Claims:

1. Isolated or substantially purified heparan sulphate HS/BMP2 which is capable of binding SEQ ID NO:1 or 6, or to BMP2, wherein the heparan sulphate HS/BMP2 is obtainable by a method comprising:

~~(i) providing a solid support having polypeptide molecules adhered to the support, wherein the polypeptide consists of the amino acid sequence QAKHKQRKRLKSSCKRHP [SEQ ID NO:1] or QAKHKQRKRLKSSCKRH [SEQ ID NO:6];~~

~~(ii)~~(i) contacting ~~the~~ a polypeptide, the polypeptide consisting of amino acid sequence QAKHKQRKRLKSSCKRHP [SEQ ID NO:1] or QAKHKQRKRLKSSCKRH [SEQ ID NO:6] and adhered to a solid support, ~~molecules~~ with a mixture comprising heparan sulphate such that polypeptide-heparan sulphate complexes ~~are allowed to~~ form;

~~(iii)~~(ii) partitioning polypeptide-heparan sulphate complexes from the ~~remainder of the~~ mixture;

~~(iv)~~(iii) dissociating glycosaminoglycans from the polypeptide-heparan sulphate complexes;

~~(v)~~(iv) collecting the dissociated heparan sulphate.

2. Isolated or substantially purified heparan sulphate HS/BMP2, wherein following digestion with heparin lyases (heparinase, heparitinase I and II) to completion and then subjecting the resulting disaccharide fragments to strong anion exchange HPLC (SAX-HPLC) the heparan sulphate HS/BMP2 has a disaccharide composition comprising:

- UA-GlcN 8.2% (±3%);
- UA-GlcNAc 17.5% (±3%);
- UA-GlcN, 6S 3.7% (±3%);
- UA, 2S-GlcN 4.5% (±3%);
- UA-GlcNS 16.2% (±3%);
- UA, 2S-GlcNS, 6S 0.5% (±3%).

3. Isolated or substantially purified HS/BMP2 according to claim ~~1~~ 2 ~~which~~ wherein the HS/BMP2 is capable of binding~~s to~~ SEQ ID NO:1 or 6.

4. Isolated or substantially purified HS/BMP2 according to any one of claims 1 to 3 which binds to SEQ ID NO: 1 with a K_D of less than 100μM.

~~3~~5. Isolated or substantially purified HS/BMP2 according to any one of claims 1 ~~or 2~~to 4 wherein the HS/BMP2 is N-sulfated.

46. Isolated or substantially purified HS/BMP2 according to any one of claims 1 to ~~3~~ 5 wherein the HS/BMP2 is 6-O-sulfated.

~~5~~7. A composition comprising Isolated or substantially purified HS/BMP2 according to any one of claims 1 to ~~4~~ 6 and BMP2 protein.

~~6~~8. A pharmaceutical composition or medicament comprising Isolated or substantially purified HS/BMP2 according to any one of claims 1 to 46.

~~7. The pharmaceutical composition or medicament of claim 6 for use in a method of treatment, the method comprising the repair and/or regeneration of a broken bone.~~

~~8~~9. The pharmaceutical composition or medicament ~~of~~ according to claim ~~6 or 7~~8 further comprising BMP2 protein.

~~9~~10. The pharmaceutical composition or medicament according to~~of~~ ~~any one of~~ claims ~~6 to~~ 8 or 9 wherein the pharmaceutical composition or medicament further comprises mesenchymal stem cells.

~~10~~11. Use of isolated or substantially purified heparan sulphate HS/BMP2 according to any one of claims 1 to ~~4~~ 6 in the manufacture of a medicament for use in a method of medical treatment.

~~11~~12. Use of isolated or substantially purified heparan sulphate HS/BMP2 according to any one of claims 1 to 6 in the manufacture of a medicament for use in ~~a method of medical treatment according to claim 10 wherein the method of medical treatment comprises a method of~~ wound healing *in vivo*.

