

CLAIMS

We claim:

1. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to human E-selectin, comprising at least one of the following:

- (a) a light chain complementarity determining region 1 (LCDR 1) comprising the amino acid sequence of SEQ ID NO:2, a LCDR 2 comprising the amino acid sequence of SEQ ID NO:3, a LCDR 3 comprising the amino acid sequence of SEQ ID NO:4, a heavy chain complementarity determining region 1 (HCDR 1) comprising the amino acid sequence of SEQ ID NO:8, a HCDR 2 comprising the amino acid sequence of SEQ ID NO:9, and a HCDR 3 comprising the amino acid sequence of SEQ ID NO:10;
- (b) a LCDR 1 amino acid sequence selected from the group consisting of the sequence of SEQ ID NO:2, 18, 47, 68, 82, 97 and 106;
- (c) a LCDR 2 amino acid sequence selected from the group consisting of the sequence of SEQ ID NO:3, 19, 48, 69, 83, 98, 107 and 120;
- (d) a LCDR 3 amino acid sequence selected from the group consisting of the sequence of SEQ ID NO:4, 20, 49, 70, 84, 99, 108 and 121;
- (e) a heavy chain complementarity determining region 1 (HCDR 1) amino acid sequence selected from the group consisting of the sequence of SEQ ID NO:8, 23, 52, 63, 77, 92, 111 and 125;
- (f) a HCDR 2 amino acid sequence selected from the group consisting of the sequence of SEQ ID NO:9, 24, 29, 38, 41, 44, 53, 64, 78, 93, 112 and 126;
- (g) a HCDR 3 amino acid sequence selected from the group consisting of the sequence of SEQ ID NO:10, 54, 65, 79, 94, 113 and 127;
- (h) the HCDR 1, HCDR 2, and HCDR 3 amino acid sequences as set forth in the amino acid sequence of SEQ ID NO:11, and the LCDR 1, LCDR 2, and LCDR 3 amino acid sequences as set forth in the amino acid sequence of SEQ ID NO:5;
- (i) the LCDR 1, LCDR 2, and LCDR 3 amino acid sequences as set forth in the amino acid sequence encoded by the insert of the plasmid deposited at the ATCC and having ATCC Accession No. PTA 126530, and HCDR 1, HCDR 2, and HCDR 3 amino acid sequences as set forth in the amino acid sequence encoded by the insert of the plasmid deposited at the ATCC and having ATCC Accession No. PTA 126529;
- (j) a heavy chain variable domain (VH) comprising an amino acid sequence selected from the group consisting of the sequence of SEQ ID NO:11, 25, 30, 35, 39, 42, 45, 55, 60,

66, 75, 80, 90, 95, 104, 114, 118 and 128, and a light chain variable domain (VL) comprising an amino acid sequence selected from the group consisting of the sequence of SEQ ID NO:5, 21, 27, 32, 50, 57, 71, 73, 85, 87, 100, 102, 109, 116 and 122;

(k) a VH comprising an amino acid sequence at least 90%, 95%, 98% or 99% identical to the sequence of SEQ ID NO:11, and a light chain variable domain (VL) comprising an amino acid sequence at least 90%, 95%, 98% or 99% identical to the sequence of SEQ ID NO:5;

(l) a VH comprising the amino acid sequence of SEQ ID NO:11 and a VL comprising the amino acid sequence of SEQ ID NO:5;

(m) a VH comprising the amino acid sequence as set forth in the amino acid sequence encoded by the insert of the plasmid deposited at the ATCC and having ATCC Accession No. PTA 126529 and a VL comprising the amino acid sequence as set forth in the amino acid sequence encoded by the insert of the plasmid deposited at the ATCC and having ATCC Accession No. PTA 126530;

(n) a heavy chain (HC) comprising an amino acid sequence selected from the group consisting of the sequence of SEQ ID NO:7, 13, 22, 28, 34, 37, 40, 43, 51, 59, 62, 74, 76, 89, 91, 103, 110, 117 and 124, and a light chain (LC) comprising an amino acid sequence selected from the group consisting of the sequence of SEQ ID NO:1, 17, 26, 31, 46, 56, 67, 72, 81, 86, 96, 101, 105, 115 and 119;

(o) a HC comprising an amino acid sequence at least 90%, 95%, 98% or 99% identical to the sequence of SEQ ID NO:7 or SEQ ID NO:13, and a LC comprising an amino acid sequence at least 90%, 95%, 98% or 99% identical to the sequence of SEQ ID NO:1;

(p) a HC comprising the amino acid sequence of SEQ ID NO:7 or SEQ ID NO:13, and a LC comprising the amino acid sequence of SEQ ID NO:1; and

(q) a HC comprising the amino acid sequence as set forth in the amino acid sequence encoded by the insert of the plasmid deposited at the ATCC and having ATCC Accession No. PTA 126529 and a LC comprising the amino acid sequence as set forth in the amino acid sequence encoded by the insert of the plasmid deposited at the ATCC and having ATCC Accession No. PTA 126530.

