

SUMMARY

[0004] The present disclosure provides a modulated effector function (MEF) antibody, wherein the MEF antibody comprises an effector function enhancing modification and an effector function diminishing modification, wherein the effector function diminishing modification comprises a biocompatible polymeric moiety (BPM) with a covalent attachment to an amino acid or post-translational modification of the MEF antibody. In some examples, the effector function diminishing modification is at least partially reversible. In some examples, the covalent attachment is cleavable, cleavage of which covalent attachment at least partially reverses the effector function diminishing modification. In some examples, the BPM comprises a cleavable moiety separate from the covalent attachment, cleavage of which moiety at least partially reverses the effector function diminishing modification.

[0004a] In one aspect, the present disclosure provides a modulated effector function (MEF) antibody, wherein the MEF antibody comprises an effector function enhancing modification and an effector function diminishing modification, wherein the effector function diminishing modification comprises a biocompatible polymeric moiety (BPM) with a covalent attachment to an amino acid or post-translational modification of the MEF antibody, wherein the effector function diminishing modification is at least partially reversible.

[0005] In some examples, the effector function enhancing modification increases a binding affinity of the MEF antibody for FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa, FcγRIIIb, or a combination thereof. In some examples, the effector function enhancing modification comprises afucosylation, a bisecting N-acetyl glucosamine, an S298A Fc region mutation, an E333A Fc region mutation, a K334A Fc region mutation, an S239D Fc region mutation, an I332E Fc region mutation, a G236A Fc region mutation, an S239E Fc region mutation, an A330L Fc region mutation, a G236A Fc region mutation, a L234Y Fc region mutation, a G236W Fc region mutation, an S296A Fc region mutation, an F243 Fc region mutation, an R292P Fc region mutation, a Y300L Fc region mutation, a V305L Fc region mutation, a P396L Fc region mutation, or a combination thereof. In some examples, the effector function enhancing modification comprises afucosylation.

[0006] In some examples, the amino acid comprises a cysteine residue or a methionine residue. In some examples, the covalent attachment to the cysteine residue comprises a disulfide bond, a thioether bond, a thioallyl bond, a vinyl thiol bond, or a combination thereof. In some examples, the disulfide bond, the thioallyl bond, or the combination thereof is cleavable. In some examples, the methionine residue couples to the BPM through a sulfanimine. In some examples, the post-translational

modification comprises glycosylation, nitrosylation, phosphorylation, citrullination, sulfenylation, or a combination thereof.

[0007] In some examples, the BPM comprises an enzymatically cleavable moiety. In some examples, the enzymatically cleavable moiety comprises a protease cleavage sequence, a glycosidic group, a carbamate, a urea, a quaternary ammonium, or a combination thereof. In some examples, the enzymatically cleavable moiety comprises a protease cleavage sequence. In some examples, the protease cleavage sequence is a tumor-associated protease cleavage sequence. In some examples, the protease cleavage sequence is a cleavage sequence of

thrombin, cathepsin, a matrix metalloproteinase, PAR-1 activating peptide, kallikrein, granzyme, caspase, ADAM, calpain, prostate-specific antigen, fibroblast activation protein, dipeptidyl peptidase IV, or a combination thereof.

[0008] In some examples, the effector function diminishing modification is at least partially reversible. In some examples, prior to the at least partial reversal of the effector function diminishing modification, the MEF antibody has between 2% and 20% of an effector function activity of an equivalent antibody lacking the BPM. In some examples, the MEF antibody has between 30% and 70% of the effector function activity of an equivalent antibody lacking the BPM following 192 hours incubation in 37 °C human plasma. In some examples, prior to the at least partial reversal of the effector function diminishing modification, the MEF antibody has between 2% and 20% of an FcγRIII binding affinity of an equivalent antibody lacking the BPM. In some examples, 192 hours after administration, the MEF antibody has between 30% and 70% of an FcγRIII binding affinity of an equivalent antibody lacking the BPM. In some examples, a rate of clearance of the MEF antibody is between 25% and 200% of a rate of the at least partial reversal of the effector function diminishing modification.

[0009] In another aspect, the present disclosure provides a modulated effector function (MEF) antibody coupled to a plurality of biocompatible polymeric moieties (BPM) and an Fc which is at least partially blocked by the BPM, or a combination thereof; wherein a BPM of the plurality of BPMs is attached to a sulfur atom of a cysteine residue by a cleavable moiety comprising a disulfide bond.

[0010] In another aspect, the present disclosure provides a modulated effector function (MEF) antibody coupled to a plurality of biocompatible polymeric moieties (BPM) and an Fc which is at least partially blocked by the BPM; wherein a BPM of the plurality of BPMs is attached to a methionine residue by a cleavable moiety.

[0011] In another aspect, the present disclosure provides a modulated effector function (MEF) antibody comprising at least one Fc region and coupled to a plurality of biocompatible polymeric moieties (BPM) comprising cleavable moieties and present in a ratio of between 6 and 10 to Fc regions of the at least one Fc region; wherein the plurality of biocompatible polymeric moieties comprise molecular weights of between 500 and 2500 Daltons (Da); and wherein the cleavable moieties comprise cleavage rates of between 0.1 and 0.5 day⁻¹ in 37 °C human plasma.

[0012] In another aspect, the present disclosure provides a modulated effector function (MEF) antibody, wherein the MEF antibody has 1, 2, 3, or 4 reduced interchain disulfide bonds and 2, 4, 6, or 8 biocompatible polymeric moieties (BPMs), respectively; wherein each BPM is covalently attached to a sulfur atom of a cysteine residue of a reduced interchain disulfide bond

of the MEF antibody via a cleavable moiety; and wherein the MEF antibody exhibits time-dependent

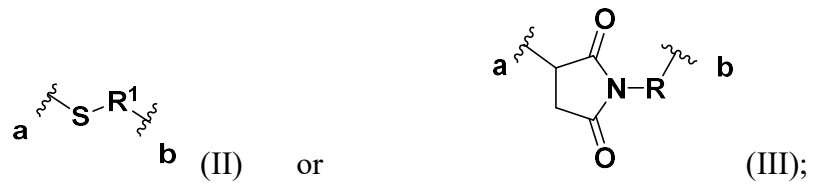
reduction in FcR binding, and thus a corresponding time-dependent reduction in an effector function, relative to that of an equivalent antibody.

[0013] In some examples, the MEF antibody has between 2% and 20% of the effector function activity of an equivalent antibody lacking the BPM. In some examples, the MEF antibody has between 2% and 10% of the effector function activity of an equivalent antibody lacking the BPM. In some examples, the MEF antibody has between 30% and 70% of the effector function activity of an equivalent antibody lacking the BPM following 192 hours incubation in 37 °C human plasma. In some examples, the MEF antibody has less than 50% of the effector function activity of an equivalent antibody lacking the BPM following cleavage of half of its BPMs. In some examples, the cleavable moiety comprises a cleavage rate of between 100% and 500% of its physiological clearance rate during *in vivo* circulation in an adult human male. In some examples, the cleavable moiety comprises a cleavage rate of between 50% and 300% of its physiological clearance rate during *in vivo* circulation in an adult human male.

[0014] In some examples, the cleavable moiety is configured to undergo a secondary reaction which diminishes a rate of its cleavage. In some examples, the cleavable moiety comprises a succinimide, and wherein the secondary reaction comprises succinimide hydrolysis. In some examples, the cleavable moiety is configured to undergo the BPM cleavage at least at twice the rate of the secondary reaction during *in vivo* circulation in an adult human male.

[0015] In some examples, each cleavable moiety is covalently attached to a sulfur atom of a cysteine residue of a reduced interchain disulfide bond of the MEF antibody through a cleavable disulfide bond, or through a cleavable thioether bond to a non-hydrolyzed succinimide moiety. In some examples, the non-hydrolyzed succinimide is configured to undergo thioether cleavage faster than hydrolysis in 37°C human plasma. In some examples, each cleavable moiety is covalently attached to a sulfur atom of a cysteine residue of a reduced interchain disulfide bond of the MEF antibody through a thioether bond to a hydrolyzed succinimide moiety. In some examples, each cleavable moiety is covalently attached to a sulfur atom of a cysteine residue of a reduced interchain disulfide bond of the MEF antibody through the cleavable disulfide bond.

[0016] In some examples, each cleavable moiety comprises a structure according either to Formula (II) or (III):



wherein:

R^1 is a C_2 - C_{12} alkylene, optionally interrupted with one of $-NH-C(=O)-$, $-C(=O)NH-$, $-NH-$, and $-O-$;

R is absent, or is a C_1 - C_{12} alkylene optionally interrupted with one or two of phenyl, $-NH-C(=O)-$, $-C(=O)NH-$, $-NH-$, $-O-$, $-O-C(=O)-$, $-C(=O)O-$, $-S-C(=O)-$, $-C(=O)S-$, $-O-C(=O)O-$, $-C(=NR^{1A})$, an acetal, $-O(SO_2)O-$, $-O-[P(=O)(-OH)]O-$, $-C(=N-OH)-$, $-C(=N-NH_2)-$, and $-C(R^{1A})=N-NH-$; and R is optionally substituted with 1-3 substituents independently selected from phenyl, oxo, and $-CO_2R^A$; C_3 - C_6 cycloalkylene; and phenyl optionally substituted with 1-3 independently selected C_1 - C_3 alkoxy;

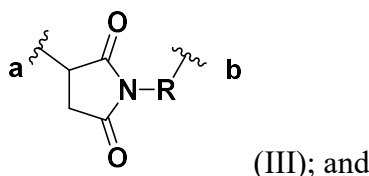
each R^A is independently hydrogen or C_1 - C_6 alkyl;

each R^{1A} is independently hydrogen or C_1 - C_6 alkyl;

wherein $\sim$ (a) represents the covalent attachment to the cysteine residue of the reduced interchain disulfide bond of the MEF antibody; and

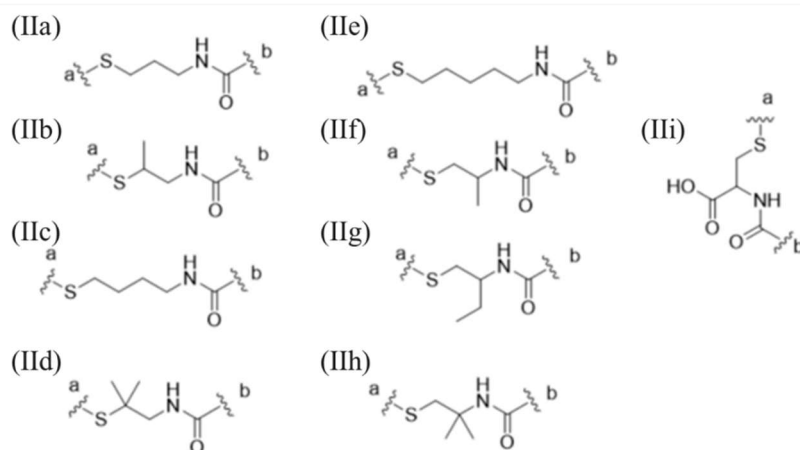
$\sim$ (b) represents the covalent attachment to a BPM or the remainder of the cleavable moiety, which retains covalent attachment to a BPM.

