Background

[0004] Various strategies are available for stimulating T cell populations in vitro, including for expanding antigen-specific T cells in vitro for use in adoptive cellular immunotherapy or cancer therapy in which infusions of such T cells have been shown to have anti-tumor reactivity in a tumor-bearing host or for use to treat viral infections. Improved strategies are needed for expanding cell populations in vitro, including for research, diagnostic and therapeutic purposes.

Summary

[0005] Provided herein are an oligomeric particle reagents comprising a plurality of streptavidin or streptavidin mutein molecules, wherein the size of the oligomeric particle reagent comprises i) a radius, e.g., a hydrodynamic radius, of greater than 25 nm, ii) a molecular weight of at least 5 x 10^6 g/mol; and/or (iii) at least 100 streptavidin or streptavidin mutein tetramers per oligomeric particle reagent.

[0005a] In one aspect, the present disclosure refers to an oligomeric particle reagent comprising a plurality of streptavidin or streptavidin mutein molecules, wherein the size of the oligomeric particle reagent comprises i) a radius of greater than 50 nm, ii) a molecular weight of at least 5 x 10^6 g/mol; and/or (iii) at least 100 streptavidin or streptavidin mutein tetramers per oligomeric particle reagent.

[0006] In particular examples of any of the oligomeric particle reagents provided herein, the streptavidin or streptavidin mutein molecules bind to or are capable of binding to biotin, a biotin analog (e.g. desthiobiotin, iminobiotin) or to a streptavidin binding peptide (e.g. Strep-tagII (WSHPQFEK, SEQ ID NO:8)). In certain examples of any of the oligomeric particle reagents provided herein, the streptavidin or streptavidin mutein molecules reversibly bind to or are capable of reversibly binding to biotin, a biotin analog or to a streptavidin binding peptide (e.g. Strep-tagII (WSHPQFEK, SEQ ID NO:8)). In some examples of any of the oligomeric particle reagents provided herein, the oligomeric particle reagent comprises a plurality of streptavidin mutein molecules, wherein the streptavidin mutein molecules comprise the amino acid sequence Val^{44}-Thr^{45}-Ala^{46}-Arg^{47} or Ile^{44}-Gly^{45}-Ala^{46}-Arg^{47} at sequence positions corresponding to positions 44 to 47 with reference to positions in streptavidin in the sequence of amino acids set forth in SEQ ID NO: 1.

[0007] In particular examples of any of the oligomeric particle reagents provided herein, the streptavidin or streptavidin mutein molecules bind to or are capable of binding to biotin, avidin, a biotin analog or mutein, an avidin analog or mutein, and/or a biologically active fragment thereof. In certain examples of any of the oligomeric particle reagents provided herein, the streptavidin or streptavidin mutein molecules reversibly bind to or are capable of reversibly binding to biotin, avidin, a biotin analog or mutein, an avidin analog or mutein,

and/or a biologically active fragment thereof. In some examples of any of the oligomeric particle reagents provided herein, the oligomeric particle reagent comprises a plurality of streptavidin mutein molecules, wherein the streptavidin mutein molecules comprise the amino acid sequence Val^{44}-Thr^{45}-Ala^{46}-Arg^{47} or Ile^{44}-Gly^{45}-Ala^{46}-Arg^{47} at sequence positions corresponding to positions 44 to 47 with reference to positions in streptavidin in the sequence of amino acids set forth in SEQ ID NO: 1.

[0008] In particular examples of any of the oligomeric particle reagents provided herein, the oligomeric particle reagent comprises a plurality of streptavidin mutein molecules that comprise: a) the sequence of amino acids set forth in any of SEQ ID NOS: 3-6, 27, 28, 60, or 61; b) a sequence of amino acids that exhibit at least 85%, 86%, 87%, 88%, 89%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to any of SEQ ID NOS: 3-6, 27, 28, 60, or 61 and contain the amino acid sequence corresponding to Val^{44}-Thr^{45}-Ala^{46}-Arg^{47} or Ile^{44}-Gly^{45}-Ala^{46}-Arg^{47} and/or reversibly bind to biotin, a biotin analog or a streptavidin-binding peptide; or and/or a sequence of amino acids that exhibit at least 85%, 86%, 87%, 88%, 89%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to any of SEQ ID NOS: 3-6, 27, 28, 60, or 61 and contain the amino acid sequence corresponding to Val^{44}-Thr^{45}-Ala^{46}-Arg^{47} or Ile^{44}-Gly^{45}-Ala^{46}-Arg^{47} and/or binds to biotin or a biologically active form thereof, a biotin analog or mutein or a biologically active fragment thereof or a streptavidin-binding peptide) a functional fragment of a) or b) that binds to biotin or a biologically active form thereof, a biotin analog or mutein or a biologically active fragment thereof or a streptavidin-binding peptide and/or reversibly bind to biotin, a biotin analog or a streptavidin-binding peptide; or c) a functional fragment of a) or b) that binds to biotin, a biotin analog or a streptavidin-binding peptide.. In certain examples of any of the oligomeric particle reagents provided herein, wherein the oligomeric particle reagent comprises a plurality of streptavidin mutein molecules that comprise the sequence of amino acids set forth in SEQ ID NO: 6 or 61. In some examples of any of the oligomeric particle reagents provided herein, the streptavidin mutein molecule further comprises an amino acid replacement or replacements at a position corresponding to 117, 120 and/or 121 with reference to positions in streptavidin in the sequence of amino acids set forth in SEQ ID NO: 1.

[0009] In particular examples of any of the oligomeric particle reagents provided herein: the amino acid replacement or replacements are selected from among Glu117, Asp117, Arg117, Ser120, Ala120, Gly120, Trp121, Tyr121 or Phe121; or the amino acid replacement or replacements are selected from one or more of Glu117, Gly120 or Tyr121; or the amino acid replacements are selected from Glu117, Gly120 or Tyr121. In certain examples of any of the oligomeric particle reagents provided herein, the oligomeric particle reagent comprises a plurality of streptavidin mutein molecules that comprise: a) the sequence of amino acids set forth in SEQ ID NO: 27 or 28; b) a sequence of amino acids that exhibits at least 85%, 86%, 87%, 88%, 89%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to SEQ ID NO: 28 and contains the amino acid sequence corresponding to Val^{44}, Thr^{45}, Ala^{46}, Arg^{47}, Glu^{117}, Gly^{120} and Tyr^{121} and/or binds to biotin or a biologically active fragment, a biotin analog or mutein or a biologically active fragment thereof or a streptavidin-binding peptide; or c) a functional fragment of a) or b) that binds to biotin or a biologically active fragment, a biotin analog or mutein or a biologically active fragment thereof or a streptavidin-binding peptide.

[0010] In particular examples of any of the oligomeric particle reagents provided herein: the amino acid replacement or replacements are selected from among Glu117, Asp117, Arg117, Ser120, Ala120, Gly120, Trp121, Tyr121 or Phe121; or the amino acid replacement or replacements are selected from one or more of Glu117, Gly120 or Tyr121; or the amino acid replacements are selected from Glu117, Gly120 or Tyr121. In certain examples of any of the oligomeric particle reagents provided herein, the oligomeric particle reagent comprises a plurality of streptavidin mutein molecules that comprise: a) the sequence of amino acids set forth in SEQ ID NO: 27 or 28; b) a sequence of amino acids that exhibits at least 85%, 86%, 87%, 88%, 89%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to SEQ ID NO: 28 and contains the amino acid sequence corresponding to Val^{44}, Thr^{45}, Ala^{46}, Arg^{47}, Glu^{117}, Gly^{120} and Tyr^{121} and/or reversibly binds to biotin, a biotin analog or a streptavidin-binding peptide; or c) a functional fragment of a) or b) that reversibly binds to biotin, a biotin analog or a streptavidin-binding peptide.

[0011] In some examples of any of the oligomeric particle reagents provided herein, the oligomeric particle reagent is bound to or is capable of binding to one or more agents via a binding partner, in which the one or more agents comprise the binding partner, such as biotin, a biotin analog or a streptavidin binding peptide. In particular examples of any of

the oligomeric particle reagents provided herein, the one or more agents comprise a binding partner, wherein the binding partner is capable of binding to one or more binding site on the oligomeric particle reagent. In certain examples of any of the oligomeric particle reagents provided herein, the binding partner comprises a streptavidin-binding peptide or biotin or a biotin analog. In some examples of any of the oligomeric particle reagents provided herein, the binding partner comprises a streptavidin-binding peptide selected from the group consisting of Trp-Ser-His-Pro-Gln-Phe-Glu-Lys (SEQ ID NO: 8), Trp-Ser-His-Pro-Gln-Phe-Glu-Lys-$(GlyGlyGlySer)_3$-Trp-Ser-His-Pro-Gln-Phe-Glu-Lys ((SEQ ID NO: 17), Trp-Ser-His-Pro-Gln-Phe-Glu-Lys-$(GlyGlyGlySer)_2$-Trp-Ser-His-Pro-Gln-Phe-Glu-Lys (SEQ ID NO: 18) and Trp-Ser-His-Pro-Gln-Phe-Glu-Lys-$(GlyGlyGlySer)_2$Gly-Gly-Ser-Ala-Trp-Ser-His-Pro-Gln-Phe-Glu-Lys (SEQ ID NO: 19). In particular examples of any of the oligomeric particle reagents provided herein, the one or more agents binds or is further capable of binding to a molecule expressed on the surface of a target cell. In certain examples of any of the oligomeric particle reagents provided herein, the one or more agents comprises an antibody, optionally a Fab or a nanobody®, for example a single domain antibody (sdAb).

