WE CLAIM

1. A tetravalent binding antibody molecule comprising:

(a) an Fc domain or fragment thereof comprising a constant heavy chain domain 3 (CH3),

(b) a bivalent low-density lipoprotein receptor-related protein 5 (LRP5) binding domain and

(c) a bivalent Frizzled (FZD) binding domain,

wherein the LRP5 binding domain is attached to one terminus of the Fc domain and the FZD binding domain is attached to the other end of the Fc domain,

wherein the LRP5 binding domain comprises a diabody that binds LRP5 and the FZD binding domain comprises two scFv or two Fab that bind FZD4.

2. The tetravalent binding antibody molecule of claim 1, wherein

(a) the LRP5 binding domain diabody is attached to the N-terminal of the Fc domain, and

(b) the FZD4 binding domain is attached to the C-terminal of the Fc domain.

3. The tetravalent binding antibody molecule of claim 2, wherein

(a) the LRP5 binding domain diabody is attached to the N-terminal of the Fc domain via a VL or VH of the diabody, and

(b) the FZD binding domain comprises two FZD binding Fabs fused to the C-terminal of the Fc, wherein each Fab is attached to the Fc domain via a heavy or light chain variable domain (VH or VL) of the Fab linked to the CH3 domain of the Fc domain.

4. A tetravalent binding antibody molecule comprising an N-terminal LRP5-binding diabody and a C-terminal domain comprising two FZD4-binding scFv, the tetravalent binding antibody molecule comprising

a dimer of a first and second monomer, wherein each monomer comprises a single-chain polypeptide comprising, from N-terminus to C-terminus:

(a) a first peptide, said first peptide comprising a first heavy chain variable domain (VH) and a first light chain variable (VL) domain that bind LRP5,

(b) an Fc region, or fragment thereof comprising a constant heavy chain domain 3 (CH3), and

(c) a second peptide, said second peptide comprising a second VL and a second VH that bind a FZD4, and

~~a first and second light chain monomer, each light chain monomer comprising from N terminus to C terminus a VL that binds the FZD4, linked to a constant light chain domain 1 (CL1 domain),~~

wherein the first and second monomers dimerize via the Fc regions or fragments thereof, the first VH and VL of each monomer pairs with the first VH and VL of the other monomer forming a diabody that binds LRP5 and the second VL and VH of each monomer pair to form a scFvs that bind FZD4, and

wherein the LRP5-binding diabody forms the N-terminal LRP5-binding domain of the tetravalent binding antibody molecule and the two FZD4-binding scFvs form the C-terminal FZD-binding domain of the tetravalent binding antibody molecule.

5. A tetravalent binding antibody molecule comprising an N-terminal LRP5-binding diabody and a C-terminal domain comprising two FZD4-binding Fab, the tetravalent binding antibody molecule comprising

(1) a first and second heavy chain monomer, wherein each heavy chain monomer comprises a single-chain polypeptide comprising, from N-terminus to C-terminus:

(a) a peptide comprising a heavy chain variable (VH) domain that binds a LRP5 co-receptor and a light chain variable (VL) domain that binds a LRP5 co-receptor, linked to,

(b) an Fc region, or fragment thereof comprising a constant heavy chain domain 3 (CH3), linked to

(c) a VH domain that binds FZD4, linked to

(d) a CH1 domain, and

(2) a first and second light chain monomer each light chain monomer comprising from N-terminus to C-terminus a VL domain that binds FZD4, and a constant light chain domain 1 (CL1)

wherein a linker between the VH and VL that binds the LRP5 is of a length that promotes the pairing of the VH and VL of the first heavy chain monomer with the VL and VH of the second heavy chain monomer thereby forming a LRP5 co-receptor binding diabody and the FZD-binding Fabs are formed by the pairing of each heavy chain monomer with a light chain monomer such that the VH that binds FZD4 and CH1 of each of the heavy chain monomer, pairs with the VL that binds FZD4 and CL1 of the light chain monomers, and

wherein the LRP5-binding diabody forms the N-terminal LRP5-binding domain of the tetravalent binding antibody molecule and the two FZD4-binding Fabs form the C-terminal FZD-binding domain of the tetravalent binding antibody molecule.

~~5. The tetravalent binding antibody molecule of claim 1, wherein the FZD binding domain is attached to the N-terminal of the Fc domain and the LRP5 binding domain is attached to the C-terminal of the Fc domain.~~

~~6. The tetravalent binding antibody molecule of claim 5, wherein~~

~~(a) the FZD binding domain comprises two Fabs that bind the FZD4, wherein each Fab is attached to N-terminal of the Fc domain via a heavy or light chain variable domain (VH or VL) of the Fab linked to the CH2 domain of the Fc domain, and~~

~~(b) the LRP5 binding domain comprises a diabody or two scFv that bind LRP5, wherein the diabody or two scFv are attached to the C-terminal of the Fc domain via a VL or VH of the diabody or scFv linked to the CH3 of the Fc domain.~~

~~7. A tetravalent binding antibody molecule comprising an Fc domain or fragment thereof comprising a constant heavy chain domain 3 (CH3), an N-terminal FZD4 binding domain~~

~~comprising two FZD4-binding Fabs and a C-terminal LRP5 binding domain comprising a LRP5 binding diabody, the tetravalent binding antibody molecule comprising~~

~~(a) a first and second heavy chain monomer, wherein each heavy chain monomer comprises a single-chain polypeptide comprising from N-terminus to C-terminus:~~

