What is claimed is:

Claims

1.- An in-vitro method ~~of~~for expanding a population of ~~cells~~lymphocytes, comprising:

contacting a sample ~~comprising~~that contains a population of ~~cells~~lymphocytes with a ~~multimerization~~multimerizing reagent~~,~~

~~wherein the multimerization reagent has reversibly immobilized thereon (bound thereto)~~ wherein a first agent ~~that provides a primary activation signal to the cells;~~

~~wherein the multimerisation reagent~~ and a second agent are reversibly bound; wherein the multimerizing reagent is in a soluble form and comprises an oligomer or polymer of streptavidin, avidin, streptavidin mutein, or avidin mutein; wherein the first agent (i) comprises at least one ~~binding site Z1 for the reversible binding~~ of ~~the~~a first ~~agent,~~

~~wherein the first agent comprises at least one~~streptavidin or a avidin binding partner ~~C1, wherein the binding partner C1 is able~~capable of reversibly binding to ~~the~~a first binding site ~~Z1~~ of the ~~multimerization reagent, wherein the first agent is bound to the multimerization reagent via the~~ multimerizing reagent and is capable of forming a reversible bond ~~formed~~ between the ~~binding partner C1 and the binding site Z1, and~~

~~wherein the~~ first ~~agent binds to a~~ streptavidin or avidin binding partner and the first binding site, (ii) capable of binding to a receptor molecule on ~~the~~a surface of ~~the cells, thereby providing~~a lymphocyte in the population and stimulating a primary ~~activation~~ signal to the ~~cells and thereby activating the cells.~~

~~2. The method of claim 1,~~lymphocyte; and wherein the ~~multimerization agent has reversibly immobilized thereon (bound thereto) a~~ second agent ~~that stimulates an accessory molecule on the surface of the cells,~~

~~wherein the second agent~~(i) comprises ~~a~~at least one of a second streptavidin or avidin binding partner ~~C2, wherein the~~ capable of reversibly binding ~~partner C2 is able of being reversibly bound~~ to a second binding site ~~Z2~~ of the ~~multimerization~~multimerizing reagent~~, wherein the second agent is bound to the multimerization reagent via the~~ and is capable of forming a reversible bond ~~formed~~ between the second streptavidin or avidin binding partner and the second binding site, (ii) capable of binding ~~partner C2 and the binding site Z2,~~

~~wherein the second agent binds to the~~to an accessory molecule on a surface of the lymphocyte, capable of stimulating an accessory ~~molecule on~~signal to the ~~surface on the surface of the cells,~~lymphocyte, and thereby capable of stimulating ~~the activated cells.~~

~~3. The method of claim 1 or 2, wherein the population of cells is~~ a lymphocyte in a population.

~~4.~~ 2. The method of claim ~~3~~1, wherein the lymphocyte population is a B cell population, a T cell population, a natural killer cell population, or a mixture ~~thereof~~of these.

~~5.~~ 3. The method of claim ~~4~~2, wherein the ~~T cell~~ population ~~is an antigen specific~~ of lymphocytes comprises a T cell population~~, a T helper cell population, a cytotoxic T cell, a memory T cell, a regulatory T cell, or a natural killer T cell population.~~ and

~~6. The method of claim 5, wherein~~ the first agent, comprises ~~a~~an MHC I: peptide complex or ~~wherein the first agent~~ stimulates a TCR/CD3 complex ~~associated~~ related signal in ~~the~~ T ~~cells.~~ cell, and/or comprises

~~7. The method of claim 6, wherein the first agent is~~ a binding reagent that ~~specifically~~ binds to CD3.

~~8.~~ 4. The method of claim ~~6 or 7~~3, wherein the accessory molecule ~~on the T cell~~ is CD28 or CD137~~.~~

~~9. The method of claim 8, wherein~~ , and/or the second agent ~~that binds the accessory molecule is~~comprises a binding reagent that ~~specifically~~ binds to CD28 or CD137, or ~~wherein the second agent is~~both are a mixture of two different ~~kinds of~~ binding reagents that ~~both~~ specifically ~~bind~~binds CD28 or CD137.

~~10.~~ 5. The method of any one of claims ~~7~~1 to ~~9~~4, wherein

saidthe first agent that specifically binds CD3.

6. The method of any one of claims 1 to 5, wherein the second agent specifically binds CD28 or CD137.

7. is selected from the group consistingThe method of any of claims 1 to 6, wherein the first agent is an anti-CD3- antibody, a divalentbivalent antibody fragment of an anti-CD3 antibody, a monovalent antibody fragment of an anti-CD3- antibody, andor a proteinaceous CD3 binding molecule withthat has an antibody-like binding properties, and/or whereincharacteristic.

the second agent that specifically binds CD28 is selected from the group consisting of an anti-CD28 antibody, a divalent antibody fragment of an anti-CD28 antibody, a monovalent antibody fragment of an anti-CD28 antibody, a proteinaceous CD28 binding molecule with antibody-like binding properties, an anti-CD137 antibody, a divalent antibody fragment of an anti-CD137 antibody, a monovalent antibody fragment of an anti-CD137 antibody, a proteinaceous CD137 binding molecule with antibody-like binding properties, 4-1BB ligand, and any mixture thereof.

11.

8. The method of claim 107, wherein the divalent antibody fragment is an $(Fab)_2$' fragment, or a divalent single-chain Fv fragment.

12. The method of claim 10, wherein the monovalent antibody fragment is selected from thea group consisting of a Fab fragment, a Fv fragment, and a single-chain Fv fragment (scFv).

13. 9. The method of claim 10any one of claims 1 to 8, wherein the proteinaceous CD3, CD28 or CD137 binding molecule with antibody-like binding properties is selected from the group of an aptamer, a mutein based on a polypeptide of the lipocalin family, a glubody, a protein based on the ankyrin scaffold, a protein based on the crystalline scaffold, an adnectin, and an avimer.

14. The method of claim 4, wherein the cell population is a B-cell population and the firstsecond agent is a binding reagent that specifically binds CD40 or CD137.

~~15. The method of claim 14, wherein the first binding reagent that specifically binds CD40 or CD137 is selected from the group consisting of an~~ an anti-~~CD40~~CD28 antibody, a bivalent antibody~~, a divalent antibody fragment~~ of an anti-~~CD40~~CD28 antibody, a monovalent antibody fragment of an anti-~~CD40~~ CD28 antibody, ~~and a~~or proteinaceous ~~CD40 binding~~CD28 molecule ~~with~~having an antibody-like binding ~~properties or an anti-CD137 antibody, a divalent antibody fragment of an anti-CD137 antibody, a monovalent antibody fragment of an anti-CD137 antibody, a proteinaceous CD137 binding molecule with antibody-like binding properties, and CD40 ligand (CD154).~~characteristic.