[0012] In some examples of any of the oligomeric particle reagents provided herein, the one or more agents is a receptor binding agent that binds to or is capable of binding to a receptor expressed on the surface of a target cell. In particular examples of any of the oligomeric particle reagents provided herein, the receptor binding agent is or comprises a stimulatory agent capable of binding to a molecule on the surface of a target cell, thereby inducing or modulating a signal in the target cell. In certain examples of any of the oligomeric particle reagents provided herein, the receptor-binding agent is capable of initiating a TCR/CD3 complex-associated signal in T cells, binds to a member of a TCR/CD3 complex; and/or specifically binds to CD3. In some examples of any of the oligomeric particle reagents provided herein, the stimulatory agent is a first receptor-binding agent and the oligomeric particle reagent comprises a second receptor-binding agent, wherein the second receptor-binding agent is capable of specifically binding to a second molecule on the surface of the target cell, which binding to the second molecule is optionally capable of inducing or modulating a signal in the target cells.

[0013] In particular examples of any of the oligomeric particle reagents provided herein, the second receptor-binding agent specifically binds to a costimulatory molecule, accessory molecule, immune checkpoint molecule, is a member of the TNF family or the TNF family receptor, cytokine receptor, chemokine receptor, or is or comprises an adhesion molecule or a factor that induces cytokine production, chemokine production and/or expression of an adhesion molecule. In certain examples of any of the oligomeric particle reagents provided herein, the receptor-binding agent specifically binds to a costimulatory molecule, accessory molecule, immune checkpoint molecule, is a member of the TNF family or the TNF family receptor, cytokine receptor, chemokine receptor, or is or comprises an adhesion molecule or a factor that induces cytokine production, chemokine production and/or expression of an adhesion molecule.

[0014] In some examples of any of the oligomeric particle reagents provided herein, the receptor-binding agent (second receptor-binding agent) binds to a costimulatory or accessory molecule and the costimulatory or accessory molecule is selected from CD28, CD90 (Thy-1), CD95 (Apo-/Fas), CD137 (4-1BB), CD154 (CD40L), ICOS, LAT, CD27, OX40 or HVEM. In particular examples of any of the oligomeric particle reagents provided herein, the receptor-binding agent (second receptor-binding agent) specifically binds to a cytokine receptor and the cytokine receptor is selected from among IL-2R, IL-1R, IL-15R, IFN-gammaR, TNF-alphaR, IL-4R, IL-10R, Type I IFNR, IL-12R, IL-15R, IL-17R, TNFR1 and TNFR2. In certain examples of any of the oligomeric particle reagents provided herein, the receptor-binding agent (second receptor-binding agent) specifically binds to a chemokine receptor and the chemokine receptor is selected from among CCR1, CCR2, CCR3, CCR4, CCR5, CCR7, CCR9, CXCR1, CXCR3 and CXCR4.

[0015] In some examples of any of the oligomeric particle reagents provided herein, the receptor-binding agent (second receptor-binding agent) is a factor that induces cytokine or chemokine production and the factor is a ligand that specifically binds to a cytokine or chemokine receptor.

[0016] In particular examples of any of the oligomeric particle reagents provided herein, the receptor-binding agent (second receptor-binding agent) is a ligand that specifically binds to a cytokine receptor, wherein the ligand specifically binds IL-2R, IL-1R, IL-15R, IFN-gammaR, TNF-alphaR, IL-4R, IL-10R, Type I IFNR, IL-12R, IL-15R, IL-17R, TNFR1 and

TNFR2; and/or the ligand is selected from among IL-2, IL-1, IL-15, IFN-gamma, TNF-alpha, IL-4, IL-10, IL-12, IL-15, IL-17 and TNF, or is a biologically active fragment thereof.

[0017] In certain examples of any of the oligomeric particle reagents provided herein, the receptor-binding agent (second receptor-binding agent) is a ligand that specifically binds to a chemokine receptor, wherein the ligand specifically binds to a chemokine receptor selected from among CCR1, CCR2, CCR3, CCR4, CCR5, CCR7, CCR9, CXCR1, CXCR3 and CXCR4; or the ligand is selected from among CXCL9, CXCL10, CCL19, CCL21 and CCL25 or is a biologically active fragment thereof. In some examples of any of the oligomeric particle reagents provided herein, the receptor-binding agent (second receptor-binding agent) is an adhesion molecule and the adhesion molecule is selected from among CD44, CD31, CD18/CD11a (LFA-1), CD29, CD54 (ICAM-1), CD62L (L-selectin), and CD29/CD49d (VLA-4), CD106 (VCAM-1) or is a biologically active fragment thereof.

[0018] In particular examples of any of the oligomeric particle reagents provided herein, the one or more agents comprises a selection agent, wherein the selection agent binds to or is capable of binding to a selection marker that is expressed on the surface of a target cell. In certain examples of any of the oligomeric particle reagents provided herein, the target cell is an immune cell. In some examples of any of the oligomeric particle reagents provided herein, the target cell is a lymphocyte or an antigen-presenting cell. In particular examples of any of the oligomeric particle reagents provided herein, the target cell is a T cell, B cell, NK cell, macrophage or dendritic cell. In certain examples of any of the oligomeric particle reagents provided herein, the target cell is a T cell. In some examples of any of the oligomeric particle reagents provided herein, the selection marker is CD25, CD28, CD62L, CCR7, CD27, CD127, CD3, CD4, CD8, CD45RA, and/or CD45RO.

[0019] In particular examples of any of the oligomeric particle reagents provided herein, the oligomeric particle reagent comprises a radius of greater than 25 nm, greater than 50 nm, greater than 60 nm, greater than 70 nm, greater than 80 nm, or greater than 90 nm. In certain examples of any of the oligomeric particle reagents provided herein, the oligomeric particle reagent comprises a radius of between 25 nm and 150 nm, between 50 nm and 150 nm, between 75 nm and 125 nm, between 80 nm and 115 nm, or between 90 nm and 110 nm, inclusive, or 90 nm ±15 nm, or 95 nm ± 20-25nm. In some examples of any of the oligomeric particle reagents provided herein, the oligomeric particle reagent has a radius of less than 150 nm. In particular examples, the radius is a hydrodynamic radius.

[0020] In particular examples of any of the oligomeric particle reagents provided herein, the oligomeric particle reagent comprises a molecular weight of at least 1 x 10^7 g/mol, at least 5 x 10^7 g/mol, or at least 1 x 10^8 g/mol. In certain examples of any of the oligomeric particle reagents provided herein, the oligomeric particle reagent comprises a molecular weight of between 1 x 10^6 g/mol and 1 x 10^{10} g/mol, between 1 x 10^7 g/mol and 1 x 10^9 g/mol, between 5 x 10^7 g/mol and 5 x 10^8 g/mol, between 1 x 10^8 g/mol and 5 x 10^8 g/mol, or between 1 x 10^8 g/mol and 2 x 10^8 g/mol. In some examples of any of the oligomeric particle reagents provided herein, the oligomeric particle reagent comprises at least 100 streptavidin or streptavidin mutein tetramers, at least 500 streptavidin or streptavidin mutein tetramers, at least 1,000 streptavidin or streptavidin mutein tetramers, at least 1,500 streptavidin or streptavidin mutein tetramers, or at least 2,000 streptavidin or streptavidin mutein tetramers.

[0021] In particular examples of any of the oligomeric particle reagents provided herein, the oligomeric particle reagent comprises between 100 and 50,000 streptavidin or streptavidin mutein tetramers, between 1,000 and 20,000 streptavidin or streptavidin mutein tetramers, between 1,000 and 10,000 streptavidin or streptavidin mutein tetramers, or between 2,000 and 5,000 streptavidin or streptavidin mutein tetramers. In certain examples of any of the oligomeric particle reagents provided herein, the plurality of streptavidin or streptavidin muteins comprise lysine residues, wherein less than 20%, 10%, 5%, 1%, of the lysine residues comprise N-substituted iminothiolane.

[0022] Provided herein is a composition comprising one or more oligomeric particle reagents. In some examples of any of the compositions provided herein, the one or more oligomeric particle reagents is a plurality of oligomeric particle reagents. In particular examples of any of the compositions provided herein, the plurality of oligomeric particle reagents comprises i) an average radius of greater than 70 nm; ii) an average molecular weight of at least 1 x 10^8 g/mol; and/or iii) an average number of streptavidin or streptavidin tetramers per oligomeric particle reagent of at least 2,000 and/or iv) a radius size distribution wherein at least 95% of the plurality of oligomeric particle reagents comprise a radius of between 10 nm to 150 nm. In certain examples, the radius size distribution is a hydrodynamic radius size distribution.

[0022a] In another aspect, the present disclosure refers to a composition comprising a plurality of the oligomeric particle reagent as disclosed herein.

[0023] In certain examples of any of the compositions provided herein, the plurality of oligomeric particle reagents comprises an average radius of greater than 25 nm, greater than 50 nm, greater than 60 nm, greater than 70 nm, greater than 80 nm, greater than 90 nm, or greater than 100 nm. In some examples of any of the compositions provided herein, the plurality of oligomeric particle reagents comprise an average radius of between 25 nm and 150 nm, between 50 nm and 150 nm, between 75 nm and 125 nm, between 80 nm and 110 nm, or between 90 nm and 110 nm, inclusive, or 90 nm ±15 nm, or 95 nm ± 20-25 nm. In particular examples of any of the compositions provided herein, at least 95% of the plurality of oligomeric particle reagents comprise a radius of between 50 and 150 nm, between 70 nm and 140 nm, between 80 nm and 120 nm, between 80 nm and 115 nm, between 80 nm and 100 nm, between 90 nm and 110 nm, and/or between 100 nm and 120 nm.