2. An isolated antibody that specifically binds to human E-selectin, comprising: an amino acid sequence comprising a LCDR 1, a LCDR 2 and a LCDR 3 as specified by the amino acid sequence of SEQ ID NO:5; and

an amino acid sequence comprising a HCDR-1, a HCDR-2 and a HCDR-3 as specified by the amino acid sequence of SEQ ID NO:11.

3. The isolated antibody of claim 2, comprising an antibody heavy chain constant region (CH) comprising the amino acid sequence of SEQ ID NO: 15 or 16, and an antibody light chain constant region (CL) comprising the amino acid sequence of SEQ ID NO:14.

4. An isolated antibody that specifically binds to human E-selectin, comprising a LG consisting of the amino acid sequence of SEQ ID NO:1, and a HC consisting of the amino acid sequence of SEQ ID NO:7 or 13.

5. An isolated antibody that specifically binds human E-selectin, comprising at least one of the following:

a) an antibody VL region comprising the LGDR1, LGDR2 and LGDR3 of the VL comprising the amino acid sequence of SEQ ID NO:5;

an antibody VH region comprising the HCDR1, HCDR2 and HCDR3 of the VH comprising the amino acid sequence of SEQ ID NO:11;

an antibody CL region comprising the amino acid sequence of SEQ ID NO:14; and

an antibody heavy chain (CH) constant region comprising the amino acid sequence of SEQ ID NO:15 or 16;

b) an antibody VL region comprising an amino acid sequence at least 95% identical to SEQ ID NO:5; and an antibody VH region comprising an amino acid sequence at least 95% identical to SEQ ID NO:11; and

c) an antibody LG region comprising an amino acid sequence at least 95% identical to SEQ ID NO:1, and an antibody HC comprising an amino acid sequence at least 95% identical to SEQ ID NO:7 or 13.

6. An isolated antibody, or antigen binding fragment thereof, that specifically binds to human E-selectin, comprising an antibody HC comprising an amino acid sequence encoded by the insert deposited with the ATCC and having the Accession Number PTA-126529, and an antibody LG comprising an amino acid sequence encoded by the insert deposited with the ATCC and having the Accession Number PTA-126530.

7. The isolated antibody, or antigen binding fragment thereof, of any one of claims 1-6,

comprising a human Fc domain selected from the group consisting of an Fc domain of IgA₁, IgA₂, IgD, IgE, IgM, IgG₁, IgG₂, IgG₃, or IgG₄; and/or a light chain constant region chosen from kappa or lambda.

- 5 8. ~~The isolated antibody or antigen binding fragment thereof, of any one of claims 1-7, wherein the antibody heavy chain isotype is IgG1 and/or wherein the light chain constant region is a kappa light chain.~~
- 10 9. ~~The isolated antibody or antigen binding fragment thereof, of any of claims 1-8, wherein the antibody is a humanized antibody, a human antibody, a murine antibody, chimeric antibody, or a camelid antibody.~~
- 15 10. ~~The isolated antibody, or antigen binding fragment thereof, of any one of claims 1-9, wherein the antibody, or antigen binding fragment thereof, binds human or cynomolgus monkey E selectin with a K_D about or less than a value selected from the group consisting of 200 nM, 175 nM, 150 nM, 125 nM, 100 nM, 90 nM, 80 nM, 70 nM, 60 nM, 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 5 nM, 2 nM, 1 nM, 900pM, 800pM, 700pM, 600pM and 500pM.~~
- 20 11. ~~The isolated antibody, or antigen binding fragment thereof, wherein the antibody or antigen binding fragment thereof, binding human or cynomolgus monkey E selectin with a K_D of about 200 nM to about 2 nM.~~
- 25 12. ~~An isolated antibody, or antigen binding fragment thereof, that specifically binds E-selectin and demonstrates at least one detectable characteristic selected from the following:~~
- 30 (i) ~~binds to human E selectin with a K_D of 200 nM or less, as measured, optionally, by SPR;~~
- (ii) ~~binds to cynomolgus monkey E selectin with a K_D of 200 nM or less, as measured, optionally, by SPR;~~
- (iii) ~~binds with an EC₅₀ of 50 nM or less, as measured, optionally, by FAC, to cell-surface expressed E selectin;~~
- (iv) ~~binds with an EC₅₀ of 350 nM or greater, as measured, optionally, by FACS, to cell-surface expressed P selectin;~~
- (v) ~~does not detectably bind to soluble rat, mouse or rabbit E selectin or soluble human L or P selectin up to 405 nM as measured, optionally, by SPR;~~