~~12~~13. Use of isolated or substantially purified heparan sulphate HS/BMP2 according to any one of claims 1 to 6 in the manufacture of a medicament for use in ~~a method of medical treatment according to claim 10 or 11 wherein the method of medical treatment comprises~~ repairing and/or ~~regeneration~~ regenerating~~of~~ connective tissue.

13~~3~~4. Use of isolated or substantially purified heparan sulphate HS/BMP2 according to any one of claims 1 to 6 in the manufacture of a medicament for use in ~~a method of medical treatment according to claim 10 or 11 wherein the method of medical treatment comprises~~ repairing and/or regeneratingon ~~of~~ a broken bone in a mammalian patient, optionally a human.

~~14. HS/BMP2 for use in a method of medical treatment according to claim 10 wherein the method of medical treatment comprises repair and/or regeneration of bone in a mammal or a human.~~

15. Use of isolated or substantially purified heparan sulphate ~~Use of~~ HS/BMP2 for use according to ~~any one of~~ claims ~~1 to 4 in the manufacture of a medicament for the~~comprising repairing and/or regeneratingon ~~of~~ a broken bone ~~in a mammal or a human~~during dental or facial or cranial surgery.

16. A biocompatible implant or prosthesis comprising a biomaterial and isolated or substantially purified HS/BMP2 according to any one of claims 1 to 6.~~which is capable of binding SEQ ID NO:1 or 6, or to BMP2, wherein the heparan sulphate HS/BMP2 is obtainable by a method comprising:~~

~~(i) providing a solid support having polypeptide molecules adhered to the support, wherein the polypeptide consists of the amino acid sequence QAKHKQRKRLKSSCKRHP [SEQ ID NO:1] or QAKHKQRKRLKSSCKRH [SEQ ID NO:6];~~

~~(ii) contacting the polypeptide molecules with a mixture comprising heparan sulphate such that polypeptide-heparan sulphate complexes are allowed to form;~~

~~(iii) partitioning polypeptide-heparan sulphate complexes from the remainder of the mixture;~~

~~(iv) dissociating glycosaminoglycans from the polypeptide-heparan sulphate complexes;~~

~~(v) collecting the dissociated heparan sulphate.~~

17. The implant or prosthesis ~~of~~ according to claim 16 wherein the implant or prosthesis is coated with HS/BMP2.

18. The implant or prosthesis according to~~of~~ claim 16 wherein the implant or prosthesis is impregnated with HS/BMP2.

19. The implant or prosthesis according to~~of~~ any one of claims 16 to 18 wherein the implant or prosthesis is further coated or impregnated with BMP2 protein and/or with mesenchymal stem cells.

20. A method of forming a biocompatible implant or prosthesis, the method comprising ~~the step of~~ coating or impregnating a biomaterial with isolated or substantially purified HS/BMP2 according to any one of claims 1 to 6.~~which is capable of binding SEQ ID NO:1 or 6, or to BMP2, wherein the heparan sulphate HS/BMP2 is obtainable by a method comprising:~~

~~(i) providing a solid support having polypeptide molecules adhered to the support, wherein the polypeptide consists of the amino acid sequence QAKHKQRKRLKSSCKRHP [SEQ ID NO:1] or QAKHKQRKRLKSSCKRH [SEQ ID NO:6];~~

~~(ii) contacting the polypeptide molecules with a mixture comprising heparan sulphate such that polypeptide-heparan sulphate complexes are allowed to form;~~

~~(iii) partitioning polypeptide-heparan sulphate complexes from the remainder of the mixture;~~

~~(iv) dissociating glycosaminoglycans from the polypeptide-heparan sulphate complexes;~~

~~(v) collecting the dissociated heparan sulphate.~~

21. The method of claim 20 ~~wherein the method~~ further comprisinges coating or impregnating the biomaterial with one or both of BMP2 protein and mesenchymal stem cells.