~~16.~~ 10. The method of claim ~~15, wherein the divalent antibody fragment is an (Fab)2' fragment, or a divalent single-chain Fv fragment.~~

~~17. The method of claim 15~~9, wherein the monovalent antibody fragment is selected from ~~the~~a group consisting of a Fab fragment, a Fv fragment, and a single-chain Fv fragment (scFv).

~~18. The method of claim 15, wherein the proteinaceous CD40 binding molecule or the proteinaceous CD137 binding molecule with antibody-like binding properties is selected from the group of an aptamer, a mutein based on a polypeptide of the lipocalin family, a glubody, a protein based on the ankyrin scaffold, a protein based on the crystalline scaffold, an adnectin, and an avimer.~~

~~19.~~ 11. The method of any one of claims ~~3 and 14~~1 to ~~18~~10, wherein the ~~accessory molecule on the B cell~~first agent is ~~CD40.~~

~~20. The method of claim 19, wherein~~an anti-CD3Fab and the second agent is ~~CD40 ligand (CD154) or CD137.~~an anti-CD28Fab.

~~21.~~ 12. The method of claim 3, wherein the population of lymphocytes comprises a B cell population, the receptor molecule is CD40 or CD137, and/or the first agent comprises a binding reagent that binds CD40 or CD137.

13. The method of any one of claims ~~2~~1 to ~~20~~12, wherein ~~the binding sites Z1 and Z2~~each subunit of the ~~multimerization reagent are identical.~~ oligomer or polymer

~~22. The method of claim 21, wherein a single multimerisation reagent~~ is ~~used~~cross-linked by a polysaccharide.

~~23.~~ 14. The method of any one of claims 1 to ~~22~~12, wherein each subunit of the ~~multimerization reagent is immobilized on a solid surface.~~

~~24. The method of claim 23, wherein the solid surface is selected from the group consisting of a magnetic bead, a polymeric bead, a cell culture plate, a microtiter plate, a membrane, a hollow fiber and combinations thereof.~~

~~25. The method of claim 24, wherein the multimerization reagent is selected from the group consisting of streptavidin, avidin, an analog of streptavidin that reversibly binds biotin, an analog of avidin that reversibly binds biotin, a reagent that comprises at least two chelating groups K, wherein the at least two chelating groups are capable of binding to a transition metal ion, thereby rendering moiety A capable of binding to an oligohistidine affinity tag, multimeric glutathione-S-transferase, multimeric calmodulin and a biotinylated carrier protein.~~

~~26. The method of any of claims 1 to 22, wherein the multimerization reagent is in a soluble form.~~

~~27. The method of claim 26, wherein the multimerization reagent comprises an oligomer or a polymer of streptavidin, an~~ oligomer or ~~a~~ polymer ~~of avidin, an oligomer or a polymer of an~~

analog of streptavidin that reversibly binds biotin, an oligomer or a polymer of an analog avidin that reversibly bind biotin, a reagent that comprises at least two chelating groups K, wherein the at least two chelating groups are capable of binding to a transition metal ion, thereby rendering the reagent capable of binding to an oligohistidine affinity tag, multimeric glutathione S-transferase, multimeric calmodulin and a biotinylated carrier protein.

is cross-linked

28. The method of claim 27, wherein the streptavidin, avidin, or the streptavidin analog or the avidin analog that reversibly binds to biotin is crosslinked by a polysaccharide or wherein the cross-linked oligomers or polymers of streptavidin, avidin or of ab analog of streptavidin or avidin that reversibly binds biotin is obtained by crosslinking via a bifunctional linker.

29. The method of claim 27 or 28, wherein the cross-linked oligomers or polymers of streptavidin, avidin, or of the analog of streptavidin or avidin that reversibly binds biotin comprise three or more streptavidin monomers.

30. The method of any of claims 1 to 29, wherein

(a) said binding partner C1 and C2 comprises independently from each other biotin and said multimerization reagent comprises a streptavidin analog or an avidin analog that reversibly binds to biotin,

(b) said binding partner C1 and C2 comprises independently from each other a biotin analog that reversibly binds to streptavidin or avidin and said multimerisation reagent comprises streptavidin, or avidin, or a streptavidin analog, or an avidin analog that reversibly binds to said biotin analog, or

(c) said binding partner C1 and C2 comprises independently from each other a streptavidin or avidin binding peptide and said multimerization reagent comprises streptavidin, or avidin, or a streptavidin analog, or an avidin analog that reversibly binds to said streptavidin or avidin binding peptide.

31. The method of claim 30, wherein said binding partner C1 and C2 comprises independently from each other the streptavidin binding peptide Trp-Ser-His-Pro-Gln-Phe-Glu-Lys and said multimerization reagent comprises a streptavidin analog that comprises the amino

~~acid sequence Va1[44] Thr[45] Ala[46] Arg[47] at sequence positions 44 to 47 of wild type streptavidin or a streptavidin analog that comprises the amino acid sequence lle[44] Gly[45] Ala[46] Arg[47] at sequence positions 44 to 47 of wild type streptavidin.~~

~~32.~~ 15. The method of any one of claims 1 to ~~31~~14, wherein the ~~binding between said binding partner C1 and the binding partner C2, respectively, and said binding sites Z1 and Z2, respectively~~oligomer or polymer of ~~said multimerization reagent occurs in the presence of a divalent cation.~~

~~33. The method of claim 32,~~

~~wherein said binding partner C1 and the binding partner C2 comprises independently from each other a calmodulin binding peptide and the said multimerization reagent comprises calmodulin, or~~

~~wherein said binding partner C comprises a FLAG peptide and said multimerization reagent comprises an antibody binding the FLAG peptide, or~~

~~wherein said first binding C comprises an oligohistidine tag and said multimerization reagent comprises an antibody binding the oligohistidine tag.~~

~~The method of claim 11 or 12, wherein the binding between said binding partner C and said binding sites Z of said multimerization reagent is disrupted by metal ion chelation.~~

~~34. The method of claim 33, wherein the metal chelation is accomplished by addition of EDTA or EGTA.~~

~~35. The method of any of claims 2 to 30, wherein the binding partners C1 and C2 are different.~~

~~36. The method of any of claims 2 to 30, wherein the binding partners C1 and C2 are identical.~~

~~37. The method of any of the foregoing claims, further comprising disrupting the binding between said binding partner C1 of the first agent and/or said binding partner C2 of the second agent and said binding sites Z1 and/or Z2 of said multimerization reagent.~~

38. The method of claim 37, wherein disrupting the binding between said binding partner C1 of the first agent and/or said binding partner C2 of the second agent and said binding sites Z1 and/or Z2 of said multimerization reagent causes termination of the stimulation of the cells.

