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(71) Applicant: JUVENA THERAPEUTICS, INC. [US/US];

2627 Hanover Street, Palo Alto, California 94304 (US).

(72) Inventors: YOUSEF, Hanadie; 2627 Hanover Street, Palo Alto, California 94304 (US). MAI, Thach; 2627 Hanover Street, Palo Alto, California 94304 (US). O'CONNELL, Jeremy; 2627 Hanover Street, Palo Alto, California 94304 (US).

(74) Agent: BRESNAHAN, Matthew J.; WILSON SONSINI GOODRICH & ROSATI, 650 Page Mill Road, Palo Alto, California 94304 (US).

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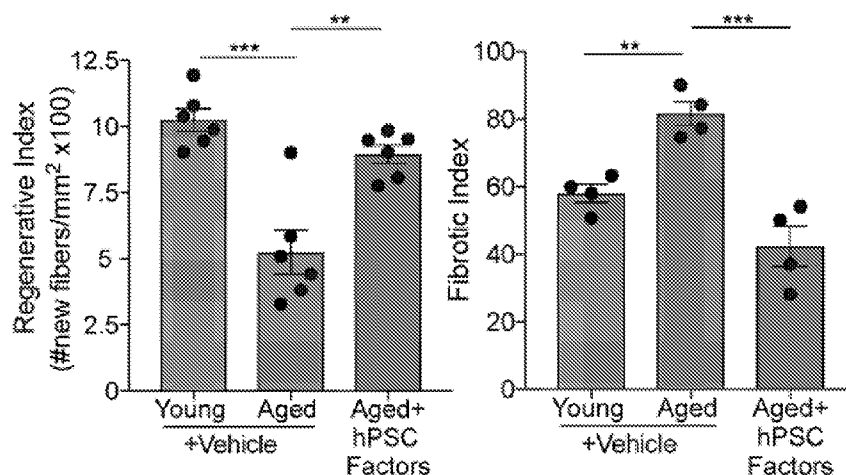


FIG. 2B

(57) Abstract: Described herein are therapeutic compositions comprising heparin-associated polypeptides useful for the treatment of soft-tissue and muscle diseases, disorders, and injuries.

HEPARIN-ASSOCIATED POLYPEPTIDES AND USES THEREOF**PRIORITY**

[0001] This application claims the benefit of U.S. Provisional Application No. 62/690,796 filed June 27, 2018, and U.S. Provisional Application No. 62/809,479 filed February 22, 2019, both of which are incorporated by reference in their entirety herein.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on June 26, 2019, is named 54275-702_601_SL.txt and is 277,008 bytes in size.

BACKGROUND

[0003] As the average life span increases, increasing emphasis is placed upon “healthy aging.” Individuals would like to live more active lifestyles as they age, and as a result, many aging disorders can have a significant impact on the quality of life of aging individuals. Treatments directed to regenerative ends have utility for treating aging diseases. Additionally, many treatments for aging disorders can be applicable to younger individuals who have suffered illness, injury, or who possess genetic or developmental defects leading to premature tissue loss, wasting, or weakening.

SUMMARY

[0004] As individuals age, tissue progenitor cells lose their regenerative potential. Described herein, in certain aspects, are heparin-associated polypeptides that can restore some or all of this regenerative potential, and are thus useful in the treatment of aging disorders that result in tissue loss or underperformance, and rehabilitation from injury. Described herein are therapeutic compositions comprising heparin-associated polypeptides and methods of treating disorders associated with aging, injury, or illness. In certain embodiments, the therapeutic compositions comprise one or more heparin-associated polypeptides that possess mitogenic (i.e., regenerative) and/or fusion promoting activity to a somatic cell, such as a tissue progenitor cell. In certain embodiments, the therapeutic compositions have activity towards muscle and soft tissue progenitor cells. In certain embodiments these compositions possess utility in treating sarcopenia, cachexia, muscular dystrophy, acute and chronic muscle wasting diseases, and muscle, ligament, or tendon injury, or any combination of these diseases or conditions.

[0005] In one aspect, described herein is a composition comprising: (a) a first therapeutic

polypeptide comprising a first polypeptide of Table 2, and (b) a second therapeutic polypeptide comprising a second polypeptide of Table 2. In certain embodiments, the first polypeptide of Table 2 is a first polypeptide of Table 1 and/or the second polypeptide of Table 2 is a second polypeptide of Table 1. In certain embodiments, the first polypeptide of Table 2 comprises THBS1, THBS2, THBS4, FGF17, VTN, POSTN, IGF2, or IL-15, or any combination thereof. In certain embodiments, the second polypeptide of Table 2 comprises THBS1, THBS2, THBS4, FGF17, VTN, POSTN, IGF2, or IL-15, or any combination thereof.

[0006] In certain embodiments, the first polypeptide of Table 2 comprises THBS1 and/or a sequence comprising at least about 90% homology to amino acids 19-1170 of SEQ ID NO: 9; and the second polypeptide of Table 2 comprises THBS2 and/or a sequence comprising at least about 90% homology to amino acids 19-1172 of SEQ ID NO: 4.

[0007] In certain embodiments, the first polypeptide of Table 2 comprises THBS1 and/or a sequence comprising at least about 90% homology to amino acids 19-1170 of SEQ ID NO: 9; and the second polypeptide of Table 2 comprises THBS4 and/or a sequence comprising at least about 90% homology to amino acids 27-961 of SEQ ID NO: 8.

[0008] In certain embodiments, the first polypeptide of Table 2 comprises THBS1 and/or a sequence comprising at least about 90% homology to amino acids 19-1170 of SEQ ID NO: 9; and the second polypeptide of Table 2 comprises FGF17 and/or a sequence comprising at least about 90% homology to amino acids 23-2165 of SEQ ID NO: 7.

[0009] In certain embodiments, the first polypeptide of Table 2 comprises THBS1 and/or a sequence comprising at least about 90% homology to amino acids 19-1170 of SEQ ID NO: 9; and the second polypeptide of Table 2 comprises VTN and/or a sequence comprising at least about 90% homology to amino acids 20-478 of SEQ ID NO: 1.

[0010] In certain embodiments, the first polypeptide of Table 2 comprises THBS1 and/or a sequence comprising at least about 90% homology to amino acids 19-1170 of SEQ ID NO: 9; and the second polypeptide of Table 2 comprises POSTN and/or a sequence comprising at least about 90% homology to amino acids 22-836 of SEQ ID NO: 6.

[0011] In certain embodiments, the first polypeptide of Table 2 comprises THBS1 and/or a sequence comprising at least about 90% homology to amino acids 19-1170 of SEQ ID NO: 9; and the second polypeptide of Table 2 comprises IGF2 and/or a sequence comprising at least about 90% homology to amino acids 25-91 of SEQ ID NO: 11.

[0012] In certain embodiments, the first polypeptide of Table 2 comprises THBS1 and/or a sequence comprising at least about 90% homology to amino acids 19-1170 of SEQ ID NO: 9; and the second polypeptide of Table 2 comprises IL-15 and/or a sequence comprising at least about 90% homology to amino acids 49-162 of SEQ ID NO: 10.

[0013] In certain embodiments, the first polypeptide of Table 2 comprises THBS2 and/or a sequence comprising at least about 90% homology to amino acids 19-1172 of SEQ ID NO: 4; and the second polypeptide of Table 2 comprises THBS4 and/or a sequence comprising at least about 90% homology to amino acids 27-961 of SEQ ID NO: 8. In certain embodiments, the composition further comprises IL-15 and/or a polypeptide comprising at least about 90% homology to amino acids 49-162 of SEQ ID NO: 10. In certain embodiments, the composition further comprises IGF2 and/or a polypeptide comprising at least about 90% homology to amino acids 25-91 of SEQ ID NO: 11.

[0014] In certain embodiments, the first polypeptide of Table 2 comprises THBS2 and/or a sequence comprising at least about 90% homology to amino acids 19-1172 of SEQ ID NO: 4; and the second polypeptide of Table 2 comprises FGF17 and/or a sequence comprising at least about 90% homology to amino acids 23-2165 of SEQ ID NO: 7.

[0015] In certain embodiments, the first polypeptide of Table 2 comprises THBS2 and/or a sequence comprising at least about 90% homology to amino acids 19-1172 of SEQ ID NO: 4; and the second polypeptide of Table 2 comprises VTN and/or a sequence comprising at least about 90% homology to amino acids 20-478 of SEQ ID NO: 1.

[0016] In certain embodiments, the first polypeptide of Table 2 comprises THBS2 and/or a sequence comprising at least about 90% homology to amino acids 19-1172 of SEQ ID NO: 4; and the second polypeptide of Table 2 comprises POSTN and/or a sequence comprising at least about 90% homology to amino acids 22-836 of SEQ ID NO: 6.

[0017] In certain embodiments, the first polypeptide of Table 2 comprises THBS2 and/or a sequence comprising at least about 90% homology to amino acids 19-1172 of SEQ ID NO: 4; and the second polypeptide of Table 2 comprises IGF2 and/or a sequence comprising at least about 90% homology to amino acids 25-91 of SEQ ID NO: 11.

[0018] In certain embodiments, the first polypeptide of Table 2 comprises THBS2 and/or a sequence comprising at least about 90% homology to amino acids 19-1172 of SEQ ID NO: 4; and the second polypeptide of Table 2 comprises IL-15 and/or a sequence comprising at least about 90% homology to amino acids 49-162 of SEQ ID NO: 10.

[0019] In certain embodiments, the first polypeptide of Table 2 comprises THBS4 and/or a sequence comprising at least about 90% homology to amino acids 27-961 of SEQ ID NO: 8; and the second polypeptide of Table 2 comprises FGF17 and/or a sequence comprising at least about 90% homology to amino acids 23-2165 of SEQ ID NO: 7.

[0020] In certain embodiments, the first polypeptide of Table 2 comprises THBS4 and/or a sequence comprising at least about 90% homology to amino acids 27-961 of SEQ ID NO: 8; and the second polypeptide of Table 2 comprises VTN and/or a sequence comprising at least about

90% homology to amino acids 20-478 of SEQ ID NO: 1.

[0021] In certain embodiments, the first polypeptide of Table 2 comprises THBS4 and/or a sequence comprising at least about 90% homology to amino acids 27-961 of SEQ ID NO: 8; and the second polypeptide of Table 2 comprises POSTN and/or a sequence comprising at least about 90% homology to amino acids 22-836 of SEQ ID NO: 6.

[0022] In certain embodiments, the first polypeptide of Table 2 comprises THBS4 and/or a sequence comprising at least about 90% homology to amino acids 27-961 of SEQ ID NO: 8; and the second polypeptide of Table 2 comprises IGF2 and/or a sequence comprising at least about 90% homology to amino acids 25-91 of SEQ ID NO: 11.

[0023] In certain embodiments, the first polypeptide of Table 2 comprises THBS4 and/or a sequence comprising at least about 90% homology to amino acids 27-961 of SEQ ID NO: 8; and the second polypeptide of Table 2 comprises IL-15 and/or a sequence comprising at least about 90% homology to amino acids 49-162 of SEQ ID NO: 10.

[0024] In certain embodiments, the first polypeptide of Table 2 comprises FGF17 and/or a sequence comprising at least about 90% homology to amino acids 23-2165 of SEQ ID NO: 7; and the second polypeptide of Table 2 comprises VTN and/or a sequence comprising at least about 90% homology to amino acids 20-478 of SEQ ID NO: 1.

[0025] In certain embodiments, the first polypeptide of Table 2 comprises FGF17 and/or a sequence comprising at least about 90% homology to amino acids 23-2165 of SEQ ID NO: 7; and the second polypeptide of Table 2 comprises POSTN and/or a sequence comprising at least about 90% homology to amino acids 22-836 of SEQ ID NO: 6.

[0026] In certain embodiments, the first polypeptide of Table 2 comprises FGF17 and/or a sequence comprising at least about 90% homology to amino acids 23-2165 of SEQ ID NO: 7; and the second polypeptide of Table 2 comprises IGF2 and/or a sequence comprising at least about 90% homology to amino acids 25-91 of SEQ ID NO: 11.

[0027] In certain embodiments, the first polypeptide of Table 2 comprises FGF17 and/or a sequence comprising at least about 90% homology to amino acids 23-2165 of SEQ ID NO: 7; and the second polypeptide of Table 2 comprises IL-15 and/or a sequence comprising at least about 90% homology to amino acids 49-162 of SEQ ID NO: 10.

[0028] In certain embodiments, the first polypeptide of Table 2 comprises VTN and/or a sequence comprising at least about 90% homology to amino acids 20-478 of SEQ ID NO: 1; and the second polypeptide of Table 2 comprises POSTN and/or a sequence comprising at least about 90% homology to amino acids 22-836 of SEQ ID NO: 6.

[0029] In certain embodiments, the first polypeptide of Table 2 comprises VTN and/or a sequence comprising at least about 90% homology to amino acids 20-478 of SEQ ID NO: 1; and

the second polypeptide of Table 2 comprises IGF2 and/or a sequence comprising at least about 90% homology to amino acids 25-91 of SEQ ID NO: 11.

[0030] In certain embodiments, the first polypeptide of Table 2 comprises VTN and/or a sequence comprising at least about 90% homology to amino acids 20-478 of SEQ ID NO: 1; and the second polypeptide of Table 2 comprises IL-15 and/or a sequence comprising at least about 90% homology to amino acids 49-162 of SEQ ID NO: 10.

[0031] In certain embodiments, the first polypeptide of Table 2 comprises POSTN and/or a sequence comprising at least about 90% homology to amino acids 22-836 of SEQ ID NO: 6; and the second polypeptide of Table 2 comprises IGF2 and/or a sequence comprising at least about 90% homology to amino acids 25-91 of SEQ ID NO: 11.

[0032] In certain embodiments, the first polypeptide of Table 2 comprises POSTN and/or a sequence comprising at least about 90% homology to amino acids 22-836 of SEQ ID NO: 6; and the second polypeptide of Table 2 comprises IL-15 and/or a sequence comprising at least about 90% homology to amino acids 49-162 of SEQ ID NO: 10.

[0033] In certain embodiments, the first polypeptide of Table 2 comprises IGF2 and/or a sequence comprising at least about 90% homology to amino acids 25-91 of SEQ ID NO: 11; and the second polypeptide of Table 2 comprises IL-15 and/or a sequence comprising at least about 90% homology to amino acids 49-162 of SEQ ID NO: 10.

[0034] In certain embodiments, the first therapeutic polypeptide has been recombinantly produced, the second polypeptide has been recombinantly produced, or both the first and second therapeutic polypeptides have been recombinantly produced. In certain embodiments, the first therapeutic polypeptide has been produced in a mammalian, yeast, insect or bacteria cell, the second polypeptide has been produced in a mammalian, yeast, insect or bacteria cell, or both the first and second therapeutic polypeptides have been produced in a mammalian, yeast, insect or bacteria cell. In certain embodiments, the first therapeutic polypeptide and/or the second therapeutic polypeptide have been produced in a mammalian cell and the mammalian cell is a human cell. In some cases the human cell is a human embryonic kidney-derived epithelial cell (e.g., HEK293 cell). In certain embodiments, the first therapeutic polypeptide has been produced in a mammalian cell and the mammalian cell is a Chinese Hamster Ovary (CHO) cell or mouse myeloma cell. In certain embodiments, the second therapeutic polypeptide has been produced in a mammalian cell and the mammalian cell is a Chinese Hamster Ovary (CHO) cell or mouse myeloma cell. In certain embodiments, the first therapeutic polypeptide and/or the second therapeutic polypeptide has been purified from a human biological sample. In some cases, the human biological sample is human plasma. In certain embodiments, the composition further comprises a pharmaceutically acceptable excipient. In certain embodiments, the composition is

formulated for administration by injection. In certain embodiments, the injection is intramuscular. In certain embodiments, the injection is subcutaneous. In certain embodiments, the injection is intravenous.

[0035] In another aspect, described herein is a composition comprising a polypeptide of Table 2 and a pharmaceutically acceptable excipient. In certain embodiments, the polypeptide comprises VTN and/or a sequence comprising at least about 90% homology to amino acids 20-478 of SEQ ID NO: 1. In certain embodiments, the polypeptide comprises POSTN and/or a sequence comprising at least about 90% homology to amino acids 22-836 of SEQ ID NO: 6. In certain embodiments, the polypeptide comprises FGF17 and/or a sequence comprising at least about 90% homology to amino acids 23-2165 of SEQ ID NO: 7. In certain embodiments, the polypeptide comprises THBS2 and/or a sequence comprising at least about 90% homology to amino acids 19-1172 of SEQ ID NO: 4. In certain embodiments, the polypeptide comprises THBS4 and/or a sequence comprising at least about 90% homology to amino acids 27-961 of SEQ ID NO: 8. In certain embodiments, the polypeptide comprises THBS1 and/or a sequence comprising at least about 90% homology to amino acids 19-1170 of SEQ ID NO: 9. In certain embodiments, the polypeptide comprises IL-15 and/or a sequence comprising at least about 90% homology to amino acids 49-162 of SEQ ID NO: 10. In certain embodiments, the polypeptide comprises IGF2 and/or a sequence comprising at least about 90% homology to amino acids 25-91 of SEQ ID NO: 11. In certain embodiments, the polypeptide has been produced in a mammalian cell and the mammalian cell is a human cell. In some cases the human cell is a human embryonic kidney-derived epithelial cell (e.g., HEK293 cells). In certain embodiments, the polypeptide has been expressed from a Chinese Hamster Ovary (CHO) cell, or mouse myeloma (NS0) cell, insect, or a bacterial cell. In some cases the bacterial cell is an *E. coli* cell. In certain embodiments, the polypeptide has been purified from a human biological sample. In some cases, the human biological sample is human plasma. In certain embodiments, the polypeptide is synthetically produced. In certain embodiments, the polypeptide possesses mitogenic and/or fusion promoting activity. Further described is a nucleic acid encoding the polypeptide described herein. Further described is a cell line comprising the nucleic acid.

[0036] Further described herein is a method of treating a disease or condition in a subject in need thereof, the method comprising administering to the subject a composition described herein. In certain embodiments, the disease or condition comprises an aging disorder, muscle wasting disorder, muscle injury, or injury to connective tissue, or a combination thereof. In certain embodiments, the subject has the aging disorder and the aging disorder comprises sarcopenia. In certain embodiments, the subject has the muscle wasting disorder and the muscle wasting disorder comprises muscular dystrophy. In certain embodiments, the subject has the muscle

wasting disorder and the muscle wasting is a result of obesity, disease progression, metabolic disorder, or therapeutic treatment, or a combination thereof. In certain embodiments, the metabolic disorder is diabetes. In some cases the diabetes is Type 2 Diabetes. In certain embodiments, the subject has the muscle wasting disorder and the muscle wasting is cachexia, e.g., muscular cachexia.

[0037] In another aspect, described herein is a composition comprising: (a) a first therapeutic polypeptide comprising THBS1, THBS2, THBS4, FGF17, VTN, POSTN, IGF2, or IL-15, and (b) a second therapeutic polypeptide comprising THBS1, THBS2, THBS4, FGF17, VTN, POSTN, IGF2, or IL-15. In certain embodiments, the first therapeutic polypeptide has been recombinantly produced, the second polypeptide has been recombinantly produced, or both the first and second therapeutic polypeptides have been recombinantly produced. In certain embodiments, the first therapeutic polypeptide has been produced in a mammalian, yeast, insect or bacteria cell, the second polypeptide has been produced in a mammalian, yeast, insect or bacteria cell, or both the first and second therapeutic polypeptides have been produced in a mammalian, yeast, insect or bacteria cell. In certain embodiments, the polypeptide has been produced in a mammalian cell and the mammalian cell is a human cell. In some cases the human cell is a human embryonic kidney-derived epithelial cell (e.g., HEK293 cells). In certain embodiments, the first therapeutic polypeptide has been produced in a mammalian cell and the mammalian cell is a Chinese Hamster Ovary (CHO) cell or mouse myeloma cell. In certain embodiments, the second therapeutic polypeptide has been produced in a mammalian cell and the mammalian cell is a Chinese Hamster Ovary (CHO) cell or mouse myeloma cell. In certain embodiments, the polypeptide has been purified from a human biological sample. In some cases, the human biological sample is human plasma.

[0038] In certain embodiments, the first therapeutic polypeptide comprises IL-15 and/or a sequence comprising at least about 90% homology to amino acids 49-162 of SEQ ID NO: 10; and the second therapeutic polypeptide comprises THBS2 and/or a sequence comprising at least about 90% homology to amino acids 19-1172 of SEQ ID NO: 4. In certain embodiments, the first therapeutic polypeptide comprises IL-15 and/or a sequence comprising at least about 90% homology to amino acids 49-162 of SEQ ID NO: 10; and the second therapeutic polypeptide comprises THBS4 and/or a sequence comprising at least about 90% homology to amino acids 27-961 of SEQ ID NO: 8. In certain embodiments, the first therapeutic polypeptide comprises IGF2 and/or a sequence comprising at least about 90% homology to amino acids 25-91 of SEQ ID NO: 11; and the second therapeutic polypeptide comprises THBS2 and/or a sequence comprising at least about 90% homology to amino acids 19-1172 of SEQ ID NO: 4. In certain embodiments, the first therapeutic polypeptide comprises IGF2 and/or a sequence comprising at least about

90% homology to amino acids 25-91 of SEQ ID NO: 11; and the second therapeutic polypeptide comprises THBS4 and/or a sequence comprising at least about 90% homology to amino acids 27-961 of SEQ ID NO: 8. In certain embodiments, the first therapeutic polypeptide comprises THBS4 and/or a sequence comprising at least about 90% homology to amino acids 27-961 of SEQ ID NO: 8; and the second therapeutic polypeptide comprises THBS2 and/or a sequence comprising at least about 90% homology to amino acids 19-1172 of SEQ ID NO: 4. In certain embodiments, the composition further comprises IL-15 and/or a sequence comprising at least about 90% homology to amino acids 49-162 of SEQ ID NO: 10. In certain embodiments, the composition further comprises IGF2 and/or a sequence comprising at least about 90% homology to amino acids 25-91 of SEQ ID NO: 11. In certain embodiments, the composition further comprises a pharmaceutically acceptable excipient. In certain embodiments, the composition is formulated for administration by injection. In certain embodiments, the injection is intramuscular. In certain embodiments, the injection is subcutaneous. In certain embodiments, the injection is intravenous.

[0039] In certain embodiments, described herein is a composition comprising THBS2 and THBS4. The composition may comprise VTN. The composition may comprise ANOS1. The composition may comprise IL-15. The composition may comprise IGF2. In certain embodiments, the composition comprises THBS2, THBS4, and VTN. In certain embodiments, the composition comprises THBS2, THBS4, and ANOS1. In certain embodiments, the composition comprises THBS2, THBS4, and IL-15. In certain embodiments, the composition comprises THBS2, THBS4, and IGF2. In certain embodiments, the composition further comprises a pharmaceutically acceptable excipient. In certain embodiments, the composition is formulated for administration by injection. In certain embodiments, the injection is intramuscular. In certain embodiments, the injection is subcutaneous. In certain embodiments, the injection is intravenous.

[0040] In certain embodiment, described herein is a composition comprising THBS1 and FGF17. In certain embodiment, described herein is a composition comprising THBS2 and VTN. In certain embodiment, described herein is a composition comprising THBS1 and VTN. In certain embodiment, described herein is a composition comprising THBS1 and THBS2. In certain embodiment, described herein is a composition comprising THBS2 and FGF17. In certain embodiment, described herein is a composition comprising THBS1 and THBS4. In certain embodiment, described herein is a composition comprising VTN and FGF17. In certain embodiment, described herein is a composition comprising THBS4 and VTN. In certain embodiment, described herein is a composition comprising THBS4 and FGF17. In certain embodiments, the composition further comprises a pharmaceutically acceptable excipient. In certain embodiments, the composition is formulated for administration by injection. In certain

embodiments, the injection is intramuscular. In certain embodiments, the injection is subcutaneous. In certain embodiments, the injection is intravenous.

[0041] Further described is a method of treating a disease or condition in a subject in need thereof, the method comprising administering to the subject a composition described herein. In certain embodiments, the disease or condition comprises an aging disorder, muscle wasting disorder, muscle injury, or injury to connective tissue, or a combination thereof. In certain embodiments, the subject has the aging disorder and the aging disorder comprises sarcopenia. In certain embodiments, the subject has the muscle wasting disorder and the muscle wasting disorder comprises muscular dystrophy. In certain embodiments, the subject has the muscle wasting disorder and the muscle wasting is a result of obesity, metabolic disorder, disease progression, or therapeutic treatment, or a combination thereof. In certain embodiments, the metabolic disorder is diabetes. In some cases the diabetes is Type 2 Diabetes. In certain embodiments, the subject has the muscle wasting disorder and the muscle wasting is cachexia, e.g., muscular cachexia.

[0042] In a certain aspect, described herein, is a composition comprising a mitogenic and/or fusion promoting polypeptide, wherein the polypeptide is a heparin-associated polypeptide secreted from a stem cell or a transformed cell line, wherein the heparin-associated polypeptide possesses mitogenic and/or fusion promoting activity. In certain embodiments, the composition comprises a plurality of mitogenic and/or fusion promoting polypeptides. In certain embodiments, the plurality comprises two, three, four, five, six, seven, eight, nine, ten or more polypeptides. In certain embodiments, the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are isolated and purified. In certain embodiments, the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are recombinantly produced. In certain embodiments, the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are secreted from a stem cell. In certain embodiments, the stem cell is a pluripotent stem cell. In certain embodiments, the stem cell is an induced pluripotent stem cell. In certain embodiments, the mitogenic activity comprises the ability to increase proliferation in a somatic cell and/or increase the ability of another heparin-associated polypeptide to increase proliferation in a somatic cell. In certain embodiments, the fusion promoting activity comprises the ability to increase fusion of a plurality of somatic cells and/or increase the ability of another heparin - associated polypeptide to increase fusion in a plurality of somatic cells. In certain embodiments, the somatic cell is a muscle, muscle progenitor cell, tenocyte, or tenocyte precursor. In certain embodiments, the somatic cell is a mammalian cell. In certain embodiments, the somatic cell is a human cell. In certain embodiments, any one of the mitogenic and/or fusion promoting

polypeptides or plurality of mitogenic and/or fusion promoting polypeptides are produced in a heterologous cellular production system. In certain embodiments, any one of the mitogenic and/or fusion promoting polypeptides or plurality of mitogenic and/or fusion promoting polypeptides are synthetically produced. In certain embodiments, the polypeptides are purified from human plasma. In certain embodiments, the polypeptides are purified from a mammalian cell, insect cell, or bacterial cell. The mammalian cell may be a human cell. In certain embodiments, the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides comprises one or more modifications to improve activity, stability, or increase polypeptide yield from a heterologous cellular production system, or any combination thereof. In certain embodiments, the modification is an alteration of one or more amino acids in the polypeptide sequence of mitogenic and/or fusion promoting polypeptide compared to the wildtype polypeptide sequence of the mitogenic and/or fusion promoting polypeptide. In certain embodiments, the mitogenic and/or fusion promoting polypeptide(s) are encoded by a nucleic acid. In certain embodiments, the cell line comprises the nucleic acid encoding the mitogenic and/or fusion promoting polypeptide(s). In certain embodiments, the cell line is a eukaryotic cell line. In certain embodiments, the composition comprises the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides and a pharmaceutically acceptable excipient, carrier, or diluent. In certain embodiments, the composition is formulated in injectable form. In certain embodiments, the composition is for use in a method of treating an aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue, or any combination thereof. In certain embodiments, the aging disorder is sarcopenia. In certain embodiments, the muscle wasting disorder is muscular dystrophy. In certain embodiments, the muscle wasting disorder is cachexia, e.g., muscular cachexia. In certain embodiments, described herein, is a method of treating an individual with aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue, or any combination thereof, the method comprising administering to the individual the composition of mitogenic and/or fusion promoting polypeptides. In certain embodiments, the aging disorder is sarcopenia. In certain embodiments, the muscle wasting disorder is muscular dystrophy. In certain embodiments, the muscle wasting disorder is cachexia, e.g., muscular cachexia. In certain embodiments, described herein, is a method of producing a composition suitable for the treatment of an aging disorder comprising admixing a pharmaceutically acceptable excipient, carrier, or diluent with the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides described herein. In certain embodiments, described herein, is a method of producing a mitogenic and/or fusion promoting polypeptide comprising culturing a cell line comprising a nucleic acid

expressing a mitogenic and/or fusion promoting polypeptide under conditions sufficient to produce the mitogenic and/or fusion promoting polypeptide.

[0043] In another aspect, described herein, is a composition comprising a mitogenic and/or fusion promoting polypeptide, wherein the mitogenic and/or fusion promoting polypeptide is identified by: (a) identifying at least one polypeptide in a mixture of a plurality of polypeptides secreted from a stem cell or a transformed cell line that can be purified with heparin coated matrix; and (b) determining the mitogenic and/or fusion promoting activity of the at least one polypeptide for a somatic cell, wherein the at least one polypeptide is identified as a mitogenic and/or fusion promoting polypeptide if the at least one polypeptide exhibits mitogenic and/or fusion promoting activity. In certain embodiments, the composition comprises a plurality of mitogenic and/or fusion promoting polypeptides. In certain embodiments, the plurality comprises three, four, five, six, seven, eight, nine, ten or more polypeptides. In certain embodiments, the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are isolated and purified. In certain embodiments, the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are recombinantly produced. In certain embodiments, the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are secreted from a stem cell. In certain embodiments, the stem cell is a pluripotent stem cell. In certain embodiments, the stem cell is an induced pluripotent stem cell. In certain embodiments, the mitogenic and/or fusion promoting activity comprises the ability to increase proliferation in a somatic cell or increase the ability of another heparin-associated polypeptide to increase proliferation in a somatic cell. In certain embodiments, the fusion promoting activity comprises the ability to increase fusion of a plurality of somatic cells or increase the ability of another heparin - associated polypeptide to increase fusion in a plurality of somatic cells. In certain embodiments, the somatic cell is a muscle, muscle progenitor cell, tenocyte, or tenocyte precursor. In certain embodiments, the somatic cell is a mammalian cell. In certain embodiments, the somatic cell is a human cell. In certain embodiments, any one of the mitogenic and/or fusion promoting polypeptides or plurality of mitogenic and/or fusion promoting polypeptides are produced in a heterologous cellular production system. In certain embodiments, any one of the mitogenic and/or fusion promoting polypeptides or plurality of mitogenic and/or fusion promoting polypeptides are synthetically produced. In certain embodiments, the polypeptides are purified from human plasma. In certain embodiments, the polypeptides are purified from a mammalian cell, insect cell, or bacterial cell. The mammalian cell may be a human cell. In certain embodiments, the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides comprises one or more modifications to improve activity,

stability, or increase polypeptide yield from a heterologous cellular production system. In certain embodiments, the modification is an alteration of one or more amino acids in the polypeptide sequence of the mitogenic and/or fusion promoting polypeptide compared to the wildtype polypeptide sequence of the mitogenic and/or fusion promoting polypeptide. In certain embodiments, the mitogenic and/or fusion promoting polypeptide(s) are encoded by a nucleic acid. In certain embodiments, the cell line comprises the nucleic acid encoding the mitogenic and/or fusion promoting polypeptide(s). In certain embodiments, the cell line is a eukaryotic cell line. In certain embodiments, the composition comprises the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides and a pharmaceutically acceptable excipient, carrier, or diluent. In certain embodiments, the composition is formulated in injectable form. In certain embodiments, the composition is for use in a method of treating an aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue, or any combination thereof. In certain embodiments, the aging disorder is sarcopenia. In certain embodiments, the muscle wasting disorder is muscular dystrophy. In certain embodiments, the muscle wasting disorder is cachexia, e.g., muscular cachexia. In certain embodiments, described herein, is a method of treating an individual with aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue, or any combination thereof, the method comprising administering to the individual the composition of mitogenic and/or fusion promoting polypeptides. In certain embodiments, the aging disorder is sarcopenia. In certain embodiments, the muscle wasting disorder is muscular dystrophy. In certain embodiments, the muscle wasting disorder is cachexia, e.g., muscular cachexia. In certain embodiments, described herein, is a method of producing a composition suitable for the treatment of an aging disorder comprising admixing a pharmaceutically acceptable excipient, carrier, or diluent with the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides described herein. In certain embodiments, described herein, is a method of producing a mitogenic and/or fusion promoting polypeptide comprising culturing a cell line comprising a nucleic acid expressing a mitogenic and/or fusion promoting polypeptide under conditions sufficient to produce the mitogenic and/or fusion promoting polypeptide.

[0044] In another aspect, described herein, is a composition comprising a mitogenic and/or fusion promoting polypeptide, wherein the mitogenic and/or fusion promoting polypeptide comprises ADAMTS12, INS-IGF2, AOC1, SOD3, CLU, ITIH1, APLP1, THBS1, COCH, ITIH2, APLP2, THBS3, COL11A1, LAMA1, APOB, TNXB, COL12A1, LAMA2, APOE, VEGFA, COL14A1, LAMA5, APOH, VTN, COL18A1, LAMB1, APP, ZNF207, COL1A1, LAMB2, CCDC80, COL1A2, LTF, CFH, COL2A1, MATN2, CLEC3B, COL3A1, MDK, COL25A1,

COL5A1, MST1, COL5A3, COL5A2, NID1, CYR61, COL6A1, NPNT, F2, COL6A2, OLFML3, FGF2, COL6A3, PCOLCE, FGFBP3, CTGF, POSTN, FSTL1, DCD, PTN, HDGF, DRAXIN, RARRES2, KNG1, ECM1, RELN, NDNF, FBLN1, SFRP1, NRP1, FBN1, SLIT3, PAFAH1B1, FBN2, SPON1, PCOLCE2, FN1, STC1, PTPRF, FST, STC2, PTPRS, HGFAC, SVEP1, RPL22, IGFBP2, THBS2, RPL29, a protein listed in Table 2, or a protein listed in Table 1, or any combination thereof. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises VTN, STC2, AGRN, POSTN, FGF17, THBS2, FST, THBS4, IGF2, IL-15, or THBS1, or a combination thereof. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises one or more of VTN, POSTN, FGF17, THBS2, IGF2, IL-15, THBS1, and THBS4. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises VTN. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises STC2. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises AGRN. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises THBS2. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises FST. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises POSTN. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises FGF17. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises THBS4. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises IGF2. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises IL-15. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises THBS1. In certain embodiments, the composition comprises a plurality of mitogenic and/or fusion promoting polypeptides. In certain embodiments, the plurality comprises three, four, five, six, seven, eight, nine, ten or more polypeptides. The plurality of polypeptides may comprise one, two, three, four, five, six, seven, eight, nine, ten or more polypeptides of Table 2. The plurality of polypeptides may comprise one, two, three, four, five, six, seven, eight, nine, ten or more polypeptides of Table 1. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises IGF2, THBS2, and THBS4. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises IL-15, THBS2, and THBS4. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2 and THBS4. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2, THBS4, and VTN. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2, THBS4, and ANOS1. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2, THBS4, and IL-15. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2, THBS4, and IGF2. In certain

embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS1 and FGF17. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2 and VTN. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS1 and VTN. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS1 and THBS2. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2 and FGF17. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS1 and THBS4. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises VTN and FGF17. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS4 and VTN. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS4 and FGF17. In certain embodiments, the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are isolated and purified. In certain embodiments, the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are recombinantly produced. In certain embodiments, the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are secreted from a stem cell. In certain embodiments, the stem cell is a pluripotent stem cell. In certain embodiments, the stem cell is an induced pluripotent stem cell. In certain embodiments, the mitogenic activity comprises the ability to increase proliferation in a somatic cell or increase the ability of another heparin-associated polypeptide to increase proliferation in a somatic cell. In certain embodiments, the fusion promoting activity comprises the ability to increase fusion of a plurality of somatic cells and/or increase the ability of another heparin-associated polypeptide to increase fusion in a plurality of somatic cells. In certain embodiments, the somatic cell is a muscle, muscle progenitor cell, tenocyte, or tenocyte precursor. In certain embodiments, the somatic cell is a mammalian cell. In certain embodiments, the somatic cell is a human cell. In certain embodiments, any one of the mitogenic and/or fusion promoting polypeptides or plurality of mitogenic and/or fusion promoting polypeptides are produced in a heterologous cellular production system. In certain embodiments, any one of the mitogenic and/or fusion promoting polypeptides or plurality of mitogenic and/or fusion promoting polypeptides are synthetically produced. In certain embodiments, the polypeptides are purified from human plasma. In certain embodiments, the polypeptides are purified from a mammalian cell, insect cell, or bacterial cell. The mammalian cell may be a human cell. In certain embodiments, the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides comprises one or more modifications to improve activity, stability, or increase polypeptide yield from a

heterologous cellular production system. In certain embodiments, the modification is an alteration of one or more amino acids in the polypeptide sequence of the mitogenic and/or fusion promoting polypeptide compared to the wildtype polypeptide sequence of the mitogenic and/or fusion promoting polypeptide. In certain embodiments, the mitogenic and/or fusion promoting polypeptide(s) are encoded by a nucleic acid. In certain embodiments, the cell line comprises the nucleic acid encoding the mitogenic and/or fusion promoting polypeptide(s). In certain embodiments, the cell line is a eukaryotic cell line. In certain embodiments, the composition comprises the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides and a pharmaceutically acceptable excipient, carrier, or diluent. In certain embodiments, the composition is formulated in injectable form. In certain embodiments, the composition is for use in a method of treating an aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue, or a combination thereof. In certain embodiments, the aging disorder is sarcopenia. In certain embodiments, the muscle wasting disorder is muscular dystrophy. In certain embodiments, the muscle wasting disorder is cachexia, e.g., muscular cachexia. In certain embodiments, described herein, is a method of treating an individual with aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue, or a combination thereof, the method comprising administering to the individual the composition of mitogenic and/or fusion promoting polypeptides. In certain embodiments, the aging disorder is sarcopenia. In certain embodiments, the muscle wasting disorder is muscular dystrophy. In certain embodiments, the muscle wasting disorder is cachexia, e.g., muscular cachexia. In certain embodiments, described herein, is a method of producing a composition suitable for the treatment of an aging disorder comprising admixing a pharmaceutically acceptable excipient, carrier, or diluent with the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides described herein. In certain embodiments, described herein, is a method of producing a mitogenic and/or fusion promoting polypeptide comprising culturing a cell line comprising a nucleic acid expressing a mitogenic and/or fusion promoting polypeptide under conditions sufficient to produce the mitogenic and/or fusion promoting polypeptide.

[0045] In another aspect, described herein, is a composition comprising a mitogenic and/or fusion promoting polypeptide, wherein the mitogenic and/or fusion promoting polypeptide comprises VTN, STC2, AGRN, POSTN, FGF17, THBS2, FST, THBS4, IGF2, IL-15, or THBS1, or a combination thereof. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises one or more of VTN, POSTN, FGF17, THBS2, THBS4, IGF2, IL-15, and THBS1. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises VTN. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises

STC2. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises AGRN. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises THBS2. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises FST. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises POSTN. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises FGF17. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises THBS4. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises IGF2. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises IL-15. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises THBS1. In certain embodiments, the composition comprises a mixture of a plurality of different mitogenic and/or fusion promoting polypeptides. In certain embodiments, the plurality of different mitogenic and/or fusion promoting polypeptides comprise three, four, or five different mitogenic and/or fusion promoting polypeptides. The plurality of polypeptides may comprise one, two, three, four, five, six, seven, eight, nine, ten or more polypeptides of Table 2. The plurality of polypeptides may comprise one, two, three, four, five, six, seven, eight, nine, ten or more polypeptides of Table 1. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises IGF2, THBS2, and THBS4. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises IL-15, THBS2, and THBS4. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2 and THBS4. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2, THBS4, and VTN. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2, THBS4, and ANOS1. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2, THBS4, and IL-15. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2, THBS4, and IGF2. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS1 and FGF17. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2 and VTN. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS1 and VTN. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS1 and THBS2. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2 and FGF17. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS1 and THBS4. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises VTN and FGF17. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS4 and VTN. In

certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS4 and FGF17. In certain embodiments, the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are isolated and purified. In certain embodiments, the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are recombinantly or synthetically produced. In certain embodiments, the polypeptides are purified from human plasma. In certain embodiments, the polypeptides are purified from a mammalian cell, insect cell, or bacterial cell. The mammalian cell may be a human cell. In certain embodiments, the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are secreted from a stem cell. In certain embodiments, the stem cell is a pluripotent stem cell. In certain embodiments, the stem cell is an induced pluripotent stem cell. In certain embodiments, the mitogenic activity comprises increasing proliferation in a muscle cell precursor. In certain embodiments, the fusion promoting activity comprises the ability to increase fusion of a plurality of somatic cells and/or increase the ability of another heparin -associated polypeptide to increase fusion in a plurality of somatic cells. In certain embodiments, the muscle cell precursor is a myoblast. In certain embodiments, the somatic cell is a mammalian cell. In certain embodiments, the somatic cell is a human cell. In certain embodiments, the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides comprise one or more modifications to improve activity, stability, or increase polypeptide yield from a heterologous cellular production system. In certain embodiments, the modification is an alteration of one or more amino acids in the polypeptide sequence of the mitogenic and/or fusion promoting polypeptide compared to the wildtype polypeptide sequence of the mitogenic and/or fusion promoting polypeptide. In certain embodiments, the modification is a fusion of a mitogenic and/or fusion promoting polypeptide to a non-mitogenic or fusion promoting polypeptide. In certain embodiments, the non-mitogenic or fusion promoting polypeptide comprises an immunoglobulin Fc region or serum albumin. In certain embodiments, the non-mitogenic or fusion promoting polypeptide is a human polypeptide. In certain embodiments, the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are concatemerized. In certain embodiments, the concatemerized polypeptides are separated by a polypeptide linker. In certain embodiments, the concatemerized polypeptides are the same polypeptide. In certain embodiments, the concatemerized polypeptides are different polypeptides. In certain embodiments, the concatemerized polypeptides are covalently concatemerized through a non-peptide linkage. In certain embodiments, the concatemerized polypeptides are non-covalently concatemerized. In certain embodiments, a nucleic acid encodes the mitogenic and/or fusion promoting polypeptide. In certain embodiments, a cell line comprises

the nucleic acid. In certain embodiments, the cell line is a eukaryotic cell line. In certain embodiments, the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides comprises a pharmaceutically acceptable excipient, carrier, or diluent. In certain embodiments, the pharmaceutically acceptable excipient, carrier, or diluent increases the function of the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides. In certain embodiments, the function comprises increasing proliferation in a muscle cell precursor, increasing stability of the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides, or increasing bioavailability of the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides. In certain embodiments, the composition is for subcutaneous, intravenous, intramuscular, or topical administration. In certain embodiments, the composition is for use in a method of treating an aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue, or a combination thereof. In certain embodiments, the aging disorder is sarcopenia. In certain embodiments, the muscle wasting disorder is muscular dystrophy. In certain embodiments, the muscle wasting disorder is cachexia, e.g., muscular cachexia. In certain embodiments, described herein, is a method of treating an individual with an aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue, or a combination thereof, the method comprising administering to the individual the composition. In certain embodiments, described herein, is a method of increasing proliferation of a muscle cell or connective tissue cell precursor in an individual comprising administering to the individual the composition. In certain embodiments, the individual is afflicted with or suspected of being afflicted with an aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue, or a combination thereof. In certain embodiments, the aging disorder is sarcopenia. In certain embodiments, the muscle wasting disorder is muscular dystrophy. In certain embodiments, the muscle wasting disorder is cachexia, e.g., muscular cachexia.

[0046] Also described is a method of producing a composition suitable for the treatment of an aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue, or a combination thereof, the method comprising admixing a pharmaceutically acceptable excipient, carrier, or diluent with the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides. Also described is a method of producing a mitogenic and/or fusion promoting polypeptide comprising culturing a cell line comprising a nucleic acid encoding mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides under conditions sufficient to produce the mitogenic and/or fusion promoting polypeptide.

BRIEF DESCRIPTION OF THE DRAWINGS

[0047] The novel features described herein are set forth with particularity in the appended claims. A better understanding of the features and advantages of the features described herein will be obtained by reference to the following detailed description that sets forth illustrative examples, in which the principles of the features described herein are utilized, and the accompanying drawings of which:

[0048] **FIG. 1** shows histology and immunofluorescence staining of injured and regenerated muscle tissue from aged mice treated with heparin-associated polypeptides or vehicle control.

[0049] **FIG. 2A** shows time-points for dosing and analysis of the effects of the entire pool of heparin-associated polypeptides in an acute injury model in aged mice. Squares denote injury inducing intramuscular injection (IM) with Barium Chloride; circles denote administration of treatment or vehicle.

[0050] **FIG. 2B** shows the results of the experiment outlined in FIG. 2A. Administration of hPSC derived factors resulted in improved new fiber formation (regenerative index, left) and reduced scarring (fibrotic index, right) in aged mice to levels similar to those in young mice, both of which were markedly better than vehicle-treated old mice. Stars indicate degree of significance from one-way ANOVA tests.

[0051] **FIG. 2C** shows time-points for dosing and analysis of the effects of the entire pool of heparin-associated polypeptides in an acute injury model in transgenic mice prone to obesity. Squares denote injury inducing intramuscular injection (IM) with Barium Chloride; circles denote administration of treatment or vehicle.

[0052] **FIG. 2D** shows the results of the experiment outlined in FIG. 2C. Administration of hPSC derived factors resulted in improved new fiber formation (regenerative index, left, $p < 3.5E-6$) and reduced scarring (fibrotic index, right, $p < 8.44E-3$) in transgenic obese mice to levels similar to those in positive control (8ng FGF19) treated mice ($p < 2.3E-5$ and $p < 2.32E-2$, respectively), both of which were markedly better than vehicle-treated transgenic obese mice. Stars indicate degree of significance from one-way ANOVA tests.

[0053] **FIGS. 3A to 3D.** Heparin-column enrichment of secreted factors from hESC and differentiated cells can be deeply profiled in an unbiased way using isobaric labeling, online reverse phase fractionation, and an SPS-MS3 instrument method. **FIG. 3A** depicts the methodology for targeted heparin purification of secreted proteins from media supernatant, isobaric labeling, reverse phase fractionation, and SPS-MS3 mass spectrometry instrument method. **FIG. 3B** depicts a silver stain gel of heparin purified proteins (left two lanes) compared to buffer only (right most lane), demonstrating enrichment of many protein species by their molecular weight. **FIG. 3C** depicts a 2D heat map of the intensity (color) of peptides separated

by m/z (y-axis) compared to elution from reverse phase nHPLC separation (x-axis). **FIG. 3D** depicts a K-means clustered heat map of all proteins found in a representative experiment demonstrating the differential abundance of many proteins specifically in the secretome of undifferentiated hPSCs. **FIG. 3E** depicts Principle Component Analysis of proteins from the same run demonstrating again the differential expressionless (PC1) as well as a high relative degree of reproducibility from undifferentiated hPSCs compared to differentiated cells.

[0054] FIGS. 4A-4B illustrate representative results from an *in vitro* assay useful to validate the regenerative capacity of factors identified by mass spectroscopy. **FIG. 4A** shows representative micrographs taken from cells treated with fusion media (neg. control), defined growth media (pos. control), Optimem, supernatant from differentiated hESC, supernatant from undifferentiated hESC, heparin binding proteins eluted from supernatant of undifferentiated hESC under two different conditions, and supernatant of undifferentiated hESC that has been depleted of heparin binding proteins. **FIG. 4B** shows data expressed as % of nuclei stained with BrdU or % cells stained for embryonic myosin heavy chain (eMyHC).

[0055] FIGS. 5A-5B show quantitation and representative images demonstrating the proliferation effect of IGFBP7(330ng/mL), POSTN(330ng/mL), SPON1(330ng/mL), MST1(330ng/mL), and RARRES2(330ng/mL) (**FIG. 5A**); and VTN(10ug/mL), FGF17(500ng/mL), IGF2(2ug/mL), FGF4(500ng/mL), FGF1(500ng/mL), and FGF6(1ug/mL) (**FIG. 5B**) in injury activated primary mouse myoblasts grown *in vitro*. **FIG. 5C** shows quantitation and representative images demonstrating the increased cellular fusion effect of THBS1(330ng/mL), THBS2(330ng/mL), and STC2(875ng/mL) in injury activated primary mouse myoblasts grown *in vitro*.

[0056] FIGS. 6A-6E show quantitation and representative immunofluorescent stained cell images demonstrating the proliferation effect specific heparin-associated polypeptides. **FIG. 6A** shows the effect of IGFBP5 at 1ug/mL, **FIG. 6B** show the effect of THBS4 at 1ug/mL, **FIG. 6C** shows the effect of VTN at 10ug/mL, **FIG. 6D** shows the effect of FGF17 at 250ng/mL, and **FIG. 6E** shows the effect of IGFBP7 at 500ng/mL – all demonstrated notable effects in injury activated primary human myoblasts, young (18 years old) and aged (both 68 years old), grown *in vitro*. **FIGS. 6F-6H**, show quantitation and representative images demonstrating the increased cellular fusion effect of SPON1(1ug/mL) (**FIG. 6F**), POSTN(1ug/mL) (**FIG. 6G**), PDGFRL(5ug/mL) (**FIG. 6H**) in injury activated primary human myoblasts, young (18 years) and old (both 69 years old), grown *in vitro*.

[0057] FIG. 7A provides an exemplary proliferative dose response of mouse myoblasts cultured with hPSC-derived factors Thrombospondin 1 (THBS1) applied at 125 ng/mL, 250 ng/mL, and 500 ng/mL, 1000 ng/ml and 200ng/ml, and Fibroblast growth factor 17 (FGF17)

applied at 12.5 ng/ml, 25 ng/ml, 50 ng/ml, 100 ng/ml, and 200 ng/ml. **FIG. 7B** shows that while THBS1 showed non-significant effects on proliferation of myoblasts (top), FGF17 produced a linear dose-dependent increase in proliferation of myoblasts (bottom). **FIG. 7C** shows that the combination of the two produced potentiation type synergy ($CI < 0.68$, $p < 7.92E-7$).

[0058] **FIGS. 7D-7M** provide examples of synergistic combinations of heparin-associated polypeptides relative to the vehicle only control (_FM) or to treatment with either of the individual heparin-associated polypeptides. Combination Index (CI) values and probability values (p-values) from statistical tests for the synergy models are reported in Table 10. **FIG. 7D** shows the synergistic effects of THBS1 with VTN. **FIG. 7E** shows the synergistic effects of THBS1 with THBS2. **FIG. 7F** shows the synergistic effects of THBS1 with THBS4. **FIG. 7G** shows the synergistic effects of lower concentrations of THBS2 with varying concentrations of THBS4. **FIG. 7H** shows the synergistic effects higher concentrations of THBS2 with varying concentrations of THBS4. **FIG. 7I** shows the synergistic effects of THBS2 with VTN. **FIG. 7J** shows the synergistic effects of THBS2 with FGF17. **FIG. 7K** shows the synergistic effects of THBS4 with VTN. **FIG. 7L** shows the synergistic effects of THBS4 with FGF17. **FIG. 7M** shows the synergistic effects of VTN with FGF17.

[0059] **FIG. 8** shows an example of the dose dependent increasing cellular fusion of mouse myoblasts cultured with a heparin-associated polypeptide. In this case Platelet derived growth factor-like (PDGFRL) proteins were applied at 625ng/mL, 1250 ng/mL, 2500 ng/mL, 5000 ng/mL, and 10000 ng/mL.

[0060] **FIG. 9A** shows the experimental schematic of time-points for dosing and analysis using an acute injury model in aged mice of the effects of individual heparin-associated polypeptides with proliferative effects in vitro. Squares denote injury inducing intramuscular injection (IM) with Barium Chloride; circles denote administration of treatment or vehicle.

[0061] **FIG. 9B** shows the results of the experiment outlined in **FIG. 9A**. Administration of 20ul of heparin-associated polypeptides FGF17 (500ng/mL, $p < 2.23E-4$), THBS1 (2ug/mL, $p < 5.83E-5$), THBS2 (2ug/mL, $p < 2.67E-4$), and VTN (10ug/mL, $p < 1.13E-2$) resulted in improved new fiber formation (regenerative index) in aged mice compared to vehicle-treated aged mice to levels similar or better than young mice. Stars indicate degree of significance from one-way ANOVA tests.

[0062] **FIG. 9C** Representative images of immunofluorescence staining of sectioned mouse muscle (tibialis anterior) demonstrated increased muscle regeneration for injured, aged mouse muscle treated with THBS1 (2ug/mL) compared to young and vehicle-treated, aged mouse muscle.

[0063] **FIG. 9D** shows the experimental schematic of time-points for dosing and analysis

using an acute injury model in aged mice of the effects of individual heparin-associated polypeptides with fusion enhancing effects in vitro. Squares denote injury inducing intramuscular injection (IM) with Barium Chloride; circles denote administration of treatment or vehicle.

[0064] FIG. 9E shows the results of the experiment outlined in FIG. 9D. Administration of 20ul of heparin-associated polypeptides PPDGFRL (5ug/mL, $p < 3.85E-2$) and IGFBP7 (1ug/mL, $p < 6.63E-3$) resulted in improved new fiber formation (regenerative index compared to vehicle-treated aged mice. Stars indicate degree of significance from one-way ANOVA tests.

[0065] FIG. 9F provides representative images of immunofluorescence staining of sectioned mouse muscle (tibialis anterior) demonstrating increased muscle regeneration for injured, aged mouse muscle treated with POSTN (1ug/mL) or IGFBP7 (1ug/mL) compared to vehicle-treated, aged mouse muscle.

[0066] FIG. 10A shows the experimental schematic of time-points for in vivo injury and individual heparin-associated polypeptide administration followed by muscle excision, dissociation, ex vivo culturing of activated myoblasts and quantitation by chemical and immunofluorescent labelling.

[0067] FIG. 10B provides resulting quantitation that demonstrates the regenerative effect of heparin-associated polypeptide administration (FGF17) of 20ul at 500ng/ml improved the regeneration of new myoblasts in aged mice above the vehicle-treated aged mice ($p < 7.57E-8$) to a level similar to those seen in young mice.

[0068] FIG. 10C provides representative immunofluorescence images for ex vivo cultured, injury activated myoblasts used for quantitative evaluation of factor efficacy.

[0069] FIG. 11A shows the experimental schematic of time-points for in vivo injury followed by muscle excision, dissociation, ex vivo culturing of activated myoblasts, then individual heparin-associated polypeptide administration and quantitation by chemical and immunofluorescent labelling.

[0070] FIG. 11B provides resulting quantitation that demonstrates the regenerative effect of administration of heparin-associated polypeptides FGF17 (500ng/ml) and THBS4 (2ug/mL) – each improved the regeneration of new myoblasts in aged mice above the vehicle-treated aged mice ($p < 1.57E-2$, $4.64E-2$ respectively, one-sided test) compared to vehicle treated control.

[0071] FIG. 11C provides representative immunofluorescence images for ex vivo cultured, injury activated myoblasts used for quantitative evaluation of factor efficacy.

[0072] FIG. 12A provides representative quantitation of immunofluorescence images demonstrating the proliferation enhancing effects of heparin-associated polypeptides administration at various doses on primary human myoblasts derived from a patient with type 1 myotonic dystrophy.

[0073] FIG. 12B provides representative quantitation of immunofluorescence images demonstrating the hypertrophy enhancing effects of heparin-associated polypeptides administration at various doses on primary human myoblasts derived from a patient with type 1 myotonic dystrophy.

DETAILED DESCRIPTION

[0074] In one aspect, described herein is a composition comprising a mitogenic and/or fusion promoting polypeptide, wherein the mitogenic and/or fusion promoting polypeptide is identified by: (a) identifying at least one polypeptide in a mixture of a plurality of polypeptides secreted from a stem cell or a transformed cell line that can be enriched through association of the mixture with heparin-conjugated beads; and (b) determining the mitogenic and/or fusion promoting activity of the at least one polypeptide for a somatic cell, wherein at least one polypeptide is identified as a mitogenic and/or fusion promoting polypeptide if at least one polypeptide exhibits mitogenic and/or fusion promoting activity.

[0075] In another aspect, described herein is a composition comprising a mitogenic and/or fusion promoting polypeptide, wherein the polypeptide is a heparin-associated polypeptide secreted from a stem cell or a transformed cell line, wherein the heparin-associated polypeptide possesses mitogenic and/or fusion promoting activity. In certain embodiments, the composition is for use in a method of treating an aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue, or a combination thereof. In certain embodiments, the composition is for use in a method of increasing proliferation of a muscle cell or connective tissue cell precursor in an individual. In certain embodiments, the individual is afflicted with or suspected of being afflicted with an aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue, or a combination thereof. In certain embodiments, the aging disorder is sarcopenia. In certain embodiments, the muscle wasting disorder is muscular dystrophy. In certain embodiments, the muscle wasting disorder is cachexia, e.g., muscular cachexia. In another aspect, described herein, is a composition comprising a mitogenic and/or fusion promoting polypeptide, wherein the mitogenic and/or fusion promoting polypeptide comprises ADAMTS12, INS-IGF2, AOC1, SOD3, CLU, ITIH1, APLP1, THBS1, COCH, ITIH2, APLP2, THBS3, COL11A1, LAMA1, APOB, TNXB, COL12A1, LAMA2, APOE, VEGFA, COL14A1, LAMA5, APOH, VTN, COL18A1, LAMB1, APP, ZNF207, COL1A1, LAMB2, CCDC80, COL1A2, LTF, CFH, COL2A1, MATN2, CLEC3B, COL3A1, MDK, COL25A1, COL5A1, MST1, COL5A3, COL5A2, NID1, CYR61, COL6A1, NPNT, F2, COL6A2, OLFML3, FGF2, COL6A3, PCOLCE, FGFBP3, CTGF, POSTN, FSTL1, DCD, PTN, HDGF, DRAXIN,

RARRES2, KNG1, ECM1, RELN, NDNF, FBLN1, SFRP1, NRP1, FBN1, SLIT3, PAFAH1B1, FBN2, SPON1, PCOLCE2, FN1, STC1, PTPRF, FST, STC2, PTPRS, HGFAC, SVEP1, RPL22, IGFBP2, THBS2, RPL29, a protein listed in Table 2, or a protein listed in Table 1, or any combination thereof. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises one or more of VTN, POSTN, FGF17, THBS2, THBS4, IGF2, IL-15, and THBS1. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises VTN. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises THBS2. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises POSTN. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises FGF17. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises THBS4. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises IGF2. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises IL-15. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises THBS1. In certain embodiments, the composition comprises a mixture of a plurality of different mitogenic and/or fusion promoting polypeptides. In certain embodiments, the plurality of different mitogenic and/or fusion promoting polypeptides comprise three, four, or five different mitogenic and/or fusion promoting polypeptides. The plurality of polypeptides may comprise one, two, three, four, five, six, seven, eight, nine, ten or more polypeptides of Table 2. The plurality of polypeptides may comprise one, two, three, four, five, six, seven, eight, nine, ten or more polypeptides of Table 1. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises IGF2, THBS2, and THBS4. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises IL-15, THBS2, and THBS4. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2 and THBS4. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2, THBS4, and VTN. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2, THBS4, and ANOS1. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2, THBS4, and IL-15. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2, THBS4, and IGF2. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS1 and FGF17. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2 and VTN. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS1 and VTN. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS1 and THBS2. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises

THBS2 and FGF17. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS1 and THBS4. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises VTN and FGF17. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS4 and VTN. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS4 and FGF17. In certain embodiments, the composition is for use in a method of treating an aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue, or any combination thereof. In certain embodiments, the composition is for use in a method of increasing proliferation of a muscle cell and/or connective tissue cell precursor in an individual. In certain embodiments, the individual is afflicted with or suspected of being afflicted with an aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue, or a combination thereof. In certain embodiments, the aging disorder is sarcopenia. In certain embodiments, the muscle wasting disorder is muscular dystrophy. In certain embodiments, the muscle wasting disorder is cachexia, e.g., muscular cachexia.

