CLAIMS

1. A pharmaceutically acceptable composition comprising an erythrocyte-binding moiety, a linker, and a tolerogenic antigen or a second binding moiety, which are recombinantly fused or chemically conjugated, wherein:

said erythrocyte-binding moiety is a petide ligand, an antibody, an antibody fragment or a single chain antigen binding domain (scFv) moiety having the ability to non-covalently specifically bind to a human erythrocyte *in situ* in blood,

said linker is a peptide, a linear or branched polymer, a covalent bond, an ionic bond, an aptamer, a nucleic acid or a particle;

said tolerogenic antigen is a foreign antigen to which patients develop an unwanted immune response, a portion of a therapeutic protein to which patients develop an unwanted immune response, a self antigen to which patients develop an unwanted immune response, or a foreign transplant antigen against which transplant recipients develop an unwanted immune response; and

said second binding moiety having the ability to specifically bind a foreign antigen to which patients develop an unwanted immune response, a therapeutic protein to which patients develop an unwanted immune response, a self antigen to which patients develop an unwanted immune response, or a foreign transplant antigen against which transplant recipients develop an unwanted immune response, or

said second binding moiety being a ligand for an endogenous circulating antibody.

2. The pharmaceutically acceptable composition of claim 1 wherein said erythrocyte-binding moiety has the ability to specifically bind Band 3, glycophorin A, glycophorin B, glycophorin C or glycophorin D.

3. The pharmaceutically acceptable composition of claim 1 wherein said erythrocyte-binding moiety comprises a 10F7 antibody, antibody fragment or ScFv, or a peptide having at least 5 consecutive amino acid residues of a sequence chosen from the group consisting of SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16 and SEQ ID NO:17 and conservative substitutions thereof.

4. The pharmaceutically acceptable composition of claim 1 characterized by having the ability to induce apoptotic- or exhausted-fate proliferation and/or deletion of $CD4^+$ and/or $CD8^+$ T-cells specific for the antigen, or the ability to induce regulatory cell phenotypes.

5. The pharmaceutically acceptable composition of claim 1 wherein the tolerogenic antigen is selected from the groups:

a) insulin, proinsulin, preproinsulin, glutamic acid decarboxylase-65 (GAD-65), GAD-67, insulinoma-associated protein 2 (IA-2), insulinoma-associated protein 2β (IA-2β), ICA69, ICA12 (SOX-13), carboxypeptidase H, Imogen 38, GLIMA 38, chromogranin-A, HSP-60, caboxypeptidase E, peripherin, glucose transporter 2, hepatocarcinoma-intestine-pancreas/pancreatic associated protein, S100β, glial fibrillary acidic protein, regenerating gene II, pancreatic duodenal homeobox 1, dystrophia myotonica kinase, islet-specific glucose-6-phosphatase catalytic subunit-related protein, and SST G-protein coupled receptors 1-5;

b) thyroglobulin (TG), thyroid peroxidase (TPO), thyrotropin receptor (TSHR), sodium iodine symporter (NIS) and megalin;

c) thyroglobulin (TG), thyroid peroxidase (TPO), thyrotropin receptor (TSHR), sodium iodine symporter (NIS), megalin, and insulin-like growth factor 1 receptor;

d) calcium sensitive receptor;

e) 21-hydroxylase, 17α-hydroxylase, P450 side chain cleavage enzyme (P450scc), ACTH receptor, P450c21 and P450c17;

f) FSH receptor and α-enolase;

g) pituitary gland-specific protein factor (PGSF) 1a, PGSF 2, and type 2 iodothyronine deiodinase;

h) myelin basic protein, myelin oligodendrocyte glycoprotein and proteolipid protein;

i) collagen II;

j) H^+,K^+-ATPase;

k) intrinsic factor;

l) tissue transglutaminase and gliadin;

m) tyrosinase, and tyrosinase related protein 1 and 2;

n) acetylcholine receptor;

o) desmoglein 3, desmoglein 1, desmoglein 4, pemphaxin, desmocollins, plakoglobin, perplakin, desmoplakins, and acetylcholine receptor;

p) BP180, BP230, plectin and laminin 5;

q) endomysium and tissue transglutaminase;

r) collagen VII;