39. The method of any of claims 1 to 38, wherein the dissociation constant (K_d) for the reversible binding between said binding site Z1 and said binding partner C1 and/or for the reversible binding between said binding site Z2 and said binding partner C2 is in the range of 10^{-2} M to 10^{-13} M.

40. The method of any of claims 1 to 39, wherein said reversible bond between said binding partner C1 of the first agent and/or said binding partner C2 of the second agent and said binding sites Z1 and /or binding sits Z2 of said multimerization reagent is disrupted by contacting said population of cells with a free first binding partner C1 or an analog of said first binding partner C1 capable of disrupting the bond between the first binding partner C1 and the binding site Z1 and/or a free partner of said second binding partner C2 or an analog of sad second binding partner C2, capable of disrupting the bond between the second binding partner C2 and the binding site Z2.

41. The method of claim 40, wherein the first free partner and/or the second free partner is a compound which is not detrimental to the cells.

42. The method of any of claims 25 to 41, wherein the reversible bond is disrupted by contacting the cells with biotin or a biotin analog, when

(a) said binding partner C1 and C2 comprises independently from each other biotin and said multimerization reagent comprises a streptavidin analog or an, avidin analog that reversibly binds to biotin,

(b) said binding partner C1 and C2 comprises independently from each other a biotin analog that reversibly binds to, streptavidin or avidin and said multimerisation reagent comprises streptavidin, or avidin, or a streptavidin analog, or an avidin analog that reversibly binds to said biotin analog, or

(c) said binding partner C1 and C2 comprises independently from each other a streptavidin or avidin binding peptide and said multimerization reagent comprises streptavidin, or avidin, or a streptavidin analog, or an avidin analog that reversibly binds to said streptavidin or avidin binding peptide.

43. The method of any of claims 25 to 39, wherein the reversible bond is disrupted by contacting the cells with a metal chelator, when the binding between said binding partner C1 and the binding partner C2, respectively, and said binding sites Z1 and Z2, respectively of said multimerization reagent occurs in the presence of a divalent cation.

44. An *in vitro* method of expanding a population of cells, comprising contacting a sample comprising a population of cells with a multimerization reagent,
wherein the multimerization reagent is in a soluble form and has immobilized thereon (bound thereto) a first agent that provides a primary activation signal to the cells;
wherein the multimerisation reagent comprises at least one binding site Z1 for the binding of the first agent,
wherein the first agent comprises at least one binding partner C1, wherein the binding partner C1 is able of binding to the binding site Z1 of the multimerization reagent, wherein the first agent is bound to the multimerization reagent via the bond formed between the binding partner C1 and the binding site Z1, and
wherein the first agent binds to a receptor molecule on the surface of the cells, thereby providing a primary activation signal to the cells and thereby activating the cells.

45. The method of claim 44, wherein the multimerization agent has immobilized thereon (bound thereto) a second agent that stimulates an accessory molecule on the surface of the cells, wherein the second agent comprises a binding partner C2, wherein the binding partner C2 is able of being bound to a binding site Z2 of the multimerization reagent, wherein the second agent is bound to the multimerization reagent via the bond formed between the binding partner C2 and the binding site Z2,
wherein the second agent binds to the accessory molecule on the surface on the surface of the cells, thereby stimulating the activated cells.

~~46. The method of claim 44 or 45, wherein the bond formed between the binding partner C1 and the binding site Z1 is irreversible and/or the bond formed between the binding partner C2 and the binding site Z2 is irreversible.~~

~~47. The method of claim 44 or 45, wherein the bond formed between the binding partner C1 and the binding site Z1 is reversible and/or the bond formed between the binding partner C2 and the binding site Z2 is reversible.~~

~~48. The method of claims 47, wherein the dissociation constant (K_d) for the reversible binding between said binding site Z1 and said binding partner C1 and/or for the reversible binding between said binding site Z2 and said binding partner C2 is in the range of 10^{-2} M to 10^{-13} M.~~

~~49. The method of any of claim 44 to 48, wherein the population of cells is a lymphocyte population.~~

~~50. The method of claim 49, wherein the lymphocyte population is B cell population, a T cell population or a natural killer cell population.~~

~~51. The method of claim 50, wherein the T cell population is an antigen specific T cell population, a T helper cell population, a cytotoxic T cell, a memory T cell, a regulatory T cell or a natural killer T cell.~~

~~52. The method of claim 51, wherein the first agent comprises an MHC I: peptide complex or wherein the first agent stimulates a TCR/CD3 complex associated signal in the T cells.~~

~~53. The method of claim 52, wherein the first agent is a binding reagent that specifically binds CD3.~~

~~54. The method of claim 52 or 53, wherein the accessory molecule on the T cell is CD28.~~

~~55. The method of claim 54, wherein the second agent that binds the accessory molecule is a binding reagent that specifically binds CD28.~~

56. The method of any of claims 53 to 55, wherein
said first binding reagent that specifically binds CD3 is selected from the group consisting of an anti-CD3 antibody, a divalent antibody fragment of an anti-CD3 antibody, a monovalent antibody fragment of an anti-CD3 antibody, and a proteinaceous CD3 binding molecule with antibody-like binding properties and/or, wherein
the second agent that specifically binds CD28 is selected from the group consisting of an anti-CD28 antibody, a divalent antibody fragment of an anti-CD28 antibody, a monovalent antibody fragment of an anti-CD28 antibody, and a proteinaceous CD28 binding molecule with antibody-like binding properties.

57. The method of claim 56, wherein the divalent antibody fragment is an $(Fab)_2$' fragment, or a divalent single-chain Fv fragment.

58. The method of claim 56, wherein the monovalent antibody fragment is selected from the group consisting of a Fab fragment, a Fv fragment, and a single-chain Fv fragment (scFv).

59. The method of claim 58, wherein the proteinaceous CD3 or CD28 binding molecule with antibody-like binding properties is selected from the group of an aptamer, a mutein based on a polypeptide of the lipocalin family, a glubody, a protein based on the ankyrin scaffold, a protein based on the crystalline scaffold, an adnectin, and an avimer.

60. The method of claim 50, wherein the first agent is a binding reagent that specifically binds CD40 or CD137.

61. The method of claim 60, wherein the first binding reagent that specifically binds CD40 or CD137 is selected from the group consisting of an anti-CD40 antibody, a divalent antibody fragment of an anti-CD40 antibody, a monovalent antibody fragment of an anti-CD40 antibody, and a proteinaceous CD40 binding molecule with antibody-like binding properties or an anti-CD137 antibody, a divalent antibody fragment of an anti-CD137 antibody, a monovalent antibody fragment of an anti-CD137 antibody, and a proteinaceous CD137 binding molecule with antibody-like binding properties.

62. The method of claim 61, wherein the divalent antibody fragment is an (Fab)2' fragment, or a divalent single-chain Fv fragment.

