; not I; and not S, for each position, respectively, and the amino acid in the position corresponding to S440 is not S, Y or W, optionally the amino acid in the position corresponding to S440 is K or R.~~

~~26. The dimeric protein according to claim 25, wherein in one or both polypeptides, e.g. each polypeptide, the amino acids in the positions corresponding to E345, E430, Y436 and S440, are R, G, I and K.~~

~~27. The dimeric protein of any one of the preceding claims, wherein in said first and/or~~ second polypeptide the amino acid residue in the position corresponding to K447 is D or E and/or the amino acid in the position corresponding to Q386 is K.

~~28~~

8. The dimeric protein of any one of claims 1 to ~~25~~7, wherein in said first and~~/or~~ second polypeptide ~~he~~the amino acid residue in the position corresponding to K447 is K, R or H and the polypeptide(s) comprise
   a) an amino acid residue in position 448 which is P; or
   b) an amino acid residue in position 448 which is K, R or H and an amino acid residue in position 449 which is P.

~~29. The dimeric protein of any one of the preceding claims, wherein in said first and/or second polypeptide the amino acid in the position corresponding to Q386 is K.~~

~~30. The dimeric protein of any one of the preceding claims, wherein the amino acid in at least one position corresponding to L234, L235, G236, G237, S239, P238, T250, M252, I253, S254, R255, T256, D265, S267, H268, D270, E272, N286, K288, N297, V303, V305, T307, V308, L309, H310, Q311, D312, K317, K322, S324, P329, P331, I332 K340, D356, K360, Q362, D376, A378, E380, E382, G385, Q386, P387, E388, N389, S400, D413, S415, S424, M428, H433, N434, H435, Y436, K439 or K447 in a human IgG1 heavy chain is not L; not L; not G; not G; not S; not P; not T; not M; not I; not S; not R; not T; not D; not S; not H; not D; not E; not N; not K; not N; not V; not V; not T; not V; not L; not H; not Q; not D; not K; not K; not S; not P; not P; not I; not K; not D; not K; not Q; not D; not A; not E; not E; not G; not Q; not P; not E; not N; not S; not D; not S; not S; not M; not H; not N; not H; not Y; and not K, respectively.~~

~~31~~9. The dimeric protein of any one of the preceding claims, comprising a drug, toxin, radiolabel, radioopaque agent, paramagnetic agent, fluorescent agent, phosphorescent

agent, ultrasound enhancing agent or polyethyleneglycol (PEG), optionally conjugated to at least one of the polypeptides via a linker.

~~32~~10. The dimeric protein of any one of the preceding claims, which is a homodimer~~.~~

~~33. The dimeric protein of any of claims 1-31, which is~~ or a heterodimer.

~~34~~11. The dimeric protein of claim ~~33~~10, wherein said first and second polypeptide are of the same isotype each comprise a CH2, CH3 and hinge regions of an ~~immunoglobulin~~human IgG1, IgG2, IgG3 or IgG4 heavy chain, and wherein

the amino acid in a position selected from K409, T366, L368, K370, D399, F405, and Y407 is not K, T, L, K, D, F and Y, respectively, in the first polypeptide e.g. K409 is R, and

the amino acid in a position selected from F405, T366, L368, K370, D399, Y407, and K409 is not F, T, L, K, D, Y and K, respectively, in the second polypeptide e.g. F405 is L.

~~35. The dimeric protein of claim 34, wherein~~

~~the amino acid in position K409 is R in the first polypeptide, and~~

~~the amino acid in position F405 is L in the second polypeptide.~~

~~36. The dimeric protein of any one of the preceding claims, which is predominantly in oligomeric form, such as hexameric form, in a phosphate buffer at a pH of about 6.8.~~

~~37. The dimeric protein of any one of claims 1 to 35, which is predominantly in monomeric form at a pH of less than 6.0, such as about 5.0.~~

~~38. An oligomer comprising at least two non covalently associated dimeric proteins, each according to any one of the preceding claims.~~

~~39~~12. A hexamer comprising six non-covalently associated dimeric proteins, each according to any one of claims 1 to ~~37~~11.