[0076] In another aspect, described herein, is a composition comprising a mitogenic and/or fusion promoting polypeptide, wherein the mitogenic and/or fusion promoting polypeptide comprises VTN, STC2, AGRN, POSTN, FGF17, THBS2, FST, or THBS4, or a combination thereof. In certain embodiments, the mitogenic of fusion promoting polypeptide comprises at least one of VTN, POSTN, FGF17, THBS2, and THBS4. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises one or more of VTN, POSTN, FGF17, THBS2, THBS4, IGF2, IL-15, and THBS1. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises VTN. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises THBS2. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises POSTN. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises FGF17. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises THBS4. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises IGF2. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises IL-15. In certain embodiments, the mitogenic and/or fusion promoting polypeptide comprises THBS1. In certain embodiments, the composition comprises a mixture of a plurality of different mitogenic and/or fusion promoting polypeptides. In certain embodiments, the plurality of different mitogenic and/or fusion promoting polypeptides comprise three, four, or five different mitogenic and/or fusion promoting polypeptides. The plurality of polypeptides may comprise one, two, three, four, five, six, seven, eight, nine, ten or more polypeptides of Table 2. The plurality of polypeptides may comprise one, two, three, four, five, six, seven, eight, nine, ten or more polypeptides of Table 1. In certain embodiments, the plurality

of mitogenic and/or fusion promoting polypeptides comprises IGF2, THBS2, and THBS4. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises IL-15, THBS2, and THBS4. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2 and THBS4. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2, THBS4, and VTN. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2, THBS4, and ANOS1. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2, THBS4, and IL-15. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2, THBS4, and IGF2. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS1 and FGF17. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2 and VTN. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS1 and VTN. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS1 and THBS2. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS2 and FGF17. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS1 and THBS4. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises VTN and FGF17. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS4 and VTN. In certain embodiments, the plurality of mitogenic and/or fusion promoting polypeptides comprises THBS4 and FGF17. In certain embodiments, the composition is for use in a method of treating an aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue, or a combination thereof. In certain embodiments, the composition is for use in a method of increasing proliferation of a muscle cell and/or connective tissue cell precursor in an individual. In certain embodiments, the individual is afflicted with or suspected of being afflicted with an aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue, or a combination thereof. In certain embodiments, the aging disorder is sarcopenia. In certain embodiments, the muscle wasting disorder is muscular dystrophy. In certain embodiments, the muscle wasting disorder is cachexia, e.g., muscular cachexia.

[0077] In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments. However, one skilled in the art will understand that the embodiments provided may be practiced without these details. Unless the context requires otherwise, throughout the specification and claims that follow, the word “comprise” and variations thereof, such as, “comprises” and “comprising” are to be construed in an open, inclusive sense, that is, as “including, but not limited to.” As used in this specification and the

appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the content clearly dictates otherwise. It should also be noted that the term “or” is generally employed in its sense including “and/or” unless the content clearly dictates otherwise. Further, headings provided herein are for convenience only and do not interpret the scope or meaning of the claimed embodiments.

[0078] As used herein a composition that is “consisting essentially” of the recited components is a composition that only has the recited elements as active ingredients, but can comprise other non-active components that do not appreciably modify the function or activity of the recited components. Any list disclosed herein that is recited as “comprising” can be recited as “consisting essentially,” to exclude non-recited polypeptide or protein components.

[0079] As used herein “heparin-associated polypeptide” means any polypeptide that directly binds to heparin with a K_D of less than 1 micromolar, or any polypeptide that associates with one or more polypeptides that bind directly to heparin with a K_D of less than 1 micromolar. This K_D can be measured using a method such as surface plasmon resonance. See e.g., Nguyen et al., “Surface plasmon resonance: a versatile technique for biosensor applications.” *Sensors (Basel)*. 2015 May 5;15(5):10481-510. Alternatively, a heparin-associated polypeptide is one that is enriched by a factor of at least 5-fold, 10-fold, 100-fold, or 1,000 from a complex mixture of polypeptides (e.g., a cell supernatant) by the use of heparin bound to a bead or other matrix support, or co-purifies with such a polypeptide.

[0080] As used herein “heparin-binding polypeptide” means any polypeptide that directly binds to heparin with a K_D of less than 1 micromolar. Heparin-binding polypeptides can interact with heparin at steady-state under normal growth conditions, but in other instances heparin-binding polypeptides may interact with heparin transiently under normal growth conditions or only under certain conditions as a result of a signaling or environmental stimulus. Heparin binding-polypeptides may interact with heparin as a result of post-translational modifications such as phosphorylation, dephosphorylation, acetylation, deacetylation, lipidation, delipidation, glycosylation, or deglycosylation, or combinations thereof.

[0081] As used herein “pluripotent stem cell” or “pluripotent cell” (PSC) means a cell that has the ability to differentiate into several different cell types that are derivatives of all of the three germinal layers (endoderm, mesoderm, and ectoderm). Pluripotent stem cells are capable of forming teratomas. Examples of pluripotent stem cells are embryonic stem cells (ESCs), embryonic germ stem cells (EGCs), embryonic Carcinoma Cells (ECCs), and induced pluripotent stem cells (iPSCs). PSC may be from any organism of interest, including, primate, human; canine; feline; murine; equine; porcine; avian; camel; bovine; ovine, and so on.

[0082] As used herein “somatic cell” means any cell of an organism that, in the absence of

experimental manipulation, does not ordinarily give rise to all types of cells in an organism. In other words, somatic cells are cells that have differentiated sufficiently that they will not naturally generate cells of all three germ layers of the body, i.e., ectoderm, mesoderm and endoderm. For example, somatic cells would include muscle cells and muscle progenitor cells, the latter of which may be able to self-renew and naturally give rise to all or some cell types of the skeletal, cardiac, or smooth muscle but cannot give rise to cells of the ectoderm or endoderm lineages.

[0083] As used herein the term “about” refers to an amount that is near the stated amount by 10% or less.

[0084] As used herein the terms “individual” “subject,” and “patient” are interchangeable. The individual can be mammal such as a horse, cow, pig, chicken, goat, rabbit, mouse, rat, dog, or cat. In certain embodiments, the individual is a human person.

[0085] The terms “polypeptide” and “protein” are used interchangeably to refer to a polymer of amino acid residues. Polypeptides, including the provided polypeptide chains and other peptides, e.g., linkers and binding peptides, may include amino acid residues including natural and/or non-natural amino acid residues. The terms also include post-translational modifications of the polypeptide, for example, glycosylation, sialylation, acetylation, phosphorylation, and the like. In some aspects, the polypeptides may contain modifications with respect to a native or natural sequence, as long as the protein maintains the desired activity. These modifications may be deliberate, as through site-directed mutagenesis, or may be accidental, such as through mutations of hosts that produce the proteins, errors due to PCR amplification, or errors in protein translation.

[0086] In some embodiments, a recombinant protein is a protein expressed in a system other than a human, e.g., the protein is expressed from bacteria, yeast, or mammalian cells in culture. In some cases, the protein is expressed from Chinese Hamster Ovary cells (CHO cells). In some cases, the protein is expressed from mouse myeloma cells, e.g., (NS0) cells. In some cases, the protein is expressed from *E. coli*.

[0087] Percent (%) sequence identity with respect to a reference polypeptide sequence is the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the reference polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are known for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Appropriate parameters for aligning sequences are

able to be determined, including algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc., and the source code has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available from Genentech, Inc., South San Francisco, Calif., or may be compiled from the source code. The ALIGN-2 program should be compiled for use on a UNIX operating system, including digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

[0088] In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows: 100 times the fraction X/Y , where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

[0089] "Exogenous" with respect to a nucleic acid or polynucleotide indicates that the nucleic acid is part of a recombinant nucleic acid construct, or is not in its natural environment. For example, an exogenous nucleic acid can be a sequence from one species introduced into another species, i.e., a heterologous nucleic acid. Typically, such an exogenous nucleic acid is introduced into the other species via a recombinant nucleic acid construct. An exogenous nucleic acid also can be a sequence that is native to an organism and that has been reintroduced into cells of that organism. An exogenous nucleic acid that includes a native sequence can often be distinguished from the naturally occurring sequence by the presence of non-natural sequences linked to the exogenous nucleic acid, e.g., non-native regulatory sequences flanking a native sequence in a recombinant nucleic acid construct. In addition, stably transformed exogenous nucleic acids typically are integrated at positions other than the position where the native sequence is found. The exogenous elements may be added to a construct, for example using genetic recombination. Genetic recombination is the breaking and rejoining of DNA strands to form new molecules of

DNA encoding a novel set of genetic information. Often exogenous nucleic acids will include a translatable sequence lacking introns that has been cloned from a cDNA.

[0090] As described herein a “mitogenic polypeptide” is one that induces one or more stages of mitosis, including interphase, prophase, metaphase, anaphase, and telophase. In certain embodiments, a mitogenic polypeptide is one that induces mitosis in any one or more of a soft-tissue cell, a soft-tissue precursor cell, a muscle cell, a muscle precursor cell, or a tenocyte.

[0091] As described herein a “fusion promoting” polypeptide is one that promotes fusion of muscle cells or muscle cell precursors. Fusion of muscle precursors like C2C12 cells is an experimental marker of differentiation and can be monitored by increases in eMyHC or increased number of nuclei per eMyHC positive cell a by a statistically measurable change of at least 25% magnitude ($p < 0.05$) relative to vehicle treated cells grown in otherwise identical conditions.

[0092] In some embodiments, reference to a fusion, fusion polypeptide, or fusion protein refers to a synthetically and/or recombinantly produced molecule in which two or more amino acid sequences are connected, *e.g.*, by a peptide bond and/or linker. In some cases, the two or more amino acid sequences are linked via a linker comprising one or more amino acids. In other cases, the two or more amino acid sequences are not linked via a linker, *e.g.*, the two sequences are directly connected by a peptide bond. In some cases, at least one of the two or more amino acid sequences comprises a polypeptide described herein. For example, the polypeptide described herein is a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS4, THBS1, IL-15, or IGF2, or a combination thereof.

[0093] In some embodiments, reference to a conjugate, polypeptide conjugate, or protein conjugate refers to a synthetically and/or recombinantly produced molecule comprising a chemical entity covalently bound to one or more amino acids of an amino acid sequence. In some cases, the conjugation is selective such that the chemical entity is connected to a specific amino acid of the amino acid sequence. In some embodiments, the amino acid sequence comprises a polypeptide described herein. For example, the polypeptide described herein is a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS4, THBS1, IL-15, or IGF2, or a combination thereof.

[0094] In some embodiments, a polypeptide described herein is a proteoform of a protein listed in Table 2. In some embodiments, as used herein a proteoform describes a molecular form of a protein product arising from a gene encoding a protein, such as a protein listed in Table 2. In some cases, a proteoform includes proteins that arise from the same gene as a result of genetic variation, alternatively spliced RNA transcripts, post-translational modifications, or polypeptide cleavage event.

Heparin-Associated Polypeptides

[0095] In one aspect, polypeptides described herein that are useful for treating an aging disease or injury comprise one or more polypeptides secreted from an induced pluripotent stem cell, an embryonic stem cell, a tissue progenitor cell, or a transformed cell line that bind to heparin. In certain embodiments, a plurality of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more heparin-associated polypeptides are included in a composition comprising a pharmaceutically acceptable excipient, carrier, or diluent. In some cases the composition comprises one, two, three, four, five, six, seven, eight, nine, ten or more polypeptides of Table 2. In some cases the composition comprises one, two, three, four, five, six, seven, eight, nine, ten or more polypeptides of Table 1.

[0096] In certain aspects, there are three biochemical features that are common across all potential therapeutic heparin-associated polypeptides: 1) they are secreted by human pluripotent stem cells; 2) they can be purified by heparin agarose beads from a complex mixture, and 3) their molecular weight equals or exceeds 3.5 kDa.

[0097] In certain aspects, there are certain structure-function relationships that potentially link disparate therapeutic polypeptides into a genus of heparin-associated therapeutic polypeptides. Included among these are the ability to be secreted, which may require: 1) an N-terminal signal sequence (approx. 15-30 amino acids in length); and/or 2) the presence of one or more post translational modifications added in the Endoplasmic Reticulum or the Golgi apparatus to promote stability, such as glycosylation or the presence of disulfide bonds. It is estimated that 2,000 to 3,000 polypeptides encoded by the human genome can be secreted by one or more cell types. In addition to being secretory polypeptides the therapeutic polypeptides may comprise a heparin-binding domain, or, alternatively associate with heparin-binding domain comprising polypeptides. Heparin is a linear polymer of saccharides in 1-4 alpha linkages that form a spiraling chain, commonly associated with its role in binding plasma proteins to reduce clotting (*See* Capila and Lindhart, "Heparin-protein interactions" *Angew Chem Int Ed Engl.* 2002 Feb 1;41(3):391-412). Currently, predicting heparin-binding from protein sequence alone is a challenge for the field due to the structural heterogeneity of heparin polymers and the large and variable number of shallow binding pockets thought to be important for stabilizing the interaction. Several hundred heparin-associated polypeptides have been empirically tested for heparin binding, using a few heparin chain configurations. Based on these studies many binding motifs have been proposed, but none have been proven necessary and sufficient. One common motif appears to be a sequence of repeating basic residues that orient onto a common surface of the secondary structure for interacting with the matching pattern of sulfate groups on heparin chains. Therefore many heparin-binding therapeutic polypeptides may contain patterns of basic residues

(arginine or lysine) clustered in some part of the protein, though agnostic to the exact sequence.

[0098] In certain embodiments, the heparin-associated therapeutic polypeptide is a secreted polypeptide. In certain embodiments, the heparin-associated therapeutic polypeptide is a secreted polypeptide that comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more disulfide bonds. In certain embodiments, the heparin-associated therapeutic polypeptide is a secreted polypeptide that comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or N-linked or O-linked glycans. In certain embodiments, the heparin-associated therapeutic polypeptide is greater than about 3.5 kilodaltons. In other embodiments, the heparin-associated is greater than about 5, 7.5, 10, 15, or 20 kilodaltons. In certain embodiments, the heparin-associated therapeutic polypeptide is one that comprises a region exhibiting enrichment for basic amino acids arginine or lysine. The region can be about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acids in length, and comprise an amount of basic residues that is greater than would be 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 100%, 150%, or 200% greater than expected given random chance. In certain embodiments, the heparin-associated therapeutic polypeptide does not comprise a basic DNA binding motif, such as those found in bZIP transcription factors. In a certain embodiment, the heparin-associated polypeptide is heparin binding polypeptide.

[0099] The heparin-associated polypeptides, described herein, can comprise one or more amino acid modifications that promote stability and/or facilitate production. In certain embodiments, the polypeptide can comprise one or more covalent modifications that promote stability (e.g., PEGylation). Other modifications of the heparin-associated polypeptide(s) are contemplated herein. For example, the heparin-associated polypeptide(s) may be linked to one of a variety of non-proteinaceous polymers, e.g., polyethylene glycol, polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol, polysialic acid, glycolic acid, or polypropylene glycol. In certain embodiments, the heparin-associated polypeptide may be fused or conjugated to another protein to increase stability and or bioavailability. In certain embodiments, the heparin-associated polypeptide may be a fusion with an Fc region of an immunoglobulin or with serum albumin.

[00100] The heparin-associated polypeptides described herein can be encapsulated in nanospheres or nanoparticles to increase stability. In certain embodiments, the nanospheres or nanoparticles are biodegradable or bioabsorbable. Certain types of nanospheres can be deployed such as polylactic acid (PLA), polyglycolic acid (PGA), or Poly(D,L-lactic-coglycolic-acid) (PLGA) microspheres or nanospheres. In certain embodiments, the heparin-associated polypeptide is included in a composition comprising a biodegradable or bioabsorbable carrier that promotes polypeptide stability. In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA), polyglycolic acid (PGA), or Poly(D,L-lactic-coglycolic-

acid) (PLGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polyglycolic acid (PGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises Poly(D,L-lactic-coglycolic-acid) (PLGA).

[00101] In certain embodiments, the heparin-associated-polypeptide may be concatemerized to increase stability and or bioavailability. In certain embodiments, the heparin-associated polypeptide(s) comprises concatemers of the same or of different heparin-associated binding polypeptides. Concatemers can be separated by polypeptide linkers, for example a Gly-Ser linker of any suitable length. In certain embodiments, the Gly-Ser linker comprises a G₄S₁ linker. In certain embodiments, the concatemers comprise 1, 2, 3, 4, 5 or more of the same heparin-associated polypeptide as a single polypeptide separated by a Gly-Ser linker. In certain embodiments, the concatemers comprise 1, 2, 3, 4, 5 or more different heparin-associated polypeptides as a single polypeptide separated by a Gly-Ser linker. In certain embodiments, the concatemers comprise 1, 2, 3, 4, 5 or more of the same heparin-associated polypeptide covalently linked through a non-peptide linkage, such as for example a disulfide bridge. In certain embodiments, the concatemers comprise 1, 2, 3, 4, 5 or more different heparin-associated polypeptides covalently linked through a non-peptide linkage, such as for example a disulfide bridge. In certain embodiments, the concatemers comprise 1, 2, 3, 4, 5 or more of the same heparin-associated polypeptide non-covalently linked, such as for example, by a streptavidin-biotin interaction or protein-protein interaction. In certain embodiments, the concatemers comprise 1, 2, 3, 4, 5 or more different heparin-associated polypeptides non-covalently linked such as for example, by a streptavidin-biotin interaction or protein-protein interaction.

[00102] Additional modifications to heparin-associated polypeptide comprise deletions of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 amino acids from the N-terminal or C-terminal ends of the heparin-associated polypeptide. In certain embodiments, the heparin-associated polypeptide comprises the deletion of known inhibitory domains or deletion of domains not associated with the heparin-associated-polypeptides functions in inducing proliferation of muscle, connective, or soft-tissue cell precursors.

[00103] The heparin-associated polypeptides herein can comprise cleavage products of a pro-protein. Cleavage of a pro-protein can result in activation or higher activity of said pro-protein. In certain embodiments, heparin-associated polypeptides are produced that correspond to a cleaved or active form of the pro-protein. In certain embodiments, the heparin-associated polypeptides comprise only the active domain of a heparin associated pro-protein (*e.g.*, the minimal portion sufficient to create a biological effect).

[00104] In certain embodiments, the heparin-associated polypeptide comprises one or more of

the polypeptides listed in Table 1 and/or Table 2. In certain embodiments, the polypeptide is at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to a polypeptide listed in Table 1 and/or Table 2, or an isoform thereof. In certain embodiments, the polypeptide is at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to a sequence selected from SEQ ID NOS: 1-44, 55, 56, and 58-70.

Table 1. Exemplary Therapeutic Polypeptides

Polypeptide	SEQ ID	Modified Amino Acid Sequences Tested
Vitronectin (VTN)	1	Asp20 to Leu478, purified from Human plasma-derived
Periostin (POSTN)	6	Asn22 to Gln836, with a C-terminal 6-His tag (SEQ ID NO: 69), purified from Mouse myeloma cell line, NS0
Thrombospondin 2 (THBS2)	4	Gly19 to Ile1172, with a C-terminal 10-His tag (SEQ ID NO: 70), purified from Mouse myeloma cell line, NS0
Thrombospondin 4 (THBS4)	8	Ala22 to Asn961, with a C-terminal 10-His tag (SEQ ID NO: 70), purified from Chinese Hamster Ovary cell line
Fibroblast growth factor 2 (FGF 2)	12	Pro143 to Ser288, purified E. coli
Fibroblast growth factor 19 (FGF 19)	13	Leu25 to Lys216, purified from E. coli
Angiogenin (ANG)	14	Gln25 to Pro147, purified from E. coli
Probetacellulin (BTC)	15	Asp32 to Tyr111, purified from E. coli
Interleukin -13 receptor alpha 2	16	Arg21 to Ala228, purified from mouse myeloma cell line, NS0
Siglec-5/CD170	17	Glu17 to Thr434, purified from mouse myeloma cell line, NS0
Interleukin-15	10	Asn49 to Ser162, purified from E. coli
Apelin receptor (APJ)	18	
Insulin-like growth factor-binding protein 2 (IGFBP-2)	19	Glu40 to Gln328, purified from mouse myeloma cell line, NS0
Chordin-Like 1 (CHRD1)	20	Glu22-Cys450, purified from mouse myeloma cell line, NS0
WAP, Kazal, immunoglobulin, Kunitz and NTR domain-containing protein 2	21	Leu35 to His 576, purified from mouse myeloma cell line, NS0
Membrane frizzled-related protein (MFRP)	22	Ser101 to Pro579, purified from mouse myeloma cell line, NS0
Interleukin -10 receptor alpha	23	His22 to Asn235, purified from human cell line HEK293
Chemokine like receptor 1, Chemerin Receptor 23 (Chem R23)	24	
HB-EGF	25	Asp63 to Leu148, purified from insect cells
fibroblast growth factor 6	26	Gly67 to Ile208, purified from E. coli
Hepatocyte Growth Factor	27	Gln32 to Ser728, purified from insect cells
Interleukin-16	28	Pro2 to Ser130, purified from E. coli
Interleukin-7 receptor alpha	29	Glu21 to Lys261, purified from mouse myeloma cell line, NS0

Tumor necrosis factor receptor superfamily member 10C	30	Ala26 to Ala221, purified from mouse myeloma cell line, NS0
Bone morphogenetic protein 6	31	Gln382 to His51,3 purified from E. coli
Interleukin-36 gamma	32	Ser18 to Asp169, purified from E. coli
interleukin-1 receptor antagonist (IL-1RA)	33	Val2 to Asp155, purified from E. coli
Kremen protein 2	34	Gln19 to Ala364, purified from mouse myeloma cell line, NS0
Tumor necrosis factor receptor superfamily member 10D	35	
C-X-C chemokine receptor type 1	36	
C-C motif chemokine 23	37	
Catenin, Beta	38	
Fibroblast growth factor 13, 1B	39	
Tumor necrosis factor ligand superfamily member 10	40	Glu108 to Leu261, purified from E. coli
C-C motif chemokine 14	41	Ser35 to Glu111, purified from E. coli
Thrombospondin 1 (THBS1)	9	Asn19-Pro1170, with Thr523Ala substitution plus 10His tag, purified from mouse myeloma cell line, NS0
Insulin-like growth factor binding protein 7	42	Asp30 to Leu282 with a K95R mutation with an N-terminal 10-His tag (SEQ ID NO: 70), purified from Mouse myeloma cell line, NS0
Fibroblast growth factor 4	43	Ser54 to Leu206, purified from E. coli
Fibroblast growth factor 17 (FGF17)	7	Thr23 to Thr216, purified from E. coli
Fibroblast growth factor 8	44	Gln23 to Arg204, purified from E. coli
Insulin-like growth factor 2 (IGF2)	11	Ala25 to Glu91, purified from E. coli
THBS1 isoform 2	58	
FGF17 isoform 2	59	
POSTN isoform 2	60	
POSTN isoform 3	61	
POSTN isoform 4	62	
POSTN isoform 5	63	
POSTN isoform 6	64	
POSTN isoform 7	65	
IGF2 isoform 2	66	
IGF2 isoform 3	67	
IL15 isoform 2	68	
STC2	2	
AGRN	3	
FST	5	

PDGFR	55	Gln22 to Ser375, purified from HEK293 cells
ANOS1	56	Ala25 to Tyr680, purified from CHO cells

Table 2. Factors enriched in the supernatants of undifferentiated human pluripotent stem cells.

Gene Name	Uniprot ID	Entrez Gene ID	Ensembl ID	Peptide No.
A1BG	P04217	1	ENSG00000121410	1
A2M	P01023	2	ENSG00000175899	2
ABCF1	Q8NE71	23	ENSG00000204574	3
ACADVL	P49748	37	ENSG00000072778	4
ACLY	P53396	47	ENSG00000131473	5
ACP1	P24666	52	ENSG00000143727	6
ACP5	P13686	54	ENSG00000102575	7
ACTG1	P63261	71	ENSG00000184009	8
ACTN1	P12814	87	ENSG00000072110	9
ACTR3	P61158	10096	ENSG00000115091	10
ADAMTS1	Q9UHI8	9510	ENSG00000154734	11
ADAMTS12	P58397	81792	ENSG00000151388	12
ADAMTS19	Q8TE59	171019	ENSG00000145808	13
ADAMTS7	Q9UKP4	11173	ENSG00000136378	14
ADAMTS8	Q9UP79	11095	ENSG00000134917	15
ADRM1	Q16186	11047	ENSG00000130706	16
AEBP1	Q8IUX7	165	ENSG00000106624	17
AFM	P43652	173	ENSG00000079557	18
AFP	P02771	174	ENSG00000081051	19
AGPS	O00116	8540	ENSG00000018510	20
AGRN	O00468	375790	ENSG00000188157	21
AGT	P01019	183	ENSG00000135744	22
AHCYL2	Q96HN2	23382	ENSG00000158467	23
AHSG	P02765	197	ENSG00000145192	24
AIMP1	Q12904	9255	ENSG00000164022	25
ALB	P02768	213	ENSG00000163631	26
ALCAM	Q13740	214	ENSG00000170017	27
ALDH9A1	P49189	223	ENSG00000143149	28
ALDOA	P04075	226	ENSG00000149925	29
ALPL	P05186	249	ENSG00000162551	30
AMBP	P02760	259	ENSG00000106927	31
ANG	P03950	283	ENSG00000214274	32
ANGPTL4	Q9BY76	51129	ENSG00000167772	33
ANOS1	P23352	3730	ENSG00000011201	34
ANXA1	P04083	301	ENSG00000135046	35
ANXA2	P07355	302	ENSG00000182718	36
ANXA2P2	A6NMY6			37
AOC1	P19801	26	ENSG00000002726	38
AP2A1	O95782	160	ENSG00000196961	39

AP2A2	O94973	161	ENSG00000183020	40
AP3D1	O14617	8943	ENSG00000065000	41
APLP2	Q06481	334	ENSG00000084234	42
APOA1	P02647	335	ENSG00000118137	43
APOA2	P02652	336	ENSG00000158874	44
APOB	P04114	338	ENSG00000084674	45
APOC3	P02656	345	ENSG00000110245	46
APOD	P05090	347	ENSG00000189058	47
APOE	P02649	348	ENSG00000130203	48
APOH	P02749	350	ENSG00000091583	49
APOM	O95445	55937	ENSG00000204444	50
ARCN1	P48444	372	ENSG00000095139	51
ARHGEF1	Q92888	9138	ENSG00000076928	52
ARHGEF28	Q8N1W1	64283	ENSG00000214944	53
ARPC1B	O15143	10095	ENSG00000130429	54
ARRB1	P49407	408	ENSG00000137486	55
ARSK	Q6UWY0	153642	ENSG00000164291	56
ART4	Q93070	420	ENSG00000111339	57
ASNA1	O43681	439	ENSG00000198356	58
ASNS	P08243	440	ENSG00000070669	59
ATP6AP2	O75787	10159	ENSG00000182220	60
ATRN	O75882	8455	ENSG00000088812	61
AZGP1	P25311	563	ENSG00000160862	62
B3GALT6	Q96L58	126792	ENSG00000176022	63
B3GNT7	Q8NFL0	93010	ENSG00000156966	64
B4GALT1	P15291	2683	ENSG00000086062	65
B4GALT4	O60513	8702	ENSG00000121578	66
B4GAT1	O43505	11041	ENSG00000174684	67
BCAM	P50895	4059	ENSG00000187244	68
BGN	P21810	633	ENSG00000182492	69
BLVRB	P30043	645	ENSG00000090013	70
BMP1	P13497	649	ENSG00000168487	71
BMP7	P18075	655	ENSG00000101144	72
BOC	Q9BWV1	91653	ENSG00000144857	73
BRD3	Q15059	8019	ENSG00000169925	74
BSG	P35613	682	ENSG00000172270	75
BTBD17	A6NE02	388419	ENSG00000204347	76
BTD	P43251	686	ENSG00000169814	77
BZW2	Q9Y6E2	28969	ENSG00000136261	78
C11orf24	Q96F05	53838	ENSG00000171067	79
C1QA	P02745	712	ENSG00000173372	80
C1QBP	Q07021	708	ENSG00000108561	81
C1QC	P02747	714	ENSG00000159189	82
C1QTNF3	Q9BXJ4	114899	ENSG00000082196	83
C1QTNF3-AMACR	E9PGA6		ENSG00000273294	84
C1QTNF4	Q9BXJ3	114900	ENSG00000172247	85
C1RL	Q9NZP8	51279	ENSG00000139178	86
C1S	P09871	716	ENSG00000182326	87
C20orf27	Q9GZN8	54976	ENSG00000101220	88
C3	P01024	718	ENSG00000125730	89
C4A	P0C0L4	720	ENSG00000206340	90
C4B	A0A140TA29		ENSG00000236625	91
C4BPA	P04003	722	ENSG00000123838	92

C5	P01031	727	ENSG00000106804	93
C7	P10643	730	ENSG00000112936	94
C8B	P07358	732	ENSG00000021852	95
C9	P02748	735	ENSG00000113600	96
CA11	O75493	770	ENSG00000063180	97
CALM2	P0DP24	801	ENSG00000143933	98
CALR	P27797	811	ENSG00000179218	99
CALU	O43852	813	ENSG00000128595	100
CAND1	Q86VP6	55832	ENSG00000111530	101
CANT1	Q8WVQ1	124583	ENSG00000171302	102
CANX	P27824	821	ENSG00000127022	103
CAPG	P40121	822	ENSG00000042493	104
CAPN1	P07384	823	ENSG00000014216	105
CAPZA2	P47755	830	ENSG00000198898	106
CARM1	Q86X55	10498	ENSG00000142453	107
CARS	P49589	833	ENSG00000110619	108
CBL	P22681	867	ENSG00000110395	109
CBX3	Q13185	11335	ENSG00000122565	110
CCAR2	Q8N163	57805	ENSG00000158941	111
CCBE1	Q6UXH8	147372	ENSG00000183287	112
CCDC80	Q76M96	151887	ENSG00000091986	113
CCK	P06307	885	ENSG00000187094	114
CCT2	P78371	10576	ENSG00000166226	115
CCT4	P50991	10575	ENSG00000115484	116
CCT7	Q99832	10574	ENSG00000135624	117
CD5	P06127	921	ENSG00000110448	118
CDC40	O60508	51362	ENSG00000168438	119
CDH1	P12830	999	ENSG00000039068	120
CDH9	Q9ULB4	1007	ENSG00000113100	121
CDON	Q4KMG0	50937	ENSG00000064309	122
CDSN	Q15517	1041	ENSG00000137197	123
CENPV	Q7Z7K6	201161	ENSG00000166582	124
CFB	P00751	629	ENSG00000241253	125
CFC1	P0CG37	55997	ENSG00000136698	126
CFD	P00746	1675	ENSG00000197766	127
CFH	P08603	3075	ENSG00000000971	128
CFI	P05156	3426	ENSG00000205403	129
CHAD	O15335	1101	ENSG00000136457	130
CHD4	Q14839	1108	ENSG00000111642	131
CHD8	Q9HCK8	57680	ENSG00000100888	132
CHGA	P10645	1113	ENSG00000100604	133
CHID1	Q9BWS9	66005	ENSG00000177830	134
CHRD1	Q9BU40	91851	ENSG00000101938	135
CHST11	Q9NPF2	50515	ENSG00000171310	136
CHST6	Q9GZX3	4166	ENSG00000183196	137
CHSY1	Q86X52	22856	ENSG00000131873	138
CHSY3	Q70JA7	337876	ENSG00000198108	139
CILP2	Q8IUL8	148113	ENSG00000160161	140
CKAP5	Q14008	9793	ENSG00000175216	141
CKMT1A	C9J8F6		ENSG00000223572	142
CKMT2	P17540	1160	ENSG00000131730	143
CLDN6	P56747	9074	ENSG00000184697	144
CLEC3B	P05452	7123	ENSG00000163815	145
CLPX	O76031	10845	ENSG00000166855	146

CLSTN3	Q9BQT9	9746	ENSG00000139182	147
CLTC	Q00610	1213	ENSG00000141367	148
CLU	P10909	1191	ENSG00000120885	149
CNOT1	A5YKK6	23019	ENSG00000125107	150
COCH	O43405	1690	ENSG00000100473	151
COL11A1	P12107	1301	ENSG00000060718	152
COL11A2	P13942	1302	ENSG00000227801	153
COL12A1	Q99715	1303	ENSG00000111799	154
COL14A1	Q05707	7373	ENSG00000187955	155
COL16A1	Q07092	1307	ENSG00000084636	156
COL18A1	P39060	80781	ENSG00000182871	157
COL1A1	P02452	1277	ENSG00000108821	158
COL1A2	P08123	1278	ENSG00000164692	159
COL22A1	Q8NFW1	169044	ENSG00000169436	160
COL25A1	Q9BXS0	84570	ENSG00000188517	161
COL26A1	Q96A83	136227	ENSG00000160963	162
COL2A1	P02458	1280	ENSG00000139219	163
COL3A1	P02461	1281	ENSG00000168542	164
COL4A1	P02462	1282	ENSG00000187498	165
COL4A2	P08572	1284	ENSG00000134871	166
COL4A3	Q01955	1285	ENSG00000169031	167
COL4A6	Q14031	1288	ENSG00000197565	168
COL5A1	P20908	1289	ENSG00000130635	169
COL5A2	P05997	1290	ENSG00000204262	170
COL5A3	P25940	50509	ENSG00000080573	171
COL6A1	P12109	1291	ENSG00000142156	172
COL6A2	P12110	1292	ENSG00000142173	173
COL6A3	P12111	1293	ENSG00000163359	174
COL9A2	Q14055	1298	ENSG00000049089	175
COLEC10	Q9Y6Z7	10584	ENSG00000184374	176
COMP	P49747	1311	ENSG00000105664	177
COPA	P53621	1314	ENSG00000122218	178
COTL1	Q14019	23406	ENSG00000103187	179
CP	P00450	1356	ENSG00000047457	180
CPA4	Q9UI42	51200	ENSG00000128510	181
CPE	P16870	1363	ENSG00000109472	182
CPN1	P15169	1369	ENSG00000120054	183
CPNE1	Q99829	8904	ENSG00000214078	184
CPVL	Q9H3G5	54504	ENSG00000106066	185
CPXM1	Q96SM3	56265	ENSG00000088882	186
CPXM2	Q8N436	119587	ENSG00000121898	187
CPZ	Q66K79	8532	ENSG00000109625	188
CRIM1	Q9NZV1	51232	ENSG00000150938	189
CRISPLD1	Q9H336	83690	ENSG00000121005	190
CRLF1	O75462	9244	ENSG00000006016	191
CRYL1	Q9Y2S2	51084	ENSG00000165475	192
CS	O75390	1431	ENSG00000062485	193
CSDE1	O75534	7812	ENSG00000009307	194
CSF2RA	P15509	1438	ENSG00000198223	195
CST1	P01037	1469	ENSG00000170373	196
CST3	P01034	1471	ENSG00000101439	197
CST4	P01036	1472	ENSG00000101441	198
CTGF	Q5M8T4	1490		199
CTNNA1	P35221	1495	ENSG00000044115	200

CTSD	P07339	1509	ENSG00000117984	201
CTSV	O60911	1515	ENSG00000136943	202
CUL2	Q13617	8453	ENSG00000108094	203
CUL3	Q13618	8452	ENSG00000036257	204
CUL4B	Q13620	8450	ENSG00000158290	205
CUTA	O60888	51596	ENSG00000112514	206
CXADR	P78310	1525	ENSG00000154639	207
CXCL12	P48061	6387	ENSG00000107562	208
CYR61	Q6FI18	3491		209
DAG1	Q14118	1605	ENSG00000173402	210
DARS	P14868	1615	ENSG00000115866	211
DBNL	Q9UJU6	28988	ENSG00000136279	212
DCD	P81605	117159	ENSG00000161634	213
DDOST	P39656	1650	ENSG00000244038	214
DDR1	Q08345	780	ENSG00000137332	215
DDX17	Q92841	10521	ENSG00000100201	216
DDX39B	Q13838	7919	ENSG00000215425	217
DENND5A	Q6IQ26	23258	ENSG00000184014	218
DHFR	P00374	1719	ENSG00000228716	219
DHX29	Q7Z478	54505	ENSG00000067248	220
DKK1	O94907	22943	ENSG00000107984	221
DKK3	Q9UBP4	27122	ENSG00000050165	222
DKK4	Q9UBT3	27121	ENSG00000104371	223
DLG3	Q92796	1741	ENSG00000082458	224
DMBT1	Q9UGM3	1755	ENSG00000187908	225
DNAAF5	Q86Y56	54919	ENSG00000164818	226
DNAJB11	Q9UBS4	51726	ENSG00000090520	227
DNAJC3	Q13217	5611	ENSG00000102580	228
DNMT1	P26358	1786	ENSG00000130816	229
DRAXIN	Q8NBI3	374946	ENSG00000162490	230
DRG1	Q9Y295	4733	ENSG00000185721	231
DSG2	Q14126	1829	ENSG00000046604	232
ECM1	Q16610	1893	ENSG00000143369	233
EDA	Q92838	1896	ENSG00000158813	234
EDIL3	O43854	10085	ENSG00000164176	235
EEF1G	P26641	1937	ENSG00000254772	236
EFEMP1	Q12805	2202	ENSG00000115380	237
EFTUD2	Q15029	9343	ENSG00000108883	238
EGFLAM	Q63HQ2	133584	ENSG00000164318	239
EIF1AY	O14602	9086	ENSG00000198692	240
EIF2B4	Q9UI10	8890	ENSG00000115211	241
EIF2S1	P05198	1965	ENSG00000134001	242
EIF2S2	P20042	8894	ENSG00000125977	243
EIF3A	Q14152	8661	ENSG00000107581	244
EIF3C	Q99613	8663	ENSG00000184110	245
EIF3F	O00303	8665	ENSG00000175390	246
EIF3H	O15372	8667	ENSG00000147677	247
EIF3M	Q7L2H7	10480	ENSG00000149100	248
EIF5	P55010	1983	ENSG00000100664	249
EIF5B	O60841	9669	ENSG00000158417	250
ELAC2	Q9BQ52	60528	ENSG00000006744	251
ELP3	Q9H9T3	55140	ENSG00000134014	252
EMILIN2	Q9BXX0	84034	ENSG00000132205	253
EPHA4	P54764	2043	ENSG00000116106	254

EPHB2	P29323	2048	ENSG00000133216	255
EPHB4	P54760	2050	ENSG00000196411	256
EPRS	P07814	2058	ENSG00000136628	257
ERBB3	P21860	2065	ENSG00000065361	258
ERLIN1	O75477	10613	ENSG00000107566	259
ERVMER34-1	Q9H9K5	100288413	ENSG00000226887	260
EXTL2	Q9UBQ6	2135	ENSG00000162694	261
EZR	P15311	7430	ENSG00000092820	262
F10	P00742	2159	ENSG00000126218	263
F13A1	P00488	2162	ENSG00000124491	264
F2	P00734	2147	ENSG00000180210	265
F5	P12259	2153	ENSG00000198734	266
FAM129B	Q96TA1	64855	ENSG00000136830	267
FAP	Q12884	2191	ENSG00000078098	268
FAT1	Q14517	2195	ENSG00000083857	269
FBLN1	P23142	2192	ENSG00000077942	270
FBLN2	P98095	2199	ENSG00000163520	271
FBN1	P35555	2200		272
FBN2	P35556	2201	ENSG00000138829	273
FERMT2	Q96AC1	10979	ENSG00000073712	274
FGB	P02675	2244	ENSG00000171564	275
FGF17	O60258	8822	ENSG00000158815	276
FGF2	P09038	2247	ENSG00000138685	277
FGF8	P55075	2253	ENSG00000107831	278
FGF4	P08620	2249	ENSG00000075388	279
FGF6	P10767	2251	ENSG00000111241	280
FGFBP3	Q8TAT2	143282	ENSG00000174721	281
FGFR1	P11362	2260	ENSG00000077782	282
FGFR2	P21802	2263	ENSG00000066468	283
FGFR4	P22455	2264	ENSG00000160867	284
FGFRL1	Q8N441	53834	ENSG00000127418	285
FH	P07954	2271	ENSG00000091483	286
FLT1	P17948	2321	ENSG00000102755	287
FN1	P02751	2335	ENSG00000115414	288
FRAS1	Q86XX4	80144	ENSG00000138759	289
FRZB	Q92765	2487	ENSG00000162998	290
FST	P19883	10468	ENSG00000134363	291
FSTL1	Q12841	11167	ENSG00000163430	292
FUCA2	Q9BTY2	2519	ENSG00000001036	293
FXR1	P51114	8087	ENSG00000114416	294
GALNT1	Q10472	2589	ENSG00000141429	295
GALNT16	Q8N428	57452	ENSG00000100626	296
GALNT2	Q10471	2590	ENSG00000143641	297
GALNT7	Q86SF2	51809	ENSG00000109586	298
GANAB	Q14697	23193	ENSG00000089597	299
GARS	P41250	2617	ENSG00000106105	300
GBA	P04062	2629	ENSG00000177628	301
GC	P02774	2638	ENSG00000145321	302
GCNT1	Q02742	2650	ENSG00000187210	303
GDF11	Q95390	10220	ENSG00000135414	304
GDF15	Q99988	9518	ENSG00000130513	305
GDF6	Q6KF10	392255	ENSG00000156466	306
GEMIN5	Q8TEQ6	25929	ENSG00000082516	307

GFAP	P14136	2670	ENSG00000131095	308
GGH	Q92820	8836	ENSG00000137563	309
GLB1	P16278	2720	ENSG00000170266	310
GLG1	Q92896	2734	ENSG00000090863	311
GM2A	P17900	2760	ENSG00000196743	312
GNAS	O95467	2778	ENSG00000087460	313
GOLM1	Q8NBJ4	51280	ENSG00000135052	314
GOT2	P00505	2806	ENSG00000125166	315
GPC1	P35052	2817	ENSG00000063660	316
GPC3	P51654	2719	ENSG00000147257	317
GPC4	O75487	2239	ENSG00000076716	318
GPI	P06744	2821	ENSG00000105220	319
GPRC5B	Q9NZH0	51704	ENSG00000167191	320
GPX4	P36969	2879	ENSG00000167468	321
GREM1	O60565	26585	ENSG00000166923	322
GRN	P28799	2896	ENSG00000030582	323
GRSF1	Q12849	2926	ENSG00000132463	324
GSN	P06396	2934	ENSG00000148180	325
GSPT1	P15170	2935	ENSG00000103342	326
GTF3C3	Q9Y5Q9	9330	ENSG00000119041	327
HABP2	Q14520	3026	ENSG00000148702	328
HADHB	P55084	3032	ENSG00000138029	329
HAPLN1	P10915	1404	ENSG00000145681	330
HAPLN3	Q96S86	145864		331
HAPLN4	Q86UW8	404037		332
HARS	P12081	3035	ENSG00000170445	333
HBB	P68871	3043	ENSG00000244734	334
HBS1L	Q9Y450	10767	ENSG00000112339	335
HDGF	P51858	3068	ENSG00000143321	336
HDGFL2	Q7Z4V5	84717	ENSG00000167674	337
HDLBP	Q00341	3069	ENSG00000115677	338
HGF	P14210	3082	ENSG00000019991	339
HGFAC	Q04756	3083	ENSG00000109758	340
HIST1H1C	P16403	3006	ENSG00000187837	341
HIST1H1E	P10412	3008	ENSG00000168298	342
HLA-C	P04222		ENSG00000225691	343
HMCN1	Q96RW7	83872	ENSG00000143341	344
HMCN2	Q8NDA2		ENSG00000148357	345
HMGB1	P09429	3146	ENSG00000189403	346
HMGB2	P26583	3148	ENSG00000164104	347
HMGB3	O15347	3149	ENSG00000029993	348
HMGN1	P05114	3150	ENSG00000205581	349
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SMARCC1	Q92922	6599	ENSG00000173473	737
SMARCD1	Q96GM5	6602	ENSG00000066117	738
SMARCD2	Q92925	6603	ENSG00000108604	739

SMC1A	Q14683	8243	ENSG00000072501	740
SMC3	Q9UQE7	9126	ENSG00000108055	741
SMOC1	Q9H4F8	64093	ENSG00000198732	742
SMOC2	Q9H3U7	64094	ENSG00000112562	743
SMPDL3B	Q92485	27293	ENSG00000130768	744
SMR3B	P02814	10879	ENSG00000171201	745
SNRPB	P14678	6628	ENSG00000125835	746
SNRPD1	P62314	6632	ENSG00000167088	747
SNRPD3	P62318	6634	ENSG00000100028	748
SOD3	P08294	6649	ENSG00000109610	749
SPARC	P09486	6678	ENSG00000113140	750
SPINT1	O43278	6692	ENSG00000166145	751
SPINT2	O43291	10653	ENSG00000167642	752
SPOCK1	Q08629	6695	ENSG00000152377	753
SPON1	Q9HCB6	10418	ENSG00000262655	754
SPP1	P10451	6696	ENSG00000118785	755
SRP14	P37108	6727	ENSG00000140319	756
SRPX	P78539	8406	ENSG00000101955	757
SRPX2	O60687	27286	ENSG00000102359	758
SRSF1	Q07955	6426	ENSG00000136450	759
SSB	P05455	6741	ENSG00000138385	760
SSC5D	A1L4H1	284297	ENSG00000179954	761
ST6GAL1	P15907	6480	ENSG00000073849	762
ST6GAL2	Q96JF0	84620	ENSG00000144057	763
STAG1	Q8WVM7	10274	ENSG00000118007	764
STC1	P52823	6781	ENSG00000159167	765
STC2	O76061	8614	ENSG00000113739	766
SUB1	P53999	10923	ENSG00000113387	767
SULF2	Q8IWU5	55959	ENSG00000196562	768
SUMF2	Q8NBJ7	25870	ENSG00000129103	769
SUPT16H	Q9Y5B9	11198	ENSG00000092201	770
SUPT6H	Q7KZ85	6830	ENSG00000109111	771
SVEP1	Q4LDE5	79987	ENSG00000165124	772
SYNCRIP	O60506	10492	ENSG00000135316	773
TAGLN2	P37802	8407	ENSG00000158710	774
TBL1XR1	Q9BZK7	79718	ENSG00000177565	775
TCN2	P20062	6948	ENSG00000185339	776
TCOF1	Q13428	6949	ENSG00000070814	777
TF	P02787	7018	ENSG00000091513	778
TFAM	Q00059	7019	ENSG00000108064	779
TFPI	P10646	7035	ENSG00000003436	780
TFRC	P02786	7037	ENSG00000072274	781
TGFB2	P61812	7042	ENSG00000092969	782
TGFBI	Q15582	7045	ENSG00000120708	783
THBS1	P07996	7057	ENSG00000137801	784
THBS2	P35442	7058	ENSG00000186340	785
THBS3	P49746	7059	ENSG00000169231	786
THBS4	P35443	7060	ENSG00000113296	787
THOC3	Q96J01	84321	ENSG00000051596	788
THSD7A	Q9UPZ6	221981	ENSG00000005108	789
TIMP1	P01033	7076	ENSG00000102265	790
TIMP2	P16035	7077	ENSG00000035862	791
TIMP3	P35625	7078	ENSG00000100234	792
TINAGL1	Q9GZM7	64129	ENSG00000142910	793

TJP1	Q07157	7082	ENSG00000104067	794
TNC	P24821	3371	ENSG00000041982	795
TNN	Q9UQP3	63923		796
TNXB	P22105	7148	ENSG00000168477	797
TOP1	P11387	7150	ENSG00000198900	798
TPM4	P67936	7171	ENSG00000167460	799
TPP2	P29144	7174	ENSG00000134900	800
TRIM28	Q13263	10155	ENSG00000130726	801
TRIP10	Q15642	9322	ENSG00000125733	802
TRMT1	Q9NXH9	55621	ENSG00000104907	803
TSKU	Q8WUA8	25987	ENSG00000182704	804
TTR	P02766	7276	ENSG00000118271	805
TUBB4A	P04350	10382	ENSG00000104833	806
TUFM	P49411	7284	ENSG00000178952	807
TWSG1	Q9GZX9	57045	ENSG00000128791	808
TXN	P10599	7295	ENSG00000136810	809
TXNDC16	Q9P2K2	57544	ENSG00000087301	810
TXNDC5	Q8NBS9	81567	ENSG00000239264	811
U2AF2	P26368	11338	ENSG00000063244	812
UBE2O	Q9C0C9	63893	ENSG00000175931	813
UBR4	Q5T4S7	23352	ENSG00000127481	814
UHL1	P09936	7345	ENSG00000154277	815
UHL3	P15374	7347	ENSG00000118939	816
UFL1	Q94874	23376	ENSG00000014123	817
UGP2	Q16851	7360	ENSG00000169764	818
USP11	P51784	8237	ENSG00000102226	819
USP14	P54578	9097	ENSG00000101557	820
USP43	Q70EL4	124739	ENSG00000154914	821
UTP4	Q969X6	84916	ENSG00000141076	822
VAR5	P26640	7407	ENSG00000096171	823
VASN	Q6EMK4	114990	ENSG00000168140	824
VCAN	P13611	1462	ENSG00000038427	825
VCP	P55072	7415	ENSG00000165280	826
VEGFA	P15692	7422	ENSG00000112715	827
VIT	Q6UXI7	5212	ENSG00000205221	828
VNN1	Q95497	8876	ENSG00000112299	829
VPS35	Q96QK1	55737	ENSG00000069329	830
VTN	P04004	7448	ENSG00000109072	831
VWF	P04275	7450	ENSG00000110799	832
WDR3	Q9UNX4	10885	ENSG00000065183	833
WDR36	Q8NI36	134430	ENSG00000134987	834
WDR4	P57081	10785	ENSG00000160193	835
WDR43	Q15061	23160	ENSG00000163811	836
WFIKKN1	Q96NZ8	117166	ENSG00000127578	837
WFIKKN2	Q8TEU8	124857	ENSG00000173714	838
XRCC5	P13010	7520	ENSG00000079246	839
XYLT1	Q86Y38	64131	ENSG00000103489	840
XYLT2	Q9H1B5	64132	ENSG00000015532	841
YBX1	P67809	4904	ENSG00000065978	842
YBX3	P16989	8531	ENSG00000060138	843
ZG16B	Q96DA0	124220	ENSG00000162078	844
ZNF207	Q43670	7756	ENSG00000010244	845
ZNF326	Q5BKZ1	284695	ENSG00000162664	846
ZNF706	Q9Y5V0	51123	ENSG00000120963	847

APLP1	P51693	333	ENSG00000105290	848
APP	P05067	351	ENSG00000142192	849
NPNT	Q6UXI9	255743	ENSG00000168743	850
RPL22	Q6UXI9	6146	ENSG00000116251	851
FGF19	O95750	9965	ENSG00000162344	852
BTC	P35070	685	ENSG00000174808	853
IL13RA2	Q14627	3598	ENSG00000123496	854
CD170	O15389		ENSG00000105501	855
IL15	P40933	3600	ENSG00000164136	856
WAP	Q8TEU8		ENSG00000173714	857
MFRP	Q9BY79	83552	ENSG00000235718	858
IL10Ra	Q13651	3587	ENSG00000110324	859
ChemR23	Q99788	1240	ENSG00000174600	860
HBEGF	Q99075	1839	ENSG00000113070	861
IL16	Q14005	3603	ENSG00000172349	862
IL7Ra	P16871	3575	ENSG00000168685	863
TNFSF10C	O14798	8794	ENSG00000173535	864
BMP6	P22004	654	ENSG00000153162	865
IL36g	P14778	56300	ENSG00000136688	866
IL1RA	P18510	3557	ENSG00000136689	867
KREMEN2	Q8NCW0	79412		868
TNFSF10D	Q9UBN6	8793	ENSG00000173530	869
CXCCR1	P49238	1524	ENSG00000168329	870
CCL23	P55773	6368	ENSG00000276114	871
Catenin	P35222	1499	ENSG00000168036	872
TNFSF10	P50591	8743	ENSG00000121858	873
CCL14	Q16627	6358	ENSG00000276409	874
IL2	P60568	3558	ENSG00000109471	875
FGF1	P05230	2246	ENSG00000113578	876

[00105] In certain embodiments, the heparin-associated polypeptide comprises one or more of the polypeptides listed in Table 2, Table 1, or a proteoform thereof. In certain embodiments, the heparin-associated polypeptide is at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to a polypeptide listed in Table 2, Table 1, or a proteoform thereof. In certain embodiments, the heparin-associated polypeptide comprises a polypeptide at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to ADAMTS12, INS-IGF2, AOC1, SOD3, CLU, ITIH1, APLP1, THBS1, COCH, ITIH2, APLP2, THBS3, COL11A1, LAMA1, APOB, TNXB, COL12A1, LAMA2, APOE, VEGFA, COL14A1, LAMA5, APOH, VTN, COL18A1, LAMB1, APP, ZNF207, COL1A1, LAMB2, CCDC80, COL1A2, LTF, CFH, COL2A1, MATN2, CLEC3B, COL3A1, MDK, COL25A1, COL5A1, MST1, COL5A3, COL5A2, NID1, CYR61, COL6A1, NPNT, F2, COL6A2, OLFML3, FGF2, COL6A3, PCOLCE, FGFBP3, CTGF, POSTN, FSTL1, DCD, PTN, HDGF, DRAXIN, RARRES2, KNG1, ECM1, RELN, NDNF, FBLN1, SFRP1, NRP1, FBN1, SLIT3, PAFAH1B1, FBN2, SPON1, PCOLCE2, FN1, STC1, PTPRF, FST, STC2, PTPRS, HGFAC, SVEP1, RPL22, IGFBP2, THBS2, or RPL29, or any combination thereof. In certain embodiments, the heparin-associated polypeptide comprises a

polypeptide at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to VTN, POSTN, FGF17, THBS2, THBS4, THBS1, IL-15, or IGF2, or any combination thereof. In certain embodiments, the heparin-associated polypeptide comprises THBS1. In certain embodiments, the heparin-associated polypeptide comprises THBS2. In certain embodiments, the heparin-associated polypeptide comprises THBS4. In certain embodiments, the heparin-associated polypeptide comprises FGF17. In certain embodiments, the heparin-associated polypeptide comprises VTN. In certain embodiments, the heparin-associated polypeptide comprises POSTN. In certain embodiments, the heparin-associated polypeptide comprises IGF2. In certain embodiments, the heparin-associated polypeptide comprises IL-15. In certain embodiments, described herein, is a composition comprising any 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more polypeptides at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to a polypeptide Table 2, Table 1, ADAMTS12, INS-IGF2, AOC1, SOD3, CLU, ITIH1, APLP1, THBS1, COCH, ITIH2, APLP2, THBS3, COL11A1, LAMA1, APOB, TNXB, COL12A1, LAMA2, APOE, VEGFA, COL14A1, LAMA5, APOH, VTN, COL18A1, LAMB1, APP, ZNF207, COL1A1, LAMB2, CCDC80, COL1A2, LTF, CFH, COL2A1, MATN2, CLEC3B, COL3A1, MDK, COL25A1, COL5A1, MST1, COL5A3, COL5A2, NID1, CYR61, COL6A1, NPNT, F2, COL6A2, OLFML3, FGF2, COL6A3, PCOLCE, FGFBP3, CTGF, POSTN, FSTL1, DCD, PTN, HDGF, DRAXIN, RARRES2, KNG1, ECM1, RELN, NDNF, FBLN1, SFRP1, NRP1, FBN1, SLIT3, PAFAH1B1, FBN2, SPON1, PCOLCE2, FN1, STC1, PTPRF, FST, STC2, PTPRS, HGFAC, SVEP1, RPL22, IGFBP2, THBS2, RPL29, a proteoform thereof, or a combination thereof; and a pharmaceutically acceptable excipient, carrier, or diluent. In certain embodiments, the composition comprises a plurality of peptides from Table 2; and optionally a pharmaceutically acceptable excipient, carrier, or diluent. In some cases the plurality comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more polypeptides of Table 2. In some cases, one or more of the plurality of polypeptides is at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to a polypeptide of Table 2. In certain embodiments, the composition comprises a plurality of peptides from Table 1; and optionally a pharmaceutically acceptable excipient, carrier, or diluent. In some cases the plurality comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more polypeptides of Table 1. In some cases, one or more of the plurality of polypeptides is at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to a polypeptide of Table 1. In certain embodiments, the composition comprises THBS1. In certain embodiments, the composition comprises THBS2. In certain embodiments, the composition comprises THBS4. In certain embodiments, the composition comprises FGF17. In certain embodiments, the composition comprises VTN. In certain embodiments, the composition comprises POSTN. In certain embodiments, the composition comprises IGF2. In certain embodiments, the composition comprises IL-15. In

certain embodiments, the composition comprises IGF2, THBS2, and THBS4. In certain embodiments, the composition comprises IL-15, THBS2, and THBS4. In certain embodiments, the composition comprises THBS2 and THBS4. In certain embodiments, the composition comprises THBS2, THBS4, and VTN. In certain embodiments, the composition comprises THBS2, THBS4, and ANOS1. In certain embodiments, the composition comprises THBS2, THBS4, and IL-15. In certain embodiments, the composition comprises THBS2, THBS4, and IGF2. In certain embodiments, the composition comprises THBS1 and FGF17. In certain embodiments, the composition comprises THBS2 and VTN. In certain embodiments, the composition comprises THBS1 and VTN. In certain embodiments, the composition comprises THBS1 and THBS2. In certain embodiments, the composition comprises THBS2 and FGF17. In certain embodiments, the composition comprises THBS1 and THBS4. In certain embodiments, the composition comprises VTN and FGF17. In certain embodiments, the composition comprises THBS4 and VTN. In certain embodiments, the composition comprises THBS4 and FGF17. In certain embodiments, described herein, is a composition comprising any 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more polypeptides at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to CTGF, THBS1, THBS2, THBS3, HGFAC, IGFBP3, IGFBP5, IGFBP7, IGFBP4, SFRP1, STC1, STC2, IGFBP2; and a pharmaceutically acceptable excipient, carrier, or diluent. In certain embodiments, described herein, is a composition comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more polypeptides, wherein one or more the polypeptides are at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4; and a pharmaceutically acceptable excipient, carrier, or diluent.