[0017] In some examples, each cleavable moiety has a structure according to Formula (III):



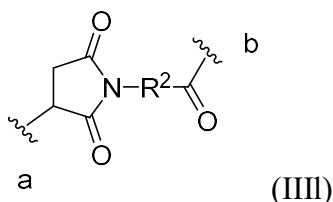
wherein R is a C_1 - C_{12} alkylene interrupted with $-C(=N-NH_2)-$ or $-C(R^{1A})=N-NH-$; or interrupted with phenyl and one of $-C(=N-NH_2)-$ and $-C(R^{1A})=N-NH-$.

[0018] In some examples, each cleavable moiety comprises a structure of any one of Formulas (IIa)-(IIi):



wherein $\sim$ (a) represents the covalent attachment to the sulfur atom of a cysteine residue of a reduced interchain disulfide bond of the MEF antibody; and $\sim$ (b) represents the covalent attachment of the cleavable moiety to a BPM.

[0019] In some examples, each cleavable moiety comprises a structure according to Formula (III):



wherein:

R^2 is C_1 - C_{15} alkyl optionally substituted with one or more instances of hydroxyl, halogen, -CN, C_1 - C_6 alkyl, C_1 - C_6 alkenyl, C_1 - C_6 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6 thioalkoxy, C_1 - C_6 cycloalkyl, $-NR^3R^4$, $-C(=O)-R^3$, $-C(=O)-OR^5$, PEG2-PEG72, or a combination thereof;

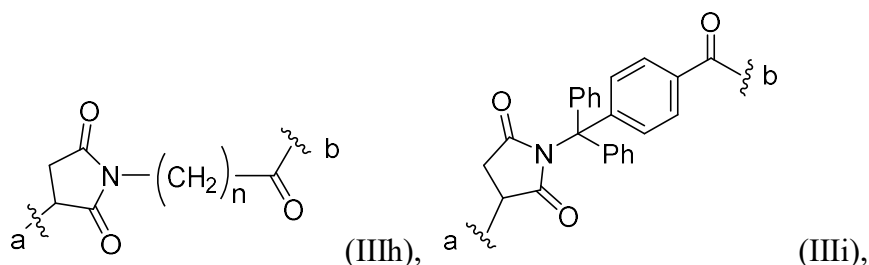
R^3 and R^4 are each independently selected from the group consisting of H,

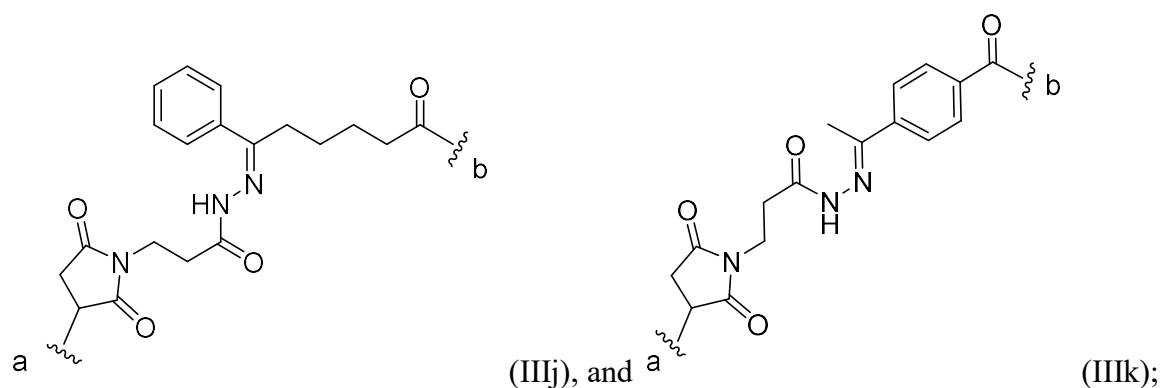
$\sim$ (a) represents the covalent attachment to the sulfur atom of a cysteine residue of a reduced interchain disulfide bond of the MEF antibody; and

$\sim$ (b) represents the covalent attachment of the cleavable moiety to a BPM.

[0020] In some examples, R^2 is C_1 - C_{15} alkyl optionally substituted with one or more instances of hydroxyl, halogen, -CN, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, or a combination thereof. In some examples, R^2 is C_1 - C_{12} alkyl optionally substituted with one or more instances of hydroxyl, halogen, -CN, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, or a combination thereof. In some examples, R^2 is C_1 - C_{12} alkyl optionally substituted with one or more instances of hydroxyl, halogen, or C_1 - C_3 alkyl.

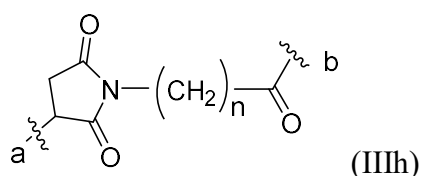
[0021] In some examples, each cleavable moiety comprises a structure of any one of Formulas (IIIh)-(IIIk):





wherein subscript n is an integer ranging from 2 to 8; and
 wherein $\sim$ (a) represents the covalent attachment to the sulfur atom of a cysteine residue of a reduced interchain disulfide bond of the MEF antibody; and $\sim$ (b) represents the covalent attachment of the cleavable moiety to a BPM.

[0022] In some examples, each cleavable moiety comprises a structure according to Formula (IIIh):

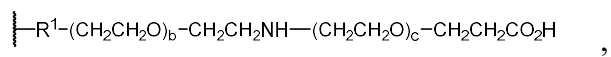
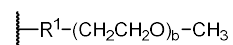
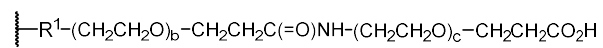
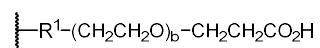


wherein subscript n is an integer ranging from 2 to 8; and
 wherein $\sim$ (a) represents the covalent attachment to the sulfur atom of a cysteine residue of a reduced interchain disulfide bond of the MEF antibody; and $\sim$ (b) represents the covalent attachment of the cleavable moiety to a BPM.

[0023] In some examples, the time-dependent reduction in FcR binding of the MEF antibody is characterized by an initial reduction in the binding of FcR from at least about 50% to about 90% relative to the equivalent antibody. In some examples, the initial reduction in FcR binding of the MEF antibody is characterized by a K_D that is about 2-fold to about 1,000-fold higher than the equivalent antibody. In some examples, the initial reduction of FcR binding is followed by a recovery of the binding as a further characteristic of the time-dependent reduction in FcR binding, wherein the recovery is correlated with BPM loss through non-enzymatic cleavage of the corresponding cleavable moiety(ies) in physiological media. In some examples, the physiological media is vertebrate plasma. In some examples, each of the cleavable moieties has a plasma half-life of from about 3 hours to about 96 hours. In some examples, the recovery substantially restores the FcR binding to that of the equivalent antibody after from about 3 hours to about 96 hours *in vitro*.

[0024] In some examples, the MEF antibody is fucosylated. In some examples, the MEF antibody is afucosylated. In some examples, the antibody of the MEF antibody is a therapeutic antibody.

[0025] In some examples, each BPM is a polyethylene glycol moiety, a polyketal moiety, a polyglycerol moiety, a polysaccharide moiety, a polysarcosine moiety, a polypeptide moiety, or a polyzwitterionic moiety. In some examples, each BPM is a monodispersed moiety. In some examples, each BPM comprises a monodispersed polyethylene glycol, polyglycerol, polypeptide, or polysaccharide moiety. In some examples, each BPM is a polydispersed moiety. In some examples, each BPM comprises a polydispersed polyethylene glycol, polyglycerol, polypeptide, or polysaccharide moiety. In some examples, each BPM independently has a weight-average molecular weight of about 100 Daltons to about 5,000 Daltons. In some examples, each BPM independently has a weight-average molecular weight of about 1,000 Daltons to about 3,000 Daltons. In some examples, each BPM independently has a hydrodynamic diameter of about 5 nm to about 25 nm. In some examples, each BPM independently has a hydrodynamic diameter of about 15 nm to about 25 nm. In some examples, each BPM independently has a hydrodynamic diameter of about 10 nm to about 20 nm. In some examples, each BPM independently has a hydrodynamic diameter of about 5 nm to about 15 nm. In some examples, each BPM independently has a hydrodynamic diameter of about 5 nm to about 10 nm. In some examples, each BPM comprises a monodispersed PEG2 to PEG72 moiety. In some examples, each BPM comprises a monodispersed PEG8 to PEG48 moiety. In some examples, each BPM comprises a monodispersed PEG12 to PEG24 moiety. In some examples, each BPM comprises a monodispersed branched PEG20 to PEG76 moiety; and wherein each branch comprises at least two contiguous ethylene glycol subunits. In some examples, each monodispersed branched PEG20 to PEG76 moiety has 2 to 8 branches. In some examples, each monodispersed branched PEG20 to PEG76 moiety has 2 to 6 branches. In some examples, each monodispersed branched PEG20 to PEG76 moiety has 2 to 4 branches. In some examples, each BPM is a PEG4(PEG8)₃ or a PEG4(PEG24)₃ moiety. In some examples, each polyethylene glycol moiety of a BPM has a cap selected from the group consisting of -CH₃, -CH₂CH₂CO₂H, and -CH₂CH₂NH₂. In some examples, each BPM has a structure selected from the group consisting of:



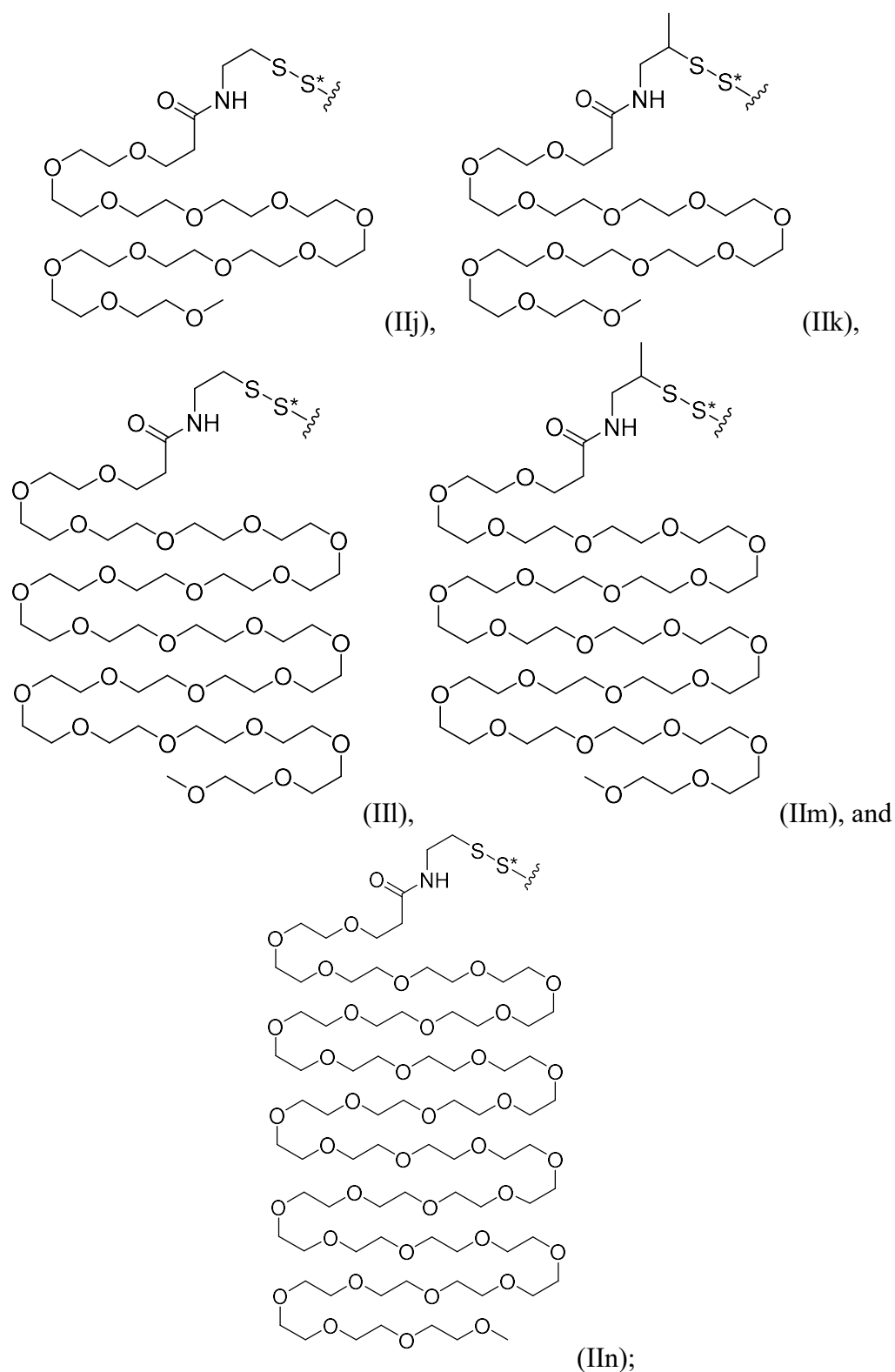
wherein R^1 is a C_2 - C_{12} alkylene, optionally interrupted with one of $-NH-C(=O)-$, $-C(=O)NH-$, $-NH-$, or $-O-$ to which the cleavable moiety is covalently attached, and optionally substituted with $-CO_2H$;

each subscript b ranges from 2 to 72;