~~40. The hexamer of claim 39, wherein at least one, such as at least two, at least three, at least four, at least five or six dimeric proteins of the hexamer are antibodies.~~

~~41~~13. A hexamer comprising six non-covalently associated molecules, at least one of which is a dimeric protein according to any one of claims 1 to ~~37~~11 and at least one of which

is an antibody comprising an Fc domain comprising at least CH2, CH3 and hinge regions, wherein the antibody is a monoclonal or polyclonal antibody.

~~42. The hexamer of claim 41, wherein the antibody is a monoclonal or polyclonal antibody.~~

14. ~~43.~~ A composition comprising the dimeric protein of any one of claims 1 to ~~37 and/or the oligomer of claim 38~~11 and/or the hexamer of any one of claims ~~39~~12 to ~~42~~13, and a pharmaceutically acceptable carrier.

~~44. A composition comprising the dimeric protein of any one of claims 1 to 37, one or more antibodies, and a pharmaceutically acceptable carrier.~~

15. ~~45.~~ A composition comprising a first dimeric protein according to any one of claims 1 to ~~37~~11, a second dimeric protein according to any one of claims 1 to ~~37~~11, and optionally a pharmaceutically acceptable carrier.

~~46.~~ 16.A composition comprising a first and second polypeptide of a first dimeric protein, wherein the amino acids at the positions corresponding to E345, E430, K439 and S440 in human IgG1 heavy chain are R, G, E and Y, respectively, and

a first and second polypeptide of a second dimeric protein, wherein the amino acids at the positions corresponding to E345, E430, Y436 and S440 in a human IgG1 heavy chain are R, G, I and K, respectively, which is predominantly in oligomeric form, in a phosphate buffer at a pH of about 6.8, which is predominantly in monomeric form at a pH of less than 6.0.

The composition of claim ~~45, comprising at least one additional dimeric protein according to any one of claims 1 to 37, such as three or six, or such as four, five, seven, eight, nine or more dimeric proteins.~~

17. ~~47. The composition of any of claims 45 and 46~~15, wherein both the first and the second dimeric proteins comprise first and second polypeptides, wherein in said first and~~/or~~ second polypeptides of said first and second dimeric proteins the amino acids at the positions corresponding to E345~~ and~~, E430 and S440 in a human IgG1 heavy chain are ~~not E,~~R, G and ~~the amino acid in at least one position selected from the~~

~~group consisting of S440, Y436, E356, T359, E382, N434, Q438, I253 and S254 is Y, K, R or W; not Y; not D or E; not T; not E; not N; not Q; not I; and not~~ , respectively; or alternatively K, G and Y, respectively; or alternatively R, S~~, for each position~~ and Y, respectively~~.~~; or alternatively R, G and W, respectively.

18. ~~48.~~ The composition of ~~any one of claims 45 to 47~~claim 15, wherein in ~~one or~~ both of said first and second polypeptides of said first and second dimeric protein the amino acids at the positions corresponding to E345, E430 and S440 in a human IgG1 heavy chain, are R, G and Y, respectively.

19. ~~49.~~ The composition of any one of claims ~~45~~15 to ~~48~~18, wherein

~~the first dimeric protein comprises first and second polypeptides, wherein in said first and/or second polypeptides the amino acid at the position corresponding to K439 is E or D, and~~

~~the second dimeric protein comprises first and second polypeptides, wherein in said first and/or second polypeptides the amino acid at the position corresponding to S440 is K or R, optionally K.~~

~~50. The composition of any one of claims 45 to 49, wherein~~

~~the first dimeric protein comprises first and second polypeptides, wherein in said first and/or second polypeptides the amino acid at the position corresponding to K439 is E or D, and~~

~~the second dimeric protein comprises first and second polypeptides, wherein in said first and/or second polypeptides the amino acid at the position corresponding to S440 is K or R, optionally K, and at least one amino acid in a position selected from the group consisting of Y436, D/E356, T359, E382, N434, Q438, I253 and S254 is not Y; not D or E; not T; not E; not N; not Q; not I; and not S, respectively.~~

~~51. The composition of claim 49, wherein~~

~~in said first and/or second polypeptide of the first dimeric protein the amino acids at the positions corresponding to E345, E430, K439 and S440 are R, G, E and Y, respectively, and~~

~~in said first and/or second polypeptide of the second dimeric protein the amino acids at the positions corresponding to E345, E430, K439 and S440 are R, G, K and K, respectively; or alternatively the amino acids at the positions corresponding to E345, E430, Y436 and S440 are R, G, I and K, respectively.~~