[0024] In certain examples of any of the compositions provided herein, at least 95% of the oligomeric particle reagents comprise a radius between ± 50%, ± 25%, ± 20%, ± 15%, ± 10%, and/or ± 5% of the average and/or the median radius of the plurality of oligomeric particle reagents. In some examples of any of the compositions provided herein, the plurality of oligomeric particle reagents comprising an average radius of between 80 nm and 115 nm and wherein at least 95% of the oligomeric particle reagents comprise a radius between ± 25% of the average radius. In particular examples of any of the compositions provided herein, the plurality of particles comprise an average molecular weight of between 1 x 10^8 g/mol and 5 x 10^8 g/mol, or between 1 x 10^8 g/mol and 2 x 10^8 g/mol, inclusive.

[0025] In certain examples of any of the compositions provided herein, the plurality of oligomeric particle reagents comprises an average number of streptavidin or streptavidin tetramers per oligomeric particle reagent of at least 100, at least 500, at least 1,000, at least 1,500, or at least 2,000. In some examples of any of the compositions provided herein, the plurality of oligomeric particle reagents comprises an average number of streptavidin or streptavidin tetramers per oligomeric particle reagent of between 100 and 50,000, between 1,000 and 20,000, between 1,000 and 10,000, or between 2,000 and 5,000,each inclusive.

[0026] In particular examples of any of the compositions provided herein, the average radius of the plurality the oligomer particles does not increase by more than 25% when stored at about or below -80°C, at about or below -20°C, and/or at about or below 4°C for at least 1 week. In certain examples of any of the compositions provided herein, the average radius

of the plurality the oligomer particles does not increase by more than 10% when stored at about or below 4°C for at least one week. In some examples of any of the compositions provided herein, the average radius of the plurality of the oligomer particles does not increase by more than 10% when stored at about or below 4°C for at least 3 weeks. In particular examples of any of the compositions provided herein, the average radius of the plurality of the oligomer particles does not increase by more than 10% when stored at about or below 4°C for at least 9 weeks, at least 27 weeks, or at least 46 weeks. In particular examples, the average radius of the plurality of the oligomer particles does not increase by more than 10% when stored at, at about, or below -20°C, -30°C, -40°C, -50°C, -60°C, -70°C,or -80°C, for at least 1 week, 3 weeks, 9 weeks, 27 weeks, or 46 weeks.

[0027] Provided herein are methods for producing an oligomeric particle reagent comprising streptavidin or a streptavidin mutein, the method comprising: incubating a plurality of activated streptavidin or streptavidin mutein molecules comprising a thiol-reactive functional group capable of reacting with a thiol functional group and a plurality of thiolated streptavidin or streptavidin mutein molecules comprising one or more thiol functional group, thereby generating oligomeric streptavidin or streptavidin mutein particles; separating the oligomeric particles from monomer and/or smaller oligomeric molecules; and contacting the oligomeric particle with a stabilizing agent, thereby producing the oligomeric particle reagent.

[0027a] In another aspect, the present disclosure refers to a method for producing an oligomeric particle reagent comprising streptavidin or a streptavidin mutein, the method comprising:

incubating a plurality of activated streptavidin or streptavidin mutein molecules comprising a thiol-reactive functional group capable of reacting with a thiol functional group and a plurality of thiolated streptavidin or streptavidin mutein molecules comprising one or more thiol functional group, thereby generating a particle composition comprising the oligomeric particles comprising streptavidin or a streptavidin mutein;

separating the oligomeric particles from monomer and/or smaller oligomeric molecules; and

contacting the oligomeric particle with a stabilization agent, thereby producing the oligomeric particle reagent.

[0028] In some examples of any of the methods provided herein, the plurality of activated streptavidin or streptavidin mutein molecules is generated by incubating a first plurality of streptavidin or streptavidin mutein molecules with an activation agent that is capable of converting one or more amines to a thiol-reactive functional group. In particular examples of any of the methods provided herein, the plurality of thiolated streptavidin or streptavidin mutein molecules is generated by incubation of a second plurality of streptavidin or streptavidin mutein molecules with a thiolating agent that adds or is capable of adding a thiol functional group to one or more lysine residue.

[0029] In another aspect, the present disclosure refers to a method for producing oligomeric particle reagents, the method comprising: (a) incubating a first plurality of streptavidin or streptavidin mutein molecules with an activation agent under conditions to convert one or more amines to a thiol-reactive group capable of reacting with a thiol functional group, thereby generating a plurality of activated streptavidin or streptavidin mutein molecules; (b) incubating a second plurality of streptavidin or streptavidin mutein molecules with a thiolating agent that adds or is capable

of adding a thiol functional group to one or more lysine residue, thereby generating a plurality of thiolated streptavidin or streptavidin mutein molecules; and (c) incubating the plurality of activated streptavidin or streptavidin mutein molecules with the plurality of thiolated streptavidin or streptavidin mutein molecules, thereby generating a particle composition comprising the oligomeric particle reagents; wherein the method is carried out under conditions in which, at the time of initiation of the incubation in (c), the plurality of thiolated streptavidin or streptavidin mutein molecules are such that at least 60% of the lysines, on average, comprise a thiol functional group, and/or at least 10 lysines, on average, per thiolated streptavidin or streptavidin mutein tetramer comprise a thiol functional group.

[0030] Certain examples further comprise separating the oligomeric particle reagents from monomer and/or smaller oligomeric streptavidin or streptavidin mutein molecules. In certain examples of any of the methods provided herein, the incubation of the first plurality of streptavidin or streptavidin mutein molecules with the activation agent is performed at a molar ratio of between 1:1 and 1:10 of streptavidin or streptavidin mutein to the activation reagent. In some examples of any of the methods provided herein, the incubation of the first plurality of streptavidin or streptavidin mutein molecules with the activation agent is performed at a molar ratio of 1:2 ± 2% of streptavidin or streptavidin mutein to the activation reagent. In particular examples of any of the methods provided herein, the activation agent comprises a heterobifunctional crosslinker. In certain examples of any of the methods provided herein, the activation agent comprises sulfosuccinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (sulfo SMCC) and/or Succinimidyl-6-[(β-maleimidopropionamido)hexanoate (SMPH).In some examples of any of the methods provided herein, the thiol-reactive functional group is a haloacetyl group, a maleimide group, an aziridine group, an acryloyl group, an arylating agent, a vinylsulfone group, a pyridyl disulfide, a TNB-thiol or a disulfide reducing agent. In particular examples of any of the methods provided herein, the thiol-reactive functional group is a maleimide group. In certain examples of any of the methods provided herein, the first plurality of streptavidin or streptavidin mutein molecules and the activation agent are incubated at a neutral pH.

[0031] In some examples of any of the methods provided herein, the first plurality of streptavidin or streptavidin mutein molecules and the activation agent are incubated at a pH of between 6.8 and 7.5. In particular examples of any of the methods provided herein, the

first plurality of streptavidin or streptavidin mutein molecules and the activation agent are incubated at a pH of between 7.0 and 7.4, optionally of or about 7.2. In certain examples of any of the methods provided herein, the first plurality of streptavidin or streptavidin mutein molecules and the activation agent are incubated at a temperature between 4°C and 39°C. In some examples of any of the methods provided herein, the first plurality of streptavidin or streptavidin mutein molecules and the activation agent are incubated at room temperature, optionally between 20°C and 25°C, optionally about 23°C or about 24°C.

[0032] In particular examples of any of the methods provided herein, the first plurality of streptavidin or streptavidin mutein molecules and the activation agent are incubated for between 15 minutes and 6 hours or 30 minutes and 2 hours, each inclusive. In certain examples of any of the methods provided herein, the first plurality of streptavidin or streptavidin mutein molecules and the activation agent are incubated for between 45 minutes and 1.5 hours, inclusive, optionally for or for about 1 hour.

[0033] In some examples of any of the methods provided herein, the incubation of the second plurality of streptavidin or streptavidin mutein molecules with the thiolating agent is performed at a molar ratio of between 10:1 and 1:1, inclusive, of the thiolating reagent to each primary amine per streptavidin or streptavidin mutein molecule. In particular examples of any of the methods provided herein, the incubation of the second plurality of streptavidin or streptavidin mutein molecules with the thiolating agent is performed at a molar ratio of between 1:50 and 1:500, inclusive, of streptavidin or streptavidin mutein to the thiolating agent. In certain examples of any of the methods provided herein, the incubation of the second plurality of streptavidin or streptavidin mutein molecules with the thiolating agent is performed at a molar ratio of or about 1:100 of streptavidin or streptavidin mutein to the activation reagent. In some examples of any of the methods provided herein, the thiolating agent is or comprises 2-iminothiolane.

[0034] In particular examples of any of the methods provided herein, the second plurality of streptavidin or streptavidin mutein molecules and the thiolating agent are incubated at a pH of 7.0 or greater, optionally between 7.0 and 8.0, inclusive. In certain examples of any of the methods provided herein, the second plurality of streptavidin or streptavidin mutein molecules and the thiolating agent are incubated at a pH of about 7.7. In some examples of any of the methods provided herein, the incubation of the second plurality of streptavidin or streptavidin mutein molecules and the thiolating agent is initiated

in the presence of a buffer with a pH of 8.0 or greater, optionally between 8.0 and 9.0, inclusive. In particular examples of any of the methods provided herein, the incubation of the second plurality of streptavidin or streptavidin mutein molecules and the thiolating agent is initiated in the presence of a buffer with a pH of or about 8.5. In certain examples of any of the methods provided herein, the buffer comprises borate. In some examples of any of the methods provided herein, the buffer comprises 10 mM to 200 mM borate or 50 mM to 100 mM borate, each inclusive, optionally about 100 mM borate.