each subscript c ranges from 1 to 72; and

~~~~ indicates site of covalent attachment to the cleavable moiety. In some examples, subscript  $b$  ranges from 6 to 72 and subscript  $c$  ranges from 1-12. In some examples, subscript  $b$  ranges from 8 to 72 and subscript  $c$  ranges from 1-12. In some examples, subscript  $b$  ranges from 10 to 72 and subscript  $c$  ranges from 1-12. In some examples, subscript  $b$  ranges from 12 to 72 and subscript  $c$  ranges from 1-12.

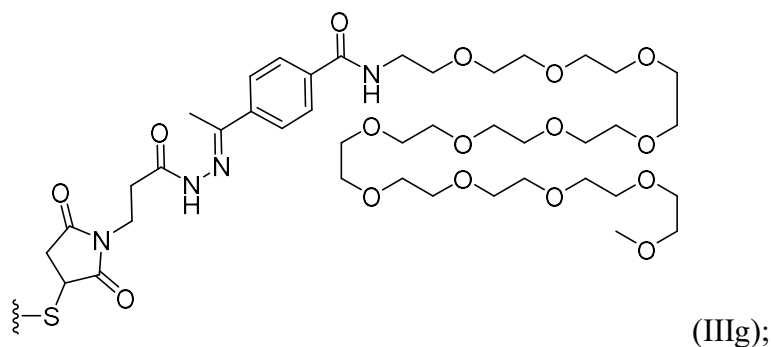
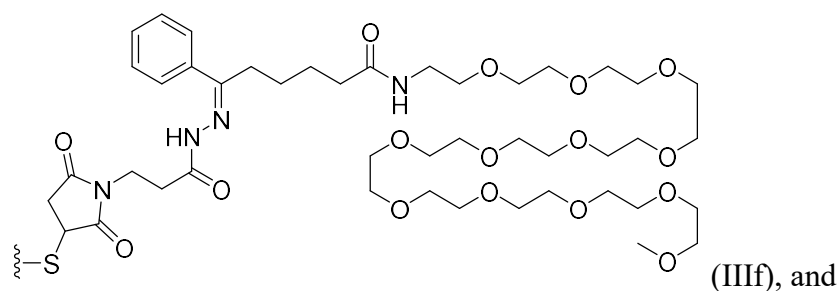
**[0026]** In some examples, each BPM and cleavable moiety, together with a sulfur atom of a cysteine residue of a reduced interchain disulfide bond of the MEF antibody to which the cleavable moiety is covalently attached, has a structure according to any one of Formulas (IIj-IIIn):



wherein S\* is a sulfur atom from a cysteine residue of a reduced interchain disulfide bond of the MEF antibody; and

wherein ~~~ indicates covalent attachment to the remainder of the MEF antibody.

**[0027]** In some examples, each BPM and cleavable moiety, together with the sulfur atom of a cysteine residue of a reduced interchain disulfide bond of the MEF antibody, has a structure according to any one of Formulas (IIIa)-(IIIg):



wherein ~~~ indicates covalent attachment to the remainder of the cysteine residue of the reduced interchain disulfide bond of the MEF antibody.

**[0028]** In some examples, the Fc receptor is present on a peripheral blood mononuclear cell (PBMC). In some examples, the Fc receptor is the Fc gamma IIIa receptor. In some examples, the PBMC is a natural killer cell. In some examples, the PBMC is enriched from plasma of a normal donor. In some examples, the normal donor is a human having the Fc gamma receptor III 158 V/V genotype. In some examples, reduction in Fc receptor binding is determined by competitive binding of the MEF antibody and a labeled isotype matched IgG Fc fragment to an orthogonally labeled Fc receptor. In some examples, the IgG Fc fragment is the labeled isotype matched Fc domain of a human IgG<sub>1</sub> antibody. In some examples, the label of the isotype matched IgG Fc fragment comprises a fluorophore. In some examples, the labeled isotype matched IgG Fc fragment is immobilized on a solid support. In some examples, the orthogonal label of the Fc receptor comprises biotin. In some examples, the isoform of the Fc receptor is Fc gamma IIIa or gamma IIIb. In some examples, the effector function that is reduced relative to the equivalent antibody on administration of the MEF antibody to a subject is antibody-dependent cellular cytotoxicity (ADCC) or antibody-dependent cellular phagocytosis (ADCP). In some examples, the subject to whom the MEF antibody is administered is a human. In some examples, the MEF antibody is an IgG<sub>1</sub> antibody. In some examples, the MEF antibody is a monoclonal antibody. In some examples, the monoclonal antibody is a chimeric antibody. In some examples, the monoclonal antibody is a humanized antibody.

**[0029]** In some examples, the MEF antibody has one or more mutations in the Fc region; wherein the MEF antibody having the one or more mutations has higher effector function relative to the equivalent antibody. In some examples, the MEF antibody is an IgG<sub>1</sub> antibody; and the one or more mutations in the Fc region are selected from the group consisting of S298A, E333A, K334A, S239D, I332E, G236A, S239E, A330L, I332E, G236A, S239D, I332E, G236A, L234Y, G236W, S296A, F243, R292P, Y300L, V305L, and P396L.

**[0030]** In some examples, the MEF antibody binds to a cancer cell. In some examples, the MEF antibody binds to an immune cell. In some examples, the MEF antibody binds to human CD40. In some examples, the antibody comprises rituximab, obinutuzumab, ofatumumab, trastuzumab, alemtuzumab, mogamulizumab, cetuximab, or dinutuximab. In some examples, the MEF antibody comprises a sequence which has at least 80% sequence identity to SEQ ID NO: 890. In some examples, the MEF antibody comprises a sequence which has at least 80% sequence identity to SEQ ID NO: 891. In some examples, the MEF antibody comprises a sequence which has at least 80% sequence identity to the heavy chain variable region of SEQ ID NO: 890. In some examples, the MEF antibody comprises a sequence which has at least 80% sequence identity to the light chain variable region of SEQ ID NO: 891. In some examples, the MEF antibody has a dissociation constant of at most 500 nM for the human CD40. In some examples, the MEF antibody has a dissociation constant of at most 10 nM for the human CD40.

**[0031]** In some examples, when the MEF antibody is introduced to a population of cells comprising one or more target cells, the binding of the MEF antibody to the one or more target cells provides a time-dependent reduction in peripheral cytokine levels relative to peripheral cytokine levels provided by binding of an equimolar amount of the equivalent antibody. In some examples, the time-dependent reduction of peripheral cytokine levels is characterized by an initial reduction of at least about 50%. In some examples, the time-dependent reduction of peripheral cytokine levels is characterized by an initial reduction of at least about 80%. In some examples, the time-dependent reduction of peripheral cytokine levels is characterized by recovery of the peripheral cytokine levels to at least about 50% relative to that from an equimolar amount of the equivalent antibody after from about 48 h to about 96 h. In some examples, the time-dependent reduction of peripheral cytokine levels is characterized by recovery of the peripheral cytokine levels to about 100% relative to that from an equimolar amount of the equivalent antibody after from about 48 h to about 96 h. In some examples, the population of cells is a biological sample; and wherein the time-dependent reduction in peripheral cytokine levels is characterized by an initial reduction in

peripheral cytokine levels in the supernatant of the biological sample relative to that from an equimolar amount of the equivalent antibody. In

some examples, the population of cells is in a subject; and wherein the peripheral cytokine levels are systemic cytokine levels in the plasma of the subject. In some examples, when the MEF antibody is introduced to a population of cells comprising one or more target cells, the binding of the MEF antibody to the one or more target cells provides an initial reduction in the rate of cell lysis of the one or more target cells relative to the rate of cell lysis provided by binding of an equimolar amount of the equivalent antibody. In some examples, the population of cells is a biological sample. In some examples, the population of cells is in a subject. In some examples, the one or more target cells comprise cancer cells comprising antigens or immune cells comprising antigens. In some examples, the target cells are radiolabeled. In some examples, the population of cells further comprises normal PBMCs. In some examples, the normal PBMCs comprise natural killer cells.

**[0032]** In some examples, administration of the MEF antibody to a subject provides a reduction of about 20% to about 75% in cytokine  $C_{\max}$  relative to administration of an equimolar amount of the equivalent antibody. In some examples, administration of the MEF antibody to a subject provides substantially the same total antibody  $AUC_{0-\infty}$  relative to administration of an equimolar amount of the equivalent antibody.

**[0033]** In another aspect, the present disclosure provides a composition comprising a distribution of MEF antibodies as disclosed herein. In some examples, the composition comprises a unit dose of the distribution of MEF antibodies. In some examples, the unit dose does not increase systemic levels of monocyte chemotactic protein-1 (MCP-1), tumor necrosis factor (TNF- $\alpha$ ), interferon gamma (IFN- $\gamma$ ), interleukin 1 beta (IL1B), interleukin 6 (IL6), or interleukin 10 (IL10) of more than 10-fold above levels prior to the administering. In some examples, the composition further comprises at least one pharmaceutically acceptable carrier.

**[0034]** The present disclosure provides a composition comprising a first population of MEF antibodies; a second population of MEF antibodies; and at least one pharmaceutically acceptable carrier; wherein the BPMs present in the first population of MEF antibodies are different than the BPMs present in the second population of MEF antibodies.

**[0035]** The present disclosure provides a composition comprising a first population of MEF antibodies; a second population of MEF antibodies; and at least one pharmaceutically acceptable carrier; wherein the cleavable moieties present in the first population of MEF antibodies are different than the cleavable moieties present in the second population of MEF antibodies.

**[0036]** In some examples, the sole active ingredient in the composition is the MEF antibody. In some examples, the percent aggregation of the MEF antibody in the composition is increased by about 1-fold to about 1.1 fold relative to an equivalent antibody. In some

examples, at least 90% of antibodies of a distribution of MEF antibodies are afucosylated. In some examples, at least 90% of antibodies of a plurality of MEF antibodies are afucosylated. In some examples, at least 98% of antibodies of a distribution of MEF antibodies are afucosylated. In some examples, at least 98% of antibodies of a plurality of MEF antibodies are afucosylated.

**[0037]** The present disclosure provides a method of treating a condition in a subject in need thereof, the method comprising: administering to the subject a therapeutically effective amount of a composition comprising a modulated effector function (MEF) antibody which comprises an effector function diminishing modification, and which effector function diminishing modification is at least partially reversible under physiological conditions; and treating the condition while maintaining a systemic level of a cytokine or an inflammatory marker to no more than 10-fold above a level prior to the administering.

**[0037a]** In another aspect, the present disclosure provides a pharmaceutical composition comprising an MEF antibody as disclosed herein or a composition as disclosed herein for use in therapy.

**[0037b]** In another aspect, the present disclosure provides use of a pharmaceutical composition comprising an MEF antibody as disclosed herein or a composition as disclosed herein in the manufacture of a medicament for treating a disease or a condition.

**[0038]** In some examples, the cytokine or the inflammatory marker is monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein-1 (MIP-1 $\beta$ ), tumor necrosis factor (TNF- $\alpha$ ), interferon gamma (IFN- $\gamma$ ), interleukin-1 receptor agonist (IL-1RA), interleukin 1 beta (IL1B), interleukin 6 (IL6), interleukin 10 (IL10), or a combination thereof. In some examples, the cytokine or the inflammatory marker is monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein-1 (MIP-1 $\beta$ ), interleukin-1 receptor agonist (IL-1RA), or a combination thereof. In some examples, the modification comprises a cleavable biocompatible polymeric moiety (BPM) covalently attached to an amino acid residue or a post-translational modification of the MEF antibody. In some examples, prior to the BPM cleavage, the MEF antibody has between 2% and 20% of the effector function activity of an equivalent antibody lacking the BPM. In some examples, 192 hours after administration, the MEF antibody has between 30% and 70% of the effector function activity of an equivalent antibody lacking the BPM. In some examples, a rate of clearance of the MEF antibody is between 25% and 200% of a rate cleavage of the BPM. In some examples, the modification which decreases the effector function of the MEF antibody decreases Fc $\gamma$ RIII binding affinity of the MEF antibody.

**[0039]** The present disclosure provides a method of decreasing the severity of an infusion related reaction in a subject associated with an antibody, comprising intravenously administering to the subject a composition consistent with the present disclosure; wherein the antibody is equivalent to an MEF antibody of the composition; and wherein the severity of the infusion related reaction is decreased from 1 to 4 units relative to intravenous administration of an equimolar amount of the antibody.

**[0039a]** In another aspect, the present disclosure provides use of a pharmaceutical composition comprising an MEF antibody as disclosed herein or a composition as disclosed herein in the manufacture of a medicament for decreasing the severity of an infusion related reaction associated with an antibody.

**[0040]** The present disclosure provides a method of reducing the incidence of and/or risk of developing an infusion related reaction in a subject associated with an antibody, comprising

intravenously administering to the subject a composition comprising a composition consistent with the present disclosure; wherein the antibody is equivalent to an MEF antibody of the composition; and wherein the incidence of and/or risk of developing the infusion related reaction is reduced relative to intravenous administration of an equimolar amount of an equivalent antibody.

