

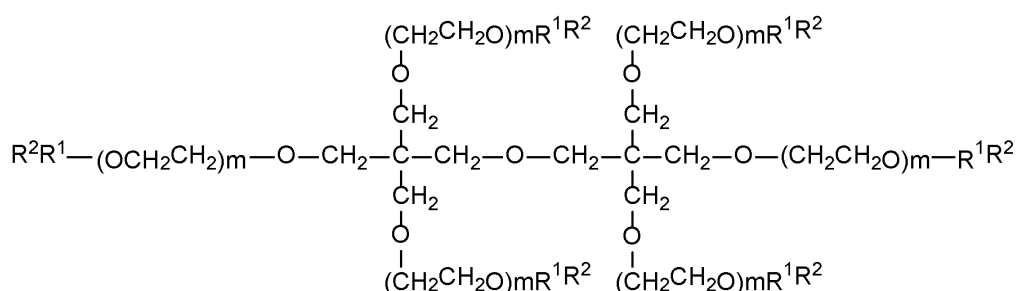
WHAT IS CLAIMED IS:

1. An isolated antibody or antigen-binding fragment thereof that specifically binds to Tie2, wherein the antibody or fragment thereof comprises:
a heavy chain variable domain (VH) comprising (a) CDR-H1 comprising the amino acid
5 sequence NTDIS (SEQ ID NO:3), (b) CDR-H2 comprising the amino acid sequence
RISPSDGNTYYADSVKG (SEQ ID NO:4), and (c) CDR-H3 comprising the amino acid
sequence RTRWASX1AX2DY (SEQ ID NO:5), where X1 is M, L, K, F, Y, R, N, Q, H or W
and/or or X2 is F, Y L, Q, I, K, or H, and a light chain variable domain (VL) comprising (d)
CDR-L1 comprising the amino acid sequence RASQDVSTAVA (SEQ ID NO:8), (e) CDR-L2
10 comprising the amino acid sequence SASFLYS (SEQ ID NO:9), and (f) CDR-L3 comprising
the amino acid sequence QQSYTTPPT (SEQ ID NO:10).
2. The antibody or antigen-binding fragment thereof according to claim 1, wherein the
CDR-H3 comprises the amino acid sequence RTRWASWAMDY (SEQ ID NO:6).
3. The antibody or antigen-binding fragment thereof according to claim 1 or 2, wherein
15 the CDR-H3 comprises the amino acid sequence RTRWASWAFDY (SEQ ID NO:7).
4. The antibody or antigen-binding fragment thereof of any one of the preceding claims,
which is a monoclonal antibody, a humanized antibody, an antibody fragment, and/or a
chimeric antibody.
5. The antibody or antigen-binding fragment thereof of any one of the preceding claims,
20 which is a Fab fragment that binds Tie2.
6. The antibody or antigen-binding fragment thereof of any one of claims 1 to 5,
comprising a VL domain comprising an amino acid sequence having at least 90% sequence
identity to the amino acid sequence of SEQ ID NO:21 and a VH domain comprising an amino
acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID
25 NO:20.
7. The antibody or antigen-binding fragment thereof of any one of claims 1 to 6,
comprising a VL domain comprising an amino acid sequence having at least 99% sequence
identity to the amino acid sequence of SEQ ID NO:21 and a VH domain comprising an amino
acid sequence having at least 99% sequence identity to the amino acid sequence of SEQ ID
30 NO:20.
8. The antibody or antigen-binding fragment thereof of any one of the preceding claims,
wherein the antibody comprises the VL sequence of SEQ ID NO:21 and a VH sequence of
SEQ ID NO:20.

9. The antibody or antigen-binding fragment thereof of any one of claims 1 to 8, wherein the antibody comprises an engineered cysteine, wherein
- the engineered cysteine is selected from a T120C, G166C, G178C, T187C, and T209C in the HC; or
- 5 the engineered cysteine is selected from Q124C, R142C, Q155C, L201C, T206C, K107C, K126C, and K149C in the LC;
- wherein the residue number of the engineered cysteine is according to EU numbering.
10. The antibody or antigen-binding fragment thereof of claim 9, wherein the engineered cysteine is selected from T209C in the HC and T206C in the LC.
- 10 11. The antibody or antigen-binding fragment thereof of claim 9 or 10, wherein the engineered cysteine is T206C in the LC.
12. The antibody or antigen-binding fragment thereof of claim 9 or 10, wherein the engineered cysteine is T209C in the HC.
13. The antibody or antigen-binding fragment thereof of any one of the preceding claims,
- 15 comprising a LC comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:25 and a HC comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:55.
14. The antibody or antigen-binding fragment thereof of any one of the preceding claims, comprising a LC comprising an amino acid sequence having at least 99% sequence identity to
- 20 the amino acid sequence of SEQ ID NO:25 and a HC comprising an amino acid sequence having at least 99% sequence identity to the amino acid sequence of SEQ ID NO:55.
15. The antibody or antigen-binding fragment thereof of any one of the preceding claims, wherein the antibody comprises a LC comprising the sequence of SEQ ID NO:25 and a HC comprising the sequence of SEQ ID NO:55.
- 25 16. The antibody or antigen-binding fragment thereof of any one of the preceding claims, wherein the HC constant regions terminates at position 221 (EU numbering).
17. An antibody or antigen-binding fragment thereof that specifically binds to Tie-2 wherein the antibody comprises a HC sequence of SEQ ID NO:55 and a LC sequence of SEQ ID NO:25.
- 30 18. An antibody or antigen-binding fragment thereof that specifically binds to Tie-2 wherein the antibody comprises a HC sequence of SEQ ID NO:23 and a LC sequence of SEQ ID NO:56.
19. An isolated nucleic acid encoding the antibody or antigen-binding fragment thereof of any of the preceding claims.

