patients on hemodialysis and Acceleron Pharma's ACE-031, an ActRIIB-Fc fusion protein has been clinically evaluated (Ph1, Ph2) for therapeutic efficacy in Duchenne muscle dystrophy (DMD) (ClinicalTrials.gov).

[007] Unfortunately, while appearing effective, the clinical potential of ACE-011 for treating osteoporosis was hampered by safety concerns (high RBC growth) and ACE-031, while demonstrating a significant muscle gain which was more pronounced than that caused by a myostatin-selective inhibitor, such as myostatin antibody, peptibody or propeptide, has been hampered by the adverse event in nose and gum bleeding seen in DMD patients, thus there was a clinical hold put on ACE-031 (Smith R.C. and Lin B.K., Curr Opin Support Palliat Care. 7(4): 352–360, 2013). Consequently, ACE-031 was discontinued in DMD Phase2 trial due to the side effect of nose and gum bleeding despite its promising sign of efficacy to improve muscle mass and function in DMD patients. It thus appears that the wild-type ActRIIB-Fc is capable of blocking BMP9 mediated Smad1/3/8 signaling that is critical in maintaining blood vessel homeostasis, and this functional blockade of BMP9 by the wild-type ActRIIB is believed to be the underlying cause of the bleeding side effect, as compelling new genetic evidence has linked loss-of-function mutations of BMP9 to vascular anomaly and bleeding syndrome in humans (Wooderchak-Donahue et. al., Am J Hum Genet., 93(3): 530–537, Sep 2013).

[008] So while there have been important advancements, there still exists a critical need to provide novel therapeutics, which are both highly effective and safe, for the treatment of muscle wasting and/or bone disease associated with the development of a number of chronic, neurological, genetic, inflammatory, fibrotic or infectious pathologies.

Incorporation by Reference

[009] All references disclosed herein are hereby incorporated by reference in their entirety for all purposes.

Summary

[009a] In one aspect, the present disclosure refers to the use of a hybrid activin IIB receptor (ActRIIB) ligand trap for the manufacture of a medicament for treating or preventing muscle wasting in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble activin IIB receptor-extracellular domain (ActRIIB-ECD)

polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

[009b] In another aspect, the present disclosure refers to the use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for treating or preventing a bone disease in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

[009c] In another aspect, the present disclosure refers to the use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for treating or preventing a metabolic disorder in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

[009d] In another aspect, the present disclosure refers to the use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for treating or preventing fibrosis in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy

or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

[009e] In another aspect, the present disclosure refers to the use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for treating or preventing an autoimmune/inflammatory disease in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

[009f] In another aspect, the present disclosure refers to the use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for treating a cardiovascular disease in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

[009g] In another aspect, the present disclosure refers to the use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for treating or preventing a cancer or cancer metastasis in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

[009h] In another aspect, the present disclosure refers to the use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for treating or preventing a chronic kidney disease (CKD) in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

[009i] In another aspect, the present disclosure refers to the use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for treating or preventing an arthritis in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted

with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

[009j] In another aspect, the present disclosure refers to the use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for treating or preventing anorexia in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

[009k] In another aspect, the present disclosure refers to the use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for treating or preventing a liver disease in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

[009l] In another aspect, the present disclosure refers to the use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for organ or tissue transplantation in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40,

S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

[009m] In another aspect, the present disclosure refers to the use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for treating or preventing an anemia disorder in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

[009n] In another aspect, the present disclosure refers to the use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for treating pain in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

[009o] In another aspect, the present disclosure refers to the use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for treating an aging condition in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide

comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

[009p] In another aspect, the present disclosure refers to the use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for inducing stem cell growth for tissue repair or organ regeneration in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

Disclosure of the Invention

[010] In one aspect, the present disclosure provides a method of treating or preventing a muscle wasting in a subject, comprising administering to the subject a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of a hybrid ActRIIB ligand trap of the present disclosure in admixture with a pharmaceutically acceptable carrier, wherein such administration attenuates the loss of muscle mass and/or loss of muscle function. In

What is claimed is:

1. Use of a hybrid activin IIB receptor (ActRIIB) ligand trap for the manufacture of a medicament for treating or preventing muscle wasting in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble activin IIB receptor-extracellular domain (ActRIIB-ECD) polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

2. A use according to claim 1, wherein the muscle wasting is associated with a disease selected from the group consisting of: muscular dystrophies, myositis, myopathies (including inherited myopathy and acquired myopathy), motorneuron diseases, neurodegenerative diseases (such as Parkinson's disease, Huntington's disease and Alzheimer's disease), peripheral nerve disease, and spinal muscular atrophy.

3. A use according to claim 2, wherein the muscular dystrophy is selected from the group consisting of: Duchenne's Muscular Dystrophy (DMD), Becker Muscular Dystrophy, Limb-Girdle Muscular Dystrophy, Myotonic Muscular Dystrophy and Facioscapulohumeral Muscular Dystrophy (FSHD).

4. A use according to claim 2, wherein the spinal muscular atrophy is selected from the group consisting of Infantile progressive spinal muscular atrophy, Intermediate spinal muscular atrophy, Juvenile spinal muscular atrophy and Adult spinal muscular atrophy.