22. Culture media comprising isolated or substantially purified HS/BMP2 according to any one of claims 1 to 6.~~which is capable of binding SEQ ID NO:1 or 6, or to BMP2, wherein the heparan sulphate HS/BMP2 is obtainable by a method comprising:~~

~~(i) providing a solid support having polypeptide molecules adhered to the support, wherein the polypeptide consists of the amino acid sequence QAKHKQRKRLKSSCKRHP [SEQ ID NO:1] or QAKHKQRKRLKSSCKRH [SEQ ID NO:6];~~

~~(ii) contacting the polypeptide molecules with a mixture comprising heparan sulphate such that polypeptide-heparan sulphate complexes are allowed to form;~~

~~(iii) partitioning polypeptide-heparan sulphate complexes from the remainder of the mixture;~~

~~(iv) dissociating glycosaminoglycans from the polypeptide-heparan sulphate complexes;~~

~~(v) collecting the dissociated heparan sulphate.~~

23. Use of isolated or substantially purified HS/BMP2 according to any one of claims 1 to 6 in cell culture *in vitro*~~, wherein the HS/BMP2 is capable of binding SEQ ID NO:1 or 6, or to BMP2, and wherein the heparan sulphate HS/BMP2 is obtainable by a method comprising:~~.

~~(i) providing a solid support having polypeptide molecules adhered to the support, wherein the polypeptide consists of the amino acid sequence QAKHKQRKRLKSSCKRHP [SEQ ID NO:1] or QAKHKQRKRLKSSCKRH [SEQ ID NO:6];~~

~~(ii) contacting the polypeptide molecules with a mixture comprising heparan sulphate such that polypeptide-heparan sulphate complexes are allowed to form;~~

~~(iii) partitioning polypeptide-heparan sulphate complexes from the remainder of the mixture;~~

~~(iv) dissociating glycosaminoglycans from the polypeptide-heparan sulphate complexes;~~

~~(v) collecting the dissociated heparan sulphate.~~

24. Use of isolated or substantially purified HS/BMP2 according to any one of claims 1 to 6 for ~~in the~~ growingth ~~of~~ connective tissue *in vitro*~~, wherein the HS/BMP2 is capable of binding SEQ ID NO:1 or 6, or to BMP2, and wherein the heparan sulphate HS/BMP2 is obtainable by a method comprising:~~.

(i) providing a solid support having polypeptide molecules adhered to the support, wherein the polypeptide consists of the amino acid sequence QAKHKQRKRLKSSCKRHP [SEQ ID NO:1] or QAKHKQRKRLKSSCKRH [SEQ ID NO:6];

(ii) contacting the polypeptide molecules with a mixture comprising heparan sulphate such that polypeptide-heparan sulphate complexes are allowed to form;

(iii) partitioning polypeptide-heparan sulphate complexes from the remainder of the mixture;

(iv) dissociating glycosaminoglycans from the polypeptide-heparan sulphate complexes;

(v) collecting the dissociated heparan sulphate.

25. A method for growing connective tissue *in vitro* comprising culturing mesenchymal stem cells in contact with exogenously added isolated or substantially purified HS/BMP2 according to any one of claims 1 to 6, wherein the HS/BMP2 is capable of binding SEQ ID NO:1 or 6, or to BMP2, and wherein the heparan sulphate HS/BMP2 is obtainable by a method comprising:

(i) providing a solid support having polypeptide molecules adhered to the support, wherein the polypeptide consists of the amino acid sequence QAKHKQRKRLKSSCKRHP [SEQ ID NO:1] or QAKHKQRKRLKSSCKRH [SEQ ID NO:6];

(ii) contacting the polypeptide molecules with a mixture comprising heparan sulphate such that polypeptide-heparan sulphate complexes are allowed to form;

(iii) partitioning polypeptide-heparan sulphate complexes from the remainder of the mixture;

(iv) dissociating glycosaminoglycans from the polypeptide-heparan sulphate complexes;

(v) collecting the dissociated heparan sulphate.

26. A method of promoting osteogenesis, the method comprising administering isolated or substantially purified HS/BMP2 according to any one of claims 1 to 6 to bone precursor cells or bone stem cells *in vitro*, wherein the HS/BMP2 is capable of binding SEQ ID NO:1 or 6, or to BMP2, and wherein the heparan sulphate HS/BMP2 is obtainable by a method comprising:.