**[0040a]** In another aspect, the present disclosure provides use of a pharmaceutical composition comprising an MEF antibody as disclosed herein or a composition as disclosed herein in the manufacture of a medicament for reducing the incidence of and/or risk of developing an infusion related reaction associated with an antibody.

**[0041]** The present disclosure provides a method of reducing one or more symptoms of an infusion related reaction in a subject associated with an antibody, comprising intravenously administering to the subject a composition comprising a composition consistent with the present disclosure; wherein the antibody is equivalent to an MEF antibody of the composition; wherein the one or more symptoms of the infusion related reaction are reduced relative to intravenous administration of an equimolar amount of an equivalent antibody.

**[0042]** The present disclosure provides a method of decreasing the  $C_{\max}$  of an active antibody, comprising intravenously administering to a subject a composition comprising a composition consistent with the present disclosure; wherein the active antibody is equivalent to an MEF antibody of the composition; and wherein the  $C_{\max}$  of the active antibody after intravenous administration of the MEF antibody composition is decreased relative to the  $C_{\max}$  after intravenous administration of an equimolar amount of the active antibody.

**[0042a]** In another aspect, the present disclosure provides use of a pharmaceutical composition comprising an MEF antibody as disclosed herein or a composition as disclosed herein in the manufacture of a medicament for decreasing the  $C_{\max}$  of an active antibody.

**[0043]** The present disclosure provides a method of delaying maximal Fc gamma receptor IIIa binding of an antibody in a subject, comprising intravenously administering to the subject a composition comprising a composition consistent with the present disclosure; wherein the antibody is equivalent to an MEF antibody of the composition; and wherein the MEF antibody delays binding to Fc gamma receptor IIIa relative to the antibody.

**[0043a]** In another aspect, the present disclosure provides use of a pharmaceutical composition comprising an MEF antibody as disclosed herein or a composition as disclosed herein in the manufacture of a medicament for delaying maximal Fc gamma receptor IIIa binding of an antibody.

**[0044]** The present disclosure provides a method of selectively increasing binding of an antibody to Fc gamma receptor IIIa in a target cell in a subject, comprising intravenously

administering to the subject a composition comprising a composition consistent with the present disclosure; wherein the antibody is equivalent to an MEF antibody of the composition; and wherein the ratio of the MEF antibody (i) bound to Fc gamma receptor IIIa at the target cell and (ii) bound to Fc gamma receptor IIIa systemically is increased relative to the ratio of the antibody (i) bound to Fc gamma receptor IIIa at the target cell and (ii) bound to Fc gamma receptor IIIa systemically.

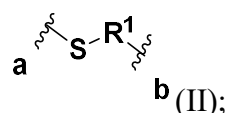
**[0045]** The present disclosure provides a method of reducing systemic Fc gamma receptor IIIa activation in a subject after administration of an antibody, comprising intravenously administering to the subject a composition comprising a composition consistent with the present disclosure; wherein the antibody is equivalent to an MEF antibody of the composition; and wherein the administration of the MEF antibody provides reduced systemic activation of Fc

gamma receptor IIIa relative to intravenous administration of an equimolar amount of the antibody.

**[0046]** The present disclosure provides a method of decreasing systemic cytokine production in a subject after administration of an antibody, comprising intravenously administering to the subject a composition comprising a composition consistent with the present disclosure; wherein the antibody is equivalent to an MEF antibody of the composition; and wherein administration of the composition comprising the MEF antibody decreases systemic cytokine production relative to intravenous administration of an equimolar amount of the antibody.

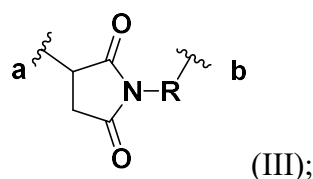
**[0046a]** In another aspect, the present disclosure provides use of a pharmaceutical composition comprising an MEF antibody as disclosed herein or a composition as disclosed herein in the manufacture of a medicament for decreasing systemic cytokine production after administration of an antibody.

**[0047]** In some examples, each cleavable moiety comprises a structure according to Formula (II):



wherein at least about 10% of the BPMs are cleaved from the MEF antibody within about 12 hours and at least about 25% of the BPMs are cleaved from the MEF antibody within 48 hours after intravenous administration.

**[0048]** In some examples, each cleavable moiety comprises a structure according to Formula (III):



wherein about 10% of the BPMs are cleaved from the MEF antibody within about 12 hours and about 25% of the BPMs are cleaved from the MEF antibody within 48 hours after intravenous administration.

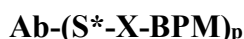
**[0049]** In some examples, at least about 10% of the BPMs are cleaved from the MEF antibody within about 12 hours and at least about 30% of the BPMs are cleaved from the MEF antibody within 48 hours after intravenous administration. In some examples, at least about 20% of the BPMs are cleaved from the MEF antibody within about 12 hours and at least about 40% of the BPMs are cleaved from the MEF antibody within 48 hours after intravenous administration. In some examples, at least about 30% of the BPMs are cleaved from

the MEF antibody within about 12 hours and at least about 50% of the BPMs are cleaved from the MEF antibody within 48 hours after intravenous administration. In some examples, at least about 50% of the BPMs are cleaved from the MEF antibody within about 12 hours and about 100% of the BPMs are cleaved from the MEF antibody within 48 hours after intravenous administration.

In some examples, at least about 50% of the BPMs are cleaved from the MEF antibody within about 12 hours.

**[0050]** In some examples, the MEF antibody is a therapeutic antibody. In some examples, the MEF antibody is selected from the group consisting of rituximab, obinutuzumab, ofatumumab, trastuzumab, alemtuzumab, mogamulizumab, cetuximab and dinutuximab.

**[0051]** In another aspect, the present disclosure provides a modulated effector function (MEF) antibody having the structure:



wherein:

each S\* is a sulfur atom from a cysteine residue of a reduced interchain disulfide of the MEF antibody;

each X is a cleavable moiety; each BPM is a polyethylene glycol moiety, a polyketal moiety, a polyglycerol moiety, a polysaccharide moiety, a polysarcosine moiety, a polypeptide moiety, or a polyzwitterionic moiety;

subscript p is 2, 4, 6, or 8; and

Ab represents the remainder of the antibody.

**[0052]** In some examples, each X is covalently attached to a sulfur atom of a cysteine residue of a reduced interchain disulfide bond of the MEF antibody through a cleavable disulfide bond, or through a cleavable thioether bond to a non-hydrolyzed succinimide moiety. In some examples, each X is covalently attached to a sulfur atom of a cysteine residue of a reduced interchain disulfide bond of the MEF antibody through the cleavable thioether bond. In some examples, each X is covalently attached to a sulfur atom of a cysteine residue of a reduced interchain disulfide bond of the MEF antibody through the cleavable disulfide bond.

**[0053]** In some examples, each X comprises a structure of either Formula (II) or (III):



wherein:

R<sup>1</sup> is a C<sub>2</sub>-C<sub>12</sub> alkylene, optionally interrupted with one of -NH-C(=O)-, -C(=O)NH-, -NH-, and -O-;

R is absent, or is a C<sub>1</sub>-C<sub>12</sub> alkylene optionally interrupted with one or two of phenyl, -NH-C(=O)-, -C(=O)NH-, -NH-, -O-, -O-C(=O)-, -C(=O)O-, -S-C(=O)-, -C(=O)S-, -O-C(=O)O-, -C(=NR<sup>1A</sup>), an acetal, -O(SO<sub>2</sub>)O-, -O-[P(=O)(-OH)]O-, -C(=N-OH)-,

$-C(=N-NH_2)-$ , and  $-C(R^{1A})=N-NH-$ ; and R is optionally substituted with 1-3 substituents independently selected from phenyl, oxo, and  $-CO_2R^A$ ;  $C_3-C_6$  cycloalkylene; and phenyl optionally substituted with 1-3 independently selected  $C_1-C_3$  alkoxy;

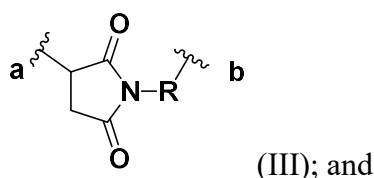
each  $R^A$  is independently hydrogen or  $C_1-C_6$  alkyl;

each  $R^{1A}$  is independently hydrogen or  $C_1-C_6$  alkyl;

wherein  $\sim$  (a) represents the covalent attachment to the cysteine residue of the reduced interchain disulfide bond of the MEF antibody; and

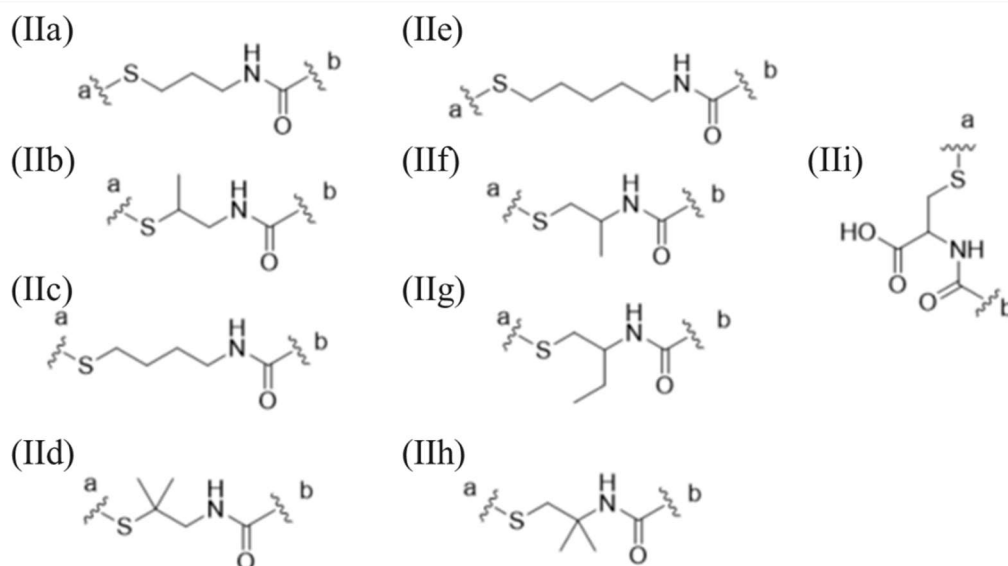
$\sim$  (b) represents the covalent attachment to a BPM or the remainder of X, which retains covalent attachment to a BPM.

**[0054]** In some examples, each X comprises a structure according to Formula (III):



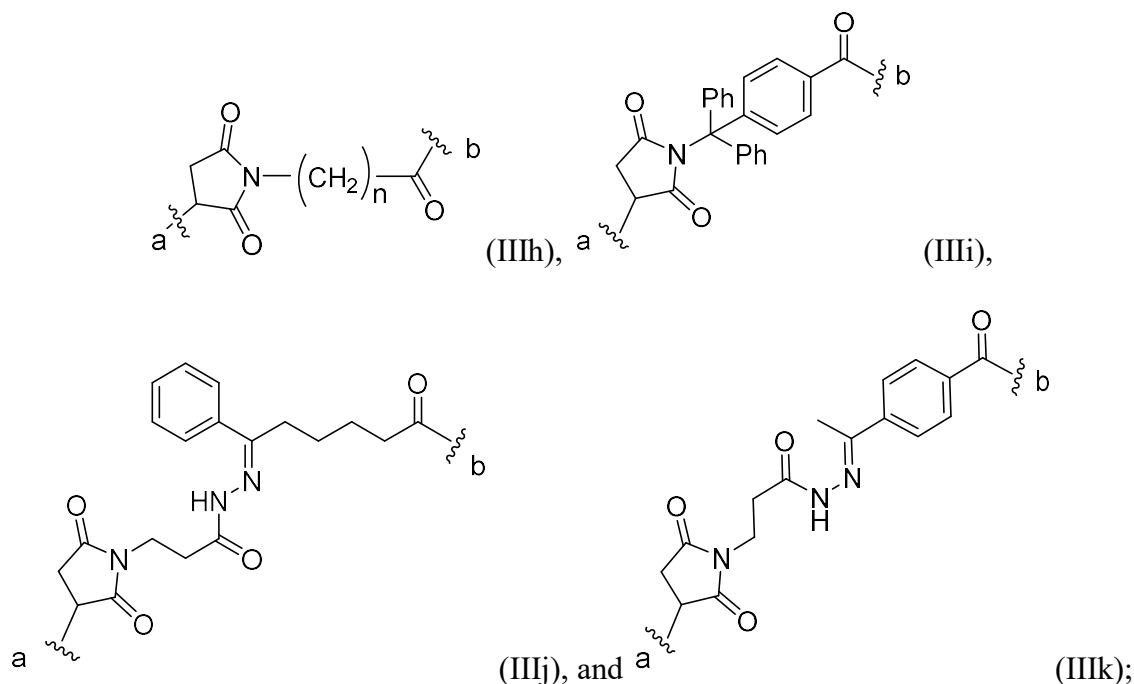
wherein R is a  $C_1-C_{12}$  alkylene interrupted with  $-C(=N-NH_2)-$  or  $-C(R^{1A})=N-NH-$ ; or interrupted with phenyl and one of  $-C(=N-NH_2)-$  and  $-C(R^{1A})=N-NH-$ .

**[0055]** In some examples, each X comprises a structure according to any one of Formulas (IIa)-(IIi):



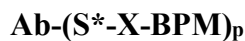
wherein  $\sim$  (a) represents the covalent attachment to the sulfur atom of a cysteine residue of a reduced interchain disulfide bond of the MEF antibody; and  $\sim$  (b) represents the covalent attachment of X to a BPM.

**[0056]** In some examples, each X comprises a structure according to any one of Formulas (IIIh)-(IIIk):

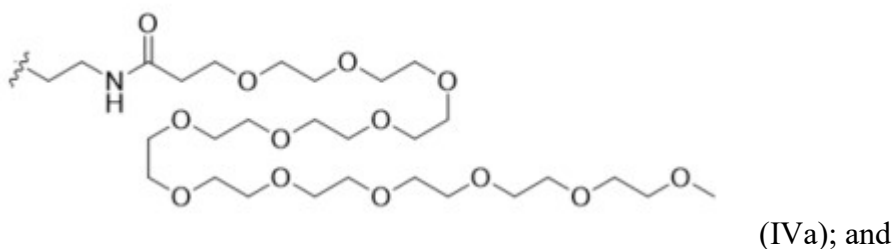


wherein subscript  $n$  is an integer ranging from 2 to 8; and wherein  $\sim$  (a) represents the covalent attachment to the sulfur atom of a cysteine residue of a reduced interchain disulfide bond of the MEF antibody; and  $\sim$  (b) represents the covalent attachment of X to a BPM.

[0057] In some examples, the MEF antibody has the structure of

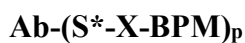


wherein each BPM moiety has a structure according to Formula (IVa):

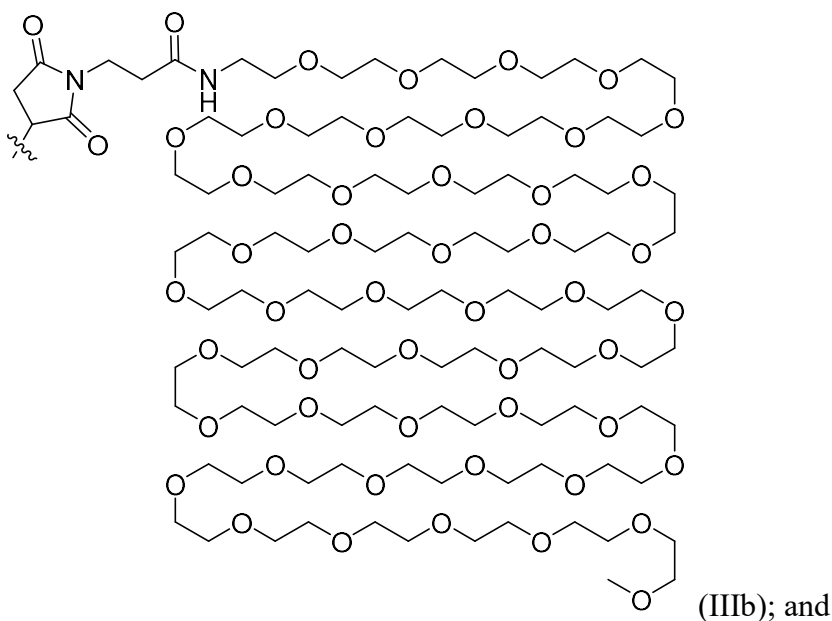


wherein  $\sim$  represents the covalent attachment to a cleavable moiety.

[0058] In some examples, the MEF antibody has the structure of:

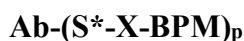


wherein each -X-BPM moiety has a structure according to Formula (IIIb):

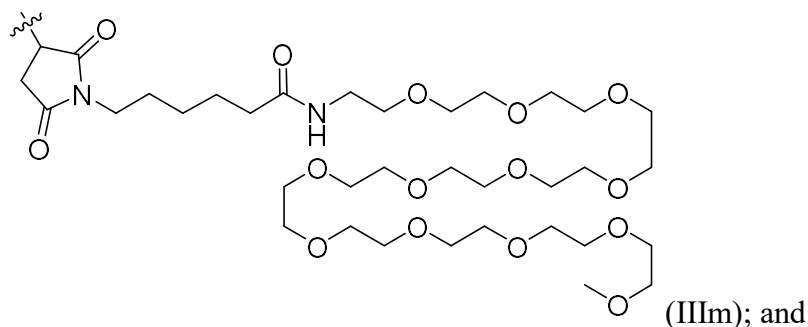


wherein ~~~ represents the covalent attachment to S\*.

[0059] In some examples, the MEF antibody has the structure of:



wherein each -X-BPM moiety has a structure according to formula (IIIIm):



wherein ~~~ represents the covalent attachment to S\*.