s) matrix metalloproteinase 1 and 3, the collagen-specific molecular chaperone heat-shock protein 47, fibrillin-1, PDGF receptor, Scl-70, U1 RNP, Th/To, Ku, Jo1, NAG-2, centromere proteins, topoisomerase I, nucleolar proteins, RNA polymerase I, II and III, PM-Slc, fibrillarin, and B23;

t) U1snRNP;

u) SS-A, SS-B, fodrin, poly(ADP-ribose) polymerase, and topoisomerase

v) SS-A, high mobility group box 1 (HMGB1), nucleosomes, histone proteins and double-stranded DNA;

w) glomerular basement membrane proteins including collagen IV;

x) cardiac myosin; and

y) aromatic L-amino acid decarboxylase, histidine decarboxylase, cysteine sulfinic acid decarboxylase, tryptophan hydroxylase, tyrosine hydroxylase, phenylalanine hydroxylase, hepatic P450 cytochromes P4501A2 and 2A6,

SOX-9, SOX-10, calcium-sensing receptor protein, and the type 1 interferons interferon alpha, beta and omega;

z) antithrombin-III, protein C, factor VIII, factor IX, growth hormone, somatotropin, insulin, pramlintide acetate, mecasermin (IGF-1), β-gluco cerebrosidase, alglucosidase-α, laronidase (α-L-iduronidase), idursuphase (iduronate-2-sulphatase), galsulphase, agalsidase-β (α-galactosidase), α-1 proteinase inhibitor, and albumin;

aa) adenosine deaminase, pancreatic lipase, pancreatic amylase, lactase, botulinum toxin type A, botulinum toxin type B, collagenase, hyaluronidase, papain, L-Asparaginase, uricase, lepirudin, streptokinase, anistreplase (anisoylated plasminogen streptokinase activator complex), antithymocyte globulin, crotalidae polyvalent immune Fab, digoxin immune serum Fab, L-arginase, and L-methionase;

ab) conarachin (Ara h 1), allergen II (Ara h 2), arachis agglutinin, conglutin (Ara h 6), 31 kda major allergen/disease resistance protein homolog (Mal d 2), lipid transfer protein precursor (Mal d 3), major allergen Mal d 1.03D (Mal d 1), α-lactalbumin (ALA), lactotransferrin, actinidin (Act c 1, Act d 1), phytocystatin, thaumatin-like protein (Act d 2), kiwellin (Act d 5), 2S albumin (Sin a 1), 11S globulin (Sin a 2), lipid transfer protein (Sin a 3), profilin (Sin a 4), profilin (Api g 4), high molecular weight glycoprotein (Api g 5), Pen a 1 allergen (Pen a 1), allergen Pen m 2 (Pen m 2), tropomyosin fast isoform, high molecular weight glutenin, low molecular weight glutenin, alpha- and gamma-gliadin, hordein, secalin, avenin, major strawberry allergy Fra a 1-E (Fra a 1), and profilin (Mus xp 1); and

ac) subunits of MHC class I and MHC class II haplotype proteins, and single-amino-acid polymorphisms on minor blood group antigens including RhCE, Kell, Kidd, Duffy and Ss.

6. The pharmaceutically acceptable composition of claim 1 wherein the

tolerogenic antigen comprises a mimotope of a protein.

7. The pharmaceutically acceptable composition of claim 1 wherein said linker is a branched polymer that increases the affinity of erythrocyte binding by avidity effects.

8. The pharmaceutically acceptable composition of claim 7 wherein said branched polymer is conjugated to more than one erythrocyte-binding moiety.

9. The pharmaceutically acceptable composition of claim 1 wherein the erythrocyte-binding moiety comprises an antibody, an antibody fragment or an ScFv derived from a hybridoma that produces an antibody against an erythrocyte, with the hybridoma being chosen from the group consisting of BRIC 4, BRIC 5, BRIC 6, BRIC 10, BRIC 14, BRIC 18, BRIC 39, BRIC 66, BRIC 68, BRIC 69, BRIC 87, BRIC 108, BRIC 110, BRIC 111, BRIC 125, BRIC 126, BRIC 128, BRIC 145, BRIC 155, BRIC 157, BRIC 163, BRIC 170, BRIC 198, BRIC 203, BRIC 216, BRIC 220, BRIC 221, BRIC 222, BRIC 229, BRIC 230, BRIC 231, BRIC 235, BRIC 256, BRAC 17, BRAC 18, BGRL 1, BGRL 2, BGRL 11, BGRL 100, BRAD 3, BIRMA D6, BIRMA D10, BIRMA K3, BIRMA K3, BIRMA 84B; 6A7; COE; and KZ1.