~~(i) a heavy chain variable domain (VH) that binds FZD4, linked to~~

~~(ii) a heavy chain constant region domain 1 (CH1 domain), linked to~~

~~(iii) the CH2 domain of the Fc region linked to~~

~~(iv) a peptide comprising a VH that binds a LRP5 co-receptor, linked to a light chain variable domain (VL) that binds a LRP5 co-receptor, and~~

~~(b) a first and second light chain monomer, each light chain monomer comprising from N terminus to C terminus a VL that binds the FZD4, linked to a constant light chain domain 1 (CL1 domain),~~

~~wherein the first and second heavy chain monomers dimerize via their Fc regions, or fragments thereof,~~

~~wherein a linker between the VH and VL that binds the LRP5 is of a length that promotes the pairing of the VH and VL of the first heavy chain monomer with the VL and VH of the second heavy chain monomer thereby forming a LRP5 co-receptor binding diabody and the FZD-binding Fabs are formed by the pairing of each heavy chain monomer with a light chain monomer such that the VH that binds FZD4 and CH1 of each of the heavy chain monomer, pairs with the VL that binds FZD4 and CL1 of the light chain monomers, and~~

~~wherein the Fabs form the FZD4-binding domain on the N-terminus of the Fc domain and the diabody forms the LRP5 co-receptor-binding domain on the C-terminus of the Fc domain.~~

~~8~~6. The tetravalent binding antibody molecule of any one of claims 1 to ~~7~~5, wherein the LRP5 binding diabody is a bispecific bivalent LRP5 binding domain that binds to two epitopes within the LRP5 co-receptor extracellular domain, preferably ~~.~~

~~9. The tetravalent binding antibody molecule of claim 8~~ wherein the LPR5 binding domain interacts with the Wnt1 and Wnt3 epitopes of the LRP5 co-receptor.

~~10~~7. The tetravalent binding antibody molecule of any one of claims 1 to ~~9~~6, wherein the FZD binding domain is monospecific.

~~11~~8. The tetravalent binding antibody molecule of any one of claims 1 to ~~10~~7, wherein

the diabody of the LRP5 binding domain binds LRP5 and comprises heavy chain complementary determining regions CDR-H1, CDR-H2 and CDR-H3 and light chain complementary determining regions CDR-L1, CDR-L2 and CDR-L3, of an antibody set forth in the sequences in Table 3 or Table 6A.

~~12~~9. The tetravalent binding antibody molecule of any one of claims 1 to ~~11~~ 8 wherein the Fc domain or fragment thereof dimerize via a knob-in-hole configuration of the Fc regions or fragments thereof.

~~13~~10. The tetravalent binding antibody molecule of claim ~~12~~9, wherein the Fc region of the first heavy chain monomer comprises the mutations T366S, L368A and Y407V, and the Fc region of the second heavy chain monomer comprises the mutation T366W, according to EU numbering.

~~14~~11. The tetravalent binding antibody molecule of claim ~~13~~10, wherein the Fc region of the first heavy chain monomer further comprises the mutations S354I and E357L, and the Fc region of the second heavy chain monomer further comprises the mutations Q347M, Y349F, T350D and L368M, according to EU numbering or~~.~~

~~15. The tetravalent binding antibody molecule of claim 13,~~ wherein an additional disulfide bond is introduced between the Fc region of the first heavy chain monomer and the second heavy chain monomer, preferably wherein the first heavy chain monomer comprises the mutation Y349C and the second heavy chain monomer comprises the mutation S354C, according to EU numbering.

~~16~~12. The tetravalent binding antibody molecule of any one of claims 1 to ~~15~~11, wherein the Fc domain lacks one or more effector functions.

~~17~~13. The tetravalent binding antibody molecule of claim ~~16~~12, wherein the Fc regions contain mutations that alter their effector function due to amino acid mutations, N297G (NG) and/or D265A (DA) variants, according to EU numbering.

~~18~~14. The tetravalent binding antibody molecule of claim ~~16~~12, wherein the Fc regions contain mutations that alter their effector function due to amino acid mutations L234A, L235A and/or P331S, according to EU numbering, such as ~~.~~

~~19. The tetravalent binding antibody molecule of claim 18,~~ wherein the Fc regions contain mutations that alter their effector function due to amino acid mutations L234A and L235A (LALA), preferably ~~.~~

~~20. The tetravalent binding antibody molecule of claim 19,~~ wherein the Fc regions contain mutations that alter their effector function due to amino acid mutations L234A, L235A and P331S (LALAPS).

~~21~~15. The tetravalent binding antibody molecule of any one of claims 1 to ~~20~~14, wherein the LRP5 binding domain and FZD binding domain are each attached to the Fc domain by a linker, preferably ~~.~~

~~22. The tetravalent binding antibody molecule of claim 21,~~ wherein the linker comprises 1 to 100, 1 to 50, 1-30, 1-25, 1- 10, 1-6 amino acids, 1-5 amino acids, or 2-4 amino acids.

~~23~~16. The tetravalent binding antibody molecule of claim ~~21~~ 15~~or 22~~, wherein the diabodies forming the LRP5 co-receptor-binding domain were fused to the Fc domain via a GGGGSGGGGSEPKSSDKTHT (SEQ ID NO: 892) linker.

~~24~~17. The tetravalent binding antibody molecule of ~~any one of claims 21 to 23~~claim 15 or claim 16, wherein the FZD4-binding Fabs are fused to the Fc region via a GGGSGGGSGGGSGGGSGSTG (SEQ ID NO: 891) linker.