~~52. The composition of any one of claims 45 to 48, wherein~~

in said first and/or second polypeptide of the first dimeric protein the amino acid at the position corresponding to K447 is D or E, and

in said first and/or second polypeptide of the second dimeric protein the amino acid at the position corresponding to K447 is K, R or H ~~and~~; an amino acid at the position corresponding to 448 is P~~.~~

~~53. The composition of any one of claims 45 to 48, wherein~~

~~in said first and/or second polypeptide of the first dimeric protein the amino acid at the position corresponding to K447 is D or E, and~~

~~in said first and/or second polypeptide of the second dimeric protein the amino acid at the position corresponding to K447 is K, R or~~ , K, R or H; ~~an amino acid at the position corresponding to 448 is K, R or H; and~~and/or an amino acid at the position corresponding to 449 is P.

20. ~~54.~~ The composition of any one of claims ~~45~~15 to ~~53~~19, wherein at least one of the first and second dimeric proteins is an antibody.

~~55.~~ The composition of claim ~~54, wherein both the first and the second dimeric proteins are antibodies.~~

~~56. The composition of claim 55, wherein the first and second antibodies bind to the same epitope of the same antigen.~~

~~57. The composition of claim 56, wherein the first and second antibodies comprise the same variable heavy and light chain region sequences.~~

21. ~~58. The composition of any one of claims 54 to 55~~20, wherein the first and second antibodies bind to different antigens or to different epitopes on the same antigen.

~~59.~~ The composition of any one of claims ~~45~~15 to ~~58~~21, wherein the pharmaceutically acceptable carrier is an aqueous buffered solution~~.~~

22. ~~60. The composition of claim 59,~~ e.g. wherein the pH of the aqueous buffered solution is at least about 6.5, such as from 6.5 to about 9.0, such as from about 7.0 to about 8.0, such as about 7.4.

~~61.~~ The composition of claim ~~60~~21, comprising a phosphate buffer system~~.~~

23. ~~62. The composition of claim 59,~~ e.g. wherein the pH of the aqueous buffered solution is less than pH 6.5, such as from about 4.0 to 6.4, such as from about 5.0 to about 6.0.

24. ~~63.~~ The composition of claim ~~62~~23, comprising an acetate, histidine, glycine, citrate, nicotinate, lactate, and/or succinate buffer system.

25. ~~64.~~ A method of increasing oligomerization in solution ~~and/or an effector function~~ of a dimeric protein comprising a first and second polypeptide, each comprising at least CH2 and CH3 regions of ~~an immunoglobulin~~a human IgG1, IgG2, IgG3 or IgG4 heavy chain, the method comprising introducing into said first and~~/or~~ second polypeptide, amino acid substitutions in at least the positions corresponding to E345, E430 and ~~in a position selected from the group consisting of S440, Y436, D/E356, T359, E382, N434, Q438, I253 and S254 in a human IgG1 heavy chain~~S440 in a human IgG1 heavy chain are R, G and Y, respectively; or alternatively K, G and Y, respectively; or alternatively R, S and Y, respectively; or alternatively R, G and W, respectively, wherein the amino acids are numbered according to the Eu numbering as set forth in Kabat.

~~65.~~ The method of claim ~~64, wherein the effector function is complement-dependent cytotoxicity (CDC).~~

~~66. The method of any one of claims 64 and 65, wherein the amino acid substitutions are in at least the positions corresponding to E345, E430 and S440 in a human IgG1 heavy chain.~~

~~67. The method of any one of claims 64 to 66, wherein the amino acids substitution in the position corresponding to E345 is selected from the group consisting of 345R, 345Q, 345N, 345K, 345Y, 345A, 345C, 345D, 345F, 345G, 345H, 345I, 345L, 345M, 345P, 345S, 345T, 345V and 345W, such as from the group consisting of 345R, 345Q, 345N, 345K and 345Y.~~

~~68. The method of any one of claims 64 to 67, wherein the amino acid substitution in the position corresponding to E430 is selected from the group consisting of 430G, 430T, 430S, 430F, 430H, 430A, 430C, 430D, 430I, 430K, 430L, 430M, 430N, 430P, 430Q, 430R, 430V, 430W and 430Y, such as from the group consisting of 430G, 430T, 430S, 430F and 430H.~~

