

We claim

1. A method for activating a Wnt signaling pathway in a cell, said method comprising contacting a cell having a Frizzled2 (FZD2) receptor or Frizzled7 (FZD7) 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) (i) a FZD2 binding domain having at least two binding sites wherein at least one binding site binds to the FZD2 receptor and comprises a light-chain variable domain (VL) that is 50%, 55%, 60%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a VL of 2890-hole-2539-2542 (having the amino acid sequence encoded by SEQ ID NO: 85) or CDRs of the VL of 2890-hole-2539-2542, and comprises a heavy-chain variable domain (VH) comprising VH of 2890-hole-2542 (having the amino acid sequence encoded by SEQ ID NO: 84), or CDRs of the VHs of 2890-hole-2539-2542 or 12735-hole-2539-2542, or (ii) a FZD7 binding domain having at least two binding sites wherein at least one binding site binds to the FZD7 receptor and comprises a light-chain variable domain (VL) that is 50%, 55%, 60%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a VL of 12735-hole-2539-2542 (having the amino acid sequence encoded by SEQ ID NO: 87) or CDRs of the VHs of 12735-hole-2539-2542 and comprises a heavy-chain variable domain (VH) comprising VH of 12735-hole-2539-2542 (having the amino acid sequence encoded by SEQ ID NO: 86), or CDRs of the VHs of 12735-hole-2539-2542, 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 FZD2 or FZD7 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 FZD2 or FZD7 binding domain comprises,

(a)(i) a diabody that binds the FZD2 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, and wherein the VL comprises the VL of 2890-hole-2539-2542(having the amino acid sequence encoded by SEQ ID NO: 85) or CDRs of the VL of 2890-hole-2539-2542 , and the VH comprises the VH of 2890-hole-2542 (having the amino acid sequence encoded by SEQ ID NO: 84), or CDRs of the VH of 2890-hole-2539-2542, or (ii) a diabody that binds the FZD7 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, and wherein the VL comprises the VL of 12735-hole-2539-2542 (having the amino acid sequence encoded by SEQ ID NO: 87) or CDRs of the VL of 12735-hole-2539-2542, and the VH comprises the VH of 12735-hole-2539-2542 (having the amino acid sequence encoded by SEQ ID NO: 86), or CDRs of the VH of 12735-hole-2539-2542, or

(b) (i) an scFv comprising a VL comprising a VL of 2890-hole-2539-2542 or (having the amino acid sequence encoded by SEQ ID NO: 85) or CDRs of the VL of 2890-hole-2539-2542 and a VH region comprising the VH of 2890-hole-2542 (having the amino acid sequence encoded by SEQ ID NO: 84), or CDRs of the VHs of 2890-hole-2539-2542 o, and binds the FZD2 receptor, or (ii) an scFv comprising a VL comprising a VL of 12735-hole-2539-2542 (having an amino acid sequence encoded by SEQ ID NO: 87) or CDRs of the VL of 2890-hole-2539-2542 or 12735-hole-2539-2542 and a VH region comprising the VH of 12735-hole-2539-2542 (having an amino acid sequence encoded by SEQ ID NO: 86), or CDRs of the VHs of 12735-hole-2539-2542, and binds the FZD7 receptor and

the Wnt co-receptor binding domain comprises

(c) 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,

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

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

3. The method of claim 1, wherein 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 1, wherein the Fc domain is an IgG Fc domain.

6. 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) (i) a FZD2 binding domain having at least two binding sites wherein at least one binding site comprises a light-chain variable domain (VL) comprising VL of 2890-hole-2539-2542 (having the amino acid sequence encoded by SEQ ID NO: 85) or CDRs of the VL of 2890-hole-2539-2542 , and comprises a heavy-chain variable domain (VH) comprising VH of 2890-hole-2542 (having the amino acid sequence encoded by SEQ ID NO: 84), or CDRs of the VHs of 2890-hole-2539-2542, and binds to the FZD2 receptor, or (ii) a FZD7 binding domain having at least two binding sites wherein at least one binding site comprises a light-chain variable domain (VL) comprising VL 12735-hole-2539-2542 (having the amino acid sequence encoded by SEQ ID NO:87) or CDRs of the VL of 12735-hole-2539-2542, and comprises a heavy-chain variable domain (VH) comprising VH of 12735-hole-2539-2542 (having the amino acid sequence encoded by SEQ ID NO: 86), or CDRs of the VHs of 2890-hole-2539-2542 or 12735-hole-2539-2542, and binds to the FZD7 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 FZD2 or FZD7 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.

7. The multivalent binding molecule of claim 6, wherein the FZD2 or FZD7 binding domain comprises,

(a)(i) a diabody that binds the FZD2 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, and wherein the VL comprises the VL of 2890-hole-2539-2542 (having an amino acid sequence encoded by SEQ ID NO: 85) or CDRs of the VL of 2890-hole-2539-2542, and the VH comprises the VH of 2890-hole-2542 (encoded by SEQ ID NO: 84), or CDRs of the VH of 2890-hole-2539-2542, or (ii) a diabody that binds the FZD7 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, and wherein the VL comprises the VL of 12735-hole-2539-2542 (having the amino acid sequence encoded by SEQ ID NO: 87) or CDRs of the VL of 12735-hole-2539-2542, and the VH comprises the VH of 12735-hole-2539-2542 (having the amino acid sequence encoded by SEQ ID NO: 86), or CDRs of the VH of 12735-hole-2539-2542, or