~~25~~18. The tetravalent binding antibody molecule of any one of claims 1 to ~~24~~17, wherein the VH that binds the LRP5 co-receptor is linked to the VL that binds a LRP5 co-receptor via a short GGGGS (SEQ ID NO: 886) linker.

~~26~~19. The tetravalent binding antibody molecule of any one of claims 1 to ~~25~~18, wherein the FZD binding domain comprises two Fabs that bind FZD4, preferably ~~.~~

~~27. The tetravalent binding antibody molecule of claim 26,~~ wherein the FZD-binding Fab comprise light chain complementary determining regions CDR-L1, CDR-L2 and CDR-L3 and heavy chain CDRs, CDR-H1, CDR-H2 and CDR-H3 of an antibody set forth in the sequences in Table 1, Table 2 or Table 6.

~~28~~20. The tetravalent binding antibody molecule of any one of claims 1 to ~~4~~ 3 and ~~8~~ 5 to ~~27~~ 19 comprising,

(a) a dimer of a first and second heavy chain monomer, each monomer comprising a single-chain polypeptide comprising, from N-terminus to C-terminus:

(1) a peptide comprising a heavy chain variable domain (VH) that binds LRP5 and a light chain variable domain (VL) that binds LRP5,

(2) an Fc region, or fragment thereof comprising the CH3,

(3) a VH that binds FZD4, and

(4) a constant heavy chain domain 1 (CH1),

wherein

(~~5~~i) the VH that binds LRP5 comprises heavy chain CDRs (CDR-H1, CDR-H2 and CDR-H3), of an antibody set forth in the sequences in Table 3 or Table 6, and

(~~b~~ii) the VL that binds LRP5 comprises light chain CDRs (CDR-L1, CDR-L2 and CDR-L3), of an antibody set forth in the sequences in Table 3 or Table 6,

(~~c~~iii) the VH that binds FZD4, comprises the heavy chain CDRs (CDR-H1, CDR-H2 and CDR-H3), of an antibody set forth in the sequences in Table 1, Table 2 or Table 6, and

(~~d~~b) a third and fourth light chain monomer each comprising a VL that binds FZD4, and a constant light chain domain 1 (CL1), the VL that binds FZD4, comprising the light chain CDRs (CDR-L1, CDR-L2 and CDR-L3), of an antibody set forth in the sequences in Table 1, Table 2 or Table 6,

wherein the first and second heavy chain monomer dimerize via their Fc regions and the VL and VH that bind LRP5 of the first monomer pair with the VH and VL that bind LRP5 of the second monomer forming a bivalent diabody that binds LRP5, and

the CL1 and VLs that bind FZD4, of the third and fourth light chain monomers pair with the CH1 and VHs that bind FZD4, of the first and second heavy chain monomers forming two Fabs that bind FZD4, wherein the diabody forms the N-terminal bivalent LRP5 binding domain and the two Fabs form the C-terminal bivalent FZD4, binding domain.

~~29. The tetravalent binding antibody molecule of any one of claims 5 to 7 comprising,~~

~~(a) a dimer of a first and second heavy chain monomer, each monomer comprising a single-chain polypeptide comprising, from N-terminus to C-terminus:~~

~~(1) a VH that binds FZD4~~

~~(2) an Fc region, or fragment thereof comprising the CH3,~~

~~(3), a peptide comprising a VH that binds LRP5 and a VL that binds LRP5 and~~

~~(4) a constant heavy chain domain 1 (CH1),~~

~~wherein~~

~~(5) the VH that binds LRP5 comprises heavy chain CDRs (CDR-H1, CDR-H2 and CDR-H3), of an antibody set forth in the sequences in Table 3 or Table 6, and~~

~~(b) the VL that binds LRP5 comprises light chain CDRs (CDR-L1, CDR-L2 and CDR-L3), of an antibody set forth in the sequences in Table 3 or Table 6,~~

~~(c) the VH that binds FZD4, comprises the heavy chain CDRs (CDR-H1, CDR-H2 and CDR-H3), of an antibody set forth in the sequences in Table 1, Table 2 or Table 6,~~

~~and~~

~~(d) a third and fourth light chain monomer each comprising from N terminus to C terminus a VL that binds FZD4, and a constant light chain domain 1 (CL1), the VL that binds FZD4, comprising the light chain CDRs (CDR-L1, CDR-L2 and CDR-L3), of an antibody set forth in the sequences in Table 1, Table 2 or Table 6,~~

~~wherein the first and second heavy chain monomer dimerize via their Fc regions and the VL and VH that bind LRP5 of the first monomer pair with the VH and VL that bind LRP5 of the second monomer forming a bivalent diabody that binds LRP5, and~~

~~the CL1 and VLs that bind FZD4, of the third and fourth light chain monomers pair with the CH1 and VHs that bind FZD4, of the first and second heavy chain monomers forming two Fabs that bind FZD4, wherein the diabody forms the C-terminal bivalent LRP5 binding domain and the two Fabs form the N-terminal bivalent FZD4, binding domain.~~

~~30~~21. The tetravalent binding antibody molecule of claim ~~28~~ 20~~or 29~~, wherein the LRP5 binding diabody is bispecific, wherein

the CDRs of the VHs that bind LRP5 of the first heavy chain monomer and the CDRs of the VHs that bind LRP5 of the second heavy chain monomer are non-identical, and

the CDRs of the VLs that bind LRP5 of the first heavy chain monomer and the CDRs of the VLs that bind LRP5 second heavy chain monomer are non-identical.