[00106] In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 1 or amino acids 20-478 of SEQ ID NO: 1, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 1. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 2, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 2. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 3, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 3. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 4 or amino acids 19-1172 of SEQ ID NO: 4,

and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 4. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 5, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 5. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 6 or amino acids 22-836 of SEQ ID NO: 6, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 6. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 7 or amino acids 23-216 of SEQ ID NO: 7, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 7. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 8 or amino acids 27-961 of SEQ ID NO: 8, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 8. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 9 or amino acids 19-1170 of SEQ ID NO: 9, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 9. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 10 or amino acids 49-162 of SEQ ID NO: 10, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 10. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 11 or amino acids 25-91 of SEQ ID NO: 11, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 11.

[00107] In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 12, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 12. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%,

95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 13, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 13. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 14, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 14. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 15 and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 15. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 16, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 16. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 17, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 17. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 18, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 18. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 19, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 19.

[00108] In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 20, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 20. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 21, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 21. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 22, and a pharmaceutically acceptable excipient, carrier, or

diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 22. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 23, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 23. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 24, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 24. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 25, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 25. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 26, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 26. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 27, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 27. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 28, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 28. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 29, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 29.

[00109] In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 30, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 30. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 31, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 31. In certain embodiments, described herein is a composition

comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 32, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 32. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 33, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 33. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 34, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 34. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 35, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 35. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 36, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 36. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 37, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 37. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 38, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 38. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 39, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 39.

[00110] In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 40, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 40. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 41, and a pharmaceutically

acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 41. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 42, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 42. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 43, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 43. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 44, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 44. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 58, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 58. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 59, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 59. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 60, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 60. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 61, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 61. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 62, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 62. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 63, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 63. In certain embodiments, described herein is a composition

comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 64, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 64. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 65, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 65. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 66, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 66. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 67, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 67. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 68, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 68. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 69, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 69. In certain embodiments, described herein is a composition comprising a polypeptide comprising at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% homology or identity to SEQ ID NO: 70, and a pharmaceutically acceptable excipient, carrier, or diluent. In some cases, the polypeptide does not comprise a signal sequence of SEQ ID NO: 70.

[00111] In certain embodiments, described herein, is a composition comprising a plurality of polypeptides at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to ADAMTS12, INS-IGF2, AOC1, SOD3, CLU, ITIH1, APLP1, THBS1, COCH, ITIH2, APLP2, THBS3, COL11A1, LAMA1, APOB, TNXB, COL12A1, LAMA2, APOE, VEGFA, COL14A1, LAMA5, APOH, VTN, COL18A1, LAMB1, APP, ZNF207, COL1A1, LAMB2, CCDC80, COL1A2, LTF, CFH, COL2A1, MATN2, CLEC3B, COL3A1, MDK, COL25A1, COL5A1, MST1, COL5A3, COL5A2, NID1, CYR61, COL6A1, NPNT, F2, COL6A2, OLFML3, FGF2, COL6A3, PCOLCE, FGFBP3, CTGF, POSTN, FSTL1, DCD, PTN, HDGF, DRAXIN, RARRES2, KNG1, ECM1, RELN, NDNF, FBLN1, SFRP1, NRP1, FBN1, SLIT3, PAFAH1B1, FBN2, SPON1, PCOLCE2, FN1, STC1, PTPRF, FST, STC2, PTPRS, HGFAC, SVEP1, RPL22, IGFBP2, THBS2, RPL29,

and combinations thereof; and a pharmaceutically acceptable excipient, carrier, or diluent. In certain embodiments, described herein, is a composition comprising a plurality of polypeptides at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to CTGF, THBS1, THBS2, THBS3, HGFAC, IGFBP3, IGFBP5, IGFBP7, IGFBP4, SFRP1, STC1, STC2, IGFBP2; and a pharmaceutically acceptable excipient, carrier, or diluent.

[00112] In certain embodiments, described herein, is a composition consisting essentially of a plurality of polypeptides at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to ADAMTS12, INS-IGF2, AOC1, SOD3, CLU, ITIH1, APLP1, THBS1, COCH, ITIH2, APLP2, THBS3, COL11A1, LAMA1, APOB, TNXB, COL12A1, LAMA2, APOE, VEGFA, COL14A1, LAMA5, APOH, VTN, COL18A1, LAMB1, APP, ZNF207, COL1A1, LAMB2, CCDC80, COL1A2, LTF, CFH, COL2A1, MATN2, CLEC3B, COL3A1, MDK, COL25A1, COL5A1, MST1, COL5A3, COL5A2, NID1, CYR61, COL6A1, NPNT, F2, COL6A2, OLFML3, FGF2, COL6A3, PCOLCE, FGFBP3, CTGF, POSTN, FSTL1, DCD, PTN, HDGF, DRAXIN, RARRES2, KNG1, ECM1, RELN, NDNF, FBLN1, SFRP1, NRP1, FBN1, SLIT3, PAFAH1B1, FBN2, SPON1, PCOLCE2, FN1, STC1, PTPRF, FST, STC2, PTPRS, HGFAC, SVEP1, RPL22, IGFBP2, THBS2, RPL29, and combinations thereof; and a pharmaceutically acceptable excipient, carrier, or diluent. In certain embodiments, described herein, is a composition consisting essentially of a plurality of polypeptides at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to CTGF, THBS1, THBS2, THBS3, HGFAC, IGFBP3, IGFBP5, IGFBP7, IGFBP4, SFRP1, STC1, STC2, IGFBP2; and a pharmaceutically acceptable excipient, carrier, or diluent.

[00113] In certain embodiments, described herein, is a composition consisting essentially of any 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more polypeptides at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to ADAMTS12, INS-IGF2, AOC1, SOD3, CLU, ITIH1, APLP1, THBS1, COCH, ITIH2, APLP2, THBS3, COL11A1, LAMA1, APOB, TNXB, COL12A1, LAMA2, APOE, VEGFA, COL14A1, LAMA5, APOH, VTN, COL18A1, LAMB1, APP, ZNF207, COL1A1, LAMB2, CCDC80, COL1A2, LTF, CFH, COL2A1, MATN2, CLEC3B, COL3A1, MDK, COL25A1, COL5A1, MST1, COL5A3, COL5A2, NID1, CYR61, COL6A1, NPNT, F2, COL6A2, OLFML3, FGF2, COL6A3, PCOLCE, FGFBP3, CTGF, POSTN, FSTL1, DCD, PTN, HDGF, DRAXIN, RARRES2, KNG1, ECM1, RELN, NDNF, FBLN1, SFRP1, NRP1, FBN1, SLIT3, PAFAH1B1, FBN2, SPON1, PCOLCE2, FN1, STC1, PTPRF, FST, STC2, PTPRS, HGFAC, SVEP1, RPL22, IGFBP2, THBS2, and RPL29; and a pharmaceutically acceptable excipient, carrier, or diluent. In certain embodiments, described herein, is a composition consisting essentially of any 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more polypeptides at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to CTGF, THBS1, THBS2, THBS3, HGFAC,

IGFBP3, IGFBP5, IGFBP7, IGFBP4, SFRP1, STC1, STC2, IGFBP2; and a pharmaceutically acceptable excipient, carrier, or diluent.

[00114] In certain embodiments, described herein, is a composition consisting of any 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more polypeptides at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to ADAMTS12, INS-IGF2, AOC1, SOD3, CLU, ITIH1, APLP1, THBS1, COCH, ITIH2, APLP2, THBS3, COL11A1, LAMA1, APOB, TNXB, COL12A1, LAMA2, APOE, VEGFA, COL14A1, LAMA5, APOH, VTN, COL18A1, LAMB1, APP, ZNF207, COL1A1, LAMB2, CCDC80, COL1A2, LTF, CFH, COL2A1, MATN2, CLEC3B, COL3A1, MDK, COL25A1, COL5A1, MST1, COL5A3, COL5A2, NID1, CYR61, COL6A1, NPNT, F2, COL6A2, OLFML3, FGF2, COL6A3, PCOLCE, FGFBP3, CTGF, POSTN, FSTL1, DCD, PTN, HDGF, DRAXIN, RARRES2, KNG1, ECM1, RELN, NDNF, FBLN1, SFRP1, NRP1, FBN1, SLIT3, PAFAH1B1, FBN2, SPON1, PCOLCE2, FN1, STC1, PTPRF, FST, STC2, PTPRS, HGFAC, SVEP1, RPL22, IGFBP2, THBS2, and RPL29; and a pharmaceutically acceptable excipient, carrier, or diluent. In certain embodiments, described herein, is a composition consisting of any 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more polypeptides at least about 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to CTGF, THBS1, THBS2, THBS3, HGFAC, IGFBP3, IGFBP5, IGFBP7, IGFBP4, SFRP1, STC1, STC2, IGFBP2; and a pharmaceutically acceptable excipient, carrier, or diluent.

[00115] In certain embodiments, compositions comprising heparin-associated polypeptides do not comprise fibroblast growth factors (FGF). In certain embodiments, compositions comprising heparin-associated polypeptides do not comprise fibroblast growth factor 2 (FGF2). In certain embodiments, compositions comprising heparin-associated polypeptides do not comprise FGF19, Angiogenin, BTC, IL-13 R alpha 2, Siglec-5/CD170, IL-15, APJ, IGFBP-2, Chordin-Like 1, GASP-1/WFIKKNRP, MFRP, IL-10 R alpha, Chem R23, HB-EGF, FGF-6, HGF, IL-16, IL-7 R alpha, TRAIL R3/TNFRSF10C, BMP-6, IL-1 F9/IL-1 H1, IL-1 beta, Kremen-2, TRAIL R4/TNFRSF10D, CXCR1/IL-8 RA, Ck beta 8-1/CCL23, Beta-catenin, FGF-13 1B, TRAIL/TNFSF10, CCL14/HCC-1/HCC-3, or FGF-4, or a combination thereof.

[00116] In certain aspects, heparin-associated binding polypeptides and compositions of heparin-associated binding polypeptides herein comprise polypeptides that increase the proliferation of muscle cell precursors, and/or increase their differentiation into muscle cells. In certain embodiments, the heparin-associated polypeptides increase proliferation of a muscle cell precursor by at least about 20%, 30%, 40%, 50%, or 100% compared to a muscle cell precursor not treated with the heparin-associated binding polypeptide. In certain embodiments, the heparin-associated polypeptides increase proliferation of a myoblast by at least about 20%, 30%, 40%, 50%, 100%, 200%, or 500% compared to a myoblast not treated with the heparin-associated

binding polypeptide. In certain embodiments, the myoblast is a human myoblast cell line. In certain embodiments, the myoblast is a mouse myoblast cell line (e.g., C2C12). Proliferation can be measured by BrdU or EdU incorporation, which can be quantified using suitable methods such as, by way of non-limiting embodiment, microscopy, flow cytometry, or ELISA.

[00117] In certain embodiments, the heparin-associated polypeptides increase differentiation and/or fusion of a muscle cell precursor by at least about 50%, 75%, 100%, 200%, or 500% compared to a muscle cell precursor not treated with the heparin-associated binding polypeptide. In certain embodiments, the heparin-associated polypeptides increase differentiation of a myoblast by at least about 50%, 75%, or 100% compared to a myoblast not treated with the heparin-associated binding polypeptide. In certain embodiments, the myoblast is a human myoblast cell line. In certain embodiments, the myoblast is a mouse myoblast cell line (e.g., C2C12). Differentiation can be measured and/or quantified by eMyHC staining, which detects fusion of a myoblast or muscle cell precursor. This staining can be quantified, for example, by microscopy or flow cytometry.

[00118] Heparin-associated polypeptides that increase muscle or connective tissue cell precursor proliferation and/or differentiation are useful in methods of treating muscle or connective tissue disorders. These disorders can arise from the normal aging process, injury related to trauma or physical exertion, genetic predispositions, or incident to other disease states.

[00119] Heparin-associated binding polypeptides that are useful for increasing muscle cell precursor differentiation or proliferation are described herein, and in certain embodiments comprise Vitronectin (VTN), Stanniocalcin-2 (STC2), Periostin (POSTN), Agrin (AGRN), Fibroblast growth factor (FGF17, also known as Fibroblast growth factor 13 or FGF13), Thrombospondin 2 (THBS2), follistatin (FST), Thrombospondin 4 (THBS4), Thrombospondin 1 (THBS1), Insulin-like growth factor 2 (IGF2), or Interleukin 15 (IL-15), or any combination thereof. In certain embodiments, any one, two, three, four, or five of VTN, STC2, AGRN, THBS2, or FST are present in a composition useful for increasing muscle cell precursor proliferation or muscle cell differentiation. In certain embodiments, any one, two, three, four, five, six, seven, or eight of VTN, POSTN, FGF17, THBS2, THBS1, IL-15, IGF2, and THBS4 are present in a composition useful for increasing muscle cell precursor proliferation or muscle cell differentiation.

[00120] In certain embodiments, a heparin-associated binding polypeptide composition comprises Vitronectin (VTN). VTN may be further included in the composition with any one, two, three, four, five, six, seven, eight, nine, or all polypeptides selected from STC2, AGRN, POSTN, FGF17, THBS2, FST, THBS1, IL-15, IGF2, and THBS4. In certain embodiments, the composition comprises VTN and STC2. In certain embodiments, the composition comprises

VTN and AGRN. In certain embodiments, the composition comprises VTN and THBS2. In certain embodiments, the composition comprises VTN and FST. In certain embodiments, the composition comprises VTN and POSTN. In certain embodiments, the composition comprises VTN and FGF17. In certain embodiments, the composition comprises VTN and THBS4. In certain embodiments, the composition comprises VTN and THBS1. In certain embodiments, the composition comprises VTN and IGF2. In certain embodiments, the composition comprises VTN and IL-15. Human VTN is disclosed in SEQ ID NO: 1. In certain embodiments, the VTN of the heparin-associated binding polypeptide composition comprises an amino acid sequence that is at least about 80%, 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 1 or amino acids 20-478 of SEQ ID NO: 1. In certain embodiments, the VTN polypeptide lacks a secretory leader sequence, *e.g.*, amino acids 1-19 of SEQ ID NO: 1. In certain embodiments, the VTN polypeptide is modified by a deletion of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acids from the N-terminal or C-terminal end of the polypeptide, including increments therein. In certain embodiments, the VTN polypeptide comprises one or more additional modifications to increase stability. In certain embodiments, the VTN polypeptide is covalently conjugated to polyethylene glycol, polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol, polysialic acid, glycolic acid, or polypropylene glycol. In certain embodiments, the heparin-associated polypeptide is fused or conjugated to another protein to increase stability and or bioavailability. In certain embodiments, the VTN polypeptide is fused with an Fc region of an immunoglobulin or with serum albumin. In certain embodiments, the VTN polypeptide is present in a concatemer with one, two, three, four or more distinct polypeptides selected from STC2, AGRN, THBS2, THBS1, THBS4, FGF17, POSTN, IGF2, IL-15 and FST. In certain embodiments, the VTN polypeptide is present in a concatemer with one, two, three, four or more distinct polypeptides selected from POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, and THBS4. In certain embodiments, the VTN polypeptide is present in a concatemer with one, two, three, four, or more distinct VTN polypeptides. In certain embodiments, the VTN polypeptide is included in a composition comprising a biodegradable or bioabsorbable carrier that promotes polypeptide stability. In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA), polyglycolic acid (PGA), or Poly(D,L-lactic-coglycolic-acid) (PLGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polyglycolic acid (PGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises Poly(D,L-lactic-coglycolic-acid) (PLGA). In some cases, the VTN polypeptide is prepared recombinantly in an expression system (*e.g.*, bacteria, yeast, mammalian, insect). In some cases, the VTN polypeptide

is prepared by chemical synthesis.

[00121] In certain embodiments, a heparin-associated binding polypeptide composition comprises Periostin (POSTN). POSTN may be further included in the composition with any one, two, three, four, five, six, or all polypeptides selected from VTN, FGF17, THBS2, THBS1, IGF2, IL-15, and THBS4. In certain embodiments, the composition comprises POSTN and VTN. In certain embodiments, the composition comprises POSTN and FGF17. In certain embodiments, the composition comprises POSTN and THBS2. In certain embodiments, the composition comprises POSTN and THBS4. In certain embodiments, the composition comprises POSTN and THBS1. In certain embodiments, the composition comprises POSTN and IGF2. In certain embodiments, the composition comprises POSTN and IL-15. Human POSTN is disclosed in SEQ ID NO: 6. In certain embodiments, the POSTN of the heparin-associated binding polypeptide composition comprises an amino acid sequence that is at least about 80%, 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 6 or amino acids 22-836 of SEQ ID NO: 6. In certain embodiments, the POSTN polypeptide lacks a secretory leader sequence, *e.g.*, amino acids 1-21 of SEQ ID NO: 6. In certain embodiments, the POSTN polypeptide is modified by a deletion of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acids from the N-terminal or C-terminal end of the polypeptide, including increments therein. In certain embodiments, the POSTN polypeptide comprises one or more additional modifications to increase stability. In certain embodiments, the POSTN polypeptide is covalently conjugated to polyethylene glycol, polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol, polysialic acid, glycolic acid, or polypropylene glycol. In certain embodiments, the heparin-associated polypeptide is fused or conjugated to another protein to increase stability and or bioavailability. In certain embodiments, the POSTN polypeptide is fused with an Fc region of an immunoglobulin or with serum albumin. In certain embodiments, the POSTN polypeptide is present in a concatemer with one, two, three, four or more distinct polypeptides selected from VTN, FGF17, THBS2, THBS1, IGF2, IL-15 and THBS4. In certain embodiments, the POSTN polypeptide is present in a concatemer with one, two, three, four, or more distinct POSTN polypeptides. In certain embodiments, the POSTN polypeptide is included in a composition comprising a biodegradable or bioabsorbable carrier that promotes polypeptide stability. In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA), polyglycolic acid (PGA), or Poly(D,L-lactic-coglycolic-acid) (PLGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polyglycolic acid (PGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises Poly(D,L-lactic-coglycolic-acid) (PLGA). In some cases, the POSTN

polypeptide is prepared recombinantly in an expression system (*e.g.*, bacteria, yeast, mammalian, insect). In some cases, the POSTN polypeptide is prepared by chemical synthesis.

[00122] In certain embodiments, a heparin-associated binding polypeptide composition comprises Fibroblast growth factor (FGF17). FGF17 may be further included in the composition with any one, two, three, four, five, six or all polypeptides selected from VTN, POSTN, THBS2, THBS1, IL-15, IGF2, and THBS4. In certain embodiments, the composition comprises FGF17 and VTN. In certain embodiments, the composition comprises FGF17 and POSTN. In certain embodiments, the composition comprises FGF17 and THBS2. In certain embodiments, the composition comprises FGF17 and THBS4. In certain embodiments, the composition comprises FGF17 and THBS1. In certain embodiments, the composition comprises FGF17 and IGF2. In certain embodiments, the composition comprises FGF17 and IL-15. Human FGF17 is disclosed in SEQ ID NO: 7. In certain embodiments, the FGF17 of the heparin-associated binding polypeptide composition comprises an amino acid sequence that is at least about 80%, 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 7, or amino acids 23-216 of SEQ ID NO: 7. In certain embodiments, the FGF17 polypeptide lacks a secretory leader sequence, *e.g.*, amino acids 1-22 of SEQ ID NO: 7. In certain embodiments, the FGF17 polypeptide is modified by a deletion of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 200, 225, 250, 275, or 300 amino acids from the N-terminal or C-terminal end of the polypeptide, including increments therein. In certain embodiments, the FGF17 polypeptide comprises one or more additional modifications to increase stability. In certain embodiments, the FGF17 polypeptide is covalently conjugated to polyethylene glycol, polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol, polysialic acid, glycolic acid, or polypropylene glycol. In certain embodiments, the heparin-associated polypeptide is fused or conjugated to another protein to increase stability and or bioavailability. In certain embodiments, the FGF17 polypeptide is fused with an Fc region of an immunoglobulin or with serum albumin. In certain embodiments, the FGF17 polypeptide is present in a concatemer with one, two, three, four or more distinct polypeptides selected from VTN, POSTN, THBS2, THBS1, IGF2, IL-15, and THBS4. In certain embodiments, the FGF17 polypeptide is present in a concatemer with one, two, three, four, or more distinct FGF17 polypeptides. In certain embodiments, the FGF17 polypeptide is included in a composition comprising a biodegradable or bioabsorbable carrier that promotes polypeptide stability. In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA), polyglycolic acid (PGA), or Poly(D,L-lactic-coglycolic-acid) (PLGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polyglycolic acid (PGA). In

certain embodiments, the biodegradable or bioabsorbable carrier comprises Poly(D,L-lactic-coglycolic-acid) (PLGA). In some cases, the FGF17 polypeptide is prepared recombinantly in an expression system (*e.g.*, bacteria, yeast, mammalian, insect). In some cases, the FGF17 polypeptide is prepared by chemical synthesis.

[00123] In certain embodiments, a heparin-associated binding polypeptide composition comprises Stanniocalcin-2 (STC2). STC-2 may be further included in the composition with any one, two, three, four or more polypeptides selected from VTN, AGRN, THBS2, THBS1, THBS4, POSTN, FGF17, IGF2, IL-15, and FST. In certain embodiments, the composition comprises STC2 and VTN. In certain embodiments, the composition comprises STC2 and AGRN. In certain embodiments, the composition comprises STC2 and THBS2. In certain embodiments, the composition comprises STC2 and FST. Human STC2 is disclosed in SEQ ID NO: 2. In certain embodiments, the STC2 of the heparin-associated binding polypeptide composition comprises an amino acid sequence that is at least about 80%, 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 2. In certain embodiments, the STC2 polypeptide lacks a secretory leader sequence. In certain embodiments, the STC2 polypeptide is modified by a deletion of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acids from the N-terminal or C-terminal end of the polypeptide, including increments therein. In certain embodiments, the STC2 polypeptide comprises one or more additional modifications to increase stability. In certain embodiments, the STC2 polypeptide is covalently conjugated to polyethylene glycol, polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol, polysialic acid, glycolic acid, or polypropylene glycol. In certain embodiments, the heparin-associated polypeptide is fused or conjugated to another protein to increase stability and or bioavailability. In certain embodiments, the STC2 polypeptide is fused with an Fc region of an immunoglobulin or with serum albumin. In certain embodiments, the STC2 polypeptide is present in a concatemer with one, two, three, four or more distinct polypeptides selected from VTN, AGRN, THBS2, THBS1, THBS4, FGF17, POSTN, IGF2, IL_15, and FST. In certain embodiments, the STC2 polypeptide is present in a concatemer with one, two, three, four, or more distinct STC2 polypeptides. In certain embodiments, the STC2 polypeptide is included in a composition comprising a biodegradable or bioabsorbable carrier that promotes polypeptide stability. In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA), polyglycolic acid (PGA), or Poly(D,L-lactic-coglycolic-acid) (PLGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polyglycolic acid (PGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises Poly(D,L-lactic-coglycolic-acid) (PLGA).

[00124] In certain embodiments, a heparin-associated binding polypeptide composition comprises Agrin (AGRN). AGRN may be further included in the composition with any one, two, three, four or more polypeptides selected from VTN, STC2, THBS2, THBS1, THBS4, FGF17, POSTN, IGF2, IL-15, and FST. In certain embodiments, the composition comprises AGRN and VTN. In certain embodiments, the composition comprises AGRN and STC2. In certain embodiments, the composition comprises AGRN and THBS2. In certain embodiments, the composition comprises AGRN and FST. Human AGRN is disclosed in SEQ ID NO: 3. In certain embodiments, the AGRN of the heparin-associated binding polypeptide composition comprises an amino acid sequence that is at least about 80%, 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 3. In certain embodiments, the AGRN polypeptide lacks a secretory leader sequence. In certain embodiments, the AGRN polypeptide is modified by a deletion of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 200, 225, 250, 275, or 300 amino acids from the N-terminal or C-terminal end of the polypeptide, including increments therein. In certain embodiments, the AGRN polypeptide comprises one or more additional modifications to increase stability. In certain embodiments, the AGRN polypeptide is covalently conjugated to polyethylene glycol, polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol, polysialic acid, glycolic acid, or polypropylene glycol. In certain embodiments, the heparin-associated polypeptide is fused or conjugated to another protein to increase stability and or bioavailability. In certain embodiments, the AGRN polypeptide is fused with an Fc region of an immunoglobulin or with serum albumin. In certain embodiments, the AGRN polypeptide is present in a concatemer with one, two, three, or four other distinct polypeptides selected from VTN, STC2, THBS2, THBS1, THBS4, FGF17, POSTN, IGF2, IL-15, and FST. In certain embodiments, the AGRN polypeptide is present in a concatemer with one, two, three, four, or more distinct AGRN polypeptides. In certain embodiments, the AGRN polypeptide is included in a composition comprising a biodegradable or bioabsorbable carrier that promotes polypeptide stability. In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA), polyglycolic acid (PGA), or Poly(D,L-lactic-coglycolic-acid) (PLGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polyglycolic acid (PGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises Poly(D,L-lactic-coglycolic-acid) (PLGA).

[00125] In certain embodiments, a heparin-associated binding polypeptide composition comprises Thrombospondin 2 (THBS2). THBS2 may be further included in the composition with any one, two, three, four, five, six or all polypeptides selected from VTN, STC2, AGRN, THBS1, IL-15, IGF2, and FST. In certain embodiments, the composition comprises THBS2 and VTN. In

certain embodiments, the composition comprises THBS2 and STC2. In certain embodiments, the composition comprises THBS2 and AGRN. In certain embodiments, the composition comprises THBS2 and FST. In certain embodiments, the composition comprises AGRN and FST. In certain embodiments, the composition comprises THBS2 and THBS1. In certain embodiments, the composition comprises THBS2 and IGF2. In certain embodiments, the composition comprises THBS2 and IL-15. THBS2 may be further included in the composition with any one, two, three, four, five, six, or all polypeptides selected from VTN, POSTN, FGF17, THBS1, IL-15, IGF2, and THBS4. In certain embodiments, the composition comprises THBS2 and VTN. In certain embodiments, the composition comprises THBS2 and POSTN. In certain embodiments, the composition comprises THBS2 and FGF17. In certain embodiments, the composition comprises THBS2 and THBS4. In certain embodiments, the composition comprises FGF17 and THBS4. Human THBS2 is disclosed in SEQ ID NO: 4. In certain embodiments, the THBS2 of the heparin-associated binding polypeptide composition comprises an amino acid sequence that is at least about 80%, 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 4 or amino acids 19-1,172 of SEQ ID NO: 4. In certain embodiments, the THBS2 polypeptide lacks a secretory leader sequence, *e.g.*, amino acids 1-18 of SEQ ID NO: 4. In certain embodiments, the THBS2 polypeptide is modified by a deletion of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 200, 225, 250, 275, or 300 amino acids from the N-terminal or C-terminal end of the polypeptide, including increments therein. In certain embodiments, the THBS2 polypeptide comprises one or more additional modifications to increase stability. In certain embodiments, the THBS2 polypeptide is covalently conjugated to polyethylene glycol, polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol, polysialic acid, glycolic acid, or polypropylene glycol. In certain embodiments, the heparin-associated polypeptide is fused or conjugated to another protein to increase stability and or bioavailability. In certain embodiments, the THBS2 polypeptide is fused with an Fc region of an immunoglobulin or with serum albumin. In certain embodiments, the THBS2 polypeptide is present in a concatemer with one, two, three, four or more distinct polypeptides selected from VTN, STC2, AGRN, THBS1, THBS4, FGF17, POSTN, IGF2, IL-15, and FST. In certain embodiments, the THBS2 polypeptide is present in a concatemer with one, two, three, four or more distinct polypeptides selected from VTN, POSTN, THBS1, IGF2, IL-15, FGF17, and THBS4. In certain embodiments, the THBS2 polypeptide is present in a concatemer with one, two, three, four, or more distinct THBS2 polypeptides. In certain embodiments, the THBS2 polypeptide is included in a composition comprising a biodegradable or bioabsorbable carrier that promotes polypeptide stability. In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA), polyglycolic acid (PGA), or Poly(D,L-lactic-coglycolic-

acid) (PLGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polyglycolic acid (PGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises Poly(D,L-lactic-coglycolic-acid) (PLGA). In some cases, the THBS2 polypeptide is prepared recombinantly in an expression system (*e.g.*, bacteria, yeast, mammalian, insect). In some cases, the THBS2 polypeptide is prepared by chemical synthesis.

[00126] In certain embodiments, a heparin-associated binding polypeptide composition comprises Thrombospondin 4 (THBS4). THBS4 may be further included in the composition with any one, two, three, four, five, six or all polypeptides selected from VTN, POSTN, FGF17, THBS1, IL-15, IGF2, and THBS2. In certain embodiments, the composition comprises THBS4 and VTN. In certain embodiments, the composition comprises THBS4 and POSTN. In certain embodiments, the composition comprises THBS4 and FGF17. In certain embodiments, the composition comprises THBS4 and THBS2. In certain embodiments, the composition comprises THBS4 and THBS1. In certain embodiments, the composition comprises THBS4 and IL-15. In certain embodiments, the composition comprises THBS4 and IGF2. Human THBS4 is disclosed in SEQ ID NO: 8. In certain embodiments, the THBS4 of the heparin-associated binding polypeptide composition comprises an amino acid sequence that is at least about 80%, 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 8 or amino acids 27-961 of SEQ ID NO: 8. In certain embodiments, the THBS4 polypeptide lacks a secretory leader sequence, *e.g.*, amino acids 1-26 of SEQ ID NO: 8. In certain embodiments, the THBS4 polypeptide is modified by a deletion of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acids from the N-terminal or C-terminal end of the polypeptide, including increments therein. In certain embodiments, the THBS4 polypeptide comprises one or more additional modifications to increase stability. In certain embodiments, the THBS4 polypeptide is covalently conjugated to polyethylene glycol, polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol, polysialic acid, glycolic acid, or polypropylene glycol. In certain embodiments, the heparin-associated polypeptide is fused or conjugated to another protein to increase stability and or bioavailability. In certain embodiments, the THBS4 polypeptide is fused with an Fc region of an immunoglobulin or with serum albumin. In certain embodiments, the THBS4 polypeptide is present in a concatemer with one, two, three, four or more distinct polypeptides selected from VTN, POSTN, FGF17, THBS1, IGF2, IL-15, and THBS2. In certain embodiments, the THBS4 polypeptide is present in a concatemer with one, two, three, four, or more distinct THBS4 polypeptides. In certain embodiments, the THBS4 polypeptide is included in a composition comprising a biodegradable or bioabsorbable carrier that promotes polypeptide stability. In certain embodiments, the biodegradable or bioabsorbable

carrier comprises polylactic acid (PLA), polyglycolic acid (PGA), or Poly(D,L-lactic-coglycolic-acid) (PLGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polyglycolic acid (PGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises Poly(D,L-lactic-coglycolic-acid) (PLGA). In some cases, the THBS4 polypeptide is prepared recombinantly in an expression system (*e.g.*, bacteria, yeast, mammalian, insect). In some cases, the THBS2 polypeptide is prepared by chemical synthesis.

[00127] In certain embodiments, a heparin-associated binding polypeptide composition comprises follistatin (FST). FST may be further included in the composition with any one, two, three, four or more polypeptides selected from VTN, STC2, AGRN, THBS1, THBS4, FGF17, POSTN, IGF2, IL-15, and THBS2. In certain embodiments, the composition comprises FST and VTN. In certain embodiments, the composition comprises FST and STC2. In certain embodiments, the composition comprises FST and AGRN. In certain embodiments, the composition comprises FST and THBS2. Human FST is disclosed in SEQ ID NO: 5. In certain embodiments, the FST of the heparin-associated binding polypeptide composition comprises an amino acid sequence that is at least about 80%, 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 5. In certain embodiments, the FST polypeptide lacks a secretory leader sequence. In certain embodiments, the FST polypeptide is modified by a deletion of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acids from the N-terminal or C-terminal end of the polypeptide, including increments therein. In certain embodiments, the FST polypeptide comprises one or more additional modifications to increase stability. In certain embodiments, the FST polypeptide is covalently conjugated to polyethylene glycol, polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol, polysialic acid, glycolic acid, or polypropylene glycol. In certain embodiments, the heparin-associated polypeptide is fused or conjugated to another protein to increase stability and or bioavailability. In certain embodiments, the FST polypeptide is fused with an Fc region of an immunoglobulin or with serum albumin. In certain embodiments, the FST polypeptide is present in a concatemer with one, two, three, four or more distinct polypeptides selected from VTN, STC2, AGRN, THBS1, THBS4, FGF17, POSTN, IGF2, IL-15, and THBS2. In certain embodiments, the FST polypeptide is present in a concatemer with one, two, three, four, or more distinct FST polypeptides. In certain embodiments, the FST polypeptide is included in a composition comprising a biodegradable or bioabsorbable carrier that promotes polypeptide stability. In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA), polyglycolic acid (PGA), or Poly(D,L-lactic-coglycolic-acid) (PLGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA). In

certain embodiments, the biodegradable or bioabsorbable carrier comprises polyglycolic acid (PGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises Poly(D,L-lactic-coglycolic-acid) (PLGA).

[00128] In certain embodiments, a heparin-associated binding polypeptide composition comprises Thrombospondin 1 (THBS1). THSB1 may be further included in the composition with any one, two, three, four, five, six, seven, eight or all polypeptides selected from VTN, STC2, AGRN, THBS4, FGF17, POSTN, IGF2, IL-15, and THBS2. In certain embodiments, the composition comprises THSB1 and VTN. In certain embodiments, the composition comprises THSB1 and STC2. In certain embodiments, the composition comprises THSB1 and AGRN. In certain embodiments, the composition comprises THSB1 and THBS2. In certain embodiments, the composition comprises THSB1 and THBS4. In certain embodiments, the composition comprises THSB1 and FGF17. In certain embodiments, the composition comprises THSB1 and POSTN. In certain embodiments, the composition comprises THSB1 and IGF2. In certain embodiments, the composition comprises THSB1 and IL-15. Human THSB1 is disclosed in SEQ ID NO: 9. In certain embodiments, the THSB1 of the heparin-associated binding polypeptide composition comprises an amino acid sequence that is at least about 80%, 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 9 or amino acids 19-1170 of SEQ ID NO: 9. In certain embodiments, the THSB1 polypeptide lacks a secretory leader sequence. In certain embodiments, the THSB1 polypeptide is modified by a deletion of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acids from the N-terminal or C-terminal end of the polypeptide, including increments therein. In certain embodiments, the THSB1 polypeptide comprises one or more additional modifications to increase stability. In certain embodiments, the THSB1 polypeptide is covalently conjugated to polyethylene glycol, polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol, polysialic acid, glycolic acid, or polypropylene glycol. In certain embodiments, the heparin-associated polypeptide is fused or conjugated to another protein to increase stability and or bioavailability. In certain embodiments, the THSB1 polypeptide is fused with an Fc region of an immunoglobulin or with serum albumin. In certain embodiments, the THSB1 polypeptide is present in a concatemer with one, two, three, four or more distinct polypeptides selected from VTN, STC2, AGRN, THBS4, FGF17, POSTN, IGF2, IL-15 and THBS2. In certain embodiments, the THSB1 polypeptide is present in a concatemer with one, two, three, four, or more distinct THSB1 polypeptides. In certain embodiments, the THSB1 polypeptide is included in a composition comprising a biodegradable or bioabsorbable carrier that promotes polypeptide stability. In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA), polyglycolic acid (PGA), or Poly(D,L-lactic-coglycolic-acid) (PLGA). In certain

embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polyglycolic acid (PGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises Poly(D,L-lactic-coglycolic-acid) (PLGA). In some cases, the THBS1 polypeptide is prepared recombinantly in an expression system (*e.g.*, bacteria, yeast, mammalian, insect). In some cases, the THBS1 polypeptide is prepared by chemical synthesis.

[00129] In certain embodiments, a heparin-associated binding polypeptide composition comprises Interleukin-15 (IL-15). IL-15 may be further included in the composition with any one, two, three, four or more polypeptides selected from VTN, STC2, AGRN, THBS1, THBS4, IGF2, POSTN, FGF17, and THBS2. In certain embodiments, the composition comprises IL-15 and VTN. In certain embodiments, the composition comprises IL-15 and STC2. In certain embodiments, the composition comprises IL-15 and AGRN. In certain embodiments, the composition comprises IL-15 and THBS2. In certain embodiments, the composition comprises IL-15 and THBS1. In certain embodiments, the composition comprises IL-15 and THBS4. In certain embodiments, the composition comprises IL-15 and IGF2. In certain embodiments, the composition comprises IL-15 and POSTN. In certain embodiments, the composition comprises IL-15 and FGF17. In certain embodiments, the composition comprises IL-15 and THBS1. Human IL-15 is disclosed in SEQ ID NO: 10. In certain embodiments, the IL-15 of the heparin-associated binding polypeptide composition comprises an amino acid sequence that is at least about 80%, 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 10 or amino acids 49-162 of SEQ ID NO: 10. In certain embodiments, the IL-15 polypeptide lacks a secretory leader sequence. In certain embodiments, the IL-15 polypeptide is modified by a deletion of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acids from the N-terminal or C-terminal end of the polypeptide, including increments therein. In certain embodiments, the IL-15 polypeptide comprises one or more additional modifications to increase stability. In certain embodiments, the IL-15 polypeptide is covalently conjugated to polyethylene glycol, polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol, polysialic acid, glycolic acid, or polypropylene glycol. In certain embodiments, the heparin-associated polypeptide is fused or conjugated to another protein to increase stability and or bioavailability. In certain embodiments, the IL-15 polypeptide is fused with an Fc region of an immunoglobulin or with serum albumin. In certain embodiments, the IL-15 polypeptide is present in a concatemer with one, two, three, four or more distinct polypeptides selected from VTN, STC2, AGRN, THBS1, THBS4, FGF17, POSTN, IGF2, and THBS2. In certain embodiments, the IL-15 polypeptide is present in a concatemer with one, two, three, four, or more distinct IL-15 polypeptides. In certain embodiments, the IL-15 polypeptide is included in

a composition comprising a biodegradable or bioabsorbable carrier that promotes polypeptide stability. In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA), polyglycolic acid (PGA), or Poly(D,L-lactic-coglycolic-acid) (PLGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polyglycolic acid (PGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises Poly(D,L-lactic-coglycolic-acid) (PLGA). In some cases, the IL-15 polypeptide is prepared recombinantly in an expression system (*e.g.*, bacteria, yeast, mammalian, insect). In some cases, the THBS1 polypeptide is prepared by chemical synthesis.

[00130] In certain embodiments, a heparin-associated binding polypeptide composition comprises Insulin-like growth factor 2 (IGF2). IGF2 may be further included in the composition with any one, two, three, four or more polypeptides selected from VTN, STC2, AGRN, THBS1, THBS4, POSTN, FGF17, IL-15 and THBS2. In certain embodiments, the composition comprises IGF2 and VTN. In certain embodiments, the composition comprises IGF2 and STC2. In certain embodiments, the composition comprises IGF2 and AGRN. In certain embodiments, the composition comprises IGF2 and THBS2. In certain embodiments, the composition comprises IGF2 and THBS1. In certain embodiments, the composition comprises IGF2 and THBS4. In certain embodiments, the composition comprises IGF2 and IL-15. In certain embodiments, the composition comprises IGF2 and POSTN. In certain embodiments, the composition comprises IGF2 and FGF17. Human IGF2 is disclosed in SEQ ID NO: 11. In certain embodiments, the IGF2 of the heparin-associated binding polypeptide composition comprises an amino acid sequence that is at least about 80%, 85%, 90%, 95%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 10 or amino acids 25-91 of SEQ ID NO: 11. In certain embodiments, the IGF2 polypeptide lacks a secretory leader sequence. In certain embodiments, the IGF2 polypeptide is modified by a deletion of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acids from the N-terminal or C-terminal end of the polypeptide, including increments therein. In certain embodiments, the IGF2 polypeptide comprises one or more additional modifications to increase stability. In certain embodiments, the IGF2 polypeptide is covalently conjugated to polyethylene glycol, polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol, polysialic acid, glycolic acid, or polypropylene glycol. In certain embodiments, the heparin-associated polypeptide is fused or conjugated to another protein to increase stability and or bioavailability. In certain embodiments, the IGF2 polypeptide is fused with an Fc region of an immunoglobulin or with serum albumin. In certain embodiments, the IGF2 polypeptide is present in a concatemer with one, two, three, four or more distinct polypeptides selected from VTN, STC2, AGRN, THBS1, THBS4, FGF17, POSTN, IL-15, and

THBS2. In certain embodiments, the IGF2 polypeptide is present in a concatemer with one, two, three, four, or more distinct IGF2 polypeptides. In certain embodiments, the IGF2 polypeptide is included in a composition comprising a biodegradable or bioabsorbable carrier that promotes polypeptide stability. In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA), polyglycolic acid (PGA), or Poly(D,L-lactic-coglycolic-acid) (PLGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polyglycolic acid (PGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises Poly(D,L-lactic-coglycolic-acid) (PLGA). In some cases, the IGF2 polypeptide is prepared recombinantly in an expression system (*e.g.*, bacteria, yeast, mammalian, insect). In some cases, the THBS1 polypeptide is prepared by chemical synthesis.

[00131] In certain embodiments, the heparin-associated binding polypeptide composition comprises any two polypeptides selected from VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, and THBS4. In certain embodiments, the composition comprises THBS1. In certain embodiments, the composition comprises THBS2. In certain embodiments, the composition comprises THBS4. In certain embodiments, the composition comprises FGF17. In certain embodiments, the composition comprises VTN. In certain embodiments, the composition comprises POSTN. In certain embodiments, the composition comprises IGF2. In certain embodiments, the composition comprises IL-15. In certain embodiments, the composition comprises VTN and POSTN. In certain embodiments, the composition comprises VTN and FGF17. In certain embodiments, the composition comprises VTN and THBS2. In certain embodiments, the composition comprises VTN and THBS1. In certain embodiments, the composition comprises VTN and IGF2. In certain embodiments, the composition comprises VTN and IL-15. In certain embodiments, the composition comprises VTN and THBS4. In certain embodiments, the composition comprises POSTN and FGF17. In certain embodiments, the composition comprises POSTN and THBS2. In certain embodiments, the composition comprises POSTN and THBS1. In certain embodiments, the composition comprises POSTN and IGF2. In certain embodiments, the composition comprises POSTN and IL-15. In certain embodiments, the composition comprises POSTN and THBS4. In certain embodiments, the composition comprises FGF17 and THBS2. In certain embodiments, the composition comprises FGF17 and THBS1. In certain embodiments, the composition comprises FGF17 and IGF2. In certain embodiments, the composition comprises FGF17 and IL-15. In certain embodiments, the composition comprises FGF17 and THBS4. In certain embodiments, the composition comprises THBS2 and THBS1. In certain embodiments, the composition comprises THBS2 and IGF2. In certain embodiments, the composition comprises THBS2 and IL-15. In certain embodiments, the composition comprises

THBS2 and THBS4. In certain embodiments, the composition comprises THBS1 and IGF2. In certain embodiments, the composition comprises THBS1 and IL-15. In certain embodiments, the composition comprises THBS1 and THBS4. In certain embodiments, the composition comprises IGF2 and IL-15. In certain embodiments, the composition comprises IGF2 and THBS4. In certain embodiments, the composition comprises IL-15 and THBS4.

[00132] In certain embodiments, the heparin-associated binding polypeptide composition comprising any two polypeptides selected from VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, and THBS4, comprises one or more additional modifications to increase stability. In certain embodiments, one or more of the heparin-associated polypeptides is covalently conjugated to polyethylene glycol, polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol, polysialic acid, glycolic acid, or polypropylene glycol. In certain embodiments, one or more of the heparin-associated polypeptides is fused or conjugated to another protein to increase stability and or bioavailability. In certain embodiments, one or more of the heparin-associated polypeptides is fused with an Fc region of an immunoglobulin or with serum albumin. In certain embodiments, one or more of the heparin-associated polypeptides is present in a concatemer with one, two, three, or four other distinct polypeptides selected from THBS2, VTN, POSTN, FGF17, THBS1, IGF2, IL-15, and THBS4. In certain embodiments, one or more of the heparin-associated polypeptides is present in a concatemer with one, two, three, four, or more distinct polypeptides. In certain embodiments, one or more of the heparin-associated polypeptides is included in a composition comprising a biodegradable or bioabsorbable carrier that promotes polypeptide stability. In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA), polyglycolic acid (PGA), or Poly(D,L-lactic-coglycolic-acid) (PLGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polyglycolic acid (PGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises Poly(D,L-lactic-coglycolic-acid) (PLGA).

[00133] In certain embodiments, the heparin-associated binding polypeptide composition comprises any three polypeptides selected from VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, and THBS4. In certain embodiments, the composition comprises THBS1. In certain embodiments, the composition comprises THBS2. In certain embodiments, the composition comprises THBS4. In certain embodiments, the composition comprises FGF17. In certain embodiments, the composition comprises VTN. In certain embodiments, the composition comprises POSTN. In certain embodiments, the composition comprises IGF2. In certain embodiments, the composition comprises IL-15. In certain embodiments, the composition comprises IGF2, THBS2, and THBS4. In certain embodiments, the composition comprises IL-15,

THBS2, and THBS4. In certain embodiments, the composition comprises THBS2 and THBS4. In certain embodiments, the composition comprises THBS2, THBS4, and VTN. In certain embodiments, the composition comprises THBS2, THBS4, and ANOS1. In certain embodiments, the composition comprises THBS2, THBS4, and IL-15. In certain embodiments, the composition comprises THBS2, THBS4, and IGF2. In certain embodiments, the composition comprises THBS1 and FGF17. In certain embodiments, the composition comprises THBS2 and VTN. In certain embodiments, the composition comprises THBS1 and VTN. In certain embodiments, the composition comprises THBS1 and THBS2. In certain embodiments, the composition comprises THBS2 and FGF17. In certain embodiments, the composition comprises THBS1 and THBS4. In certain embodiments, the composition comprises VTN and FGF17. In certain embodiments, the composition comprises THBS4 and VTN. In certain embodiments, the composition comprises THBS4 and FGF17.

[00134] In certain embodiments, the composition comprises VTN, POSTN, and FGF17. In certain embodiments, the composition comprises VTN, POSTN, and THBS2. In certain embodiments, the composition comprises VTN, POSTN, and FGF17. In certain embodiments, the composition comprises VTN, POSTN, THBS2. In certain embodiments, the composition comprises VTN, POSTN, and THBS1. In certain embodiments, the composition comprises VTN, POSTN, IGF2. In certain embodiments, the composition comprises VTN, POSTN, and IL-15. In certain embodiments, the composition comprises VTN, POSTN, and THBS4.

[00135] In certain embodiments, the composition comprises VTN, FGF17, and THBS2. In certain embodiments, the composition comprises VTN, FGF17, and POSTN. In certain embodiments, the composition comprises VTN, FGF17, and THBS2. In certain embodiments, the composition comprises VTN, FGF17, and THBS1. In certain embodiments, the composition comprises VTN, FGF17, and IGF2. In certain embodiments, the composition comprises VTN, FGF17, and IL-15. In certain embodiments, the composition comprises VTN, FGF17, and THBS4.

[00136] In certain embodiments, the composition comprises VTN, THBS2, and POSTN. In certain embodiments, the composition comprises VTN, THBS2, and FGF17. In certain embodiments, the composition comprises VTN, THBS2, and THBS1. In certain embodiments, the composition comprises VTN, THBS2, and IGF2. In certain embodiments, the composition comprises VTN, THBS2, and IL-15. In certain embodiments, the composition comprises VTN, THBS2, and THBS4.

[00137] In certain embodiments, the composition comprises VTN, THBS1, and POSTN. In certain embodiments, the composition comprises VTN, THBS1, and FGF17. In certain embodiments, the composition comprises VTN, THBS1, and THBS2. In certain embodiments,

the composition comprises VTN, THBS1, and IGF2. In certain embodiments, the composition comprises VTN, THBS1, and IL-15. In certain embodiments, the composition comprises VTN, THBS1, and THBS4.

[00138] In certain embodiments, the composition comprises VTN, IGF2, and POSTN. In certain embodiments, the composition comprises VTN, IGF2, and FGF17. In certain embodiments, the composition comprises VTN, IGF2, and THBS2. In certain embodiments, the composition comprises VTN, IGF2, and THBS1. In certain embodiments, the composition comprises VTN, IGF2, and IL-15. In certain embodiments, the composition comprises VTN, IGF2, and THBS4.

[00139] In certain embodiments, the composition comprises VTN, IL-15, and POSTN. In certain embodiments, the composition comprises VTN, IL-15, and FGF17. In certain embodiments, the composition comprises VTN, IL-15, and THBS2. In certain embodiments, the composition comprises VTN, IL-15, and THBS1. In certain embodiments, the composition comprises VTN, IL-15, and IGF2. In certain embodiments, the composition comprises VTN, IL-15, and THBS4.

[00140] In certain embodiments, the composition comprises VTN, TBHS4, and POSTN. In certain embodiments, the composition comprises VTN, TBHS4, and FGF17. In certain embodiments, the composition comprises VTN, TBHS4, and THBS2. In certain embodiments, the composition comprises VTN, TBHS4, and THBS1. In certain embodiments, the composition comprises VTN, TBHS4, and IGF2. In certain embodiments, the composition comprises VTN, TBHS4, and IL-15.

[00141] In certain embodiments, the composition comprises POSTN, FGF17, and VTN. In certain embodiments, the composition comprises POSTN, FGF17, and TBHS2. In certain embodiments, the composition comprises POSTN, FGF17, and THBS1. In certain embodiments, the composition comprises POSTN, FGF17, and IGF2. In certain embodiments, the composition comprises POSTN, FGF17, and IL-15. In certain embodiments, the composition comprises POSTN, FGF17, and THBS4.

[00142] In certain embodiments, the composition comprises POSTN, THBS2, and VTN. In certain embodiments, the composition comprises POSTN, THBS2, and FGF17. In certain embodiments, the composition comprises POSTN, THBS2, and THBS1. In certain embodiments, the composition comprises POSTN, THBS2, and IGF2. In certain embodiments, the composition comprises POSTN, THBS2, and IL-15. In certain embodiments, the composition comprises POSTN, THBS2, and THBS4.

[00143] In certain embodiments, the composition comprises POSTN, THBS1, and VTN. In certain embodiments, the composition comprises POSTN, THBS1, and FGF17. In certain

embodiments, the composition comprises POSTN, THBS1, and THBS2. In certain embodiments, the composition comprises POSTN, THBS1, and IGF2. In certain embodiments, the composition comprises POSTN, THBS1, and IL-15. In certain embodiments, the composition comprises POSTN, THBS1, and THBS4.

[00144] In certain embodiments, the composition comprises POSTN, IGF2, and VTN. In certain embodiments, the composition comprises POSTN, IGF2, and FGF17. In certain embodiments, the composition comprises POSTN, IGF2, and THBS2. In certain embodiments, the composition comprises POSTN, IGF2, and THBS1. In certain embodiments, the composition comprises POSTN, IGF2, and IL-15. In certain embodiments, the composition comprises POSTN, IGF2, and THBS4.

[00145] In certain embodiments, the composition comprises POSTN, IL-15, and VTN. In certain embodiments, the composition comprises POSTN, IL-15, and FGF17. In certain embodiments, the composition comprises POSTN, IL-15, and THBS2. In certain embodiments, the composition comprises POSTN, IL-15, and THBS1. In certain embodiments, the composition comprises POSTN, IL-15, and IGF2. In certain embodiments, the composition comprises POSTN, IL-15, and THBS4.

[00146] In certain embodiments, the composition comprises POSTN, THBS4, and VTN. In certain embodiments, the composition comprises POSTN, THBS4, and FGF17. In certain embodiments, the composition comprises POSTN, THBS4, and THBS2. In certain embodiments, the composition comprises POSTN, THBS4, and THBS1. In certain embodiments, the composition comprises POSTN, THBS4, and IGF2. In certain embodiments, the composition comprises POSTN, THBS4, and IL-15.

[00147] In certain embodiments, the composition comprises FGF17, THBS2, and VTN. In certain embodiments, the composition comprises FGF17, THBS2, and POSTN. In certain embodiments, the composition comprises FGF17, THBS2, and THBS1. In certain embodiments, the composition comprises FGF17, THBS2, and IGF2. In certain embodiments, the composition comprises FGF17, THBS2, and IL-15. In certain embodiments, the composition comprises FGF17, THBS2, and THBS4.

[00148] In certain embodiments, the composition comprises FGF17, THBS1, and VTN. In certain embodiments, the composition comprises FGF17, THBS1, and POSTN. In certain embodiments, the composition comprises FGF17, THBS1, and THBS2. In certain embodiments, the composition comprises FGF17, THBS1, and IGF2. In certain embodiments, the composition comprises FGF17, THBS1, and IL-15. In certain embodiments, the composition comprises FGF17, THBS1, and THBS4.

[00149] In certain embodiments, the composition comprises FGF17, IGF2, and VTN. In

certain embodiments, the composition comprises FGF17, IGF2, and POSTN. In certain embodiments, the composition comprises FGF17, IGF2, and THBS2. In certain embodiments, the composition comprises FGF17, IGF2, and THBS1. In certain embodiments, the composition comprises FGF17, IGF2, and IL-15. In certain embodiments, the composition comprises FGF17, IGF2, and THBS4.

[00150] In certain embodiments, the composition comprises FGF17, IL-15, and VTN. In certain embodiments, the composition comprises FGF17, IL-15, and POSTN. In certain embodiments, the composition comprises FGF17, IL-15, and THBS2. In certain embodiments, the composition comprises FGF17, IL-15, and THBS1. In certain embodiments, the composition comprises FGF17, IL-15, and IGF2. In certain embodiments, the composition comprises FGF17, IL-15, and THBS4.

[00151] In certain embodiments, the composition comprises FGF17, THBS4, and VTN. In certain embodiments, the composition comprises FGF17, THBS4, and POSTN. In certain embodiments, the composition comprises FGF17, THBS4, and THBS2. In certain embodiments, the composition comprises FGF17, THBS4, and THBS1. In certain embodiments, the composition comprises FGF17, THBS4, and IGF2. In certain embodiments, the composition comprises FGF17, THBS4, and IL-15.

[00152] In certain embodiments, the composition comprises THBS2, THBS1, and VTN. In certain embodiments, the composition comprises THBS2, THBS1, and POSTN. In certain embodiments, the composition comprises THBS2, THBS1, and FGF17. In certain embodiments, the composition comprises THBS2, THBS1, and IGF2. In certain embodiments, the composition comprises THBS2, THBS1, and IL-15. In certain embodiments, the composition comprises THBS2, THBS1, and THBS4.

[00153] In certain embodiments, the composition comprises THBS2, IGF2, and VTN. In certain embodiments, the composition comprises THBS2, IGF2, and POSTN. In certain embodiments, the composition comprises THBS2, IGF2, and FGF17. In certain embodiments, the composition comprises THBS2, IGF2, and THBS1. In certain embodiments, the composition comprises THBS2, IGF2, and IL-15. In certain embodiments, the composition comprises THBS2, IGF2, and THBS4.

[00154] In certain embodiments, the composition comprises THBS2, IL-15, and VTN. In certain embodiments, the composition comprises THBS2, IL-15, and POSTN. In certain embodiments, the composition comprises THBS2, IL-15, and FGF17. In certain embodiments, the composition comprises THBS2, IL-15, and THBS1. In certain embodiments, the composition comprises THBS2, IL-15, and IGF2. In certain embodiments, the composition comprises THBS2, IL-15, and THBS4.

[00155] In certain embodiments, the composition comprises THBS2, THBS4, and VTN. In certain embodiments, the composition comprises THBS2, THBS4, and POSTN. In certain embodiments, the composition comprises THBS2, THBS4, and FGF17. In certain embodiments, the composition comprises THBS2, THBS4, and THBS1. In certain embodiments, the composition comprises THBS2, THBS4, and IGF2. In certain embodiments, the composition comprises THBS2, THBS4, and IL-15.

[00156] In certain embodiments, the composition comprises THBS1, IGF2, and VTN. In certain embodiments, the composition comprises THBS1, IGF2, and POSTN. In certain embodiments, the composition comprises THBS1, IGF2, and FGF17. In certain embodiments, the composition comprises THBS1, IGF2, and THBS2. In certain embodiments, the composition comprises THBS1, IGF2, and IL-15. In certain embodiments, the composition comprises THBS1, IGF2, and THBS4.

[00157] In certain embodiments, the composition comprises THBS1, IL-15, and VTN. In certain embodiments, the composition comprises THBS1, IL-15, and POSTN. In certain embodiments, the composition comprises THBS1, IL-15, and FGF17. In certain embodiments, the composition comprises THBS1, IL-15, and THBS2. In certain embodiments, the composition comprises THBS1, IL-15, and IGF2. In certain embodiments, the composition comprises THBS1, IL-15, and THBS4.

[00158] In certain embodiments, the composition comprises THBS1, and THBS4, and VTN. In certain embodiments, the composition comprises THBS1, and THBS4, and POSTN. In certain embodiments, the composition comprises THBS1, and THBS4, and FGF17. In certain embodiments, the composition comprises THBS1, and THBS4, and THBS2. In certain embodiments, the composition comprises THBS1, and THBS4, and IGF2. In certain embodiments, the composition comprises THBS1, and THBS4, and IL-15.

[00159] In certain embodiments, the composition comprises IGF2, IL-15, and VTN. In certain embodiments, the composition comprises IGF2, IL-15, and POSTN. In certain embodiments, the composition comprises IGF2, IL-15, and FGF17. In certain embodiments, the composition comprises IGF2, IL-15, and THBS2. In certain embodiments, the composition comprises IGF2, IL-15, and THBS1. In certain embodiments, the composition comprises IGF2, IL-15, and THBS4.

[00160] In certain embodiments, the composition comprises IGF2, THBS4, and VTN. In certain embodiments, the composition comprises IGF2, THBS4, and POSTN. In certain embodiments, the composition comprises IGF2, THBS4, and FGF17. In certain embodiments, the composition comprises IGF2, THBS4, and THBS2. In certain embodiments, the composition comprises IGF2, THBS4, and THBS1. In certain embodiments, the composition comprises IGF2, THBS4, and IL-15.

[00161] In certain embodiments, the composition comprises IL-15, and THBS4, and VTN. In certain embodiments, the composition comprises IL-15, and THBS4, and POSTN. In certain embodiments, the composition comprises IL-15, and THBS4, and FGF17. In certain embodiments, the composition comprises IL-15, and THBS4, and THBS2. In certain embodiments, the composition comprises IL-15, and THBS4, and THBS1. In certain embodiments, the composition comprises IL-15, and THBS4, and IGF2.