[0060] Provided herein are antibodies having biocompatible polymeric moieties (BPMs) covalently attached via cleavable moieties, providing adjustable magnitudes of Fc receptor interaction. The resulting antibodies initially exhibit decreased Fc receptor binding upon administration, but exhibit an increase in Fc receptor affinity over time.

[0061] Some examples provide a MEF antibody, wherein: the MEF antibody has 1, 2, 3, or 4 reduced interchain disulfide bonds and 2, 4, 6, or 8 biocompatible polymeric moieties (BPMs), respectively; wherein each BPM is covalently attached to each sulfur atom of the cysteine residues of each reduced interchain disulfide bond of the MEF antibody via a cleavable moiety; and wherein the MEF antibody exhibits time-dependent reduction in FcR binding, and thus a corresponding time-dependent reduction in an effector function, relative to that of an equivalent antibody.

**[0062]** Some examples provide a composition comprising a distribution of MEF antibodies, as described herein. In some examples, the MEF antibodies of the distribution differ primarily in the number of covalently attached BPMs.

**[0063]** Some examples provide a composition comprising a first population of an MEF antibody composition; a second population of an MEF antibody; and at least one pharmaceutically acceptable carrier; wherein the BPMs present in the first population of MEF antibodies are different than the BPMs present in the second population of MEF antibodies.

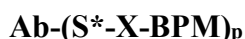
**[0064]** Some examples provide a composition comprising a first population of an MEF antibody composition; a second population of an MEF antibody composition; and at least one pharmaceutically acceptable carrier; wherein the cleavable moieties present in the first population of MEF antibodies are different than the cleavable moieties present in the second population of MEF antibodies.

**[0065]** The disclosure provides a method of decreasing the severity of an infusion related reaction in a subject associated with an antibody, comprising intravenously administering to the subject a composition comprising an MEF antibody; wherein the severity of the infusion related reaction is decreased from 1 to 4 units relative to intravenous administration of an equimolar amount of the antibody; and wherein the antibody is equivalent to the MEF antibody.

**[0066]** The disclosure provides a method of reducing the incidence of and/or risk of developing an infusion related reaction in a subject associated with an antibody, comprising intravenously administering to the subject a composition comprising an MEF antibody; wherein the antibody is equivalent to the MEF antibody; and wherein the incidence of and/or risk of developing the infusion related reaction is reduced relative to intravenous administration of an equimolar amount of the antibody.

**[0067]** The disclosure provides a method of reducing one or more symptoms of an infusion related reaction in a subject associated with an antibody, comprising intravenously administering to the subject a composition comprising an MEF antibody; wherein the antibody is equivalent to the MEF antibody; and wherein the one or more symptoms of the infusion related reaction are reduced relative to intravenous administration of an equimolar amount of the antibody.

**[0068]** The disclosure provides an MEF antibody having the structure:



wherein: each S\* is a sulfur atom from a cysteine residue of a reduced interchain disulfide bond of the MEF antibody; each X is a cleavable moiety; each BPM is a polyethylene glycol moiety, a polyketal moiety, a polyglycerol moiety, a polysaccharide moiety, a polysarcosine moiety, a

polypeptide moiety, or a polyzwitterionic moiety; subscript p is 2, 4, 6, or 8; and Ab represents the remainder of the antibody.

**[0069]** The disclosure provides a method of decreasing the  $C_{\max}$  of an active antibody, comprising intravenously administering to a subject a composition comprising a MEF antibody;

**[0070]** wherein the active antibody is equivalent to the MEF antibody; wherein the  $C_{\max}$  of the active antibody after intravenous administration of the MEF antibody composition is decreased relative to the  $C_{\max}$  after intravenous administration of an equimolar amount of the active antibody.

**[0071]** The disclosure provides a method of delaying maximal Fc gamma receptor IIIa binding of an antibody, comprising intravenously administering to a subject a composition comprising an MEF antibody to the subject in need thereof; wherein the antibody is equivalent to the MEF antibody; and wherein the MEF antibody delays binding to Fc gamma receptor IIIa relative to the antibody.

**[0072]** The disclosure provides a method of selectively increasing binding of an antibody to Fc gamma receptor IIIa in a target cell in a subject, comprising intravenously administering a composition comprising an MEF antibody to the subject; wherein the antibody is equivalent to the MEF antibody; and wherein the ratio of the MEF antibody (i) bound to Fc gamma receptor IIIa at the target cell and (ii) bound to Fc gamma receptor IIIa systemically is increased relative to the ratio of the antibody (i) bound to Fc gamma receptor IIIa at the target cell and (ii) bound to Fc gamma receptor IIIa systemically.

**[0073]** The disclosure provides a method of reducing systemic Fc gamma receptor IIIa activation in a subject after administration of an antibody, comprising intravenously administering a composition comprising an MEF antibody to the subject, wherein the antibody is equivalent to the MEF antibody; and wherein the administration of the MEF antibody provides reduced systemic activation of Fc gamma receptor IIIa relative to intravenous administration of an equimolar amount of the antibody.

**[0074]** The disclosure provides a method of decreasing systemic cytokine production in a subject after administration of an antibody, comprising intravenously administering a composition comprising an MEF antibody to the subject; wherein the antibody is equivalent to the MEF antibody; and wherein administration of the composition comprising the MEF antibody decreases systemic cytokine production relative to intravenous administration of an equimolar amount of the antibody.

**[0075]** The disclosure provides a method of selectively activating an antibody, comprising intravenously administering a composition comprising a distribution of MEF antibodies; wherein at least about 10% of the BPMs are cleaved from the MEF antibody

within about 12 hours and at least about 25% of the BPMs are cleaved from the MEF antibody within 48 hours.

**[0076]** The disclosure provides a method of selectively activating an antibody, comprising intravenously administering a composition comprising a distribution of MEF antibodies; wherein at least about 25% of the BPMs are cleaved from the MEF antibody within about 12 hours and at least about 75% of the BPMs are cleaved from the MEF antibody within 24 hours.

**[0077]** The disclosure provides a method of selectively activating an antibody, comprising intravenously administering a composition comprising a distribution of MEF antibodies; wherein about 25% to about 75% of the BPMs are cleaved from the MEF antibody within about 48 hours.

**[0078]** The disclosure provides a method of selectively activating an antibody, comprising intravenously administering a composition comprising a distribution of MEF antibodies; wherein about 25% to about 75% of the BPMs are cleaved from the MEF antibody within about 72 hours.

### **BRIEF DESCRIPTION OF THE FIGURES**

**[0079]** **FIGS. 1A-B** illustrates the stability of modified antibodies Anti-CD40-AF-12 (**FIG. 1A**) and Anti-CD40-AF-1 (**FIG. 1B**) in rat plasma as assessed by the WES capillary gel electrophoresis assay.

**[0080]** **FIG. 2** illustrates FcγRIIIa NFAT activity and EC<sub>50</sub> values of various modified antibodies (Anti-CD40-WT, Anti-CD40-AF, ANTI-CD40-AF-10, ANTI-CD40-AF-14, ANTI-CD40-AF-15, and ANTI-CD40-AF-17) versus control hIgG1k.

**[0081]** **FIGS. 3A-C** illustrates three time courses of FcγRIIIa NFAT activity of modified antibodies (Anti-CD40-WT, Anti-CD40-AF, Anti-CD40-AF-1, Anti-CD40-AF-12, Anti-BCMA-WT, Anti-BCMA-AF, and Anti-BCMA-AF-12) versus control hIgG1k in rat plasma (time in h).

**[0082]** **FIG. 4** illustrates saturation binding of various modified antibodies (Anti-TIGIT-WT, Anti-TIGIT-AF, Anti-TIGIT-null Fc, Anti-TIGIT-AF-1 and Anti-TIGIT-AF-12) to CHO cells expressing human FcγRIIIa.

**[0083]** **FIGS. 5A-D** illustrates cytokine activity of human PBMCs dosed with various modified antibodies (Anti-CD40-WT, Anti-CD40-AF, Anti-CD40-AF-NEM, Anti-CD40-AF-12 and Anti-CD40-AF-19) versus control hIgG1k. The cytokine activity was measured for IP-10 (**FIG. 5A**), MIP-1b (**FIG. 5B**), TNFa (**FIG. 5C**), and MIP-1a (**FIG. 5D**).

**[0084]** **FIGS. 6A-D** illustrates cytokine production 2, 8, 24, 48, 72 hours post-dose in mice with transgenic human CD40 treated with various modified antibodies (Anti-CD40-WT, Anti-CD40-AF, Anti-CD40-AF-9, Anti-CD40-AF-10, and Anti-CD40-AF-12) versus untreated mouse. The

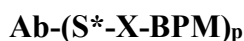
cytokine production was measured for MCP-1 (**FIG. 6A**), KC (**FIG. 6B**), IP-10 (**FIG. 6C**), and MIP-1b (**FIG. 6D**).

**[0085] FIGS. 7A-B** illustrates cytokine production 2, 8, 24, 48, 72 hours post-dose in mice with transgenic human CD40 treated with various modified antibodies (Anti-CD40-WT, Anti-CD40-

## CLAIMS

WHAT IS CLAIMED IS:

1. A modulated effector function (MEF) antibody having the structure:



wherein:

each S\* is a sulfur atom from a cysteine residue of a reduced interchain disulfide of the MEF antibody;

each X is a cleavable moiety; each BPM is a polyethylene glycol moiety, a polyketal moiety, a polyglycerol moiety, a polysaccharide moiety, a polysarcosine moiety, a polypeptide moiety, or a polyzwitterionic moiety;

subscript p is 2, 4, 6, or 8; and

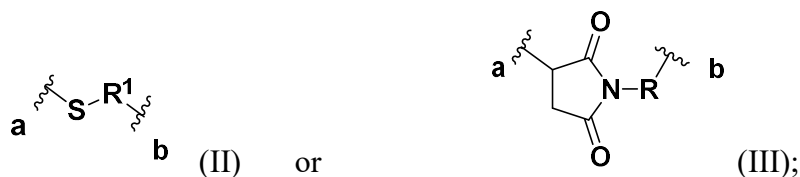
Ab represents the remainder of the antibody.

2. The MEF antibody of Claim 1, wherein each X is covalently attached to the sulfur atom of the cysteine residue of the reduced interchain disulfide bond of the MEF antibody through a cleavable disulfide bond or through a cleavable thioether bond.

3. The MEF antibody of Claim 1 or Claim 2, wherein each X is covalently attached to the sulfur atom of the cysteine residue of the reduced interchain disulfide bond of the MEF antibody through the cleavable thioether bond.

4. The MEF antibody of Claim 1 or Claim 2, wherein each X is covalently attached to the sulfur atom of the cysteine residue of the reduced interchain disulfide bond of the MEF antibody through the cleavable disulfide bond.

5. The MEF antibody of any one of Claims 1 to 4, wherein each X comprises a structure of either Formula (II) or (III):



wherein:

R<sup>1</sup> is a C<sub>2</sub>-C<sub>12</sub> alkylene, optionally interrupted with one of -NH-C(=O)-, -C(=O)NH-, -NH-, and -O-;

R is absent, or is a C<sub>1</sub>-C<sub>12</sub> alkylene optionally interrupted with one or two of phenyl, -NH-C(=O)-, -C(=O)NH-, -NH-, -O-, -O-C(=O)-, -C(=O)O-, -S-C(=O)-, -C(=O)S-, -O-C(=O)O-, -C(=NR<sup>1A</sup>), an acetal, -O(SO<sub>2</sub>)O-, -O-[P(=O)(-OH)]O-, -C(=N-OH)-, -C(=N-NH<sub>2</sub>)-, and -C(R<sup>1A</sup>)=N-NH-; and R is optionally substituted with 1-3 substituents independently selected from phenyl, oxo, and -CO<sub>2</sub>R<sup>A</sup>; C<sub>3</sub>-C<sub>6</sub> cycloalkylene; and phenyl optionally substituted with 1-3 independently selected C<sub>1</sub>-C<sub>3</sub> alkoxy;

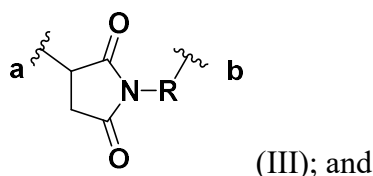
each R<sup>A</sup> is independently hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl;

each R<sup>1A</sup> is independently hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl;

wherein ~~~(a) represents the covalent attachment to the cysteine residue of the reduced interchain disulfide bond of the MEF antibody; and

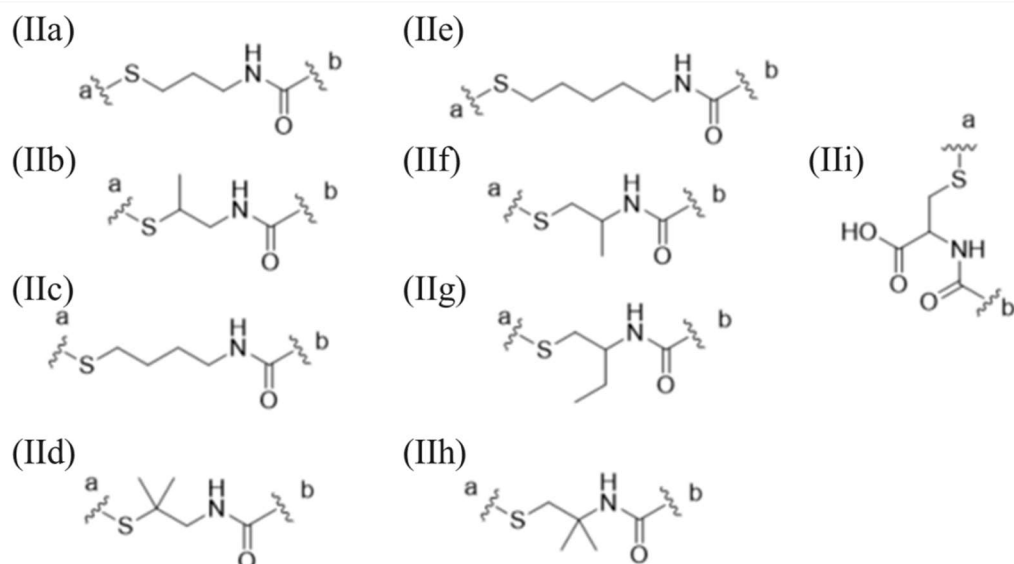
~~~(b) represents the covalent attachment to a BPM or the remainder of X, which retains covalent attachment to a BPM.