~~31~~22. The tetravalent binding antibody molecule of claim ~~30~~21, wherein

in the first heavy chain monomer

(a) the CDR-H1 and CDR-H2 of the VH that binds LRP5 comprise respectively FSSSSI (SEQ ID NO: 528) and SISSSYGYTY (SEQ ID NO: 553), or the CDR-H1 and CDR-H2 of the VH that binds LRP5 comprise respectively LSYYYM (SEQ ID NO: 527) and SIYSSYGYTY (SEQ ID NO: 552) and

(b) the CDR-L2 and CDR-L3 of the VL that binds LRP5 comprise respectively SASDLYS (SEQ ID NO: 491) and YAGAGLI (SEQ ID NO: 510), or the CDR-L2 and CDR-L3 of the VL that binds LRP5 comprise respectively SASSLYS (SEQ ID NO: 2) and SSYSLI (SEQ ID NO: 130), and

in the second heavy chain monomer

(c) the CDR-H1 and CDR-H2 of the VH that binds LRP5 comprises respectively FTAYAM (SEQ ID NO: 536) and SIYPSGGYTA (SEQ ID NO: 566), or the CDR-H1 and CDR-H2 of the VH that binds LRP5 comprises respectively FSSSSI (SEQ ID NO: 528) and SISSSYGYTY (SEQ ID NO: 553) and

(d) the CDR-L2 and the CDR-L3 of the VL that binds LRP5 comprises respectively SASSLYS (SEQ ID NO: 2) and YWAYYSPI (SEQ ID NO: 493), or the CDR-L2 and the CDR-L3 of the VL that binds LRP5 comprises respectively SASSLYS (SEQ ID NO: 2) and ASYAPI (SEQ ID NO: 492).

~~32~~23. The tetravalent binding antibody molecule of any one of claims ~~28~~ 20 to ~~31~~22, wherein in the first and second heavy chain monomer the CDR-H1 and CDR-H2 of the VH that binds FZD4 comprises respectively LSSYSM (SEQ ID NO: 24) and YISSYYGYTY (SEQ ID NO: 51), or the CDR-H1 and CDR-H2 of the VH that binds FZD4 comprises respectively LSSYSM (SEQ ID NO: 24) and YISSYDSITD (SEQ ID NO: 61).

~~33~~24. The tetravalent binding antibody molecule of any one of claims ~~28~~ 20 to ~~32~~23, wherein in the third and fourth light chain monomers the CDR-L1 and CDR-L2 of the VL that bind FZD4 comprise respectively SVSSA (SEQ ID NO: 1) and SASSLYS (SEQ ID NO: 2), and the CDR-L3 of the VL that binds FZD4 comprises WYYAPI (SEQ ID NO: 3) or WYNAPI (SEQ ID NO: 12).

~~34~~25. The tetravalent binding antibody molecule of any one of claims ~~28~~20, ~~29, 30~~21, ~~32~~ 23 and ~~33~~24, comprising a bivalent, bispecific LRP5 binding domain, wherein

(a) in the first heavy chain monomer,

the VH that binds LRP-5 comprises CDR-H1 of SEQ ID NO: 528, CDR-H2 of SEQ ID NO: 553 and CDR-H3 of SEQ ID NO: 586, and the VL that binds LRP-5 comprises CDR-L1 of SEQ ID NO: 1, CDR-L2 of SEQ ID NO: 491 and CDR-L3 of SEQ ID NO: 510 of ANT16-Hole of Table 6A, or

the VH that binds LRP-5 comprises CDR-H1 of SEQ ID NO: 527, CDR-H2 of SEQ ID NO: 552 and CDR-H3 of SEQ ID NO: 584 and the VL that binds LRP-5 comprises CDR-L1 of SEQ ID NO: 1, CDR-L2 of SEQ ID NO: 2 and CDR-L3 of SEQ ID NO: 130 of ANT18-Hole of Table 6A, or

the VH that binds LRP-5 comprises CDR-H1 of SEQ ID NO: 527, CDR-H2 of SEQ ID NO: 552 and CDR-H3 of SEQ ID NO: 584 and the VL that binds LRP-5 comprises CDR-L1 of SEQ ID NO: 1, CDR-L2 of SEQ ID NO: 491 and CDR-L3 of SEQ ID NO: 510 of ANT20-Hole of Table 6A, or

the VH that binds LRP-5 comprises CDR-H1 of SEQ ID NO: 528, CDR-H2 of SEQ ID NO: 553 and CDR-H3 of SEQ ID NO: 586 and the VL that binds LRP-5 comprises CDR-L1 of SEQ ID NO: 1, CDR-L2 of SEQ ID NO: 2 and CDR-L3 of SEQ ID NO: 130 of ANT21-Hole of Table 6A, or

the VH that binds LRP-5 comprises CDR-H1 of SEQ ID NO: 527, CDR-H2 of SEQ ID NO: 552 and CDR-H3 of SEQ ID NO: 584 and the VL that binds LRP-5 comprises CDR-L1 of SEQ ID NO: 1, CDR-L2 of SEQ ID NO: 2 and CDR-L3 of SEQ ID NO: 130 of ANT36-Hole of Table 6A, or