- (vi) binds with an EC_{50} of 2 nM or less, as measured, optionally, by ELISA, to soluble human E-selectin;
- (vii) neutralizes binding with an EC_{50} of 2 nM or less as measured, optionally, by AlphaLisa competition assay, of a sialyl Lewis A ligand to soluble human E-selectin;
- (viii) binds with an IC_{50} of about 1 nM to about 3 nM to free soluble human E-selectin in human serum;
- (ix) neutralizes binding with an IC_{50} of 100 nM or less, as measured, optionally, by competition ELISA under static conditions, of a sialyl Lewis A ligand to soluble human E-selectin;
- (x) neutralizes binding with an IC_{50} of 50 nM or less, as measured, optionally, by competition ELISA under static conditions, of a sialyl Lewis A ligand to cell surface expressed human E-selectin;
- (xi) inhibits adhesion with an IC_{50} of 100 nM or less, as measured, optionally, under static conditions, of cells expressing an E-selectin ligand (e.g., E-selectin ligand, PSGL-1 and other sialyl Lewis ligands) to cell surface expressed human E-selectin;
- (xii) inhibits adhesion with an IC_{50} of 100 nM or less, as measured, optionally, under physiological flow conditions, of cells expressing an E-selectin ligand (e.g., E-selectin ligand, PSGL-1 and other sialyl Lewis ligands) to cell surface expressed human E-selectin;
- (xiii) inhibits adhesion with an IC_{50} of about 6.17 nM to about 18.66 nM as measured, optionally, under physiologic flow conditions, of blood cells from SCD patients to soluble human E-selectin;
- (xiv) binds to at least one amino acid residue of human E-selectin selected from: T7, E8, A9, M10, T11, P46, S47, Y48, N82, N83, Q85, E88, E92, Y94, R97, N105, E107, R108, S110, K111, K112 and K113;
- (xv) has a mean half life of about 14.4 days (345 hours) following IV administration at a dose of 10 mg/kg;
- (xvi) has a mean half life of about 21.5 days (518 hours) following SC administration at a dose of about 3 mg/kg;
- (xvii) has a viscosity of 33.4 cP at 185.7 mg/mL when measured at 25°C by, optionally an Anton Parr method;
- (xviii) exhibits commercially suitable formulation properties, including a high degree of

thermal stability and minimal aggregation at high concentration; and
(xix) ~~exhibits reproducible expression and purity under large scale manufacturing conditions.~~

13. ~~An isolated antibody or antigen binding fragment thereof that competes for binding to
5 human E-selectin with at least one antibody or antigen binding fragment thereof of any one of
claims 1-12.~~

14. ~~An isolated nucleic acid molecule encoding the antibody, or antigen binding fragment
thereof, of any one of claims 1-13.~~

15. ~~An isolated nucleic acid molecule comprising at least one of the following:
a) the nucleic acid sequence of SEQ ID NO:136, the nucleic acid sequence of SEQ ID
NO:137, or both;
b) a nucleic acid sequence selected from the group consisting of the sequence of SEQ
15 ID NO:136, 144, 146, 148, 150, 151, 152, 153, 155, 157, 159, 161, 163, 165, 167,
169, 171 and 173 or a nucleic acid sequence selected from the group consisting of
the sequence of SEQ ID NO:137, 145, 147, 149, 154, 156, 158, 160, 162, 164, 166,
168, 170, 172 and 174, or both;
c) a nucleic acid sequence of SEQ ID NO:206 or 138, the nucleic acid sequence of
20 SEQ ID NO:139, or both; and
d) the nucleic acid sequence of the insert of the plasmid deposited with the ATCC and
having the Accession Number PTA-126529, the nucleic acid sequence of the insert
of the plasmid deposited with the ATCC and having the Accession Number PTA-
126530, or both.~~

16. ~~A vector comprising the nucleic acid of claim 14 or 15.~~

17. ~~A host cell comprising the vector of claim 16.~~

18. ~~The host cell of claim 17, wherein said host cell is a mammalian cell selected from the
group consisting of a CHO cell, a COS cell, a HEK-293 cell, an NS0 cell, a PER.C6® cell, or an
Sp2.0 cell.~~

19. ~~A method of making an antibody, or antigen binding fragment thereof, comprising~~

culturing the host cell of claim 17 or 18 under a condition wherein said antibody, or antigen binding fragment thereof, is expressed by said host cell.