~~69. The method of any one of claims 64 to 68, wherein the amino acid substitution in the position corresponding to S440 is 440Y or 440W.~~

~~70. The method of any one of claims 64 to 69, wherein the amino acid substitutions in the positions corresponding to E345, E430 and S440 are 345R, 430G and 440Y, respectively, or alternatively 345K, 430G and 440Y, respectively; or alternatively 345R, 430S and 440Y, respectively; or alternatively 345R, 430G and 440W, respectively; or alternatively 345R, 430G, and 440K, respectively; or alternatively the amino acid substitutions in the positions corresponding to E345, E430 and Y436 are 345R, 430G and 436I, respectively.~~

~~71. The method of any one of claims 64 to 70, wherein the isotype of the heavy chain sequence is selected from the group consisting of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgM and IgE.~~

~~72. The method of any one of claims 64 to 71, wherein the heavy chain is of primate or murine origin, such as human.~~

~~73. The method of any one of claims 64 to 72, wherein each polypeptide comprises an immunoglobulin heavy chain variable region associated with an immunoglobulin light chain sequence comprising light chain variable and constant regions to form a first and a second antigen-binding region, optionally binding the same antigen.~~

~~74. The method of claim 73, wherein each polypeptide of the dimeric protein comprises a full-length heavy chain constant region, such as a full-length human IgG1 heavy chain constant region.~~

26. ~~75. The method of any one of claims 64 to 74~~25, wherein the dimeric protein is an antibody.

~~76. A variant dimeric protein prepared by the method of any one of claims 64 to 75.~~

27. ~~77.~~ A kit-of-parts comprising a first dimeric protein according to any one of claims 1 to ~~37~~11 and a second dimeric protein according to any one of claims 1 to ~~37~~11 for simultaneous, separate or sequential use in imaging, diagnostics or therapy.

28. ~~78. The~~Use of the dimeric protein~~, oligomer~~, hexamer, composition or kit-of-parts according to any one of claims 1 to ~~63, 76, 77 and 79,~~24 and 27, in the manufacture of a medicament for ~~use in~~ the treatment of a disease, such as a bacterial, viral or

parasitic infection, autoimmune disease, cancer, inflammation, and/or reducing the risk for septic shock caused by a bacterial infection.

29. ~~79.~~ The dimeric protein, ~~oligomer,~~ hexamer, composition or kit-of-parts of any one of claims 1 to ~~63, 76, 77~~ 24, 27 and ~~79~~28, wherein the dimeric protein comprises a binding region specifically binding to a lipopolysaccharide (LPS), a lipooligosaccharide (LOS), a delta endotoxin, Botulinum toxin, Corynebacterium diphtheriae exotoxin, a bacterial superantigen, a heat-stable enterotoxin, cytolysin, a channel-forming toxin, an enzymatically active toxin, or a mycotoxin.

~~80~~30. The dimeric protein, ~~oligomer,~~ hexamer, composition or kit-of-parts according to any one of the claims 1 to ~~63, 76, 77~~24, 28 and ~~79~~29, for use in imaging at least a part of the body of a human or other mammal.

~~81. A method for imaging of at least a part of the body of a human or other mammal, comprising administering a~~The dimeric protein, ~~oligomer,~~ hexamer, composition or kit-of-parts according to any one of the claims 1 to ~~63, 76, 77~~24, 28, 29 and ~~79.~~

31. ~~82. A method~~30 for ~~treating~~use in treatment of a bacterial, viral or parasitic infection, for imaging of at least a part of the body of human or other mammal, or for modulating clearance of a target molecule from the body of a human or other

mammal~~, comprising administering a dimeric protein, oligomer, hexamer, composition or kit-of-parts according to any one of the claims 1 to 63, 76, 77 and 79~~.

32. ~~83. A method~~Use of the dimeric protein, hexamer, composition, kit-of-parts according to any one of the claims 1 to 24 and 28 in the manufacture of a medicament for ~~preventing or treating a disease, such as~~the treatment of cancer, auto-immune diseases, organ transplant rejections, and C1q depletion in the humoral system~~, comprising administration of~~ in a ~~dimeric protein, oligomer, hexamer, composition, kit-of parts according to any one of the claims 1 to 63, 76, 77 and 79~~human.