the VH that binds LRP-5 comprises CDR-H1 of SEQ ID NO: 528, CDR-H2 of SEQ ID NO: 553 and CDR-H3 of SEQ ID NO: 586 and the VL that binds LRP-5 comprises CDR-L1 of SEQ ID NO: 1, CDR-L2 of SEQ ID NO: 491 and CDR-L3 of SEQ ID NO: 510 of ANT39-Hole of Table 6A,

and

the VH that binds FZD4 comprises the FZD4 VH CDRs CDR-H1 of SEQ ID NO: 24, a CDR-H2 of SEQ ID NO: 51 and a CDR-H3 of SEQ ID NO: 79 of ANT16 Hole of Table 6B, or

the VH that binds FZD4 comprises the FZD4 VH CDRs CDR-H1 of SEQ ID NO: 24, a CDR-H2 of SEQ ID NO: 51 and a CDR-H3 of SEQ ID NO: 79 of ANT18-Hole of Table 6B, or

the VH that binds FZD4 comprises the FZD4 VH CDRs CDR-H1 of SEQ ID NO: 24, a CDR-H2 of SEQ ID NO: 51 and a CDR-H3 of SEQ ID NO: 79 of ANT20-Hole of Table 6B, or

the VH that binds FZD4 comprises the FZD4 VH CDRs CDR-H1 of SEQ ID NO: 24, a CDR-H2 of SEQ ID NO: 51 and a CDR-H3 of SEQ ID NO: 79 of ANT21-Hole of Table 6B, or

the VH that binds FZD4 comprises the FZD4 VH CDRs CDR-H1 of SEQ ID NO: 24, a CDR-H2 of SEQ ID NO: 61 and a CDR-H3 of SEQ ID NO: 90 of ANT36-Hole of Table 6B, or

the VH that binds FZD4 comprises the FZD4 VH CDRs CDR-H1 of SEQ ID NO: 24, a CDR-H2 of SEQ ID NO: 61 and a CDR-H3 of SEQ ID NO: 90 of ANT39-Hole of Table 6B,

wherein the FZD CDR-L1 and CDR-L2 are respectively SVSSA (SEQ ID NO: 1) and SASSLYS (SEQ ID NO: 2), and

(b) in the second heavy chain monomer

the VH that binds LRP5 comprises CDR-H1 of SEQ ID NO: 536, CDR-H2 of SEQ ID NO: 566 and CDR-H3 of SEQ ID NO: 603 and the VL that binds LRP5 comprises CDR-L1 of SEQ ID NO: 1, CDR-L2 of SEQ ID NO: 2 and CDR-L3 of SEQ ID NO: 493 of ANT16-Knob of Table 6A, or

the VH that binds LRP5 comprises CDR-H1 of SEQ ID NO: 528, CDR-H2 of SEQ ID NO: 553 and CDR-H3 of SEQ ID NO: 585 and the VL that binds LRP5 comprises CDR-L1 of SEQ ID NO: 1, CDR-L2 of SEQ ID NO: 2 and CDR-L3 of SEQ ID NO: 492 of ANT18-Knob of Table 6A, or

the VH that binds LRP5 comprises CDR-H1 of SEQ ID NO: 536, CDR-H2 of SEQ ID NO: 566 and CDR-H3 of SEQ ID NO: 603 and the VL that binds LRP5 comprises CDR-L1 of SEQ ID NO: 1, CDR-L2 of SEQ ID NO: 2 and CDR-L3 of SEQ ID NO: 492 of ANT20-Knob of Table 6A, or

the VH that binds LRP5 comprises CDR-H1 of SEQ ID NO: 528, CDR-H2 of SEQ ID NO: 553 and CDR-H3 of SEQ ID NO: 585 and the VL that binds LRP5 comprises CDR-L1 of SEQ ID NO: 1, CDR-L2 of SEQ ID NO: 2 and CDR-L3 of SEQ ID NO: 493 of ANT21-Knob of Table 6A, or

the VH that binds LRP5 comprises CDR-H1 of SEQ ID NO: 528, CDR-H2 of SEQ ID NO: 553 and CDR-H3 of SEQ ID NO: 585 and the VL that binds LRP5 comprises CDR-L1 of SEQ ID NO: 1, CDR-L2 of SEQ ID NO: 2 and CDR-L3 of SEQ ID NO: 492 of ANT36-Knob of Table 6A, or the VH that binds LRP5 comprises CDR-H1 of SEQ ID NO: 536, CDR-H2 of SEQ ID NO: 566 and CDR-H3 of SEQ ID NO: 603 and the VL that binds LRP5 comprises CDR-L1 of SEQ ID NO: 1, CDR-L2 of SEQ ID NO: 2 and CDR-L3 of SEQ ID NO: 493 of ANT39-Knob of Table 6A,

and the VH that binds FZD4 comprises,

FZD4 Fab CDR-H1 of SEQ ID NO: 24, a CDR-H2 of SEQ ID NO: 51 and a CDR-H3 of SEQ ID NO: 79 of ANT16 Knob of Table 6B, or

FZD4 Fab CDR-H1 of SEQ ID NO: 24, a CDR-H2 of SEQ ID NO: 51 and a CDR-H3 of SEQ ID NO: 79 of ANT18 Knob of Table 6B, or

FZD4 Fab CDR-H1 of SEQ ID NO: 24, a CDR-H2 of SEQ ID NO: 51 and a CDR-H3 of SEQ ID NO: 79 of ANT20 Knob of Table 6B, or