20. A host cell comprising the nucleic acid of claim 19.
21. A conjugate that binds to Tie2, wherein the conjugate comprises at least two, at least three, at least four, at least five, at least six, at least seven, or at least eight antibodies or antigen-binding fragment thereof according to any one of claims 1 to 18, wherein each of the
- 5 antibodies or antigen-binding fragment thereof is linked to a multimerizing moiety.
22. The conjugate of claim 21, wherein the conjugate causes a reduction in Tie2 protein levels in an in vitro assay by less than 25%, less than 50% or less than 75%.
23. The conjugate of claim 21 or 22, wherein the conjugate does not cause a reduction in Tie-2 protein levels in an in vitro assay by more than 25%, more than 50%, or more than 75%.
- 10 24. The conjugate of any one of claims 21 to 23, wherein the multimerizing moiety comprises a polyol, a polypeptide, and/or a peptide.
25. The conjugate of any one of claims 21 to 24, wherein the multimerizing moiety comprising a polyol, wherein the polyol is a multi-armed polyol, selected from a dimer, a tetramer, a hexamer, and an octamer.
- 15 26. The conjugate of claim 25, wherein the multi-armed polyol is a hexamer.
27. The conjugate of any one of claims 24 to 26, wherein the polyol is a polyethylene glycol (PEG).
28. The conjugate of any one of claims 24 to 27, wherein the polyol is covalently linked to the at least two antibodies or antigen-binding fragment thereof through a free sulfhydryl group
- 20 of an engineered cysteine amino acid, wherein the engineered cysteine is selected from the group consisting of
- T120C, G166C, G178C, T187C, and T209C in the HC; or
- the engineered cysteine is selected from the group consisting of Q124C, R142C, Q155C, L201C, T206C, K107C, K126C, and K149C in the LC;
- 25 wherein the residue number is according to EU numbering.
29. The conjugate of claim 28, wherein the engineered cysteine is T206C in the LC, wherein the residue number is according to EU numbering.
30. The conjugate of claim 28, wherein the engineered cysteine is T209C in the HC, wherein the residue number is according to EU numbering.
- 30 31. The conjugate of any one of claims 25 to 27, wherein the polyol is covalently linked to the at least one antibody through a free amino group of a lysine amino acid.
32. The conjugate according to any one of claims 27 to 31, wherein the PEG has a weight average molecular weight of from about 500 Daltons (Da) to about 300,000 Da.

33. The conjugate according to any one of claims 27 to 32, wherein the PEG has the structure of general formula (Ib):

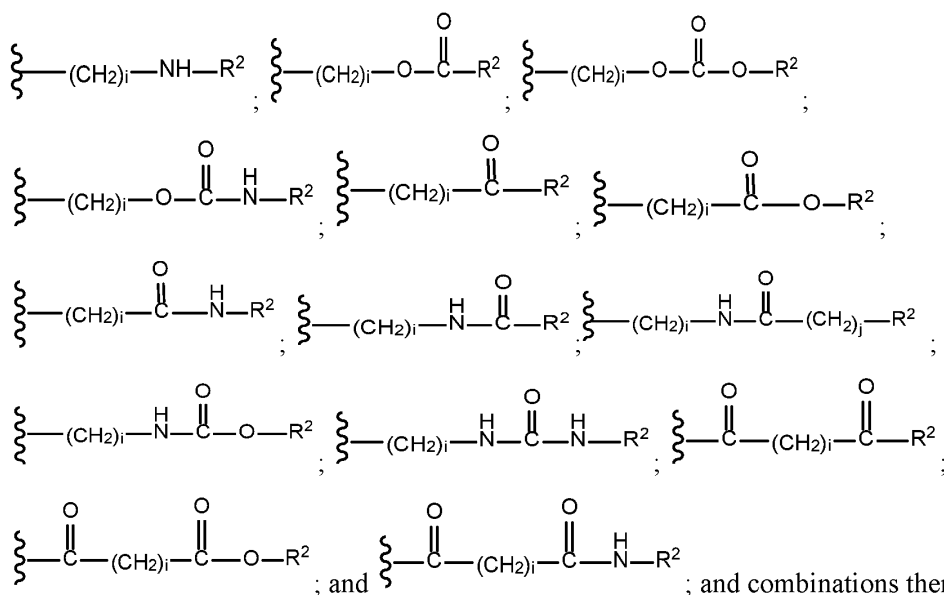


where each m is independently an integer from 3-250; each R^1 is independently either
 5 absent or is a linking group; and each R^2 is independently either hydrogen or a terminal reactive group;

where at least one R^2 is a terminal reactive group and is covalently linked to the antibody or antigen-binding fragment thereof of any one of claims 1 to 14.