[0035] In particular examples of any of the methods provided herein, the second plurality of streptavidin or streptavidin mutein molecules and the thiolating agent are incubated at a temperature between 4°C and 39°C. In certain examples of any of the methods provided herein, the second plurality of streptavidin or streptavidin mutein molecules and the thiolating agent are incubated at room temperature, optionally between 20°C and 25°C, optionally at or about 23°C or at or about 24°C. In some examples of any of the methods provided herein, the second plurality of streptavidin or streptavidin mutein molecules and the thiolating agent are incubated for between 15 minutes and 2 hours or 15 minutes and 1.5 hours. In particular examples of any of the methods provided herein the second plurality of streptavidin or streptavidin mutein molecules and the thiolating agent are incubated for between 15 minutes and 2 hours or 25 minutes and 1 hour, each inclusive. In certain examples of any of the methods provided herein the second plurality of streptavidin molecules and the thiolating agent are incubated for or for about 1 hour.

[0036] In some examples of any of the methods provided herein the second plurality of streptavidin or streptavidin mutein molecules and the thiolating agent are incubated for or for about 25 minutes. In particular examples of any of the methods provided herein the plurality of activated streptavidin or streptavidin mutein molecules to the plurality of thiolated streptavidin or streptavidin mutein molecules during the incubation is at a molar ratio of X:1, wherein X is the number of lysine residues available to be thiolated per molecule of streptavidin or streptavidin mutein. In certain examples of any of the methods provided herein the molar ratio is from 1:1 to 8:1 or 2:1 to 6:1, optionally of or about 4:1. In certain examples, the molar ratio is from 1:1 to 1:8 or 1:2 to 1:6, optionally of or about 1:4.

[0037] In some examples of any of the methods provided herein the plurality of activated streptavidin or streptavidin mutein molecules and the plurality of thiolated streptavidin or streptavidin mutein molecules, are incubated at a pH of between 6.8 and 7.5,

inclusive. In particular examples of any of the methods provided herein the plurality of activated streptavidin or streptavidin mutein molecules and the plurality of thiolated streptavidin or streptavidin mutein molecules, are incubated at a pH of between 7.0 and 7.4, inclusive. In certain examples of any of the methods provided herein the plurality of activated streptavidin or streptavidin mutein molecules and the plurality of thiolated streptavidin or streptavidin mutein molecules, are incubated at a pH of or about 7.2.

[0038] In some examples of any of the methods provided herein the plurality of activated streptavidin or streptavidin mutein molecules and the plurality of thiolated streptavidin or streptavidin mutein molecules, are incubated at a temperature between 4°C and 39°C, inclusive. In particular examples of any of the methods provided herein the plurality of activated streptavidin or streptavidin mutein molecules and the plurality of thiolated streptavidin or streptavidin mutein molecules, are incubated at room temperature, optionally between 20°C and 25°C, inclusive, optionally at or about 23°C or at or about 24°C. In certain examples of any of the methods provided herein the plurality of activated streptavidin molecules and the plurality of thiolated streptavidin molecules, are incubated for between 15 minutes and 6 hours or 30 minutes and 2 hours, each inclusive. In some examples of any of the methods provided herein the plurality of activated streptavidin molecules and the plurality of thiolated streptavidin molecules, are incubated for between 45 minutes and 1.5 hours, inclusive, optionally for or for about 1 hour. In particular examples of any of the methods provided herein the incubation of activated streptavidin or streptavidin mutein molecules and the thiolated streptavidin or streptavidin mutein molecules is ended by contacting the molecules with N-ethylmaleimide (NEM).

[0039] In certain examples of any of the methods provided herein at least a portion of the incubating of the first plurality of streptavidin or streptavidin mutein molecules with the activation agent and at least a portion of the incubating of the second plurality of streptavidin or streptavidin mutein molecules with the thiolating agent are carried out separately at the same time. In some examples of any of the methods provided herein the incubating of the first plurality of streptavidin or streptavidin mutein molecules with the activation agent and the incubating of the second plurality of streptavidin or streptavidin mutein molecules with the thiolating agent are carried out for substantially the same amount of time and/or are completed at substantially the same time. In particular examples of any of the methods provided herein, wherein, prior to incubating the thiolated streptavidin or streptavidin mutein

molecules and the activated streptavidin or streptavidin mutein molecules, the method comprises (i) removing the activation agent from the composition comprising the activated streptavidin or streptavidin mutein molecules; and/or (ii) removing the thiolating agent from the composition comprising the thiolated streptavidin or streptavidin mutein molecules. .

[0040] In certain examples of any of the methods provided herein wherein the incubation of the plurality of activated streptavidin or streptavidin mutein molecules and the plurality of thiolated streptavidin or streptavidin mutein molecules is initiated within 15 minutes after the incubating of the second plurality of streptavidin molecules with the thiolating agent is ended and/or after the removing of the thiolating agent from composition comprising the thiolated streptavidin or streptavidin mutein molecules..

[0041] Provided herein are methods producing oligomeric particle reagents, comprising: incubating a first plurality of streptavidin or streptavidin mutein molecules with Succinimidyl-6-[(β-maleimidopropionamido)hexanoate (SMPH) for or for about 1 hour at a pH of or of about 7.2, thereby generating a plurality of activated streptavidin or streptavidin mutein molecules comprising a maleimide thiol-reacting functional group; incubating a second plurality of streptavidin or streptavidin mutein molecules with 2-iminothiolane for or for about 1 hour at a pH of between 7.5 and 8.5, inclusive, thereby generating a plurality of thiolated streptavidin molecules comprising one or more thiol functional groups; and incubating the plurality of activated streptavidin or streptavidin mutein molecules with the plurality of thiolated streptavidin molecules for or for about 1 hour at a pH of or of about 7.2, thereby generating a composition comprising the oligomeric particle reagents; wherein the incubating of the plurality of activated streptavidin molecules with the plurality of thiolated streptavidin molecules is initiated within 10 minutes after the incubation of the second plurality of streptavidin molecules with 2-iminothiolane ends.

[0041a] In another aspect, the present disclosure refers to a method for producing oligomeric particle reagents, comprising: incubating a first plurality of streptavidin or streptavidin mutein molecules with Succinimidyl-6-[(β-maleimidopropionamido)hexanoate (SMPH) for or for about 1 hour at a pH of or of about 7.2, thereby generating a plurality of activated streptavidin or streptavidin mutein molecules comprising a maleimide thiol-reacting functional group; incubating a second plurality of streptavidin or streptavidin mutein molecules with 2-iminothiolane for or for about 1 hour at a pH of between 7.5 and 8.5, inclusive, thereby generating a plurality of thiolated streptavidin molecules comprising one or more thiol functional groups; and incubating the plurality of activated streptavidin or streptavidin mutein molecules with the plurality of thiolated streptavidin molecules for or for about 1 hour at a pH of or of about 7.2, thereby generating a particle composition comprising the oligomeric particle reagents; wherein the incubating of the plurality of activated streptavidin molecules with the plurality of thiolated streptavidin molecules is initiated within 10 minutes after the incubation of the second plurality of streptavidin molecules with 2-iminothiolane ends.

[0042] In some examples of any of the methods provided herein the method further comprises contacting the oligomeric particle reagents with a stabilization agent. In particular examples of any of the methods provided herein the stabilization agent reduces an amount of N-substituted iminothiolane present on lysine residues of the oligomeric particle reagents. In certain examples of any of the methods provided herein the stabilization agent reduces an amount of N-substituted iminothiolane present on lysine residues of the oligomeric particle reagents by at least 25%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%,

or at least 95%. In some examples of any of the methods provided herein the stabilization agent comprises hydroxylamine.

[0043] In particular examples of any of the methods provided herein the oligomeric particle reagents have a radius of less than 150 nm. Certain examples of any of the methods provided herein further comprise filter sterilizing the oligomeric particle reagents. In some examples of any of the methods provided herein the oligomeric particle reagents are separated from the monomer or smaller oligomeric streptavidin or streptavidin mutein molecules by size exclusion chromatography. In particular examples of any of the methods provided herein, the size exclusion limit is greater than or greater than about 100 kDa, 500 kDa, 750 kDa, 1000 kDa or 2000 kDa. In certain examples of any of the methods provided herein, the size exclusion limit is from or from about 500 kDa to 1000 kDa. In some examples of any of the methods provided herein, the size exclusion limit is or is about 750 kDa.

[0044] Particular examples of any of the methods provided herein comprise collecting one or more fractions comprising the void volume, thereby separating oligomeric particle reagents from the monomer or smaller oligomeric streptavidin or streptavidin mutein molecules. In certain examples the methods further comprise storing the oligomeric particle reagents at a temperature at about or below 4°C, at about or below -20°C, or about or below -80°C. In some examples the methods further comprise mixing the oligomeric particle reagents with one or more agents under conditions to reversibly bind the one or more agents to the oligomeric particle reagents.

[0045] Also provided herein are methods of multimerizing one or more agents to an oligomeric particle reagent, the method comprising mixing an oligomeric particle reagent produced by the methods provided herein with one or more agents under conditions to reversibly bind the one or more agents to the oligomeric particle reagents. In particular examples of any of the methods provided herein, the one or more agents comprise a binding partner, wherein the binding partner is capable of binding to one or more binding site on the oligomeric particle reagent. In certain examples of any of the methods provided herein, the binding partner comprises a streptavidin-binding peptide.

[0045a] In another aspect, the present disclosure refers to a method of multimerizing one or more agent to an oligomeric particle reagent, the method comprising mixing an oligomeric particle reagent as disclosed herein, a composition comprising a plurality of oligomeric particle reagents as disclosed herein, or an oligomeric particle reagent produced by the method as disclosed herein, with one or more agents under conditions to reversibly bind the one or more agents to the oligomeric particle reagents.