FZD4 Fab CDR-H1 of SEQ ID NO: 24, a CDR-H2 of SEQ ID NO: 51 and a CDR-H3 of SEQ ID NO: 79 of ANT21 Knob of Table 6B, or

FZD4 Fab CDR-H1 of SEQ ID NO: 24, a CDR-H2 of SEQ ID NO: 61 and a CDR-H3 of SEQ ID NO: 90 of ANT36 Knob of Table 6B, or

FZD4 Fab CDR-H1 of SEQ ID NO: 24, a CDR-H2 of SEQ ID NO: 61 and a CDR-H3 of SEQ ID NO: 90 of ANT39 Knob of Table 6B,

and

(c) in each of the third and fourth light chain monomers

the VL comprises the FZD4 Fab CDR-L1, CDR-L2 and CDR-L3 of SEQ ID NO: 3 of ANT16- Knob of Table 6B, or

the VL comprises the FZD4 Fab CDR-L1, CDR-L2 and CDR-L3 of SEQ ID NO: 3 of ANT18- Knob of Table 6B, or

the VL comprises the FZD4 Fab CDR-L1, CDR-L2 and CDR-L3 of SEQ ID NO: 3 of ANT20- Knob of Table 6B, or

the VL comprises the FZD4 Fab CDR-L1, CDR-L2 and CDR-L3 of SEQ ID NO: 3 of ANT21- Knob of Table 6B, or

the VL comprises the FZD4 Fab CDR-L1, CDR-L2 and CDR-L3 of SEQ ID NO: 12 of ANT36- Knob of Table 6B, or

the VL comprises the FZD4 Fab CDR-L1, CDR-L2 and CDR-L3 of SEQ ID NO: 12 of ANT39- Knob of Table 6B,

wherein the FZD4 Fab CDR-L1 comprises SVSSA (SEQ ID NO: 1) and CDR-L2 comprises SASSLYS (SEQ ID NO: 2).

~~35. The tetravalent binding antibody molecule of any one of claims 1 to 34 wherein the tetravalent binding antibody molecule does not comprise a FZD binding domain comprising the~~

~~CDRs of the FZD-binding antibody 5044 in combination with the Wnt co-receptor binding domain comprising the CDRs of LRP6-binding antibody 2542 and/or antibody 2539.~~

26. The tetravalent binding antibody molecule of any one of claims 20, 21, 23 and 24, comprising a bivalent, bispecific LRP5 binding domain, wherein

(a) in the first heavy chain monomer, the VH that binds LRP5 comprises CDR-H1 of SEQ ID NO: 528, CDR-H2 of SEQ ID NO: 553 and CDR-H3 of SEQ ID NO: 586 and the VL that binds LRP5 comprises CDR-L1 of SEQ ID NO: 1, CDR-L2 of SEQ ID NO: 491 and CDR-L3 of SEQ ID NO: 510

and the VH that binds FZD4 comprises the FZD4 VH CDRs CDR-H1 of SEQ ID NO: 24, a CDR-H2 of SEQ ID NO: 61 and a CDR-H3 of SEQ ID NO: 90

(b) in the second heavy chain monomer, the VH that binds LRP5 comprises CDR-H1 of SEQ ID NO: 536, CDR-H2 of SEQ ID NO: 566 and CDR-H3 of SEQ ID NO: 603 and the VL that binds LRP5 comprises CDR-L1 of SEQ ID NO: 1, CDR-L2 of SEQ ID NO: 2 and CDR-L3 of SEQ ID NO: 493

and the VH that binds FZD4 comprises the FZD4 VH CDRs CDR-H1 of SEQ ID NO: 24, a CDR-H2 of SEQ ID NO: 61 and a CDR-H3 of SEQ ID NO: 90

and

(c) in each of the third and fourth light chain monomers, the VL that binds FZD4 comprises the CDR-L1 of SEQ ID NO: 1, CDR-L2 of SEQ ID NO: 2 and CDR-L3 of SEQ ID NO: 12.

~~36~~27. The tetravalent binding antibody molecule of ~~any one of~~ claim~~s~~ 1 ~~to 35~~, wherein the tetravalent binding antibody molecule comprises

(a) a first heavy chain monomer comprising the amino acid sequence of the hole heavy chain construct of SEQ ID NO: 898, a second heavy chain monomer comprising the amino acid ~~a~~ of the knob heavy chain construct of SEQ ID NO: 897 and a light chain monomer comprising the amino acid sequence of the light chain construct of SEQ ID

NO: 899 wherein the amino acid sequence of the CDRs are the amino acid sequence of the CDRs of ANT16; or

(b) a first heavy chain monomer comprising the amino acid sequence of the hole heavy chain construct of SEQ ID NO: 901, a second heavy chain monomer comprising the amino acid of the ~~a~~ knob heavy chain construct of SEQ ID NO: 900 and a light chain monomer comprising the amino acid sequence of the light chain construct of SEQ ID NO: 902 wherein the amino acid sequence of the CDRs are the amino acid sequence of the CDRs of ANT 18; or

(c) a first heavy chain monomer comprising the amino acid sequence of the hole heavy chain construct of SEQ ID NO: 904, a second heavy chain monomer comprising the amino acid of the ~~a~~ knob heavy chain construct of SEQ ID NO: 903 and a light chain monomer comprising the amino acid sequence of the light chain construct of SEQ ID NO: 902 wherein the amino acid sequence of the CDRs are the amino acid sequence of the CDRs of ANT20; or