~~(i) providing a solid support having polypeptide molecules adhered to the support, wherein the polypeptide consists of the amino acid sequence QAKHKQRKRLKSSCKRHP [SEQ ID NO:1] or QAKHKQRKRLKSSCKRH [SEQ ID NO:6];~~

~~(ii) contacting the polypeptide molecules with a mixture comprising heparan sulphate such that polypeptide-heparan sulphate complexes are allowed to form;~~

~~(iii) partitioning polypeptide-heparan sulphate complexes from the remainder of the mixture;~~

~~(iv) dissociating glycosaminoglycans from the polypeptide-heparan sulphate complexes;~~

~~(v) collecting the dissociated heparan sulphate.~~

27. The method of claim 26 wherein the HS/BMP2 and a BMP2 are administered to the bone precursor cells or bone stem cells ~~are contacted with BMP2 protein~~ simultaneously ~~with HS/BMP2~~.

28. The method of claim 26 or claim 27 wherein the bone precursor or bone stem cells are mesenchymal stem cells.

29. Use of isolated or substantially purified heparan sulphate HS/BMP2 according to any one of claims 1 to 6 in the manufacture of a medicament for use in promoting osteogenesis.

~~29~~30. Bone tissue obtained by *in vitro* culture of mesenchymal stem cells in the presence of isolated or substantially purified HS/BMP2 according to any one of claims 1 to 6~~, wherein the HS/BMP2 is capable of binding SEQ ID NO:1 or 6, or to BMP2, and wherein the heparan sulphate HS/BMP2 is obtainable by a method comprising:~~

~~(i) providing a solid support having polypeptide molecules adhered to the support, wherein the polypeptide consists of the amino acid sequence QAKHKQRKRLKSSCKRHP [SEQ ID NO:1] or QAKHKQRKRLKSSCKRH [SEQ ID NO:6];~~

~~(ii) contacting the polypeptide molecules with a mixture comprising heparan sulphate such that polypeptide-heparan sulphate complexes are allowed to form;~~

~~(iii) partitioning polypeptide-heparan sulphate complexes from the remainder of the mixture;~~

~~(iv) dissociating glycosaminoglycans from the polypeptide-heparan sulphate complexes;~~

~~(v) collecting the dissociated heparan sulphate.~~

~~30~~31. Bone tissue ~~as claimed in~~according to claim 29, wherein the mesenchymal stem cells are cultured in the presence of BMP2 protein.

~~31~~32. A method of culturing mesenchymal stem cells comprising culturing mesenchymal stem cells in contact with isolated or substantially purified HS/BMP2 according to any one of claims 1 to 6.~~, wherein the HS/BMP2 is capable of binding SEQ ID NO:1 or 6, or to BMP2, and wherein the heparan sulphate HS/BMP2 is obtainable by a method comprising:~~

~~(i) providing a solid support having polypeptide molecules adhered to the support, wherein the polypeptide consists of the amino acid sequence QAKHKQRKRLKSSCKRHP [SEQ ID NO:1] or QAKHKQRKRLKSSCKRH [SEQ ID NO:6];~~

~~(ii) contacting the polypeptide molecules with a mixture comprising heparan sulphate such that polypeptide-heparan sulphate complexes are allowed to form;~~

~~(iii) partitioning polypeptide-heparan sulphate complexes from the remainder of the mixture;~~

~~(iv) dissociating glycosaminoglycans from the polypeptide-heparan sulphate complexes;~~

~~(v) collecting the dissociated heparan sulphate.~~

~~32~~33. A kit comprising a predetermined amount of isolated or substantially purified HS/BMP2 according to any one of claims 1 to 6 and a predetermined amount of BMP2.~~,~~

~~wherein the HS/BMP2 is capable of binding SEQ ID NO:1 or 6, or to BMP2, and wherein the heparan sulphate HS/BMP2 is obtainable by a method comprising:~~

~~(i) providing a solid support having polypeptide molecules adhered to the support, wherein the polypeptide consists of the amino acid sequence QAKHKQRKRLKSSCKRHP [SEQ ID NO:1] or QAKHKQRKRLKSSCKRH [SEQ ID NO:6];~~