~~63. The method of claim 61, wherein the monovalent antibody fragment is selected from the group consisting of a Fab fragment, a Fv fragment, and a single chain Fv fragment (scFv).~~

~~64. The method of claim 61, wherein the proteinaceous CD40 binding molecule or proteinaceous CD137 binding molecule with antibody like binding properties is selected from the group of an aptamer, a~~, or avidin mutein ~~based on a polypeptide of the lipocalin family, a glubody, a protein based on the ankyrin scaffold, a protein based on the crystalline scaffold, an adnectin, and an avimer.~~comprises three or more monomers of streptavidin, avidin, streptavidin mutein, or avidin mutein.

~~65~~16. The method of any one of claims ~~50 and 60~~1 to ~~64~~15, wherein the ~~accessory molecule on the B cell is CD40.~~

~~66. The method of claim 65, wherein the second agent is CD40 ligand (CD154) or CD137.~~

~~67. A reagent kit for expanding a population of cells, the kit comprising~~
~~(i) a multimerization reagent,~~
~~wherein the multimerisation reagent comprises at least one binding site Z for the reversible binding of a first agent,~~
~~(ii) a first agent that binds to a receptor molecule on the surface of the cells, thereby providing a primary activation signal to the cells and thereby activating the cells,~~
~~wherein the first agent comprises at least one binding partner C1, wherein the binding partner C1 is able of reversibly binding to a binding site Z1 of the multimerization reagent, wherein the first agent is bound to the multimerization reagent via the reversible bond formed between the binding partner C1 and the binding site Z1, and~~
~~(iii) a second agent that stimulates an accessory molecule on the surface of the cells,~~
~~wherein the second agent comprises a binding partner C2, wherein the binding partner C2 is able of reversibly binding to a binding site Z2 of the multimerization reagent, wherein the second agent is bound to the multimerization reagent via the bond formed between the binding partner C2 and the binding site Z2,~~

~~wherein the second agent binds to the accessory molecule on the surface on the surface of the cells, thereby stimulating the activated cells.~~

~~68. A reagent kit for expanding a population of cells, the kit comprising~~
~~(i) a multimerization reagent,~~
~~wherein the multimerisation reagent is in soluble form and comprises at least one binding site Z for the reversible binding of a first agent,~~
~~(ii) a first agent that binds to a receptor molecule on the surface of the cells, thereby providing a primary activation signal to the cells and thereby activating the cells,~~
~~wherein the first agent comprises at least one binding partner C1, wherein the binding partner C1 is able of binding to a binding site Z1 of the multimerization reagent, wherein the first agent is bound to the multimerization reagent via the reversible bond formed between the binding partner C1 and the binding site Z1.~~

~~69. The reagent kit of claim 68, further comprising~~
~~(iii) a second agent that stimulates an accessory molecule on the surface of the cells,~~
~~wherein the second agent comprises a binding partner C2, wherein the binding partner C2 is able of binding to a binding site Z2 of the multimerization reagent, wherein the second agent is bound to the multimerization reagent via the bond formed between the binding partner C2 and the binding site Z2.~~

~~70. The kit of any of claims 67 to 69, wherein the population of cells is a lymphocyte population.~~

~~71. The kit of claim 70, wherein the lymphocyte population is B cell population, a T cell population or a natural killer cell population.~~

~~72. The kit of claim 71, wherein the T cell population is an antigen-specific T cell population, a T helper cell population, a cytotoxic T cell, a memory T cell, a regulatory T cell or a natural killer T cell.~~

~~73. The kit of any of claims 67 to72, wherein the first agent comprises an MHC I : peptide complex or wherein the first agent stimulates a TCR/CD3 complex-associated signal in the T cells.~~

74. The kit of claim 73, wherein the first agent is a binding reagent that specifically binds CD3.

75. The kit of any of claim 72 to 74, wherein the accessory molecule on the T cell is CD28.

76. The kit of claim 75, wherein the second agent that binds the accessory molecule is a binding reagent that specifically binds CD28.

77. The kit of any of claims 74 to 76, wherein
said first binding reagent that specifically binds CD3 is selected from the group consisting of an anti-CD3-antibody, a divalent antibody fragment of an anti-CD3 antibody, a monovalent antibody fragment of an anti-CD3-antibody, and a proteinaceous CD3 binding molecule with antibody-like binding properties and/or, wherein
the second agent that specifically binds CD28 is selected from the group consisting of an anti-CD28-antibody, a divalent antibody fragment of an anti-CD28 antibody, a monovalent antibody fragment of an anti-CD28-antibody, and a proteinaceous CD28 binding molecule with antibody-like binding properties.

78. The kit of claim 67, wherein the multimerization agent is immobilized on a solid surface.

79. The kit of claim 78, wherein the solid surface is selected from the group consisting of a magnetic bead, a polymeric bead, a cell culture plate, a microtiter plate, a membrane, a hollow fiber and combinations thereof.

80. The kit of claim 79, wherein the multimerization reagent is the multimerization reagent is selected from the group consisting of streptavidin, avidin, an analog of streptavidin that reversibly binds biotin, an analog of avidin that reversibly binds biotin, a reagent that comprises at least two chelating groups K, wherein the at least two chelating groups are capable of binding to a transition metal ion, thereby rendering moiety A capable of binding to an oligohistidine affinity tag, multimeric glutathione-S-transferase, multimeric calmodulin and a biotinylated carrier protein.

81. The kit of claim 67, wherein the multimerization reagent is in a soluble form.

82. The kit of any of claims 68 to 78 or claim 81, wherein the multimerization reagent is selected from the group consisting of streptavidin, avidin, an analog of streptavidin that reversibly binds biotin, an analog of avidin that reversibly binds biotin, a reagent that comprises at least two chelating groups K, wherein the at least two chelating groups are capable of binding to a transition metal ion, thereby rendering the reagent capable of binding to an oligohistidine affinity tag, multimeric glutathione-S-transferase, multimeric calmodulin and a biotinylated carrier protein.

83. The kit of claim 82, wherein the streptavidin, avidin, or the streptavidin analog or the avidin analog that reversibly binds to biotin is crosslinked by a polysaccharide or wherein the cross-linked oligomers or polymers of streptavidin, avidin or of ab analog of streptavidin or avidin that reversibly binds biotin is obtained by crosslinking via a bifunctional linker.