(d) a first heavy chain monomer comprising the amino acid sequence of the hole heavy chain construct of SEQ ID NO: 906, a second heavy chain monomer comprising the amino acid of the ~~a~~ knob heavy chain construct of SEQ ID NO: 905 and a light chain monomer comprising the amino acid sequence of the light chain construct of SEQ ID NO: 902 wherein the amino acid sequence of the CDRs are the amino acid sequence of the CDRs of ANT21; or

(e) a first heavy chain monomer comprising the amino acid sequence of the hole heavy chain construct of SEQ ID NO: 908, a second heavy chain monomer comprising the amino acid of the ~~a~~ knob heavy chain construct of SEQ ID NO: 907 and a light chain monomer comprising the amino acid sequence of the light chain construct of SEQ ID NO: 909 wherein the amino acid sequence of the CDRs are the amino acid sequence of the CDRs of ANT39; or

(f) a first heavy chain monomer comprising the amino acid sequence of the hole heavy chain construct selected from the group consisting of SEQ ID NO: 921; SEQ ID NO:

922; SEQ ID NO: 923; SEQ ID NO: 924; SEQ ID NO: 925; SEQ ID NO: 926; SEQ ID NO: 927; and SEQ ID NO: 928; a second heavy chain monomer comprising the amino acid of a knob heavy chain construct selected from the group consisting of SEQ ID NO: 929; SEQ ID NO: 930; SEQ ID NO: 931; SEQ ID NO: 932; SEQ ID NO: 933; SEQ ID NO: 934; SEQ ID NO: 935; and SEQ ID NO: 936; and a light chain monomer comprising the amino acid sequence of the light chain construct selected from the group consisting of SEQ ID NO: 909 and SEQ ID NO: 952.

~~37~~28. The tetravalent binding antibody molecule of any one of claims 1 to ~~35~~27, wherein the tetravalent binding antibody molecule comprises

(a) a first heavy chain monomer comprising the amino acid sequence of the hole heavy chain construct of SEQ ID NO: 921 or SEQ ID NO: 925, a second heavy chain monomer comprising the amino acid ~~a~~ of the knob heavy chain construct of SEQ ID NO: 929 or SEQ ID NO: 933, and a light chain monomer comprising the amino acid sequence of the light chain construct of SEQ ID NO: 909 or SEQ ID NO: 952; or

b) a first heavy chain monomer comprising the amino acid sequence of the hole heavy chain construct of SEQ ID NO: 922 or SEQ ID NO: 926, a second heavy chain monomer comprising the amino acid of the ~~a~~ knob heavy chain construct of SEQ ID NO: 930 or SEQ ID NO: 934, and a light chain monomer comprising the amino acid sequence of the light chain construct of SEQ ID NO: 909 or SEQ ID NO: 952; or

c) a first heavy chain monomer comprising the amino acid sequence of the hole heavy chain construct of SEQ ID NO: 923 or SEQ ID NO: 927, a second heavy chain monomer comprising the amino acid of the ~~a~~ knob heavy chain construct of SEQ ID NO: 931 or SEQ ID NO: 935, and a light chain monomer comprising the amino acid sequence of the light chain construct of SEQ ID NO: 909 or SEQ ID NO: 952; or

d) a first heavy chain monomer comprising the amino acid sequence of the hole heavy chain construct of SEQ ID NO: 924 or SEQ ID NO: 928, a second heavy chain monomer comprising the amino acid of the ~~a~~ knob heavy chain construct of SEQ ID NO: 932 or

SEQ ID NO: 936, and a light chain monomer comprising the amino acid sequence of the light chain construct of SEQ ID NO: 909 or SEQ ID NO: 952; or

e) a first heavy chain monomer comprising the amino acid sequence of the hole heavy chain construct of SEQ ID NO: 908 or SEQ ID NO: 940, a second heavy chain monomer comprising the amino acid of the ~~a~~ knob heavy chain construct of SEQ ID NO: 944 or SEQ ID NO: 948, and a light chain monomer comprising the amino acid sequence of the light chain construct of SEQ ID NO: 909 or SEQ ID NO: 952; or

f) a first heavy chain monomer comprising the amino acid sequence of the hole heavy chain construct of SEQ ID NO: 937 or SEQ ID NO: 941, a second heavy chain monomer comprising the amino acid of the ~~a~~ knob heavy chain construct of SEQ ID NO: 945 or SEQ ID NO: 949, and a light chain monomer comprising the amino acid sequence of the light chain construct of SEQ ID NO: 909 or SEQ ID NO: 952; or

g) a first heavy chain monomer comprising the amino acid sequence of the hole heavy chain construct of SEQ ID NO: 938 or SEQ ID NO: 942, a second heavy chain monomer comprising the amino acid of the ~~a~~ knob heavy chain construct of SEQ ID NO: 946 or SEQ ID NO: 950, and a light chain monomer comprising the amino acid sequence of the light chain construct of SEQ ID NO: 909 or SEQ ID NO: 952; or

h) a first heavy chain monomer comprising the amino acid sequence of the hole heavy chain construct of SEQ ID NO: 939 or SEQ ID NO: 943, a second heavy chain monomer comprising the amino acid of the ~~a~~ knob heavy chain construct of SEQ ID NO: 947 or SEQ ID NO: 951, and a light chain monomer comprising the amino acid sequence of the light chain construct of SEQ ID NO: 909 or SEQ ID NO: 952.