20. A pharmaceutical composition comprising an antibody, or antigen binding fragment thereof, of any one of claims 1-13, and a pharmaceutically acceptable carrier or excipient.

21. The pharmaceutical composition of claim 20, comprising i) an antibody or antigen-binding fragment thereof comprising an antibody heavy chain encoded by the amino acid sequence of SEQ ID NO:7 and an antibody light chain encoded by the amino acid sequence of SEQ ID NO:1, ii) an antibody or antigen binding fragment thereof comprising an antibody heavy chain encoded by the amino acid sequence of SEQ ID NO:13 and an antibody light chain encoded by the amino acid sequence of SEQ ID NO:1, or iii) both.

22. A method of treating a medical condition, disease or disorder mediated by or associated with expression of E-selectin and/or binding of E-selectin to a ligand, in a subject in need thereof, wherein the method comprises administering a therapeutically effective amount of an antibody, or antigen binding fragment thereof, of any one of claims 1-13 that specifically binds to E-selectin.

23. The method of claim 22, wherein the medical condition, disease or disorder is SCD, a skin disease (e.g., psoriasis), inflammatory disease (e.g., rheumatoid arthritis) and/or complications of diabetes.

24. A method of treating SCD, in a subject in need thereof, wherein the method comprises administering a therapeutically effective amount of an antibody, or antigen binding fragment thereof, of any one of claims 1-13 that specifically binds to E-selectin and, treating, preventing and/or ameliorating at least one sign and/or symptom of SCD selected from the group consisting of those affecting the cardiothoracic system (e.g., chronic restrictive lung disease, left ventricular diastolic disease, pulmonary hypertension, acute chest syndrome, dysrhythmias, sudden death, vaso-occlusive crisis (VOC)), the nervous system (e.g., hemorrhagic stroke, venous sinus thrombosis, silent cerebral infarction of the brain, chronic pain, acute ischemic stroke of the brain, proliferative retinopathy, orbital infarction, cognitive impairment) the reticuloendothelial system (e.g., splenic sequestration, functional hyposplenism, anemia, hemolysis), the musculoskeletal system (e.g., avascular necrosis, skin ulcerations), the

urogenital system (e.g., papillary necrosis, proteinuria, renal failure, hematuria, nocturnal enuresis, priapism) and the gastrointestinal system (e.g., cholelithiasis, cholangiopathy, hepatopathy, mesenteric vaso-occlusion).

5 25. The method of treating SCD of claim 24, wherein treatment of VOC includes i) treatment of acute VOC by decreasing the duration and/or intensity of the VOC, ii) prevention, or reduction in the occurrence, of VOC or iii) both.

10 26. A method of decreasing an E-selectin biological activity in a subject in need thereof, wherein the method comprises administering a therapeutically effective amount of an antibody, or antigen binding fragment thereof, of any one of claims 1-13 that specifically binds to E-selectin.

15 27. The method of claim 26, wherein the antibody, or antigen binding fragment thereof decreases at least one detectable E-selectin biological activity wherein the decreased activity is selected from the group consisting of (a) leukocyte tethering to endothelial cells; (b) activation of stable adhesion to endothelial cells; (c) slow rolling of leukocytes to arrest; (d) efficient trans-endothelial migration of leukocytes; (e) affinity and avidity of E-selectin to CD18 integrins; (f) trafficking of leukocytes to sites of acute inflammation; (g) cytosolic calcium; (h) tyrosine phosphorylation that activates p38 MAP kinase and Syk kinase; (i) recruitment of platelets and leukocytes from the blood to the vascular endothelium; and (j) creation of a pro-inflammatory environment.

25 28. The method of any one of claims 22-27, comprising administration of a therapeutically effective amount of at least one additional therapeutically active compound or treatment modality which additional compound and modality is effective in treating and/or preventing at least one sign and/or symptom of SCD.

30 29. The method of claim 28, wherein the at least one additional therapeutically active compound is selected from the group consisting of penicillin prophylaxis, hydroxyurea (DROXIA, HYDREA), L-glutamine (ENDARI), crizanlizumab (ADAKVEO), voxelotor (OXBRYTA), apixaban (ELIQUIS), rivaroxaban (XARELTO), a non-steroidal anti-inflammatory drug, an analgesic (e.g., an opioid analgesic), IW-1701, riociguat (ADEMPAS), ticagrelor (BRILINTA), memantine (NAMENDA), and a combination thereof.