84. An *in vitro* method of serially expanding a population of lymphocytes, wherein the population of lymphocytes comprises T cells, the method comprising
contacting a sample comprising the T cell comprising population of lymphocytes with a multimerization reagent,
wherein the multimerization reagent is in a soluble form and has reversibly immobilized thereon (i) a first agent that provides a primary activation signal to the T cells and (ii) a second agent which stimulates an accessory molecule on the surface of the T cells,
wherein the multimerisation reagent comprises at least one binding site Z1 for the reversible binding of the first agent,
wherein the first agent comprises at least one binding partner C1, wherein the binding partner C1 is able of reversibly binding to the binding site Z1 of the multimerization reagent, wherein the first agent is bound to the multimerization reagent via the reversible bond formed between the binding partner C1 and the binding site Z1,
wherein the multimerisation reagent comprises at least one binding site Z2 for the reversible binding of the second agent,
wherein the second agent comprises at least one binding partner C2, wherein the binding partner C2 is able of reversibly binding to the binding site Z2 of the multimerization reagent, wherein the first agent is bound to the multimerization reagent via the reversible bond formed between the binding partner C2 and the binding site Z2,

~~wherein the first agent binds to a receptor molecule on the surface of the T cells, thereby providing a primary activation signal to the cells and thereby activating the T cells,~~
~~wherein the second agent binds to the accessory molecule on the surface of the T cells, thereby stimulating the activated cells, the first agent and the second agent thereby together inducing the T cells to expand.~~

~~85. The method of claim 84, wherein contacting the sample comprising the T cell comprising population of lymphocytes with the multimerization reagent results having immobilized thereon the first and second agent results in specific binding of T cells to the multimerisation reagent.~~

~~86. The method of claim 84 or 85, further comprising separating the T cells bound to the multimerisation agent from unbound cells of the lymphocyte population.~~

~~87. The method of any of claims 84 to 86, wherein contacting the sample comprising the T cell comprising population of lymphocytes with the multimerization reagent results having immobilized thereon the first and second agent is carried out in a bioreactor such as a culture plate, a hollow-fiber bioreactor or a plastic bag bioreactor.~~

~~88. The method of any of claims 84 to 88, further comprising contacting the population of lymphocytes (reaction mixture containing the T cells bound to the multimerization reagent via the first agent and the second agent) with (i) a free first binding partner C1 or an analogue thereof capable of disrupting the bond between the first binding partner C1 and the binding site Z1 and (ii) a free second binding partner C2 or an analogue thereof, capable of disrupting the bond between the second binding partner C2 and the binding site Z2,~~
~~wherein said reversible bond between said binding partner C1 of the first agent and said binding sites Z1 as well as the reversible bond between said binding partner C2 of the second agent and said binding site Z2 of said multimerization reagent is disrupted, thereby releasing, the T cells, from the soluble multimerization reagent, and from the first agent and the second agent and stopping the expansion of the T cells.~~

~~89. The method of claim 88, comprising collecting an eluate containing the released T cells, the soluble multimerization reagent, the first agent and/or the second agent, the free binding partner C1 or the analogue thereof and the free binding partner C2 or the analogue thereof.~~

90. The method of any of claims 84 to 89, wherein the binding sites Z1 and Z2 of the multimerization reagent are identical.

91. The method of claim 90, wherein a single multimerisation reagent is used.

92. The method of any of claims 89 to 91, further comprising exposing the eluate to chromatography on a suitable stationary phase, the stationary phase being a gel filtration matrix and/or affinity chromatography matrix, wherein the gel filtration and/or affinity chromatography matrix comprises an affinity reagent, wherein the affinity reagent comprises a binding site Z1 and/or Z2 specifically binding to the binding partner C1 and/or C2 comprised in the first agent or the second agent, thereby immobilizing the first agent, the second agent, the first binding partner C1 or the analogue thereof and/or the free second binding partner C2 or the analogue thereof on the stationary phase.

93. The method of any of claim 88 to 92, wherein the stationary phase is fluidly connected to the bioreactor.

94. The method of claim 93, wherein the T cells are separated from the soluble multimerization reagent.

95. The method of claim 93, wherein the mixture comprising the T cells and the multimerization reagent are exposed to chromatography on a suitable stationary phase, the stationary phase being a gel filtration matrix and/or affinity chromatography matrix, wherein the gel filtration and/or affinity chromatography matrix comprises an affinity reagent, wherein the affinity reagent comprises a binding partner D that (specifically) binds to the binding site Z1 of the multimerization reagent, thereby immobilizing the multimerization reagent on the stationary phase.

96. The method of any of claims 84 to 95, wherein the first agent stimulates a TCR/CD3 complex-associated signal in the T cells.

97. The method of claim 96, wherein the first agent is a binding reagent that specifically binds CD3.

~~98. The method of any of claims 84 to 97, wherein the accessory molecule on the T cell is CD28.~~

~~99. The method of claim 98, wherein the second agent that binds the accessory molecule is a binding reagent that specifically binds CD28.~~

~~100. The method of any of claims 97 to 99, wherein~~
~~said first agent that specifically binds CD3 is selected from the group consisting of an anti-CD3-antibody, a divalent antibody fragment of an anti-CD3 antibody, a monovalent antibody fragment of an anti-CD3-antibody, and a proteinaceous CD3 binding molecule with antibody-like binding properties and/or wherein~~
~~the second agent that specifically binds CD28 is selected from the group consisting of an anti-CD28-antibody, a divalent antibody fragment of an anti-CD28 antibody, a monovalent antibody fragment of an anti-CD28-antibody, and a proteinaceous CD28 binding molecule with antibody-like binding properties.~~

~~101. The method of claim 100, wherein the divalent antibody fragment is an $(Fab)_2$'-fragment, or a divalent single-chain Fv fragment.~~

~~102. The method of claim 101, wherein the monovalent antibody fragment is selected from the group consisting of a Fab fragment, a Fv fragment, and a single-chain Fv fragment (scFv).~~

~~103. The method of any of claims 84 to 102, wherein the multimerization~~multimerizing reagent comprises an oligomer or a polymer of streptavidin~~, an oligomer or a polymer of avidin, an oligomer or a polymer of an analog of streptavidin that reversibly binds biotin, an oligomer or a polymer of an analog avidin that reversibly bind biotin.~~ mutein.

~~104.~~ 17. The method of ~~claim 103~~any one of claims 1 to 16, wherein the first streptavidin~~,~~ or avidin~~, or the streptavidin analog or the avidin analog that reversibly binds to biotin is crosslinked by a polysaccharide or wherein the cross-linked oligomers or polymers of~~

~~streptavidin, avidin or of an analog of streptavidin or avidin that reversibly binds biotin is obtained by crosslinking via a bifunctional linker.~~

~~105. The method of claim 103 or 104, wherein the cross-linked oligomers or polymers of streptavidin, avidin, or of the analog of streptavidin or avidin that reversibly binds biotin comprise three or more streptavidin monomers.~~

~~106. The method of any of claims 84 to 105, wherein~~

~~(a) said~~ binding partner ~~C1 and C2 comprises independently from each other biotin and said multimerization reagent comprises a streptavidin analog or an avidin analog that reversibly binds to biotin,~~

~~(b) said~~ and/or the second streptavidin or avidin binding partner ~~C1 and C2~~ comprises ~~independently from each other a biotin analog that reversibly binds to streptavidin or avidin and said multimerisation reagent comprises streptavidin, or avidin, or a streptavidin analog, or an avidin analog that reversibly binds to said biotin analog, or~~

~~(c) said binding partner C1 and C2 comprises independently from each other a~~ streptavidin or avidin binding peptide ~~and said multimerization reagent comprises~~.

