Claims

1. An activin-binding ActRIIa polypeptide having an amino acid sequence that is at least 95% identical to SEQ ID NO: 7, wherein the N-terminus is ILGRSETQE (SEQ ID NO: 11).

2. The activin-binding ActRIIA polypeptide of claim 1, wherein the polypeptide has an amino acid sequence comprising SEQ ID NO:7.

3. The activin-binding ActRIIa polypeptide of claims 1 or 2, wherein the polypeptide is at least 95% pure, with respect to protein contaminants, as determined by size exclusion chromatography.

4. The activin-binding ActRIIa polypeptide of any of claims 1-3, wherein the polypeptide exhibits at least 10-fold selectivity in dissociation constant for activin versus GDF-11.

5. A pharmaceutical preparation comprising the activin-binding ActRIIa polypeptide of any of claims 1-4 and at least one pharmaceutically acceptable excipient.

6. The pharmaceutical preparation of claim 5, wherein said preparation is substantially pyrogen free.

7. An isolated polynucleotide comprising a coding sequence for the activin-binding ActRIIa polypeptide of any of claims 1-4.

8. The isolated polynucleotide of claim 7, wherein the isolated polynucleotide comprises a sequence of SEQ ID NO:14.

9. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claims 7 or 8.

10. A cell transformed with a recombinant polynucleotide of any of claims 7-9.

11. The cell of claim 10, wherein the cell is a mammalian cell.

12. The cell of claim 11, wherein the cell is a CHO cell or a human cell, wherein the human cell is not a human embryonic stem cell or a human germ cell.

13. A method of making an activin-binding ActRIIa polypeptide, comprising: a) culturing a cell under conditions suitable for expression of the soluble ActRIIa polypeptide, wherein said cell is transformed with a recombinant polynucleotide of any of claims 7-9; and b) recovering the activin-binding ActRIIa polypeptide so expressed.

14. A polypeptide having an amino acid sequence that is at least 95% identical to SEQ ID NO: 7, wherein the N-terminus of the polypeptide is ILGRSETQE (SEQ ID NO:11), for use in promoting bone growth, increasing bone density or increasing bone strength.

15. The polypeptide of claim 14, wherein the polypeptide has an amino acid sequence comprising SEQ ID NO:7.

16. The polypeptide of claims 14 or 15, wherein the polypeptide has one or more of the following characteristics: i) binds to an ActRIIa ligand with a K_D of at least 10^{-7} M; and ii) inhibits ActRIIa signaling in a cell.

17. The polypeptide of any of claims 14-16, wherein said polypeptide includes one or more modified amino acid residues selected from: a glycosylated amino acid, a PEGylated amino acid, a farnesylated amino acid, an acetylated amino acid, a biotinylated amino acid, an amino acid conjugated to a lipid moiety, and an amino acid conjugated to an organic derivatizing agent.

18. A polypeptide having an amino acid sequence that is at least 95% identical to SEQ ID NO: 7, wherein the N-terminus of the polypeptide is ILGRSETQE (SEQ ID NO:11), for use in treating a bone-related disorder.

19. The polypeptide of claim 18, wherein the polypeptide has an amino acid sequence comprising SEQ ID NO:7.

20. The polypeptide of claims 18 or 19, wherein the polypeptide has one or more of the following characteristics: i) binds to an ActRIIa ligand with a K_D of at least 10^{-7} M; and ii) inhibits ActRIIa signaling in a cell.

21. The polypeptide of any of claims 18-20, wherein said polypeptide includes one or more modified amino acid residues selected from: a glycosylated amino acid, a PEGylated amino acid, a farnesylated amino acid, an acetylated amino acid, a biotinylated amino acid, an amino acid conjugated to a lipid moiety, and an amino acid conjugated to an organic derivatizing agent.

22. The polypeptide of any of claims 18-21, wherein the bone-related disorder is selected from the group consisting of: primary osteoporosis and secondary osteoporosis.

23. The polypeptide of any of claims 18-21, wherein the bone-related disorder is selected from the group consisting of: post-menopausal osteoporosis, hypogonadal bone loss, tumor-induced bone loss, cancer therapy induced bone loss, bony metastases, multiple myeloma and Paget's disease.

24. A combination comprising (a) a polypeptide having an amino acid sequence that is at least 95% identical to SEQ ID NO: 7, wherein the N-terminus of the polypeptide is ILGRSETQE (SEQ ID NO:11); and (b) an agent selected from the group consisting of: a bisphosphonate, an estrogen, a selective estrogen receptor modulator, a parathyroid hormone, a calcitonin, a calcium supplement and a vitamin D supplement, for use in treating a bone-related disorder.

25. The combination of claim 24, wherein the polypeptide has an amino acid sequence comprising SEQ ID NO:7.

26. A pharmaceutical preparation comprising: (a) a polypeptide having an amino acid sequence that is at least 95% identical to SEQ ID NO: 7, wherein the N-terminus of the polypeptide is ILGRSETQE (SEQ ID NO:11); and (b) an agent selected from the group consisting of: a bisphosphonate, an estrogen, a selective estrogen receptor modulator, a parathyroid hormone, a calcitonin, a calcium supplement and a vitamin D supplement.