[00162] In certain embodiments, the composition comprises VTN, POSTN, and FGF17. In certain embodiments, the composition comprises VTN, POSTN, and THBS2. In certain embodiments, the composition comprises VTN, POSTN, and THBS4. In certain embodiments, the composition comprises VTN, FGF17, and POSTN. In certain embodiments, the composition comprises VTN, FGF17, and THBS2. In certain embodiments, the composition comprises VTN, FGF17, and THBS4. In certain embodiments, the composition comprises VTN, THBS2, and POSTN. In certain embodiments, the composition comprises VTN, THBS2, and FGF17. In certain embodiments, the composition comprises VTN, THBS2, and THBS4. In certain embodiments, the composition comprises VTN, THBS4, and POSTN. In certain embodiments, the composition comprises VTN, THBS4, and FGF17. In certain embodiments, the composition comprises VTN, THBS4, and THBS2. In certain embodiments, the composition comprises POSTN, VTN, and THBS4. In certain embodiments, the composition comprises POSTN, VTN, and FGF17. In certain embodiments, the composition comprises POSTN, VTN, and THBS2. In certain embodiments, the composition comprises POSTN, FGF17, and THBS4. In certain embodiments, the composition comprises POSTN, FGF17, and VTN. In certain embodiments, the composition comprises POSTN, FGF17, and THBS2. In certain embodiments, the composition comprises POSTN, THBS2, and THBS4. In certain embodiments, the composition comprises POSTN, THBS2, and VTN. In certain embodiments, the composition comprises POSTN, THBS2, and FGF17. In certain embodiments, the composition comprises POSTN, THBS4, and THBS2. In certain embodiments, the composition comprises POSTN, THBS4, and VTN. In certain embodiments, the composition comprises POSTN, THBS4, and FGF17. In certain embodiments, the composition comprises FGF17, VTN, and THBS2. In certain embodiments, the composition comprises FGF17, VTN, and THBS4. In certain embodiments, the composition comprises FGF17, VTN, and POSTN. In certain embodiments, the composition comprises FGF17, POSTN, and THBS2. In certain embodiments, the composition comprises FGF17, POSTN, and THBS4. In certain embodiments, the composition comprises FGF17, POSTN, and VTN. In certain embodiments, the composition comprises FGF17, THBS2, and POSTN. In certain embodiments, the composition comprises FGF17, THBS2, and THBS4. In certain embodiments, the composition comprises FGF17, THBS2, and VTN. In certain

embodiments, the composition comprises FGF17, THBS4, and POSTN. In certain embodiments, the composition comprises FGF17, THBS4, and THBS2. In certain embodiments, the composition comprises FGF17, THBS4, and VTN. In certain embodiments, the composition comprises THBS2, VTN, and POSTN. In certain embodiments, the composition comprises THBS2, VTN, and FGF17. In certain embodiments, the composition comprises THBS2, VTN, and THBS4. In certain embodiments, the composition comprises THBS2, POSTN, and VTN. In certain embodiments, the composition comprises THBS2, POSTN, and FGF17. In certain embodiments, the composition comprises THBS2, POSTN, and THBS4. In certain embodiments, the composition comprises THBS2, FGF17, and VTN. In certain embodiments, the composition comprises THBS2, FGF17, and POSTN. In certain embodiments, the composition comprises THBS2, FGF17, and THBS4. In certain embodiments, the composition comprises THBS2, THBS4, and VTN. In certain embodiments, the composition comprises THBS2, THBS4, and POSTN. In certain embodiments, the composition comprises THBS2, THBS4, and FGF17. In certain embodiments, the composition comprises THBS4, VTN, and THBS2. In certain embodiments, the composition comprises THBS4, VTN, and POSTN. In certain embodiments, the composition comprises THBS4, VTN, and FGF17. In certain embodiments, the composition comprises THBS4, POSTN, and THBS2. In certain embodiments, the composition comprises THBS4, POSTN, and VTN. In certain embodiments, the composition comprises THBS4, POSTN, and FGF17. In certain embodiments, the composition comprises THBS4, FGF17, and THBS2. In certain embodiments, the composition comprises THBS4, FGF17, and VTN. In certain embodiments, the composition comprises THBS4, FGF17, and POSTN. In certain embodiments, the composition comprises THBS4, THBS2, and FGF17. In certain embodiments, the composition comprises THBS4, THBS2, and VTN. In certain embodiments, the composition comprises THBS4, THBS2, and POSTN.

[00163] In certain embodiments, the heparin-associated binding polypeptide composition comprising any three polypeptides selected from VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, and THBS4, comprises one or more additional modifications to increase stability. In certain embodiments, one or more of the heparin-associated polypeptides is covalently conjugated to polyethylene glycol, polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol, polysialic acid, glycolic acid, or polypropylene glycol. In certain embodiments, one or more of the heparin-associated polypeptides is fused or conjugated to another protein to increase stability and or bioavailability. In certain embodiments, one or more of the heparin-associated polypeptides is fused with an Fc region of an immunoglobulin or with serum albumin. In certain embodiments, one or more of the heparin-associated polypeptides is present in a concatemer with one, two, three, or four other distinct polypeptides selected from

THBS2, VTN, POSTN, FGF17, THBS1, IGF2, IL-15, and THBS4. In certain embodiments, one or more of the heparin-associated polypeptides is present in a concatemer with one, two, three, four, or more distinct polypeptides. In certain embodiments, one or more of the heparin-associated polypeptides is included in a composition comprising a biodegradable or bioabsorbable carrier that promotes polypeptide stability. In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA), polyglycolic acid (PGA), or Poly(D,L-lactic-coglycolic-acid) (PLGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polyglycolic acid (PGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises Poly(D,L-lactic-coglycolic-acid) (PLGA).

[00164] In certain embodiments, the heparin-associated binding polypeptide composition comprises any four polypeptides selected from VTN, POSTN, FGF17, THBS1, IGF2, IL-15, THBS2, and THBS4. In certain embodiments, the composition comprises VTN, POSTN, FGF17, and THBS2. In certain embodiments, the composition comprises VTN, POSTN, FGF17, and THBS4. In certain embodiments, the composition comprises VTN, POSTN, THBS2, and FGF17. In certain embodiments, the composition comprises VTN, POSTN, THBS2, and THBS4. In certain embodiments, the composition comprises VTN, POSTN, THBS4, and FGF17. In certain embodiments, the composition comprises VTN, POSTN, THBS4, and THBS2. In certain embodiments, the composition comprises VTN, FGF17, POSTN, and THBS4. In certain embodiments, the composition comprises VTN, FGF17, POSTN, and THBS2. In certain embodiments, the composition comprises VTN, FGF17, THBS2, and THBS4. In certain embodiments, the composition comprises VTN, FGF17, THBS2, and POSTN. In certain embodiments, the composition comprises VTN, FGF17, THBS4, and THBS2. In certain embodiments, the composition comprises VTN, FGF17, THBS4, and POSTN. In certain embodiments, the composition comprises VTN, THBS2, POSTN, and FGF17. In certain embodiments, the composition comprises VTN, THBS2, POSTN, and THBS4. In certain embodiments, the composition comprises VTN, THBS2, FGF17, and POSTN. In certain embodiments, the composition comprises VTN, THBS2, FGF17, and THBS4. In certain embodiments, the composition comprises VTN, THBS2, THBS4, and POSTN. In certain embodiments, the composition comprises VTN, THBS2, THBS4, and FGF17. In certain embodiments, the composition comprises VTN, THBS4, POSTN, and THBS2. In certain embodiments, the composition comprises VTN, THBS4, POSTN, and FGF17. In certain embodiments, the composition comprises VTN, THBS4, FGF17, and THBS2. In certain embodiments, the composition comprises VTN, THBS4, FGF17, and POSTN. In certain embodiments, the composition comprises VTN, THBS4, THBS2, and FGF17. In certain

embodiments, the composition comprises VTN, THBS4, THBS2, and POSTN. In certain embodiments, the composition comprises POSTN, VTN, THBS4, and FGF17. In certain embodiments, the composition comprises POSTN, VTN, THBS4, and THBS2. In certain embodiments, the composition comprises POSTN, VTN, FGF17, and THBS4. In certain embodiments, the composition comprises POSTN, VTN, FGF17, and THBS2. In certain embodiments, the composition comprises POSTN, VTN, THBS2, and THBS4. In certain embodiments, the composition comprises POSTN, VTN, THBS2, and FGF17. In certain embodiments, the composition comprises POSTN, FGF17, THBS4, and THBS2. In certain embodiments, the composition comprises POSTN, FGF17, THBS4, and VTN. In certain embodiments, the composition comprises POSTN, FGF17, VTN, and THBS2. In certain embodiments, the composition comprises POSTN, FGF17, VTN, and THBS4. In certain embodiments, the composition comprises POSTN, FGF17, THBS2, and VTN. In certain embodiments, the composition comprises POSTN, FGF17, THBS2, and THBS4. In certain embodiments, the composition comprises POSTN, THBS2, THBS4, and VTN. In certain embodiments, the composition comprises POSTN, THBS2, THBS4, and FGF17. In certain embodiments, the composition comprises POSTN, THBS2, VTN, and THBS4. In certain embodiments, the composition comprises POSTN, THBS2, VTN, and FGF17. In certain embodiments, the composition comprises POSTN, THBS2, FGF17, and THBS4. In certain embodiments, the composition comprises POSTN, THBS2, FGF17, and VTN. In certain embodiments, the composition comprises POSTN, THBS4, THBS2, and FGF17. In certain embodiments, the composition comprises POSTN, THBS4, THBS2, and VTN. In certain embodiments, the composition comprises POSTN, THBS4, VTN, and FGF17. In certain embodiments, the composition comprises POSTN, THBS4, VTN, and THBS2. In certain embodiments, the composition comprises POSTN, THBS4, FGF17, and VTN. In certain embodiments, the composition comprises POSTN, THBS4, FGF17, and THBS2. In certain embodiments, the composition comprises FGF17, VTN, THBS2, and THBS4. In certain embodiments, the composition comprises FGF17, VTN, THBS2, and POSTN. In certain embodiments, the composition comprises FGF17, VTN, THBS4, and THBS2. In certain embodiments, the composition comprises FGF17, VTN, THBS4, and POSTN. In certain embodiments, the composition comprises FGF17, VTN, POSTN, and THBS2. In certain embodiments, the composition comprises FGF17, VTN, POSTN, and THBS4. In certain embodiments, the composition comprises FGF17, POSTN, THBS2, and VTN. In certain embodiments, the composition comprises FGF17, POSTN, THBS2, and THBS4. In certain embodiments, the composition comprises FGF17, POSTN, THBS4, and VTN. In certain embodiments, the composition comprises FGF17, POSTN, THBS4, and THBS2. In certain

embodiments, the composition comprises FGF17, POSTN, VTN, and THBS4. In certain embodiments, the composition comprises FGF17, POSTN, VTN, and THBS2. In certain embodiments, the composition comprises FGF17, THBS2, POSTN, and THBS4. In certain embodiments, the composition comprises FGF17, THBS2, POSTN, and VTN. In certain embodiments, the composition comprises FGF17, THBS2, THBS4, and POSTN. In certain embodiments, the composition comprises FGF17, THBS2, THBS4, and VTN. In certain embodiments, the composition comprises FGF17, THBS2, VTN, and POSTN. In certain embodiments, the composition comprises FGF17, THBS2, VTN, and THBS4. In certain embodiments, the composition comprises FGF17, THBS4, POSTN, and VTN. In certain embodiments, the composition comprises FGF17, THBS4, POSTN, and THBS2. In certain embodiments, the composition comprises FGF17, THBS4, THBS2, and VTN. In certain embodiments, the composition comprises FGF17, THBS4, THBS2, and POSTN. In certain embodiments, the composition comprises FGF17, THBS4, VTN, and THBS2. In certain embodiments, the composition comprises FGF17, THBS4, VTN, and POSTN. In certain embodiments, the composition comprises THBS2, VTN, POSTN, and FGF17. In certain embodiments, the composition comprises THBS2, VTN, POSTN, and THBS4. In certain embodiments, the composition comprises THBS2, VTN, FGF17, and POSTN. In certain embodiments, the composition comprises THBS2, VTN, FGF17, and THBS4. In certain embodiments, the composition comprises THBS2, VTN, THBS4, and POSTN. In certain embodiments, the composition comprises THBS2, VTN, THBS4, and FGF17. In certain embodiments, the composition comprises THBS2, POSTN, VTN, and THBS4. In certain embodiments, the composition comprises THBS2, POSTN, VTN, and FGF17. In certain embodiments, the composition comprises THBS2, POSTN, FGF17, and THBS4. In certain embodiments, the composition comprises THBS2, POSTN, FGF17, and VTN. In certain embodiments, the composition comprises THBS2, POSTN, THBS4, and FGF17. In certain embodiments, the composition comprises THBS2, POSTN, THBS4, and VTN. In certain embodiments, the composition comprises THBS2, FGF17, VTN, and POSTN. In certain embodiments, the composition comprises THBS2, FGF17, VTN, and THBS4. In certain embodiments, the composition comprises THBS2, FGF17, POSTN, and VTN. In certain embodiments, the composition comprises THBS2, FGF17, POSTN, and THBS4. In certain embodiments, the composition comprises THBS2, FGF17, THBS4, and VTN. In certain embodiments, the composition comprises THBS2, FGF17, THBS4, and POSTN. In certain embodiments, the composition comprises THBS2, THBS4, VTN, and FGF17. In certain embodiments, the composition comprises THBS2, THBS4, VTN, and POSTN. In certain embodiments, the composition comprises THBS2, THBS4, POSTN, and FGF17. In certain

embodiments, the composition comprises THBS2, THBS4, POSTN, and VTN. In certain embodiments, the composition comprises THBS2, THBS4, FGF17, and POSTN. In certain embodiments, the composition comprises THBS2, THBS4, FGF17, and VTN. In certain embodiments, the composition comprises THBS4, VTN, THBS2, and POSTN. In certain embodiments, the composition comprises THBS4, VTN, THBS2, and FGF17. In certain embodiments, the composition comprises THBS4, VTN, POSTN, and THBS2. In certain embodiments, the composition comprises THBS4, VTN, POSTN, and FGF17. In certain embodiments, the composition comprises THBS4, VTN, FGF17, and THBS2. In certain embodiments, the composition comprises THBS4, VTN, FGF17, and POSTN. In certain embodiments, the composition comprises THBS4, POSTN, THBS2, and FGF17. In certain embodiments, the composition comprises THBS4, POSTN, THBS2, and VTN. In certain embodiments, the composition comprises THBS4, POSTN, VTN, and FGF17. In certain embodiments, the composition comprises THBS4, POSTN, VTN, and THBS2. In certain embodiments, the composition comprises THBS4, POSTN, FGF17, and VTN. In certain embodiments, the composition comprises THBS4, POSTN, FGF17, and THBS2. In certain embodiments, the composition comprises THBS4, FGF17, THBS2, and VTN. In certain embodiments, the composition comprises THBS4, FGF17, THBS2, and POSTN. In certain embodiments, the composition comprises THBS4, FGF17, VTN, and THBS2. In certain embodiments, the composition comprises THBS4, FGF17, VTN, and POSTN. In certain embodiments, the composition comprises THBS4, FGF17, POSTN, and THBS2. In certain embodiments, the composition comprises THBS4, FGF17, POSTN, and VTN. In certain embodiments, the composition comprises THBS4, THBS2, FGF17, and POSTN. In certain embodiments, the composition comprises THBS4, THBS2, FGF17, and VTN. In certain embodiments, the composition comprises THBS4, THBS2, VTN, and POSTN. In certain embodiments, the composition comprises THBS4, THBS2, VTN, and FGF17. In certain embodiments, the composition comprises THBS4, THBS2, POSTN, and VTN. In certain embodiments, the composition comprises THBS4, THBS2, POSTN, and FGF17.

[00165] In certain embodiments, the composition comprises VTN, POSTN, FGF17, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, POSTN, THBS2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, POSTN, FGF17, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, POSTN, THBS2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition

comprises VTN, POSTN, THBS1, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, POSTN, IGF2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, POSTN, IL-15, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, POSTN, THBS4, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00166] In certain embodiments, the composition comprises VTN, FGF17, THBS2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, FGF17, POSTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, FGF17, THBS2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, FGF17, THBS1, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, FGF17, IGF2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, FGF17, IL-15, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, FGF17, THBS4, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00167] In certain embodiments, the composition comprises VTN, THBS2, POSTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, THBS2, FGF17, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, THBS2, THBS1, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, THBS2, IGF2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, THBS2, IL-15, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, THBS2, THBS4, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00168] In certain embodiments, the composition comprises VTN, THBS1, POSTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, THBS1, FGF17, and a polypeptide

comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, THBS1, THBS2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, THBS1, IGF2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, THBS1, IL-15, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, THBS1, THBS4, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00169] In certain embodiments, the composition comprises VTN, IGF2, POSTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, IGF2, FGF17, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, IGF2, THBS2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, IGF2, THBS1, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, IGF2, IL-15, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, IGF2, THBS4, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00170] In certain embodiments, the composition comprises VTN, IL-15, POSTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, IL-15, FGF17, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, IL-15, THBS2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, IL-15, THBS1, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, IL-15, IGF2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, IL-15, THBS4, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00171] In certain embodiments, the composition comprises VTN, THBS4, POSTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In

certain embodiments, the composition comprises VTN, TBHS4, FGF17, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, TBHS4, THBS2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, TBHS4, THBS1, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, TBHS4, IGF2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises VTN, TBHS4, IL-15, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00172] In certain embodiments, the composition comprises POSTN, FGF17, VTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, FGF17, TBHS2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, FGF17, THBS1, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, FGF17, IGF2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, FGF17, IL-15, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, FGF17, THBS4, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00173] In certain embodiments, the composition comprises POSTN, THBS2, VTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, THBS2, FGF17, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, THBS2, THBS1, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, THBS2, IGF2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, THBS2, IL-15, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, THBS2, THBS4, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00174] In certain embodiments, the composition comprises POSTN, THBS1, VTN, and a

polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, THBS1, FGF17, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, THBS1, THBS2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, THBS1, IGF2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, THBS1, IL-15, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, THBS1, THBS4, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00175] In certain embodiments, the composition comprises POSTN, IGF2, VTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, IGF2, FGF17, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, IGF2, THBS2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, IGF2, THBS1, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, IGF2, IL-15, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, IGF2, THBS4, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00176] In certain embodiments, the composition comprises POSTN, IL-15, VTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, IL-15, FGF17, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, IL-15, THBS2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, IL-15, THBS1, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, IL-15, IGF2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, IL-15, THBS4, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00177] In certain embodiments, the composition comprises POSTN, THBS4, VTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, THBS4, FGF17, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, THBS4, THBS2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, THBS4, THBS1, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, THBS4, IGF2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises POSTN, THBS4, IL-15, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00178] In certain embodiments, the composition comprises FGF17, THBS2, VTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises FGF17, THBS2, POSTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises FGF17, THBS2, THBS1, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises FGF17, THBS2, IGF2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises FGF17, THBS2, IL-15, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises FGF17, THBS2, THBS4, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00179] In certain embodiments, the composition comprises FGF17, THBS1, VTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises FGF17, THBS1, POSTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises FGF17, THBS1, THBS2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises FGF17, THBS1, IGF2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises FGF17, THBS1, IL-15, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises FGF17, THBS1, THBS4, and a polypeptide comprising VTN, POSTN, FGF17,

THBS2, THBS1, IGF2, IL-15, or THBS4.

[00180] In certain embodiments, the composition comprises FGF17, IGF2, VTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises FGF17, IGF2, POSTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises FGF17, IGF2, THBS2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises FGF17, IGF2, THBS1, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises FGF17, IGF2, IL-15, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises FGF17, IGF2, THBS4, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00181] In certain embodiments, the composition comprises FGF17, IL-15, VTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises FGF17, IL-15, POSTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises FGF17, IL-15, THBS2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises FGF17, IL-15, THBS1, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises FGF17, IL-15, IGF2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises FGF17, IL-15, THBS4, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00182] In certain embodiments, the composition comprises FGF17, THBS4, VTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises FGF17, THBS4, POSTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises FGF17, THBS4, THBS2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises FGF17, THBS4, THBS1, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises FGF17, THBS4, IGF2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the

composition comprises FGF17, THBS4, IL-15, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00183] In certain embodiments, the composition comprises THBS2, THBS1, VTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS2, THBS1, POSTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS2, THBS1, FGF17, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS2, THBS1, IGF2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS2, THBS1, IL-15, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS2, THBS1, THBS4, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00184] In certain embodiments, the composition comprises THBS2, IGF2, VTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS2, IGF2, POSTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS2, IGF2, FGF17, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS2, IGF2, THBS1, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS2, IGF2, IL-15, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS2, IGF2, THBS4, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00185] In certain embodiments, the composition comprises THBS2, IL-15, VTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS2, IL-15, POSTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS2, IL-15, FGF17, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS2, IL-15, THBS1, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS2, IL-15, IGF2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2,

THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS2, IL-15, THBS4, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00186] In certain embodiments, the composition comprises THBS2, THBS4, VTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS2, THBS4, POSTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS2, THBS4, FGF17, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS2, THBS4, THBS1, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS2, THBS4, IGF2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS2, THBS4, IL-15, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00187] In certain embodiments, the composition comprises THBS1, IGF2, VTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS1, IGF2, POSTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS1, IGF2, FGF17, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS1, IGF2, THBS2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS1, IGF2, IL-15, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS1, IGF2, THBS4, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00188] In certain embodiments, the composition comprises THBS1, IL-15, VTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS1, IL-15, POSTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS1, IL-15, FGF17, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS1, IL-15, THBS2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition

comprises THBS1, IL-15, IGF2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS1, IL-15, THBS4, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00189] In certain embodiments, the composition comprises THBS1, and THBS4, VTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS1, THBS4, POSTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS1, THBS4, FGF17, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS1, THBS4, THBS2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS1, THBS4, IGF2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises THBS1, THBS4, IL-15, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00190] In certain embodiments, the composition comprises IGF2, IL-15, VTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises IGF2, IL-15, POSTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises IGF2, IL-15, FGF17, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises IGF2, IL-15, THBS2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises IGF2, IL-15, THBS1, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises IGF2, IL-15, THBS4, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00191] In certain embodiments, the composition comprises IGF2, THBS4, VTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises IGF2, THBS4, POSTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises IGF2, THBS4, FGF17, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises IGF2, THBS4, THBS2, and a polypeptide comprising VTN, POSTN,

FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises IGF2, THBS4, THBS1, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises IGF2, THBS4, IL-15, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00192] In certain embodiments, the composition comprises IL-15, THBS4, VTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises IL-15, THBS4, POSTN, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises IL-15, THBS4, FGF17, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises IL-15, THBS4, THBS2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises IL-15, THBS4, THBS1, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4. In certain embodiments, the composition comprises IL-15, THBS4, IGF2, and a polypeptide comprising VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, or THBS4.

[00193] In certain embodiments, the heparin-associated binding polypeptide composition comprising any four polypeptides selected from VTN, POSTN, FGF17, THBS2, THBS1, IGF2, IL-15, and THBS4, comprises one or more additional modifications to increase stability. In certain embodiments, one or more of the heparin-associated polypeptides is covalently conjugated to polyethylene glycol, polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol, polysialic acid, glycolic acid, or polypropylene glycol. In certain embodiments, one or more of the heparin-associated polypeptides is fused or conjugated to another protein to increase stability and or bioavailability. In certain embodiments, one or more of the heparin-associated polypeptides is fused with an Fc region of an immunoglobulin or with serum albumin. In certain embodiments, one or more of the heparin-associated polypeptides is present in a concatemer with one, two, three, four or more distinct polypeptides selected from THBS2, VTN, POSTN, FGF17, THBS1, IL-15, IGF2, and THBS4. In certain embodiments, one or more of the heparin-associated polypeptides is present in a concatemer with one, two, three, four, or more distinct polypeptides. In certain embodiments, one or more of the heparin-associated polypeptides is included in a composition comprising a biodegradable or bioabsorbable carrier that promotes polypeptide stability. In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA), polyglycolic acid (PGA), or Poly(D,L-lactic-coglycolic-acid) (PLGA). In certain embodiments, the biodegradable or

bioabsorbable carrier comprises polylactic acid (PLA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polyglycolic acid (PGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises Poly(D,L-lactic-co-glycolic-acid) (PLGA).

[00194] In certain embodiments, the heparin-associated binding polypeptide composition comprises any three polypeptides selected from VTN, STC2, AGRN, THBS2, and FST. In certain embodiments, the composition comprises VTN, STC2, and AGRN. In certain embodiments, the composition comprises VTN, STC2, and THBS2. In certain embodiments, the composition comprises VTN, STC2, and FST. In certain embodiments, the composition comprises VTN, AGRN, and STC2. In certain embodiments, the composition comprises VTN, AGRN, and THBS2. In certain embodiments, the composition comprises VTN, AGRN, and FST. In certain embodiments, the composition comprises VTN, THBS2, and STC2. In certain embodiments, the composition comprises VTN, THBS2, and AGRN. In certain embodiments, the composition comprises VTN, THBS2, and FST. In certain embodiments, the composition comprises VTN, FST, and STC2. In certain embodiments, the composition comprises VTN, FST, and AGRN. In certain embodiments, the composition comprises VTN, FST, and THBS2. In certain embodiments, the composition comprises STC2, VTN, and FST. In certain embodiments, the composition comprises STC2, VTN, and AGRN. In certain embodiments, the composition comprises STC2, VTN, and THBS2. In certain embodiments, the composition comprises STC2, AGRN, and FST. In certain embodiments, the composition comprises STC2, AGRN, and VTN. In certain embodiments, the composition comprises STC2, AGRN, and THBS2. In certain embodiments, the composition comprises STC2, THBS2, and FST. In certain embodiments, the composition comprises STC2, THBS2, and VTN. In certain embodiments, the composition comprises STC2, THBS2, and AGRN. In certain embodiments, the composition comprises STC2, FST, and THBS2. In certain embodiments, the composition comprises STC2, FST, and VTN. In certain embodiments, the composition comprises STC2, FST, and AGRN. In certain embodiments, the composition comprises AGRN, VTN, and THBS2. In certain embodiments, the composition comprises AGRN, VTN, and FST. In certain embodiments, the composition comprises AGRN, VTN, and STC2. In certain embodiments, the composition comprises AGRN, STC2, and THBS2. In certain embodiments, the composition comprises AGRN, STC2, and FST. In certain embodiments, the composition comprises AGRN, STC2, and VTN. In certain embodiments, the composition comprises AGRN, THBS2, and STC2. In certain embodiments, the composition comprises AGRN, THBS2, and FST. In certain embodiments, the composition comprises AGRN, THBS2, and VTN. In certain embodiments, the composition comprises AGRN, FST, and STC2. In certain embodiments, the composition comprises AGRN, FST, and THBS2. In certain embodiments, the composition comprises AGRN, FST, and VTN. In certain

embodiments, the composition comprises THBS2, VTN, and STC2. In certain embodiments, the composition comprises THBS2, VTN, and AGRN. In certain embodiments, the composition comprises THBS2, VTN, and FST. In certain embodiments, the composition comprises THBS2, STC2, and VTN. In certain embodiments, the composition comprises THBS2, STC2, and AGRN. In certain embodiments, the composition comprises THBS2, STC2, and FST. In certain embodiments, the composition comprises THBS2, AGRN, and VTN. In certain embodiments, the composition comprises THBS2, AGRN, and STC2. In certain embodiments, the composition comprises THBS2, AGRN, and FST. In certain embodiments, the composition comprises THBS2, FST, and VTN. In certain embodiments, the composition comprises THBS2, FST, and STC2. In certain embodiments, the composition comprises THBS2, FST, and AGRN. In certain embodiments, the composition comprises FST, VTN, and THBS2. In certain embodiments, the composition comprises FST, VTN, and STC2. In certain embodiments, the composition comprises FST, VTN, and AGRN. In certain embodiments, the composition comprises FST, STC2, and THBS2. In certain embodiments, the composition comprises FST, STC2, and VTN. In certain embodiments, the composition comprises FST, STC2, and AGRN. In certain embodiments, the composition comprises FST, AGRN, and THBS2. In certain embodiments, the composition comprises FST, AGRN, and VTN. In certain embodiments, the composition comprises FST, AGRN, and STC2. In certain embodiments, the composition comprises FST, THBS2, and AGRN. In certain embodiments, the composition comprises FST, THBS2, and VTN. In certain embodiments, the composition comprises FST, THBS2, and STC2. In certain embodiments, one or more of the heparin-associated polypeptides comprise one or more additional modifications to increase stability. In certain embodiments, one or more of the heparin-associated polypeptides is covalently conjugated to polyethylene glycol, polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol, polysialic acid, glycolic acid, or polypropylene glycol. In certain embodiments, one or more of the heparin-associated polypeptide is fused or conjugated to another protein to increase stability and or bioavailability. In certain embodiments, one or more of the heparin-associated polypeptides is fused with an Fc region of an immunoglobulin or with serum albumin. In certain embodiments, one or more of the heparin-associated polypeptides is present in a concatemer with one, two, three, four or more distinct polypeptides selected from THBS2, VTN, STC2, AGRN, or FST. In certain embodiments, one or more of the heparin-associated polypeptides is present in a concatemer with one, two, three, four, or more distinct polypeptides. In certain embodiments, one or more of the heparin-associated polypeptides is included in a composition comprising a biodegradable or bioabsorbable carrier that promotes polypeptide stability. In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA), polyglycolic acid (PGA), or Poly(D,L-lactic-coglycolic-

acid) (PLGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polyglycolic acid (PGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises Poly(D,L-lactic-co-glycolic-acid) (PLGA).

[00195] In certain embodiments, the heparin-associated binding polypeptide composition comprises any four polypeptides selected from VTN, STC2, AGRN, THBS2, and FST. In certain embodiments, the composition comprises VTN, STC2, AGRN, and THBS2. In certain embodiments, the composition comprises VTN, STC2, AGRN, and FST. In certain embodiments, the composition comprises VTN, STC2, THBS2, and AGRN. In certain embodiments, the composition comprises VTN, STC2, THBS2, and FST. In certain embodiments, the composition comprises VTN, STC2, FST, and AGRN. In certain embodiments, the composition comprises VTN, STC2, FST, and THBS2. In certain embodiments, the composition comprises VTN, AGRN, STC2, and FST. In certain embodiments, the composition comprises VTN, AGRN, STC2, and THBS2. In certain embodiments, the composition comprises VTN, AGRN, THBS2, and FST. In certain embodiments, the composition comprises VTN, AGRN, THBS2, and STC2. In certain embodiments, the composition comprises VTN, AGRN, FST, and THBS2. In certain embodiments, the composition comprises VTN, AGRN, FST, and STC2. In certain embodiments, the composition comprises VTN, THBS2, STC2, and AGRN. In certain embodiments, the composition comprises VTN, THBS2, STC2, and FST. In certain embodiments, the composition comprises VTN, THBS2, AGRN, and STC2. In certain embodiments, the composition comprises VTN, THBS2, AGRN, and FST. In certain embodiments, the composition comprises VTN, THBS2, FST, and STC2. In certain embodiments, the composition comprises VTN, THBS2, FST, and AGRN. In certain embodiments, the composition comprises VTN, FST, STC2, and THBS2. In certain embodiments, the composition comprises VTN, FST, STC2, and AGRN. In certain embodiments, the composition comprises VTN, FST, AGRN, and THBS2. In certain embodiments, the composition comprises VTN, FST, AGRN, and STC2. In certain embodiments, the composition comprises VTN, FST, THBS2, and AGRN. In certain embodiments, the composition comprises VTN, FST, THBS2, and STC2. In certain embodiments, the composition comprises STC2, VTN, FST, and AGRN. In certain embodiments, the composition comprises STC2, VTN, FST, and THBS2. In certain embodiments, the composition comprises STC2, VTN, AGRN, and FST. In certain embodiments, the composition comprises STC2, VTN, AGRN, and THBS2. In certain embodiments, the composition comprises STC2, VTN, THBS2, and FST. In certain embodiments, the composition comprises STC2, VTN, THBS2, and AGRN. In certain embodiments, the composition comprises STC2, AGRN, FST, and THBS2. In certain embodiments, the composition comprises STC2, AGRN, FST, and VTN. In certain embodiments,

the composition comprises STC2, AGRN, VTN, and THBS2. In certain embodiments, the composition comprises STC2, AGRN, VTN, and FST. In certain embodiments, the composition comprises STC2, AGRN, THBS2, and VTN. In certain embodiments, the composition comprises STC2, AGRN, THBS2, and FST. In certain embodiments, the composition comprises STC2, THBS2, FST, and VTN. In certain embodiments, the composition comprises STC2, THBS2, FST, and AGRN. In certain embodiments, the composition comprises STC2, THBS2, VTN, and FST. In certain embodiments, the composition comprises STC2, THBS2, VTN, and AGRN. In certain embodiments, the composition comprises STC2, THBS2, AGRN, and FST. In certain embodiments, the composition comprises STC2, THBS2, AGRN, and VTN. In certain embodiments, the composition comprises STC2, FST, THBS2, and AGRN. In certain embodiments, the composition comprises STC2, FST, THBS2, and VTN. In certain embodiments, the composition comprises STC2, FST, VTN, and AGRN. In certain embodiments, the composition comprises STC2, FST, VTN, and THBS2. In certain embodiments, the composition comprises STC2, FST, AGRN, and VTN. In certain embodiments, the composition comprises STC2, FST, AGRN, and THBS2. In certain embodiments, the composition comprises AGRN, VTN, THBS2, and FST. In certain embodiments, the composition comprises AGRN, VTN, THBS2, and STC2. In certain embodiments, the composition comprises AGRN, VTN, FST, and THBS2. In certain embodiments, the composition comprises AGRN, VTN, FST, and STC2. In certain embodiments, the composition comprises AGRN, VTN, STC2, and THBS2. In certain embodiments, the composition comprises AGRN, VTN, STC2, and FST. In certain embodiments, the composition comprises AGRN, STC2, THBS2, and VTN. In certain embodiments, the composition comprises AGRN, STC2, THBS2, and FST. In certain embodiments, the composition comprises AGRN, STC2, FST, and VTN. In certain embodiments, the composition comprises AGRN, STC2, FST, and THBS2. In certain embodiments, the composition comprises AGRN, STC2, VTN, and FST. In certain embodiments, the composition comprises AGRN, STC2, VTN, and THBS2. In certain embodiments, the composition comprises AGRN, THBS2, STC2, and FST. In certain embodiments, the composition comprises AGRN, THBS2, STC2, and VTN. In certain embodiments, the composition comprises AGRN, THBS2, FST, and STC2. In certain embodiments, the composition comprises AGRN, THBS2, FST, and VTN. In certain embodiments, the composition comprises AGRN, THBS2, VTN, and STC2. In certain embodiments, the composition comprises AGRN, THBS2, VTN, and FST. In certain embodiments, the composition comprises AGRN, FST, STC2, and VTN. In certain embodiments, the composition comprises AGRN, FST, STC2, and THBS2. In certain embodiments, the composition comprises AGRN, FST, THBS2, and VTN. In certain embodiments, the composition comprises AGRN, FST, THBS2, and STC2. In certain embodiments, the

composition comprises AGRN, FST, VTN, and THBS2. In certain embodiments, the composition comprises AGRN, FST, VTN, and STC2. In certain embodiments, the composition comprises THBS2, VTN, STC2, and AGRN. In certain embodiments, the composition comprises THBS2, VTN, STC2, and FST. In certain embodiments, the composition comprises THBS2, VTN, AGRN, and STC2. In certain embodiments, the composition comprises THBS2, VTN, AGRN, and FST. In certain embodiments, the composition comprises THBS2, VTN, FST, and STC2. In certain embodiments, the composition comprises THBS2, VTN, FST, and AGRN. In certain embodiments, the composition comprises THBS2, STC2, VTN, and FST. In certain embodiments, the composition comprises THBS2, STC2, VTN, and AGRN. In certain embodiments, the composition comprises THBS2, STC2, AGRN, and FST. In certain embodiments, the composition comprises THBS2, STC2, AGRN, and VTN. In certain embodiments, the composition comprises THBS2, STC2, FST, and AGRN. In certain embodiments, the composition comprises THBS2, STC2, FST, and VTN. In certain embodiments, the composition comprises THBS2, AGRN, VTN, and STC2. In certain embodiments, the composition comprises THBS2, AGRN, VTN, and FST. In certain embodiments, the composition comprises THBS2, AGRN, STC2, and VTN. In certain embodiments, the composition comprises THBS2, AGRN, STC2, and FST. In certain embodiments, the composition comprises THBS2, AGRN, FST, and VTN. In certain embodiments, the composition comprises THBS2, AGRN, FST, and STC2. In certain embodiments, the composition comprises THBS2, FST, VTN, and AGRN. In certain embodiments, the composition comprises THBS2, FST, VTN, and STC2. In certain embodiments, the composition comprises THBS2, FST, STC2, and AGRN. In certain embodiments, the composition comprises THBS2, FST, STC2, and VTN. In certain embodiments, the composition comprises THBS2, FST, AGRN, and STC2. In certain embodiments, the composition comprises THBS2, FST, AGRN, and VTN. In certain embodiments, the composition comprises FST, VTN, THBS2, and STC2. In certain embodiments, the composition comprises FST, VTN, THBS2, and AGRN. In certain embodiments, the composition comprises FST, VTN, STC2, and THBS2. In certain embodiments, the composition comprises FST, VTN, STC2, and AGRN. In certain embodiments, the composition comprises FST, VTN, AGRN, and THBS2. In certain embodiments, the composition comprises FST, VTN, AGRN, and STC2. In certain embodiments, the composition comprises FST, STC2, THBS2, and AGRN. In certain embodiments, the composition comprises FST, STC2, THBS2, and VTN. In certain embodiments, the composition comprises FST, STC2, VTN, and AGRN. In certain embodiments, the composition comprises FST, STC2, VTN, and THBS2. In certain embodiments, the composition comprises FST, STC2, AGRN, and VTN. In

certain embodiments, the composition comprises FST, STC2, AGRN, and THBS2. In certain embodiments, the composition comprises FST, AGRN, THBS2, and VTN. In certain embodiments, the composition comprises FST, AGRN, THBS2, and STC2. In certain embodiments, the composition comprises FST, AGRN, VTN, and THBS2. In certain embodiments, the composition comprises FST, AGRN, VTN, and STC2. In certain embodiments, the composition comprises FST, AGRN, STC2, and THBS2. In certain embodiments, the composition comprises FST, AGRN, STC2, and VTN. In certain embodiments, the composition comprises FST, THBS2, AGRN, and STC2. In certain embodiments, the composition comprises FST, THBS2, AGRN, and VTN. In certain embodiments, the composition comprises FST, THBS2, VTN, and STC2. In certain embodiments, the composition comprises FST, THBS2, VTN, and AGRN. In certain embodiments, the composition comprises FST, THBS2, STC2, and VTN. In certain embodiments, the composition comprises FST, THBS2, STC2, and AGRN. In certain embodiments, one or more of the heparin-associated polypeptides comprise one or more additional modifications to increase stability. In certain embodiments, one or more of the heparin-associated polypeptides is covalently conjugated to polyethylene glycol, polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol, polysialic acid, glycolic acid, or polypropylene glycol. In certain embodiments, one or more of the heparin-associated polypeptides is fused or conjugated to another protein to increase stability and or bioavailability. In certain embodiments, one or more of the heparin-associated polypeptides is fused with an Fc region of an immunoglobulin or with serum albumin. In certain embodiments, one or more of the heparin-associated polypeptides is present in a concatemer with one, two, three, or four other distinct polypeptides selected from THBS2, VTN, STC2, AGRN, or FST. In certain embodiments, one or more of the heparin-associated polypeptides is present in a concatemer with one, two, three, four, or more distinct polypeptides. In certain embodiments, one or more of the heparin-associated polypeptides is included in a composition comprising a biodegradable or bioabsorbable carrier that promotes polypeptide stability. In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA), polyglycolic acid (PGA), or Poly(D,L-lactic-coglycolic-acid) (PLGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polyglycolic acid (PGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises Poly(D,L-lactic-coglycolic-acid) (PLGA).

[00196] In some embodiments, a composition herein comprises polypeptide 1 and one or more polypeptides from Table 2. In some embodiments, a composition herein comprises polypeptide 2 and one or more polypeptides from Table 2. In some embodiments, a composition herein comprises polypeptide 3 and one or more polypeptides from Table 2. In some embodiments, a

[illegible]

[illegible]

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[illegible]

[illegible]

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[00198] In some embodiments, a composition herein comprises polypeptide 201 and one or

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

comprises polypeptide 499 and one or more polypeptides from Table 2. In some embodiments, a composition herein comprises polypeptide 500 and one or more polypeptides from Table 2.

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

some embodiments, a composition herein comprises polypeptide 797 and one or more polypeptides from Table 2. In some embodiments, a composition herein comprises polypeptide 798 and one or more polypeptides from Table 2. In some embodiments, a composition herein comprises polypeptide 799 and one or more polypeptides from Table 2. In some embodiments, a composition herein comprises polypeptide 800 and one or more polypeptides from Table 2.

[illegible]

[illegible]

[illegible]

[00203] In some cases, the one or more polypeptides from Table 2 comprises IL-15. In some cases, the one or more polypeptides from Table 2 comprises THBS4. In some cases, the one or more polypeptides from Table 2 comprises POSTN. In some cases, the one or more polypeptides from Table 2 comprises THBS1. In some cases, the one or more polypeptides from Table 2 comprises THBS2. In some cases, the the one or more polypeptides from Table 2 comprises VTN. In some cases, the one or more polypeptides from Table 2 comprises FGF17. In some

cases, the one or more polypeptides from Table 2 comprises IGF2. In some cases, the one or more polypeptides from Table 2 comprises polypeptide 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664,

665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 810, 811, 812, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838, 839, 840, 841, 842, 843, 844, 845, 846, 847, 848, 849, 850, 851, 852, 853, 854, 855, 856, 857, 858, 859, 860, 861, 862, 863, 864, 865, 866, 867, 868, 869, 870, 871, 872, 873, 874, 875, or 876. In some cases, one or a plurality of the polypeptides of the composition are heparin-associated polypolypeptides. In some cases, one or a plurality of the polypeptides of the composition are mitogenic and/or fusion promoting polypolypeptides. In certain embodiments, one or more of the polypeptides of the composition comprise one or more additional modifications to increase stability. In certain embodiments, one or more of the polypeptides is covalently conjugated to polyethylene glycol, polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol, polysialic acid, glycolic acid, or polypropylene glycol. In certain embodiments, one or more of the polypeptides is fused or conjugated to another protein to increase stability and or bioavailability. In certain embodiments, one or more of the polypeptides is fused with an Fc region of an immunoglobulin or with serum albumin. In certain embodiments, one or more of the polypeptides is present in a concatemer with one, two, three, four or more distinct polypeptides selected from Table 2 and/or Table 1. In certain embodiments, one or more of the polypeptides is present in a concatemer with one, two, three, four, or more distinct polypeptides. In certain embodiments, one or more of the polypeptides is included in the composition with a biodegradable or bioabsorbable carrier that promotes polypeptide stability. In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA), polyglycolic acid (PGA), or Poly(D,L-lactic-coglycolic-acid) (PLGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polylactic acid (PLA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises polyglycolic acid (PGA). In certain embodiments, the biodegradable or bioabsorbable carrier comprises Poly(D,L-lactic-coglycolic-acid) (PLGA).

[00204] In certain embodiments, the heparin-associated polypeptides increase the mitogenic (e.g., proliferative capacity) of a somatic cell that is a tissue cell or a tissue precursor, such as: a muscle cell, a muscle precursor cell, a tenocyte, a tenocyte precursor cell, a chondrocyte, a

chondrocyte precursor, a mesenchymal stem cell, or a fibroblast. The cell can be a precursor cell derived from any mammal, such as, monkeys, apes, dogs, cats, horses, rats, mice, or humans. In certain embodiments, the precursor cell is a human precursor cell. In certain embodiments, the heparin-associated polypeptides increase the proliferative capacity of a mouse myoblast by at least about 1.5-fold, about 2-fold, about 3-fold, or about 4-fold as measured by BrdU or EdU incorporation.

Therapeutic Indications

[00205] In certain aspects, heparin-associated polypeptides and compositions comprising heparin-associated polypeptides, described herein, are useful for treating diseases and disorders that involve soft-tissue injury, degradation, or destruction. Aging disorders that result in the deterioration and loss of muscle tissue are such soft-tissue disorders. Sarcopenia, for example, is the degenerative loss of skeletal muscle mass quality, and strength associated with aging. Injuries that result in acute muscle damage are other such disorders. The disorders include muscle ruptures, strains, and contusions. A rupture is a separating of the muscle tissues. Muscle strains are contraction-induced injuries in which muscle fibers tear due to extensive mechanical stress, and can be classified as a grade I, II, or III. Muscle contusions are muscle hematomas. Muscle injury can also be caused by non-mechanical stresses such as cachexia. Cachexia may be caused by malnutrition, cancer, AIDS, coeliac disease, chronic obstructive pulmonary disease, multiple sclerosis, rheumatoid arthritis, congestive heart failure, tuberculosis, familial amyloid polyneuropathy, mercury poisoning (acrodynia), Crohn's disease, untreated/severe type 1 diabetes mellitus, anorexia nervosa, chemotherapy, muscular dystrophy or other genetic diseases which cause immobility, and hormonal deficiencies. Certain disorders that are weaknesses of specific muscles such as dysphagia or facioscapulohumeral muscular dystrophy may also be treated by the polypeptides described herein. Additional soft-tissues disorders that may be treated using the heparin-associated polypeptides described herein are those that inflict injury to the tendons, ligaments or cartilage. In certain embodiments, the muscle wasting disease is a muscular dystrophy. In certain embodiments, the muscular dystrophy comprises myotonic muscular dystrophy, Duchenne muscular dystrophy, Becker muscular dystrophy, Limb-girdle muscular dystrophy, facioscapulohumeral muscular dystrophy, congenital, muscular dystrophy, oculopharyngeal muscular dystrophy, or distal muscular dystrophy. In certain embodiments, the muscular dystrophy is Becker muscular dystrophy. In certain embodiments, the heparin-associated polypeptides useful for treating a soft-tissue disorder comprise any one, two, three, four, or five heparin-associated polypeptides selected from Vitronectin (VTN), Periostin (POSTN), Fibroblast growth factor (FGF17), Thrombospondin 2 (THBS2), Thrombospondin 4

(THBS4), Thrombospondin 1 (THBS1), Insulin-like growth factor 2 (IGF2), and Interleukin 15 (IL-15). In certain embodiments, the heparin-associated polypeptides useful for treating a soft-tissue disorder comprise any one, two, three, four, or five heparin-associated polypeptides selected from Vitronectin (VTN), Stanniocalcin-2 (STC2), Agrin (AGRN), Thrombospondin 2 (THBS2), follistatin (FST), Periostin (POSTN), Fibroblast growth factor (FGF17), Thrombospondin 4 (THBS4), Thrombospondin 1 (THBS1), Insulin-like growth factor 2 (IGF2), and Interleukin 15 (IL-15).

[00206] In certain embodiments, the heparin-associated polypeptides and compositions comprising heparin-associated polypeptides, described herein, are for use in treating an individual with an aging disorder, a muscle wasting disorder, a muscle injury, an injury to a connective tissue, or an injury to a non-muscle soft-tissue, or any combination thereof. In certain embodiments, the aging disorder is sarcopenia. In certain embodiments, the muscle wasting disorder is cachexia. In certain embodiments, the cachexia is a result of a cancer. In certain embodiments, the cachexia is a result of AIDS. In certain embodiments, the injury is a muscle injury. In certain embodiments, the muscle wasting is atrophy do to limb immobilization or disuse. In certain embodiments, the muscle injury is a strain or a tear. In certain embodiments, the muscle injury is a Grade III strain. In certain embodiments, sarcopenia contributes to the incidence of the muscle injury. In certain embodiments, the injury is ligament damage. In certain embodiments, the ligament damage is a rupture or a tear. In certain embodiments, the injury is tendon damage. In certain embodiments, the tendon damage is a rupture or a tear. In certain embodiments, the injury is cartilage damage. In certain embodiments, the heparin-associated polypeptides comprise any one, two, three, four, five or more heparin-associated polypeptides selected from Vitronectin (VTN), Periostin (POSTN), Fibroblast growth factor (FGF17), Thrombospondin 2 (THBS2), Thrombospondin 4 (THBS4), Thrombospondin 1 (THBS1), Insulin-like growth factor 2 (IGF2), and Interleukin 15 (IL-15). In certain embodiments, the heparin-associated polypeptides comprise any one, two, three, four, five or more heparin-associated polypeptides selected from Vitronectin (VTN), Stanniocalcin-2 (STC2), Agrin (AGRN), Thrombospondin 2 (THBS2), and follistatin (FST).

[00207] In certain embodiments, the heparin-associated polypeptides and compositions comprising heparin-associated polypeptides, described herein, are for use in a method of treating myositis. In certain embodiments, the myositis comprises dermatomyositis, polymyositis, necrotizing myopathy (also called necrotizing autoimmune myopathy or immune-mediated necrotizing myopathy), juvenile myositis, or sporadic inclusion-body myositis. In certain embodiments, the heparin-associated polypeptides comprise any one, two, three, four, five or more heparin-associated polypeptides selected from Vitronectin (VTN), Periostin (POSTN),

Fibroblast growth factor (FGF17), Thrombospondin 2 (THBS2), Thrombospondin 4 (THBS4), Thrombospondin 1 (THBS1), Insulin-like growth factor 2 (IGF2), and Interleukin 15 (IL-15). In certain embodiments, the heparin-associated polypeptides comprise any one, two, three, four, or five heparin-associated polypeptides selected from Vitronectin (VTN), Stanniocalcin-2 (STC2), Agrin (AGRN), Thrombospondin 2 (THBS2), and follistatin (FST).

[00208] In certain embodiments, the heparin-associated polypeptides and compositions comprising heparin-associated polypeptides, described herein, are for use in a method of increasing proliferation or promoting survival of a cell associated with soft-tissue damage. In certain embodiments, the heparin-associated polypeptides described herein are useful in a method of increasing proliferation or promoting survival of any one or more of a muscle cell, a muscle precursor cell, a tenocyte, a tenocyte precursor cell, a chondrocyte, a chondrocyte precursor cell, a mesenchymal stem cell, or a fibroblast. In certain embodiments, the heparin-associated polypeptides comprise any one, two, three, four, five or more heparin-associated polypeptides selected from Vitronectin (VTN), Periostin (POSTN), Fibroblast growth factor (FGF17), Thrombospondin 2 (THBS2), Thrombospondin 4 (THBS4), Thrombospondin 1 (THBS1), Insulin-like growth factor 2 (IGF2), and Interleukin 15 (IL-15). In certain embodiments, the heparin-associated polypeptides comprise any one, two, three, four, or five heparin-associated polypeptides selected from Vitronectin (VTN), Stanniocalcin-2 (STC2), Agrin (AGRN), Thrombospondin 2 (THBS2), and follistatin (FST).

[00209] The heparin-associated polypeptides compositions described herein can be administered separately or as a mixture of 2, 3, 4, 5, 6, 7, 8, 9, 10 or more heparin-binding or heparin-associated polypeptides for the treatment of any disorder associated with muscle or soft-tissue.

[00210] In certain aspects, a method of treating a disease or condition, such as those described herein, in a subject in need thereof comprises administering to the subject a composition comprising a polypeptide of Table 2. In some embodiments, the polypeptide of Table 2 is a polypeptide of Table 1. In some embodiments, the composition comprises a pharmaceutically acceptable excipient, such as described herein. In some embodiments, the disease or condition comprises an aging disorder, muscle wasting disorder, muscle injury, or injury to connective tissue, or a combination thereof. In some embodiments, the aging disorder comprises sarcopenia. In some embodiments, the muscle wasting disorder comprises muscular dystrophy. In some embodiments, the muscle wasting is a result of obesity. In certain embodiments, the muscle wasting is the result of a metabolic disorder. In some cases the metabolic disorder is diabetes. In some cases the diabetes is Type 2 Diabetes. In some embodiments, muscle wasting is a result of disease progression. In some embodiments, muscle wasting is a result of therapeutic treatment. In

some embodiments, the muscle wasting is cachexia. In some embodiments, the therapeutic polypeptide promotes fusion of myocytes.

[00211] In some embodiments, the polypeptide is a heparin-associated binding polypeptide as described herein. In some embodiments, the polypeptide is a mitogenic and/or fusion promoting polypeptide as described herein. In some embodiments, a composition comprising a plurality of heparin-associated binding polypeptides as described herein is administered. In some embodiments, a composition comprising a plurality of mitogenic and/or fusion promoting polypeptides as described herein is administered.

[00212] In some embodiments, the polypeptide has been recombinantly produced. In some embodiments, the polypeptide has been produced in a mammalian cell culture. In certain embodiments, the polypeptide has been produced in a mammalian cell and the mammalian cell is a human cell. In some cases the human cell is a human embryonic kidney-derived epithelial cell (e.g., HEK293 cells). In some embodiments, the mammalian cell culture is a mouse myeloma cell culture. In some embodiments, the mammalian cell culture is a Chinese Hamster Ovary (CHO) cell culture. In some embodiments, the polypeptide has been produced in a non-mammalian cell culture, e.g., in bacteria, yeast, or insect cells. In certain embodiments, the polypeptide has been purified from a human biological sample. In some cases, the human biological sample is human plasma. In some embodiments, the composition is formulated for administration by injection to the subject. In some embodiments, the composition comprises one or more polypeptides having at least about 90% homology to a sequence selected from SEQ ID NOS: 1-44, 55, 56, and 58-70. In some embodiments, the composition comprises polypeptide 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296,

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[00213] In some embodiments, the polypeptide comprises VTN. In some cases, the VTN comprises a polypeptide comprising at least about 90% homology or identity to SEQ ID NO: 1. In some cases, the VTN comprises a polypeptide comprising at least about 90% homology or identity to amino acids 20-478 of SEQ ID NO: 1. In some cases, the VTN is purified from human

plasma.

[00214] In some embodiments, the polypeptide comprises POSTN. In some cases, the POSTN comprises a polypeptide comprising at least about 90% homology or identity to SEQ ID NO: 6. In some cases, the POSTN comprises a polypeptide comprising at least about 90% homology or identity to amino acids 22-836 of SEQ ID NO: 6. In some cases, the POSTN is expressed in a mouse myeloma cell line.

[00215] In some embodiments, the polypeptide comprises FGF17. In some cases, the FGF17 comprises a polypeptide comprising at least about 90% homology or identity to SEQ ID NO: 7. In some cases, the FGF17 comprises a polypeptide comprising at least about 90% homology or identity to amino acids 23-216 of SEQ ID NO: 7. In some cases, the FGF17 is expressed in a bacterial cell. In some embodiments, the bacterial cell is *E. coli*.

[00216] In some embodiments, the polypeptide comprises THBS2. In some cases, the THBS2 comprises a polypeptide comprising at least about 90% homology or identity to SEQ ID NO: 4. In some cases, the THBS2 comprises a polypeptide comprising at least about 90% homology or identity to amino acids 19-1172 of SEQ ID NO: 4. In some cases, the THBS2 is expressed in a mouse myeloma cell line.

[00217] In some embodiments, the polypeptide comprises THBS4. In some cases, the THBS4 comprises a polypeptide comprising at least about 90% homology or identity to SEQ ID NO: 8. In some cases, the THBS4 comprises a polypeptide comprising at least about 90% homology or identity to amino acids 27-961 of SEQ ID NO: 8. In some cases, the THBS4 is expressed in Chinese hamster ovary cell.

[00218] In some embodiments, the polypeptide comprises IGF2. In some cases, the IGF2 comprises a polypeptide comprising at least about 90% homology or identity to SEQ ID NO: 11. In some cases, the IGF2 comprises a polypeptide comprising at least about 90% homology or identity to amino acids 25-91 of SEQ ID NO: 11. In some cases, the IGF2 is expressed in a bacterial cell. In some embodiments, the bacterial cell is *E. coli*.

[00219] In some embodiments, the polypeptide comprises IL-15. In some cases, the IL-15 comprises a polypeptide comprising at least about 90% homology or identity to SEQ ID NO: 10. In some cases, the IL-15 comprises a polypeptide comprising at least about 90% homology or identity to amino acids 49-162 of SEQ ID NO: 10. In some cases, the IL-15 is expressed in a bacterial cell. In some embodiments, the bacterial cell is *E. coli*.

[00220] In some embodiments, the polypeptide comprises THBS1. In some cases, the THBS1 comprises a polypeptide comprising at least about 90% homology or identity to SEQ ID NO: 9. In some cases, the THBS1 comprises a polypeptide comprising at least about 90% homology or identity to amino acids 19-1170 of SEQ ID NO: 9. In some cases, the THBS1 is expressed in a

mouse myeloma cell line.

[00221] In some embodiments, the polypeptide comprises IL-15, and the composition further comprises THBS2. In some embodiments, the polypeptide comprises IL-15, and the composition further comprises THBS4. In some embodiments, the polypeptide comprises THBS4, and the composition further comprises THBS2. In some embodiments, the polypeptide comprises IL-15, and the composition further comprises THBS2 and THBS4.

[00222] In some embodiments, the polypeptide comprises IGF2, and the composition further comprises THBS2. In some embodiments, the polypeptide comprises IGF2, and the composition further comprises THBS4. In some embodiments, the polypeptide comprises THBS4, and the composition further comprises THBS2. In some embodiments, the polypeptide comprises IGF2, and the composition further comprises THBS2 and THBS4.