18. The method of any one of claims 1 to 17, wherein the first streptavidin~~,~~ or avidin~~,~~ binding partner and/or ~~a streptavidin analog, or an avidin analog that reversibly binds to said~~the second streptavidin or avidin binding ~~peptide.~~

~~107. The method of claim 106, wherein said binding~~ partner ~~C~~independently comprises ~~the~~a streptavidin- binding peptide Trp-Ser-His-Pro-Gln-Phe-Glu-Lys ~~and said multimerization reagent comprises~~ (SEQ ID NO. 1) or a streptavidin binding peptide SAWSHPQFEK$(GGGS)_2$GGSAWSHPQFEK (SEQ. ID NO. 7).

19. ~~analog that comprises~~The method of any one of claims 1 to 18, wherein the multimerizing reagent comprises streptavidin mutein comprising amino acid sequence Val^{44}-Thr^{45}-Ala^{46}-Arg^{47} ~~at~~in sequence positions 44 to 47 of a wild type streptavidin, or ~~a~~ streptavidin ~~analog~~mutein

comprising ~~the~~ amino acid sequence ~~Ile~~^{44}Ile^{44}-Gly^{45}-Ala^{46}-Arg^{47} ~~at~~in sequence positions 44 to 47 of a wild type streptavidin.

20. The method of claim 19, wherein an N-terminal amino acid residue of the streptavidin mutein is within a region of amino acids 10 to 16 of a wild type streptavidin amino acid sequence, and a C-terminal amino acid residue of the streptavidin mutein is within a region of amino acids 133 to 142 of a wild type streptavidin amino acid sequence.

21. The method of any of claims 1 to 20, wherein the first or second streptavidin or avidin binding partners are identical.

~~22.108. The method of any of claims 84 to 107, wherein the dissociation constant (K_d) for the reversible binding between said binding site Z1 and said binding partner C1 and/or for the reversible binding between said binding site Z2 and said binding partner C2 is in the range of 10^{-2} M to 10^{-13} M.~~

~~109.~~ The method of any of claims 1 to 20, wherein the first and second streptavidin or avidin binding partner are different.

23. The method of any of claims 1 to 22, further comprising separating a bond between the first streptavidin or avidin binding partner of the first agent and the first binding site of the multimerizing reagent, and/or separating a bond between the second streptavidin or avidin binding partner of the second agent and the second binding site of the multimerizing reagent.

24.~~89 to 108~~ The method of claim 23, wherein the ~~first free partner and/or the second free partner is a compound which is not detrimental~~separating causes the stimulation of a primary signal and/or an accessory signal to a lymphocyte to ~~the cells~~end.

~~110.~~ 25. The method of ~~claim 109~~any of claims 1 to 24, wherein dissociation constant (K_d) of a reversible bond between the first streptavidin or avidin binding partner and the first binding site and/or a dissociation constant (K_d) of reversible bond between the second streptavidin or avidin binding partner and the second binding site is in a range of 10^{-2}M to 10^{-13}M.

26.~~the~~ The method of any one of claims 1 to 25, wherein a reversible bond ~~is disrupted~~between the first streptavidin or avidin binding partner and the first binding site and/or a reversible bond between the second streptavidin or avidin binding partner and the second binding site is separated by contacting ~~the cells~~a population of lymphocytes with biotin or a biotin analog.

~~111.~~ 27. The method of any of claims ~~92~~1 to 26, wherein contacting the sample with the multimerizing reagent causes a specific binding property of a T cell towards the multimerizing reagent.

28.~~110~~ The method of claim 27, further comprising separating the T cell bound to the multimerizing reagent from a non-bound cell of the cell population.

29. The method of claim 27 or 28, wherein a T cell receptor or a ~~chimeric~~chimera antigen receptor is introduced ~~into the~~to a T ~~cells~~cell either after ~~expansion~~stimulation or during ~~expansion.~~stimulation.

~~112.~~ 30. The method of claim ~~111~~29, wherein the T ~~cells are~~cell is stimulated ~~with~~by a third agent that binds to the introduced T cell receptor ~~or~~of the ~~chimeric~~chimera antigen receptor.

~~113.~~ 31. The method of any one of claims ~~84~~1 to ~~112~~30, wherein the population of lymphocytes ~~that comprises T cells~~ is a population of peripheral blood ~~mononucleated~~mononuclear cells (PBMC) or a population of ~~enriched~~concentrated or purified T cells.

32. The multimerizing reagent that reversibly binds to the first agent and the second agent, wherein the multimerizing reagent is in a soluble form and comprises an oligomer or polymer of streptavidin, avidin, streptavidin mutein, or avidin mutein, wherein; the first agent comprises (i) a first streptavidin or avidin binding peptide capable of reversibly binding to a first binding site of the multimerizing reagent, and (ii) a first antibody or an antigen-binding fragment thereof that binds to a receptor molecule on a surface of a lymphocyte and stimulates a signal to the lymphocyte; and the second agent comprises (i) a second streptavidin or avidin binding peptide capable of reversibly binding to a second binding site of the multimerizing reagent, and (ii) a second antibody or an antigen binding fragment thereof that binds to an accessory molecule on a surface of a lymphocyte and provides a co-stimulating signal to the lymphocyte.

33.~~114. An arrangement of a bioreactor and a (first) stationary phase for chromatography, wherein the bioreactor is suitable for the expansion of cells, wherein the (first) stationary phase is suitable for cell separation and removal of reagents, the stationary phase being a gel filtration matrix and/or affinity chromatography matrix, wherein the gel filtration and/or affinity chromatography matrix comprises an affinity reagent, wherein the affinity reagent comprises a binding site Z1 specifically binding to a binding partner C1 comprised in a first agent and/or the affinity reagent comprises a binding site Z2 specifically binding to a binding partner C2 comprised in a second agent, thereby being suitable of immobilizing on the stationary phase the first agent and/or the second agent, the first binding partner C1 and/or the free second binding partner C2, wherein the bioreactor and the stationary phase are fluidly connected.~~

~~115. The arrangement of claim 114, wherein the first stationary phase is either comprised in a chromatography column or is a planar stationary phase.~~

116. The arrangement of claim 115, further comprising a second stationary phase, the second stationary phase being fluidly connected to the first stationary phase.