34. The conjugate according to claim 33, wherein at least one R^1 is a linking group,

10 wherein R^1 and R^2 when taken together are selected from: $\text{---}(\text{CH}_2)\text{---R}^2$;



wherein each i is independently an integer of 0-10; j is an integer of 0-10; and R^2 is a terminal reactive group selected from the group consisting of a thiol reactive group, an amino reactive group, and combinations thereof.

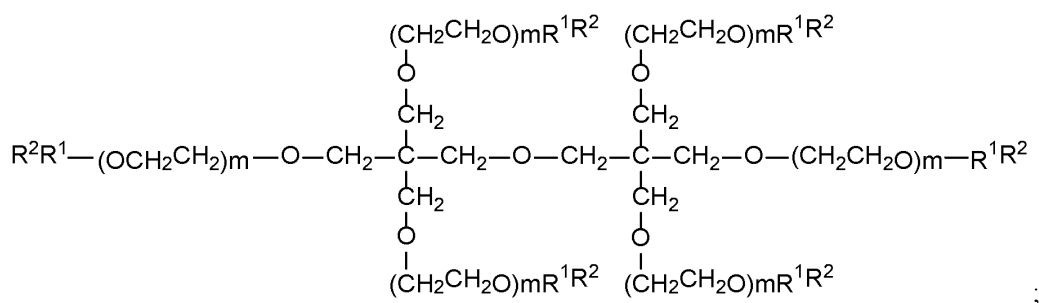
35. The conjugate according to claim 33 or claim 34, wherein at least 1 R^2 is a maleamide
 20 and is covalently linked to the antibody or antigen-binding fragment thereof.

36. The conjugate according to any one of claims 33 to 35, wherein each R² is a maleamide.

37. A conjugate which binds Tie2 comprising:

a Fab comprising a HC having SEQ ID NO:55 and a LC having SEQ ID NO:25;

5 conjugated to a polyol which has the structure of Formula 1(b)



where each m is independently an integer from 20-30, where R¹ and R² taken together

has the structure $\text{S}-(\text{CH}_2)_l-\text{N}-\overset{\text{O}}{\parallel}{\text{C}}-(\text{CH}_2)_j-\text{R}^2$, where R² is a maleamide; and

wherein the polyol is linked to the Fab HC at residue C209 (EU numbering).

10 38. A pharmaceutical composition comprising the conjugate according to any one of claims 21 to 37 and a pharmaceutically acceptable carrier.

39. The pharmaceutical composition of claim 38, further comprising an additional therapeutic agent, wherein the additional therapeutic agent is selected from the group consisting of a VEGF antagonist, an Ang2 antagonist, an HtrA1 antagonist, and IL33

15 antagonist, a complement component antagonist, and a second Tie2 agonist.

40. A long acting delivery device for ocular delivery comprising the pharmaceutical composition of claim 38 or 39 and a means for delivering the composition intravitreally to a patient, wherein the composition remains effective on site for a prolonged period of time.

41. A method of treating a Tie2 pathway-mediated disorder in a subject in need thereof, comprising administering to the subject an effective amount of the antibody or antigen-binding fragment thereof of any one of claims 1 to 18, the conjugate of any one of claims 21 to 36, or the pharmaceutical composition of any one of claims 37 to 38.

42. The method of claim 41, wherein the Tie2 pathway-mediated disorder is a vascular permeability disorder.

25 43. The method of claim 41 or 42, wherein the Tie2 pathway-mediated disorder is an eye condition.

44. The method of claim 43, wherein the eye condition is selected from diabetic macular edema (DME), diabetic retinopathy, age-related macular degeneration (AMD), including dry and wet (non-exudative and exudative) forms, choroidal neovascularization (CNV), uveitis, ischemia-related retinopathy, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, glaucoma, and retinal neovascularization.
45. The method of claim 43 or 44, wherein the eye condition is DME.
46. The antibody of any one of claims 1 to 18 or the conjugate of any one of claims 21 to 39 for use as a medicament.
47. The antibody of any one of claims 1 to 18 or the conjugate of any one of claims 21 to 39 for use in treating a Tie2 pathway-mediated disorder and/or an ocular disorder in a subject in need thereof.
48. Use of the antibody of any one of claims 1 to 18 or the conjugate of any one of claims 21 to 39 in the manufacture of a medicament for the treatment of a Tie2 pathway-mediated disorder and/or an ocular disorder in a subject in need thereof.