10. The pharmaceutically acceptable composition of claim 1 having an erythrocyte-binding moiety, a linker and a second binding moiety that together form a bi-specific protein construct.

11. The pharmaceutically acceptable composition of claim 10 wherein said second binding moiety is a ligand for an endogenous circulating antibody.

12. A method of treating an unwanted immune response comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutically

acceptable composition, the composition being an erythrocyte-binding moiety, a linker, and a tolerogenic antigen or a second binding moiety, which are recombinantly fused or chemically conjugated, wherein:

said erythrocyte-binding moiety is a peptide ligand, an antibody, an antibody fragment or a single chain antigen binding domain (scFv) moiety having the ability to non-covalently specifically bind to a human erythrocyte *in situ* in blood,

said linker is a peptide, a linear or branched polymer, a covalent bond, an ionic bond, an aptamer, a nucleic acid or a particle;

said tolerogenic antigen is a foreign antigen to which patients develop an unwanted immune response, a therapeutic protein to which patients develop an unwanted immune response, a self antigen to which patients develop an unwanted immune response, or a foreign transplant antigen against which transplant recipients develop an unwanted immune response; and

said second binding moiety being a ligand for an endogenous circulating antibody.

13. The method of claim 12 wherein said erythrocyte-binding moiety has the ability to specifically bind Band 3, glycophorin A, glycophorin B, glycophorin C or glycophorin D.

14. The method of claim 12 wherein said erythrocyte-binding moiety comprises a 10F7 antibody, antibody fragment or ScFv, or a peptide having at least 5 consecutive amino acid residues of a sequence chosen from the group consisting of SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16 and SEQ ID NO:17 and conservative substitutions thereof.

15. The method of claim 12 characterized by having the ability to induce apoptotic- or exhausted-fate proliferation and/or deletion of $CD4^+$ and/or $CD8^+$ Tcells

specific for the antigen, or the ability to induce regulatory cell phenotypes.

16. The method of claim 12 wherein said composition is administered to a patient prior to an unwanted immune response to the antigen, wherein said treatment prevents or minimizes the unwanted immune response.

17. The method of claim 12 wherein said composition is administered to a patient having an unwanted immune response to the antigen, wherein said treatment reverses or minimizes the unwanted immune response.

18. The method of claim 12 where the unwanted immune response is selected from the group: type 1 diabetes mellitus; autoimmune diseases of the thyroid, including Hashimoto's thyroiditis and Graves' disease; thyroid-associated ophthalmopathy and dermopathy; hypoparathyroidism; Addison's disease; premature ovarian failure; autoimmune hypophysitis or pituitary autoimmune disease; multiple sclerosis; rheumatoid arthritis; immunogastritis; pernicious angemis; celiac disease; vitiligo; myasthenia gravis; pemphigus vulgaris and variants; bullous pemphigoid; dermatitis herpetiformis Duhring; epidermolysis bullosa acquisita; systemic sclerosis; mixed connective tissue disease; Sjogren's syndrome; systemic lupus erythematosus; Goodpasture's syndrome; rheumatic heart disease; and autoimmune polyglandular syndrome type 1.

19. The method of claim 12 where the tolerogenic antigen is selected from the groups:

a) insulin, proinsulin, preproinsulin, glutamic acid decarboxylase-65 (GAD-65), GAD-67, insulinoma-associated protein 2 (IA-2), insulinoma-associated protein 2β (IA-2β), ICA69, ICA12 (SOX-13), carboxypeptidase H, Imogen 38, GLIMA 38, chromogranin-A, HSP-60, caboxypeptidase E, peripherin, glucose transporter 2, hepatocarcinoma-intestine-pancreas/pancreatic associated protein, S100β, glial fibrillary acidic protein, regenerating gene II, pancreatic

duodenal homeobox 1, dystrophia myotonica kinase, islet-specific glucose-6-phosphatase catalytic subunit-related protein, and SST G-protein coupled receptors 1-5;

b) thyroglobulin (TG), thyroid peroxidase (TPO), thyrotropin receptor (TSHR), sodium iodine symporter (NIS) and megalin;