6. The MEF antibody of any one of Claims 1 to 5, wherein each X comprises a structure according to Formula (III):



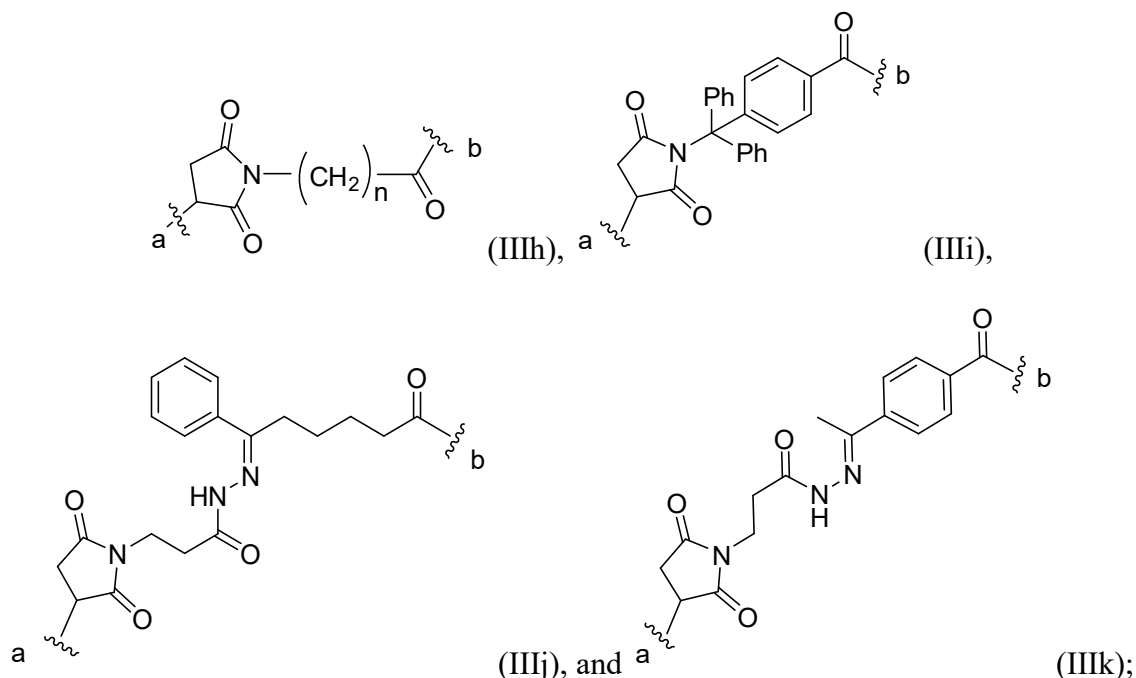
wherein R is a C₁-C₁₂ alkylene interrupted with -C(=N-NH₂)- or -C(R^{1A})=N-NH-; or interrupted with phenyl and one of -C(=N-NH₂)- and -C(R^{1A})=N-NH-.

7. The MEF antibody of any one of Claims 1 to 6, wherein each X comprises a structure according to any one of Formulas (IIa)-(IIi):



wherein $\sim$ (a) represents the covalent attachment to the sulfur atom of a cysteine residue of a reduced interchain disulfide bond of the MEF antibody; and $\sim$ (b) represents the covalent attachment of X to a BPM.

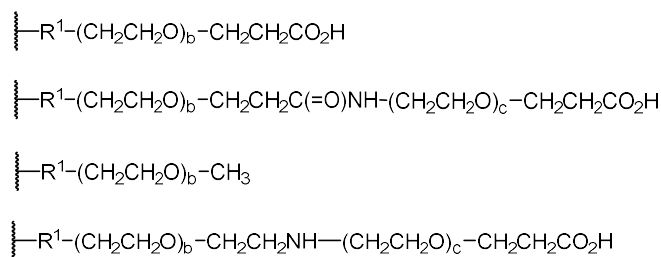
8. The MEF antibody of any one of Claims 1 to 7, wherein each X comprises a structure according to any one of Formulas (IIIh)-(IIIk):



wherein subscript n is an integer ranging from 2 to 8; and

wherein $\sim$ (a) represents the covalent attachment to the sulfur atom of a cysteine residue of a reduced interchain disulfide bond of the MEF antibody; and $\sim$ (b) represents the covalent attachment of X to a BPM.

9. The MEF antibody of any one of Claims 1 to 8, wherein the MEF antibody comprises an effector function enhancing modification.
10. The MEF antibody of Claim 9, wherein the effector function enhancing modification increases a binding affinity of the MEF antibody for FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa, FcγRIIIb, or a combination thereof.
11. The MEF antibody of Claim 9 or Claim 10, wherein the effector function enhancing modification comprises afucosylation, a bisecting N-acetyl glucosamine, an S298A Fc region mutation, an E333A Fc region mutation, a K334A Fc region mutation, an S239D Fc region mutation, an I332E Fc region mutation, a G236A Fc region mutation, an S239E Fc region mutation, an A330L Fc region mutation, a G236A Fc region mutation, a L234Y Fc region mutation, a G236W Fc region mutation, an S296A Fc region mutation, an F243 Fc region mutation, an R292P Fc region mutation, a Y300L Fc region mutation, a V305L Fc region mutation, a P396L Fc region mutation, or a combination thereof.
12. The MEF antibody of any one of Claims 1 to 11, wherein the MEF antibody has between 2% and 20% of an effector function activity of an equivalent antibody lacking the BPM.
13. The MEF antibody of any one of Claims 1 to 12, wherein the MEF antibody has between 30% and 70% of the effector function activity of an equivalent antibody lacking the BPM following 192 hours incubation in 37 °C human plasma.
14. The MEF antibody of any one of Claims 1 to 13, wherein a rate of clearance of the MEF antibody is between 25% and 200% of a rate of the at least partial reversal of the effector function diminishing modification.
15. The MEF antibody of any one of Claims 1 to 14, wherein each BPM is a monodispersed moiety.
16. The MEF antibody of any one of Claims 1 to 15, wherein each BPM independently has a weight-average molecular weight of about 100 Daltons to 5000 Daltons.
17. The MEF antibody of any one of Claims 1 to 16, wherein each BPM independently has a hydrodynamic diameter of about 5 nm to about 25 nm.
18. The MEF antibody of any one of Claims 1 to 17, wherein each BPM has a structure selected from the group consisting of:



wherein R¹ is a C₂-C₁₂ alkylene, optionally interrupted with one of –NH-C(=O)–, –C(=O)NH–, –NH–, or –O– to which the cleavable moiety is covalently attached, and optionally substituted with –CO₂H;

each subscript b ranges from 2 to 72;

each subscript c ranges from 1 to 72; and

~ indicates site of covalent attachment to the cleavable moiety.