30. The method of claim 28, wherein the at least one additional therapeutically active compound is selected from the group consisting of an anti-P-selectin antibody, a compound that modulates HbS so as to maintain it in its R state (i.e., oxygenated), a compound that modulates oxygen affinity of HbS, a compound that targets HbS polymerization by modulating generation of 2,3-disphosphoglyceric acid, a compound that targets HbS polymerization by inducing expression of fetal hemoglobin (HbF), a compound that targets dysfunctional cellular adhesion, vascular dysfunction and/or inflammation, a compound that increases levels of nitric oxide (NO) in the blood as compared with the level of NO before administration of the compound, intravenous IG, a compound that targets hypercoagulability, a compound that blocks NMDA receptor binding and a combination thereof.

31. The method of claim 30, wherein the compound that modulates HbS so as to maintain it in its R state (i.e., oxygenated) is selected from the group consisting of 6-((1S)-1-((2-amino-6-fluoroquinolin-3-yl)oxy)ethyl)-5-(1H-pyrazol-1-yl)pyridin-2-ol, (S)-6-(1-((2-amino-6-fluoroquinolin-3-yl)oxy)ethyl)-5-(1H-pyrazol-1-yl)pyridin-2(1H)-one and a combination thereof.

32. The method of claim 28, wherein the at least one additional therapeutically active treatment modality is selected from the group consisting of supplemental oxygen, blood transfusion, optionally with iron chelation, bone marrow transplant, gene therapy, a gene editing therapy by CRISPR or a zinc finger technique and a combination thereof.

33. The method of any one of claims 28-32, wherein the administration of the at least one additional therapeutically active compound or treatment modality, which is effective in treating and/or preventing at least one sign and/or symptom of SCD, is simultaneous, sequential or separate from the administration of the therapeutically effective amount of the anti-E-selectin antibody, or antigen-binding fragment thereof.

34. A kit for the treatment of SCD, comprising a therapeutically effective amount of an anti-E-selectin antibody of any one of claims 1-13.

35. The kit of claim 34, further comprising a synergistic therapeutically effective amount of an at least one additional therapeutically active compound or treatment modality which is effective in treating and/or preventing at least one sign and/or symptom of SCD.

36. ~~An antibody, or antigen-binding fragment thereof, of any one of claims 1-13, or the pharmaceutical composition of claims 20 or 21 for use in treating and/or preventing a disease, disorder or condition associated with, or mediated by, E-selectin expression and/or E-selectin binding to a ligand.~~

37. ~~The antibody, or antigen-binding fragment thereof, or the pharmaceutical composition for use of claim 36, wherein the disease, disorder or condition is SCD.~~

38. ~~Use of an antibody, or antigen-binding fragment thereof, of any one of claims 1-13 in the manufacture of a medicament for treating and/or preventing a disease, disorder or condition associated with, or mediated by, E-selectin expression and/or E-selectin binding to a ligand.~~

39. ~~The use of claim 38, wherein the disease, disorder or condition is SCD.~~

40. ~~The antibody or antigen-binding fragment thereof according to any of claims 1-13, or the pharmaceutical composition of claims 20 or 21 for use in reducing E-selectin activity in a subject in need thereof, for treatment of SCD.~~

CLAIMS

We claim:

1. An isolated antibody that specifically binds to human E-selectin, comprising at least one of the following:

- (a) a light chain complementarity determining region 1 (LCDR-1) comprising the amino acid sequence of SEQ ID NO:2, a LCDR-2 comprising the amino acid sequence of SEQ ID NO:3, a LCDR-3 comprising the amino acid sequence of SEQ ID NO:4, a heavy chain complementarity determining region 1 (HCDR-1) comprising the amino acid sequence of SEQ ID NO:8, a HCDR-2 comprising the amino acid sequence of SEQ ID NO:9, and a HCDR-3 comprising the amino acid sequence of SEQ ID NO:10;
- (b) the HCDR-1, HCDR-2, and HCDR-3 amino acid sequences as set forth in the amino acid sequence of SEQ ID NO:11, and the LCDR-1, LCDR-2, and LCDR-3 amino acid sequences as set forth in the amino acid sequence of SEQ ID NO:5;
- (c) the LCDR-1, LCDR-2, and LCDR-3 amino acid sequences as set forth in the amino acid sequence encoded by the insert of the plasmid deposited at the ATCC and having ATCC Accession No. PTA-126530, and HCDR-1, HCDR-2, and HCDR-3 amino acid sequences as set forth in the amino acid sequence encoded by the insert of the plasmid deposited at the ATCC and having ATCC Accession No. PTA-126529;
- (d) a heavy chain variable domain (VH) comprising an amino acid sequence at least 98% identical to the amino acid sequence of SEQ ID NO:11, and a light chain variable domain (VL) comprising an amino acid sequence at least 98% identical to the amino acid sequence of SEQ ID NO:5;
- (e) a VH comprising the amino acid sequence of SEQ ID NO:11 and a VL comprising the amino acid sequence of SEQ ID NO:5;
- (f) a VH comprising the amino acid sequence as set forth in the amino acid sequence encoded by the insert of the plasmid deposited at the ATCC and having ATCC Accession No. PTA-126529 and a VL comprising the amino acid sequence as set forth in the amino acid sequence encoded by the insert of the plasmid deposited at the ATCC and having ATCC Accession No. PTA-126530;
- (g) a heavy chain (HC) comprising an amino acid sequence at least 98% identical to the amino acid sequence of SEQ ID NO:7 or SEQ ID NO:13, and a light chain (LC) comprising an amino acid sequence at least 98% identical to the amino acid sequence of SEQ ID NO:1;
- (h) a HC comprising the amino acid sequence of SEQ ID NO:7 or SEQ ID NO:13, and a