Schedules routes of administration and amounts

[00223] In certain embodiments, the heparin-associated polypeptides can be administered by any suitable route such as, for example, subcutaneous, intravenous, or intramuscular. In certain embodiments, the heparin-associated polypeptides are administered on a suitable dosage schedule, for example, weekly, twice weekly, monthly, twice monthly, once every three weeks, or once every four weeks. The heparin-associated polypeptides can be administered in any therapeutically effective amount. In certain embodiments, the therapeutically acceptable amount is about 0.001 mg/kg to about 1 mg/kg. In certain embodiments, the therapeutically acceptable amount is about 0.001 mg/kg to about 0.002 mg/kg, about 0.001 mg/kg to about 0.005 mg/kg, about 0.001 mg/kg to about 0.01 mg/kg, about 0.001 mg/kg to about 0.02 mg/kg, about 0.001 mg/kg to about 0.05 mg/kg, about 0.001 mg/kg to about 0.1 mg/kg, about 0.001 mg/kg to about 0.2 mg/kg, about 0.001 mg/kg to about 0.5 mg/kg, about 0.001 mg/kg to about 1 mg/kg, about 0.002 mg/kg to about 0.005 mg/kg, about 0.002 mg/kg to about 0.01 mg/kg, about 0.002 mg/kg to about 0.02 mg/kg, about 0.002 mg/kg to about 0.05 mg/kg, about 0.002 mg/kg to about 0.1 mg/kg, about 0.002 mg/kg to about 0.2 mg/kg, about 0.002 mg/kg to about 0.5 mg/kg, about 0.002 mg/kg to about 1 mg/kg, about 0.005 mg/kg to about 0.01 mg/kg, about 0.005 mg/kg to about 0.02 mg/kg, about 0.005 mg/kg to about 0.05 mg/kg, about 0.005 mg/kg to about 0.1 mg/kg, about 0.005 mg/kg to about 0.2 mg/kg, about 0.005 mg/kg to about 0.5 mg/kg, about 0.005 mg/kg to about 1 mg/kg, about 0.01 mg/kg to about 0.02 mg/kg, about 0.01 mg/kg to about 0.05 mg/kg, about 0.01 mg/kg to about 0.1 mg/kg, about 0.01 mg/kg to about 0.2 mg/kg, about 0.01 mg/kg to about 0.5 mg/kg, about 0.01 mg/kg to about 1 mg/kg, about 0.02 mg/kg to about 0.05 mg/kg, about 0.02 mg/kg to about 0.1 mg/kg, about 0.02 mg/kg to about 0.2 mg/kg, about 0.02 mg/kg to about 0.5 mg/kg, about 0.02 mg/kg to about 1 mg/kg, about 0.05 mg/kg to about

0.1 mg/kg, about 0.05 mg/kg to about 0.2 mg/kg, about 0.05 mg/kg to about 0.5 mg/kg, about 0.05 mg/kg to about 1 mg/kg, about 0.1 mg/kg to about 0.2 mg/kg, about 0.1 mg/kg to about 0.5 mg/kg, about 0.1 mg/kg to about 1 mg/kg, about 0.2 mg/kg to about 0.5 mg/kg, about 0.2 mg/kg to about 1 mg/kg, or about 0.5 mg/kg to about 1 mg/kg. In certain embodiments, the therapeutically acceptable amount is about 0.001 mg/kg, about 0.002 mg/kg, about 0.005 mg/kg, about 0.01 mg/kg, about 0.02 mg/kg, about 0.05 mg/kg, about 0.1 mg/kg, about 0.2 mg/kg, about 0.5 mg/kg, or about 1 mg/kg. In certain embodiments, the therapeutically acceptable amount is at least about 0.001 mg/kg, about 0.002 mg/kg, about 0.005 mg/kg, about 0.01 mg/kg, about 0.02 mg/kg, about 0.05 mg/kg, about 0.1 mg/kg, about 0.2 mg/kg, or about 0.5 mg/kg. In certain embodiments, the therapeutically acceptable amount is at most about 0.002 mg/kg, about 0.005 mg/kg, about 0.01 mg/kg, about 0.02 mg/kg, about 0.05 mg/kg, about 0.1 mg/kg, about 0.2 mg/kg, about 0.5 mg/kg, or about 1 mg/kg. In certain embodiments, the therapeutically acceptable amount is about 0.1 mg/kg to about 50 mg/kg. In certain embodiments, the therapeutically acceptable amount is about 0.1 mg/kg to about 0.2 mg/kg, about 0.1 mg/kg to about 0.5 mg/kg, about 0.1 mg/kg to about 1 mg/kg, about 0.1 mg/kg to about 2 mg/kg, about 0.1 mg/kg to about 5 mg/kg, about 0.1 mg/kg to about 10 mg/kg, about 0.1 mg/kg to about 20 mg/kg, about 0.1 mg/kg to about 50 mg/kg, about 0.2 mg/kg to about 0.5 mg/kg, about 0.2 mg/kg to about 1 mg/kg, about 0.2 mg/kg to about 2 mg/kg, about 0.2 mg/kg to about 5 mg/kg, about 0.2 mg/kg to about 10 mg/kg, about 0.2 mg/kg to about 20 mg/kg, about 0.2 mg/kg to about 50 mg/kg, about 0.5 mg/kg to about 1 mg/kg, about 0.5 mg/kg to about 2 mg/kg, about 0.5 mg/kg to about 5 mg/kg, about 0.5 mg/kg to about 10 mg/kg, about 0.5 mg/kg to about 20 mg/kg, about 0.5 mg/kg to about 50 mg/kg, about 1 mg/kg to about 2 mg/kg, about 1 mg/kg to about 5 mg/kg, about 1 mg/kg to about 10 mg/kg, about 1 mg/kg to about 20 mg/kg, about 1 mg/kg to about 50 mg/kg, about 2 mg/kg to about 5 mg/kg, about 2 mg/kg to about 10 mg/kg, about 2 mg/kg to about 20 mg/kg, about 2 mg/kg to about 50 mg/kg, about 5 mg/kg to about 10 mg/kg, about 5 mg/kg to about 20 mg/kg, about 5 mg/kg to about 50 mg/kg, about 10 mg/kg to about 20 mg/kg, about 10 mg/kg to about 50 mg/kg, or about 20 mg/kg to about 50 mg/kg. In certain embodiments, the therapeutically acceptable amount is about 0.1 mg/kg, about 0.2 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 2 mg/kg, about 5 mg/kg, about 10 mg/kg, about 20 mg/kg, or about 50 mg/kg. In certain embodiments, the therapeutically acceptable amount is at least about 0.1 mg/kg, about 0.2 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 2 mg/kg, about 5 mg/kg, about 10 mg/kg, or about 20 mg/kg. In certain embodiments, the therapeutically acceptable amount is at most about 0.2 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 2 mg/kg, about 5 mg/kg, about 10 mg/kg, about 20 mg/kg, or about 50 mg/kg.

Nucleic Acids**Table 3.** Nucleic acid sequences.

Protein Name	Size (AA)	UniProtKB	Protein accession#	mRNA accession#	Gene ID	SEQ ID
FGF17	216	O60258.1	NP_003858.1	NM_003867.4	8822	45
THBS1	1170	P07996.2	NP_003237.2	NM_003246.4	7057	46
THBS2	1172	P35442.2	NP_003238.2	NM_003247.3	7058	47
THBS4	961	P35443.2	NP_003239.2	NM_003248.6	7060	48
IGF2	180	P01344.1	NP_000603.1	NM_000612.6	3481	49
IL15	162	P40933.1	NP_000576.1	NM_000585.5	3600	50
IGFBP7	282	Q16270.1	NP_001544.1	NM_001553.3	3490	51
VTN	478	P04004	NP_000629.3	NM_000638.4	7448	52
POSTN	836	Q15063.2	NP_006466.2	NM_006475.3	10631	53
PDGFRL	375	Q15198.1	NP_006198.1	NM_006207.2	5157	54
ANOS1	3730	P23352	NP_000207.2	NM_000216.4	3730	57

[00224] In certain embodiments, described herein, are nucleic acids that encode the heparin-associated polypeptides described herein. In certain embodiments, the nucleic acids are exogenous. In certain embodiments, the nucleic acid is a plasmid. In certain embodiments, the nucleic acid is a viral vector. In certain embodiments, the viral vector is an adenovirus, lentivirus, retrovirus, adeno-associated virus, or vaccinia virus. In certain embodiments, the nucleic acid comprises RNA. In certain embodiments, the nucleic acid encodes any of the polypeptides listed in Table 1 or Table 2, or VTN, STC2, AGRN, POSTN, FGF17, THBS2, FST, THBS1, IL-15, IGF2, or THBS4. In certain embodiments, the nucleic acid encodes any one or more polypeptide embodiments described herein. Nucleic acids according to this description can comprise additional nucleic acid sequences sufficient to propagate the vector or express a polypeptide encoded by the vector. In certain embodiments, the nucleic acid comprises a universal promoter, such as the CMV promoter, or an inducible promoter system such as a TET_{ON}, TET_{OFF} or GAL4. In certain embodiments, the nucleic acid is expressed via a tissue specific promoter or one compatible with a eukaryotic or prokaryotic cellular expression system. The nucleic acid can further comprise a sequence encoding a suitable purification tag (e.g., HIS-tag, V5, FLAG, MYC).

Production of heparin-associated or heparin-binding polypeptides

[00225] Once a polypeptide is determined as a heparin-associated or heparin-binding polypeptide it can be purified or synthesized in any suitable manner. A nucleic acid encoding the polypeptide can be cloned into a suitable vector and expressed in a suitable cellular system. In

certain embodiments, the cellular system is a prokaryotic cell system. In certain embodiments, the cellular system is a eukaryotic cell system. In certain embodiments, the cellular system is a mammalian cell system. The supernatants from such an expression system can be subjected to one or more purification steps involving centrifugation, ultracentrifugation, filtration, diafiltration, tangential-flow filtration, dialysis, chromatography (e.g., cation exchange, ion exchange, hydrophobic interaction, reverse phase, affinity, or size exclusion). The polypeptides can be purified to an extent suitable for human administration. Additionally, polypeptides can be synthesized for inclusion in a formulation to be administered to a human subject. In certain embodiments, the polypeptides can be produced by a suitable peptide synthesis method, such as solid-phase synthesis.

Master cell bank and transgenic cells

[00226] In a certain embodiment, described herein is a master cell bank comprising a cell that comprises a nucleic acid encoding one or more heparin-associated polypeptides integrated into its genome creating a transgenic cell-line. In some embodiments, the master cell bank comprises a plurality of cells that each comprise a nucleic acid encoding a heparin-associated polypeptide. In certain embodiments, the nucleic acid is maintained extrachromosomally on a plasmid or yeast artificial chromosome. In certain embodiments, the nucleic acid is integrated into a chromosomal location. In certain embodiments, the cell is a yeast cell. In certain embodiments, the yeast is *Pichia pastoris* or *Saccharomyces cerevisiae*. In certain embodiments, the cell is a mammalian cell. In certain embodiments, the mammalian cell is a 293T cell or derivative thereof (e.g., 293T-Rex). In certain embodiments, the cell is a bacterial cell.

[00227] In certain embodiments, the transgenic mammalian, yeast, or bacterial cell is a master cell bank that comprises a cryopreservative suitable for freezing to at least about -80° or below. In certain embodiments, the master cell bank comprises glycerol at between about 10 and about 30%, and is suitable for long-term storage at about -80° or below. In certain embodiments, the master cell bank can preserve a transgenic mammalian, yeast, or bacterial strain for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more years.

Pharmaceutically acceptable excipients, carriers, and diluents

[00228] The heparin-associated polypeptide(s) described herein can be administered in a pharmaceutical composition that comprises one or more pharmaceutically acceptable excipients, carriers, or diluents. The exact components can differ based upon the preferred route of administration. The excipients used in a pharmaceutical composition can provide additional function to the polypeptide by making the polypeptide suitable for a particular route of administration (e.g., intravenous, topical, subcutaneous, or intramuscular), increasing polypeptide stability, increasing penetration of a desired tissue (e.g., muscle or skin), increasing residence

time at particular site, increasing solubility, enhancing the efficacy of the polypeptide, and/or reducing inflammatory reactions coincident with administration.

[00229] In certain embodiments, the heparin-associated polypeptide(s) described herein are included in a pharmaceutical composition with a solubilizing emulsifying, or dispersing agent. In certain embodiments, the solubilizing agent can allow high-concentration solutions of heparin-associated polypeptides that exceed at least about 2 mg/mL, 5 mg/mL, 10 mg/mL, 15 mg/mL, or 20 mg/mL. Carbomers in an aqueous pharmaceutical composition serve as emulsifying agents and viscosity modifying agents. In certain embodiments, the pharmaceutically acceptable excipient comprises or consists of a carbomer. In certain embodiments, the carbomer comprises or consists of carbomer 910, carbomer 934, carbomer 934P, carbomer 940, carbomer 941, carbomer 1342, or combinations thereof. Cyclodextrins in an aqueous pharmaceutical composition serve as solubilizing and stabilizing agents. In certain embodiments, the pharmaceutically acceptable excipient comprises or consists of a cyclodextrin. In certain embodiments, the cyclodextrin comprises or consists of alpha cyclodextrin, beta cyclodextrin, gamma cyclodextrin, or combinations thereof. Lecithin in a pharmaceutical composition may serve as a solubilizing agent. In certain embodiments, the solubilizing agent comprises or consists of lecithin. Poloxamers in a pharmaceutical composition serve as emulsifying agents, solubilizing agents, and dispersing agents. In certain embodiments, the pharmaceutically acceptable excipient comprises or consists of a poloxamer. In certain embodiments, the poloxamer comprises or consists of poloxamer 124, poloxamer 188, poloxamer 237, poloxamer 338, poloxamer 407, or combinations thereof. Polyoxyethylene sorbitan fatty acid esters in a pharmaceutical composition serve as emulsifying agents, solubilizing agents, surfactants, and dispersing agents. In certain embodiments, the pharmaceutically acceptable excipient comprises or consists of a polyoxyethylene sorbitan fatty acid ester. In certain embodiments, the polyoxyethylene sorbitan fatty acid ester comprises or consists of polysorbate 20, polysorbate 21, polysorbate 40, polysorbate 60, polysorbate 61, polysorbate 65, polysorbate 80, polysorbate 81, polysorbate 85, polysorbate 120, or combinations thereof. Polyoxyethylene stearates in a pharmaceutical composition serve as emulsifying agents, solubilizing agents, surfactants, and dispersing agents. In certain embodiments, the pharmaceutically acceptable excipient comprises or consists of a polyoxyethylene stearate. In certain embodiments, the polyoxyethylene stearate comprises or consists of polyoxyl 2 stearate, polyoxyl 4 stearate, polyoxyl 6 stearate, polyoxyl 8 stearate, polyoxyl 12 stearate, polyoxyl 20 stearate, polyoxyl 30 stearate, polyoxyl 40 stearate, polyoxyl 50 stearate, polyoxyl 100 stearate, polyoxyl 150 stearate, polyoxyl 4 distearate, polyoxyl 8 distearate, polyoxyl 12 distearate, polyoxyl 32 distearate, polyoxyl 150 distearate, or

combinations thereof. Sorbitan esters in a pharmaceutical composition serve as emulsifying agents, solubilizing agents, and non-ionic surfactants, and dispersing agents. In certain embodiments, the pharmaceutically acceptable excipient comprises or consists of a sorbitan ester. In certain embodiments, the sorbitan ester comprises or consists of sorbitan laurate, sorbitan oleate, sorbitan palmitate, sorbitan stearate, sorbitan trioleate, sorbitan sesquioleate, or combinations thereof. In certain embodiments, solubility can be achieved with a protein carrier. In certain embodiments the protein carrier comprises recombinant human albumin.

[00230] In certain embodiments, the heparin-associated polypeptide(s) of the current disclosure are formulated to increase stability. Polypeptides in aqueous formulations may require stabilization to prevent degradation. In certain embodiments, the stabilizer comprises pH buffers, salts, amino acids, polyols/disaccharides/polysaccharides, liposomes, surfactants, antioxidants, reducing agents, or chelating agents. In certain embodiments, the stabilizer comprises or consists of a polyol/non-reducing sugar. In certain embodiments, the non-reducing sugar comprises or consists of sucrose, mannitol, trehalose, raffinose, stachyose, xylitol, starch, verbascose, or combinations thereof. Polypeptides can be encapsulated in liposomes to increase stability. In certain embodiments, the stabilizer comprises or consists of liposomes. In certain embodiments, the liposomes comprise or consists of ipalmitoylphosphatidylcholine (DPPC) liposomes, phosphatidylcholine:cholesterol (PC:Chol) (70:30) liposomes, or dipalmitoylphosphatidylcholine: dipalmitoylphosphatidylserine (DPPC:DPPS) liposomes (70:30). Non-ionic surfactants can increase the stability of a polypeptide. In certain embodiments, the stabilizer comprises or consists of a non-ionic surfactant. In certain embodiments, the non-ionic surfactant comprises or consists of polysorbates (e.g., poly sorbate 80, poly sorbate 20), alkylsaccharides alkyl ethers and alkyl glyceryl ethers, polyoxyethelene (4) lauryl ether; polyoxyethylene cetyl ethers, polyoxyethylene stearyl ethers, sorbitan fatty acid esters, polyoxyethylene fatty acid esters, or combinations thereof. In certain embodiments, the polypeptide is formulated with a protein surfactant, such as recombinant human serum albumin as a stabilizer. Antioxidants or reducing agents can increase the stability of a polypeptide. In certain embodiments, the stabilizer comprises or consists of an antioxidant or reducing agent. In certain embodiments, the reducing agent comprises or consists of dithiothreitol, ethylenediaminetetraacetic acid, 2-Mercaptoethanol, Tris(2-carboxyethyl)phosphine hydrochloride, Tris(hydroxypropyl)phosphine, or combinations thereof. In certain embodiments, the antioxidant comprises or consists of methionine, ascorbic acid, citric acid, alpha tocopherol, sodium bisulfite, ascorbyl palmitate, erythorbic acid, or combinations thereof. Chelating agents can stabilize polypeptides by reducing the activity of proteases. In certain embodiments, the stabilizer comprises or consists of a chelating agent. In certain embodiments, the chelating agent

comprises or consists of ethylenediaminetetraacetic acid (EDTA), ethylene glycol-bis(β -aminoethyl ether)-N,N,N',N'-tetraacetic acid (EGTA), metal complexes (e.g. Zn-protein complexes), or combinations thereof. Buffer agents can stabilize polypeptides by reducing the acid hydrolysis of polypeptides. In certain embodiments, the stabilizer comprises or consists of a buffer agent. In certain embodiments, the buffer agent comprises or consists sucrose octa-sulfate, ammonium carbonate, ammonium phosphate, boric acid, sodium citrate, potassium citrate, lactic acid, 3-(N-morpholino)propanesulfonic acid (MOPS), 2-(N-morpholino)ethanesulfonic acid (MES), hydroxymethylaminomethane (Tris), calcium carbonate, calcium phosphate or combinations thereof.

[00231] The heparin-associated polypeptide(s) also may be entrapped in or associated with microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization (for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively), in colloidal delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules), or in macroemulsions. Such techniques are disclosed in *Remington's Pharmaceutical Sciences*, 16th edition, Oslo, A., Ed., (1980).

[00232] The heparin-associated polypeptide(s) of the current disclosure may be formulated or delivered with an anti-inflammatory agent. In certain embodiments, the anti-inflammatory agent comprises or consists of a corticosteroid. In certain embodiments, the corticosteroid comprises or consists of hydrocortisone, cortisone, ethamethasoneb (Celestone), prednisone (Prednisone Intensol), prednisolone (Orapred, Prelone), triamcinolone (Aristospan Intra-Articular, Aristospan Intralesional, Kenalog), methylprednisolone (Medrol, Depo-Medrol, Solu-Medrol), or dexamethasone (Dexamethasone Intensol). In certain embodiments, the anti-inflammatory comprises or consists of a non-steroidal anti-inflammatory (NSAID). In certain embodiments, the NSAID comprises or consists of aspirin, celecoxib, diclofenac, diflunisal, etodolac, ibuprofen, indomethacin, ketoprofen, ketorolac, nabumetone, naproxen, oxaprozin, piroxicam, salsalate, sulindac, or tolmetin.

[00233] In certain embodiments, the heparin-associated polypeptide(s) of the current disclosure are included in a pharmaceutical composition suitable for intravenous administration comprising one or more pharmaceutically acceptable excipients, carriers, and diluents. In certain embodiments, the polypeptides of the current disclosure are administered suspended in a sterile solution. In certain embodiments, the solution is one commonly used for administration of biological formulations, and comprises, for example, about 0.9% NaCl or about 5% dextrose. In certain embodiments, the solution further comprises one or more of: buffers, for example, acetate, citrate, histidine, succinate, phosphate, potassium phosphate, bicarbonate and

hydroxymethylaminomethane (Tris); surfactants, for example, polysorbate 80 (Tween 80), polysorbate 20 (Tween 20), and poloxamer 188; polyol/disaccharide/polysaccharides, for example, glucose, dextrose, mannose, mannitol, sorbitol, sucrose, trehalose, and dextran 40; amino acids, for example, glycine, histidine, leucine, or arginine; antioxidants, for example, ascorbic acid, methionine; or chelating agents, for example, EDTA, or EGTA.

[00234] In certain embodiments, the heparin-associated polypeptide(s) of the current disclosure are included in a pharmaceutical composition suitable for intramuscular or subcutaneous administration comprising one or more pharmaceutically acceptable excipients, carriers, and diluents. Formulations suitable for intramuscular or subcutaneous injection can include physiologically acceptable sterile aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and non-aqueous carriers, diluents, solvents, or vehicles include ethanol, polyols (inositol, propyleneglycol, polyethylene-glycol, glycerol, cremophor and the like) and suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity is maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. Formulations suitable for subcutaneous injection also contain optional additives such as preserving, wetting, emulsifying, and dispensing agents.

[00235] In certain embodiments, the heparin-associated polypeptide(s) of the current disclosure are formulated for topical administration as a cream, gel, paste, ointment, or emulsion. Excipients in a cream, gel, paste, ointment, or emulsion can comprise gelatin, casein, lecithin, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecyl sulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, sugars, and starches.

[00236] The excipient used with the heparin-associated polypeptide(s) described herein will allow for storage, formulation, or administration of highly concentrated formulations. In certain embodiments, a highly concentrated heparin-associated polypeptide(s) comprises at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50 or more milligrams per milliliter.

[00237] In certain embodiments, the polypeptides of the current disclosure are shipped/stored lyophilized and reconstituted before administration. In certain embodiments, lyophilized heparin-

associated polypeptide formulations comprise a bulking agent such as, mannitol, sorbitol, sucrose, trehalose, and dextran 40. The lyophilized formulation can be contained in a vial comprised of glass. The heparin-associated polypeptides when formulated, whether reconstituted or not, can be buffered at a certain pH, generally less than 7.0. In certain embodiments, the pH can be between 4.5 and 6.5, 4.5 and 6.0, 4.5 and 5.5, 4.5 and 5.0, or 5.0 and 6.0.

Further Embodiments

[00238] 1. A composition comprising a mitogenic and/or fusion promoting polypeptide, wherein the polypeptide is a heparin-associated polypeptide secreted from a stem cell or a transformed cell line, wherein the heparin-associated polypeptide possesses mitogenic and/or fusion promoting activity. 2. The composition of embodiment 1, comprising a plurality of mitogenic and/or fusion promoting polypeptides. 3. The composition of embodiment 2, wherein the plurality comprises three, four, five, six, seven, eight, nine, ten or more mitogenic and/or fusion promoting polypeptides. 4. The composition of embodiment 1 to 3, wherein the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are isolated and purified. 5. The composition of embodiment 1 to 3, wherein the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are recombinantly produced. 6. The composition of embodiment 1 to 3, wherein the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are secreted from a stem cell. 7. The composition of embodiment 1 to 3, wherein the stem cell is a pluripotent stem cell. 8. The composition of embodiment 1 to 3, wherein the stem cell is an induced pluripotent stem cell. 9. The composition of embodiment 1 to 3, wherein the mitogenic activity comprises the ability to increase proliferation in a somatic cell or increase the ability of another heparin-associated polypeptide to increase proliferation in a somatic cell. 10. The composition of embodiment 1 to 3, wherein the fusion promoting activity comprises the ability to increase fusion of a plurality of somatic cells or increase the ability of another heparin-associated polypeptide to increase fusion in a plurality of somatic cells. 11. The composition of embodiment 10, wherein the somatic cell is a muscle, muscle progenitor cell, tenocyte, or tenocyte precursor. 12. The composition of embodiment 11, wherein the somatic cell is a mammalian cell. 13. The composition of embodiment 11, wherein the somatic cell is a human cell. 14. The composition of any one of embodiments 1 to 13, wherein any one of the mitogenic and/or fusion promoting polypeptides or plurality of mitogenic and/or fusion promoting polypeptides are produced in a heterologous cellular production system. 15. The composition of any one of embodiments 1 to 13, wherein any one of the mitogenic and/or fusion promoting polypeptides or plurality of mitogenic and/or fusion promoting polypeptides are synthetically produced. 16. The composition of any one of embodiments 1 to 15, wherein the mitogenic and/or

fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides comprise one or more modifications to improve activity, stability, or increase polypeptide yield from a heterologous cellular production system. 17. The composition of embodiment 16, wherein the modification is an alteration of one or more amino acids in the polypeptide sequence of the mitogenic and/or fusion promoting polypeptide compared to the wildtype polypeptide sequence of the mitogenic polypeptide. 18. A nucleic acid encoding at least one mitogenic and/or fusion promoting polypeptide of any one of embodiments 1 to 17. 19. A cell line comprising the nucleic acid of embodiment 18. 20. The cell line of embodiment 19, wherein the cell line is a eukaryotic cell line. 21. The composition comprising the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides of any one of embodiments 1 to 17, and a pharmaceutically acceptable excipient, carrier, or diluent. 22. The composition of any one of embodiments 1 to 17 or 21, formulated in injectable form. 23. Use of the composition of any one of embodiments 1 to 17, 21, or 22 in a method of treating an aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue. 24. The use of embodiment 23, wherein the aging disorder is sarcopenia. 25. The use of embodiment 23, wherein the muscle wasting disorder is a muscular dystrophy. 26. A method of treating an individual with aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue comprising administering to the individual the composition of any one of embodiments 1 to 17, 21, or 22. 27. The method of embodiment 26, wherein the muscle wasting disorder is sarcopenia. 28. The method of embodiment 26, wherein the aging disorder is a muscular dystrophy. 29. A method of producing a composition suitable for the treatment of an aging disorder comprising admixing a pharmaceutically acceptable excipient, carrier, or diluent with the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides of any one of embodiments 1 to 17. 30. A method of producing a mitogenic and/or fusion promoting polypeptide comprising culturing the cell line of embodiment 19 under conditions sufficient to produce the mitogenic and/or fusion promoting polypeptide.

[00239] 31. A composition comprising a mitogenic and/or fusion promoting polypeptide, wherein the mitogenic and/or fusion promoting polypeptide is identified by: a) identifying at least one polypeptide in a mixture of a plurality of polypeptides secreted from a stem cell or a transformed cell line that binds heparin; and b) determining the mitogenic and/or fusion promoting activity of the at least one polypeptide for a somatic cell, wherein the at least one polypeptide is identified as a mitogenic and/or fusion promoting polypeptide if the at least one polypeptide exhibits mitogenic and/or fusion promoting activity. 32. The composition of embodiment 31, wherein the composition comprises a mixture of a plurality of mitogenic and/or fusion promoting polypeptides. 33. The composition of embodiment 32, wherein the plurality of

mitogenic and/or fusion promoting polypeptides comprises three, four, five, six, seven, eight, nine, ten or more polypeptides. 34. The composition of any one of embodiments 31 to 33, wherein the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are isolated and purified. 35. The composition of any one of embodiments 31 to 33, wherein the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are recombinantly produced. 36. The composition of any one of embodiments 31 to 33, wherein the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are secreted from a stem cell. 37. The composition of any one of embodiments 31 to 33, wherein the stem cell is a pluripotent stem cell. 38. The composition of any one of embodiments 31 to 33, wherein the stem cell is an induced pluripotent stem cell. 39. The composition of any one of embodiments 31 to 33, wherein the mitogenic activity comprises the ability to increase proliferation in a somatic cell or increase the ability of another heparin -associated polypeptide to increase proliferation in a somatic cell. 40. The composition of any one of embodiments 31 to 33, wherein the fusion promoting activity comprises the ability to increase fusion of a plurality of somatic cells or increase the ability of another heparin-associated polypeptide to increase fusion in a plurality of somatic cells. 41. The composition of embodiment 40, wherein the somatic cell is a muscle, muscle progenitor cell, tenocyte, or tenocyte precursor. 42. The composition of embodiment 41, wherein the somatic cell is a mammalian cell. 43. The composition of embodiment 41, wherein the somatic cell is a human cell. 44. The composition of any one of embodiments 31 to 43, wherein any one of the mitogenic and/or fusion promoting polypeptides or plurality of mitogenic and/or fusion promoting polypeptides are produced in a heterologous cellular production system. 45. The composition of any one of embodiments 31 to 43, wherein any one of the mitogenic and/or fusion promoting polypeptides or plurality of mitogenic and/or fusion promoting polypeptides are synthetically produced. 46. The composition of any one of embodiments 31 to 43, wherein the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides comprise one or more modifications to improve activity, stability, or increase polypeptide yield from a heterologous cellular production system. 47. The composition of embodiment 46, wherein the modification is an alteration of one or more amino acids in the polypeptide sequence of the mitogenic and/or fusion promoting polypeptide compared to the wildtype polypeptide sequence of the mitogenic and/or fusion promoting polypeptide. 48. A nucleic acid encoding at least one mitogenic and/or fusion promoting polypeptide of any one of embodiments 31 to 47. 49. A cell line comprising the nucleic acid of embodiment 48. 50. The cell line of embodiment 49, wherein the cell line is a eukaryotic cell line. 51. The composition comprising the mitogenic and/or fusion promoting polypeptide or

plurality of mitogenic and/or fusion promoting polypeptides of any one of embodiments 31 to 47, and a pharmaceutically acceptable excipient, carrier, or diluent. 52. The composition of any one of embodiments 31 to 47 or 51, formulated in injectable form. 53. Use of the composition of any one of embodiments 31 to 47, 51, or 52 in a method of treating an aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue. 54. The use of embodiment 53, wherein the aging disorder is sarcopenia. 55. The use of embodiment 53, wherein the muscle wasting disorder is muscular dystrophy. 56. A method of treating an individual with an aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue comprising administering to the individual the composition of any one of embodiments 31 to 47, 51, or 52. 57. The method of embodiment 56, wherein the aging disorder is sarcopenia. 58. The method of embodiment 56, wherein the muscle wasting disorder is a muscular dystrophy. 59. A method of producing a composition suitable for the treatment of an aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue comprising admixing a pharmaceutically acceptable excipient, carrier, or diluent with the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides of any one of embodiments 31 to 47. 60. A method of producing a mitogenic and/or fusion promoting polypeptide comprising culturing the cell line of embodiment 59 under conditions sufficient to produce the mitogenic and/or fusion promoting polypeptide.

[00240] 61. A composition comprising a mitogenic and/or fusion promoting polypeptide, wherein the mitogenic and/or fusion promoting polypeptide comprises a protein listed in Table 2, and combinations thereof. 62. The composition of embodiment 61, wherein the mitogenic and/or fusion promoting polypeptide comprises VTN, POSTN, FGF17, THBS2, or THBS4. 63. The composition of embodiment 61, wherein the mitogenic and/or fusion promoting polypeptide comprises VTN. 64. The composition of embodiment 61, wherein the mitogenic and/or fusion promoting polypeptide comprises POSTN. 65. The composition of embodiment 61, wherein the mitogenic and/or fusion promoting polypeptide comprises FGF17. 66. The composition of embodiment 61, wherein the mitogenic and/or fusion promoting polypeptide comprises THBS2. 67. The composition of embodiment 61, wherein the mitogenic and/or fusion promoting polypeptide comprises THBS4. 68. The composition of any one of embodiments 61 to 67, wherein the composition comprises a mixture of a plurality of mitogenic and/or fusion promoting polypeptides. 69. The composition of embodiment 68, wherein the plurality of mitogenic and/or fusion promoting polypeptides comprises three, four, five, six, seven, eight, nine, ten or more mitogenic and/or fusion promoting polypeptides. 70. The composition of any one of embodiments 61 to 69, wherein the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are isolated and purified. 71. The composition of

any one of embodiments 61 to 69, wherein the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are recombinantly produced. 72. The composition of any one of embodiments 61 to 69, wherein the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are secreted from a stem cell. 73. The composition of any one of embodiments 61 to 69, wherein the stem cell is a pluripotent stem cell. 74. The composition of any one of embodiments 61 to 69, wherein the stem cell is an induced pluripotent stem cell. 75. The composition of any one of embodiments 61 to 69, wherein the mitogenic activity comprises the ability to increase proliferation in a somatic cell or increase the ability of another heparin -associated polypeptide to increase proliferation in a somatic cell. 76. The composition of any one of embodiments 61 to 69, wherein the fusion promoting activity comprises the ability to increase fusion of a plurality of somatic cells or increase the ability of another heparin -associated polypeptide to increase fusion in a plurality of somatic cells. 77. The composition of embodiment 76, wherein the somatic cell is a muscle, muscle progenitor cell, tenocyte, or tenocyte precursor. 78. The composition of embodiment 77, wherein the somatic cell is a mammalian cell. 79. The composition of embodiment 77, wherein the somatic cell is a human cell. 80. The composition of any one of embodiments 61 to 79, wherein any one of the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are produced in a heterologous cellular production system. 81. The composition of any one of embodiments 61 to 79, wherein any one of the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are synthetically produced. 82. The composition of any one of embodiments 61 to 79, wherein the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides comprise one or more modifications to improve activity, stability, or increase polypeptide yield from a heterologous cellular production system. 83. The composition of embodiment 82, wherein the modification is an alteration of one or more amino acids in the polypeptide sequence of the mitogenic and/or fusion promoting polypeptide compared to the wildtype polypeptide sequence of the mitogenic and/or fusion promoting polypeptide. 84. A nucleic acid encoding at least one mitogenic and/or fusion promoting polypeptide of any one of embodiments 61 to 83. 85. A cell line comprising the nucleic acid of embodiment 84. 86. The cell line of embodiment 85, wherein the cell line is a eukaryotic cell line. 87. The composition comprising the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides of any one of embodiments 61 to 83, and a pharmaceutically acceptable excipient, carrier, or diluent. 88. The composition of any one of embodiments 61 to 83, formulated in injectable form. 89. Use of the composition of any one of embodiments 61 to 83 in a method of treating an aging disorder, a muscle wasting disorder, a

muscle injury, or an injury to a connective tissue. 90. The use of embodiment 89, wherein the aging disorder is sarcopenia. 91. The use of embodiment 89, wherein the muscle wasting disorder is muscular dystrophy. 92. A method of treating an individual with an aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue comprising administering to the individual the composition of any one of embodiments 61 to 83. 93. The method of embodiment 92, wherein the aging disorder is sarcopenia. 94. The method of embodiment 92, wherein the muscle wasting disorder is a muscular dystrophy. 95. A method of producing a composition suitable for the treatment of an aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue comprising admixing a pharmaceutically acceptable excipient, carrier, or diluent with the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides of any one of embodiments 61 to 83. 96. A method of producing a mitogenic and/or fusion promoting polypeptide comprising culturing the cell line of embodiment 95 under conditions sufficient to produce the mitogenic and/or fusion promoting polypeptide.

[00241] 97. A composition comprising a mitogenic and/or fusion promoting polypeptide, wherein the mitogenic and/or fusion promoting polypeptide comprises VTN, POSTN, FGF17, THBS2, or THBS4. 98. The composition of embodiment 97, wherein the mitogenic and/or fusion promoting polypeptide comprises VTN. 99. The composition of embodiment 97, wherein the mitogenic and/or fusion promoting polypeptide comprises POSTN. 100. The composition of embodiment 97, wherein the mitogenic and/or fusion promoting polypeptide comprises FGF17. 101. The composition of embodiment 97, wherein the mitogenic and/or fusion promoting polypeptide comprises THBS2. 102. The composition of embodiment 97, wherein the mitogenic and/or fusion promoting polypeptide comprises THBS4. 103. The composition of any one of embodiments 97 to 102, wherein the composition comprises a mixture of a plurality of different mitogenic and/or fusion promoting polypeptides. 104. The composition of embodiment 103, wherein the plurality of different mitogenic and/or fusion promoting polypeptides comprise three, four, or five different mitogenic and/or fusion promoting polypeptides. 105. The composition of any one of embodiments 97 to 104, wherein the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are isolated and purified. 106. The composition of any one of embodiments 97 to 105, wherein the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are recombinantly or synthetically produced. 107. The composition of any one of embodiments 97 to 105, wherein the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are secreted from a stem cell. 108. The composition embodiment 107, wherein the stem cell is a pluripotent stem cell. 109. The composition of embodiment 108,

wherein the stem cell is an induced pluripotent stem cell. 110. The composition of any one of embodiments 97 to 109, wherein the mitogenic activity comprises the ability to increase proliferation in a somatic cell or increase the ability of another heparin-associated polypeptide to increase proliferation in a somatic cell. 111. The composition of any one of embodiments 97 to 109, wherein the fusion promoting activity comprises the ability to increase fusion of a plurality of somatic cells or increase the ability of another heparin-associated polypeptide to increase fusion in a plurality of somatic cells. 112. The composition of embodiment 111, wherein the muscle cell precursor is a myoblast. 113. The composition of embodiment 112, wherein the somatic cell is a mammalian cell. 114. The composition of embodiment 112, wherein the somatic cell is a human cell. 115. The composition of any one of embodiments 97 to 114, wherein the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides comprise one or more modifications to improve activity, stability, or increase polypeptide yield from a heterologous cellular production system. 116. The composition of embodiment 115, wherein the modification is an alteration of one or more amino acids in the polypeptide sequence of the mitogenic and/or fusion promoting polypeptide compared to the wildtype polypeptide sequence of the mitogenic and/or fusion promoting polypeptide. 117. The composition of embodiment 115, wherein the modification is a fusion of a mitogenic and/or fusion promoting polypeptide to a non-mitogenic and/or fusion promoting polypeptide. 118. The composition of embodiment 117, wherein the non-mitogenic and/or fusion promoting polypeptide comprises an immunoglobulin Fc region or serum albumin. 119. The composition of embodiment 117 or 108, wherein the non-mitogenic or fusion promoting polypeptide is a human polypeptide. 120. The composition of any one of embodiments 97 to 114, wherein the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides are concatemerized. 121. The composition of embodiment 120, wherein the concatemerized polypeptides are separated by a polypeptide linker. 122. The composition of embodiment 120 or 121, wherein the concatemerized polypeptides are the same polypeptide. 123. The composition of embodiment 120 or 121, wherein the concatemerized polypeptides are different polypeptides. 124. The composition of embodiment 120 or 123, wherein the concatemerized polypeptides are covalently concatemerized through a non-peptide linkage. 125. The composition of embodiment 120 or 123, wherein the concatemerized polypeptides are non-covalently concatemerized. 126. A nucleic acid encoding a mitogenic and/or fusion promoting polypeptide of any one of embodiments 97 to 125. 127. A cell line comprising the nucleic acid of embodiment 126. 128. The cell line of embodiment 127, wherein the cell line is a eukaryotic cell line. 129. The composition comprising the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides of any one of embodiments 97 to

125, and a pharmaceutically acceptable excipient, carrier, or diluent. 130. The composition comprising the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides of embodiment 129, wherein the pharmaceutically acceptable excipient, carrier, or diluent increases the function of the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides. 131. The composition comprising the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides of embodiment 130, wherein the function comprises increasing proliferation in a muscle cell precursor, increasing stability of the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides, or increasing bioavailability of the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides. 132. The composition of any one of embodiments 97 to 131, formulated for subcutaneous, intravenous, intramuscular, or topical administration. 133. Use of the composition of any one of embodiments 97 to 132, in a method of treating an aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue. 134. The use of embodiment 133, wherein the aging disorder is sarcopenia. 135. The use of embodiment 133, wherein the muscle wasting disorder is a muscular dystrophy. 136. A method of treating an individual with an aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue comprising administering to the individual the composition of any one of embodiments 97 to 132. 137. A method of increasing proliferation of a muscle cell precursor or connective tissue cell precursor in an individual comprising administering to the individual the composition of any one of embodiments 97 to 132. 138. The method of embodiment 137, wherein the individual is afflicted with or suspected of being afflicted with an aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue. 139. The method of embodiment 138, wherein the aging disorder is sarcopenia. 140. The method of embodiment 138, wherein the muscle wasting disorder is a muscular dystrophy. 141. A method of producing a composition suitable for the treatment of an aging disorder, a muscle wasting disorder, a muscle injury, or an injury to a connective tissue comprising admixing a pharmaceutically acceptable excipient, carrier, or diluent with the mitogenic and/or fusion promoting polypeptide or plurality of mitogenic and/or fusion promoting polypeptides of any one of embodiments 97 to 125. 142. A method of producing a mitogenic and/or fusion promoting polypeptide comprising culturing the cell line of embodiment 127, under conditions sufficient to produce the mitogenic and/or fusion promoting polypeptide.

EXAMPLES

[00242] The following illustrative examples are representative of embodiments of the compositions and methods described herein and are not meant to be limiting in any way.

Example 1 – Isolation of heparin-associated polypeptides

[00243] hESC secretome collection (differentiated vs undifferentiated): Human embryonic or induced pluripotent stem cells (H1, H9, H7 lines, and 2 iPSC lines derived from 1 healthy young adult female (18-25 years) and 1 aged female (greater than 65 year) donor), were cultured in triplicate on 10 cm plates on diluted Matrigel (1:30), in mTeSR-1 (Stem Cell Technologies), for a total media volume of 10 mL per plate. Another triplicate set of hPSCs/iPSCs were cultured on 10 cm plates and differentiated after plating in mTeSR-1 by changing the medium to DMEM/F12 with 10% Bovine Growth Serum (Hyclone), and culturing for an additional 7 days. hPSCs/iPSCs and differentiated hPSCs/iPSCs (6 plates in total) were washed twice with Opti-MEM (Gibco) and then cultured in Opti-MEM for 16 hours. 10ml media was then collected per plate as hPSCs/iPSCs -secretome or differentiated hPSCs/iPSCs -secretome containing media. Media was spun for 5 min at 1000g and transferred to new tubes to remove cell debris, aliquoted and flash frozen at 2 mL per plate as 0.5 mL aliquots and stored at -80C; remaining 8 mL/ plate was used immediately for heparin-associated protein purification.

Heparin-associated protein purification

[00244] 10 mL of Heparin-Agarose Type I Beads (H 6508, Sigma Aldrich) was washed with molecular grade water and preconditioned in 1 mL OptiMEM as recommended by manufacturer. 8-9ml secretome containing media was incubated with 1 ml Heparin-Agarose Beads for 2 hours shaking at 4°C to allow binding. Remaining heparin-depleted hPSCs/iPSCs -conditioned medium or differentiated hPSCs/iPSCs -conditioned medium was aliquoted in 15 mL tubes, flash frozen and stored at -80C to serve as negative controls for efficacy testing. Protein bound heparin beads were washed twice via a 10 minute incubation at 4°C in 1 mL sterile PBS + 0.05% Tween. Proteins were eluted twice for 15 minutes at 4°C in 400µl of elution buffer A (Eluted-A) (0.01M HEPES pH 7.5 +1.5M NaCl + 0.1%BSA) per 10 cm plate for the first two plates, or elution buffer B (Eluted-B) lacking BSA (0.01M HEPES pH 7.5 +1.5M NaCl)** for the 3rd 10 cm plate, to collect proteins in a total of 800µl of elute per original plate. The proteins were desalted by diffusion dialysis (3500 MWCO) (by a 2 hour dialysis shaking at 4C in 500ml McCoy's 5A Medium or similar tissue culture medium (Gibco) followed by overnight (not more than 16 hours) dialysis shaking at 4C in 200 ml OptiMEM (Gibco). The collected eluate was aliquoted in appropriately capped tubes, flash frozen and stored at -80C.

Secretome heparin-associated fraction validation assays:

[00245] BCA assay (Pierce) was performed for total protein yield in the eluate using 2ul per sample in triplicate according to manufacturer's instructions from each Elution A sample and Elution B.

[00246] SDS-PAGE Silver Stain/SDS-PAGE Coomassie was performed for protein integrity and rough MW analysis (loading <5-10ug per lane for each sample).

Mouse myoblast proliferation assay

[00247] Reduced regeneration from an individual's tissue progenitor cells is a hallmark of aging, therefore assays that measure mitogenic capacity in tissue progenitor cells serve as a read-out for potential success of any given heparin-associated polypeptide as a regenerative factor. Measuring the increased proliferation rate of treated mouse or human muscle progenitor cells will provide good basis for potentially therapeutic regenerative factors for treating individuals who have suffered illness, injury, or who possess genetic or developmental defects leading to premature tissue loss, wasting, or weakening. As a control, the assay will also be performed on proteins purified from differentiated cells, which result in no in myoblast proliferation, cultured in medium conditioned by differentiated cells, or purified heparin-associated fractions.

[00248] Mouse muscle progenitor cells (early passage myoblasts) were cultured and expanded in mouse growth medium: Ham's F-10 (Gibco), 20% Bovine Growth Serum (Hyclone), 5 ng/mL FGF2 and 1% penicillin-streptomycin on Matrigel coated plates (1:300 matrigel: PBS), at 37°C and 5% CO₂. For experimental conditions, cells were plated at 40,000 cells/well on Matrigel coated 8-well chamber slides in 250-500 uL medium per well (1:100 matrigel: PBS) in mouse fusion medium: DMEM (Gibco) + 2% horse serum (Hyclone). One hour after plating, mouse myoblasts were treated with 50% respective medias:

Table 4. 8-well Chamber Slide A: Eluted Heparin-associated Proteins from H9/H7 hPSCs and 2 iPSC lines - 4 slides total, 1 for each cell line tested.

Fusion Media (FM) (250 uL)	50% FM/ 50% Eluted-A Heparin-associated proteins	50% FM/ 50% Differentiated hPSC-conditioned OptiMem	50% FM/ 50% Differentiated hPSC-conditioned OptiMem
50% FM (125 uL) / 50% Growth Media (125 uL)	50% FM/ 50% hPSC-conditioned OptiMEM	50% FM/ 50% Heparin-depleted hESC-conditioned OptiMEM	50% FM/ 50% Eluted-B Heparin-associated proteins (no BSA)

Table 5. Assay for Eluted heparin-associated proteins purified from Differentiated hPSSs/iPSCs (Control). 50% FM/ 50% OptiMEM	50% FM/ 50% Eluted-A Heparin-associated proteins	50% FM/ 50% Differentiated hPSC-conditioned OptiMem	50% FM/ 50% Eluted-B Heparin-associated proteins (no BSA)
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Table 6. 8-well Chamber Slide B: Eluted Heparin-associated Protein Serial Dilution.

Fusion Media (FM) (250 uL)	50% FM/ 50% Eluted-A Heparin-associated protein	75% FM/ 25% Eluted-A Heparin-associated protein	75% FM/ 12.5% Eluted-A Heparin-associated protein
81.25% FM/ 6.25% Eluted-A Heparin-associated protein	84.375% FM/ 3.125% Eluted-A Heparin-associated protein	98.44% FM/ 1.56% Eluted-A Heparin-associated protein	75% FM/ 25% hPSC-conditioned OptiMEM

Mouse Myoblasts were cultured for 24 hours in the above conditions, at 37°C in 10% CO₂ incubator. BrdU (300µM) in DMSO was added for 2 hours prior to fixation with cold 70% ethanol and stored at 4°C until staining.

Quantifying Regenerative Index

[00249] Following permeabilization in PBS + 0.25% Triton X-100, antigen retrieval was performed via a 10 minute 4 N HCl treatment followed by PBS washes. Primary staining was performed overnight at 4°C in PBS +2%FBS. Primary antibodies include: a species-specific monoclonal antibody for mouse anti-embryonic Myosin Heavy Chain (eMyHC, hybridoma clone 1.652, Developmental Studies Hybridoma Bank) and Rat-anti-BrdU (Abcam Inc. ab6326). Secondary staining with fluorophore-conjugated, species-specific antibodies (Donkey anti-Rat-488, #712-485-150; Donkey anti-Mouse-488, #715-485-150; all secondary antibodies from Jackson ImmunoResearch) was performed for 1 hour at room temperature at a 1:500 dilution in PBS +2%FBS. Nuclei are visualized by Hoechst staining. For cell quantification, 5 images per well were collected at 20x in each of the channels as well as DIC to achieve at least 2000 imaged cells per condition. Using the Hoechst stain to tally cell number, the percent of cells positive for BrdU and eMyHC were tabulated and reported.

[00250] Human muscle progenitor cells (myoblasts) were similarly activated to proliferate when conditioned with hPSC-secreted heparin-associated proteins. Proliferation assays were performed on human myoblasts to test protein candidate factors for enhanced precursor cell activity in an *in vitro* screening assay. Conditions for culturing human muscle cells were optimized to reflect the slower rate of growth and differentiation of human muscle cells, where

early passage human myoblasts were cultured for 72 hours with daily medium changes rather 24 hours, and pulsed for 4 hours with BrdU instead of 2 hours.

Example 2-Characterization of the protein components of the heparin bead binding hPSC secretomes

Protein Quantification

[00251] The protein concentration in the eluted sample was determined using the bicinchoninic acid (BCA) protein assay (Thermo Fisher Scientific, Waltham, MA). The protocol was performed as follows: A volume containing 100ug protein was extracted and disulfide bonds were reduced with 5 mM tris-(2-carboxyethyl)-phosphine (TCEP), at room temperature for 25 min, and alkylated with 10 mM iodoacetamide at room temperature for 30 min in the dark). Excess iodoacetamide was quenched with 15 mM dithiothreitol (room temperature, 15 min in the dark). At this point the sample were split, with 20 µg analyzed immediately via SDS-PAGE Silver Stain, 20 µg saved for SDS-PAGE Coomassie stained gel band analysis, and 60ug proceeded to in-solution mass spectrometry sample preparation.

Quantify the size distribution of proteins

[00252] Silver staining provides a sensitive, rapid, low cost way to survey the complexity and general molecular weight distribution of the proteins in a complex mixture. By running a matched sample treated to remove glycans, the presence of this PTM common secreted proteins can be determined by the resulting shift in apparent molecular weight. Additional rounds of selective glycosylation reactions can then be run to gain insight into the identity and structure of glycan modifications on proteins of interest. Five micrograms of sample can be removed and treated with Protein Deglycosylation Mix II (NEB) to remove all N-linked and simple O-linked glycans as well as some complex O-linked glycans, which can be visualized by molecular weight shifts relative to an untreated control on a silver stained SDS-PAGE gel.

[00253] A 4-12% acrylamide gel (BioRad) in 1x MOPS buffer was loaded gel with samples (>0.20ug/lane) and ladder (as per manufacturer's instructions), run at 200V for 45 minutes or until sample front neared the bottom of the gel, and incubated in 50% methanol/50% LC grade water > 1 hour. Stain solution was prepared adding a solution of 0.8g AgNO₃ in 4mL LC grade H₂O dropwise into a solution of 1mL 0.36% NaOH + 1.4mL 14.8M ammonium hydroxide under constant stirring followed by the addition of LC grade water to a final volume of 100mL. Gel staining proceeded by incubating gel in stain solution for 15 minutes, before washing twice with LC grade water, allowing 5-8 minutes of incubation per wash step. The silver stain was developed by incubation in a solution of 0.25mL 1% citric acid + 25uL 37% formaldehyde in 50mL LC grade water for 10-15 minutes in the dark (or until desired density was achieved).

Developer solution was removed and the gel washed with LC grade water to slow development for an imaging series, or development was stopped by incubation in a solution of 45% methanol, 10% acetic acid.

In-solution mass spectrometry sample preparation

[00254] Methanol-chloroform precipitation was performed prior to protease digestion (a standard trichloroacetic acid-based precipitation protocol would be substituted here if protein yield from the heparin bead eluates are below 25ug total). In brief, four parts neat methanol was added to each sample and vortexed, one part chloroform was added to the sample and vortexed, and three parts water was added to the sample and vortexed. The sample was centrifuged at 4,000 RPM for 15 min at room temperature and subsequently washed twice with 100% methanol, prior to air-drying. Samples were resuspended in 50 mM HEPES pH 8.5 and digested at room temperature for 12 hrs with LysC protease at a 100:1 protein-to-protease ratio. Trypsin was then added at a 100:1 protein-to-protease ratio and the reaction was incubated 6 hours at 37° C. Peptide concentrations in the digests were measured using the Quantitative Colorimetric Peptide assay kit (Pierce). From each sample 10ug of peptide digestion solution was taken and enzymatic activity quenched with formic acid to a final pH of <2 before de-salting via C-18 Stagetips, using a standard formic acid/acetonitrile buffer system. Stagetips were eluted directly into autosampler vials in a buffer of 70% acetonitrile and 1% formic acid, dried in a vacuum concentrator, and stored at -80C until being resuspended to ~1ug/μl of Buffer A (typically ~0.2% formic acid, 5% acetonitrile) for mass spectrometry analysis.

SDS-PAGE Coomassie and in-gel band mass spectrometry sample preparation

[00255] A gel based sample preparation pipeline may be employed if the abundance distribution of the sample is heavily skewed, or where only a few species of proteins account for a substantial majority of the molecules in the sample. This size based separation method has been shown to effectively improve depth of proteomic coverage in biochemically purified protein mixtures.

[00256] Briefly, the protocol begins by running >20ug per lane of sample out on an SDS-PAGE as in the Silver Stain method above, staining and destaining by Coomassie as per manufacturer's instructions, excising sections of the gel containing potentially interesting proteins, and cutting excised gel sections into 1mm x 1mm squares. Ensure gel pieces are at neutral pH by adding 50-100 μl 100mM Ammonium bicarbonate, let sit for 10 minutes and discard. Wash gel pieces with 100-150 μl 50mM Ammonium bicarbonate/ 50% acetonitrile for 10 minutes, vortexing every 5 minutes to dehydrate. Depending on intensity of stain, repeat step 9 until the gel pieces are clear. Discard solution phase and dry samples in speed vac for 5-10 minutes. To digest proteins add 5 pmol sequencing grade trypsin (Promega Corp.) in 50mM Ammonium

bicarbonate and 0.02% Protease Max to each sample and incubate overnight in 37°C on a shaking heatblock. Spin down samples at 1000G for 2 minutes, pull off all liquid, and transfer to a glass autosampler vial. Add 40-50 µl 1% formic acid, 66% acetonitrile 33% 100mM Ammonium bicarbonate and incubate for 10 minutes at 37° C to increase peptide release from gel. Spin at 10,000G for 2 minutes to pellet insoluble protein or detergent degradation production. Extract all solution being sure to avoid pellet areas and combine into autosampler vial. Speed vac total combined extracts to dryness and store at -80C until being resuspended to ~1ug/µl of Buffer A (typically ~0.2% formic acid, 5% acetonitrile) for mass spectrometry analysis.

nHPLC-MS2 Instrumentation and Analysis

[00257] Two, 3-hr gradients were collected per sample using an Orbitrap Fusion instrument coupled to a Waters liquid chromatography (LC) pump (Thermo Fisher Scientific). Peptides are fractionated on a 100 µm inner diameter microcapillary column packed with ~25 cm of Accucore 150 resin (1.2 µm, 150 Å, ThermoFisher Scientific). For each analysis, 1 µg per sample was loaded onto the column. Peptides were separated using a 3 hr gradient of 6 to 46% acetonitrile in 0.2% formic acid at a flow rate of ~400 nL/min. Instrument settings for the Orbitrap fusion were as follows: FTMS1 resolution (120,000), ITMS2 isolation window (0.4 m/z), ITMS2 max ion time (120 ms), ITMS2 AGC (2E4), ITMS2 CID energy (35%), dynamic exclusion window (90 sec). A TOP10 method was used where each FTMS1 scan was used to select up to 10 FTMS2 precursors for interrogation by HCD-MS2 with readout in the orbitrap.

Data analysis

[00258] Resulting mass spectra were searched using commercially available analysis software (e.g., Byonic) against a human database publicly available from Uniprot which was concatenated with common contaminants and reversed sequences of the human and contaminant proteins as decoys for FDR determination. Searches restricted the precursor ion tolerance to 20 ppm, and product ion tolerance window was set to 0.5 m/z. Searches allowed up to two missed cleavages, including static carbamidomethylation of cysteine residues (+57.021 Da) and variable oxidation of methionine residues (+15.995 Da). Additional variable modifications may be included, particularly glycosylations, based on the results of the gel shift assay following de-glycosylation treatment or the preview search PTM scan. Results were filtered to a 1% FDR at the protein level per sample.

Example 3- In Vitro Screening of stem cell secreted factors

[00259] A deeper understanding of a given protein factor's contribution to the regenerative effects of the pool of heparin-associated hPSC secretome will be gained by screening against an established panel of assays for cellular age. Assays include measurements of reactive oxygen

species (ROS) production or tolerance, cytoplasmically and in the mitochondria, telomerase activity, measurements of proteostasis capacity via lysosomal, autophagy, and proteasomal routes, epigenetic re-patterning, and cellular energy balance (e.g., ATP/ADP and NAD/NADH ratios). Many of these assay leverage the high-throughput automated microscopy described above to make these measurements in a variety of cell types, including fibroblast, endothelial cells, mesenchymal stem cells, and chondrocytes. Collectively these metrics can inform both the pathway and the mechanisms by which the heparin-associated hPSC secretome or its individual components enact their regenerative effects.

[00260] To begin screening and validating potential regenerative protein factors protein coding sequences will be collected from a publicly available source, such as used for the proteomics analysis (e.g., UniProt). The sequence for each of the proteins will be used to construct a DNA sequence encoding the proteins. The sequences are then each cloned into a plasmid vector system tailored for inducible or constitutive high-copy expression (in mammalian or prokaryotic settings). Alternatively such a plasmid vector system may be designed *in silico*. Such a plasmid can be transformed into a pool of cells where the encoded protein was transiently expressed from the plasmid. Alternatively the gene of interest could be incorporated in the genomes of a pool of cells (e.g. lentiviral transduction for mammalian cells or homologous recombination for *S. cerevisiae*) to create stable cell lines for recombinant protein production.

[00261] To de-bulk the target factor list and validate recombinant expression for factor production, a viable route would be to express the construct in a human cell line (like 293T-REx), which exploits: 1) that proteins of interest naturally purify themselves during the secretion process; and 2) will be processed in a natural context, potentially preserving important post translational processing steps. T-REx cells will be grown on 10 cm plates to ~50% confluence in DMEM with 10% Bovine Growth Serum (Hyclone), 2 mM L-glutamine, and 1% Pen-Strep before initiating translation of a target protein of interest for 48hr. The media would be collected, spun at 2,000g to purify, and the supernatant used for heparin-associated enrichment of target factors in mouse myoblast regeneration assays.

Machine learning classifier

[00262] By combining and statistically comparing the information from the Regenerative index assay, the Panel of Cellular Age Makers, the Proteomics we can create deep feature vectors for each protein factor, the pool of all factors (from each repeat of the assays), and the negative control pool (from each repeat of the assays). Treating the pool of all factors (or known factors such as FGF-2) as True Positives, and the negative control pool (or known non-functional proteins such as BSA) as True Negatives a supervised clustering algorithm can be trained to classify protein factors. Using a standard 10-fold cross validation scheme to assess the relative

accuracy, recall, and confusion matrix graphs of the output of various algorithms' outputs (eg, Naive Bayes, Support Vector Machine, Linear Regression, or Random Forest) trained classifier most likely to successfully distinguish proteins with regenerative potential from the set of target factors can be selected. Target factors (or tested combinations) can then be rank ordered by the probability they derive from the regenerative set compared to the null set. A number of the top scoring target factors (or tested combinations) will then be selected for GMP-grade production for *in vivo* and *in vitro* validation.

[00263] Based on the complexity of the original heparin-associated fraction of the hPSC secretome and the limits to which individual proteins can recapitulate the activity of the whole pool, we will test combinations of factors as well. In the simplest approach, we would combine the 293T-REx secretome containing media from two or more cell lines each producing a given factor, and test their combined regenerative efficacy across a range of concentrations in an isobologram analysis using the regenerative index from the Myoblast Regeneration assay.