c) thyroglobulin (TG), thyroid peroxidase (TPO), thyrotropin receptor (TSHR), sodium iodine symporter (NIS), megalin, and insulin-like growth factor 1 receptor;

d) calcium sensitive receptor;

e) 21-hydroxylase, 17α-hydroxylase, P450 side chain cleavage enzyme (P450scc), ACTH receptor, P450c21 and P450c17;

f) FSH receptor and α-enolase;

g) pituitary gland-specific protein factor (PGSF) 1a, PGSF 2, and type 2 iodothyronine deiodinase;

h) myelin basic protein, myelin oligodendrocyte glycoprotein and proteolipid protein;

i) collagen II;

j) H^+,K^+-ATPase;

k) intrinsic factor;

l) tissue transglutaminase and gliadin;

m) tyrosinase, and tyrosinase related protein 1 and 2;

n) acetylcholine receptor;

o) desmoglein 3, desmoglein 1, desmoglein 4, pemphaxin, desmocollins, plakoglobin, perplakin, desmoplakins, and acetylcholine receptor;

p) BP180, BP230, plectin and laminin 5;

q) endomysium and tissue transglutaminase;

r) collagen VII;

s) matrix metalloproteinase 1 and 3, the collagen-specific molecular chaperone heat-shock protein 47, fibrillin-1, PDGF receptor, Scl-70, U1 RNP, Th/To, Ku,

Jo1, NAG-2, centromere proteins, topoisomerase I, nucleolar proteins, RNA polymerase I, II and III, PM-Slc, fibrillarin, and B23;

t) U1snRNP;

u) SS-A, SS-B, fodrin, poly(ADP-ribose) polymerase, and topoisomerase

v) SS-A, high mobility group box 1 (HMGB1), nucleosomes, histone proteins and double-stranded DNA;

w) glomerular basement membrane proteins including collagen IV;

x) cardiac myosin; and

y) aromatic L-amino acid decarboxylase, histidine decarboxylase, cysteine sulfinic acid decarboxylase, tryptophan hydroxylase, tyrosine hydroxylase, phenylalanine hydroxylase, hepatic P450 cytochromes P4501A2 and 2A6, SOX-9, SOX-10, calcium-sensing receptor protein, and the type 1 interferons interferon alpha, beta and omega;

z) antithrombin-III, protein C, factor VIII, factor IX, growth hormone, somatotropin, insulin, pramlintide acetate, mecasermin (IGF-1), β-gluco cerebrosidase, alglucosidase-α, laronidase (α-L-iduronidase), idursuphase (iduronate-2-sulphatase), galsulphase, agalsidase-β (α-galactosidase), α-1 proteinase inhibitor, and albumin;

aa) adenosine deaminase, pancreatic lipase, pancreatic amylase, lactase, botulinum toxin type A, botulinum toxin type B, collagenase, hyaluronidase, papain, L-Asparaginase, uricase, lepirudin, streptokinase, anistreplase (anisoylated plasminogen streptokinase activator complex), antithymocyte globulin, crotalidae polyvalent immune Fab, digoxin immune serum Fab, L-arginase, and L-methionase;

ab) conarachin (Ara h 1), allergen II (Ara h 2), arachis agglutinin, conglutin (Ara h 6), 31 kda major allergen/disease resistance protein homolog (Mal d 2), lipid transfer protein precursor (Mal d 3), major allergen Mal d 1.03D (Mal d 1), α-lactalbumin (ALA), lactotransferrin, actinidin (Act c 1, Act d 1), phytocystatin, thaumatin-like protein (Act d 2), kiwellin (Act d 5), 2S albumin

(Sin a 1), 11S globulin (Sin a 2), lipid transfer protein (Sin a 3), profilin (Sin a 4), profilin (Api g 4), high molecular weight glycoprotein (Api g 5), Pen a 1 allergen (Pen a 1), allergen Pen m 2 (Pen m 2), tropomyosin fast isoform, high molecular weight glutenin, low molecular weight glutenin, alpha- and gamma-gliadin, hordein, secalin, avenin, major strawberry allergy Fra a 1-E (Fra a 1), and profilin (Mus xp 1); and

ac) subunits of MHC class I and MHC class II haplotype proteins, and single-amino-acid polymorphisms on minor blood group antigens including RhCE, Kell, Kidd, Duffy and Ss.