5. A use according to claim 2, wherein the peripheral nerve disease is Charcot-Marie Tooth disease.

6. A use according to claim 2, wherein the motorneuron disease is amyotrophic lateral sclerosis (ALS).

7. A use according to claim 2, wherein the medicament is suitable for administration by a method selected from the group consisting of: subcutaneous, intramuscular, intravenous, or intrathecal administration.

8. A use according to claim 2, wherein the medicament comprising a hybrid ActRIIB ligand trap is to be administered to the subject in a combination therapy regimen, wherein the combination therapy regimen comprises administering to the subject the medicament comprising a hybrid ActRIIB ligand trap and a separate composition comprising a second therapeutic agent, wherein the second therapeutic agent is selected from the group consisting of gene therapy, gene targeting therapy, and antisense oligonucleotide therapy.

9. A use according to any of claims 2-8, wherein the medicament comprising a hybrid ActRIIB ligand trap is to be administered to the subject concurrently with the administration of a separate composition comprising a second therapeutic agent.

10. A use according to any of claims 2-8, wherein the medicament comprising a hybrid ActRIIB ligand trap is to be administered before a separate composition comprising a second therapeutic agent is to be administered to the subject.

11. A use according to any of claims 2-8, wherein the medicament comprising a hybrid ActRIIB ligand trap is to be administered after a separate composition comprising a second therapeutic agent is to be administered to the subject.

12. Use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for treating or preventing a bone disease in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or

T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

13. A use according to claim 12, wherein the bone disease is selected from the group consisting of: osteoporosis, osteomalacia, osteogenesis imperfecta, fibrodysplasia ossificans progressiva, corticosteroid-induced bone loss, bone fracture, and bone metastasis.

14. Use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for treating or preventing a metabolic disorder in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

15. A use according to claim 14, wherein the metabolic disorder is selected from the group consisting of: obesity, dyslipidemia, sarcopenic obesity, non-alcoholic fatty liver disease such as non-alcoholic steatohepatitis, alcoholic fatty liver disease, insulin resistance, diabetes and metabolic syndrome, as well as diabetic myopathy, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, and hemochromatosis.

16. Use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for treating or preventing fibrosis in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted

with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

17. A use according to claim 16, wherein the fibrosis is selected from the group consisting of: interstitial lung disease, idiotypic pulmonary fibrosis, cystic fibrosis, liver fibrosis, cirrhosis, cardiac fibrosis, renal fibrosis, myelofibrosis, idiopathic retroperitoneal fibrosis, nephrogenic fibrosing dermopathy, inflammatory bowel disease, keloid, scleroderma and arthrofibrosis.

18. Use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for treating or preventing an autoimmune/inflammatory disease in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

19. A use according to claim 18, wherein the autoimmune/inflammatory disease is selected from the group consisting of: multiple sclerosis, systemic sclerosis, type-1 diabetes, glomerulonephritis, myasthenia gravis, psoriasis, systemic lupus erythematosus, polymyositis, Crohn's disease, ulcerative colitis, and primary biliary cirrhosis.

20. Use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for treating a cardiovascular disease in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted

with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

21. A use according to claim 20, wherein the cardiovascular disease is selected from the group consisting of: heart failure, cardiac atrophy, hypertension, myocarditis, coronary artery disease, myocardial infarction, cardiac arrhythmias, heart valve disease, cardiomyopathy, pericardial disease, aorta disease and Marfan syndrome.

22. Use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for treating or preventing a cancer or cancer metastasis in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

23. A use according to claim 22, wherein the cancer is selected from the group consisting of: pancreatic cancer, gastric cancer, ovarian cancer, colorectal cancer, melanoma, leukemia, myelodysplastic syndrome, lung cancer, prostate cancer, brain cancer, bladder cancer, head-neck cancer, and rhabdomyosarcoma.

24. Use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for treating or preventing a chronic kidney disease (CKD) in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107,

A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

25. A use according to claim 24, wherein the CKD is selected from the group consisting of: renal failure, interstitial fibrosis, kidney dialysis, renal osteodystrophy, and protein energy wasting (PEW) associated with CKD.

26. Use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for treating or preventing an arthritis in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

27. A use according to claim 26, wherein the arthritis is selected from the group consisting of: rheumatoid arthritis and osteoarthritis.

28. Use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for treating or preventing anorexia in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

29. A use according to claim 28, wherein the anorexia is selected from anorexia nervosa and anorexia-cachexia syndrome.

30. Use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for treating or preventing a liver disease in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

31. A use according to claim 31, wherein the liver disease is selected from the group consisting of non-alcoholic steatohepatitis, liver fibrosis or cirrhosis, liver failure, autoimmune hepatitis, and hepatocellular carcinoma.

32. Use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for organ or tissue transplantation in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

33. A use according to claim 32, wherein the transplantation is selected from the group consisting of: organ transplantations of the heart, kidneys, liver, lungs, pancreas, intestine and

thymus and tissues transplantations of the bones, tendons, cornea, skin, heart valves, nerves and veins.