(b) (i) an scFv comprising VL and VH regions that bind the FZD2 receptor, wherein the VL comprises the VL of 2890-hole-2539-2542 (having the amino acid sequence encoded by SEQ ID NO: 85) or CDRs of the VL of 2890-hole-2539-2542 or 12735-hole-2539-2542, and the VH comprises the VH of 2890-hole-2542 (having the amino acid sequence encoded by SEQ ID NO: 86), or CDRs of the VH of 2890-hole-2539-2542, or (ii) an scFv comprising VL and VH regions that bind the FZD7 receptor, wherein the VL comprises the VL of 12735-hole-2539-2542 (having the amino acid sequence encoded by SEQ ID NO: 87) or CDRs of the VL of 12735-hole-2539-2542, and the VH comprises the VH of 12735-hole-2539-2542 (having the amino acid sequence encoded by SEQ ID NO: 86), or CDRs of the VH of 12735-hole-2539-2542, and

the Wnt co-receptor binding domain comprises

(d) a diabody that binds the coreceptor, 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, wherein the VL comprises the VL of 2890-hole-2539-2542, 2890-knob-2539-2542, 12735-hole-2539-2542 or 12735-knob-2539-2542 (having the amino acid sequence encoded by SEQ ID NO: 50 or 52) or CDRs of the VL of 2890-hole-2539-2542 or 12735-hole-2539-2542 or 12735-knob-2539-2542, and the VH comprises the VH of 2890-hole-2542, 2890-knob-2542, 12735-hole-2539-2542 or 12735-knob-2539-2542 (having the amino acid sequence encoded by SEQ ID NO: 49 or 53), or CDRs of the VH of 2890-hole-2539-2542 or 12735-hole-2539-2542, or,

(e) an scFv comprising VL and VH regions that bind the co-receptor, wherein the VL comprises the VL of 2890-hole-2539-2542, 2890-knob-2539-2542 or 12735-hole-2539-2542, or 12735-knob-2539-2542 (having the amino acid sequence encoded by SEQ ID NO: 50 or 52) or CDRs of the VL of 2890-hole-2539-2542 or 12735-hole-2539-2542, and the VH comprises the VH of 2890-hole-2542, 2890-hole-2539-2542 or 12735-hole-2539-2542 or 12735-knob-2539-2542 (having the amino acid sequence encoded by SEQ ID NO: 49 or 53), or CDRs of the VH of 2890-hole-2539-2542 or 12735-hole-2539-2542.

8. The multivalent binding molecule of claim 6, wherein at least one of the binding domains is bispecific.
9. The multivalent binding molecule of claim 6, comprising a first peptide comprising SEQ ID NO: 77 and a second peptide comprises SEQ ID NO: 79 and binds FZD2.
10. The multivalent binding molecule of 6, comprising a first peptide comprising SEQ ID NO: 81 and a second peptide comprising SEQ ID NO: 83 and binds FZD7.
11. The multivalent binding molecule of claim 6, comprising a first peptide consisting essentially of SEQ ID NO: 77 and a second peptide consisting essentially of SEQ ID NO: 79 and binds FZD2.
12. The multivalent binding molecule of 6, comprising a first peptide consisting essentially of SEQ ID NO: 81 and a second peptide consisting essentially of SEQ ID NO: 83.

13. A pharmaceutical composition comprising a multivalent binding molecule of any one of claims 6-12 and a pharmaceutically acceptable carrier.
14. Use of a multivalent binding molecule of any one of claims 6 to 12 in the manufacture of a medicament for method for enhancing tissue regeneration in a subject in need thereof, or treating a subject having a condition associated with reduced Wnt signaling, wherein the multivalent binding molecule are to be administered to the subject in an amount sufficient to enhance tissue regeneration or alleviate symptoms associated with the condition.
15. The use of claim 14, wherein the tissue is bone tissue or intestinal tissue.
16. A method for facilitating the interaction of a FZD2 or FZD7 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 FZD2 or FZD7 receptor binding domain comprising the VL that binds the FZD2 receptor of 2890-hole-2539-2542 or the FZD7 receptor of 12735-hole-2539-2542 (having the amino acid sequence encoded by SEQ ID NO 85 or 87 respectively) or CDRs of the VL of 2890-hole-2539-2542 or 12735-hole-2539-2542, and the VH comprises the VH of 2890-hole-2542 or 12735-hole-2539-2542 (having the amino acid sequence encoded by SEQ ID NO: 84 or 86 respectively), or CDRs of the VH of 2890-hole-2539-2542 or 12735-hole-2539-2542, 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 FZD2 or FZD7 receptor and Wnt co-receptor under conditions wherein the tetravalent binding molecule binds to the FZD2 or FZD7 receptor and the Wnt co-receptor thereby activating the Wnt signaling pathway.
17. The method of claim 16, wherein the bivalent FZD2 or FZD7 receptor binding domain comprises a diabody comprising the VL of 2890-hole-2539-2542 or of 12735-hole-2539-2542 (having the amino acid sequence encoded by SEQ ID NO 85 or 87) or CDRs of the VL of 2890-hole-2539-2542 or of 12735-hole-2539-2542, and the VH comprises the VH of 2890-hole-2542 or of 12735-hole-2539-2542 (having the amino acid sequence encoded by SEQ ID NO 84 or 86), or CDRs of the VH of 2890-hole-2539-2542 or of 12735-hole-2539-

2542 and the bivalent Wnt receptor binding domain comprises a diabody that binds a Wnt co-receptor.

18. The method of claim 17, 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.