Example 4-In vivo testing of stem cell secreted factors

[00264] There are two main aspects of muscle degeneration with aging, acute loss following trauma and chronic wasting (sarcopenia), and both of them will be tested. As the therapeutic approach to each case is expected to be different two arms for the *in vivo* validation is envisioned to specifically test each use-case for the factors as therapeutics in humans. The following Acute Injury Model and Sarcopenia/Chronic Administration Model for the most promising proteins emerging from the machine learning classifier can be carried out.

Acute Injury Model

[00265] Animals were kept under standard animal husbandry condition. Animals were fed standard chow, and have ad libitum access to food and water. Temperature were kept at 22°C and 12 h light/12 h dark cycles. Animals were acclimated prior to study initiation. The experimental design was: C57BL/6J male mice, N = 18; Young: 12-13 week old (3-month-old) mice, n=6; Aged: 77-78 week old (18-month-old) mice, n=12. This design was used to test any single factor identified and validated in *in vitro* assays or complex mixtures of 2 or more factors.

Table 7. Experimental design of acute injury model.

No	Group	n	Test	Dose (mg/kg)	Administration	Blood collection	Tissue collection
1	Young, Vehicle	6	vehicle	n/a	i.m, q.d; into injured muscle site on day 0, and 2	terminal	TA/GA muscles into 25% sucrose; Brain, liver, heart, and lung into 4%
2	Aged, Vehicle	6	vehicle	n/a			

3	Aged, Test factor	6	Test factor	0.1			PFA
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[00266] On Day 0, mice were weighed and underwent muscle injury with focal injection of barium chloride (BaCl₂, 10 μ L, 1.2% w/v in saline, Sigma-Aldrich) in the Tibialis anterior (TA; Day 0) of both the right and left hindlegs. Injections of vehicle or factor A (0.1 mg/kg) were co-administered intramuscularly (i.m.) following the BaCl₂ into the TA injured hindleg sites, and again 48 hours later on day 2 (i.m.) into the TA injured hindleg sites. Also on day 2, BaCl₂ (Ctx; 10 μ L, 1.2% w/v in saline, Sigma-Aldrich) was injected into the Gastrocnemius (GA, Day 2, i.m.) muscles of both right and left hind legs. Injections of vehicle or a factor were sequentially administered (i.m.) following the BaCl₂ into the TA hindleg sites post-injury, and again 48 hours later on day 4 (i.m.) into the GA injured hind leg sites. Bromodeoxyuridine (BrdU) was be administered (100 mg/kg, i.p.) once daily for 3 days, day 2-4, before sacrifice to label proliferating cells.

[00267] On day 5, animals were sacrificed and animal weight recorded followed by collecting 0.5 ml of terminal blood via cardiac puncture which was processed to plasma and stored at 80 °C. We then perfused the animal with 1xPBS, carefully dissected the skin from the GA/TA muscles of each hind leg and took photos (prior to excision). After excision of exclusively the GA or TA muscle, excised tissue was photographed, weighed, then placed into 25% sucrose in PBS at 4°C for 4 hr rinsed in 1x PBS, immersed in Tissue-TEK OCT and rapidly frozen before storing the muscles tissues frozen at 80 °C. Cryosectioning and H&E were performed to ensure muscle injury site was appropriately visualized. A diagram of the time points for these experiments can be seen in **FIG. 2A**. Muscle tissue composition from new skeletal muscle fibers, fibrotic tissue, and adipose (fat), were measured. Muscle regeneration, as defined as the number of number of new myofibers with centrally located nuclei per millimeter, fibrosis as defined as the area of fibrotic scarring, size of the fibers, as defined as the width and area, adipose tissue, as defined by the amount of fat surrounding the muscle, were measured to assess level of regeneration.

[00268] Young muscle regeneration after acute focal injury had the highest regenerative index (measured as the number of new myofibers with centrally located nuclei per millimeter squared). Aged muscle regeneration following acute injuries performed on average 30-50% less than young muscle regeneration, in part due to the reduction of mitogenic muscle precursor/progenitor cell activity (**FIG. 2B**). It was predicted that systemic treatment of aged animals, injured animals, animals with genetic diseases causing muscle wasting, or animals injured by radiation or other tissue damaging treatment, the heparin-associated polypeptides, individually or in various combinations, will improve skeletal muscle regeneration by 20-50%, approaching comparable

levels to young healthy animals. It was also predicted that the composition of fibrous scar tissue and fat tissue will be reduced to levels comparable to younger animals by treatment with the heparin-associated polypeptides. And indeed, treatment with the heparin-associated polypeptides did improve the skeletal muscle regeneration of sarcopenic mice to level indistinguishable from the young by both the number of new myoblasts and the reduction in fibrous scar tissue (**FIG. 2B**).

Sarcopenia/Chronic Administration Model

[00269] After arrival, animals will be kept under standard animal husbandry condition. Animals will be fed standard chow, and have *ad libitum* access to food and water. Temperature will be kept at 22 °C and 12 h light/12 h dark cycles. Animals will be acclimated prior to study initiation, including any *in vivo* assay acclimation, if necessary. The experimental design was C57BL/6J male mice, N = 18; Young: 12-13 week old (3-month-old) mice, n=6; Aged: 77-78 week old (18-month-old) mice, n=12. This design can be used to test any single factor identified and validated in *in vitro* assays or complex mixtures of 2 or more factors.

Table 8. Design of sarcopenia/chronic administration model.

No	Group	n	Test	Dose (mg/kg)	Administration	<i>In vivo</i> assay	Blood collection	Tissue collection
1	Young, Vehicle	6	vehicle	n/a	i.p, q.d; on day -8 to +5	2 sets of: Animal weight, grip strength, running wheel performance; horizontal bar 1 set of: In capacitance	terminal	TA/GA muscles into 25% sucrose; Brain, liver, heart, and lung into 4% PFA
2	Aged, Vehicle	6	vehicle	n/a				
3	Aged, Test factor	6	Test factor	0.1				

[00270] On Day -10, mice will have the following *in vivo* healthspan measurements will be performed over 1 day as a baseline for age-based parameters: Weight, running wheel performance, grip strength, and horizontal bar. Each assay should be run for 4 trials per assay per animal. These healthspan assays will be repeated on day -1. After one day of rest on day -9, mice will begin 1x daily injections (0.1 mg/kg) of vehicle or factor A for the remainder of the experiment until sacrifice (days -8 to +5, 13 days of dosing). On day -4, 6 days after dosing begins, mice will undergo a repeat of the healthspan assays. On day 0, 5 days prior to sacrifice, mice will undergo muscle injury with focal injection of cardiotoxin (Ctx; 10 µg, Sigma-Aldrich) in the Tibialis anterior (TA; Day 0) of the right hindleg only. On day 2, the Gastrocnemius (GA; Day 2) muscle of the right hind leg will then receive cardiotoxin (Ctx; 10 µg, Sigma-Aldrich). BrdU will be administered (100 mg/kg, i.p.) once daily for 3 days, day 2-4, before sacrifice. On

day +5, prior to take-down, the animals will have an in vivo incapacitance assay run. On day +5, animals will be sacrificed and animal weight recorded. Collect 0.5 ml of blood via cardiac puncture, process to plasma and store plasma samples at 80 °C. The animals will then be perfused with 1xPBS. Carefully dissect the skin from the GA/TA muscles of each hind leg and take photos (prior to excision). After excision of exclusively the GA or TA muscle, weigh the muscles, then place muscles into 25% sucrose in PBS at 4°C for 4 hr. Then rinse the muscles in 1x PBS, adding Tissue-TEK OCT and storing the muscles tissues frozen at 80 °C. Perform cryosectioning and H&E, ensuring muscle injury site is appropriately visualized. Carefully excise the inguinal white adipose tissue (WAT) and weigh tissue. Discard WAT post-weighing.

[00271] Collected brain, liver, heart and lung can be post-fixed in 4% PFA for 72 hours, after 72 hours, transferred into 30% sucrose in 1xPBS and stored at -4 °C (brain, liver, heart, lung).

[00272] Muscle tissue composition, from new skeletal muscle fibers, fibrotic tissue, and adipose (fat), will be measured. Muscle regeneration, as defined as the number of number of new myofibers with centrally located nuclei per millimeter, fibrosis, as defined as the area of fibrotic scarring, size of the fibers, as defined as the width and area, adipose tissue, as defined by the amount of fat surrounding the muscle, will be measured to assess level of regeneration. Weights of the animals during the duration of treatment with heparin-associated polypeptide(s), as well as healthspan assays including performance on a running wheel (speed, distance, duration), grip strength, and performance on a horizontal bar will take into account the phenotypic outcomes of treatment of the aged animals systemically with the heparin-associated polypeptides for sarcopenia.

[00273] The horizontal bar test is performed as described previously (Malinowska et al. 2010) at 8 months (n = 6 WT, n = 7 MPS IIIB) and 10 months (n = 3 WT, n = 4 MPS IIIB) of age. In brief, a 300-mm metal wire, 2 mm in diameter, was secured between two posts 320 mm above a padded surface. The mouse was allowed to grip the center of the wire and the time to fall or reach the side was recorded, and after 2 min the test was stopped. Crossing the bar in x seconds was scored as 240-x, remaining on the bar was scored as 120, and falling off the bar after y seconds was recorded as the value of y. The test was repeated three times as a practice run followed by a 10-min rest prior to three tests where the score was recorded.

[00274] Young muscle regeneration after acute focal injury has the highest regenerative index (measured as the number of new myofibers with centrally located nuclei per millimeter squared). Aged muscle regeneration following acute injuries performs on average 30-50% less than young muscle regeneration, in part due to the reduction of mitogenic muscle precursor/progenitor cell activity. We predict systemic treatment of aged animals, injured animals, animals with genetic diseases causing muscle wasting, or animals injured by radiation or other tissue damaging

treatment, the heparin-associated polypeptides, individually or in various combinations, will improve skeletal muscle regeneration by 20-50%, approaching comparable levels to young healthy animals. We also predict the composition of fibrous scar tissue and fat tissue will be reduced to levels comparable to younger animals by treatment with the heparin-associated polypeptides.

[00275] Animals will also have better healthspan outcomes: reduced weight, fat composition, scar tissue around muscles, increased running speed, duration, and distance, increased grip strength, and enhanced performance on the horizontal bar test.

Example 5-Additional tests for pro-regenerative factors

[00276] Mechanistic insight into a given heparin-associated polypeptide factor's pathway of action will be gained by establishing and screening against a panel of assays for cellular age. Assays include measurements of reactive oxygen species (ROS) production or tolerance cytoplasmically and in the mitochondria, telomerase activity, measurements of proteostasis capacity via lysosomal, autophagy, and proteasomal routes, epigenetic re-patterning, and cellular energy balance (e.g., ATP/ADP and NAD/NADH ratios). Many of these assay leverage high-throughput automated microscopy to make these measurements in a variety of cell types, including fibroblast, endothelial cells, mesenchymal stem cells, and chondrocytes. Collectively these metrics can inform both the pathway and the mechanisms by which the heparin-associated hPSC secretome or its individual components enact their regenerative effects. These deep profile vectors can be crucial for approaching combinations of factors rationally, and for machine learning predictions.

[00277] To test the cellular effects of secretomes toward reversing the hallmarks of aging, high-throughput automated imaging and quantification of single cells to achieve deep population level statistical power can be employed. Cellular component state profiles of Young, Aged, and Aged+Treatment in human fibroblasts and epithelial cells, myoblasts, mesenchymal stem cells, chondrocytes, and neural progenitor cells will be compared. Some examples of tests and methods include:

- 1) **Epigenetic reprogramming:** repressive mark H3K9me3, the heterochromatin-associated protein HP1 γ , nuclear lamina support protein LAP2 α
- 2) **Nuclear membrane Folding/Blebbing:** immunofluorescence of the nuclear membrane protein Lamin A/C
- 3) **Proteolytic Activity:** Cleavage of fluorescent-tagged chymotrypsin like substrate corresponds to proteasome 20S core particle activity. Wells are first stained with PrestoBlue Cell Viability dye (Life Technologies) for 10 minutes. Well signals are read

using a TECAN fluorescence plate reader as a measure of cell count. Then cells are washed with HBSS/Ca/Mg before switching to original media containing the chymotrypsin like fluorogenic substrate LLVY-R110 (Sigma) which is cleaved by the proteasome 20S core particle. Cells are then incubated at 37°C in 5% CO₂ for 2 hours before signals are again read on the TECAN fluorescence plate reader. Readings are then normalized by PrestoBlue cell count.

- 4) **Formation of autophagosomes:** Autophagosome number and volume are measured by staining with CellTracker Deep Red (Sigma). The cells are then incubated at 37°C in 5% CO₂ for 20 minutes, washed 2 times using HBSS/Ca/Mg, and stained for 15 minutes using CellTracker Deep Red cell labeling dye. Cells are then switched to HBSS/Ca/Mg for single cell imaging using the Operetta High Content Imaging System (Perkin Elmer).
- 5) **Energy Metabolism:** ATP in the cells is measured using colorimetric assay using an ATP assay kit (ab83355; Abcam, Cambridge, MA) following manufacturer's instructions. Cells are washed in cold phosphate buffered saline and homogenized and centrifuged to collect the supernatant. The samples are loaded with assay buffer in triplicate. ATP reaction mix and background control (50 µL) is added to the wells and incubated for 30 min in dark. The plate is read at OD 570 nm using SpectraMax M2e (Molecular Devices, Sunnyvale, CA). The mean optical density is used to estimate of the intracellular ATP concentration relative to the standard curve.
- 6) **Mitochondrial Activity:** To measure **Mitochondria Membrane Potential**, cells are washed twice with Ham's F10 (no serum or pen/strep). Subsequently, MuSCs are stained with MitoTracker Green FM (ThermoFisher, M7514) and DAPI for 30 minutes at 37°C, washed three times with Ham's F10, and analyzed using a BD FACSAria III flow cytometer. To measure
- 7) **Mitochondrial ROS Measurement.** Cells are washed with HBSS/Ca/Mg and then switched to HBSS/Ca/Mg containing MitoSOX (Thermo), a live cell permeant fluorogenic dye that is selectively targeted to mitochondria and fluoresces when oxidized by superoxide. Cells are incubated for 10 minutes at 37°C in 5% CO₂. Cells are then washed twice with HBSS/Ca/Mg, and stained for 15 minutes using CellTracker Deep Red. Finally, cells are imaged in fresh HBSS/Ca/Mg using the Operetta High Content Imaging System (Perkin Elmer).
- 8) **Deregulated Nutrient Sensing:** levels of SIRT1 are measured.
- 9) **Senescence:** Senescence-associated beta-galactosidase staining is measured in cells washed twice with PBS then fixed with 15% Paraformaldehyde in PBS for 6 minutes. Cells are rinsed 3 times with PBS before staining with X-gal chromogenic substrate,

which is cleaved by endogenous Beta galactosidase. Plates are kept in the staining solution, Parafilm, to prevent from drying out, and incubated overnight at 37°C with ambient CO₂. The next day, cells are washed again with PBS before switching to a 70% glycerol solution for imaging under a Leica brightfield microscope.

10) **Secretome of the cells:** Mass-Spec or O-Link for inflammatory cytokines profiles.

11) **Soft Tissue Deposition:** Immunofluorescence for SOX9, MMP3, MMP13, and COL2A1 expression, the decrease of which is characterized by cartilage loss, pain, cleft-lip, and joint destruction.

Example 6-Identification of pro-regenerative factors by mass spectroscopy

[00278] Factors enriched in the secretome of undifferentiated hPSCs can be determined by Mass spectroscopy. A schematic of a type of mass spectroscopy experiment employed herein is shown in **FIG. 3A**.

[00279] Five confluent, 15 cm plates of cells per biological replicate were washed with OptiMEM- a basal, synthetic medium-, and then incubated in OptiMEM for 16 hours, yielding roughly 100ml of media. The media, now containing secreted factors, was collected, cells and cell debris removed by centrifugation, and flash frozen for storage at -80C until processing. The target factors were enriched via affinity purification for heparin binding using heparin-agarose bead columns. Heparin-agarose beads (Sigma) were washed with water twice, and once with OptiMEM (minus phenol red), before incubating with factor containing culture media for 2h at 4°C shaking at 100 rpm. The ratio of bead slurry (~50% beads) to media can be effective at 1:10, 1:20, 1:30, 1:40, and 1:50. Heparin-agarose beads were then collected into a column by centrifugation in an Amicon Pro Purification System column set in a 50ml conical tube at 1000g for 5 min, washed with 10x column volumes of PBS + 0.05% tween at 4°C twice. Factors were eluted via two repeats of the following: addition of a high salt solution (1.5M NaCl, 0.01M HEPES, pH 7.2, at ratio of 0.4ml elution buffer per milliliter of bead slurry), incubated at 4°C for 10 minutes at 100 rpm, and centrifugation at 1000g for 5 min into a fresh collection tube.

[00280] Protein concentration in the eluted fraction was assayed by silver stain densitometry as shown in **FIG. 3B**, and a BCA assay against standard curves for bovine serum albumin. Protein disulfide bonds were reduced by incubation in 5 mM tris-(2-carboxyethyl)-phosphine (TCEP) for 25 min, and the free cysteines alkylated with 10 mM iodoacetamide at room temperature for 30 min in the dark. Excess iodoacetamide was quenched with 15 mM dithiotreitol during a 15 min incubation. The eluates from all samples were then further purified by protein precipitation using trichloroacetic acid, prior to resuspending in digest buffer and 16hr of digestion using a mixture of modified Trypsin and Lys-C to yield peptides predominantly with

terminal arginine or lysine residues. The resulting peptide concentration were measured using a quantitative colorimetric peptide assay (Promega), and equimolar amounts of peptides from each biological replicate labeled at their free amines with tandem mass tags (TMT) using manufacturer recommended conditions before mixing the peptides. The mixed sample was desalted via reverse phase separation on a C18 StageTip prior to analysis via nHPLC-SPS/MS3 on a Fusion Lumos (Thermo Fisher). A TOP10 method was used to select up to 10 MS2 precursors for identification by CID-MS2 analyzed in the ion trap. For synchronous precursor selection of up to 10 ion windows, the FTMS3 isolation window was 0.4 m/z, max ion time 150 ms, automatic gain control 1.5E5, and FTMS3 resolution was 50,000. Resulting spectra were searched using commercial MS analysis software against the Uniprot human database (2018) protein sequences (Swiss-Prot and TrEMBL) concatenated with their reversed sequences as decoys for FDR determination, appended to common contaminant sequences. Searches restricted the precursor ion tolerance to 50 ppm and the product ion tolerance window to 0.9 m/z (or 50ppm), allowed no more than two missed cleavages, included static modification of lysine residues, arginine residues and peptide N-termini with TMT tags (+229.163 Da), static carbamidomethylation of cysteine residues (+57.021 Da), and variable oxidation of methionine residues (+15.995 Da).

[00281] Results were filtered to a 1% FDR at the peptide and then protein level using the target-decoy strategy. Peptides were assigned to protein groups, and individual proteins by the parsimony principle. Proteins were quantified by summing reporter ion intensities across all PSMs with greater than 70% of their spectral intensity deriving from matched ions and a summed signal to noise intensity greater than 200, normalizing channel level intensities, and computing the percent contribution of a given channel to the total signal. These values were then used for additional statistical modelling of differential abundance.

[00282] Heparin-associated proteins from undifferentiated and differentiated supernatants generated distinct sets of secreted factors as indicated by **FIG. 3C, 3D and 3E**. Combined results from such experiments are summarized in Table 2 shown previously herein, by the gene name, UniProt ID, Entrez Gene ID, and Ensembl ID.

Example 7-Validation of pro-regenerative factors in vitro using high-throughput imaging

[00283] Mass spectroscopy can define candidate pro-regenerative factors, however, as shown in example 6, these experiments can generate large amounts of data that need to be further validated in relevant *in vitro* and *in vivo* models. The use of high-throughput imaging can help define individual factors and mixtures of factors that possess regenerative potential. Mouse muscle progenitor cells can be cultured with BrdU or Edu, in the presence or absence of specific

potential pro-regenerative factors, and the degree of proliferation determined using high-throughput microscopy. BrdU or Edu staining indicates proliferation, while embryonic Myosin Heavy-Chain (eMyHC) staining indicates terminal differentiation of the progenitor cells. **FIG. 4A** and **4B** shows an example of data generated using high-throughput imaging.

[00284] Many of the factors detailed in Table 2 were tested individually for their ability to promote proliferation and/or fusion of mouse muscle progenitor cells *in vitro* **FIG. 5** and **FIG. 6**.

[00285] The effect of the candidate factors on myogenic activity was assayed in biological triplicate across a range of concentrations centered around expected physiological levels by adding each factor to mouse myoblasts for 48 hours or human myoblasts for 72 hours with daily media changes (DMEM +2% horse serum) and a second pulse of factors. After 24 hours, cells were pulsed for 2-5 hours with EdU (30uM), ethanol fixed, stained with Hoescht 3342, immunostained for proliferation -as measured by the percent of cells staining positive for EdU (%EdU)-, and immunostained for differentiation -as measured by the increase in cellular area staining positive for embryonic myosin heavy chain (%eMyHC) relative to the negative controls, which received media and vehicle only. Wells were imaged on a Keyence BZ-100 at 4x, the images quantified in Cell Profiler, and the statistics were computed in R. **FIGS. 7A-7B** show an example of the proliferation dose response for two of the factors tested. Results for additional factors are summarized below in Table 9.

Table 9. Effect of individual factors on mouse myoblast growth and fusion					
		Proliferation (% EdU)		Fusion (%eMyHC)	
Factor Name	Concentration (ug/mL)	Effect Size (% relative to control)	Statistical Significance (p-value)	Effect Size (% relative to control)	Statistical Significance (p-value)
FST	0.33	72%	0.001	202%	0.005
CTGF	5			154%	0.00005
THBS1	5			157%	0.004
THBS2	0.33			161%	0.006
IGFBP3	0.33	131%	0.03		
IGFBP5	2	69%	0.04		
IGFBP7	0.33	78%	0.03		
STC2	2.5	133%	0.02	-31%	0.003
SPON1	0.33	139%	0.04		
MST1	0.33	144%	0.02		
POSTN	0.33	139%	0.01		
RARRES2	0.33	141%	0.03		
AGRN	2.5	148%	0.008		

CHRD1	1.25	150%	0.00009		
VTN	5	125%	0.004		
FGF17	0.5	244%	0.0004		
ANOS1	1	165%	0.03		
FGF4	0.3	239%	4.6E-13		
HGF	0.56	114%	1.6E-10		
IGF2	1	97%	1.3E-5		
FGF1	1	96%	2.3E-7		
FGF6	0.002	115%	1.8E-5		
MST1	0.33	79%	0.002		
PDGFD	0.1	89%	4E-5		

[00286] The effect of the combination of candidate factors on myogenic activity was assayed in biological triplicate across a range of concentrations centered around expected physiological levels by adding each factor to mouse myoblasts for 48 hours or human myoblasts for 72 hours with daily media changes (DMEM +2% horse serum) and a second pulse of factors. After 24 hours, cells were pulsed for 2-5 hours with EdU (30uM), ethanol fixed, stained with Hoescht 3342, immunostained for proliferation -as measured by the percent of cells staining positive for EdU (%EdU)-, and immunostained for differentiation -as measured by the increase in cellular area staining positive for embryonic myosin heavy chain (%eMyHC) relative to the negative controls, which received media, individual factors, or vehicle only. Wells were imaged on a Keyence BZ-100 at 4x, the images quantified in Cell Profiler, and the statistics were computed in R. **FIGS. 7C-7M** show examples of the proliferation dose response for two or more of the factors tested individually and as a combination to test for synergy. Statistical metrics for increased myogenetic activity from the pair of factors relative to the controls are summarized below in Tables 10-14. Each polypeptide was produced using the method listed in Table 1. The magnitude of the combinations' effects relative to control (FM – negative control, hESC factors – positive control) is shown. The Combination Index (CI) for synergy was calculated using the Highest Single Agent (HAS) model due to the linear dose responses for the individual factor, e.g. **FIG. 7B**.

Table 10. Synergistic combinations of heparin-associated polypeptides.

Factor 1		Factor 2		Factor 3		p-value	CI (HSA)
Name	ug/mL	Name	ug/mL	Name	ug/mL		
THBS2	0.125	THBS4	0.25	VTN	1	<0.05	0.886
THBS2	0.125	THBS4	0.25	ANOS1	1	<0.005	0.532
THBS2	0.125	THBS4	0.25			<0.005	0.633

THBS1	0.0625	FGF17	0.025			<0.005	0.667
THBS1	0.125	FGF17	0.1			<0.005	0.679
THBS2	0.125	THBS4	0.25	IL-15	1	<0.005	0.680
THBS2	0.125	THBS4	0.25	IGF2	0.05	<0.05	0.733
THBS2	0.0625	VTN	1.25			<0.005	0.763
THBS2	0.125	VTN	1.25			<0.005	0.763
THBS2	0.125	VTN	0.3125			<0.005	0.771
THBS2	0.0625	THBS4	0.125			<0.005	0.772
THBS2	0.125	THBS4	0.0625			<0.005	0.779
THBS1	0.0625	FGF17	0.1			<0.005	0.796
THBS1	0.0625	VTN	0.315			<0.005	0.840
THBS2	0.0625	THBS4	0.25			<0.005	0.850
THBS1	0.25	THBS2	0.25			<0.05	0.859
THBS2	0.0625	FGF17	0.1			<0.005	0.871
THBS2	0.0625	VTN	0.625			<0.005	0.876
THBS2	0.125	THBS4	0.125			<0.005	0.878
THBS1	0.0625	VTN	1.25			<0.05	0.880
THBS1	0.25	THBS4	0.0625			<0.005	0.888
THBS2	0.0625	FGF17	0.025			<0.005	0.890
THBS1	0.0625	THBS2	0.0625			<0.05	0.900
THBS1	0.25	VTN	1.25			<0.005	0.907
THBS2	0.125	FGF17	0.025			<0.005	0.913
VTN	0.3125	FGF17	0.025			<0.05	0.915
THBS4	0.25	VTN	0.3125			<0.05	0.922
THBS2	0.125	FGF17	0.1			<0.005	0.923
THBS1	0.25	VTN	0.625			<0.005	0.930
THBS2	0.0625	THBS4	0.0625			<0.05	0.942
THBS4	0.25	FGF17	0.1			<0.005	0.945
THBS4	0.0625	VTN	0.625			<0.05	0.950
VTN	0.625	FGF17	0.1			<0.005	0.952
THBS4	0.25	VTN	1.25			<0.05	0.954

Table 11. Additional data regarding synergistic combinations of heparin-associated polypeptides (mouse myoblasts)

Factor Name	Single Dose @ saturation (ug/mL)	Single Dose % of EB	Single Dose %EdU Fold Change to FM	Single Dose %EdU	Combo Dose (ug/mL)	Combo Dose % of EB	Combo Dose %EdU Fold Change to FM	Combo Dose %EdU	HSA CI
THBS1	2	50%	1.7	15%	0.125	64%	1.16	14%	
FGF17	0.5	239%	4.5	69%	0.1	148%	2.89	33%	
Combo						163%	3.63	29%	0.6790 91

THBS2	2	50%	1.25	13%	0.125	46%	0.88	10%	
THBS4	2	40%	1.87	10%	0.25	53%	1.11	12%	
Combo						71%	1.39	17%	0.6325 48
THBS1	2	50%	1.7	15%	0.0625	44.08%	0.75	10.63%	
VTN	10	50%	1.5	16%	10	59.18%	1.01	14.27%	
Combo						69.47%	1.19	16.75%	0.8518 42
THBS2	2	50%	1.25	13%	0.125	31.08%	0.85	7.86%	
THBS4	2	40%	1.87	10%	0.25	29.33%	0.8	7.41%	
IL15	0.5	52%	1.4	12.50%	1	47.25%	1.28	11.90%	
Combo						57.91%	1.66	16.21%	0.6795 78
THBS2	2	50%	1.25	13%	0.125	45.08%	0.79	9.64%	
THBS4	2	40%	1.87	10%	0.25	61.15%	1.08	13.08%	
VTN	10	50%	1.5	16%	10	54.46%	0.94	12.67%	

Table 12. Additional data regarding synergistic combinations of heparin-associated polypeptides (mouse myoblasts)

Factor	Single Dose (ug/mL)	Single Dose % of Eb	Single Dose %EdU	Combo Dose (ug/mL)	Combo Dose % of EB	Combo Dose %EdU Fold Change to FM	Combo Dose %EdU
THBS1	2	50%	15%	0.125	64%	1.16	14%
FGF17	0.5	239%	69%	0.1	148%	2.89	33%
Combo					163%	3.63	29%
THBS2	2	50%	13%	0.125	46%	0.88	10%
THBS4	2	40%	10%	0.25	53%	1.11	12%
Combo					71%	1.39	17%
THBS1	2	50%	15%	0.0625	44.08%	0.75	10.63%
VTN	10	50%	16%	10	59.18%	1.01	14.27%
Combo					69.47%	1.19	16.75%
THBS2	2	50%	13%	0.125	31.08%	0.85	7.86%
THBS4	2	40%	10%	0.25	29.33%	0.8	7.41%
IL15	0.5	52%	12.50%	1	47.25%	1.28	11.90%
Combo					57.91%	1.66	16.21%

THBS2	2	50%	13%	0.125	45.08%	0.79	9.64%
THBS4	2	40%	10%	0.25	61.15%	1.08	13.08%
VTN	10	50%	16%	1	54.46%	0.94	12.67%
Combo					69.02%	1.22	14.76%
THBS2	2	50%	13%	0.125	58.62%	0.86	15.23%
THBS4	2	40%	10%	0.25	62.99%	0.93	16.37%
IGF2	2	89%	23%	0.5	85.78%	1.27	22.29%
Combo					116.95%	1.72	30.39%

Table 13. Additional data regarding synergistic combinations of heparin-associated polypeptides (human myoblasts)

Factor Name	Single Dose @ saturation (ug/mL)	Single Dose % of EB	Single Dose %EdU Fold Change to FM	Single Dose %EdU	Combo Dose (ug/mL)	Combo Dose % of EB	Combo Dose %EdU Fold Change to FM	Combo Dose %EdU	HSA CI
THBS1	7.5	98.93	1.61	10.99	0.5	78.22	0.85	8.95	
FGF17	0.25	222.09	3.62	24.67	0.05	121.74	1.33	13.93	
Combo						157.29	1.72	18	0.77
THBS2	7.5	112.84 69	1.2	12.53 448	0.125	57.09	0.95	7.82	
THBS4	0.5	126.70 02	2.07	14.07 323	0.25	62.67	1.04	8.59	
IL15	0.1	67.81	1.13	9.29	0.1	67.81	1.13	9.29	
Combo						69	1.15	9.46	0.98

Table 14. Additional data regarding synergistic combinations of heparin-associated polypeptides (human myoblasts)

Factor Name	Single Dose @ saturation (ug/mL)	Single Dose % of EB	Single Dose %EdU Fold Change to FM	Single Dose %EdU	Combo Dose (ug/mL)	Combo Dose % of EB	Combo Dose %EdU Fold Change to FM	Combo Dose %EdU
THBS1	7.5	98.93	1.61	10.99	0.5	78.22	0.85	8.95
FGF17	0.25	222.09	3.62	24.67	0.05	121.74	1.33	13.93
Combo						157.29	1.72	18

Example 8-In vivo testing of hPSC factors increases regenerative index and reduces fibrotic index in an acute injury model in aged mice

[00287] FIGS. 9A-9F show that aged mice (18 months) administered isolated, heparin-agarose bead purified hPSC show improved regenerative index and reduced fibrotic index. **FIG.**

9A shows a schematic of the experiment in this example. This experiment shows that hPSC derived factors can improve histological metrics of muscle health and function. As shown in **FIG. 9B** heparin-associated polypeptides isolated from human pluripotent stem cells increase regenerative potential and reduce muscle fibrosis in aged mice subjected to a model of acute muscle injury. As shown in **FIG. 9C**, there was increased muscle regeneration for injured, aged mouse muscle treated with THBS1 (2ug/mL) compared to young and vehicle-treated, aged mouse muscle.

[00288] **FIG. 9D** shows the experimental schematic of time-points for dosing and analysis using an acute injury model in aged mice of the effects of individual heparin-associated polypeptides with fusion enhancing effects in vitro. Square denote injury inducing intramuscular injection (IM) with Barium Chloride while circles denote administration of treatment or vehicle. **FIG. 9E** shows the results of the experiment outlined in **FIG. 9D** shows that administration of 20ul of heparin-associated polypeptides PPDGFRL (5ug/mL, $p < 3.85E-2$) and IGFBP7 (1ug/mL, $p < 6.63E-3$) resulted in improved new fiber formation (regenerative index compared to vehicle treated aged mice. Stars indicate degree of significance from one-way ANOVA tests. **FIG. 9F** provides representative images of immunofluorescence staining of sectioned mouse muscle (tibialis anterior) demonstrating increased muscle regeneration for injured, aged mouse muscle treated with POSTN (1ug/mL) or IGFBP7 (1ug/mL) compared to vehicle-treated, aged mouse muscle.

[00289] Other models for in vivo testing of hSPC factors include:

Disuse-Reload injury model

[00290] This mouse model is a way to observe muscle atrophy in a non-invasive way by contracting the hind limbs of a mouse and preventing extension and flexion, thus reducing the size and strength. The model will serve as an important measurement of muscle regeneration with biologic candidates.

[00291] The hind limb will be immobilized with Cast Tape extended position using sports tape to prevent flexion of the limb. Once the sports tape is in place, a strip of casting tape will be wrapped over the sports tape from the ankle upward, and air dried. The extension of the hind limb should stay rigid in its position of the duration of the study parameters.

[00292] The study begins after mice are acclimated and on Day -3, in which mice from all groups will be weighed. Assigned animals will be given daily i.p. injections of Vehicle control or Candidate Biologic for 3 days before undergoing hind limb immobilization on Day 0 for 7 days with continuous daily i.p. injections. Hind limbs will be observed for any adverse effects due to immobilization. On Day 7 of the study, all animals will be sacrificed and muscle tissue weighed and harvested for further analysis.

Force Measurement

[00293] This study will be used to measure the force of pull in the hind limbs that the animal exerts upon skeletal muscle injury of the tibialis anterior (TA) and gastrocnemius (GA) muscles after injury induction with Barium chloride (BaCl_2). This model will serve to determine which of our biological candidates are efficacious in muscle regeneration.

[00294] Skeletal Muscle Injury Induction: Under anesthesia, BaCl_2 will be administered in two sites on the TA and four sites on the GA (as previously described). Hair will be shaved on the left and right hind limbs prior to injection with small animal hair clippers. On Day 0 of the study, the TA muscle will undergo BaCl_2 induced injury on two sites (previously described). On Day 4 of the study, the GA muscle will follow with BaCl_2 induced injury on four sites. Candidate biologic will be administered on Days 0 and 2 in the injury sites of the TA and GA muscles. BrdU will be injected via IP (QD) on days 4-7 to label proliferating muscle precursor and fibrotic cells in order to measure their regenerative potential.

[00295] On terminal day 7, animals will be deeply anesthetized and a force transducer will be used to measure twitch reactions in the hind limbs of each mouse being tested in the study, via a small incision in the TA to a small metal hook. This will be a terminal procedure. Grip strength measurements: the mice will rest on an angled mesh, facing away from the force meter and with its hind limbs at least one-half of the way down the length of the mesh. The mouse's tail is pulled directly toward the meter and parallel to the mesh. During this procedure, the mouse resists by grasping the mesh with all four limbs. Pulling is continued toward the meter until the hind limbs release.

Ex vivo regenerative measurement

[00296] To confirm these data with age matched, primary muscle stem cells, injury-activated satellite cells associated with myofibers will be isolated from young and old muscle by dissecting the muscle groups of interest and dissociating the tissue to single cell suspensions by incubating in digestion medium (250 U/mL Collagenase type II in DMEM medium, buffered with 30 mM HEPES, pH 7.4) at 37C for 1hr., triturating the cell suspension, the myofibers were collected by centrifugation and myofibers further digested with 1 U/mL Dispase and 40 U/mL Collagenase type II in 30mM HEPES at 37C for 1hr to free muscle stem cells. Muscle stem cells can then be plated and cultured growth media containing serum (2-5%) from the same mouse. The regenerative and fusion potential of the cells will then be assayed as described above in in Example 7 and as demonstrated in **FIGS. 10B, 10C, 11B, and 11C**. This has the advantage of testing the effect of treatment while maintaining the exogenous, often inhibitory extracellular environmental cues contributed by the age appropriate serum.

Example 9- Modelling treatment of a muscular dystrophy with pro-regenerative factors in vitro using high-throughput imaging

[00297] Muscular dystrophies (MD) encompass a variety of muscular degeneration diseases typically due to genetic mutations in genes encoding proteins responsible for forming and stabilizing skeletal muscle. The phenotypic consequence of these genetic mutations is the progressive loss of muscle mass and strength over time, similar to sarcopenia but with different underlying causes. As heparin-associated polypeptides provided phenotypic improvements on sarcopenic muscle, we tested for similar improvements in a model for MD.

[00298] Many of the factors detailed in Table 2 were tested individually for their ability to promote proliferation and/or fusion of human muscle progenitor cells from a patient with myotonic dystrophy type 1 (hMD) - a muscular dystrophy caused by mutations in the DMPK1 gene.

[00299] The effect of the candidate factors on myogenic activity was assayed in biological triplicate across a range of concentrations centered around expected physiological levels by adding each factor to hMD myoblasts for 72 hours with daily media changes (DMEM +2% horse serum) and a second pulse of factors at the first media change. After 72 hours, cells were pulsed for 2-5 hours with EdU (30uM), ethanol fixed, stained with Hoescht 3342, immunostained for proliferation -as measured by the percent of cells staining positive for EdU (%EdU)-, and immunostained for differentiation -as measured by the increase in cellular area staining positive for embryonic myosin heavy chain (%eMyHC) relative to the negative controls, which received media and vehicle only. Wells were imaged on a Keyence BZ-100 at 4x, the images quantified in Cell Profiler, and the statistics were computed in R. **FIGS. 12A** and **12B** show examples of the quantitation of the proliferation response and fusion response for several of the factors tested, respectively. Results those and additional factors are summarized below in Table 15.

Table 15. Effect of individual factors on dystrophic human myoblast growth and fusion

		Proliferation (% EdU)		Fusion (%eMyHC)	
Factor Name	Concentration (ug/mL)	Effect Size (% relative to -control)	Statistical Significance (p-value)	Effect Size (% relative to -control)	Statistical Significance (p-value)
FGF17	0.2	208%	<9E-14		
FGF4	0.0125	269%	9.52E-13		
FGF4	0.025	244%	6.83E-12		
FGF4	0.05	235%	7.22E-10		
FGF4	0.1	213%	8.11E-07		
FGF4	0.2	184%	1.46E-02		
IGF2	0.2	53%	2.57E-02		

FGF1	0.05	157%	1.65E-06		
FGF1	0.1	217%	2.87E-06		
FGF1	0.2	213%	1.10E-10		
FGF6	0.0125	277%	1.34E-09		
FGF6	0.025	272%	4.54E-09		
FGF6	0.05	261%	4.75E-08		
FGF6	0.1	243%	1.03E-07		
FGF6	0.2	237%	8.49E-06		
PDGFRL	0.03125			2580%	1.47E-06
PDGFRL	0.0625			2240%	6.34E-07
PDGFRL	0.125			1410%	4.53E-03
PDGFRL	0.25			2570%	1.86E-08
PDGFRL	0.5			3440%	5.75E-11

Example 10 Assess hPSC factors in vivo using rodent models of Becker muscular dystrophy for their ability to improve muscle regeneration and muscle mass

[00300] Mdx ^{-/-} mice will receive intramuscular injections of the top 3 select hPSC secreted factors selected from the in vitro screen. Indications of enhanced functional regeneration will be assessed through quantification of twitch force measurements and walking track analysis. The Mdx ^{-/-} mouse model for BMD is chosen as it has a spontaneous point mutation in the dystrophin gene leading to near complete absence of dystrophin protein. Despite having phenotypic markers of myopathy there are only mild skeletal muscle defects, suggesting that the model best reflects Becker muscular dystrophy. This animal model also mimics the complex paracrine signaling environment, where immune cells and other systemic factors would be involved. Thus, a screen in injured dystrophic muscle for regeneration will efficiently narrow the candidate list for those proteins needed for the ultimate goal of restoring muscle mass and strength to the BMD patients. Myogenesis in a muscle regeneration model will be compared between controls (vehicle-treated) and with the top 3-5 efficacious, dose-optimized factors. Hind limb muscles, the Tibialis anterior (TA) and gastrocnemius (GA) muscle will receive i.m. injection of vehicle control or candidate factor every day for 7 days (t=5 days). BrdU will be also be injected 3 days prior to tissue collection for *ex vivo* analysis. Muscle regeneration will be assessed in 10 micrometer muscle cryosections. The histological analysis of hematoxylin and eosin staining and immunodetection of eMyHC and BrdU will be used to quantify the numbers of de-novo eMyHC⁺ myofibers with centrally-located BrdU⁺ nuclei throughout the injury site. Additionally, myofiber size and muscle weights will also be assessed. For twitch force measurements, mice hindlimbs will be immobilize to a frame. A small incision will be made in the skin directly above the tibialis anterior (TA) muscle to hook to a thin metal hook and then attached to a 300C-LR force

transducer (Aurora Scientific). A bipolar electrical stimulation cuff will wrap around the TA and stimulate with a single 0.1-ms pulse for 3 seconds.

[00301] It is expected that administration of select pro-myogenic factors will increase Delta/Notch and MapK signaling, dependent on BMP signaling in Mdx ^{-/-} myogenic cells, resulting in increased proliferation, allowing the injury site to heal similar to wildtype muscle - with new muscle fibers - instead of filling with fibrotic scar tissue or adipose tissue as is common in dystrophic muscle. Administration of candidate factors to Mdx ^{-/-} injured TA muscle is expected to improve regeneration indicated by quantification of muscle fiber repair and twitch force measurement.

Example 11-Clinical testing of pro-regenerative factors

[00302] The purpose of this study is to determine the efficacy of repeat dosing with multiple dose levels of heparin-associated proteins on patient physical function, skeletal muscle mass and strength in older adults with sarcopenia. In addition, this study will generate data on the safety, tolerability, and pharmacokinetics of heparin-associated proteins in older adults with sarcopenia. Individuals will administered placebo or heparin-associated binding proteins and monitored for 25 weeks of study. The following primary and secondary outcome measures will be assessed:

Primary Outcome Measures:

[00303] Short Physical Performance Battery (SPPB) [Time Frame: Baseline, week 25]. Change from baseline to week 25.

Secondary Outcome Measures:

[00304] Safety and tolerability as assessed by various measures such as adverse events. Assessed by various measures such as adverse events over 24 weeks.

[00305] Change in 6-minute walk test [Time Frame: baseline, week 25]. Change from baseline to week 25.

[00306] Gait speed [Time Frame: baseline, week 25]. Change from baseline to week 25.

[00307] Change in total lean body mass and appendicular skeletal muscle index measured by DXA from baseline to week 25.

Inclusion Criteria:

[00308] Otherwise healthy adults aged at least 70 years; Low muscle mass as confirmed by DXA; Low gait speed; SPPB score less than or equal to 9; Weigh at least 35 kg; with adequate dietary intake as determined by patient interview.

Protocol

[00309] Patients will be i.v.-administered placebo (5% dextrose solution) or heparin-associated binding proteins (in 5% dextrose). Starting on day 1, week 1 and repeated every other

week (day one of weeks 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, and 23. At the end of week 12 and 24 patients will be assessed by the above methods for improvement. Doses will be selected from a traditional 3 + 3 design, and selected as the top two-doses that lack dose-limiting toxicity.

[00310] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention.

[00311] All publications, patent applications, issued patents, and other documents referred to in this specification are herein incorporated by reference as if each individual publication, patent application, issued patent, or other document was specifically and individually indicated to be incorporated by reference in its entirety. Definitions that are contained in text incorporated by reference are excluded to the extent that they contradict definitions in this disclosure.

CLAIMS**WHAT IS CLAIMED IS:**

1. A composition comprising: (a) a first therapeutic polypeptide comprising a first polypeptide of Table 2, and (b) a second therapeutic polypeptide comprising a second polypeptide of Table 2.
2. The composition of claim 1, provided that the first polypeptide of Table 2 is a first polypeptide of Table 1 and/or the second polypeptide of Table 2 is a second polypeptide of Table 1.
3. The composition of claim 1 or claim 2, provided that the first polypeptide of Table 2 comprises THBS1, THBS2, THBS4, FGF17, VTN, POSTN, IGF2, or IL-15, or any combination thereof.
4. The composition of any one of claims 1 to 3, provided that the second polypeptide of Table 2 comprises THBS1, THBS2, THBS4, FGF17, VTN, POSTN, IGF2, or IL-15, or any combination thereof.
5. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises THBS1 and/or a sequence comprising at least about 90% homology to amino acids 19-1170 of SEQ ID NO: 9; and the second polypeptide of Table 2 comprises THBS2 and/or a sequence comprising at least about 90% homology to amino acids 19-1172 of SEQ ID NO: 4.
6. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises THBS1 and/or a sequence comprising at least about 90% homology to amino acids 19-1170 of SEQ ID NO: 9; and the second polypeptide of Table 2 comprises THBS4 and/or a sequence comprising at least about 90% homology to amino acids 27-961 of SEQ ID NO: 8.
7. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises THBS1 and/or a sequence comprising at least about 90% homology to amino acids 19-1170 of SEQ ID NO: 9; and the second polypeptide of Table 2 comprises FGF17 and/or a sequence comprising at least about 90% homology to amino acids 23-2165 of SEQ ID NO: 7.
8. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises THBS1 and/or a sequence comprising at least about 90% homology to amino acids 19-1170 of SEQ ID NO: 9; and the second polypeptide of Table 2 comprises VTN and/or a sequence comprising at least about 90% homology to amino acids 20-478 of SEQ ID NO: 1.
9. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises THBS1 and/or a sequence comprising at least about 90% homology to amino acids 19-1170 of SEQ ID NO: 9; and the second polypeptide of Table 2 comprises POSTN and/or a sequence comprising at least about 90% homology to amino acids 22-836 of SEQ ID NO: 6.

10. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises THBS1 and/or a sequence comprising at least about 90% homology to amino acids 19-1170 of SEQ ID NO: 9; and the second polypeptide of Table 2 comprises IGF2 and/or a sequence comprising at least about 90% homology to amino acids 25-91 of SEQ ID NO: 11.
11. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises THBS1 and/or a sequence comprising at least about 90% homology to amino acids 19-1170 of SEQ ID NO: 9; and the second polypeptide of Table 2 comprises IL-15 and/or a sequence comprising at least about 90% homology to amino acids 49-162 of SEQ ID NO: 10.
12. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises THBS2 and/or a sequence comprising at least about 90% homology to amino acids 19-1172 of SEQ ID NO: 4; and the second polypeptide of Table 2 comprises THBS4 and/or a sequence comprising at least about 90% homology to amino acids 27-961 of SEQ ID NO: 8.
13. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises THBS2 and/or a sequence comprising at least about 90% homology to amino acids 19-1172 of SEQ ID NO: 4; and the second polypeptide of Table 2 comprises FGF17 and/or a sequence comprising at least about 90% homology to amino acids 23-2165 of SEQ ID NO: 7.
14. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises THBS2 and/or a sequence comprising at least about 90% homology to amino acids 19-1172 of SEQ ID NO: 4; and the second polypeptide of Table 2 comprises VTN and/or a sequence comprising at least about 90% homology to amino acids 20-478 of SEQ ID NO: 1.
15. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises THBS2 and/or a sequence comprising at least about 90% homology to amino acids 19-1172 of SEQ ID NO: 4; and the second polypeptide of Table 2 comprises POSTN and/or a sequence comprising at least about 90% homology to amino acids 22-836 of SEQ ID NO: 6.
16. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises THBS2 and/or a sequence comprising at least about 90% homology to amino acids 19-1172 of SEQ ID NO: 4; and the second polypeptide of Table 2 comprises IGF2 and/or a sequence comprising at least about 90% homology to amino acids 25-91 of SEQ ID NO: 11.
17. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises THBS2 and/or a sequence comprising at least about 90% homology to amino acids 19-1172 of SEQ ID NO: 4; and the second polypeptide of Table 2 comprises IL-15 and/or a sequence comprising at least about 90% homology to amino acids 49-162 of SEQ ID NO: 10.
18. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises THBS4 and/or a sequence comprising at least about 90% homology to amino acids

- 27-961 of SEQ ID NO: 8; and the second polypeptide of Table 2 comprises FGF17 and/or a sequence comprising at least about 90% homology to amino acids 23-2165 of SEQ ID NO: 7.
19. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises THBS4 and/or a sequence comprising at least about 90% homology to amino acids 27-961 of SEQ ID NO: 8; and the second polypeptide of Table 2 comprises VTN and/or a sequence comprising at least about 90% homology to amino acids 20-478 of SEQ ID NO: 1.
20. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises THBS4 and/or a sequence comprising at least about 90% homology to amino acids 27-961 of SEQ ID NO: 8; and the second polypeptide of Table 2 comprises POSTN and/or a sequence comprising at least about 90% homology to amino acids 22-836 of SEQ ID NO: 6.
21. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises THBS4 and/or a sequence comprising at least about 90% homology to amino acids 27-961 of SEQ ID NO: 8; and the second polypeptide of Table 2 comprises IGF2 and/or a sequence comprising at least about 90% homology to amino acids 25-91 of SEQ ID NO: 11.
22. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises THBS4 and/or a sequence comprising at least about 90% homology to amino acids 27-961 of SEQ ID NO: 8; and the second polypeptide of Table 2 comprises IL-15 and/or a sequence comprising at least about 90% homology to amino acids 49-162 of SEQ ID NO: 10.
23. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises FGF17 and/or a sequence comprising at least about 90% homology to amino acids 23-2165 of SEQ ID NO: 7; and the second polypeptide of Table 2 comprises VTN and/or a sequence comprising at least about 90% homology to amino acids 20-478 of SEQ ID NO: 1.
24. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises FGF17 and/or a sequence comprising at least about 90% homology to amino acids 23-2165 of SEQ ID NO: 7; and the second polypeptide of Table 2 comprises POSTN and/or a sequence comprising at least about 90% homology to amino acids 22-836 of SEQ ID NO: 6.
25. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises FGF17 and/or a sequence comprising at least about 90% homology to amino acids 23-2165 of SEQ ID NO: 7; and the second polypeptide of Table 2 comprises IGF2 and/or a sequence comprising at least about 90% homology to amino acids 25-91 of SEQ ID NO: 11.
26. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises FGF17 and/or a sequence comprising at least about 90% homology to amino acids 23-2165 of SEQ ID NO: 7; and the second polypeptide of Table 2 comprises IL-15 and/or a sequence comprising at least about 90% homology to amino acids 49-162 of SEQ ID NO: 10.

27. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises VTN and/or a sequence comprising at least about 90% homology to amino acids 20-478 of SEQ ID NO: 1; and the second polypeptide of Table 2 comprises POSTN and/or a sequence comprising at least about 90% homology to amino acids 22-836 of SEQ ID NO: 6.
28. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises VTN and/or a sequence comprising at least about 90% homology to amino acids 20-478 of SEQ ID NO: 1; and the second polypeptide of Table 2 comprises IGF2 and/or a sequence comprising at least about 90% homology to amino acids 25-91 of SEQ ID NO: 11.
29. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises VTN and/or a sequence comprising at least about 90% homology to amino acids 20-478 of SEQ ID NO: 1; and the second polypeptide of Table 2 comprises IL-15 and/or a sequence comprising at least about 90% homology to amino acids 49-162 of SEQ ID NO: 10.
30. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises POSTN and/or a sequence comprising at least about 90% homology to amino acids 22-836 of SEQ ID NO: 6; and the second polypeptide of Table 2 comprises IGF2 and/or a sequence comprising at least about 90% homology to amino acids 25-91 of SEQ ID NO: 11.
31. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises POSTN and/or a sequence comprising at least about 90% homology to amino acids 22-836 of SEQ ID NO: 6; and the second polypeptide of Table 2 comprises IL-15 and/or a sequence comprising at least about 90% homology to amino acids 49-162 of SEQ ID NO: 10.
32. The composition of any one of claims 1 to 4, provided that the first polypeptide of Table 2 comprises IGF2 and/or a sequence comprising at least about 90% homology to amino acids 25-91 of SEQ ID NO: 11; and the second polypeptide of Table 2 comprises IL-15 and/or a sequence comprising at least about 90% homology to amino acids 49-162 of SEQ ID NO: 10.
33. The composition of claim 12, further comprising IL-15 and/or a polypeptide comprising at least about 90% homology to amino acids 49-162 of SEQ ID NO: 10.
34. The composition of claim 12, further comprising IGF2 and/or a polypeptide comprising at least about 90% homology to amino acids 25-91 of SEQ ID NO: 11.
35. The composition of any one of claims 1 to 34, provided that the first therapeutic polypeptide has been recombinantly produced, the second polypeptide has been recombinantly produced, or both the first and second therapeutic polypeptides have been recombinantly produced.
36. The composition of any one of claims 1 to 35, provided that the first therapeutic polypeptide has been produced in a mammalian, yeast, insect or bacteria cell, the second polypeptide has

- been produced in a mammalian, yeast, insect or bacteria cell, or both the first and second therapeutic polypeptides have been produced in a mammalian, yeast, insect or bacteria cell.
37. The composition of any one of claims 1 to 35, provided that the first therapeutic polypeptide and/or the second therapeutic polypeptide has been purified from a human biological sample.
38. The composition of claim 36, provided that the first therapeutic polypeptide and/or the second therapeutic polypeptide has been produced in a mammalian cell and the mammalian cell is a human cell, Chinese Hamster Ovary (CHO) cell or mouse myeloma cell.
39. The composition of any one of claims 1 to 38, further comprising a pharmaceutically acceptable excipient.
40. The composition of any one of claims 1 to 39, formulated for administration by injection.
41. The composition of claim 40, provided that the injection is intramuscular injection, subcutaneous injection, or intravenous injection.
42. A composition comprising a polypeptide of Table 2 and a pharmaceutically acceptable excipient.
43. The composition of claim 42, provided that the polypeptide comprises VTN and/or a sequence comprising at least about 90% homology to amino acids 20-478 of SEQ ID NO: 1.
44. The composition of claim 42 or claim 43, provided that the polypeptide comprises POSTN and/or a sequence comprising at least about 90% homology to amino acids 22-836 of SEQ ID NO: 6.
45. The composition of any one of claims 42 to 44, provided that the polypeptide comprises FGF17 and/or a sequence comprising at least about 90% homology to amino acids 23-2165 of SEQ ID NO: 7.
46. The composition of any one of claims 42 to 45, provided that the polypeptide comprises THBS2 and/or a sequence comprising at least about 90% homology to amino acids 19-1172 of SEQ ID NO: 4.
47. The composition of any one of claims 42 to 46, provided that the polypeptide comprises THBS4 and/or a sequence comprising at least about 90% homology to amino acids 27-961 of SEQ ID NO: 8.
48. The composition of any one of claims 42 to 47, provided that the polypeptide comprises THBS1 and/or a sequence comprising at least about 90% homology to amino acids 19-1170 of SEQ ID NO: 9.
49. The composition of any one of claims 42 to 48, provided that the polypeptide comprises IL-15 and/or a sequence comprising at least about 90% homology to amino acids 49-162 of SEQ ID NO: 10.

50. The composition of any one of claims 42 to 49, provided that the polypeptide comprises IGF2 and/or a sequence comprising at least about 90% homology to amino acids 25-91 of SEQ ID NO: 11.
51. The composition of any one of claims 42 to 50, provided that the polypeptide has been expressed from a human cell, Chinese Hamster Ovary (CHO) cell, or mouse myeloma (NS0) cell, or a bacterial cell.
52. The composition of any one of claims 42 to 50, provided that the polypeptide is synthetically produced, or has been purified from a human biological sample.
53. The composition of any one of claims 42 to 52, provided that the polypeptide possesses mitogenic and/or fusion promoting activity.
54. A nucleic acid encoding the polypeptide of any one of claims 42 to 53.
55. A cell line comprising the nucleic acid of claim 54.
56. A method of treating a disease or condition in a subject in need thereof, the method comprising administering to the subject the composition of any one of claims 1 to 53.
57. The method of claim 56, provided that the disease or condition comprises an aging disorder, muscle wasting disorder, muscle injury, or injury to connective tissue, or a combination thereof.
58. The method of claim 57, provided that the subject has the aging disorder and the aging disorder comprises sarcopenia.
59. The method of claim 57, provided that the subject has the muscle wasting disorder and the muscle wasting disorder comprises muscular dystrophy.
60. The method of claim 57, provided that the subject has the muscle wasting disorder and the muscle wasting is a result of obesity, disease progression, metabolic disorder, or therapeutic treatment, or a combination thereof.
61. The method of claim 57, provided that the subject has the muscle wasting disorder and the muscle wasting is cachexia.
62. The method of claim 60, provided that the metabolic disorder is diabetes.