34. Use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for treating or preventing an anemia disorder in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

35. A use according to claim 34, wherein the anemia disorder is selected from the group consisting of: iron deficiency anemia, iron overload, thalassemia, hemolytic anemia, sickle cell anemia, pernicious anemia, fanconi anemia and aplastic anemia (such as cancer-associated anemia and chemotherapy-induced anemia).

36. Use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for treating pain in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

37. A use according to claim 36, wherein the pain is selected from the group consisting of: neuropathic pain, somatic pain, visceral pain, inflammatory pain, cancer pain, back pain, and joint pain.

38. Use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for treating an aging condition in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

39. A use according to claim 38, wherein the aging condition is selected from the group consisting of: frailty of the elderly, age-related sarcopenia, and osteoarthritis.

40. Use of a hybrid ActRIIB ligand trap for the manufacture of a medicament for inducing stem cell growth for tissue repair or organ regeneration in a subject, wherein the medicament comprises a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of the hybrid ActRIIB ligand trap in admixture with a pharmaceutically acceptable carrier, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least one of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, E94, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 is substituted with another amino acid, and wherein administration of the hybrid ActRIIB ligand trap to the subject attenuates the loss of muscle mass and/or loss of muscle function.

41. A use according to claim 40, wherein the stem cell is selected from the group consisting of: muscle stem (satellite) cell, cardiac stem cell, bone marrow-derived mesynchymal stem cell and pluripotent stem cell.

42. A use according to any one of claims 1 to 41, wherein the hybrid ActRIIB ligand trap protein comprises a hybrid soluble ActRIIB-ECD polypeptide, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104, SEQ ID NO: 105, SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 115, SEQ ID NO: 116, and SEQ ID NO: 117.

43. A use according to any one of claims 1 to 41, wherein said hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 1, wherein at least two of amino acid residues R3, I6, Y7, Y8, L14, E15, S20, L22, R24, E26, E28, Q29, L33, L48, Y36, S38, R40, S42, T45, K51, F58, Q64, E65, A68, T69, E70, E71, N72, Q74, F84, R88, T90, H91, L92, A95, G96, G97, P98, E99, V100, Y102, E103, P105, P106, T107, A108, or T110 are substituted with the corresponding amino acid residues of SEQ ID NO: 2, and wherein the hybrid ActRIIB-ECD polypeptide is capable of binding myostatin and activin A, but demonstrates a decreased binding affinity for bone morphogenic protein 9 (BMP9) relative to a wild-type ActRIIB-ECD polypeptide.

44. A use according to any one of claims 1 to 43, wherein the hybrid ActRIIB ligand trap protein comprises an human Fc domain derived from a human immunoglobulin Fc domain

comprising an amino acid sequence selected from the group consisting of: SEQ ID NO: 38, SEQ ID NO: 40, and SEQ ID NO: 42.

45. A use according to claim 44, wherein the hybrid ActRIIB ligand trap protein comprises a human Fc domain comprising the amino acid sequence selected from the group consisting of: SEQ ID NO: 39, SEQ ID NO: 41, and SEQ ID NO: 43 linked to the hybrid soluble ActRIIB-ECD polypeptide.

46. A use according to claim 44 or 45, wherein a linker is used to link the human Fc domain to the hybrid soluble ActRIIB-ECD polypeptide.

47. A use according to claim 46, wherein a peptide linker comprising the amino acid sequence set forth in SEQ ID NO: 44 is used with a hinge linker comprising the amino acid sequence set forth in SEQ ID NO: 118 to link the human Fc domain to the hybrid soluble ActRIIB-ECD polypeptide.

48. A use according to any one of claims 1 to 47, wherein the hybrid ActRIIB ligand trap comprises a hybrid soluble ActRIIB-ECD polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 16 and SEQ ID NO: 29.

49. A use according to claim 48, wherein the hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 16 attached to a human Fc domain having an amino acid sequence of SEQ ID NO: 43.

50. A use according to claim 48, wherein the hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 29 attached to a human Fc domain having an amino acid sequence of SEQ ID NO: 43.

51. A use according to claim 49, wherein the hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 16, and wherein said hybrid soluble ActRIIB-ECD polypeptide is fused to a peptide linker comprising the amino acid sequence set forth in SEQ ID NO: 44, wherein said peptide linker is fused to a hinge linker comprising the amino acid sequence set forth in SEQ ID NO: 118, and wherein said hinge linker is fused to a human Fc domain comprising the amino acid sequence of SEQ ID NO: 43.

52. A use according to claim 50, wherein the hybrid soluble ActRIIB-ECD polypeptide comprises the amino acid sequence of SEQ ID NO: 29, and wherein said hybrid soluble ActRIIB-ECD polypeptide is fused to a peptide linker comprising the amino acid sequence set forth in SEQ ID NO: 44, wherein said peptide linker is fused to a hinge linker comprising the amino acid sequence set forth in SEQ ID NO: 118, and wherein said hinge linker is fused to a human Fc domain comprising the amino acid sequence of SEQ ID NO: 43.