~~38~~29. A pharmaceutical composition comprising a tetravalent binding antibody molecule of any one of claims 1 to ~~37~~ 28 and a pharmaceutically acceptable carrier.

~~39~~30. A method for promoting endothelial cell barrier functions in a tissue comprising administering an effective amount of a tetravalent binding antibody molecule of any one of claims 1 to ~~37~~ 28 to a tissue, such as ~~.~~

~~40. The method of claim 39,~~ wherein the tissue is brain, kidney or eye tissue~~,~~ preferably ~~.~~

~~41. The method of claim 40,~~ wherein the tetravalent binding antibody molecule is administered to eye tissue by intravitreal injection.

~~42~~31. A method for increasing retinal or brain endothelial cell barrier functions, decreasing endothelial cell permeability, enhancing or restoring blood retina and blood brain barrier maintenance in a subject in need thereof comprising contacting an endothelial cell comprising an FZD4 receptor and an LRP5 in a subject in need thereof with an effective amount of a tetravalent binding antibody molecule of any one of claim 1 to ~~37~~28.

~~43~~32. The method of claim ~~42~~31, wherein the tetravalent binding antibody molecule is administered to the subject in need thereof by injection, topically, or orally~~,~~ or ~~.~~

~~44. The method of claim 42,~~ wherein the tetravalent binding antibody molecule is administered subcutaneously, intravenously, intraperitoneally, intrathecally, intravitreously, or intraocularly.

~~45. The tetravalent binding antibody molecule of any one of claims 1 to 37 or the pharmaceutical composition of claim 38 for use as a medicament.~~

~~46. The tetravalent binding antibody molecule or pharmaceutical composition of claim 45 for use in the treatment or prevention of a disorder or condition characterized by defective retinal or brain angiogenesis and/or characterized by reduced endothelial cell barrier function and/or vascular leakage.~~

~~47. A method of treating or preventing a disorder or condition characterized by defective retinal or brain angiogenesis and/or reduced endothelial cell barrier function and/or vascular leakage comprising administering to a person in need thereof a therapeutically effective amount of the tetravalent binding antibody molecule of any one of claims 1 to 37 or the pharmaceutical composition of claim 38.~~

~~48~~33. Use of the tetravalent binding antibody molecule of claims 1 to ~~37~~ 28 or the pharmaceutical composition of claim ~~38~~ 29 for the manufacture of a medicament for the treatment or prevention of a disorder or condition characterized by defective retinal or brain

angiogenesis and/or reduced endothelial cell barrier function and/or vascular leakage, preferably .

~~49. The tetravalent binding antibody molecule or pharmaceutical composition for use, method or use of any one of claims 46 to 48~~ wherein the disorder is selected from diabetic retinopathy, retinopathy of prematurity, Coats' disease, FEVR, Norrie disease, macular degeneration, diabetic macular edema, pediatric vitreoretinopathies, Alzheimer's disease, epilepsy, multiple sclerosis, stroke and ischemia.

~~50. The tetravalent binding antibody molecule of any one of claims 1 to 37 or the pharmaceutical composition of claim 37, for use in the treatment or prevention of an ocular disorder e.g. a disorder of the retina or macula e.g. selected from diabetic retinopathy, retinopathy of prematurity, Coats' disease, FEVR, Norrie disease, macular degeneration, diabetic macular edema and pediatric vitreoretinopathies or in the treatment or prevention of a disorder selected from Alzheimer's disease, epilepsy, multiple sclerosis, stroke and ischemia.~~

~~51. A method of treating or preventing an ocular disorder e.g. a disorder of the retina or macula e.g. selected from diabetic retinopathy, retinopathy of prematurity, Coats' disease, FEVR, Norrie disease, macular degeneration, diabetic macular edema and pediatric vitreoretinopathies or in the treatment or prevention of a disorder selected from Alzheimer's disease, epilepsy, multiple sclerosis, stroke and ischemia comprising administering to a person in need thereof a therapeutically effective amount of the tetravalent binding antibody molecule of any one of claims 1 to 37 or the pharmaceutical composition of claim 38.~~

~~52~~34. Use of the tetravalent binding antibody molecule of claims 1 to ~~36~~ 28 or the pharmaceutical composition of claim ~~38~~ 29 for the manufacture of a medicament for the treatment or prevention of an ocular disorder e.g. a disorder of the retina or macula e.g. selected from diabetic retinopathy, retinopathy of prematurity, Coats' disease, FEVR, Norrie disease, macular degeneration, diabetic macular edema and pediatric vitreoretinopathies or in the treatment or prevention of a disorder selected from Alzheimer's disease, epilepsy, multiple sclerosis, stroke and ischemia.

~~53~~35. A nucleic acid molecule encoding a polypeptide of the tetravalent binding antibody molecules of any one of claims 1 to ~~37~~28.

~~54~~36. A vector comprising the nucleic acid molecule of claim ~~53~~35, preferably~~.~~

~~55. The vector of claim 54,~~ wherein said vector is an animal virus, such as a virus selected from reverse transcriptase virus (including lentivirus), adenovirus, adeno-associated virus, herpes virus, chicken pox virus, baculovirus, papilloma virus, and papova virus.

~~56~~37. A host cell expressing the vector of claim ~~54~~ 36~~or claim 55~~.

~~57~~38. A pharmaceutical composition comprising the nucleic acid molecule according to claim ~~53~~ 35 or the vector according to claim ~~54~~ 36~~or claim 55~~, and a pharmaceutical acceptable carrier, diluent or excipient.