19. The MEF antibody of any one of Claims 1 to 18, wherein each BPM comprises a PEG2 to PEG72 moiety.

20. The MEF antibody of any one of Claims 1 to 19, wherein:

- i) the MEF antibody is an IgG₁ antibody;
- ii) the MEF antibody is a monoclonal antibody;
- iii) the monoclonal antibody is a chimeric antibody;
- iv) the monoclonal antibody is a humanized antibody; or
- v) a combination thereof.

21. The MEF antibody of any one of Claims 1 to 20, wherein the MEF antibody binds to a cancer cell or an immune cell.

22. The MEF antibody of any one of Claims 1 to 21, wherein the antibody comprises rituximab, obinutuzumab, ofatumumab, trastuzumab, alemtuzumab, mogamulizumab, cetuximab, or dinutuximab.

23. The MEF antibody of any one of Claims 1 to 22, wherein the MEF antibody comprises a sequence which has at least 80% sequence identity to SEQ ID NO: 890 and the MEF antibody comprises a sequence which has at least 80% sequence identity to SEQ ID NO: 891.

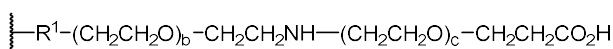
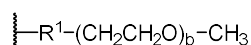
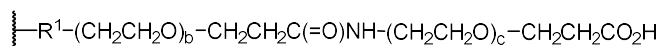
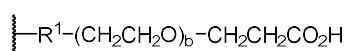
24. A modulated effector function (MEF) antibody, wherein the MEF antibody comprises an effector function enhancing modification and an effector function diminishing modification, wherein the effector function diminishing modification comprises a biocompatible polymeric moiety (BPM) with a covalent attachment to an amino acid or post-translational modification of the MEF antibody, wherein the effector function diminishing modification is at least partially reversible.

25. The MEF antibody of Claim 24, wherein the covalent attachment is cleavable, cleavage of which covalent attachment at least partially reverses the effector function diminishing modification.

26. A modulated effector function (MEF) antibody coupled to a plurality of biocompatible polymeric moieties (BPM) and an Fc which is at least partially blocked by the BPM, or a combination thereof; wherein a BPM of the plurality of BPMs is attached to a sulfur atom of a cysteine residue by a cleavable moiety comprising a disulfide bond.

27. The MEF antibody of Claim 26, wherein:

- i) the MEF antibody has between 2% and 20% of the effector function activity of an equivalent antibody lacking the BPM;
- ii) the cleavable moiety comprises a cleavage rate of between 50% and 300% of its physiological clearance rate during *in vivo* circulation in an adult human male;
- iii) the cleavable moiety is configured to undergo a secondary reaction that diminishes a rate of its cleavage;
- iv) each BPM comprises a PEG2 to PEG72 moiety;
- v) each BPM has a structure selected from the group consisting of:



wherein R¹ is a C₂-C₁₂ alkylene, optionally interrupted with one of –NH-C(=O)–, –C(=O)NH–, –NH–, or –O– to which the cleavable moiety is covalently attached, and optionally substituted with –CO₂H;

each subscript b ranges from 2 to 72;

each subscript c ranges from 1 to 72; and

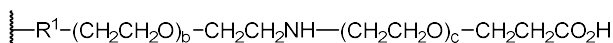
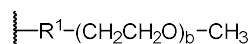
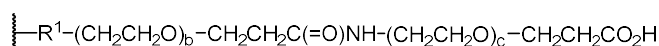
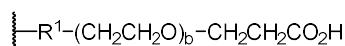
~ indicates site of covalent attachment to the cleavable moiety; or

vi) a combination thereof.

28. A modulated effector function (MEF) antibody coupled to a plurality of biocompatible polymeric moieties (BPM) and an Fc which is at least partially blocked by the BPM; wherein a BPM of the plurality of BPMs is attached to a methionine residue by a cleavable moiety.

29. The MEF antibody of Claim 28, wherein:

- i) the MEF antibody has between 2% and 20% of the effector function activity of an equivalent antibody lacking the BPM;
- ii) the cleavable moiety comprises a cleavage rate of between 50% and 300% of its physiological clearance rate during *in vivo* circulation in an adult human male;
- iii) the cleavable moiety is configured to undergo a secondary reaction that diminishes a rate of its cleavage;
- iv) each BPM comprises a PEG2 to PEG72 moiety;
- v) each BPM has a structure selected from the group consisting of:



wherein R¹ is a C₂-C₁₂ alkylene, optionally interrupted with one of –NH-C(=O)–, –C(=O)NH–, –NH–, or –O– to which the cleavable moiety is covalently attached, and optionally substituted with –CO₂H;

each subscript b ranges from 2 to 72;

each subscript c ranges from 1 to 72; and

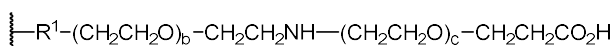
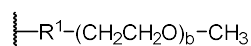
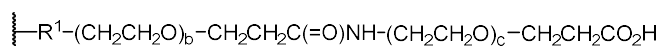
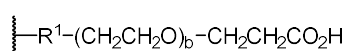
~ indicates site of covalent attachment to the cleavable moiety; or

vi) a combination thereof.

30. A modulated effector function (MEF) antibody comprising at least one Fc region and coupled to a plurality of biocompatible polymeric moieties (BPM) comprising cleavable moieties and present in a ratio of between 6 and 10 to Fc regions of the at least one Fc region; wherein the plurality of biocompatible polymeric moieties comprise molecular weights of between 500 and 2500 Daltons (Da); and wherein the cleavable moieties comprise cleavage rates of between 0.1 and 0.5 day⁻¹ in 37 °C human plasma.

31. The MEF antibody of Claim 30, wherein:

- i) the MEF antibody has between 2% and 20% of the effector function activity of an equivalent antibody lacking the BPM;
- ii) the cleavable moiety comprises a cleavage rate of between 50% and 300% of its physiological clearance rate during *in vivo* circulation in an adult human male;
- iii) the cleavable moieties are configured to undergo a secondary reaction that diminishes their cleavage rates;
- iv) each BPM comprises a PEG2 to PEG72 moiety;
- v) each BPM has a structure selected from the group consisting of:



wherein R¹ is a C₂-C₁₂ alkylene, optionally interrupted with one of -NH-C(=O)-, -C(=O)NH-, -NH-, or -O- to which the cleavable moiety is covalently attached, and optionally substituted with -CO₂H;

each subscript b ranges from 2 to 72;

each subscript c ranges from 1 to 72; and

~ indicates site of covalent attachment to the cleavable moiety; or

vi) a combination thereof.

32. A modulated effector function (MEF) antibody, wherein the MEF antibody has 1, 2, 3, or 4 reduced interchain disulfide bonds and 2, 4, 6, or 8 biocompatible polymeric moieties (BPMs), respectively; wherein each BPM is covalently attached to a sulfur atom of a cysteine residue of a reduced interchain disulfide bond of the MEF antibody via a cleavable moiety; and wherein the MEF antibody exhibits time-dependent reduction in FcR binding, and thus a corresponding time-dependent reduction in an effector function, relative to that of an equivalent antibody.

33. The MEF antibody of Claim 32, wherein:

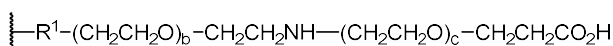
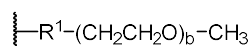
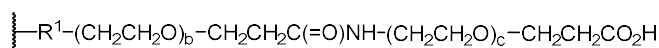
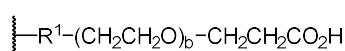
i) the MEF antibody has between 2% and 20% of the effector function activity of an equivalent antibody lacking the BPM;

ii) the cleavable moiety comprises a cleavage rate of between 50% and 300% of its physiological clearance rate during *in vivo* circulation in an adult human male;

iii) the cleavable moiety is configured to undergo a secondary reaction which diminishes a rate of its cleavage;

iv) each BPM comprises a PEG2 to PEG72 moiety;

v) each BPM has a structure selected from the group consisting of:



wherein R¹ is a C₂-C₁₂ alkylene, optionally interrupted with one of -NH-C(=O)-, -C(=O)NH-, -NH-, or -O- to which the cleavable moiety is covalently attached, and optionally substituted with -CO₂H;

each subscript b ranges from 2 to 72;

each subscript c ranges from 1 to 72; and

~ indicates site of covalent attachment to the cleavable moiety; or

vi) a combination thereof.

34. A composition comprising a distribution of MEF antibodies according to any one of Claims 1 to 33.

35. The composition of Claim 34, further comprising at least one pharmaceutically acceptable carrier.

36. The composition of Claim 34 or 35, wherein the composition comprises a unit dose of the distribution of MEF antibodies that does not increase systemic levels of monocyte chemotactic protein-1 (MCP-1), tumor necrosis factor (TNF- α), interferon gamma (IFN- γ), interleukin 1 beta (IL1B), interleukin 6 (IL6), or interleukin 10 (IL10) of more than 10-fold above levels prior to administration.

37. The composition of any one of claims 34 to 36, wherein the sole active ingredient in the composition is the MEF antibody.

38. Use of a pharmaceutical composition comprising an MEF antibody according to any one of Claims 1 to 33 or a composition according to any one of Claims 34 to 37 in the manufacture of a medicament for treating a disease or a condition.

39. The use of Claim 38, wherein the disease is cancer.

40. Use of a pharmaceutical composition comprising an MEF antibody according to any one of Claims 1 to 33 or a composition according to any one of Claims 34 to 37 in the manufacture of a medicament for decreasing the severity of an infusion related reaction associated with an antibody.

41. Use of a pharmaceutical composition comprising an MEF antibody according to any one of Claims 1 to 33 or a composition according to any one of Claims 34 to 37 in the manufacture of a medicament for reducing the incidence of and/or risk of developing an infusion related reaction associated with an antibody.

42. Use of a pharmaceutical composition comprising an MEF antibody according to any one of Claims 1 to 33 or a composition according to any one of Claims 34 to 37 in the manufacture of a medicament for decreasing the $C_{\max}$ of an active antibody.
43. Use of a pharmaceutical composition comprising an MEF antibody according to any one of Claims 1 to 33 or a composition according to any one of Claims 34 to 37 in the manufacture of a medicament for delaying maximal Fc gamma receptor IIIa binding of an antibody.
44. Use of a pharmaceutical composition comprising an MEF antibody according to any one of Claims 1 to 33 or a composition according to any one of Claims 34 to 37 in the manufacture of a medicament for decreasing systemic cytokine production after administration of an antibody.
45. A pharmaceutical composition comprising an MEF antibody according to any one of Claims 1 to 33 or a composition according to any one of Claims 34 to 37 for use in therapy.