27. The pharmaceutical preparation of claim 26, wherein the polypeptide has an amino acid sequence comprising SEQ ID NO:7.

28. A polypeptide having an amino acid sequence that is at least 95% identical to SEQ ID NO: 7, wherein the N-terminus of the polypeptide is ILGRSETQE (SEQ ID NO:11), for use in preventing a bone-related disorder.

29. Use of a polypeptide having an amino acid sequence that is at least 95% identical to SEQ ID NO: 7, wherein the N-terminus of the polypeptide is ILGRSETQE (SEQ ID NO:11), in the manufacture of a medicament for preventing a bone-related disorder.

30. The polypeptide of claim 28 or use of claim 29, wherein the polypeptide has an amino acid sequence comprising SEQ ID NO:7.

31. The polypeptide of claims 28 or 30 or use of claims 29 or 30, wherein the bone related disorder is cancer that is associated with bone metastases.

32. The polypeptide of any of claims 28 or 30-31 or use of any of claims 29-31, wherein the bone related disorder is bone loss associated with a cancer treatment regimen.

33. The polypeptide of any of claims 28 or 30-31 or use of any of claims 29-31, wherein the bone related disorder is cancer associated with bone loss.

34. The activin-binding ActRIIa polypeptide of any of claims 1-4, the pharmaceutical preparation of any of claims 5-6 or 26-27, the polypeptide of any of claims 14-23, 28 or 30-33, or use of any of claims 29-33 wherein the polypeptide is glycosylated.

35. The polypeptide of any of claims 14-23, 28 or 30-33, or use of any of claims 29-33, wherein the amino acid sequence of the polypeptide consists of SEQ ID NO: 7.

36. An ActRIIa-Fc fusion protein, wherein the ActRIIa fusion protein comprises an amino acid sequence that is at least 95% identical to SECT ID NO: 7, wherein the N-terminus of the polypeptide is ILGRSETQE (SEQ ID NO:11), for use in promoting bone growth and inhibiting bone resorption in a patient.

37. The fusion of claim 36, wherein the polypeptide has an amino acid sequence comprising SEQ ID NO:7.

38. The fusion of any of claims 36-37, wherein the ActRIIa-Fc fusion protein causes less than 10% increase in the patient's skeletal muscle mass.

39. The fusion of any of claims 36-38, wherein the ActRIIa-Fc fusion protein is intended to be administered so as to reach a serum concentration in the patient of at least 0.2 pg/kg.

40. The fusion of any of claims 36-39, wherein the ActRIIa-Fc fusion protein consists of the amino acid sequence of SEQ ID NO:7.

41. The fusion of any of claims 36-40, wherein the ActRIIa-Fc fusion protein has a serum half-life of between 15 and 30 days.

42. The fusion of any of claims 36-41, wherein the ActRIIa-Fc fusion protein is administered to the patient no more frequently than once per week.

43. The fusion of any of claims 36-41, wherein the ActRIIa-Fc fusion protein is administered to the patient no more frequently than once per month.

We claim:

1. A soluble polypeptide comprising an amino acid sequence that is at least 95% identical to SEQ ID NO: 7, wherein the N-terminus of the polypeptide is ILGRSETQE (SEQ ID NO: 11), and wherein the polypeptide binds activin A.

2. A polypeptide according to claim 1 which comprises an amino acid sequence that is at least 97% identical to SEQ ID NO: 7.

3. A polypeptide according to claim 2 comprising an amino acid sequence that is at least 99% identical to SEQ ID NO: 7.

4. A polypeptide according to claim 3 comprising the amino acid sequence of SEQ ID NO: 7.

5. A polypeptide according to claim 1 which is an antagonist of activin A.

6. A polypeptide according to claim 1 which promotes bone growth *in vivo*.

7. A polypeptide according to claim 6 comprising an amino acid sequence that is at least 97% identical to SEQ ID NO: 7.

8. A polypeptide according to claim 7 comprising an amino acid sequence that is at least 99% identical to SEQ ID NO: 7.

9. A polypeptide according to claim 8 comprising the amino acid sequence of SEQ ID NO: 7.

10. A polypeptide according to claim 1 which has a serum half life greater than two weeks.

11. A polypeptide according to claim 10 which has a serum half life of 20-30 days.

12. A polypeptide according to claim 1 which is glycosylated and has a mammalian glycosylation pattern.

13. A polypeptide according to claim 12, which has a glycosylation patter obtainable from a chinese hamster ovary (CHO) cell line.

14. A composition comprising a polypeptide according to claim 1 and a pharmaceutically acceptable carrier, wherein the polypeptide is at least 98% pure as determined by size exclusion chromatography.

15. A composition according to claim 14 wherein the polypeptide comprises an amino acid sequence that is at least 97% identical to SEQ ID NO: 7.

16. A composition according to claim 15 wherein the polypeptide comprises an amino acid sequence that is at least 99% identical to SEQ ID NO: 7.

17. A composition according to claim 16 wherein the polypeptide comprises the amino acid sequence of SEQ ID NO: 7.