117. The arrangement of claim 116, wherein the secondary stationary phase is a gel filtration matrix and/or affinity chromatography matrix, wherein the gel filtration and/or affinity chromatography matrix comprises an affinity reagent, wherein the affinitymultimerizing reagent comprises a binding partner D that (specifically) binds to the binding site Z1 of the multimerization reagent, thereby being suitable of immobilizing the multimerization reagent on the stationary phase.

118. The arrangement of claim 117, wherein the second stationary phase and the bioreactor are fluidly connected to each other.

119. An apparatus for purification and expansion of target cells, the apparatus comprising at least one arrangement of of claim 32, capable of stimulating a bioreactor and of at least one stationary phase for chromatography as defined in claims 114 to 118.

120. The apparatus of claim 119, comprising a sample inlet being fluidly connected to the bioreactor of the arrangement of a bioreactor and the at least one stationary phase for chromatography.

121. The apparatus of any of claims 119 or 120, comprising a sample outlet for purified and expanded target cells, the sample outlet being fluidly connected to the stationary phase of the arrangement of a bioreactor and the at least one stationary phase for chromatography.

122. The apparatus of any of claims 119 to 121, wherein the apparatus is a functionally closed system.

123. A multimerization reagent capable of expanding alymphocyte population of cells,.

wherein the multimerisation reagent is in soluble form and comprises at least one binding site Z1 for the reversible binding of a first agent that provides a primary activation signal to the cells, wherein the multimerization reagent has reversibly immobilized thereon (bound thereto) said first agent that provides a primary activation signal to the cells;

~~wherein the first agent comprises at least one binding partner C1, wherein the binding partner C1 is able of reversibly binding to the at least one binding site Z1 of the multimerization reagent, wherein the first agent is bound to the multimerization reagent via the reversible bond formed between the binding partner C1 and the binding site Z1.~~

~~124.~~

34. The ~~multimerization~~multimerizing reagent of claim ~~123,~~

~~wherein the multimerization reagent further comprises at least one binding site Z2 for the reversible binding of a second agent that stimulates an accessory molecule on the surface of the cells,~~

~~wherein the multimerization reagent has reversibly immobilized thereon (bound thereto) said second agent that stimulates an accessory molecule on the surface of the cells,~~

~~wherein the second agent comprises a binding partner C2, wherein the binding partner C2 is able of binding to the at least one binding site Z2 of the multimerization reagent, wherein the second agent is bound to the multimerization reagent via the bond formed between the binding partner C2 and the binding site Z2.~~

~~125. The multimerization reagent of claim 123 or 124, wherein the multimerization reagent is capable of expanding a lymphocyte population.~~

~~126. The multimerization reagent if claim 125~~33, wherein the lymphocyte population to be ~~expanded~~stimulated is a B cell population, ~~a~~ T cell population, or a natural killer cell population.

~~127.~~ 35. The ~~multimerization~~multimerizing reagent of ~~claim 126, wherein the T cell population is an antigen-specific T cell population, a T helper cell population, a cytotoxic T cell, a memory T cell, a regulatory T cell, or a natural killer T cell population.~~

~~128. The multimerization reagent~~any one of ~~claim 127~~claims 32 to 34, wherein the first agent comprises an MHC I–: peptide complex or the first agent stimulates a TCR/CD3 complex-~~associated~~ related signal in the T ~~cells.~~cell.

~~129~~36. The ~~multimerization~~multimerizing reagent of ~~claim 128~~any one of claims 32 to 35, wherein the first agent ~~is a binding reagent that~~ specifically binds CD3.

37. ~~130.~~ The ~~multimerization~~multimerizing reagent of any one of claims ~~124~~32 to ~~129~~36, wherein the second agent that binds the accessory molecule is a binding ~~reagent~~agent that specifically binds CD28 or CD137.

~~131.~~ 38. The ~~multimerization~~multimerizing reagent of any one of claims ~~128~~32 to ~~130~~37, wherein

~~said~~the first agent ~~that~~ specifically binds CD3 and is selected from ~~the~~a group consisting of an anti-CD3~~-~~ antibody, a ~~divalent~~bivalent antibody fragment of an anti-CD3 antibody, and a monovalent antibody fragment of an anti-CD3~~-~~ antibody~~,~~; and ~~a proteinaceous CD3 binding molecule with antibody-like binding properties, and wherein~~

the second agent ~~that~~ specifically binds CD28 or CD137 and is selected from ~~the~~a group consisting of an anti-CD28~~-~~ antibody, a ~~divalent~~bivalent antibody fragment of an anti-CD28 antibody, and a monovalent antibody fragment of an anti-CD28~~ antibody, a proteinaceous CD28 binding molecule with antibody-like binding properties,~~ antibody, an anti-CD137~~-~~ antibody, a ~~divalent~~bivalent antibody fragment of an anti-CD137 antibody, and a monovalent antibody fragment of an anti-CD137~~ antibody, a proteinaceous CD137 binding molecule with antibody-like binding properties, 4-1BB ligand, and any mixture thereof.~~ antibody.

~~132.~~ 39. The ~~multimerization~~multimerizing reagent of claim ~~131~~38, wherein the ~~divalent~~bivalent antibody fragment is ~~an (Fab)$_2$'~~ a F(ab')$_2$ fragment~~,~~ or a ~~divalent~~bivalent single-chain Fv fragment.

~~133.~~ 40. The ~~multimerization~~multimerizing reagent of claim ~~131~~38, wherein the monovalent antibody fragment is selected from ~~the~~a group consisting of a Fab fragment, a Fv fragment, and a single-chain Fv fragment (scFv).

~~134.~~ 41. The ~~multimerization~~multimerizing reagent of claim ~~133~~40, wherein the ~~proteinaceous CD3, CD28 or CD137 binding molecule with~~first agent is a monovalent antibody~~-like binding properties is selected from the group~~ fragment of an ~~aptamer, a mutein based on a polypeptide of the lipocalin family, a glubody, a protein based on the ankyrin scaffold, a protein based on the crystalline scaffold, an adnectin~~anti-CD3 antibody that is Fab, and ~~an avimer.~~the second agent is a monovalent antibody fragment of an anti-CD28 antibody that is Fab.

~~135.~~ 42. The ~~multimerization~~multimerizing reagent any one of ~~claim 126~~claims 32 to 34, wherein the first agent is a binding reagent that specifically binds CD40 or CD137, and ~~wherein the cell~~ a population ~~is~~of lymphocytes comprises a B cell ~~population.~~.

