CLAIMS

1. An anti-ActRIIB therapeutic antibody or functional protein.

2. An anti-ActRIIB antibody or functional protein that binds to the ligand binding domain of ActRIIB.

3. An anti-ActRIIB antibody or functional protein that binds to ActRIIB between amino acids 19-134 of SEQ ID NO: 181.

4. An anti-ActRIIB antibody or functional protein according to any previous claim, which binds to ActRIIB with a K_D of 1nM or less, preferably 100pM or less.

5. An anti-ActRIIB antibody according to any previous claim, wherein said antibody inhibits myostatin binding to ActRIIB.

6. An anti-ActRIIB antibody according to any previous claim, wherein said antibody inhibits myostatin induced signalling as measured by a Smad dependent reporter gene assay.

7. An anti-ActRIIB antibody according to any previous claim, wherein said antibody binds to ActRIIB with a 10-fold or greater affinity than it binds to ActRIIA.

8. The antibody or functional protein according to any previous claim, wherein said antibody comprises at least one complementarity determining region having at least 95% identity to at least one of the CDRs recited in SEQ ID NOs: 1-84.

9. The antibody or functional protein according to any of claims 1-7, wherein said antibody comprises at least one complementarity determining region having at least 95% identity to at least one CDR3 recited in SEQ ID NOs: 29-42.

10. The antibody or functional protein according to any of claims 1-7, wherein said antibody comprises a VH polypeptide sequence having at least 95% sequence identity to at least one of SEQ ID NOs: 99-112.

11. The antibody or functional protein according to any of claims 1-7, wherein said antibody comprises a VL polypeptide sequence having at least 95% sequence identity to at least one of SEQ ID NOs: 85-98.

12. The antibody or functional protein according to any of claims 1-7, wherein said antibody comprises a VH polypeptide sequence having at least 95% sequence identity to at least one

of SEQ ID NOs: 99-112 and a VL polypeptide sequence having at least 95% sequence identity to at least one of SEQ ID NOs: 85-98.

13. The antibody or functional protein according to any of claims 1-7, wherein said antibody comprises a heavy chain variable region CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-14; a heavy chain variable region CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 15-28; a heavy chain variable region CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 29-42; a light chain variable region CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 43-56; a light chain variable region CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 57-70; and a light chain variable region CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 71-84.

14. An antibody or functional protein according to any one of claims 1-7 comprising:

(a) a heavy chain variable region CDR1 of SEQ ID NO: 1; a heavy chain variable region CDR2 of SEQ ID NO: 15; a heavy chain variable region CDR3 of SEQ ID NO: 29; a light chain variable region CDR1 of SEQ ID NO: 43; a light chain variable region CDR2 of SEQ ID NO: 57; and a light chain variable region CDR3 of SEQ ID NO: 71,

(b) a heavy chain variable region CDR1 of SEQ ID NO: 2 a heavy chain variable region CDR2 of SEQ ID NO: 16; a heavy chain variable region CDR3 of SEQ ID NO: 30; a light chain variable region CDR1 of SEQ ID NO: 44; a light chain variable region CDR2 of SEQ ID NO: 58; and a light chain variable region CDR3 of SEQ ID NO: 72,

(c) a heavy chain variable region CDR1 of SEQ ID NO: 3; a heavy chain variable region CDR2 of SEQ ID NO: 17; a heavy chain variable region CDR3 of SEQ ID NO: 31; a light chain variable region CDR1 of SEQ ID NO: 45; a light chain variable region CDR2 of SEQ ID NO: 59; and a light chain variable region CDR3 of SEQ ID NO: 73,

(d) a heavy chain variable region CDR1 of SEQ ID NO: 4; a heavy chain variable region CDR2 of SEQ ID NO: 18; a heavy chain variable region CDR3 of SEQ ID NO: 32; a light chain variable region CDR1 of SEQ ID NO: 46; a light chain variable region CDR2 of SEQ ID NO: 60; and a light chain variable region CDR3 of SEQ ID NO: 74,

(e) a heavy chain variable region CDR1 of SEQ ID NO: 5; a heavy chain variable region CDR2 of SEQ ID NO: 19; a heavy chain variable region CDR3 of SEQ ID NO: 33; a light

chain variable region CDR1 of SEQ ID NO: 47; a light chain variable region CDR2 of SEQ ID NO: 61; and a light chain variable region CDR3 of SEQ ID NO: 75,

