

We claim

1. A method for activating a Wnt signaling pathway in a cell, said method comprising contacting a cell having a Frizzled (FZD) receptor and a Wnt co-receptor with a multivalent binding molecule, wherein the multivalent binding molecule comprises

- (a) an Fc domain, or fragment thereof comprising a CH3 domain, having a C-terminus and an N-terminus,
- (b) a FZD binding domain having at least two binding sites wherein at least one binding site binds to the FZD receptor and
- (c) a Wnt co-receptor domain having at least two binding sites wherein at least one binding site binds to the Wnt co-receptor,

wherein the FZD binding domain is attached to one terminus of the Fc domain or one terminus of the fragment thereof, and the Wnt co-receptor binding domain is attached to the other terminus of the Fc domain or the other terminus of the fragment thereof.

2. The method of claim 1, wherein the FZD binding domain comprises,

- (a) a diabody that binds the FZD receptor, said diabody comprising two peptides each peptide comprising a heavy-chain variable domain (VH) linked to a light-chain variable domain (VL) wherein the VH and the VL from one peptide pair to the VL and VH of the other peptide thereby forming the diabody, or
- (b) an scFv comprising VL and VH regions that binds the FZD receptor or
- (c) an endogenous ligand of the FZD receptor, and

the Wnt co-receptor binding domain comprises

- (d) a diabody that binds the Wnt co receptor, said diabody comprising two peptides each peptide comprising a heavy-chain variable domain (VH) linked to a light-chain variable domain (VL) wherein the VH and the VL from one peptide pair to the VL and VH of the other peptide thereby forming the diabody, or,
- (e) an scFv comprising VL and VH regions that binds the co-receptor, or

(f) an endogenous ligand of the co-receptor or a fragment of such ligand that binds the co-receptor.

3. The method of claim 2, wherein the FZD binding domain binds to a Wnt ligand binding site on the FZD receptor, or the Wnt co-receptor binding domain binds to a Wnt ligand binding site on the Wnt co-receptor.
4. The method of claim 3, wherein the Wnt co-receptor binding domain binds to Wnt3 and/or Wnt1 binding sites.
5. The method of claim 3, wherein the VH and VL are derived from a multivalent binding molecule listed in Table 1.
6. The method of claim 1, wherein the FZD binding domain binds one or more FZD receptor.
7. The method of claim 1, wherein the Fc domain is an IgG Fc domain.
8. The method of any of the foregoing claims, wherein the FZD receptor is FZD1, FZD2, FZD4, FZD5, FZD7 or FZD8 and the Wnt co-receptor is LRP5, LRP6, ROR1, ROR2, RYK, PTK7, GPR124, or TSPAN12.
9. A multivalent binding molecule, wherein the multivalent binding molecule comprises
 - (a) an Fc domain, or fragment thereof comprising a CH3 domain, having a C-terminus and an N-terminus,
 - (b) a FZD binding domain having at least two binding sites wherein at least one binding site binds to the FZD receptor and
 - (c) a Wnt co-receptor binding domain having at least two binding sites wherein at least one binding site binds to the Wnt co-receptor,wherein the FZD binding domain is attached to one terminus of the Fc domain and the Wnt co-receptor binding domain is attached to the other terminus of the Fc domain.
10. The multivalent binding molecule of claim 9, wherein the FZD binding domain comprises,

(a) a diabody that binds the FZD receptor, said diabody comprising two peptides each peptide comprising a heavy-chain variable domain (VH) linked to a light-chain variable domain (VL) wherein the VH and the VL from one peptide pair to the VL and VH of the other peptide thereby forming the diabody, or

(b) an scFv comprising VL and VH regions that binds the FZD receptor or

(c) an endogenous ligand of the FZD receptor, and

the Wnt co-receptor binding domain comprises

(d) a diabody that binds the co receptor, said diabody comprising two peptides each peptide comprising a heavy-chain variable domain (VH) linked to a light-chain variable domain (VL) wherein the VH and the VL from one peptide pair to the VL and VH of the other peptide thereby forming the diabody, or,

(e) an scFv comprising VL and VH regions that binds the co-receptor, or

(f) an endogenous ligand of the Wnt co-receptor or a fragment of such ligand that binds the Wnt co-receptor.

11. The multivalent binding molecule of claim 9, wherein at least one of the binding domains is bispecific.

12. The multivalent binding molecule of claim 10, wherein the VH and VL are derived from an antibody that binds the FZD receptor and optionally inhibits binding of a Wnt ligand to the FZD receptor, or the VH and VL are derived from an antibody that binds to the Wnt co-receptor and optionally inhibits binding of a Wnt ligand to the co-receptor.

13. The multivalent binding molecule of claim 10, wherein the VH and VL are derived from a multivalent binding molecule listed in Table 1.

14. The multivalent binding molecule of any one of claims 9 to 13, wherein

(a) the FZD binding domain binds one or more of FZD1, FZD2, FZD3, FZD4, FZD5, FZD6, FZD7, FZD8, FZD9, or FZD10 receptor or

(b) the Wnt co-receptor binding domain binds one or more of LRP5, LRP6, ROR1, ROR2, RYK, PTK7, GPR124, or TSPAN12 or

(c) the FZD binding domain binds one or more of FZD1, FZD2, FZD3, FZD4, FZD5, FZD6, FZD7, FZD8, FZD9, or FZD10 receptor and the Wnt co-receptor binding domain binds one or more of LRP5, LRP6, ROR1, ROR2, RYK, PTK7, GPR124, or TSPAN12.

15. A pharmaceutical composition comprising a multivalent binding molecule of any one of claims 9 to 14 and a pharmaceutically acceptable carrier.

16. A method for enhancing tissue regeneration in a subject in need thereof, or treating a subject having a condition associated with reduced Wnt signaling comprising administering a multivalent binding molecule of any one of claims 9 to 14 to the subject in an amount sufficient to enhance tissue regeneration or alleviate symptoms associated with the condition.

17. A method for facilitating the interaction of a FZD receptor and a Wnt co-receptor on a cell thereby activating a Wnt signaling pathway in the cell comprising,

- a) selecting an Fc domain, or fragment thereof comprising a CH3 domain, having a C-terminus and an N-terminus
- b) linking a bivalent FZD receptor binding domain on one terminus of the Fc domain and linking a bivalent Wnt co-receptor binding domain on the other terminus of the Fc domain thereby forming a tetravalent binding molecule;
- c) contacting said tetravalent binding molecule with the cell expressing said FZD receptor and Wnt co-receptor under conditions wherein the tetravalent binding molecule binds to the FZD receptor and the Wnt co-receptor thereby activating the Wnt signaling pathway.

18. The method of claim 17 wherein the bivalent FZD receptor binding domain comprises a diabody that binds a FZD receptor and the bivalent Wnt receptor binding domain comprises a diabody that binds a Wnt co-receptor.

19. The method of claim 18 wherein the diabody that binds a Wnt co-receptor binds to one or both of Wnt1 or Wnt3a binding sites on the Wnt co-receptor.