~~136. The multimerization reagent of claim 135, wherein the first binding reagent that specifically binds CD40 or CD137 is selected from the group consisting of an anti-CD40-antibody, a divalent antibody fragment of an anti-CD40 antibody, a monovalent antibody fragment of an anti-CD40-antibody, and a proteinaceous CD40 binding molecule with antibody-like binding properties or an anti-CD137-antibody, a divalent antibody fragment of an anti-CD137 antibody, a monovalent antibody fragment of an anti-CD137-antibody, a proteinaceous CD137 binding molecule with antibody-like binding properties, and CD40 ligand (CD154).~~

~~137. The multimerization reagent of claim 136, wherein the divalent antibody fragment is an (Fab)2'-fragment, or a divalent single-chain Fv fragment.~~

~~138. The multimerization reagent of claim 136, wherein the monovalent antibody fragment is selected from the group consisting of a Fab fragment, a Fv fragment, and a single-chain Fv fragment (scFv).~~

~~139. The multimerization reagent of claim 136, wherein the proteinaceous CD40 binding molecule or the proteinaceous CD137 binding molecule with antibody-like binding properties is selected from the group of an aptamer, a mutein based on a polypeptide of the lipocalin family, a glubody, a protein based on the ankyrin scaffold, a protein based on the crystalline scaffold, an adnectin, and an avimer.~~

~~140. The multimerization reagent of claims 126, wherein the accessory molecule on the B-cell is CD40 or CD137 or a mixture thereof.~~

~~141. The multimerization reagent of claim 140, wherein the second agent is CD40 ligand (CD154), CD137 or a mixture thereof and the cell population is a B-cell population.~~

~~142. The multimerization reagent of any of claims 124 to 141, wherein the binding sites Z1 and Z2 of the multimerization reagent are identical.~~

~~143. The multimerization~~43. The multimerizing reagent of any one of claims 32 to 42, wherein the oligomer or polymer of streptavidin, avidin, streptavidin mutein, or avidin mutein is cross-linked by a polysaccharide or via a bifunctional linker.

44. The multimerizing reagent of any ~~of claim 124 to 142, wherein the multimerization reagent comprises an oligomer or a polymer of streptavidin, an oligomer or a polymer of avidin, an~~ one of claims 32 to 43, wherein the oligomer or ~~a~~ polymer of ~~an analog of streptavidin that reversibly binds biotin, an oligomer or a polymer of an analog avidin that reversibly bind biotin, a reagent that comprises at least two chelating groups K, wherein the at least two chelating groups are capable of binding to a transition metal ion, thereby rendering the reagent capable of binding to an oligohistidine affinity tag, multimeric glutathione-S-transferase, multimeric calmodulin and a biotinylated carrier protein.~~

~~144. The multimerization reagent of claim 143, wherein the streptavidin, avidin, or the streptavidin analog or the avidin analog that reversibly binds to biotin is crosslinked by a polysaccharide or wherein the cross-linked oligomers or polymers of streptavidin, avidin or of an~~

analog of streptavidin or avidin that reversibly binds biotin is obtained by crosslinking via a bifunctional linker.

145. The multimerization reagent of claim 143 or 144, wherein the cross-linked oligomers or polymers of streptavidin, avidin, or of the analog of streptavidin mutein, or avidin that reversibly binds biotin comprise mutein comprises three or more monomers of streptavidin monomers., avidin, streptavidin mutein, or avidin mutein.

146. 45. The multimerizationmultimerizing reagent of any one of claims 12332 to 14544, wherein

(a) said binding partner C1 and C2 comprises independently from each other biotin and said multimerization reagent comprises a streptavidin analog or an avidin analog that reversibly binds to biotin,

(b) said binding partner C1 and C2 comprises independently from each other a biotin analog that reversibly binds tothe first streptavidin or avidin binding peptide and said multimerisation reagent comprises second streptavidin, or avidin, or a binding peptide independently comprises streptavidin analog, or an avidin analog that reversibly binds to said biotin analog, or

(c) said binding partner C1 and C2 comprises independently from each other a streptavidin or avidin binding peptide and said multimerization reagent comprises streptavidin, or avidin, or a streptavidin analog, or an avidin analog that reversibly binds to said streptavidin or avidin binding peptide.

147. The multimerization reagent of claim 146, wherein said binding partner C1 and C2 comprises independently from each other the streptavidin binding peptide Trp-Ser-His-Pro-Gln-Phe-Glu-Lys (SEQ. ID NO. 1) or streptavidin binding peptide SAWSHPQFEK(GGGS)$_2$GGSAWSHPQFEK (SEQ. ID NO. 7).

46.and said multimerization reagent comprises a streptavidin analog that comprises the The multimerizing reagent of any one of claims 32 to 45, wherein the multimerizing reagent comprises streptavidin mutein comprising amino acid sequence Val^{44}-Thr^{45}-Ala^{46}-Arg^{47} atin sequence

positions 44 to 47 of ~~———~~a wild type streptavidin, or streptavidin mutein comprising amino acid sequence Ile^{44}-Gly^{45}-Ala^{46}-Arg^{47} in sequence positions 44 to 47 of a wild type streptavidin.

47. The multimerizing reagent of claim 46, wherein the N-terminal amino acid residue of the streptavidin mutein is within a region of amino acids 10 to 16 of a wild type streptavidin ~~or a~~amino acid sequence, and the C-terminal amino acid residue of the streptavidin ~~analog that comprises the amino acid sequence Ile^{44}-Gly^{45}-Ala^{46}-Arg^{47} at sequence positions 44~~mutein is within a region of amino acids 133 to ~~47~~142 of a wild type streptavidin~~.~~

~~148. A composition capable of expanding a population of cells comprising~~
~~(i) a first multimerization reagent,~~
~~wherein the first multimerisation reagent is in soluble form and comprises at least one binding site Z1 for the reversible binding of a first agent that provides a primary activation signal to the cells,~~
~~wherein the first multimerization reagent has reversibly immobilized thereon (bound thereto) said first agent that provides a primary activation signal to the cells;~~
~~wherein the first agent comprises at least one binding partner C1, wherein the binding partner C1 is able of reversibly binding to the at least one binding site Z1 of the multimerization reagent,~~
~~wherein the first agent is bound to the multimerization reagent via the reversible bond formed between the binding partner C1 and the binding site Z1, and~~
~~(ii) a second multimerization reagent,~~
~~wherein the second multimerization reagent is in soluble form and comprises at least one binding site Z2 for the reversible binding of a second agent that stimulates an accessory molecule on the surface of the cells,~~
~~wherein the multimerization reagent has reversibly immobilized thereon (bound thereto) said second agent that stimulates an accessory molecule on the surface of the cells,~~
~~wherein the second agent comprises a binding partner C2, wherein the binding partner C2 is able of binding to the at least one binding site Z2 of the multimerization reagent, wherein the second agent is bound to the multimerization reagent via the bond formed between the binding partner C2 and the binding site Z2.~~

amino acid sequence.