(f) a heavy chain variable region CDR1 of SEQ ID NO: 6; a heavy chain variable region CDR2 of SEQ ID NO: 20; a heavy chain variable region CDR3 of SEQ ID NO: 34; a light chain variable region CDR1 of SEQ ID NO: 48; a light chain variable region CDR2 of SEQ ID NO: 62; and a light chain variable region CDR3 of SEQ ID NO: 76,

(g) a heavy chain variable region CDR1 of SEQ ID NO: 7; a heavy chain variable region CDR2 of SEQ ID NO: 21; a heavy chain variable region CDR3 of SEQ ID NO: 35; a light chain variable region CDR1 of SEQ ID NO: 49; a light chain variable region CDR2 of SEQ ID NO: 63; and a light chain variable region CDR3 of SEQ ID NO: 77,

(h) a heavy chain variable region CDR1 of SEQ ID NO: 8; a heavy chain variable region CDR2 of SEQ ID NO: 22; a heavy chain variable region CDR3 of SEQ ID NO: 36; a light chain variable region CDR1 of SEQ ID NO: 50 a light chain variable region CDR2 of SEQ ID NO: 64; and a light chain variable region CDR3 of SEQ ID NO: 78,

(i) a heavy chain variable region CDR1 of SEQ ID NO: 9; a heavy chain variable region CDR2 of SEQ ID NO: 23; a heavy chain variable region CDR3 of SEQ ID NO: 37; a light chain variable region CDR1 of SEQ ID NO: 51; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 79,

(j) a heavy chain variable region CDR1 of SEQ ID NO: 10; a heavy chain variable region CDR2 of SEQ ID NO: 24; a heavy chain variable region CDR3 of SEQ ID NO: 38; a light chain variable region CDR1 of SEQ ID NO: 52; a light chain variable region CDR2 of SEQ ID NO: 66; and a light chain variable region CDR3 of SEQ ID NO: 80,

(k) a heavy chain variable region CDR1 of SEQ ID NO: 11; a heavy chain variable region CDR2 of SEQ ID NO: 25; a heavy chain variable region CDR3 of SEQ ID NO: 39; a light chain variable region CDR1 of SEQ ID NO: 53; a light chain variable region CDR2 of SEQ ID NO: 67; and a light chain variable region CDR3 of SEQ ID NO: 81,

(l) a heavy chain variable region CDR1 of SEQ ID NO: 12; a heavy chain variable region CDR2 of SEQ ID NO: 26; a heavy chain variable region CDR3 of SEQ ID NO: 40; a light chain variable region CDR1 of SEQ ID NO: 54; a light chain variable region CDR2 of SEQ ID NO: 68; and a light chain variable region CDR3 of SEQ ID NO: 82,

(m) a heavy chain variable region CDR1 of SEQ ID NO: 13; a heavy chain variable region CDR2 of SEQ ID NO: 27; a heavy chain variable region CDR3 of SEQ ID NO: 41; a light chain variable region CDR1 of SEQ ID NO: 55; a light chain variable region CDR2 of SEQ ID NO: 69; and a light chain variable region CDR3 of SEQ ID NO: 83, or

(n) a heavy chain variable region CDR1 of SEQ ID NO: 14; a heavy chain variable region CDR2 of SEQ ID NO: 28; a heavy chain variable region CDR3 of SEQ ID NO: 42; a light chain variable region CDR1 of SEQ ID NO: 56; a light chain variable region CDR2 of SEQ ID NO: 70; and a light chain variable region CDR3 of SEQ ID NO: 84.

15. The antibody or functional protein according to any of claims 1-7, wherein said antibody comprises a full length heavy chain amino acid sequence having at least 95% sequence identity to at least one sequence selected from the group consisting of SEQ ID NOs:146-150 and 156-160.

16. The antibody or functional protein according to any of claims 1-7, wherein said antibody comprises a full length light chain amino acid sequence having at least 95% sequence identity to at least one sequence selected from the group consisting of SEQ ID NOs:141-145 and 151-155.