~~(ii) contacting the polypeptide molecules with a mixture comprising heparan sulphate such that polypeptide-heparan sulphate complexes are allowed to form;~~

~~(iii) partitioning polypeptide-heparan sulphate complexes from the remainder of the mixture;~~

~~(iv) dissociating glycosaminoglycans from the polypeptide-heparan sulphate complexes;~~

~~(v) collecting the dissociated heparan sulphate.~~

~~33~~34. Products containing therapeutically effective amounts of:

(i) isolated or substantially purified HS/BMP2 according to any one of claims 1 to 6.; and one or both of

(ii) BMP2 protein;

(iii) Mesenchymal stem cells,

for simultaneous, separate or sequential use in a method of medical treatment~~, wherein the HS/BMP2 is capable of binding SEQ ID NO:1 or 6, or to BMP2, and wherein the heparan sulphate HS/BMP2 is obtainable by a method comprising:~~ .

(i) providing a solid support having polypeptide molecules adhered to the support, wherein the polypeptide consists of the amino acid sequence QAKHKQRKRLKSSCKRHP [SEQ ID NO:1] or QAKHKQRKRLKSSCKRH [SEQ ID NO:6];

(ii) contacting the polypeptide molecules with a mixture comprising heparan sulphate such that polypeptide-heparan sulphate complexes are allowed to form;

(iii) partitioning polypeptide-heparan sulphate complexes from the remainder of the mixture;

(iv) dissociating glycosaminoglycans from the polypeptide-heparan sulphate complexes;

(v) collecting the dissociated heparan sulphate.

Claims:

1. Isolated or substantially purified heparan sulphate HS/BMP2 which is capable of binding SEQ ID NO: 1 or 6, or to BMP2, wherein the heparan sulphate HS/BMP2 is obtainable by a method comprising:

(i) contacting a polypeptide, the polypeptide consisting of amino acid sequence QAKHKQRKRLKSSCKRHP [SEQ ID NO:1] or QAKHKQRKRLKSSCKRH [SEQ ID NO:6] and adhered to a solid support, with a mixture comprising heparan sulphate such that polypeptide-heparan sulphate complexes form;

(ii) partitioning polypeptide-heparan sulphate complexes from the mixture;

(iii) dissociating glycosaminoglycans from the polypeptide-heparan sulphate complexes;

(iv) collecting the dissociated heparan sulphate.

2. Isolated or substantially purified heparan sulphate HS/BMP2, wherein following digestion with heparin lyases (heparinase, heparitinase I and II) to completion and then subjecting the resulting disaccharide fragments to strong anion exchange HPLC (SAX-HPLC) the heparan sulphate HS/BMP2 has a disaccharide composition comprising:

- UA-GlcN 8.2% (±3%);
- UA-GlcNAc 17.5% (±3%);
- UA-GlcN, 6S 3.7% (±3%);
- UA, 2S-GlcN 4.5% (±3%);
- UA-GlcNS 16.2% (±3%);
- UA, 2S-GlcNS, 6S 0.5% (±3%).

3. Isolated or substantially purified HS/BMP2 according to claim 2 wherein the HS/BMP2 is capable of binding SEQ ID NO: 1 or 6.

4. Isolated or substantially purified HS/BMP2 according to any one of claims 1 to 3 which binds to SEQ ID NO: 1 with a K_D of less than 100μM.

5. Isolated or substantially purified HS/BMP2 according to any one of claims 1 to 4 wherein the HS/BMP2 is N-sulfated.

6. Isolated or substantially purified HS/BMP2 according to any one of claims 1 to 5 wherein the HS/BMP2 is 6-O-sulfated.

7. A composition comprising Isolated or substantially purified HS/BMP2 according to any one of claims 1 to 6 and BMP2 protein.

8. A pharmaceutical composition or medicament comprising Isolated or substantially purified HS/BMP2 according to any one of claims 1 to 6.