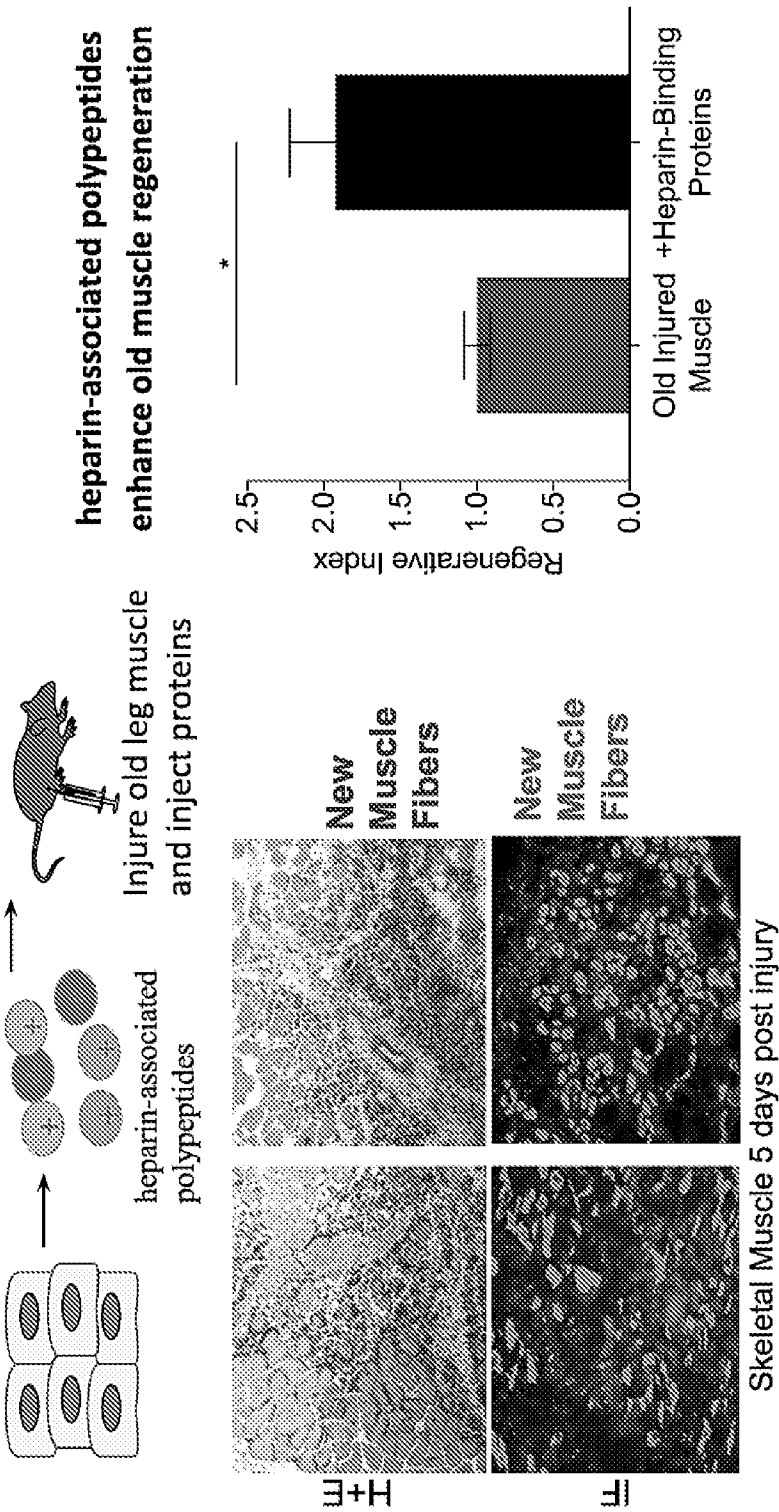


FIG. 1

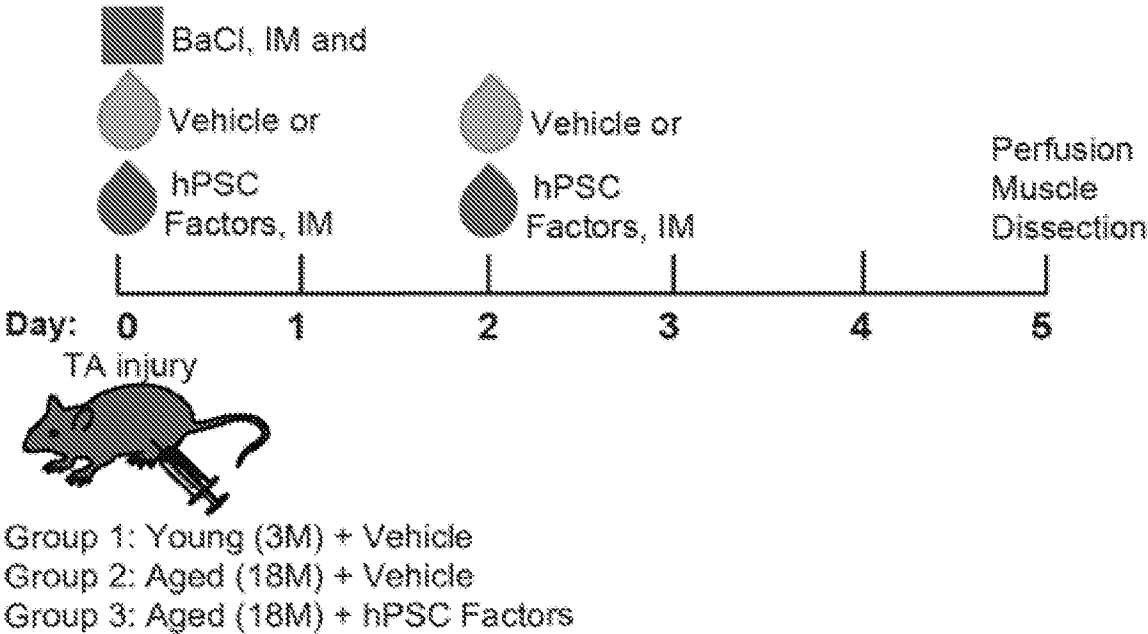


FIG. 2A

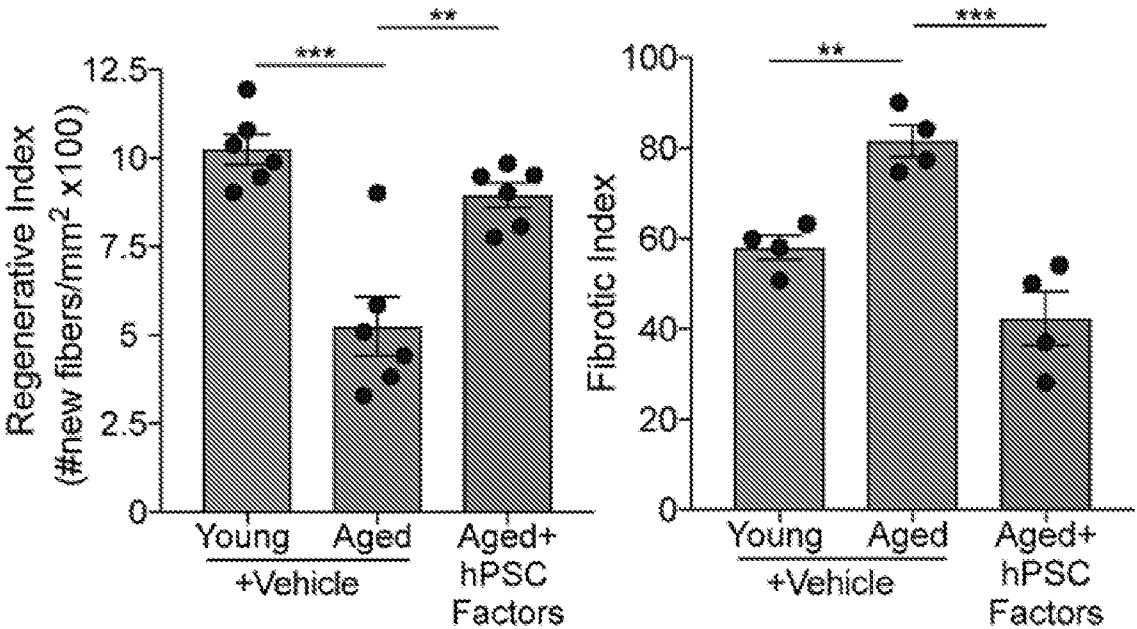


FIG. 2B

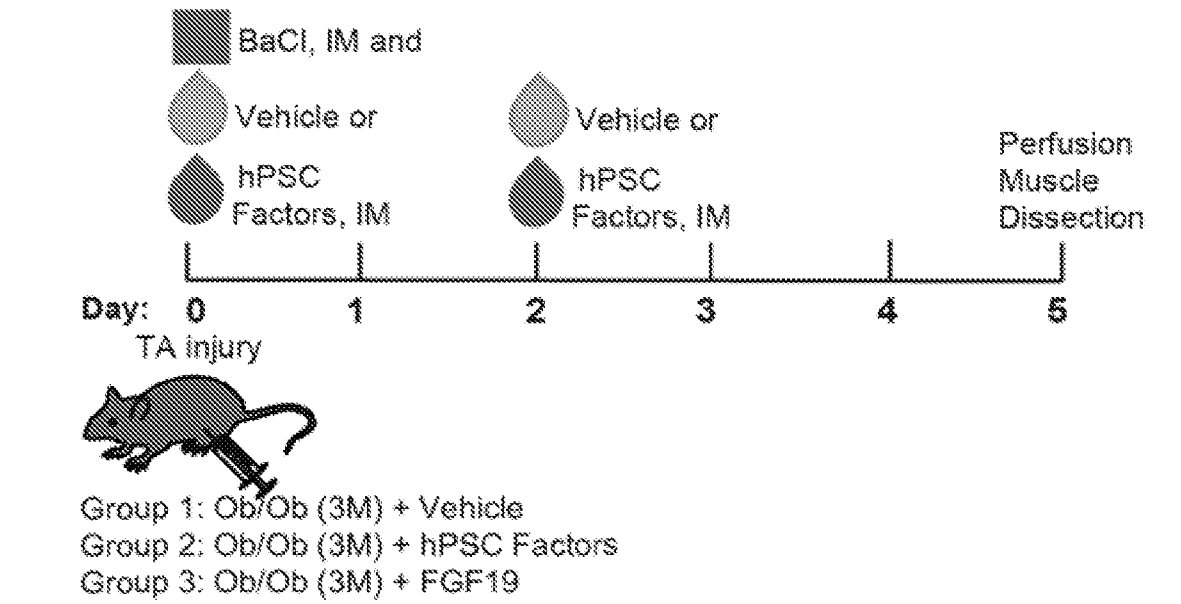


FIG. 2C

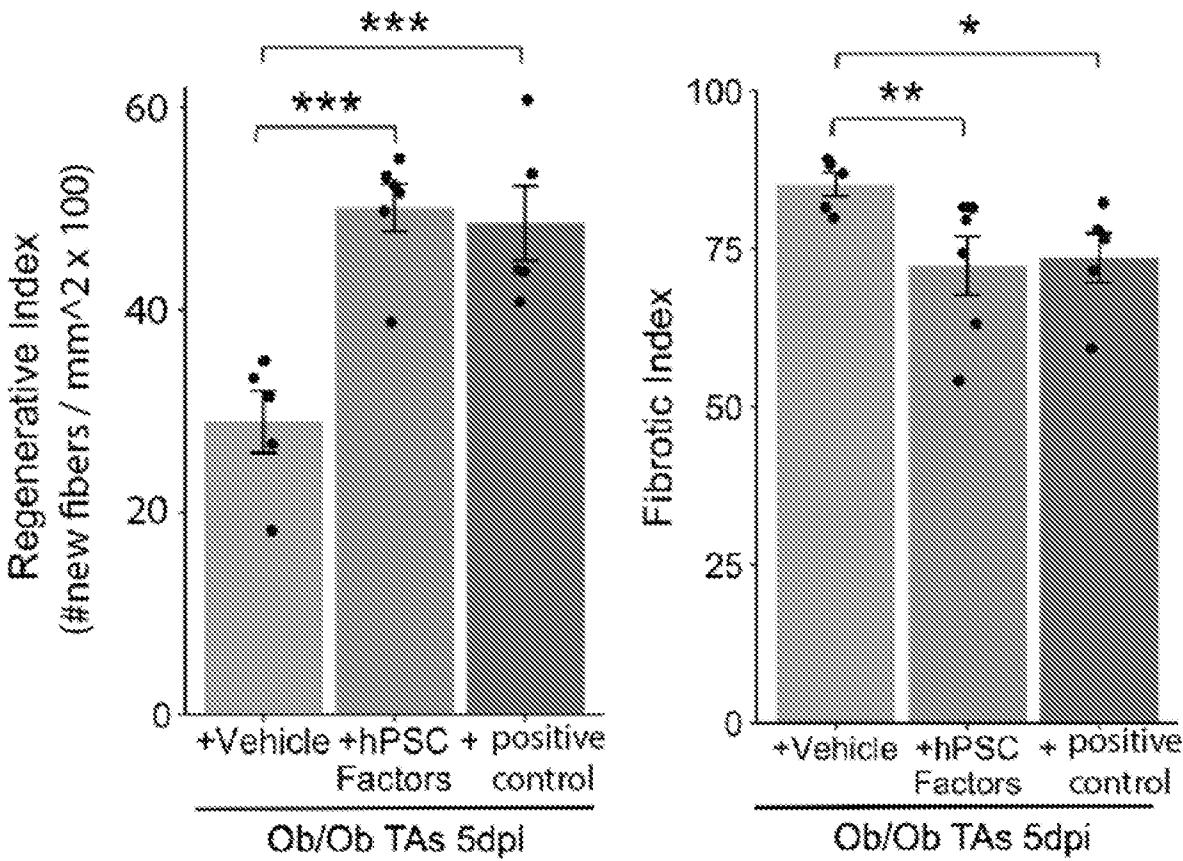


FIG. 2D

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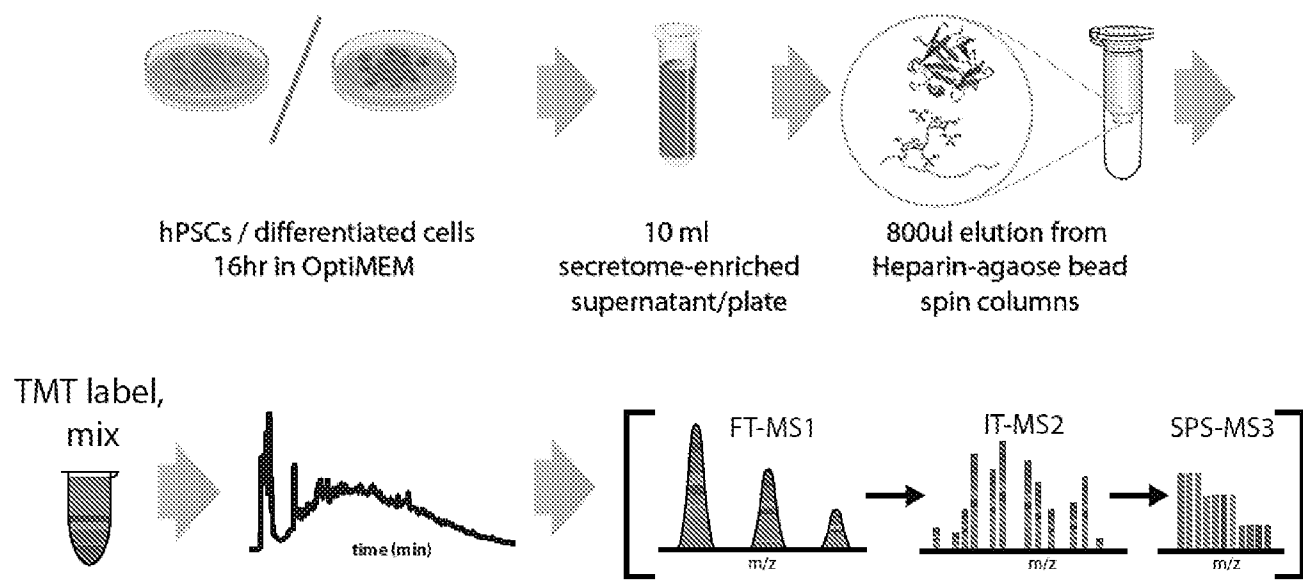


FIG. 3A

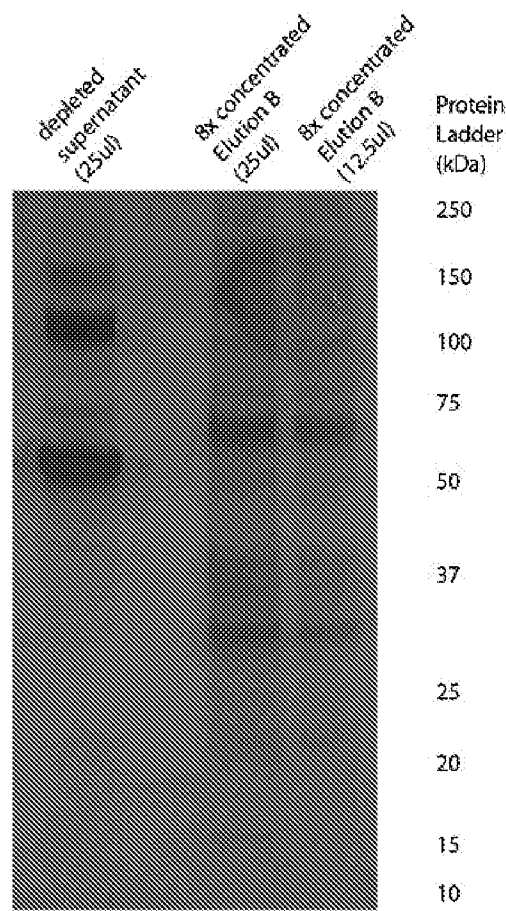


FIG. 3B

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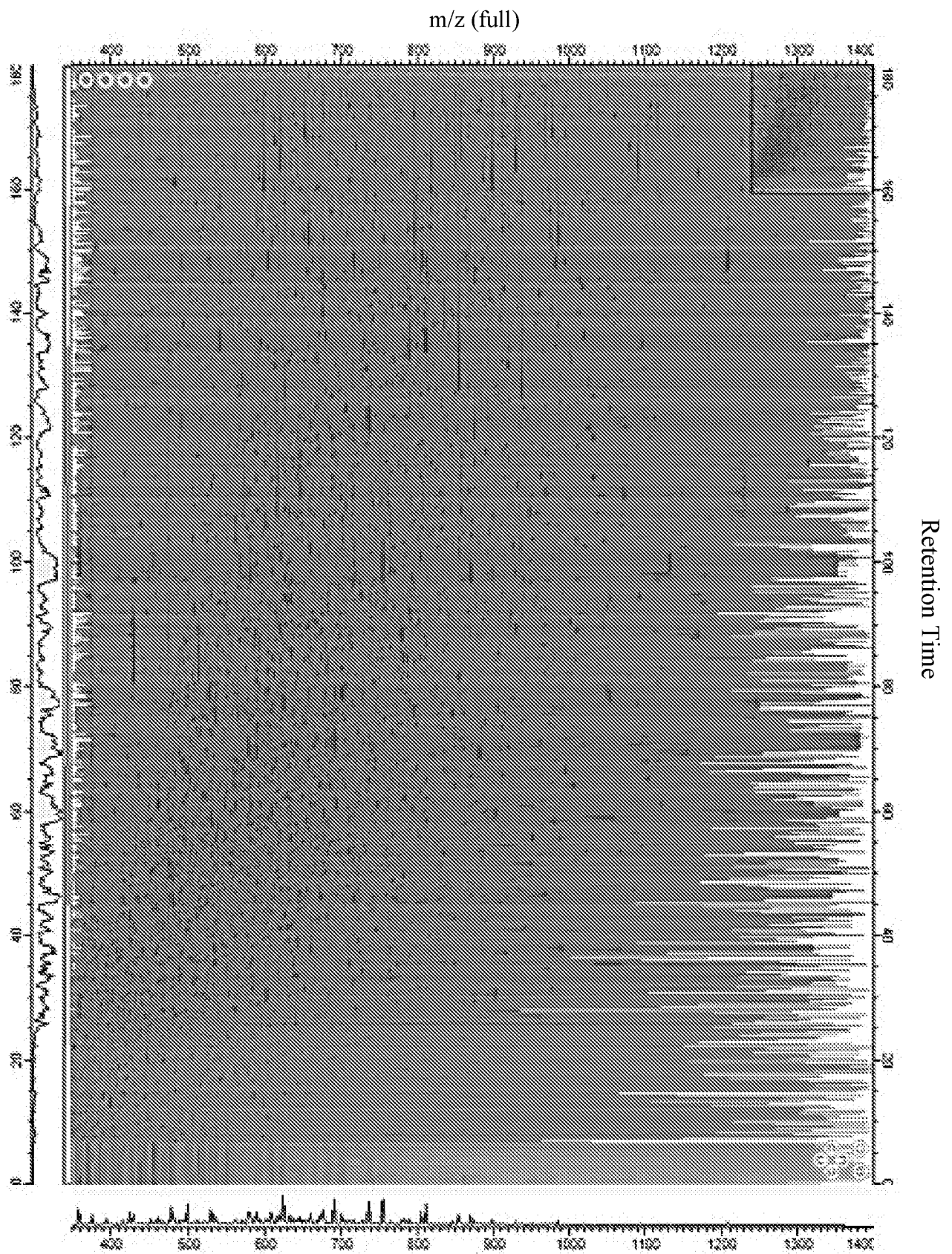