17. An antibody comprising:

(a) the variable heavy chain sequence of SEQ ID NO: 85 and variable light chain sequence of SEQ ID NO: 99;

(b) the variable heavy chain sequence of SEQ ID NO: 86 and variable light chain sequence of SEQ ID NO: 100;

(c) the variable heavy chain sequence of SEQ ID NO: 87 and variable light chain sequence of SEQ ID NO: 101;

(d) the variable heavy chain sequence of SEQ ID NO: 88 and variable light chain sequence of SEQ ID NO: 102;

(e) the variable heavy chain sequence of SEQ ID NO: 89 and variable light chain sequence of SEQ ID NO: 103;

(f) the variable heavy chain sequence of SEQ ID NO: 90 and variable light chain sequence of SEQ ID NO: 104;

(g) the variable heavy chain sequence of SEQ ID NO: 91 and variable light chain sequence of SEQ ID NO: 105;

(h) the variable heavy chain sequence of SEQ ID NO: 92 and variable light chain sequence of SEQ ID NO: 106;

(i) the variable heavy chain sequence of SEQ ID NO: 93 and variable light chain sequence of SEQ ID NO: 107;

(j) the variable heavy chain sequence of SEQ ID NO: 94 and variable light chain sequence of SEQ ID NO: 108;

(k) the variable heavy chain sequence of SEQ ID NO: 95 and variable light chain sequence of SEQ ID NO: 109;

(l) the variable heavy chain sequence of SEQ ID NO: 96 and variable light chain sequence of SEQ ID NO: 110;

(m) the variable heavy chain sequence of SEQ ID NO: 97 and variable light chain sequence of SEQ ID NO: 111; or

(n) the variable heavy chain sequence of SEQ ID NO: 98 and variable light chain sequence of SEQ ID NO: 112.

18. An antibody comprising:

(a) the heavy chain sequence of SEQ ID NO: 146 and light chain sequence of SEQ ID NO: 141;

(b) the heavy chain sequence of SEQ ID NO: 147 and light chain sequence of SEQ ID NO: 142;

(c) the heavy chain sequence of SEQ ID NO: 148 and light chain sequence of SEQ ID NO: 143;

(d) the heavy chain sequence of SEQ ID NO: 149 and light chain sequence of SEQ ID NO: 144;

(e) the heavy chain sequence of SEQ ID NO: 150 and light chain sequence of SEQ ID NO: 145;

(f) the heavy chain sequence of SEQ ID NO: 156 and light chain sequence of SEQ ID NO: 151;

(g) the heavy chain sequence of SEQ ID NO: 157 and light chain sequence of SEQ ID NO: 152;

(h) the heavy chain sequence of SEQ ID NO: 158 and light chain sequence of SEQ ID NO: 153;

(i) the heavy chain sequence of SEQ ID NO: 159 and light chain sequence of SEQ ID NO: 154; or

(j) the heavy chain sequence of SEQ ID NO: 160 and light chain sequence of SEQ ID NO: 155.

19. An antibody or functional protein which cross-blocks or is cross blocked by at least one antibody of claim 18 from binding to ActRIIB.

20. An antibody or functional protein according to any one of claims 1-17 which cross-blocks or is cross blocked by at least one antibody of claim 18 from binding to ActRIIB.

21. An antibody or functional protein that binds to an epitope recognised by an antibody of claim 17 or claim 18.

22. An antibody or functional protein according to any one of claims 1-16 that binds to an epitope recognised by an antibody of claim 17 or claim 18.

23. An antibody according to any one of claims 1-18 which binds to an epitope comprising or consisting of:

(a) amino acids 78-83 of SEQ ID NO: 181 (WLDDFN – SEQ ID NO:188);

(b) amino acids 76-84 of SEQ ID NO: 181 (GCWLDDFNC – SEQ ID NO:186);

(c) amino acids 75-85 of SEQ ID NO: 181 (KGCWLDDFNCY – SEQ ID NO:190);

(d) amino acids 52-56 of SEQ ID NO: 181 (EQDKR – SEQ ID NO:189);

(e) amino acids 49-63 of SEQ ID NO: 181 (CEGEQDKRLHCYASW – SEQ ID NO:187); or

(f) amino acids 78-83 of SEQ ID NO: 181 (WLDDFN) and amino acids 52-56 of SEQ ID NO: 181 (EQDKR).

24. The antibody or functional protein of any one of claims 19-22 wherein cross blocking or binding to the same epitope is detected in a BIAcore assay or an ELISA.