[0046] In some examples of any of the methods provided herein, the binding partner comprises a streptavidin-binding peptide selected from the group consisting of Trp-Ser-His-Pro-Gln-Phe-Glu-Lys (SEQ ID NO: 8), Trp-Ser-His-Pro-Gln-Phe-Glu-Lys-$(GlyGlyGlySer)_3$-

Trp-Ser-His-Pro-Gln-Phe-Glu-Lys ((SEQ ID NO: 17), Trp-Ser-His-Pro-Gln-Phe-Glu-Lys-$(GlyGlyGlySer)_2$-Trp-Ser-His-Pro-Gln-Phe-Glu-Lys (SEQ ID NO: 18) and Trp-Ser-His-Pro-Gln-Phe-Glu-Lys-$(GlyGlyGlySer)_2$Gly-Gly-Ser-Ala-Trp-Ser-His-Pro-Gln-Phe-Glu-Lys (SEQ ID NO: 19).

[0047] In particular examples of any of the methods provided herein, the one or more agents binds or is capable of binding to a molecule expressed on the surface of a target cell. In certain examples of any of the methods provided herein, the one or more agents comprise an antibody, optionally a Fab. In some examples of any of the methods provided herein, the one or more agents is a receptor binding-agent that binds to or is capable of binding to a receptor expressed on the surface of a target cell. In particular examples of any of the methods provided herein, the receptor binding agent is or comprises a stimulatory agent capable of binding to a molecule on the surface of a target cell, thereby inducing or modulating a signal in the target cell.

[0048] In certain examples of any of the methods provided herein, the receptor-binding agent is capable of initiating a TCR/CD3 complex-associated signal in T cells, binds to a member of a TCR/CD3 complex; and/or specifically binds to CD3. In some examples of any of the methods provided herein, the stimulatory agent is a first receptor-binding agent and the method further comprises reversibly binding to the oligomeric particle reagent a second receptor-binding agent, wherein the second receptor-binding agent is capable of specifically binding to a second molecule on the surface of the target cell, which binding to the second molecule is optionally capable of inducing or modulating a signal in the target cells.

[0049] In particular examples of any of the methods provided herein, the second receptor-binding agent specifically binds to a costimulatory molecule, accessory molecule, immune checkpoint molecule, is a member of the TNF family or the TNF family receptor, cytokine receptor, chemokine receptor, or is or comprises an adhesion molecule or a factor that induces cytokine production, chemokine production and/or expression of an adhesion molecule. In certain examples of any of the methods provided herein, the receptor-binding agent specifically binds to a costimulatory molecule, accessory molecule, immune checkpoint molecule, is a member of the TNF family or the TNF family receptor, cytokine receptor, chemokine receptor, or is or comprises an adhesion molecule or a factor that induces cytokine production, chemokine production and/or expression of an adhesion molecule.

[0050] In some examples of any of the methods provided herein, the receptor-binding agent (second receptor-binding agent) binds to a costimulatory or accessory molecule and the costimulatory or accessory molecule is selected fromCD28, CD90 (Thy-1), CD95 (Apo-/Fas), CD137 (4-1BB), CD154 (CD40L), ICOS, LAT, CD27, OX40 or HVEM. In particular examples of any of the methods provided herein, the receptor-binding agent (second receptor-binding agent) specifically binds to a cytokine receptor and the cytokine receptor is selected from among IL-2R, IL-1R, IL-15R, IFN-gammaR, TNF-alphaR, IL-4R, IL-10R, Type I IFNR, IL-12R, IL-15R, IL-17R, TNFR1 and TNFR2. In certain examples of any of the methods provided herein, the receptor-binding agent (second receptor-binding agent) specifically binds to a chemokine receptor and the chemokine receptor is selected from among CCR1, CCR2, CCR3, CCR4, CCR5, CCR7, CCR9, CXCR1, CXCR3 and CXCR4.

[0051] In some examples of any of the methods provided herein, the receptor-binding agent (second receptor-binding agent) is a factor that induces cytokine or chemokine production and the factor is a ligand that specifically binds to a cytokine or chemokine receptor. In particular examples of any of the methods provided herein, the receptor-binding agent (second receptor-binding agent) is a ligand that specifically binds to a cytokine receptor, wherein the ligand specifically binds IL-2R, IL-1R, IL-15R, IFN-gammaR, TNF-alphaR, IL-4R, IL-10R, Type I IFNR, IL-12R, IL-15R, IL-17R, TNFR1 and TNFR2; and/or the ligand is selected from among IL-2, IL-1, IL-15, IFN-gamma, TNF-alpha, IL-4, IL-10, IL-12, IL-15, IL-17 and TNF, or is a biologically active fragment thereof.

[0052] In certain examples of any of the methods provided herein, the receptor-binding agent (second receptor-binding agent) is a ligand that specifically binds to a chemokine receptor, wherein the ligand specifically binds to a chemokine receptor selected from among CCR1, CCR2, CCR3, CCR4, CCR5, CCR7, CCR9, CXCR1, CXCR3 and CXCR4; or the ligand is selected from among CXCL9, CXCL10, CCL19, CCL21 and CCL25 or is a biologically active fragment thereof. In some examples of any of the methods provided herein, the receptor-binding agent (second receptor-binding agent) is an adhesion molecule and the adhesion molecule is selected from among CD44, CD31, CD18/CD11a (LFA-1), CD29, CD54 (ICAM-1), CD62L (L-selectin), and CD29/CD49d (VLA-4), CD106 (VCAM-1) or is a biologically active fragment thereof.

[0053] In particular examples of any of the methods provided herein, the one or more agents comprises a selection agent, wherein the selection agent binds to or is capable of binding to a selection marker that is expressed on the surface of a target cell. In certain examples of any of the methods provided herein, the target cell is an immune cell. In some examples of any of the methods provided herein, the target cell is a lymphocyte or an antigen-presenting cell. In particular examples of any of the methods provided herein, the target cell is a T cell, B cell, NK cell, macrophage or dendritic cell. In certain examples of any of the methods provided herein, the target cell is a T cell. In some examples of any of the methods provided herein, the selection marker is CD25, CD28, CD62L, CCR7, CD27, CD127, CD3, CD4, CD8, CD45RA, and/or CD45RO.

[0054] Particular examples are directed to a composition comprising oligomeric particle reagents produced by the method of any of example provided herein. In another aspect, the present disclosure refers to a composition comprising a plurality of the oligomeric particle reagents produced by the method as disclosed herein. Certain examples are directed to an article of manufacture, comprising the oligomeric particle reagent of any of examples provided herein or the composition of any of examples provided herein.

[0054a] In another aspect, the present disclosure refers to an oligomeric particle reagent produced by the method as disclosed herein.

[0054b] In another aspect, the present disclosure refers to an article of manufacture, comprising the oligomeric particle reagent as disclosed herein, the composition comprising a plurality of oligomeric reagents as disclosed herein or the oligomeric reagent produced by the method as disclosed herein.

[0055] Provided herein are methods for modulating cells, the method comprising incubating a cell composition comprising target cells in the presence of the oligomeric particle reagent of any of examples provided herein or in the presence of the composition of any of examples provided herein, thereby modulating the target cells. In some examples of any of the methods provided herein, modulating the target cells comprises activating, enriching, and/or expanding the target cells.

[0055a] In another aspect, the present disclosure refers to a method for modulating cells, the method comprising incubating a cell composition comprising target cells in the presence of the oligomeric particle reagent as disclosed herein, the composition comprising a plurality of oligomeric reagents as disclosed herein, or an oligomeric reagent produced by the method as disclosed herein, thereby modulating the target cells.

[0056] Provided herein are methods for culturing cells, the method comprising incubating a cell composition comprising target cells in the presence of the oligomeric particle reagent of any of examples provided herein or in the presence of the composition of any of examples provided herein. In certain examples of any of the methods provided herein, the oligomeric particle reagent comprises are reversibly bound to one or more agents. In particular examples of any of the methods provided herein, the one or more agents binds or is capable of binding to a molecule expressed on the surface of a target cell. In some examples of any of the methods provided herein, the one or more agents comprise an antibody, optionally a Fab.

[0056a] In another aspect, the present disclosure refers to a method for culturing cells, the method comprising incubating a cell composition comprising target cells in the presence of the oligomeric particle reagent as disclosed herein, the composition comprising a plurality of oligomeric reagents as disclosed herein, or an oligomeric reagent produced by the method as disclosed herein.

[0057] In certain examples of any of the methods provided herein, the one or more agents is a receptor binding-agent that binds to or is capable of binding to a receptor expressed on the surface of a target cell. In particular examples of any of the methods provided herein, the receptor binding agent is or comprises a stimulatory agent capable of binding to a molecule on the surface of a target cell, thereby inducing or modulating a signal in the target cell.

[0058] In some examples of any of the methods provided herein, the receptor-binding agent is capable of initiating a TCR/CD3 complex-associated signal in T cells, binds to a member of a TCR/CD3 complex; and/or specifically binds to CD3. In certain examples of any of the methods provided herein, the stimulatory agent is a first receptor-binding agent and the method further comprises reversibly binding to the oligomeric particle reagent a second receptor-binding agent, wherein the second receptor-binding agent is capable of specifically binding to a second molecule on the surface of the target cell, which binding to the second molecule is optionally capable of inducing or modulating a signal in the target cells.

[0059] In particular examples of any of the methods provided herein, the second receptor-binding agent specifically binds to a costimulatory molecule, accessory molecule, immune checkpoint molecule, is a member of the TNF family or the TNF family receptor, cytokine receptor, chemokine receptor, or is or comprises an adhesion molecule or a factor that induces cytokine production, chemokine production and/or expression of an adhesion molecule. In some examples of any of the methods provided herein, the receptor-binding agent specifically binds to a costimulatory molecule, accessory molecule, immune checkpoint molecule, is a member of the TNF family or the TNF family receptor, cytokine receptor, chemokine receptor, or is or comprises an adhesion molecule or a factor that induces cytokine production, chemokine production and/or expression of an adhesion molecule.