LC comprising the amino acid sequence of SEQ ID NO:1; and

- (i) a HC comprising the amino acid sequence as set forth in the amino acid sequence encoded by the insert of the plasmid deposited at the ATCC and having ATCC Accession No. PTA-126529 and a LC comprising the amino acid sequence as set forth in the amino acid sequence encoded by the insert of the plasmid deposited at the ATCC and having ATCC Accession No. PTA-126530.

2. An isolated antibody that specifically binds to human E-selectin, comprising:
a VL amino acid sequence comprising a LCDR-1, a LCDR-2 and a LCDR-3 of the amino acid sequence of SEQ ID NO:5; and
a VH amino acid sequence comprising a HCDR-1, a HCDR-2 and a HCDR-3 of the amino acid sequence of SEQ ID NO:11.

3. The isolated antibody of claim 2, comprising an antibody heavy chain constant region (CH) comprising the amino acid sequence of SEQ ID NO:15 or SEQ ID NO:16, and an antibody light chain constant region (CL) comprising the amino acid sequence of SEQ ID NO:14.

4. An isolated antibody that specifically binds to human E-selectin, comprising a LC comprising of the amino acid sequence of SEQ ID NO:1, and a HC comprising of the amino acid sequence of SEQ ID NO:7 or SEQ ID NO:13.

5. An isolated antibody that specifically binds human E-selectin, comprising
an antibody VL comprising an amino acid sequence at least 98% identical to the amino acid sequence of SEQ ID NO:5 and comprising a LCDR-1 consisting of the amino acid sequence of SEQ ID NO:2, a LCDR-2 consisting of the amino acid sequence of SEQ ID NO:3, and a LCDR-3 consisting of the amino acid sequence of SEQ ID NO:4; and
an antibody VH comprising an amino acid sequence at least 98% identical to the amino acid sequence of SEQ ID NO:11 and comprising a HCDR-1 consisting of the amino acid sequence of SEQ ID NO:8, a HCDR-2 consisting of the amino acid sequence of SEQ ID NO:9, and a HCDR-3 consisting of the amino acid sequence of SEQ ID NO:10.

6. An isolated antibody that specifically binds to human E-selectin, comprising an antibody HC comprising an amino acid sequence encoded by the insert deposited with the ATCC and having the Accession Number PTA-126529, and an antibody LC comprising an amino acid

sequence encoded by the insert deposited with the ATCC and having the Accession Number PTA-126530.

7. The isolated antibody of any one of claims 1-6, comprising a human Fc domain selected from the group consisting of an Fc domain of IgA₁, IgA₂, IgD, IgE, IgM, IgG₁, IgG₂, IgG₃, or IgG₄, a light chain constant region chosen from kappa or lambda, and a combination thereof.

8. The isolated antibody of any one of claims 1-7, wherein the antibody heavy chain isotype is IgG1, wherein the light chain constant region is a kappa light chain, or both.

9. The isolated antibody of any one of claims 1-8, wherein the antibody binds human or cynomolgus monkey E-selectin with a K_D of about 200 nM to about 2 nM.