25. An anti-ActRIIB antibody according to any previous claim, wherein said antibody is of the IgG1 isotype.

26. An anti-ActRIIB antibody according to any previous claim, which has altered effector function through mutation of the Fc region.

27. An isolated polynucleotide sequence encoding an antibody or functional protein according to any previous claim.

28. An isolated polynucleotide sequence according to claim 27, comprising one or more of SEQ ID NOs: 113-140 or 161-180.

29. A cloning or expression vector comprising one or more isolated polynucleotide sequences according to claim 27 or claim 28.

30. A vector according to claim 29, wherein said vector comprises one or more of SEQ ID NOs: 113-140 or 161-180, or fragment thereof encoding at least one CDR region.

31. A host cell comprising one or more vectors according to claim 29 or claim 30.

32. A process for the production of an antibody or functional protein of any one of claims 1-26, comprising culturing the host cell of claim 31 and isolating said antibody or functional protein.

33. A pharmaceutical composition comprising an antibody or functional protein according to any one of claims 1-26 or a polynucleotide sequence according to claim 27 or claim 28.

34. A pharmaceutical composition according to claim 33, further comprising a pharmaceutically acceptable diluent or carrier.

35. A pharmaceutical composition according to claim 33 or 34, further comprising one or more additional active agents.

36. A pharmaceutical composition according to claim 35, wherein said additional active agent is selected from IGF-1, IGF-2 or variants of IGF-1 or IGF-2, an anti-myostatin antibody, a myostatin propeptide, a myostatin decoy protein that binds ActRIIB but does not activate it, a beta 2 agonist, a Ghrelin agonist, a SARM, GH agonists/mimetics or follistatin.

37. A method of treating a patient suffering from a musculoskeletal disease or disorder; acute and/or chronic renal disease or failure; liver fibrosis or cirrhosis; cancer such as breast cancer; Parkinson's Disease; conditions associated with neuronal death, such as ALS, brain atrophy, or dementia and anemia; liver, kidney and pulmonary fibrosis; age-related conditions; and cancers examplified by but not restricted to rhabdomyosarcomas, bone-loss inducing cancers, hepatocellular carcinomas, gastrointestinal cancers, comprising

administering an effective dose of an antibody or functional protein according to any one of claims 1-26 to said patient.

38. The antibody or functional protein according to any one of claims 1-26, the polynucleotide sequence according to claim 27 or claim 28, or the pharmaceutical composition according to any one of claims 33-36 for use as a medicament.

39. Use of an antibody or functional protein according to any one of claims 1-26, the polynucleotide sequence according to claim 27 or claim 28, or the pharmaceutical composition according to any one of claims 33-36 in the manufacture of a medicament for the treatment of a musculoskeletal disease or disorder; acute and/or chronic renal disease or failure; liver fibrosis or cirrhosis; cancer such as breast cancer; Parkinson's Disease; conditions associated with neuronal death, such as ALS, brain atrophy, or dementia and anemia; liver, kidney and pulmonary fibrosis; age-related conditions; and cancers examplified by but not restricted to rhabdomyosarcomas, bone-loss inducing cancers, hepatocellular carcinomas, gastrointestinal cancers.

40. The antibody or functional protein according to any one of claims 1-26, the polynucleotide sequence according to claim 27 or claim 28, or the pharmaceutical composition according to any one of claims 33-36 for use in the treatment of a musculoskeletal disease or disorder; acute and/or chronic renal disease or failure; liver fibrosis or cirrhosis; cancer such as breast cancer; Parkinson's Disease; conditions associated with neuronal death, such as ALS, brain atrophy, or dementia and anemia; liver, kidney and pulmonary fibrosis; and cancers examplified by but not restricted to rhabdomyosarcomas, bone-loss inducing cancers, hepatocellular carcinomas, gastrointestinal cancers.

41. The use of claim 39 or 40, wherein said muscuoskeletal disease or disorder is muscle atrophy, for example caused by a myopathy, such as myotonia, a congential myopathy, including nemalene myopathy, multi/minicore myopathy and myotubular (centronuclear)

myopathy, mitochondrial myopathy, familial periodic paralysis, inflammatory myopathy, metabolic myopathy, such as caused by a glycogen or lipid storage disease, dermatomyositisis, polymyositis, inclusion body myositis, myositis ossificans, rhabdomyolysis and myoglobinurias; a dystrophy, such as Duchenne, Becker, myotonic, fascioscapulohumeral, Emery-Dreifuss, oculopharyngeal, scapulohumeral, limb girdle, Fukuyama, a congenital muscular dystrophy, or hereditary distal myopathy; osteoporosis; a bone fracture; short stature; dwarfism; prolonged bed rest; voluntary inactivity; or involuntary inactivity.