[0060] In certain examples of any of the methods provided herein, the receptor-binding agent (second receptor-binding agent) binds to a costimulatory or accessory molecule and the costimulatory or accessory molecule is selected from CD28, CD90 (Thy-1), CD95 (Apo-/Fas), CD137 (4-1BB), CD154 (CD40L), ICOS, LAT, CD27, OX40 or HVEM. In particular examples of any of the methods provided herein, the receptor-binding agent (second receptor-binding agent) specifically binds to a cytokine receptor and the cytokine receptor is selected from among IL-2R, IL-1R, IL-15R, IFN-gammaR, TNF-alphaR, IL-4R, IL-10R,

Type I IFNR, IL-12R, IL-15R, IL-17R, TNFR1 and TNFR2. In some examples of any of the methods provided herein, the receptor-binding agent (second receptor-binding agent) specifically binds to a chemokine receptor and the chemokine receptor is selected from among CCR1, CCR2, CCR3, CCR4, CCR5, CCR7, CCR9, CXCR1, CXCR3 and CXCR4.

[0061] In certain examples of any of the methods provided herein, the receptor-binding agent (second receptor-binding agent) is a factor that induces cytokine or chemokine production and the factor is a ligand that specifically binds to a cytokine or chemokine receptor. In particular examples of any of the methods provided herein, the receptor-binding agent (second receptor-binding agent) is a ligand that specifically binds to a cytokine receptor, wherein the ligand specifically binds IL-2R, IL-1R, IL-15R, IFN-gammaR, TNF-alphaR, IL-4R, IL-10R, Type I IFNR, IL-12R, IL-15R, IL-17R, TNFR1 and TNFR2; and/or the ligand is selected from among IL-2, IL-1, IL-15, IFN-gamma, TNF-alpha, IL-4, IL-10, IL-12, IL-15, IL-17 and TNF, or is a biologically active fragment thereof.

[0062] In some examples of any of the methods provided herein, the receptor-binding agent (second receptor-binding agent) is a ligand that specifically binds to a chemokine receptor, wherein the ligand specifically binds to a chemokine receptor selected from among CCR1, CCR2, CCR3, CCR4, CCR5, CCR7, CCR9, CXCR1, CXCR3 and CXCR4; or the ligand is selected from among CXCL9, CXCL10, CCL19, CCL21 and CCL25 or is a biologically active fragment thereof.

[0063] In certain examples of any of the methods provided herein, the receptor-binding agent (second receptor-binding agent) is an adhesion molecule and the adhesion molecule is selected from among CD44, CD31, CD18/CD11a (LFA-1), CD29, CD54 (ICAM-1), CD62L (L-selectin), and CD29/CD49d (VLA-4), CD106 (VCAM-1) or is a biologically active fragment thereof.

[0064] In particular examples of any of the methods provided herein, the one or more agents comprises a selection agent, wherein the selection agent binds to or is capable of binding to a selection marker that is expressed on the surface of a target cell. In some examples of any of the methods provided herein, the target cell is an immune cell. In certain examples of any of the methods provided herein, the target cell is a lymphocyte or an antigen-presenting cell. In particular examples of any of the methods provided herein, the target cell is a T cell, B cell, NK cell, macrophage or dendritic cell. In some examples of any of the methods provided herein, the target cell is a T cell. In certain examples of

any of the methods provided herein, the selection marker is CD25, CD28, CD62L, CCR7, CD27, CD127, CD3, CD4, CD8, CD45RA, and/or CD45RO. In certain examples, the target cells comprise blood cells, leukocytes, lymphocytes, B cells, a population of B cells, T cells, a population of T cells, NK cells, dendritic cells and/or macrophages. In particular examples of any of the methods provided herein, the target cells express a recombinant receptor. In some examples of any of the methods provided herein, the target cells express a recombinant T cell receptor and/or a chimeric antigen receptor (CAR).

[0065] In certain examples of any of the methods provided herein, the target cells express a CAR that binds to an antigen associated with a disease and/or a cancer. In particular examples of any of the methods provided herein, the antigen is αvβ6 integrin (avb6 integrin), B cell maturation antigen (BCMA), B7-H6, carbonic anhydrase 9 (CA9, also known as CAIX or G250), a cancer-testis antigen, cancer/testis antigen 1B (CTAG, also known as NY-ESO-1 and LAGE-2), carcinoembryonic antigen (CEA), a cyclin, cyclin A2, C-C Motif Chemokine Ligand 1 (CCL-1), CD19, CD20, CD22, CD23, CD24, CD30, CD33, CD38, CD44, CD44v6, CD44v7/8, CD123, CD138, CD171, chondroitin sulfate proteoglycan 4 (CSPG4), epidermal growth factor protein (EGFR), truncated epidermal growth factor protein (tEGFR), type III epidermal growth factor receptor mutation (EGFR vIII), epithelial glycoprotein 2 (EPG-2), epithelial glycoprotein 40 (EPG-40), ephrinB2, ephrine receptor A2 (EPHa2), estrogen receptor, Fc receptor like 5 (FCRL5; also known as Fc receptor homolog 5 or FCRH5), fetal acetylcholine receptor (fetal AchR), a folate binding protein (FBP), folate receptor alpha, fetal acetylcholine receptor, ganglioside GD2, O-acetylated GD2 (OGD2), ganglioside GD3, glycoprotein 100 (gp100), G Protein Coupled Receptor 5D (GPCR5D), Her2/neu (receptor tyrosine kinase erbB2), Her3 (erb-B3), Her4 (erb-B4), erbB dimers, human high molecular weight-melanoma-associated antigen (HMW-MAA), hepatitis B surface antigen, Human leukocyte antigen A1 (HLA-AI), human leukocyte antigen A2 (HLA-A2), IL-22 receptor alpha(IL-22Ra), IL-13 receptor alpha 2 (IL-13Ra2), kinase insert domain receptor (kdr), kappa light chain, L1 cell adhesion molecule (L1CAM), CE7 epitope of L1-CAM, Leucine Rich Repeat Containing 8 Family Member A (LRRC8A), Lewis Y, melanoma-associated antigen (MAGE)-A1, MAGE-A3, MAGE-A6, mesothelin, c-Met, murine cytomegalovirus (CMV), mucin 1 (MUC1), MUC16, natural killer group 2 member D (NKG2D) ligands, melan A (MART-1), neural cell adhesion molecule (NCAM), oncofetal antigen, preferentially expressed antigen of melanoma (PRAME), progesterone receptor, a

prostate specific antigen, prostate stem cell antigen (PSCA), prostate specific membrane antigen (PSMA), receptor tyrosine kinase like orphan receptor 1 (RORl), survivin, Trophoblast glycoprotein (TPBG also known as 5T4), tumor-associated glycoprotein 72 (TAG72), vascular endothelial growth factor receptor (VEGFR), vascular endothelial growth factor receptor 2 (VEGFR2), Wilms tumor 1 (WT-1), a pathogen-specific antigen or an antigen associated with a universal tag, and/or biotinylated molecules, and/or molecules expressed by HIV, HCV, HBV or other pathogens.

[0066] Some examples of any of the methods provided herein further comprise disrupting the reversible binding between the one or more agent and the oligomeric particle reagent. In certain examples of any of the methods provided herein, said disruption comprises introducing to the target cells a composition comprising a substance capable of reversing the bond between the one or more agent and the oligomeric particle reagent. In particular examples of any of the methods provided herein, the substance is a free binding partner and/or is a competition agent.

[0067] In some examples of any of the methods provided herein, said disruption terminates or lessens the signal induced or modulated by the one or more agent in the target cells, optionally T cells. In certain examples of any of the methods provided herein, the substance comprises a streptavidin-binding peptide, biotin or a biologically active fragment, optionally a D-biotin, or a biotin analog (or biologically active fragment)

[0068] In particular examples of any of the methods provided herein, the substance is a streptavidin-binding peptide is selected from the group consisting of Trp-Ser-His-Pro-Gln-Phe-Glu-Lys (SEQ ID NO: 8), Trp-Ser-His-Pro-Gln-Phe-Glu-Lys-$(GlyGlyGlySer)_3$-Trp-Ser-His-Pro-Gln-Phe-Glu-Lys ((SEQ ID NO: 17), Trp-Ser-His-Pro-Gln-Phe-Glu-Lys-$(GlyGlyGlySer)_2$-Trp-Ser-His-Pro-Gln-Phe-Glu-Lys (SEQ ID NO: 18) and Trp-Ser-His-Pro-Gln-Phe-Glu-Lys-$(GlyGlyGlySer)_2$Gly-Gly-Ser-Ala-Trp-Ser-His-Pro-Gln-Phe-Glu-Lys (SEQ ID NO: 19). In some examples of any of the methods provided herein, the disruption is carried out within 5 days after initiation of said incubation.

Brief Description of the Drawings

[0069] **FIG. 1** depicts levels of thiol functional groups attached to streptavidin mutein tetramers during a time course incubation of the exemplary streptavidin mutein STREP-TACTIN® M2 with 2-iminothiolane in the presence of 100 mM borate.

CLAIMS

WHAT IS CLAIMED:

1. An oligomeric particle reagent comprising a plurality of streptavidin or streptavidin mutein molecules, wherein the size of the oligomeric particle reagent comprises i) a radius of greater than 50 nm, ii) a molecular weight of at least 5 x 10^6 g/mol; and/or (iii) at least 100 streptavidin or streptavidin mutein tetramers per oligomeric particle reagent.