10. The isolated antibody of any one of claims 1-9 that specifically binds human E-selectin and demonstrates at least one detectable characteristic selected from the following:

- (i) binds to human E-selectin with a K_D of 200 nM or less, as measured optionally by SPR;
- (ii) binds to cynomolgus monkey E-selectin with a K_D of 200 nM or less, as measured optionally by SPR;
- (iii) binds with an EC₅₀ of 50 nM or less to cell-surface expressed E-selectin, as measured optionally by FAC;
- (iv) binds with an EC₅₀ of 2 nM or less to soluble human E-selectin, as measured optionally by ELISA;
- (v) neutralizes binding with an EC₅₀ of 2 nM or less of a sialyl-Lewis A ligand to soluble human E-selectin, as measured optionally by an AlphaLISA competition assay;
- (vi) binds with an IC₅₀ of about 1 nM to about 3 nM to free soluble human E-selectin in human serum;
- (vii) neutralizes binding with an IC₅₀ of 100 nM or less of a sialyl-Lewis A ligand to soluble human E-selectin, as measured optionally by competition ELISA under static conditions;
- (viii) neutralizes binding with an IC₅₀ of 50 nM or less of a sialyl-Lewis A ligand to cell-surface expressed human E-selectin, as measured optionally by competition ELISA under static conditions;

- (ix) inhibits adhesion with an IC₅₀ of 100 nM or less of cells expressing an E-selectin ligand to cell-surface expressed human E-selectin, as measured optionally under static conditions;
- (x) inhibits adhesion with an IC₅₀ of 100 nM or less of cells expressing an E-selectin ligand to cell-surface expressed human E-selectin, as measured optionally under physiological flow conditions;
- (xi) inhibits adhesion with an IC₅₀ of about 6.17 nM to about 18.66 nM of blood cells from Sickle Cell disease (SCD) patients to soluble human E-selectin, as measured optionally under physiologic flow conditions;
- (xii) binds to at least one amino acid residue of human E-selectin selected from: T7, E8, A9, M10, T11, P46, S47, Y48, N82, N83, Q85, E88, E92, Y94, R97, N105, E107, R108, S110, K111, K112 and K113;
- (xiii) has a mean half-life of about 14.4 days (345 hours) following IV administration at a dose of 10 mg/kg;
- (xiv) has a mean half-life of about 21.5 days (518 hours) following SC administration at a dose of about 3 mg/kg;
- (xv) has a viscosity of 33.4 cP at 185.7 mg/mL when measured at 25°C by, optionally an Anton Parr method;
- (xvi) exhibits commercially suitable formulation properties, including a high degree of thermal stability and minimal aggregation at high concentration; and
- (xvii) exhibits reproducible expression and purity under large-scale manufacturing conditions.

11. An isolated antibody that competes for binding to human E-selectin with at least one antibody of any one of claims 1-10.

12. An isolated nucleic acid molecule encoding the antibody of any one of claims 1-11.

13. An isolated nucleic acid molecule comprising at least one of the following:

- a) a nucleic acid encoding the VH, VL or both of an antibody that specifically binds human E-selectin, wherein the nucleic acid comprises the nucleic acid sequence of SEQ ID NO:136, the nucleic acid sequence of SEQ ID NO:137, or both;
- b) a nucleic acid encoding the HC, LC or both of an antibody that specifically binds

- human E-selectin, wherein the nucleic acid comprises the nucleic acid sequence of SEQ ID NO: 138 or SEQ ID NO:206, the nucleic acid sequence of SEQ ID NO:139, or both; and
- c) a nucleic acid encoding the VH, VL or both of an antibody that specifically binds human E-selectin, wherein the nucleic acid comprises the nucleic acid sequence of the insert of the plasmid deposited with the ATCC and having the Accession Number PTA-126529, the nucleic acid sequence of the insert of the plasmid deposited with the ATCC and having the Accession Number PTA-126530, or both.
14. A vector comprising the nucleic acid of claim 12 or 13.
15. A host cell comprising the vector of claim 14.
16. The host cell of claim 15, wherein said host cell is a mammalian cell selected from the group consisting of a CHO cell, a COS cell, a HEK-293 cell, an NS0 cell, a PER.C6 cell, or an Sp2.0 cell.
17. A method of making an antibody comprising culturing the host cell of claim 15 or 16 under a condition wherein the antibody is expressed by the host cell.
18. A pharmaceutical composition comprising an antibody of any one of claims 1-11, and a pharmaceutically acceptable carrier or excipient.
19. The pharmaceutical composition of claim 18, comprising i) an antibody comprising an antibody HC comprising the amino acid sequence of SEQ ID NO:7 and an antibody LC comprising the amino acid sequence of SEQ ID NO:1, ii) an antibody comprising an antibody HC comprising the amino acid sequence of SEQ ID NO:13 and an antibody LC comprising the amino acid sequence of SEQ ID NO:1, or iii) both i) and ii).
20. An antibody of any one of claims 1-11, or the pharmaceutical composition of claim 18 or 19, for use in the treatment of a medical condition, disease or disorder mediated by or associated with expression of E-selectin, binding of E-selectin to a ligand, or both in a subject in

need thereof.