42. The use according to claim 41, wherein the patient being treated has been pre-treated with IGF-1, IGF-2 or variants of IGF-1 or IGF-2, an anti-myostatin antibody, a myostatin propeptide, a myostatin decoy protein that binds ActRIIB but does not activate it, a beta 2 agonist, a Ghrelin agonist, a SARM, GH agonists/mimetics or follistatin.

43. The use according to claim 41, wherein the patient being treated has previously been refractive to treatment with IGF-1, IGF-2 or variants of IGF-1 or IGF-2, an anti-myostatin antibody, a myostatin propeptide, a myostatin decoy protein that binds ActRIIB but does not activate it, a beta 2 agonist, a Ghrelin agonist, a SARM, GH agonists/mimetics or follistatin.

44. The use according to claim 41, wherein the patient being treated is elderly, has spent time in a zero gravity environment or has undergone a period of inactivity.

45. A method of ameliorating the muscle wasting effects of enforced inactivity or time spent in a zero gravity environment comprising administering an effective dose of an antibody or functional protein according to any one of claims 1-26 prior to said period of enforced inactivity or time spent in a zero gravity environment.

46. The use according to claim 41, wherein the patient being treated has a fracture to a limb (i.e. leg or arm) or joint (i.e. knee or hip).

47. The use according to claim 41, wherein the patient has undergone or is about to undergo, hip or knee replacement surgery.

48. An antibody encoded by pBW522 (DSM22873) or pBW524 (DSM22874).

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An isolated anti-ActRIIB antibody or functional protein that binds to ActRIIB between amino acids 19-134 of SEQ ID NO: 181 which binds to ActRIIB with a K_D of 1nM or less, preferably 100pM or less, wherein said antibody inhibits myostatin-induced ActRIIB signalling, and wherein said antibody or functional protein comprises heavy chain complementarity determining regions 1-3 and light chain complementarity determining regions 1-3 having at least 95% identity to the CDR 1 recited in SEQ ID NO: 9, the heavy chain variable regions CDR2 recited in SEQ ID NOs: 18-28, the heavy chain variable region CDR3 recited in SEQ ID NO: 37, the light chain variable region CDR1 recited in SEQ ID NO: 51, light chain variable region CDR2 recited in SEQ ID NO: 65, light chain variable regions CDR3 recited in SEQ ID NOs: 71-73 and 79.

2. An anti-ActRIIB antibody according to claim 1, wherein said antibody inhibits myostatin induced signalling as measured by a Smad dependent reporter gene assay.

3. An anti-ActRIIB antibody according to claim 1 or claim 2, wherein said antibody binds to ActRIIB with a 10-fold or greater affinity than it binds to ActRIIA.

4. The antibody or functional protein according to any one of claims 1 to 3, wherein said antibody comprises a VH polypeptide sequence having at least 95% sequence identity to at least one of SEQ ID NOs: 99, 103, 104, 106, 107, 109-112 and a VL polypeptide sequence having at least 95% sequence identity to at least one of SEQ ID NOs: 85-88.

5. The antibody or functional protein according to any one of claims 1 to 4, wherein said antibody comprises a heavy chain variable region CDR1 comprising an amino acid sequence of SEQ ID NO: 9; a heavy chain variable region CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 18-28; a heavy chain variable region CDR3 comprising an amino acid sequence of SEQ ID NO: 37; a light chain variable region CDR1 comprising an amino acid sequence of SEQ ID NO: 51; a light chain variable region CDR2 comprising an amino acid sequence of SEQ ID NO: 65; and a light chain variable region CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 71-73 and 79.

