

CLAIMS

1. An *in vitro* method for activating a Wnt signaling pathway in a cell, said method comprising contacting a cell having a Frizzled (FZD) receptor and a low density lipoprotein receptor protein 5 or 6 (LRP5/6) with a multivalent binding molecule, wherein the multivalent binding molecule is tetravalent and 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 two FZD receptor binding sites and
 - (c) a LRP 5/6 binding domain having two LRP5/6 binding sites formed by a diabody comprising a binding site that binds a Wnt1 binding site on LRP5 or LRP6 and a binding site that binds Wnt3 binding site on LRP5 or LRP6, said diabody comprising two peptides with each peptide comprising a heavy-chain variable domain (VH) linked to a light-chain variable domain (VL) that bind the LRP5 or LRP6 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 FZD binding domain is attached to one terminus of the Fc domain, or one terminus of the fragment thereof, and the LRP5/6-binding diabody 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 an antibody fragment that binds the cysteine-rich domain (CRD) of the FZD receptor.
3. The method of claim 1, wherein the FZD binding domain comprises,
 - (a) a diabody comprising the two FZD receptor binding sites, 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 bind the FZD receptor.~~ (b) two scFvs forming the two FZD receptor binding sites, each scFv comprising VIL and VH regions that bind the FZD receptor.

4. The method of claim 1, wherein the FZD binding domain binds to a Wnt ligand binding site on the FZD receptor.
5. The method of claim 1 wherein the FZD binding domain binds to the FZD receptor without inhibiting WNT binding to the FZD receptor.
6. The method of claim 3, wherein the VH and VL are derived from the VH and VL of a multivalent binding molecule listed in Table 1B.
7. The method of claim 1, wherein the FZD binding domain binds one or more FZD receptor.
8. The method of claim 1, wherein the Fc domain is an IgG Fc domain.
9. The method of any of the foregoing claims, wherein the FZD receptor is FZD1, FZD2, FZD4, FZD5, FZD6, FZD7, FZD8, FZD9 or FZD10.
10. A tetravalent binding molecule, wherein the tetravalent binding molecule is a Wnt signalling pathway agonist and 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 two FZD binding sites that bind to the FZD receptor and
 - (c) a diabody comprised of a binding site that binds a Wnt1 binding site on LRP5 or LRP6 and a binding site that binds a Wnt3 binding site on LRP5 or LRP6, the 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 that binds LRP5/6,

wherein the FZD binding domain is attached to one terminus of the Fc domain, or fragment thereof comprising a CH3 domain, and the diabody is attached to the other terminus of the Fc domain, or fragment thereof comprising a CH3 domain.

11. The tetravalent binding molecule of claim 10, wherein the FZD binding domain comprises,
 - (a) a diabody comprising the two FZD receptor binding sites, said diabody comprising two peptides with 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) two scFvs forming the two FZD receptor binding sites, each scFv comprising VL and VH regions that bind the FZD receptor.
12. The tetravalent binding molecule of claim 10, wherein at least one of the binding domains is bispecific.
13. The tetravalent binding molecule of claim 11, wherein the VH and VL of the FZD binding domain 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 of the LRP5/6-binding diabody are derived from an antibody that binds to ~~the~~ a Wnt co-receptor and optionally inhibits binding of a Wnt ligand to the co-receptor.
14. The tetravalent binding molecule of claim 11, wherein the VH and VL are derived from a VH and VL of the multivalent binding molecules listed in Table 1B.
15. The tetravalent binding molecule of any one of claims 10 to 14, wherein the FZD binding domain binds one or more of FZD1, FZD2, FZD3, FZD4, FZD5, FZD6, FZD7, FZD8, FZD9, or FZD10 receptor.
16. A pharmaceutical composition comprising a tetravalent binding molecule of any one of claims 10 to 15 and a pharmaceutically acceptable carrier.
17. Use of ~~an~~ a sufficient amount of a tetravalent binding molecule of any one of claims 10 to 15 in the manufacture of a medicament for enhancing tissue regeneration in ~~a subject in need thereof, or for treating~~ a subject having a degenerative condition associated with reduced Wnt signaling and/or no Wnt signaling.

18. An *in vitro* method for facilitating the interaction of a FZD receptor and an LRP5 or LRP6 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, the bivalent FZD binding domain comprising two binding sites that bind the FZD, and linking a bivalent LRP5 or LRP6 binding diabody that comprises both a binding site that binds the Wnt1 binding site on LRP5 or LRP6 and a binding site that binds the Wnt3 binding site on LRP5 or LRP6 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 LRP5 or LRP6 under conditions wherein the tetravalent binding molecule binds to the FZD receptor and the LRP5 or LRP6 thereby activating the Wnt signaling pathway.
19. The method of claim 18 wherein the bivalent FZD receptor binding domain comprises a diabody comprising the two FZD binding sites that binds the FZD receptor.