21. The antibody or pharmaceutical composition of claim 20, wherein the medical condition, disease or disorder is SCD.

22. An antibody of any one of claims 1-11 or the pharmaceutical composition of claim 18 or 19 that specifically binds to E-selectin for use in the treatment of SCD, in a subject in need thereof, wherein the use comprises the treatment, the prevention and/or the amelioration of at least one sign or symptom of SCD selected from the group consisting of those affecting the cardiothoracic system, the nervous system, the reticuloendothelial system, the musculoskeletal system, the urogenital system, the gastrointestinal system and a combination thereof.

23. The antibody or pharmaceutical composition of claim 22, wherein the at least one sign or symptom of SCD affecting the cardiothoracic system is selected from the group consisting of chronic restrictive lung disease, left ventricular diastolic disease, pulmonary hypertension, acute chest syndrome, dysrhythmias, sudden death, vaso-occlusive crisis (VOC) and a combination thereof.

24. The antibody or pharmaceutical composition of claim 23, wherein treatment of VOC includes i) treatment of acute VOC by decreasing the duration of the VOC, the intensity of the VOC, or both ii) prevention or reduction in the occurrence of VOC or iii) both i) and ii).

25. An antibody of any one of claims 1-11 or the pharmaceutical composition of claim 18 or 19 that specifically binds human E-selectin for use in decreasing an E-selectin biological activity in a subject in need thereof.

26. The antibody or pharmaceutical composition of claim 25, wherein the antibody decreases at least one detectable E-selectin biological activity and wherein the decreased activity is selected from the group consisting of (a) leukocyte tethering to endothelial cells; (b) activation of stable adhesion to endothelial cells; (c) slow rolling of leukocytes to arrest; (d) efficient trans-endothelial migration of leukocytes; (e) affinity and avidity of E-selectin to CD18 integrins; (f) trafficking of leukocytes to sites of acute inflammation; (g) cytosolic calcium; (h) tyrosine phosphorylation that activates p38 MAP kinase and Syk kinase; (i) recruitment of platelets and leukocytes from the blood to the vascular endothelium; (j) creation of a pro-

inflammatory environment and (k) a combination thereof.

27. The antibody or pharmaceutical composition of any one of claims 20-26, comprising use with a therapeutically effective amount of at least one additional therapeutically active compound or treatment modality which additional compound and modality is effective in the treatment of at least one sign or symptom of SCD.

28. The antibody or pharmaceutical composition of claim 27, wherein the at least one additional therapeutically active compound is selected from the group consisting of penicillin prophylaxis, hydroxyurea (DROXIA, HYDREA), L-glutamine (ENDARI), crizanlizumab (ADAKVEO), voxelotor (OXBRYTA), apixaban (ELIQUIS), rivaroxaban (XARELTO), a non-steroidal anti-inflammatory drug, an analgesic, IW-1701, riociguat (ADEMPAS), ticagrelor (BRILINTA), memantine (NAMENDA), and a combination thereof.

29. The antibody or pharmaceutical composition of claim 27, wherein the at least one additional therapeutically active compound is selected from the group consisting of an anti-P-selectin antibody, a compound that modulates HbS so as to maintain it in its R state, a compound that modulates oxygen affinity of HbS, a compound that targets HbS polymerization by modulating generation of 2,3-disphosphoglyceric acid, a compound that targets HbS polymerization by inducing expression of fetal hemoglobin (HbF), a compound that targets dysfunctional cellular adhesion, vascular dysfunction and/or inflammation, a compound that increases levels of nitric oxide (NO) in the blood as compared with the level of NO before administration of the compound, intravenous IG, a compound that targets hypercoagulability, a compound that blocks NMDA receptor binding and a combination thereof.

30. The antibody or pharmaceutical composition of claim 27, wherein the at least one additional therapeutically active treatment modality is selected from the group consisting of supplemental oxygen, blood transfusion, iron chelation, bone marrow transplant, gene therapy, a gene editing therapy by CRISPR or a zinc finger technique and a combination thereof.

31. A kit for the treatment of SCD, comprising a therapeutically effective amount of an anti-E-selectin antibody of any one of claims 1-11.

32. The kit of claim 31, further comprising a therapeutically effective amount of an at least

one additional therapeutically active compound or treatment modality which is effective in the treatment and/or the prevention of at least one sign or symptom of SCD.

33. Use of an antibody of any one of claims 1-11 in the manufacture of a medicament for the treatment and/or prevention of a disease, disorder or condition associated with, or mediated by, E-selectin expression, E-selectin binding to a ligand or both.

34. The use of claim 33, wherein the disease, disorder or condition is SCD.

35. The antibody according to any of claims 1-11, or the pharmaceutical composition of claims 18 or 19 for use in reducing E-selectin activity in a subject in need thereof for treatment of SCD.