6. An antibody or functional protein according to any one of claims 1 to 5 comprising:

(a) a heavy chain variable region CDR1 of SEQ ID NO: 9; a heavy chain variable region CDR2 of SEQ ID NO: 18; a heavy chain variable region CDR3 of SEQ ID NO: 37; a light chain variable region CDR1 of SEQ ID NO: 51; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 71,

(b) a heavy chain variable region CDR1 of SEQ ID NO: 9 a heavy chain variable region CDR2 of SEQ ID NO: 18; a heavy chain variable region CDR3 of SEQ ID NO: 37; a light chain variable region CDR1 of SEQ ID NO: 51; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 72,

(c) a heavy chain variable region CDR1 of SEQ ID NO: 9; a heavy chain variable region CDR2 of SEQ ID NO: 18; a heavy chain variable region CDR3 of SEQ ID NO: 37; a light chain variable region CDR1 of SEQ ID NO: 51; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 73,

(d) a heavy chain variable region CDR1 of SEQ ID NO: 9; a heavy chain variable region CDR2 of SEQ ID NO: 18; a heavy chain variable region CDR3 of SEQ ID NO: 37; a light chain variable region CDR1 of SEQ ID NO: 51; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 79,

(e) a heavy chain variable region CDR1 of SEQ ID NO: 9; a heavy chain variable region CDR2 of SEQ ID NO: 19; a heavy chain variable region CDR3 of SEQ ID NO: 37; a light chain variable region CDR1 of SEQ ID NO: 51; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 71,

(f) a heavy chain variable region CDR1 of SEQ ID NO: 9; a heavy chain variable region CDR2 of SEQ ID NO: 20; a heavy chain variable region CDR3 of SEQ ID NO: 37; a light chain variable region CDR1 of SEQ ID NO: 51; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 71,

(g) a heavy chain variable region CDR1 of SEQ ID NO: 9; a heavy chain variable region CDR2 of SEQ ID NO: 19; a heavy chain variable region CDR3 of SEQ ID NO: 37; a light chain variable region CDR1 of SEQ ID NO: 51; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 79,

(h) a heavy chain variable region CDR1 of SEQ ID NO: 9; a heavy chain variable region CDR2 of SEQ ID NO: 22; a heavy chain variable region CDR3 of SEQ ID NO: 37; a light chain variable region CDR1 of SEQ ID NO: 51 a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 79,

(i) a heavy chain variable region CDR1 of SEQ ID NO: 9; a heavy chain variable region CDR2 of SEQ ID NO: 20; a heavy chain variable region CDR3 of SEQ ID NO: 37; a light chain variable region CDR1 of SEQ ID NO: 51; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 79,

(j) a heavy chain variable region CDR1 of SEQ ID NO: 9; a heavy chain variable region CDR2 of SEQ ID NO: 25; a heavy chain variable region CDR3 of SEQ ID NO: 37; a light chain variable region CDR1 of SEQ ID NO: 51; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 79,

(k) a heavy chain variable region CDR1 of SEQ ID NO: 9; a heavy chain variable region CDR2 of SEQ ID NO: 26; a heavy chain variable region CDR3 of SEQ ID NO: 37; a light chain variable region CDR1 of SEQ ID NO: 51; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 79,

(l) a heavy chain variable region CDR1 of SEQ ID NO: 9; a heavy chain variable region CDR2 of SEQ ID NO: 27; a heavy chain variable region CDR3 of SEQ ID NO: 37; a light chain variable region CDR1 of SEQ ID NO: 51; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 79, or

(m) a heavy chain variable region CDR1 of SEQ ID NO: 9; a heavy chain variable region CDR2 of SEQ ID NO: 28; a heavy chain variable region CDR3 of SEQ ID NO: 37; a light chain variable region CDR1 of SEQ ID NO: 51; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 79.

7. An antibody or functional protein according to any one of claims 1 to 6, wherein said antibody comprises a full length heavy chain amino acid sequence having at least 95% sequence identity to at least one sequence selected from the group consisting of SEQ ID NOs: 146-150 and 156-160, and wherein said antibody comprises a full length light chain amino acid sequence having at least 95% sequence identity to at least one sequence selected from the group consisting of SEQ ID NO: 141.