9. The pharmaceutical composition or medicament according to claim 8 further comprising BMP2 protein.

10. The pharmaceutical composition or medicament according to claim 8 or 9 wherein the pharmaceutical composition or medicament further comprises mesenchymal stem cells.

11. Use of isolated or substantially purified heparan sulphate HS/BMP2 according to any one of claims 1 to 6 in the manufacture of a medicament for use in a method of medical treatment.

12. Use of isolated or substantially purified heparan sulphate HS/BMP2 according to any one of claims 1 to 6 in the manufacture of a medicament for use in wound healing *in vivo*.

13. Use of isolated or substantially purified heparan sulphate HS/BMP2 according to any one of claims 1 to 6 in the manufacture of a medicament for use in repairing and/or regenerating connective tissue.

14. Use of isolated or substantially purified heparan sulphate HS/BMP2 according to any one of claims 1 to 6 in the manufacture of a medicament for use in repairing and/or regenerating a broken bone in a mammalian patient, optionally a human.

15. Use of isolated or substantially purified heparan sulphate HS/BMP2 for use according to claim 14 comprising repairing and/or regenerating a broken bone during dental or facial or cranial surgery.

16. A biocompatible implant or prosthesis comprising a biomaterial and isolated or substantially purified HS/BMP2 according to any one of claims 1 to 6.

17. The implant or prosthesis according to claim 16 wherein the implant or prosthesis is coated with HS/BMP2.

18. The implant or prosthesis according to claim 16 wherein the implant or prosthesis is impregnated with HS/BMP2.

19. The implant or prosthesis according to any one of claims 16 to 18 wherein the implant or prosthesis is further coated or impregnated with BMP2 protein and/or with mesenchymal stem cells.

20. A method of forming a biocompatible implant or prosthesis, the method comprising coating or impregnating a biomaterial with isolated or substantially purified HS/BMP2 according to any one of claims 1 to 6.

21. The method of claim 20 further comprising coating or impregnating the biomaterial with one or both of BMP2 protein and mesenchymal stem cells.

22. Culture media comprising isolated or substantially purified HS/BMP2 according to any one of claims 1 to 6.

23. Use of isolated or substantially purified HS/BMP2 according to any one of claims 1 to 6 in cell culture *in vitro*.

24. Use of isolated or substantially purified HS/BMP2 according to any one of claims 1 to 6 for growing connective tissue *in vitro*.

25. A method for growing connective tissue *in vitro* comprising culturing mesenchymal stem cells in contact with exogenously added isolated or substantially purified HS/BMP2 according to any one of claims 1 to 6.

26. A method of promoting osteogenesis, the method comprising administering isolated or substantially purified HS/BMP2 according to any one of claims 1 to 6 to bone precursor cells or bone stem cells *in vitro*.

27. The method of claim 26 wherein the HS/BMP2 and a BMP2 are administered to the bone precursor cells or bone stem cells simultaneously.

28. The method of claim 26 or claim 27 wherein the bone precursor or bone stem cells are mesenchymal stem cells.

29. Use of isolated or substantially purified heparan sulphate HS/BMP2 according to any one of claims 1 to 6 in the manufacture of a medicament for use in promoting osteogenesis.

30. Bone tissue obtained by *in vitro* culture of mesenchymal stem cells in the presence of isolated or substantially purified HS/BMP2 according to any one of claims 1 to 6.

31. Bone tissue according to claim 29, wherein the mesenchymal stem cells are cultured in the presence of BMP2 protein.

32. A method of culturing mesenchymal stem cells comprising culturing mesenchymal stem cells in contact with isolated or substantially purified HS/BMP2 according to any one of claims 1 to 6.

33. A kit comprising a predetermined amount of isolated or substantially purified HS/BMP2 according to any one of claims 1 to 6 and a predetermined amount of BMP2.

34. Products containing therapeutically effective amounts of:

(i) isolated or substantially purified HS/BMP2 according to any one of claims 1 to 6.; and one or both of

(ii) BMP2 protein;

(iii) Mesenchymal stem cells,

for simultaneous, separate or sequential use in a method of medical treatment.