2. The oligomeric particle reagent of claim 1, wherein the plurality of streptavidin or streptavidin mutein molecules reversibly bind to or are capable of reversibly binding to biotin, a biotin analog or a streptavidin-binding peptide.

3. The oligomeric particle reagent of any of claims 1-2, wherein the oligomeric particle reagent comprises streptavidin mutein molecules and each of the streptavidin mutein molecules comprises the amino acid sequence Val^{44}-Thr^{45}-Ala^{46}-Arg^{47} or Ile^{44}-Gly^{45}-Ala^{46}-Arg^{47} at sequence positions corresponding to positions 44 to 47 with reference to positions in streptavidin in the sequence of amino acids set forth in SEQ ID NO: 1.

4. The oligomeric particle reagent of any of claims 1-3, wherein the oligomeric particle reagent comprises streptavidin mutein molecules and each of the plurality of streptavidin mutein molecules comprises:

a) the sequence of amino acids set forth in any of SEQ ID NOS: 3-6, 27, 28, 60, or 61;

b) a sequence of amino acids that exhibit at least 85%, 86%, 87%, 88%, 89%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to any of SEQ ID NOS: 3-6, 27, 28, 60, or 61 and contain the amino acid sequence corresponding to Val^{44}-Thr^{45}-Ala^{46}-Arg^{47} or Ile^{44}-Gly^{45}-Ala^{46}-Arg^{47} and/or reversibly bind to biotin, a biotin analog or a streptavidin-binding peptide; or

c) a functional fragment of a) or b) that reversibly binds to biotin, a biotin analog or a streptavidin-binding peptide.

5. The oligomeric particle reagent of any of claims 1-4, wherein the oligomeric particle reagent is bound to one or more agents, wherein each of the one or more agents

comprises a streptavidin-binding peptide and the streptavidin-binding peptide reversibly binds to a binding site of the streptavidin or streptavidin mutein on the oligomeric particle reagent.

6. The oligomeric particle reagent of claim 5, wherein the streptavidin-binding peptide is selected from the group consisting of Trp-Ser-His-Pro-Gln-Phe-Glu-Lys (SEQ ID NO: 8), Trp-Ser-His-Pro-Gln-Phe-Glu-Lys-$(GlyGlyGlySer)_3$-Trp-Ser-His-Pro-Gln-Phe-Glu-Lys ((SEQ ID NO: 17), Trp-Ser-His-Pro-Gln-Phe-Glu-Lys-$(GlyGlyGlySer)_2$-Trp-Ser-His-Pro-Gln-Phe-Glu-Lys (SEQ ID NO:18) and Trp-Ser-His-Pro-Gln-Phe-Glu-Lys-$(GlyGlyGlySer)_2$Gly-Gly-Ser-Ala-Trp-Ser-His-Pro-Gln-Phe-Glu-Lys (SEQ ID NO: 19).

7. The oligomeric particle reagent of claim 5 or claim 6, wherein the one or more agents is an antibody or an antigen-binding fragment thereof.

8. The oligomeric particle reagent of claim 7, wherein the one or more agents is or comprises a monovalent antibody fragment, optionally a Fab.

9. The oligomeric particle reagent of any of claims 5-8, wherein the one or more agents is a receptor-binding agent that binds to or is capable of binding to a receptor expressed on the surface of a target cell, optionally wherein the receptor-binding agent is a stimulatory agent capable of binding to a molecule on the surface of a target cell, wherein binding induces or modulates a signal in the target cell.

10. The oligomeric particle reagent of claim 9, wherein the receptor-binding agent is capable of initiating a TCR/CD3 complex-associated signal in T cells, binds to a member of a TCR/CD3 complex; and/or specifically binds to CD3.

11. The oligomeric particle reagent of claim 9 or claim 10, wherein the stimulatory agent is a first receptor-binding agent and the oligomeric particle reagent comprises a second receptor-binding agent that binds to a costimulatory molecule on the surface of the target cell, wherein binding to the costimulatory molecule induces or modulates a signal in the target cells, optionally wherein the costimulatory molecule is CD28.

12. The oligomeric particle reagent of any of claims 5-11, wherein the one or more agents is an anti-CD3 antibody and an anti-CD28 antibody, optionally an anti-CD3 Fab and an anti-CD28 Fab.

13. The oligomeric particle reagent of any of claims 1-12, wherein the oligomeric particle reagent comprises:

a radius of between 50 nm and 150 nm, between 75 nm and 125 nm, between 80 nm and 115 nm, or between 90 nm and 110 nm, inclusive;

a molecular weight between 5 x 10^7 g/mol and 5 x 10^8 g/mol, between 1 x 10^8 g/mol and 5 x 10^8 g/mol, or between 1 x 10^8 g/mol and 2 x 10^8 g/mol; and/or

between 1,000 and 10,000 streptavidin or streptavidin mutein tetramers, or between 2,000 and 5,000 streptavidin or streptavidin mutein tetramers.

14. The oligomeric particle reagent of any of claims 1-13, wherein the plurality of streptavidin or streptavidin mutein comprise lysine residues, wherein less than 20%, 10%, 5%, 1%, of the lysine residues comprise N-substituted iminothiolane.

15. A composition comprising a plurality of the oligomeric particle reagent of any of claims 1-14.

16. The composition of claim 15, wherein the plurality of oligomeric particle reagents comprises i) an average radius of greater than 70 nm; ii) an average molecular weight of at least 1 x 10^8 g/mol; and/or iii) an average number of streptavidin or streptavidin tetramers per oligomeric particle reagent of at least 2,000 and/or iv) a radius size distribution wherein at least 95% of the plurality of oligomeric particle reagents comprise a radius of between 10 nm to 150 nm.

17. The composition of claim 15 or 16, wherein:

the plurality of oligomeric particle reagents comprises an average radius of between 50 nm and 150 nm, between 75 nm and 125 nm, between 80 nm and 110 nm, or between 90 nm and 110 nm, inclusive; or an average radius of 90 nm ±15 nm, 95 nm ± 20-25nm; or 97 ± 10 nm;

at least 95% of the plurality of oligomeric particle reagents comprise a radius of between 50 and 150 nm, between 70 nm and 140 nm, between 80 nm and 120 nm, between 80 nm and 115 nm, between 80 nm and 100 nm, between 90 nm and 110 nm, and/or between 100 nm and 120 nm; and/or

at least 95% of the plurality of oligomeric particle reagents comprise a radius between ± 50%, ± 25%, ± 20%, ± 15%, ± 10%, and/or ± 5% of the average and/or the median radius of the plurality of oligomeric particle reagents.

18. The composition of any of claims 15-17, wherein the plurality of oligomeric particle reagents comprising an average radius of between 80 nm and 115 nm and wherein at least 95% of the oligomeric particle reagents comprise a radius between ± 25% of the average radius.

19. The composition of any of claims 15-18, wherein the plurality of particles comprises:

(i) an average molecular weight of between 1 x 10^8 g/mol and 5 x 10^8 g/mol, or between 1 x 10^8 g/mol and 2 x 10^8 g/mol, inclusive; and/or

(ii) an average number of streptavidin or streptavidin tetramers per oligomeric particle reagent of at least 100, at least 500, at least 1,000, at least 1,500, or at least 2,000, or between 1,000 and 20,000, between 1,000 and 10,000, or between 2,000 and 5,000, each inclusive.

20. The composition of any of claims 15-19, wherein the average radius of the plurality of oligomer particles does not increase by more than 25% or 10% when stored at about or below -80°C, at about or below -20°C, and/or at about or below 4°C for at least 1 week.

21. A method for producing an oligomeric particle reagent comprising streptavidin or a streptavidin mutein, the method comprising:

incubating a plurality of activated streptavidin or streptavidin mutein molecules comprising a thiol-reactive functional group capable of reacting with a thiol functional group and a plurality of thiolated streptavidin or streptavidin mutein molecules comprising one or more thiol functional group, thereby generating a particle composition comprising the oligomeric particles comprising streptavidin or a streptavidin mutein;

separating the oligomeric particles from monomer and/or smaller oligomeric molecules; and

contacting the oligomeric particle with a stabilization agent, thereby producing the oligomeric particle reagent.

22. The method of claim 21, wherein:

the plurality of activated streptavidin or streptavidin mutein molecules is generated by incubating a first plurality of streptavidin or streptavidin mutein molecules with an activation agent that is capable of converting one or more amines to a thiol-reactive functional group; and/or

the plurality of thiolated streptavidin or streptavidin mutein molecules is generated by incubation of a second plurality of streptavidin or streptavidin mutein molecules with a thiolating agent that adds or is capable of adding a thiol functional group to one or more lysine residue.

23. A method for producing oligomeric particle reagents, the method comprising:

(a) incubating a first plurality of streptavidin or streptavidin mutein molecules with an activation agent under conditions to convert one or more amines to a thiol-reactive group capable of reacting with a thiol functional group, thereby generating a plurality of activated streptavidin or streptavidin mutein molecules;

(b) incubating a second plurality of streptavidin or streptavidin mutein molecules with a thiolating agent that adds or is capable of adding a thiol functional group to one or more lysine residue, thereby generating a plurality of thiolated streptavidin or streptavidin mutein molecules; and

(c) incubating the plurality of activated streptavidin or streptavidin mutein molecules with the plurality of thiolated streptavidin or streptavidin mutein molecules, thereby generating a particle composition comprising the oligomeric particle reagents;

wherein the method is carried out under conditions in which, at the time of initiation of the incubation in (c), the plurality of thiolated streptavidin or streptavidin mutein molecules are such that at least 60% of the lysines, on average, comprise a thiol functional group, and/or at least 10 lysines, on average, per thiolated streptavidin or streptavidin mutein tetramer comprise a thiol functional group.