8. An antibody according to claim 1 comprising:

(a) the variable light chain sequence of SEQ ID NO: 85 and variable heavy chain sequence of SEQ ID NO: 99;

(b) the variable light chain sequence of SEQ ID NO: 86 and variable heavy chain sequence of SEQ ID NO: 99;

(c) the variable light chain sequence of SEQ ID NO: 87 and variable heavy chain sequence of SEQ ID NO: 99;

(d) the variable light chain sequence of SEQ ID NO: 88 and variable heavy chain sequence of SEQ ID NO: 99;

(e) the variable light chain sequence of SEQ ID NO: 85 and variable heavy chain sequence of SEQ ID NO: 103;

(f) the variable light chain sequence of SEQ ID NO: 85 and variable heavy chain sequence of SEQ ID NO: 104;

(g) the variable light chain sequence of SEQ ID NO: 88 and variable heavy chain sequence of SEQ ID NO: 103;

(h) the variable light chain sequence of SEQ ID NO: 88 and variable heavy chain sequence of SEQ ID NO: 106;

(i) the variable light chain sequence of SEQ ID NO: 88 and variable heavy chain sequence of SEQ ID NO: 107;

(j) the variable light chain sequence of SEQ ID NO: 88 and variable heavy chain sequence of SEQ ID NO: 104;

(k) the variable light chain sequence of SEQ ID NO: 88 and variable heavy chain sequence of SEQ ID NO: 109;

(l) the variable light chain sequence of SEQ ID NO: 88 and variable heavy chain sequence of SEQ ID NO: 110;

(m) the variable light chain sequence of SEQ ID NO: 88 and variable heavy chain sequence of SEQ ID NO: 111; or

(n) the variable light chain sequence of SEQ ID NO: 88 and variable heavy chain sequence of SEQ ID NO: 112.

9. An antibody according to claim 1 comprising:

(a) the heavy chain sequence of SEQ ID NO: 146 and light chain sequence of SEQ ID NO: 141;

(b) the heavy chain sequence of SEQ ID NO: 147 and light chain sequence of SEQ ID NO: 141;

(c) the heavy chain sequence of SEQ ID NO: 148 and light chain sequence of SEQ ID NO: 141;

(d) the heavy chain sequence of SEQ ID NO: 149 and light chain sequence of SEQ ID NO: 141;

(e) the heavy chain sequence of SEQ ID NO: 150 and light chain sequence of SEQ ID NO: 141;

(f) the heavy chain sequence of SEQ ID NO: 156 and light chain sequence of SEQ ID NO: 141;

(g) the heavy chain sequence of SEQ ID NO: 157 and light chain sequence of SEQ ID NO: 141;

(h) the heavy chain sequence of SEQ ID NO: 158 and light chain sequence of SEQ ID NO: 141;

(i) the heavy chain sequence of SEQ ID NO: 159 and light chain sequence of SEQ ID NO: 141; or

(j) the heavy chain sequence of SEQ ID NO: 160 and light chain sequence of SEQ ID NO: 141.

10. An antibody or functional protein according to any one of claims 1 to 8 which cross-blocks or is cross blocked by at least one antibody of claim 9 from binding to ActRIIB.

11. An antibody or functional protein according to any one of claims 1 to 7 that binds to an epitope recognised by an antibody of claim 8 or claim 9.

12. An antibody according to any one of claims 1 to 9 which binds to an epitope comprising or consisting of:

(a) amino acids 78-83 of SEQ ID NO: 181 (WLDDFN – SEQ ID NO: 188);

(b) amino acids 76-84 of SEQ ID NO: 181 (GCWLDDFNC – SEQ ID NO: 186);

(c) amino acids 75-85 of SEQ ID NO: 181 (KGCWLDDFNCY – SEQ ID NO: 190);

(d) amino acids 52-56 of SEQ ID NO: 181 (EQDKR – SEQ ID NO: 189);

(e) amino acids 49-63 of SEQ ID NO: 181 (CEGEQDKRLHCYASW – SEQ ID NO: 187); or

(f) amino acids 78-83 of SEQ ID NO: 181 (WLDDFN) and amino acids 52-56 of SEQ ID NO: 181 (EQDKR).

13. An antibody or functional protein according to claim 10, wherein cross blocking or binding to the same epitope is detected in a BIAcore assay or an ELISA.

14. An anti-ActRIIB antibody according to any one of claims 1 to 13, wherein said antibody is of the IgG1 isotype.

15. An anti-ActRIIB antibody according to any one of claims 1 to 14, which has altered effector function through mutation of the Fc region.

16. An isolated polynucleotide sequence encoding an antibody or functional protein according to any one of claims 1 to 15.