24. The method of claim 23, further comprising separating the oligomeric particle reagents from monomer and/or smaller oligomeric streptavidin or streptavidin mutein molecules.

25. The method of any of claims 22-24, wherein the incubation of the first plurality of streptavidin or streptavidin mutein molecules with the activation agent is performed at a molar ratio of between 1:1 and 1:10 of streptavidin or streptavidin mutein to the activation reagent, optionally a molar ratio of 1:2 ± 2% of streptavidin or streptavidin mutein to the activation reagent.

26. The method of any of claims 22-25, wherein the activation agent comprises a heterobifunctional crosslinker, optionally wherein the activation agent is sulfosuccinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (sulfo SMCC) and/or Succinimidyl-6-[(β-maleimidopropionamido)hexanoate (SMPH), and/or optionally wherein the thiol-reactive functional group is a maleimide group.

27. The method of any of claims 22-26, wherein:

the first plurality of streptavidin or streptavidin mutein molecules and the activation agent are incubated at pH of between 6.8 and 7.5, or pH of between 7.0 and 7.4, each inclusive, optionally at or at about 7.2; and/or

the plurality of activated streptavidin or streptavidin mutein molecules and the plurality of thiolated streptavidin or streptavidin mutein molecules, are incubated at a pH of between 6.8 and 7.5, or between 7.0 and 7.4, each inclusive, optionally at a pH of or of about 7.2.

28. The method of any of claims 22-27, wherein:

the incubation of the second plurality of streptavidin or streptavidin mutein molecules with the thiolating agent is performed at a molar ratio of between 10:1 and 1:1, inclusive, of the thiolating reagent to each primary amine per streptavidin or streptavidin mutein molecule; and/or the incubation of the second plurality of streptavidin or streptavidin mutein molecules with the thiolating agent is performed at a molar ratio of between 1:50 and 1:500, inclusive, of streptavidin or streptavidin mutein tetramer to the thiolating agent, optionally at or about 1:100 of streptavidin or streptavidin mutein tetramer to the activation reagent.

29. The method of any of claims 22-28, wherein the thiolating agent is or comprises 2-iminothiolane.

30. The method of any of claims 22-29, wherein:

the second plurality of streptavidin or streptavidin mutein molecules and the thiolating agent are incubated at a pH of 7.0 or greater, optionally between 7.0 and 8.0, inclusive, optionally at a pH of about 7.7; and/or

the incubation of the second plurality of streptavidin or streptavidin mutein molecules and the thiolating agent is initiated in the presence of a buffer with a pH of 8.0 or greater, optionally between 8.0 and 9.0, inclusive, optionally at or at about 8.5.

31. The method of any of claims 22-30, wherein the plurality of activated streptavidin or streptavidin mutein molecules to the plurality of thiolated streptavidin or streptavidin mutein molecules during the incubation is, at a molar ratio of X:1, wherein X is the number of lysine residues available to be thiolated per molecule of streptavidin or streptavidin mutein, optionally wherein the molar ratio is from 1:1 to 8:1 or 2:1 to 6:1, optionally of or about 4:1.

32. The method of any of claims 22-31, wherein generating the particle composition comprising the oligomeric streptavidin or streptavidin mutein particles further comprises ending the reaction of the activated streptavidin or streptavidin mutein molecules and the thiolated streptavidin or streptavidin mutein molecules by contacting the molecules with N-ethylmaleimide (NEM).

33. The method of any of claims 23-33, wherein, prior to incubating the thiolated streptavidin or streptavidin mutein molecules and the activated streptavidin or streptavidin mutein molecules, the method comprises:

(i) removing the activation agent from the composition comprising the activated streptavidin or streptavidin mutein molecules; and/or

(ii) removing the thiolating agent from the composition comprising the thiolated streptavidin or streptavidin mutein molecules.

34. The method of claim 33, wherein the incubation of the plurality of activated streptavidin or streptavidin mutein molecules and the plurality of thiolated streptavidin or streptavidin mutein molecules is initiated within 15 minutes after the incubating of the second plurality of streptavidin molecules with the thiolating agent is ended and/or after the removing of the thiolating agent from composition comprising the thiolated streptavidin or streptavidin mutein molecules.

35. A method for producing oligomeric particle reagents, comprising:

incubating a first plurality of streptavidin or streptavidin mutein molecules with Succinimidyl-6-[(β-maleimidopropionamido)hexanoate (SMPH) for or for about 1 hour at a pH of or of about 7.2, thereby generating a plurality of activated streptavidin or streptavidin mutein molecules comprising a maleimide thiol-reacting functional group;

incubating a second plurality of streptavidin or streptavidin mutein molecules with 2-iminothiolane for or for about 1 hour at a pH of between 7.5 and 8.5, inclusive, thereby generating a plurality of thiolated streptavidin molecules comprising one or more thiol functional groups; and

incubating the plurality of activated streptavidin or streptavidin mutein molecules with the plurality of thiolated streptavidin molecules for or for about 1 hour at a pH of or of about 7.2, thereby generating a particle composition comprising the oligomeric particle reagents;

wherein the incubating of the plurality of activated streptavidin molecules with the plurality of thiolated streptavidin molecules is initiated within 10 minutes after the incubation of the second plurality of streptavidin molecules with 2-iminothiolane ends.

36. The method of any of claims 23-35, wherein the method further comprises contacting the oligomeric particle reagents with a stabilization agent, wherein the stabilization agent reduces an amount of N-substituted iminothiolane present on lysine residues of the oligomeric particle reagents, optionally wherein the stabilization agent comprises hydroxylamine.

37. The method of any of claims 21-36, further comprising filter sterilizing the oligomeric particle reagents.

38. The method of any of claims 21, 22, and 24-37, wherein the oligomeric particle reagents are separated from the monomer or smaller oligomeric streptavidin or streptavidin mutein molecules by size exclusion chromatography (SEC), optionally wherein the SEC comprises a size exclusion limit and the size exclusion limit is a size from or from about 500 kDa to 1000 kDa, optionally a size that is or is about 75 kDa.

39. An oligomeric particle reagent produced by the method of any of claims 21-38.

40. A method of multimerizing one or more agent to an oligomeric particle reagent, the method comprising mixing an oligomeric particle reagent of any of claims 1-14, a composition comprising a plurality of oligomeric particle reagents of any of claims 15-20, or an oligomeric particle reagent produced by the method of any of claims 21-38, with one or more agents under conditions to reversibly bind the one or more agents to the oligomeric particle reagents.

41. The method of claim 40, wherein each of the one or more agents comprises a streptavidin-binding peptide, wherein the streptavidin-binding peptide is capable of binding to a binding site of the streptavidin or streptavidin mutein on the oligomeric particle reagent.

42. The method of claim 41, wherein the streptavidin-binding peptide is selected from the group consisting of Trp-Ser-His-Pro-Gln-Phe-Glu-Lys (SEQ ID NO: 8), Trp-Ser-His-Pro-Gln-Phe-Glu-Lys-(GlyGlyGlySer)$_3$-Trp-Ser-His-Pro-Gln-Phe-Glu-Lys ((SEQ ID NO: 17), Trp-Ser-His-Pro-Gln-Phe-Glu-Lys-(GlyGlyGlySer)$_2$-Trp-Ser-His-Pro-Gln-Phe-Glu-Lys (SEQ ID NO: 18) and Trp-Ser-His-Pro-Gln-Phe-Glu-Lys-(GlyGlyGlySer)$_2$Gly-Gly-Ser-Ala-Trp-Ser-His-Pro-Gln-Phe-Glu-Lys (SEQ ID NO: 19).

43. The method of any of claims 40-42, wherein the one or more agents is or comprises an antibody or an antigen-binding fragment thereof.

44. The method of claim 43, wherein the one or more agents is or comprises a monovalent antibody fragment, optionally a Fab.

45. The method of any of claims 40-44, wherein the one or more agents is a receptor binding agent that binds to or is capable of binding to a receptor expressed on the surface of a target cell, optionally wherein the receptor-binding agent is a stimulatory agent capable of binding to a molecule on the surface of a target cell, wherein binding induces or modulates a signal in the target cell.

46. A composition comprising a plurality of the oligomeric particle reagents produced by the method of any of claim 21-38.

47. An article of manufacture, comprising the oligomeric particle reagent of any of claims 1-14, the composition comprising a plurality of oligomeric reagents of any of claims 15-20 and 46 or the oligomeric reagent produced by the method of any of claims 21-38.

48. A method for modulating cells, the method comprising incubating a cell composition comprising target cells in the presence of the oligomeric particle reagent of any of claims 1-14, the composition comprising a plurality of oligomeric reagents of any of claims 15-20 and 46, or an oligomeric reagent produced by the method of any of claims 21-38, thereby modulating the target cells.

49. A method for culturing cells, the method comprising incubating a cell composition comprising target cells in the presence of the oligomeric particle reagent of any of claims 1-14, the composition comprising a plurality of oligomeric reagents of any of claims 15-20 and 46, or an oligomeric reagent produced by the method of any of claims 21-38.

50. The method of claim 48 or claim 49, wherein the oligomeric particle reagent is reversibly bound to one or more receptor-binding agent that binds to or is capable of binding to a receptor expressed on the surface of a target cell, optionally wherein the receptor-binding agent is a stimulatory agent capable of binding to a molecule on the surface of a target cell, wherein binding induces or modulates a signal in the target cell.

51. The method of any of claims 48-50, wherein the target cell is a T cell.

52. The method of claim 50 or claim 51, further comprising disrupting the reversible binding between the one or more agent and the oligomeric particle reagent, said disrupting comprising introducing to the target cells a substance capable of reversing or competing with the bond between the one or more agent and the oligomeric particle reagent, optionally wherein the substance comprises biotin or a biotin analog or optionally comprises D-biotin.