17. An isolated polynucleotide sequence according to claim 16, comprising one or more of SEQ ID NOs: 113-140 or 161-180.

18. A cloning or expression vector comprising one or more isolated polynucleotide sequences according to claim 16 or claim 17.

19. A vector according to claim 18, wherein said vector comprises one or more of SEQ ID NOs: 113-140 or 161-180, or fragment thereof encoding at least one CDR region.

20. A host cell comprising one or more vectors according to claim 18 or claim 19.

21. A process for the production of an antibody or functional protein of any one of claims 1 to 15, comprising culturing the host cell of claim 20 and isolating said antibody or functional protein.

22. A pharmaceutical composition comprising an antibody or functional protein according to any one of claims 1 to 15 or a polynucleotide sequence according to claim 16 or claim 17.

23. A pharmaceutical composition according to claim 22, further comprising a pharmaceutically acceptable diluent or carrier.

24. A pharmaceutical composition according to claim 22 or claim 23, further comprising one or more additional active agents.

25. A pharmaceutical composition according to claim 24, wherein said additional active agent is selected from IGF-1, IGF-2 or variants of IGF-1 or IGF-2, an anti-myostatin antibody, a myostatin propeptide, a myostatin decoy protein that binds ActRIIB but does not activate it, a beta 2 agonist, a Ghrelin agonist, a SARM, GH agonists/mimetics or follistatin.

26. Use of an antibody or functional protein according to any one of claims 1 to 15, a polynucleotide sequence according to claim 16 or claim 17, or a pharmaceutical composition according to any one of claims 22 to 25 in the manufacture of a medicament for the treatment of a musculoskeletal disease or disorder; acute and/or chronic renal disease or failure; liver fibrosis or cirrhosis; cancer such as breast cancer; Parkinson's Disease; conditions associated with neuronal death, such as ALS, brain atrophy, or dementia and anemia; liver, kidney and pulmonary fibrosis; age-related conditions; and cancers examplified by but not restricted to rhabdomyosarcomas, bone-loss inducing cancers, hepatocellular carcinomas, gastrointestinal cancers.

27. The use according to claim 26, wherein said musculoskeletal disease or disorder is muscle atrophy, for example caused by a myopathy, such as myotonia, a congential myopathy, including nemalene myopathy, multi/minicore myopathy and myotubular (centronuclear) myopathy, mitochondrial myopathy, familial periodic paralysis, inflammatory myopathy, metabolic myopathy, such as caused by a glycogen or lipid storage disease, dermatomyositisis, polymyositis, inclusion body myositis, myositis ossificans, rhabdomyolysis and myoglobinurias; a dystrophy, such as Duchenne, Becker, myotonic, fascioscapulohumeral, Emery-Dreifuss, oculopharyngeal, scapulohumeral, limb girdle, Fukuyama, a congenital muscular dystrophy, or hereditary distal myopathy; osteoporosis; a bone fracture; short stature; dwarfism; prolonged bed rest; voluntary inactivity; or involuntary inactivity.

28. The use according to claim 27, wherein the patient being treated has been pre-treated with IGF-1, IGF-2 or variants of IGF-1 or IGF-2, an anti-myostatin antibody, a myostatin propeptide, a myostatin decoy protein that binds ActRIIB but does not activate it, a beta 2 agonist, a Ghrelin agonist, a SARM, GH agonists/mimetics or follistatin.

29. The use according to claim 27, wherein the patient being treated has previously been refractive to treatment with IGF-1, IGF-2 or variants of IGF-1 or IGF-2, an anti-myostatin antibody, a myostatin propeptide, a myostatin decoy protein that binds ActRIIB but does not activate it, a beta 2 agonist, a Ghrelin agonist, a SARM, GH agonists/mimetics or follistatin.

30. The use according to claim 27, wherein the patient being treated is elderly, has spent time in a zero gravity environment or has undergone a period of inactivity.

31. The use according to claim 27, wherein the patient being treated has a fracture to a limb (i.e. leg or arm) or joint (i.e. knee or hip).

32. The use according to claim 27, wherein the patient has undergone or is about to undergo, hip or knee replacement surgery.

33. A therapeutic ActRIIB antibody encoded by pBW522 (DSM22873) or pBW524 (DSM22874), wherein said antibody inhibits myostatin-induced ActRIIB signalling.