FIG. 3C

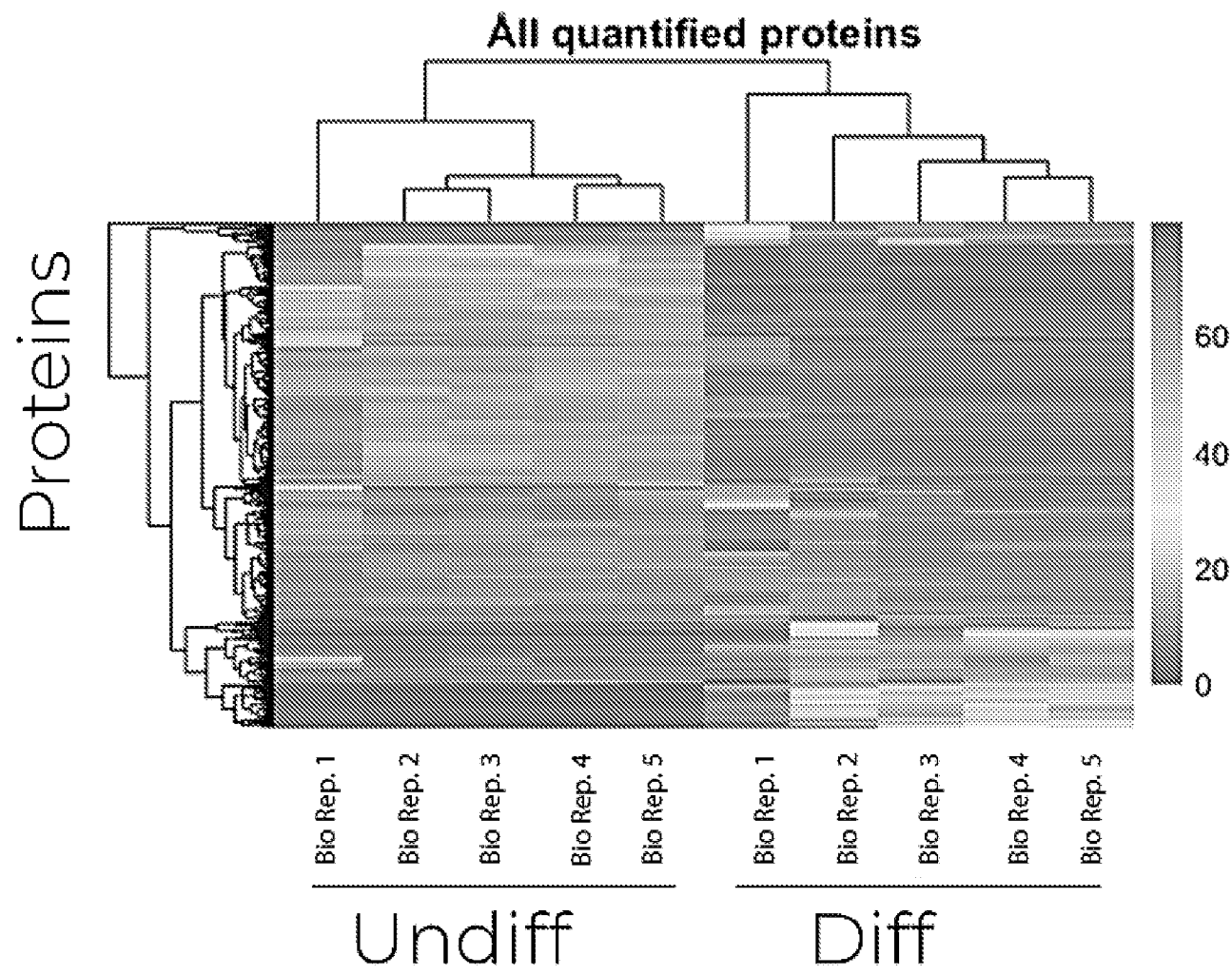


FIG. 3D

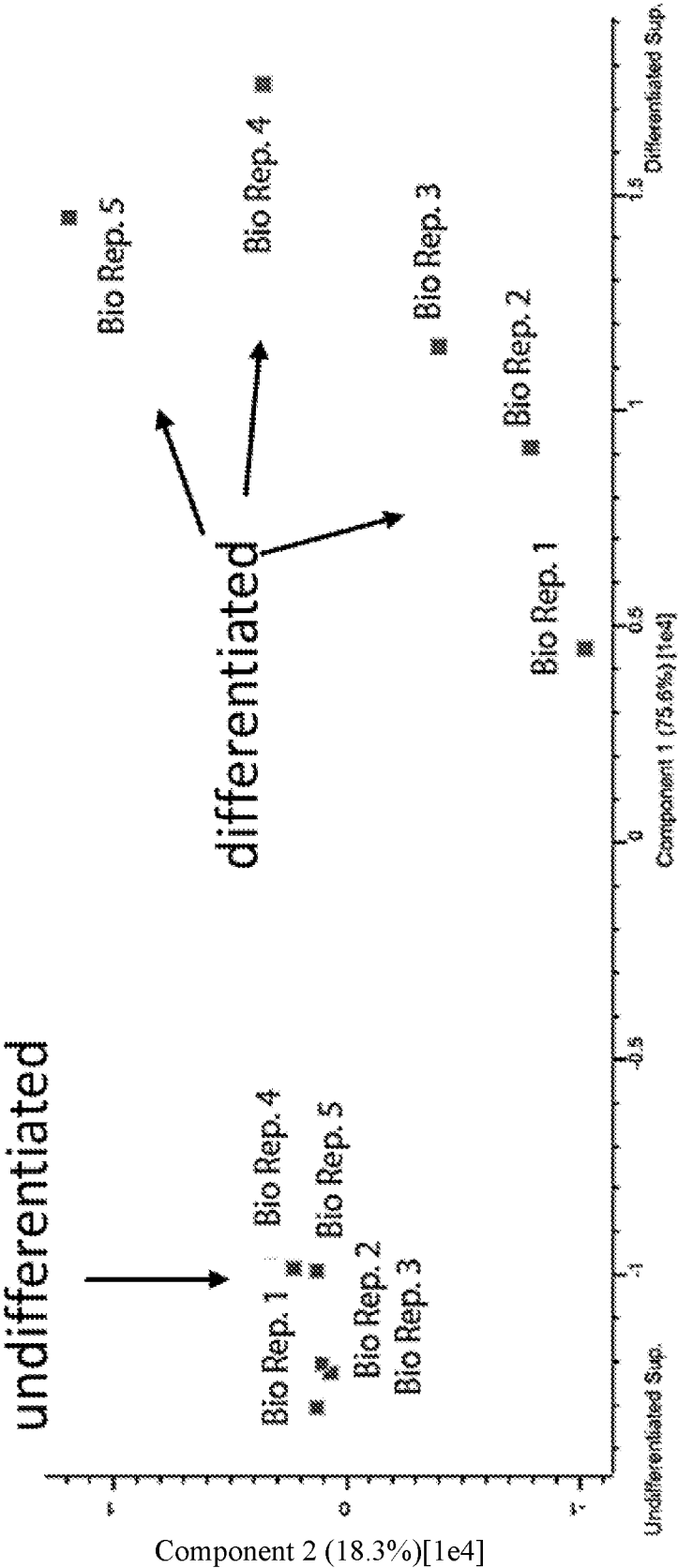


FIG. 3E

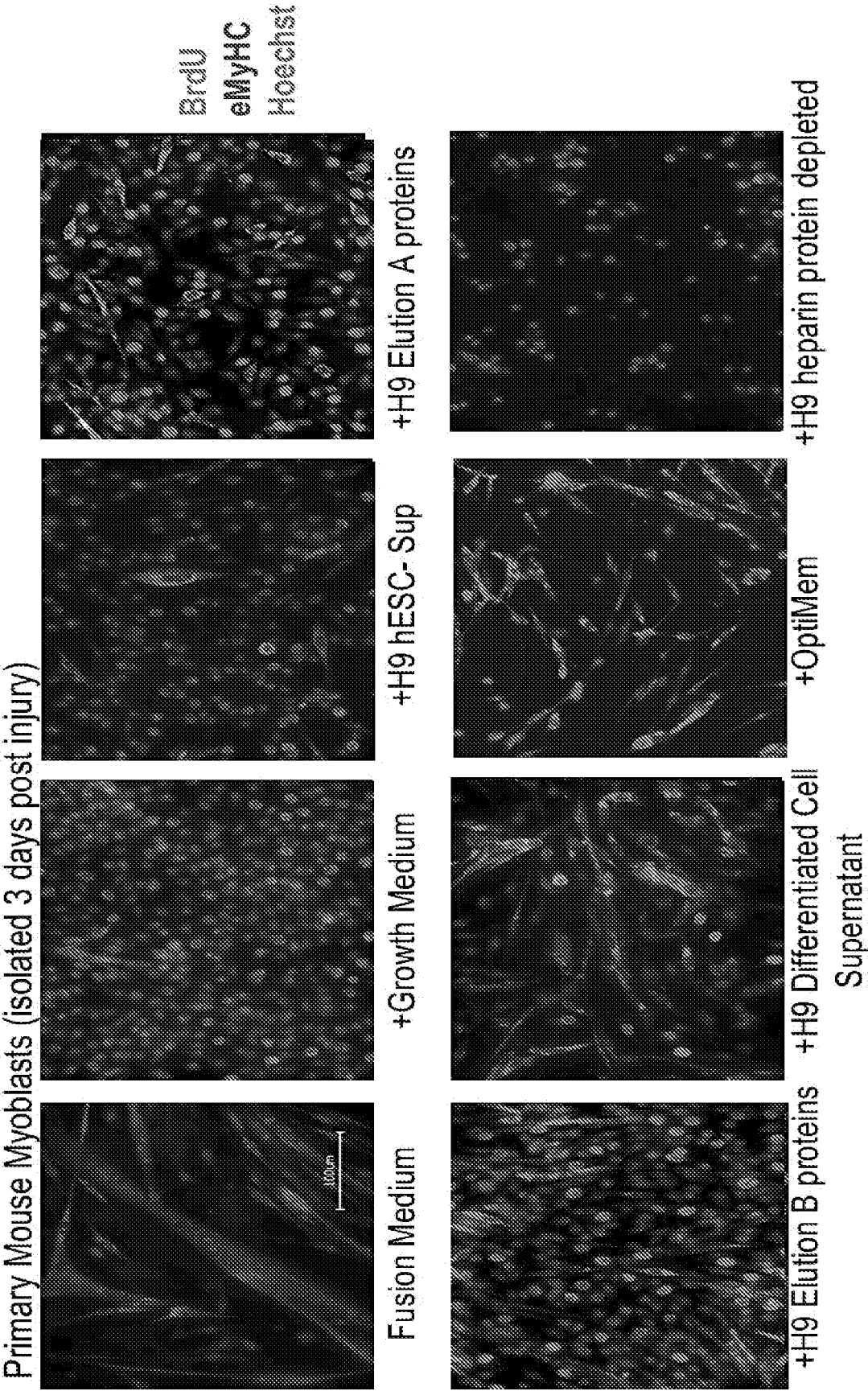


FIG. 4A

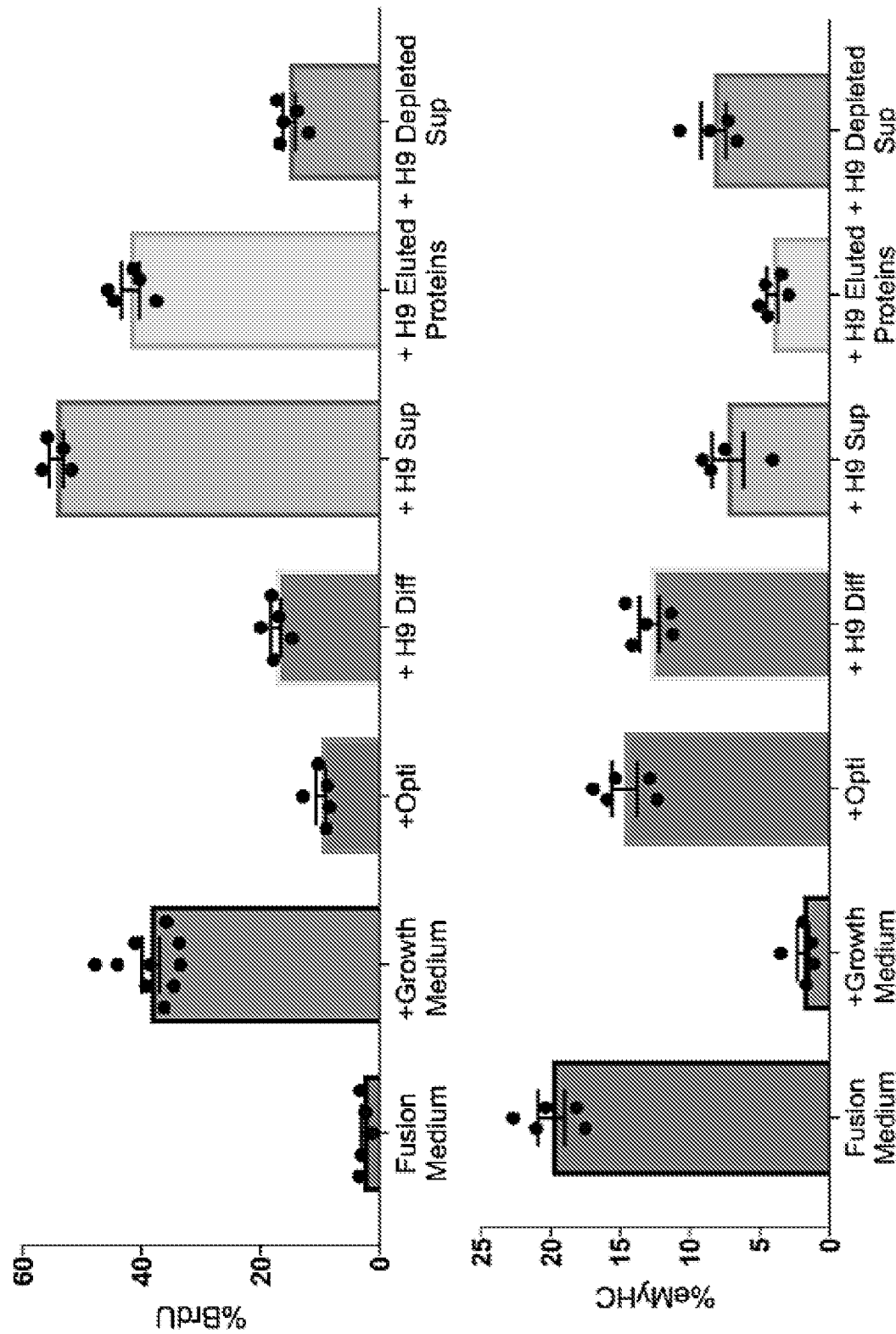


FIG. 4B

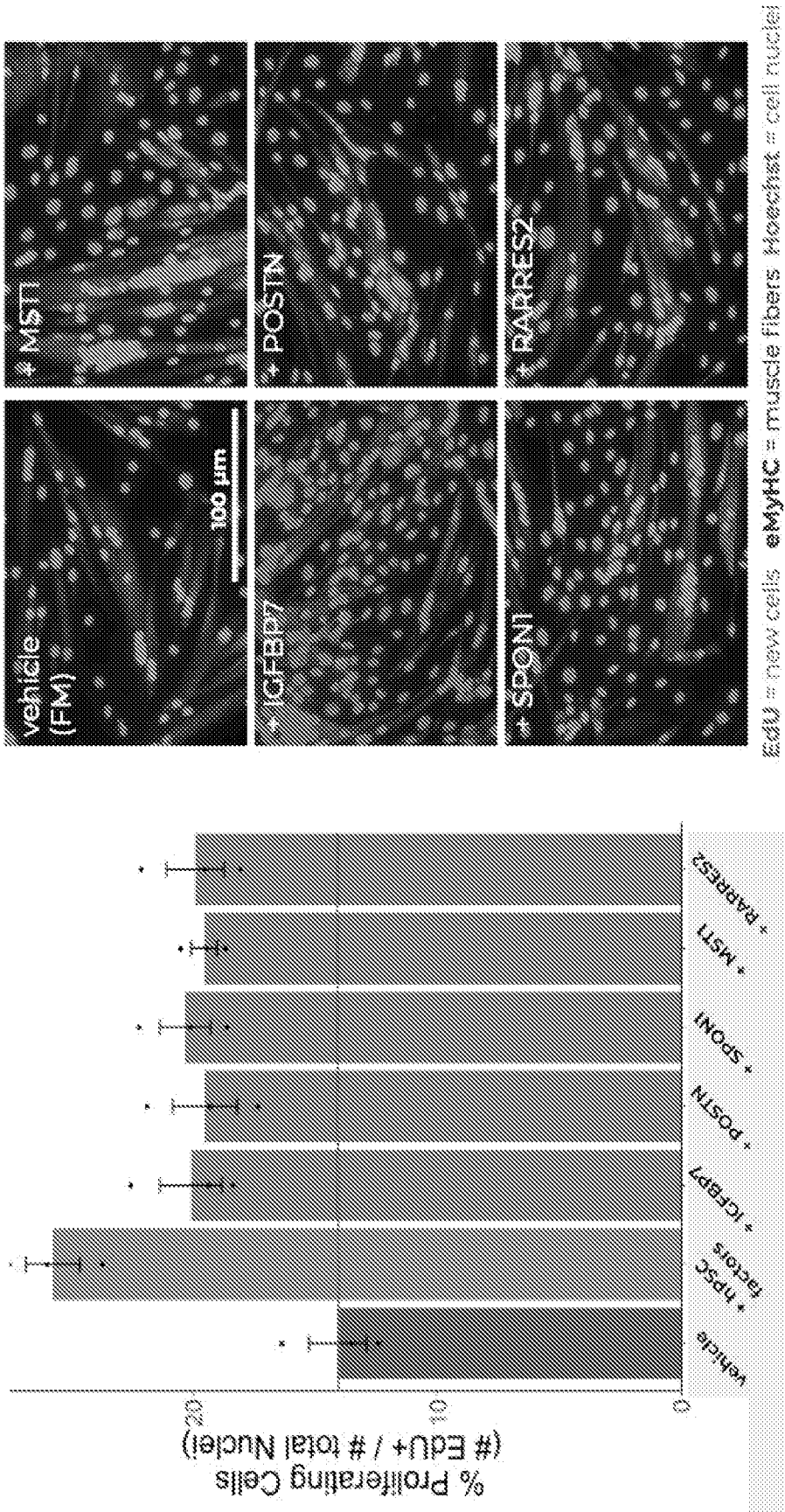


FIG. 5A

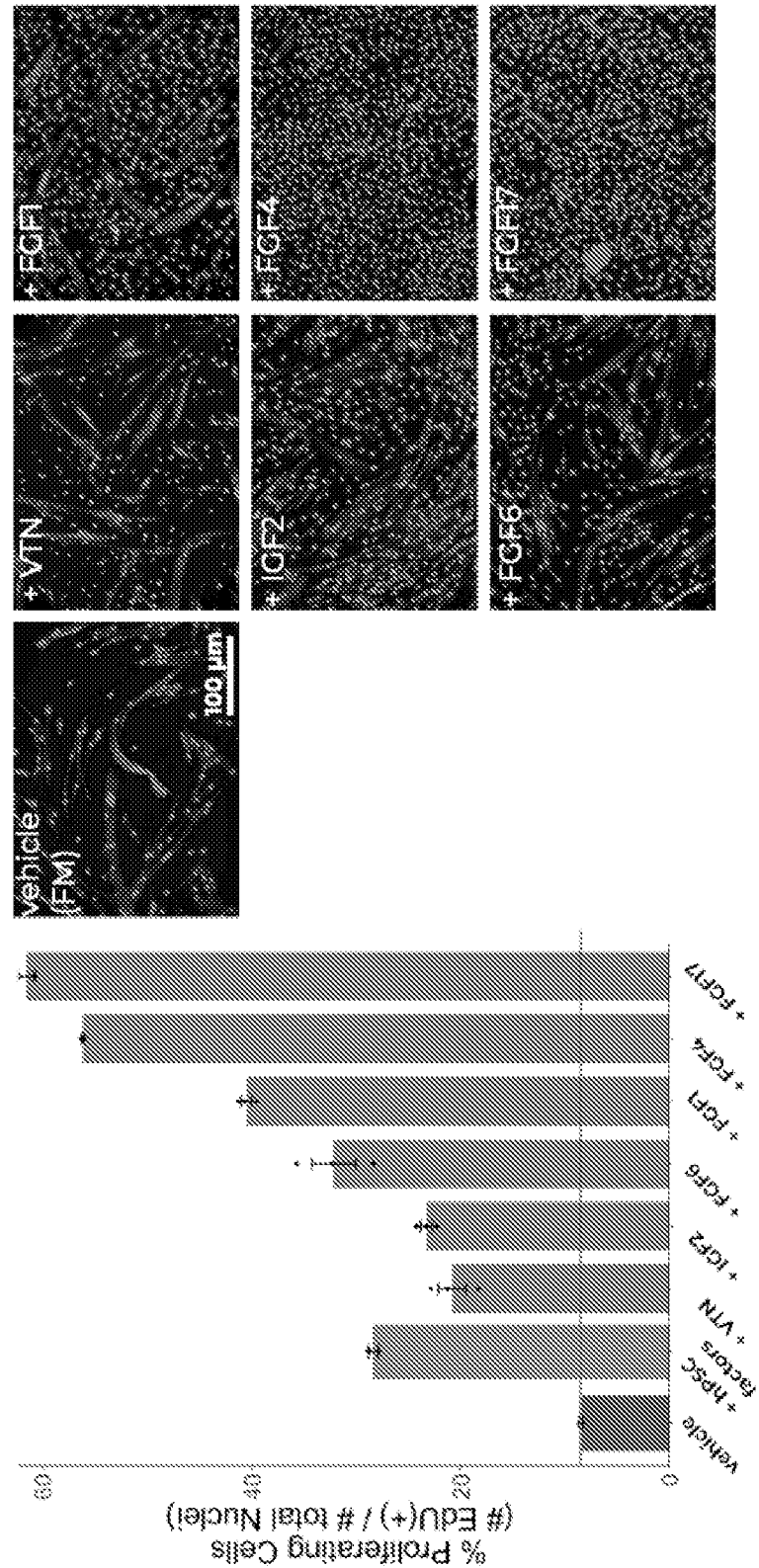


FIG. 5B

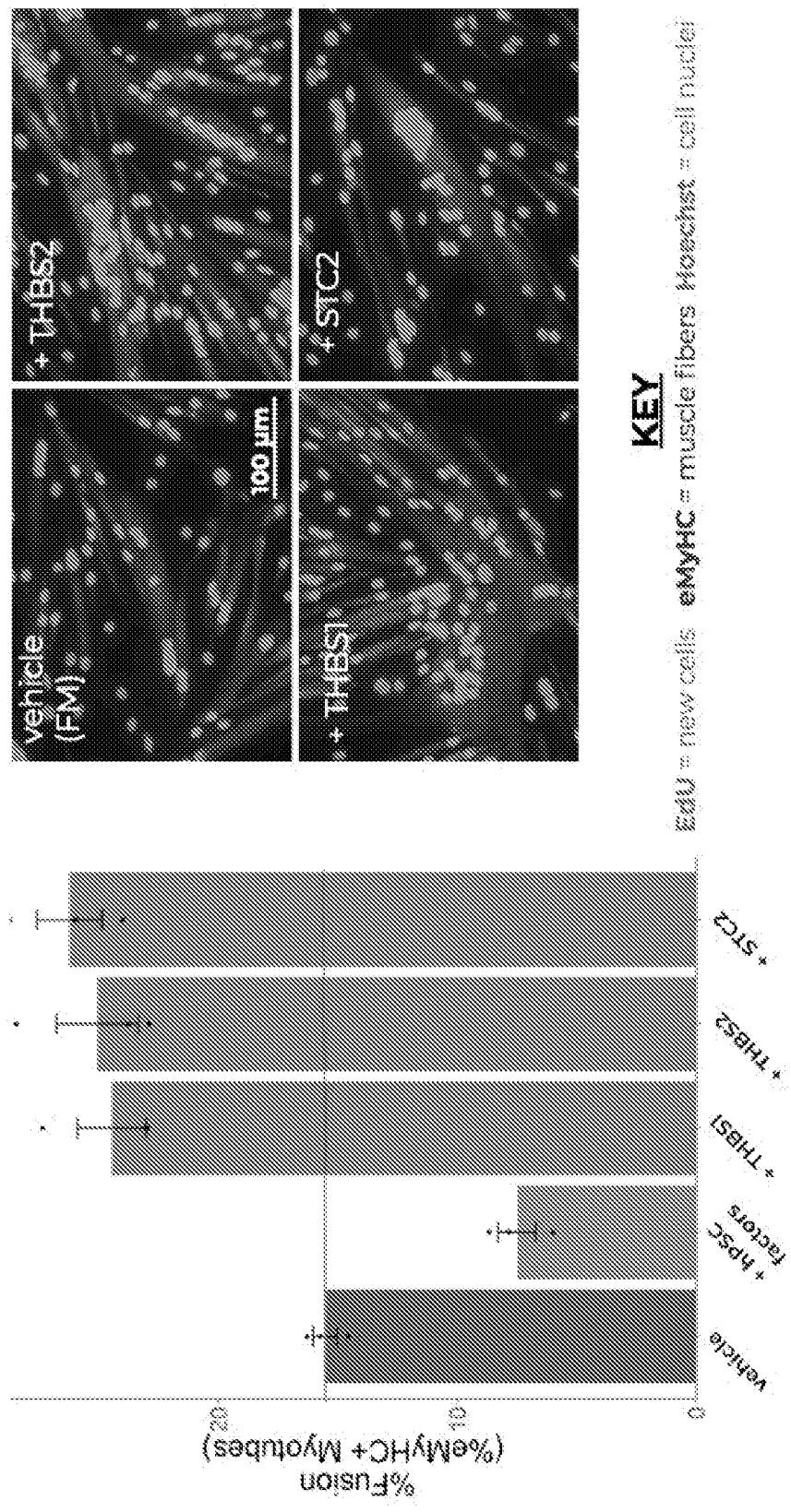


FIG. 5C

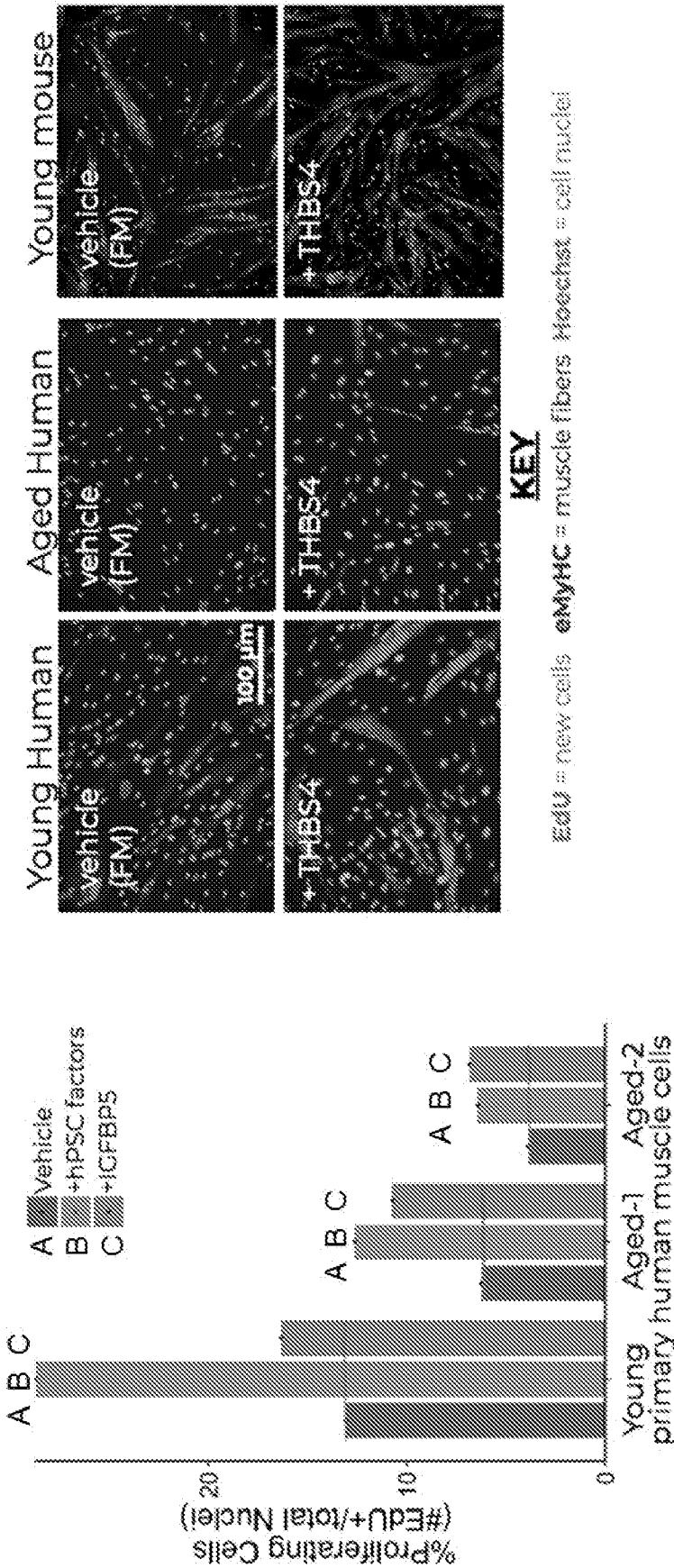


FIG. 6A

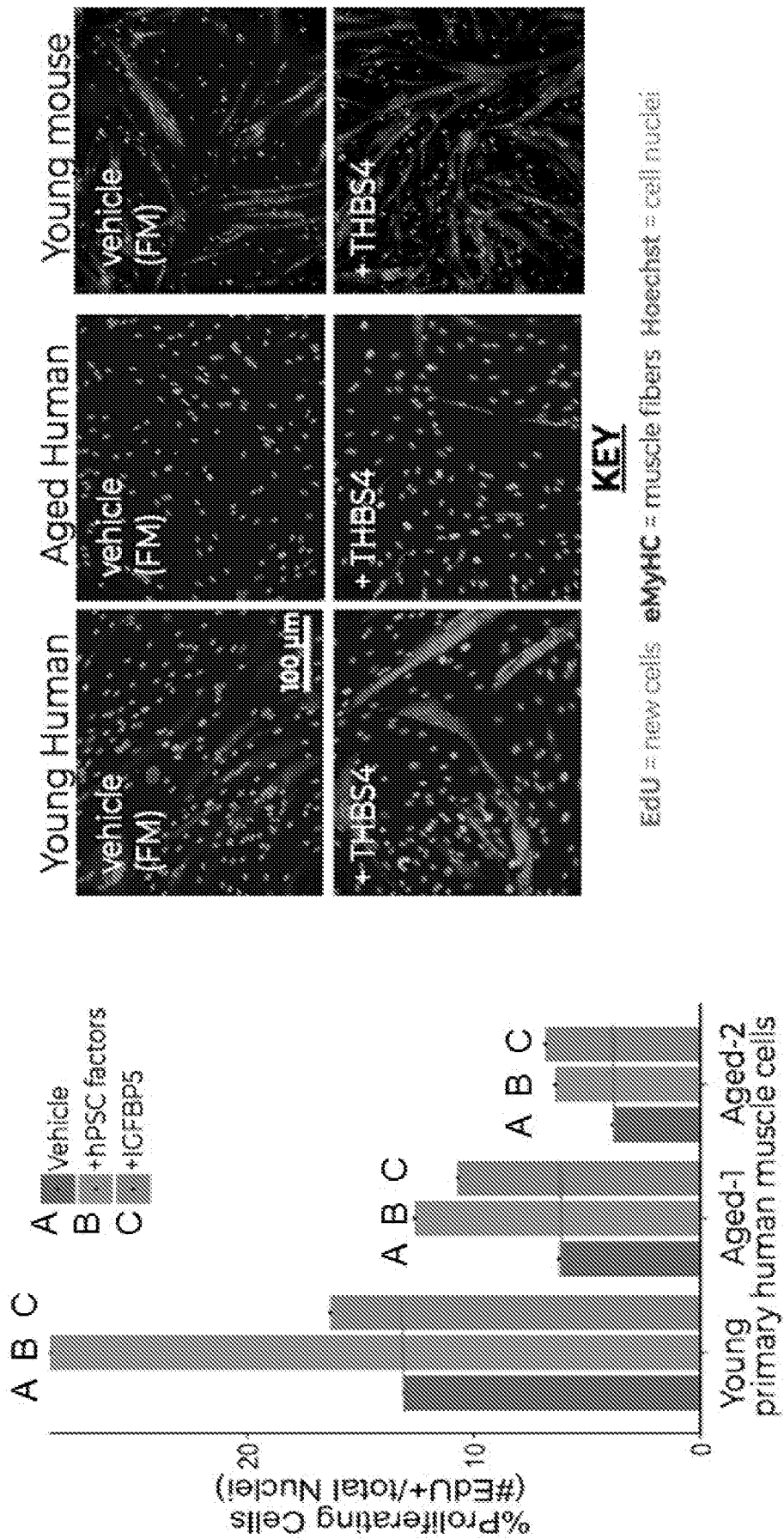


FIG. 6B

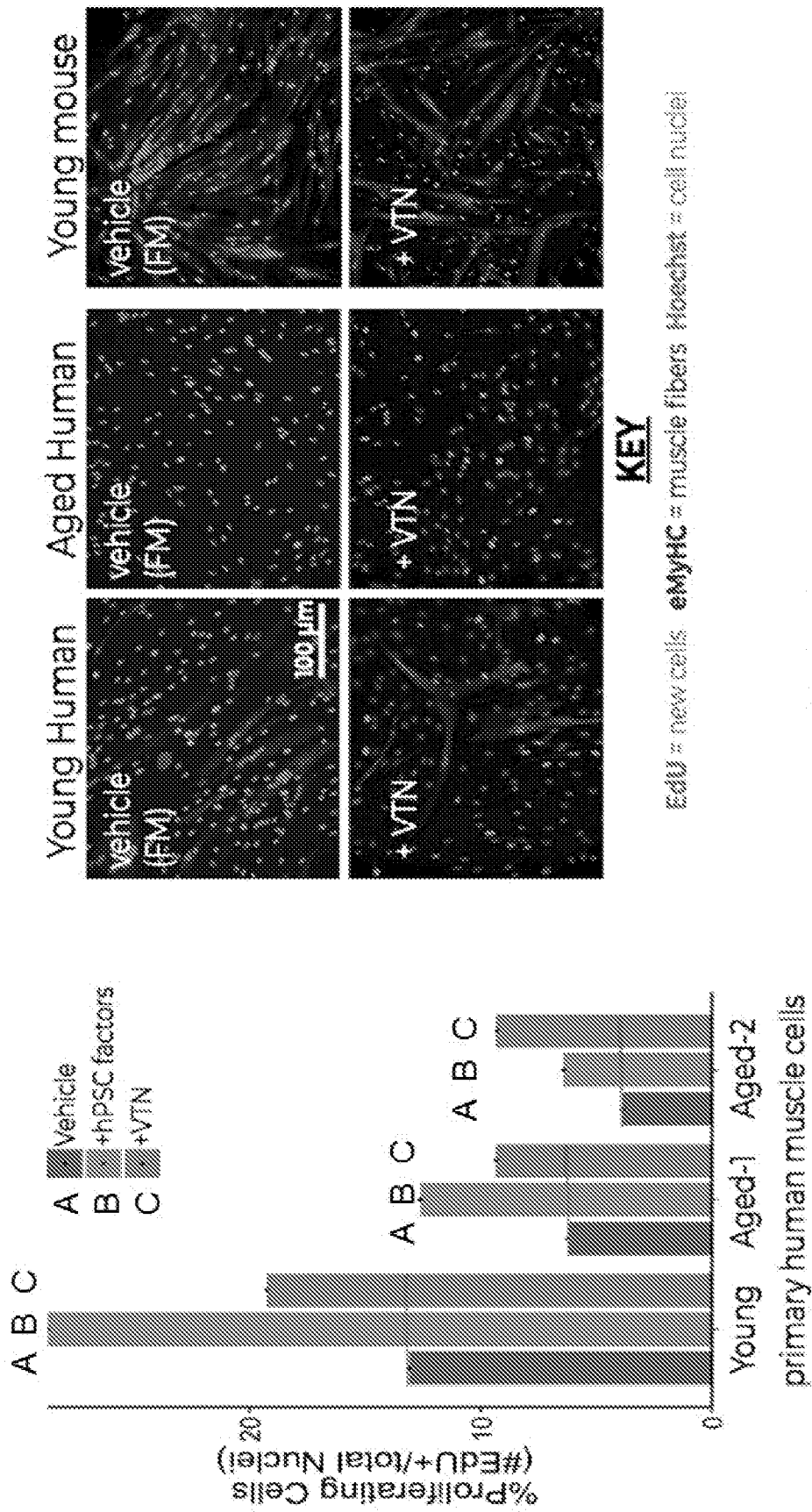


FIG. 6C

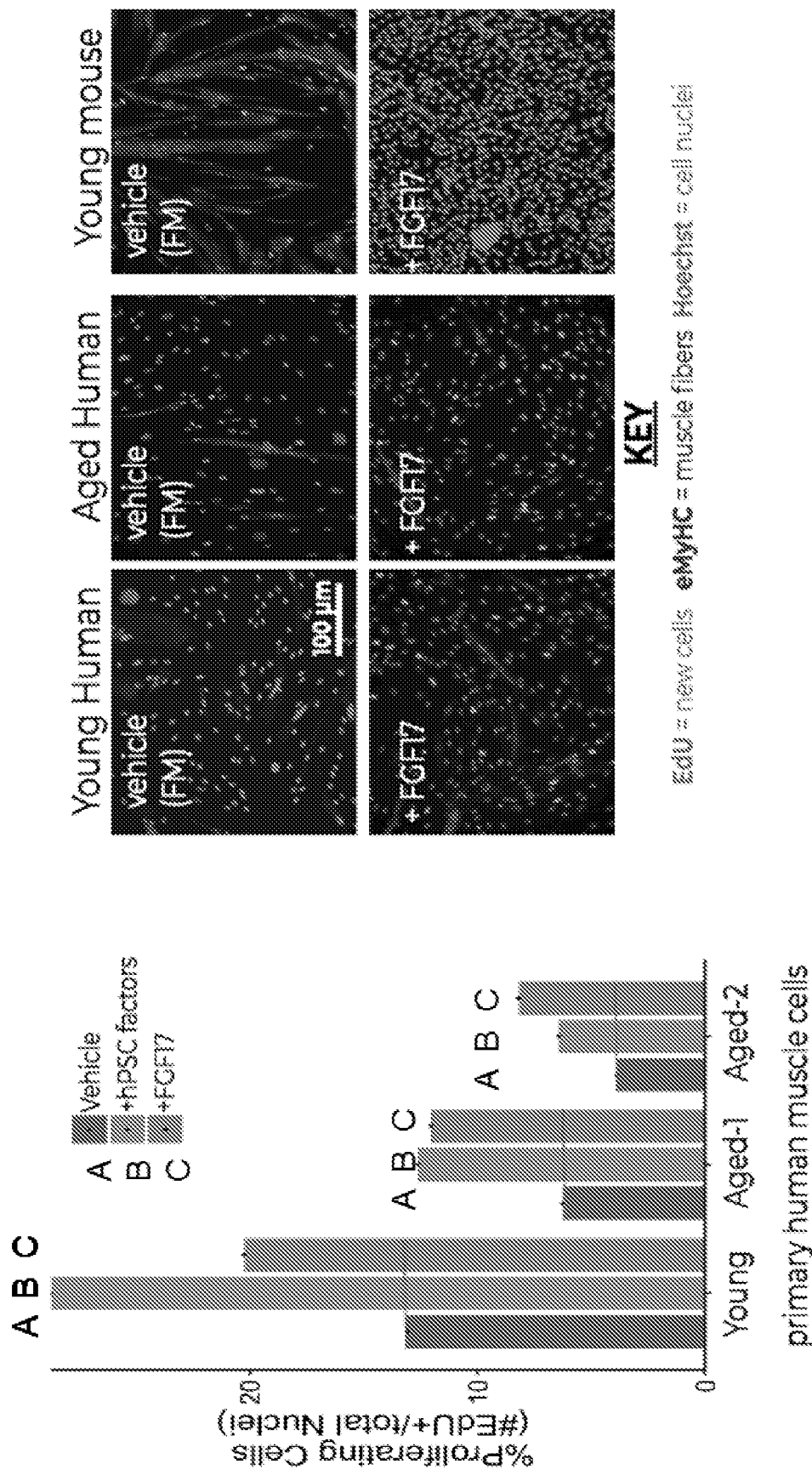


FIG. 6D

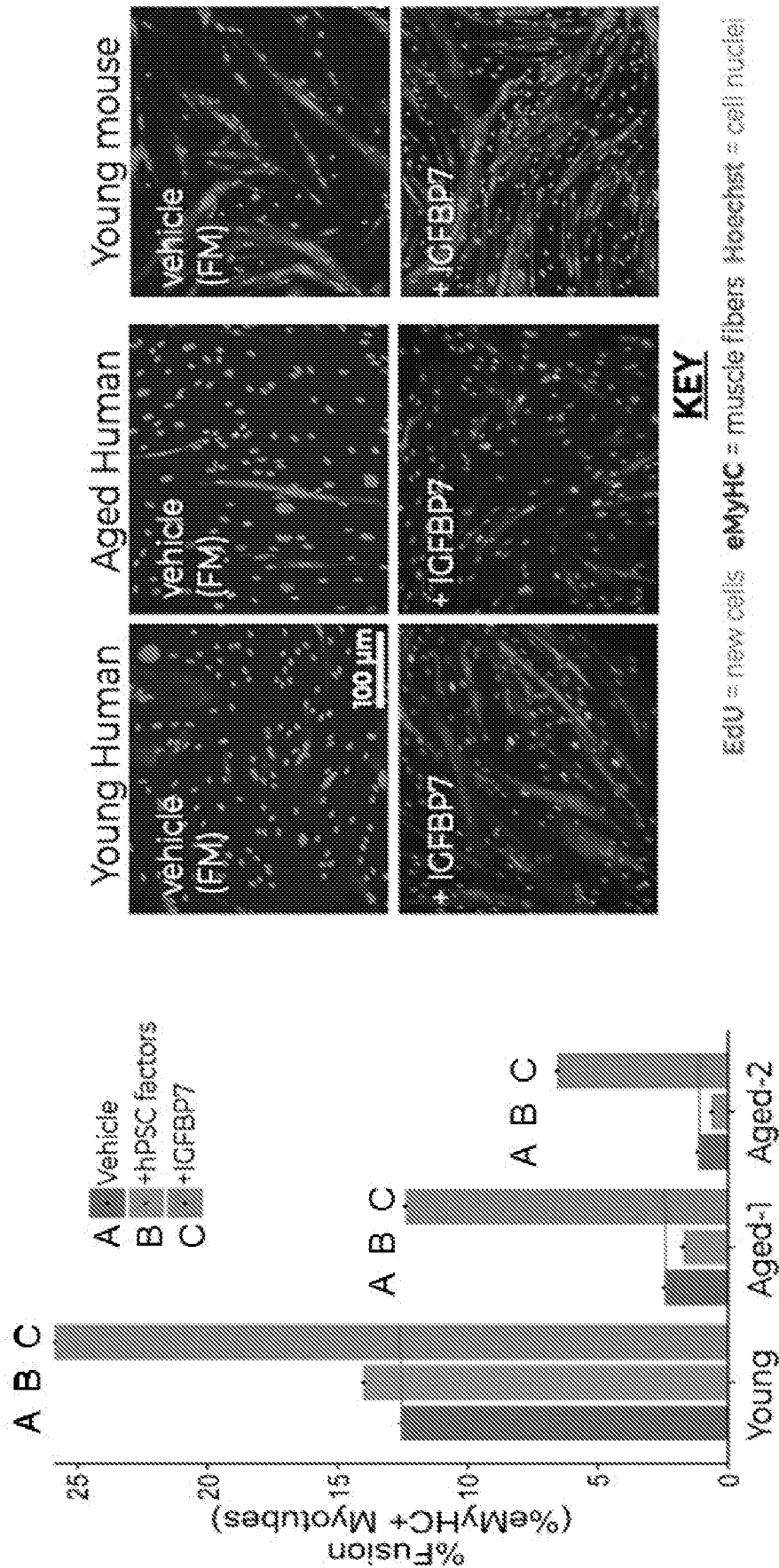


FIG. 6E

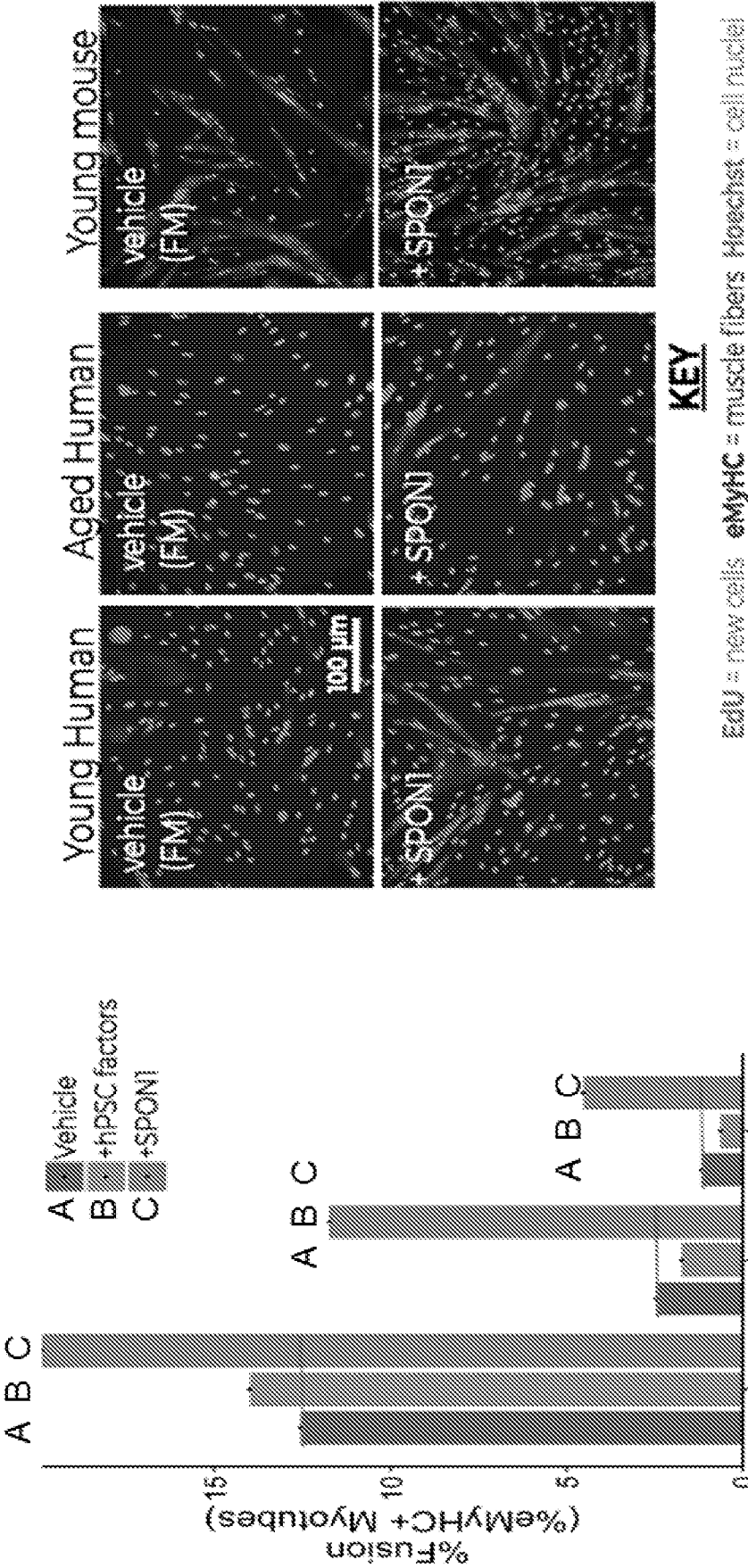


FIG. 6F

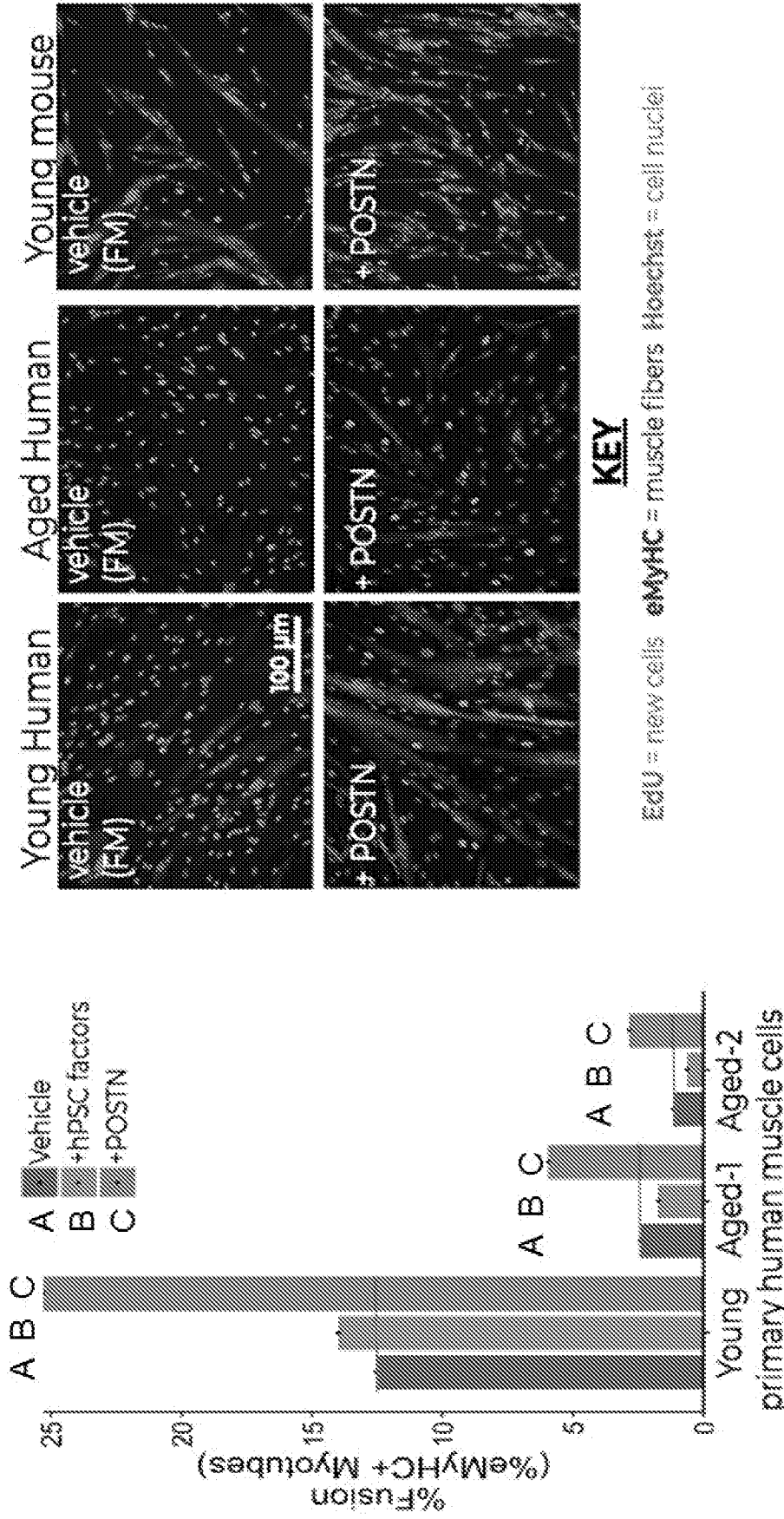
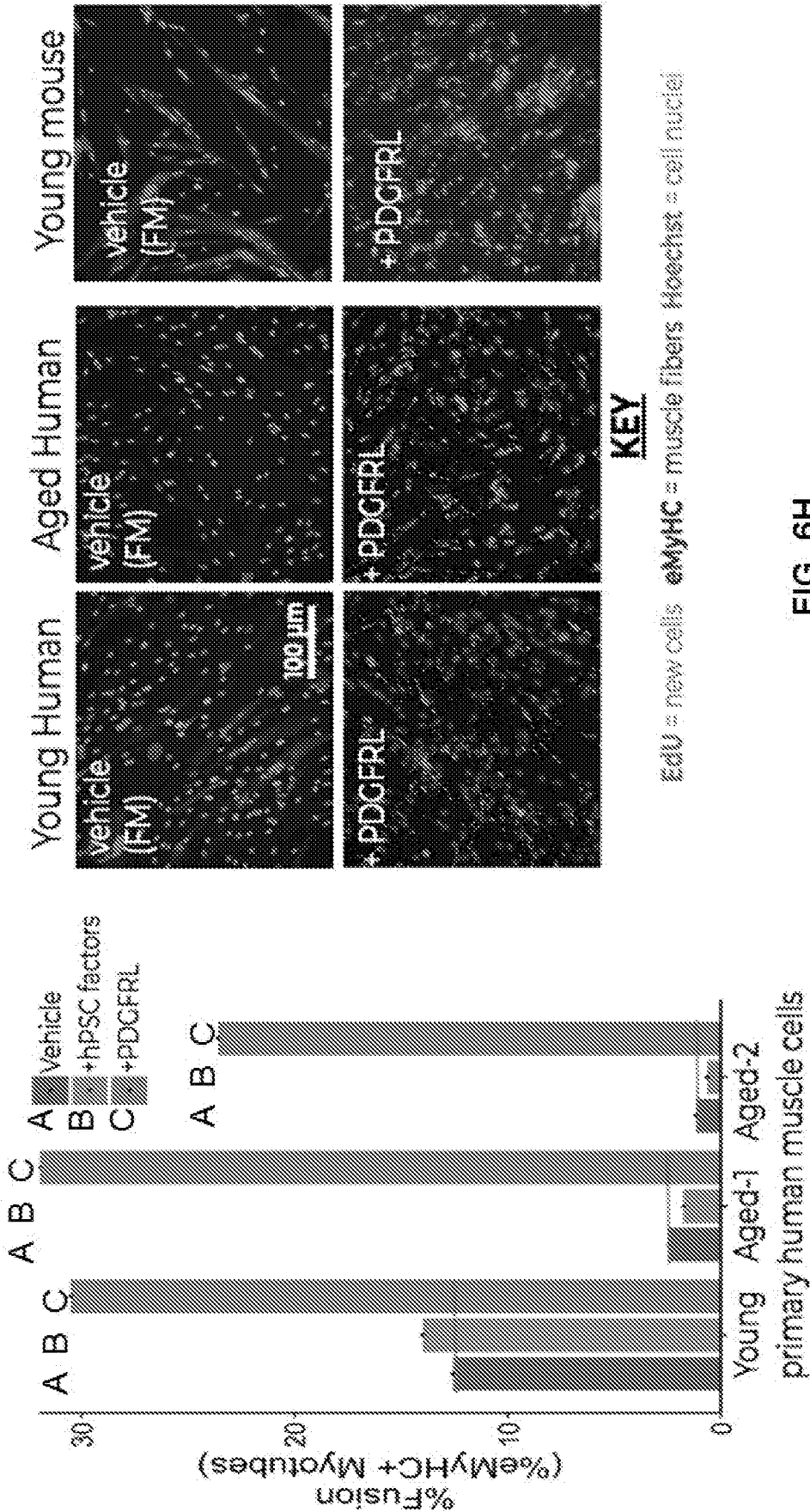


FIG. 6G



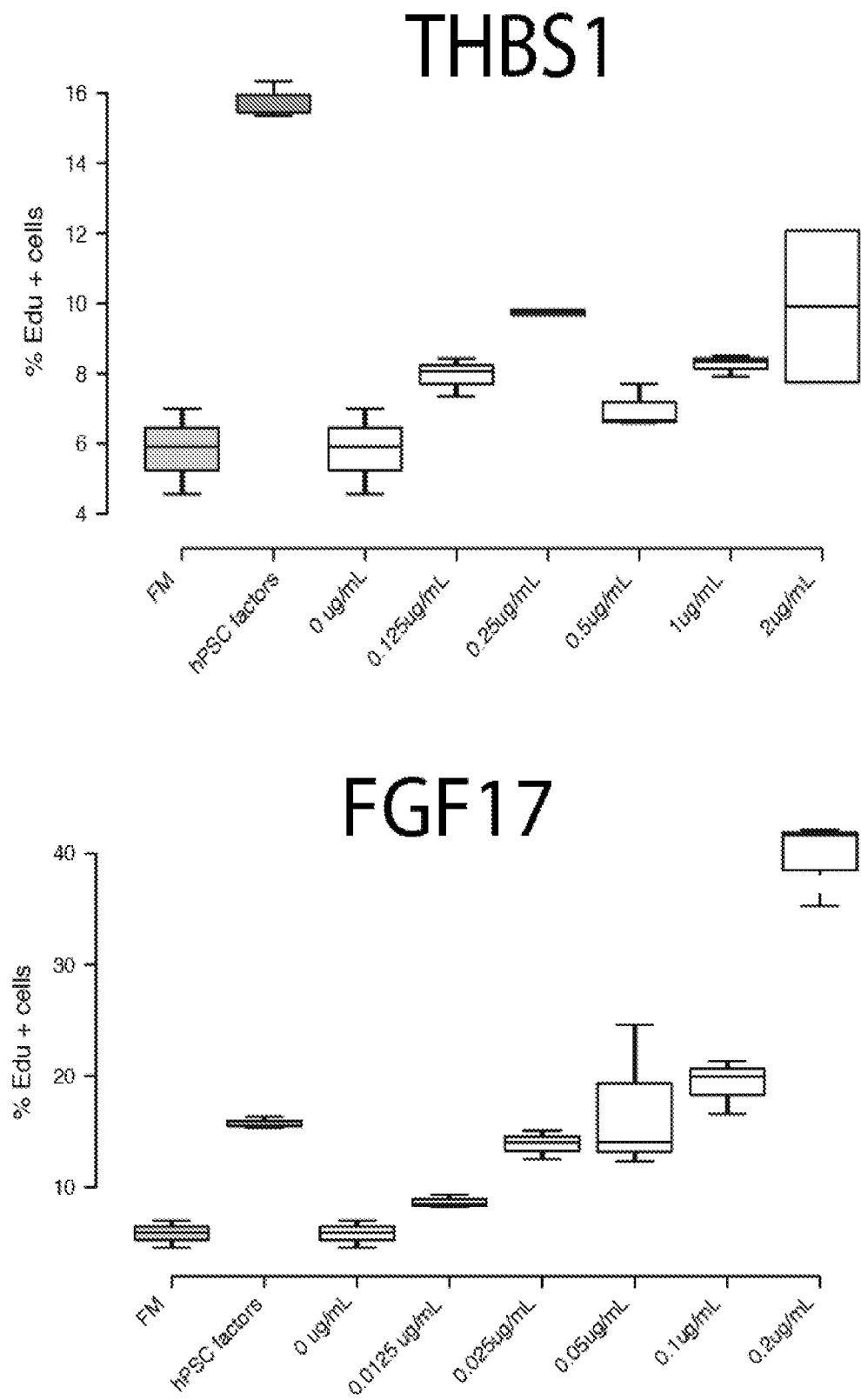


FIG. 7A

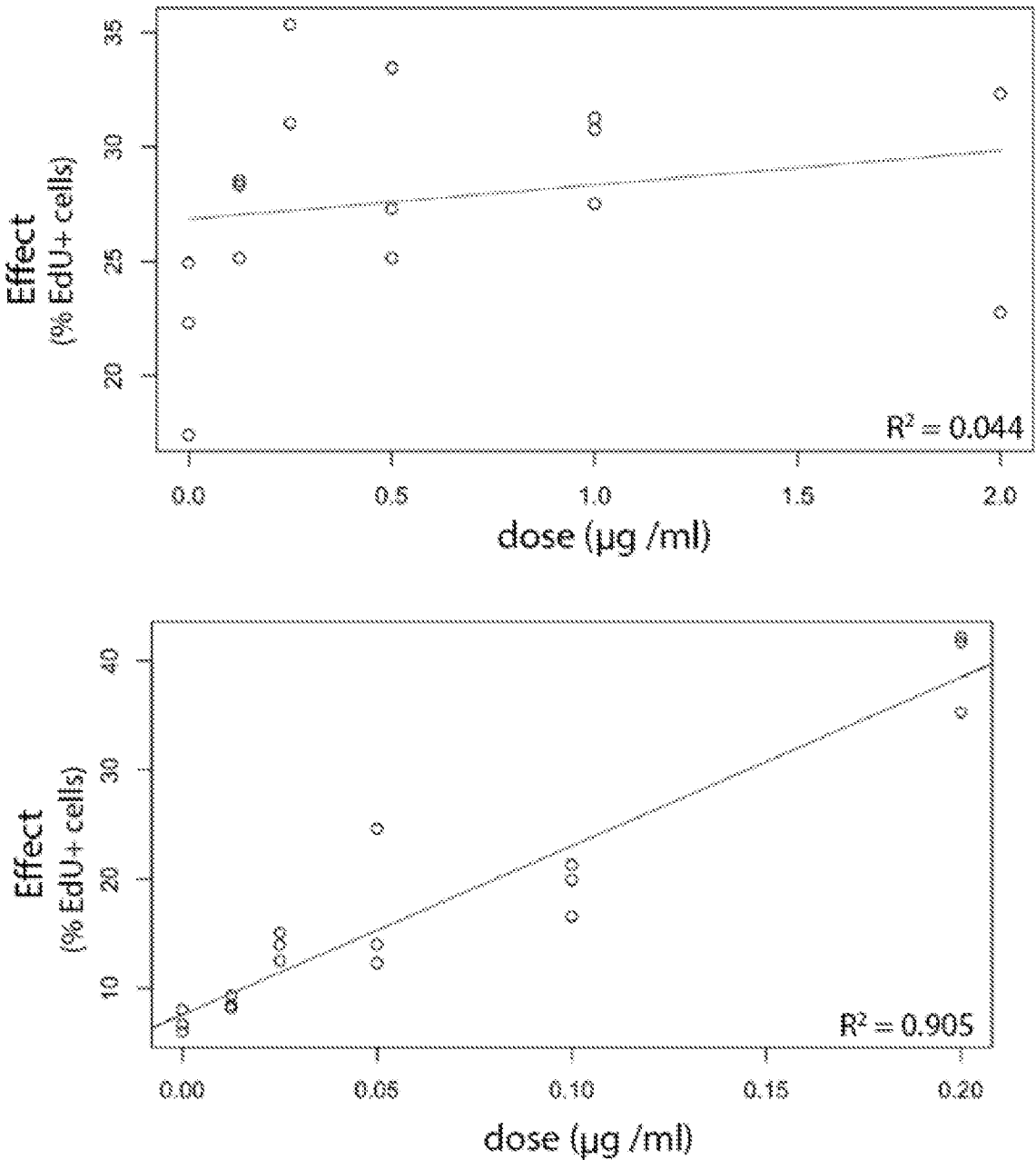


FIG. 7B

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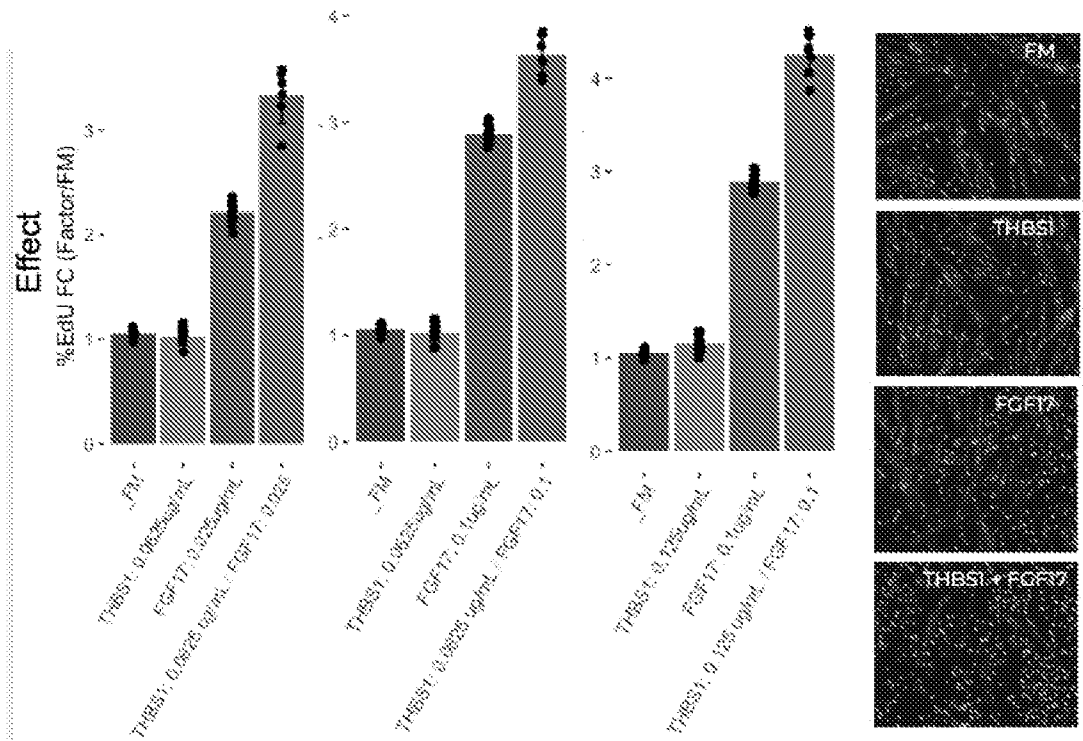


FIG. 7C

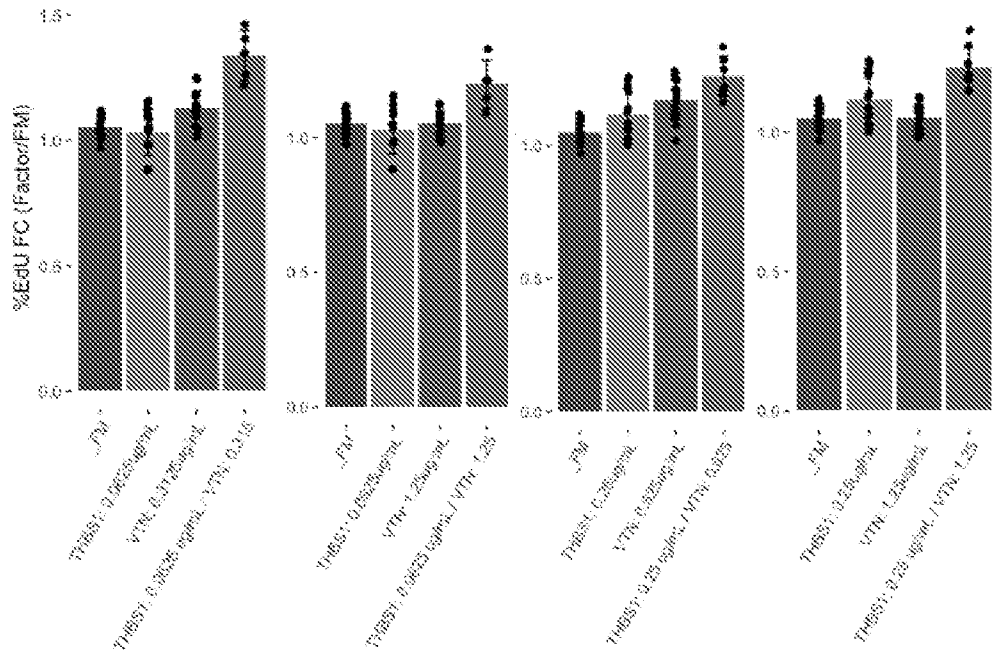


FIG. 7D

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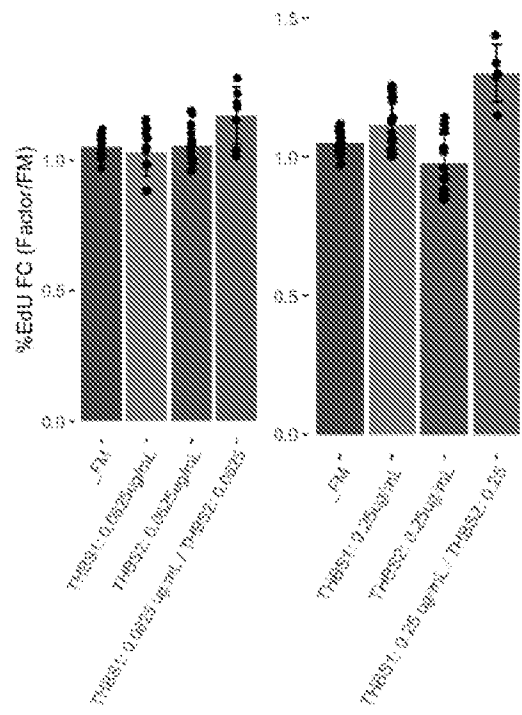


FIG. 7E

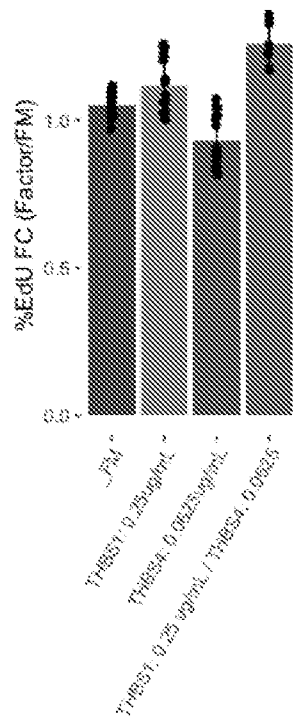


FIG. 7F

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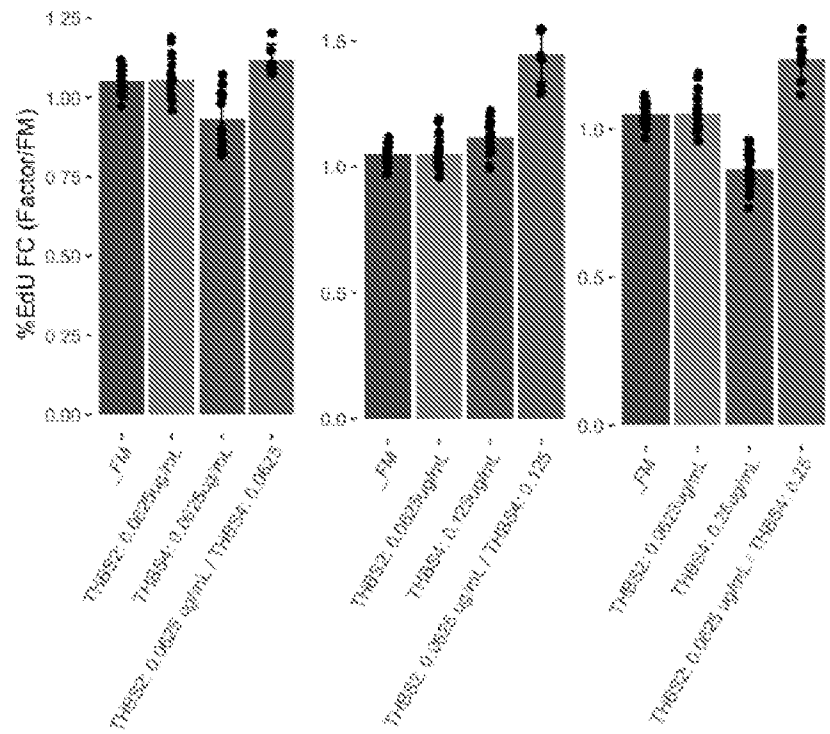


FIG. 7G

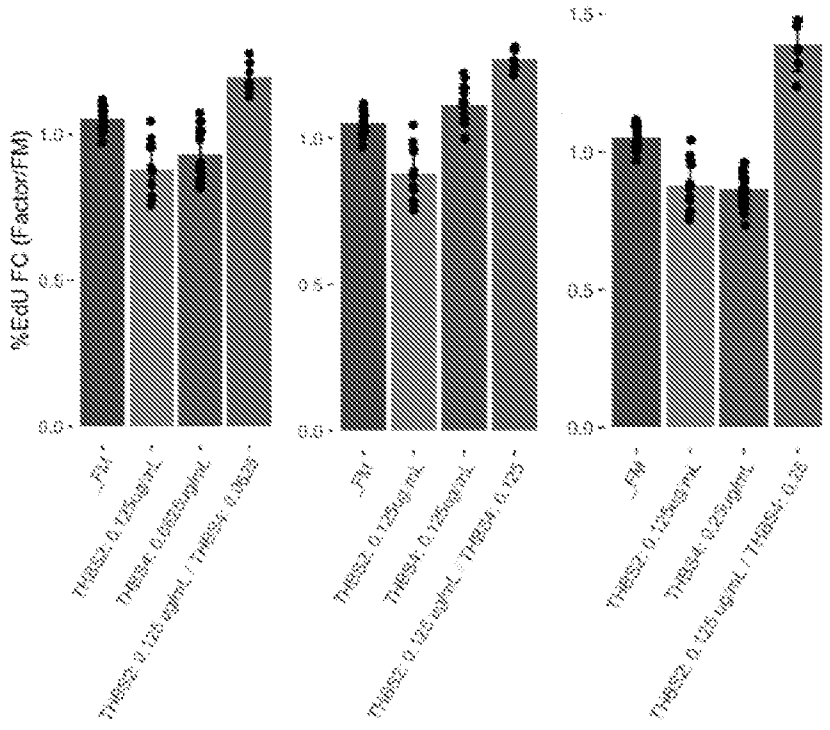


FIG. 7H

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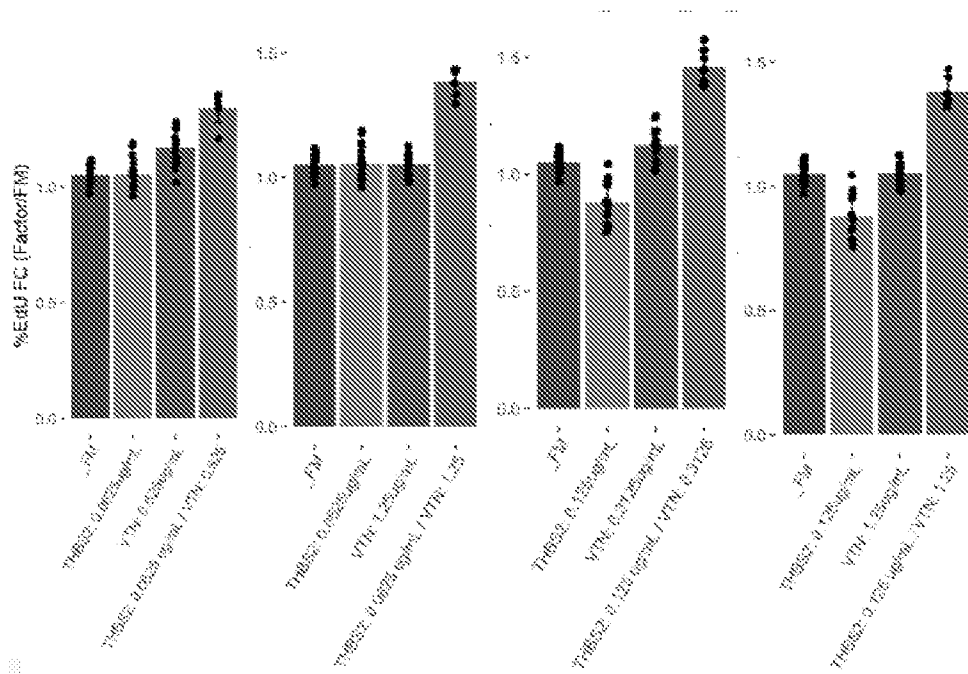


FIG. 7I

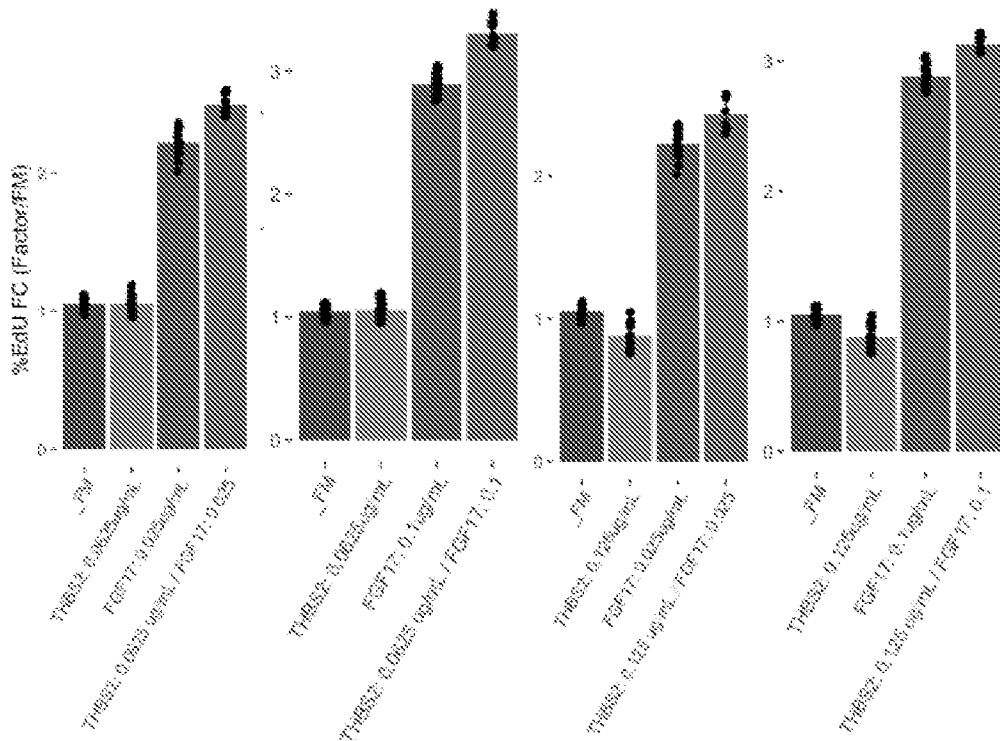


FIG. 7J

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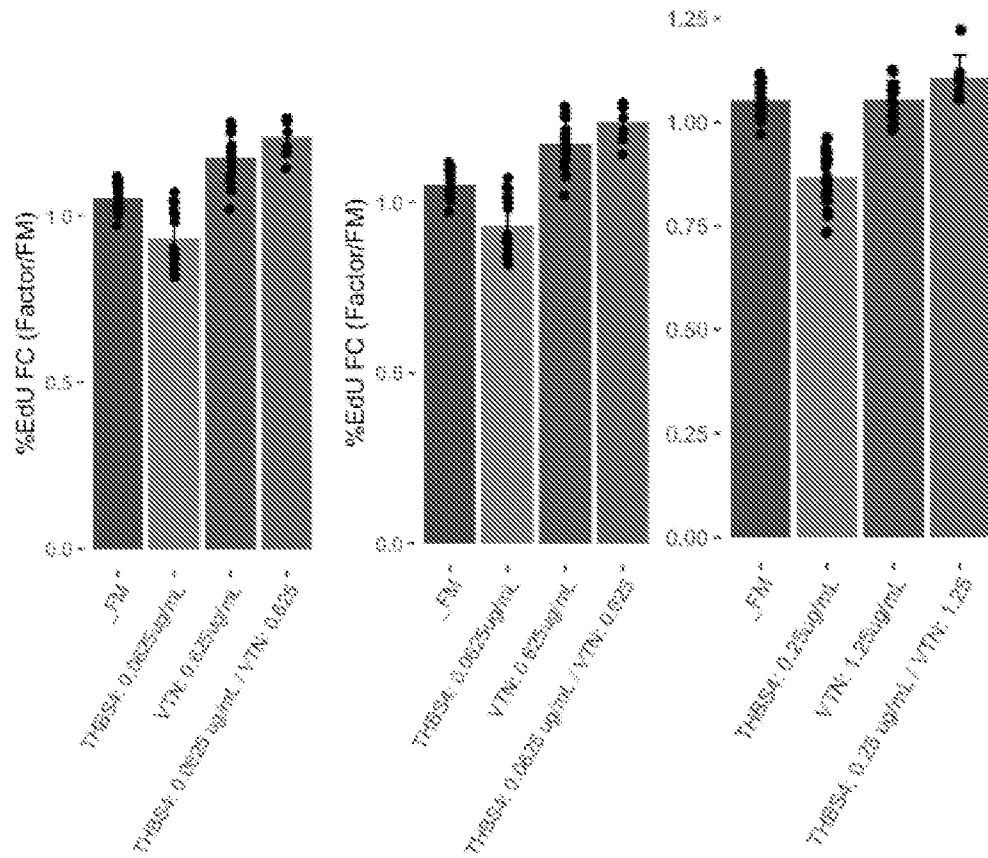


FIG. 7K

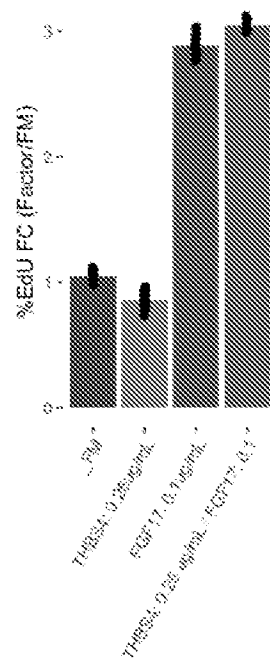


FIG. 7L

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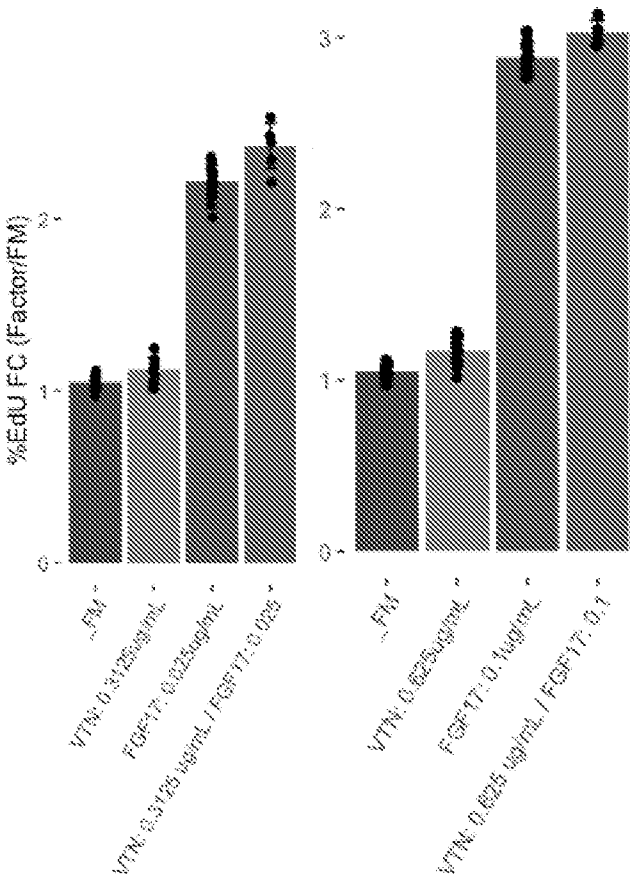


FIG. 7M

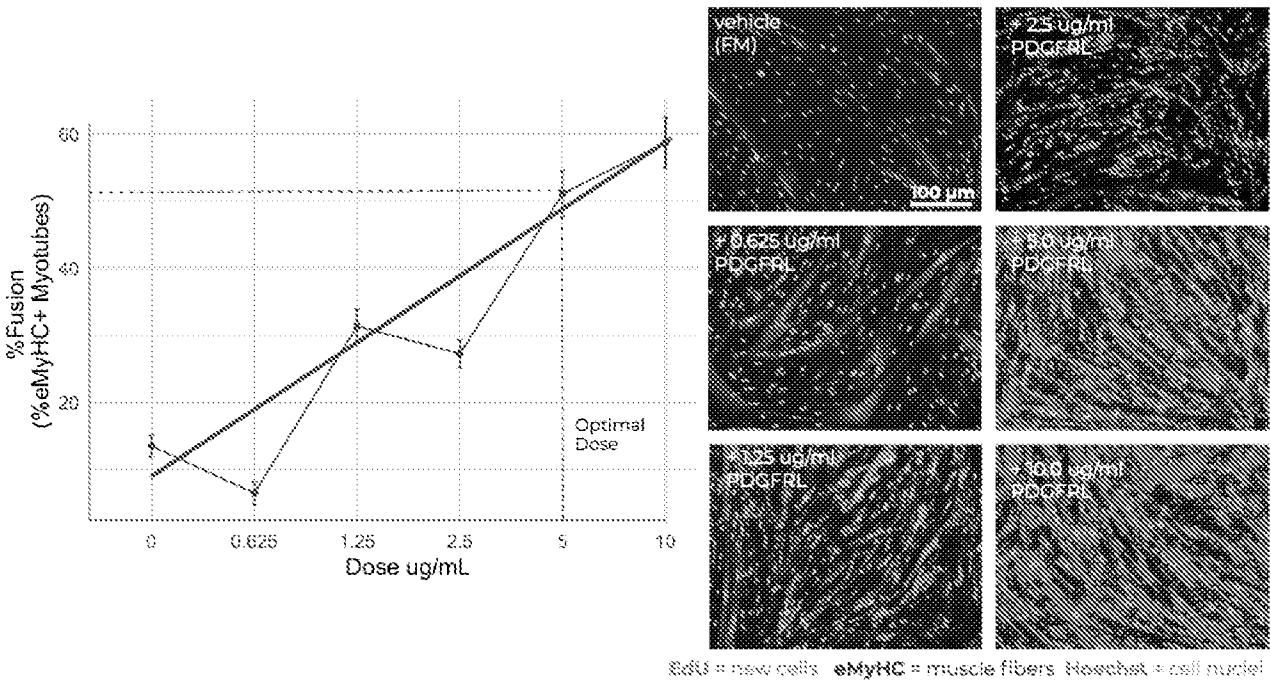


FIG. 8

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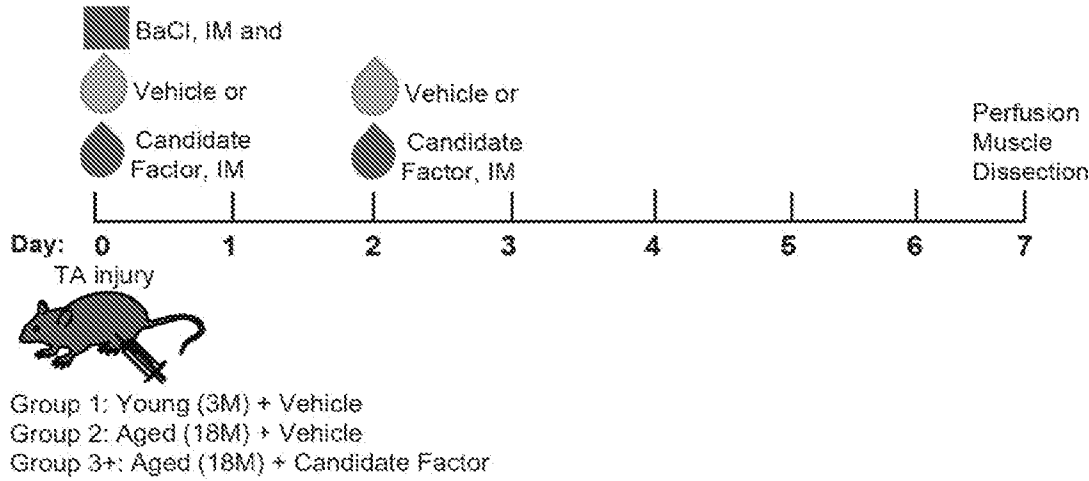


FIG. 9A

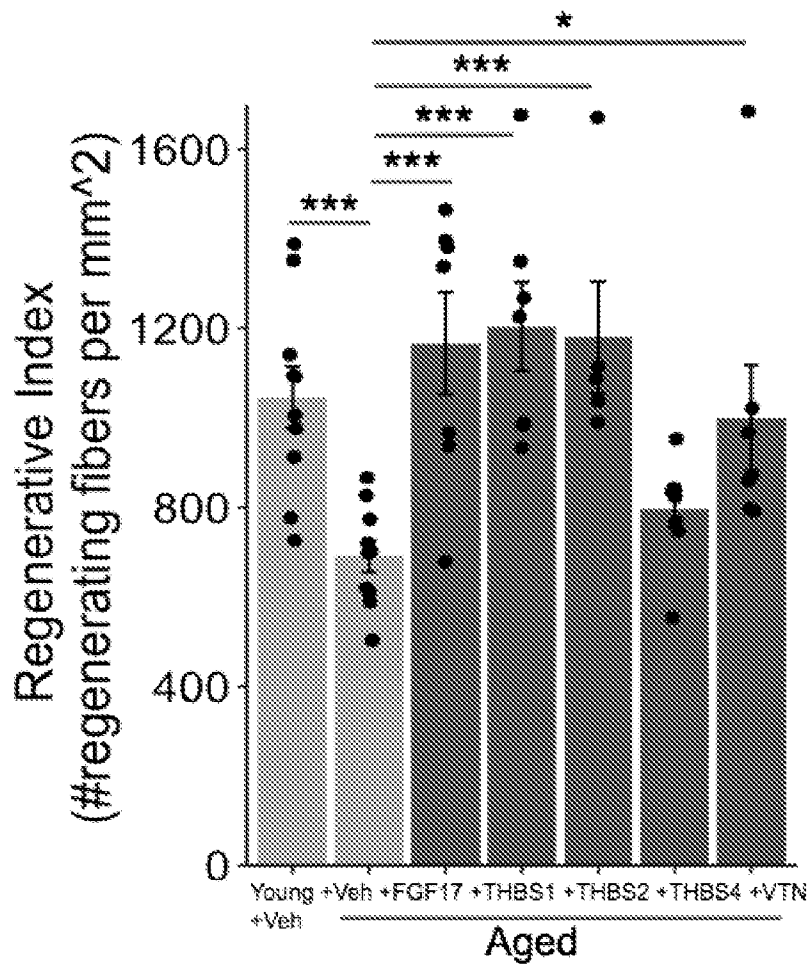


FIG. 9B

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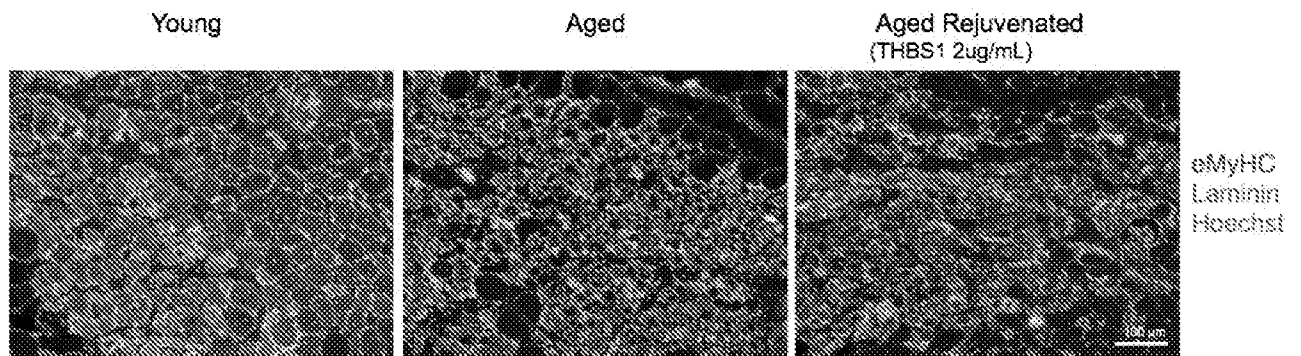


FIG. 9C

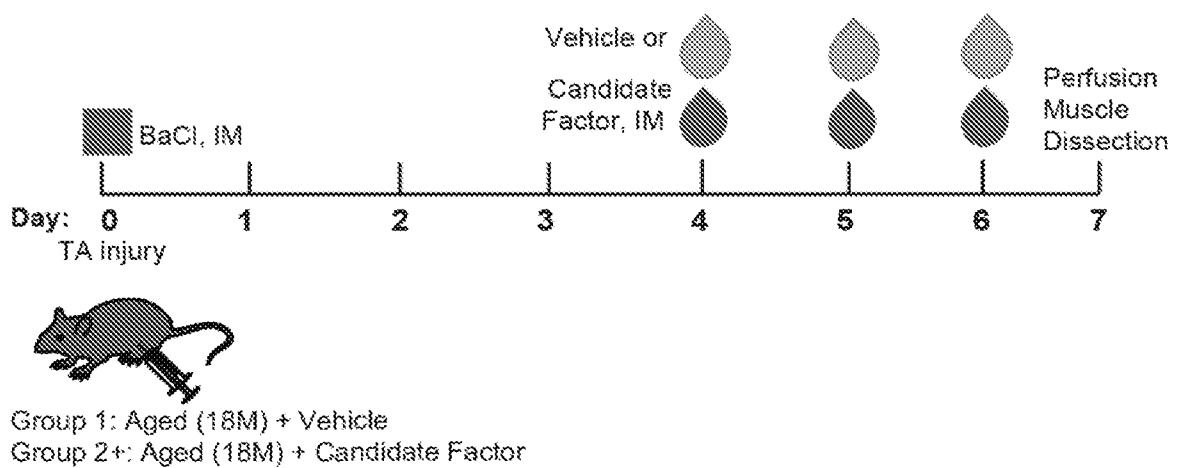


FIG. 9D

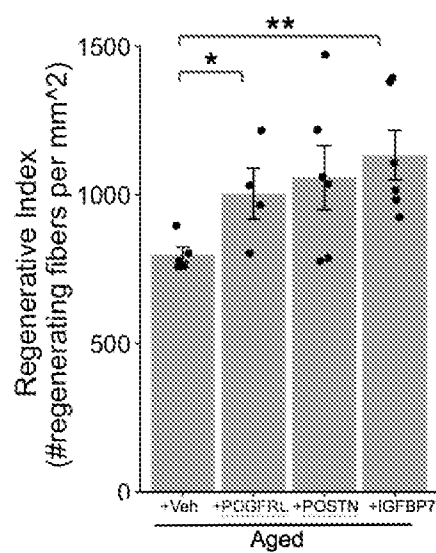


FIG. 9E

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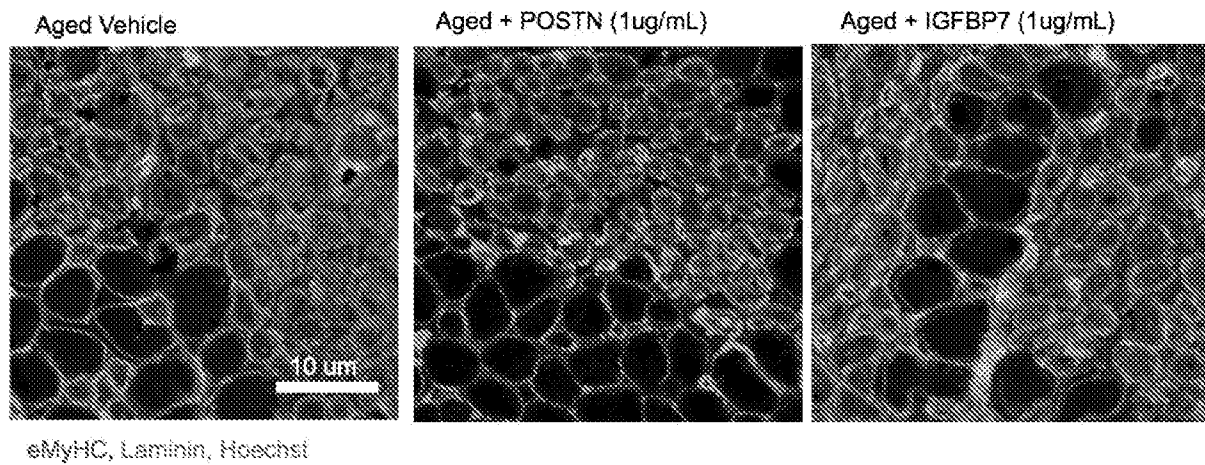


FIG. 9F

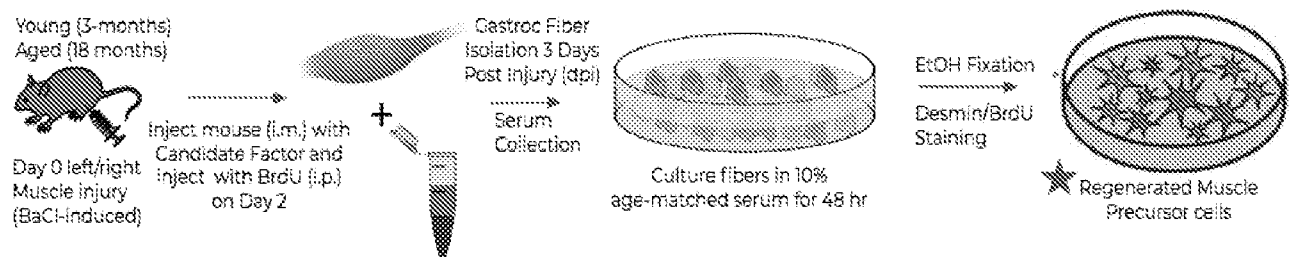


FIG. 10A

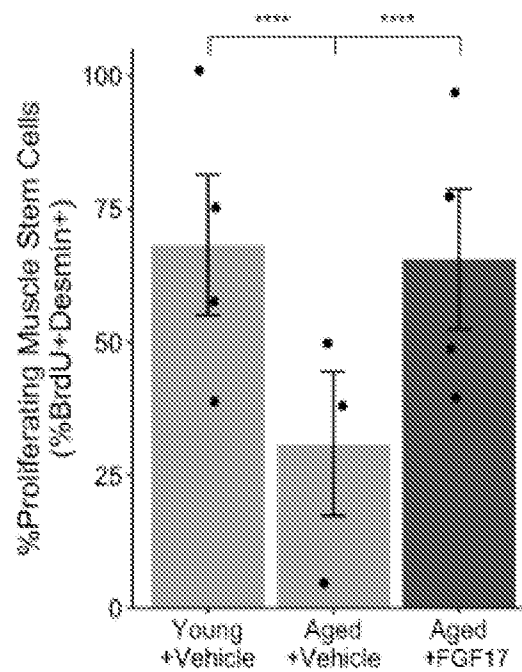


FIG. 10B

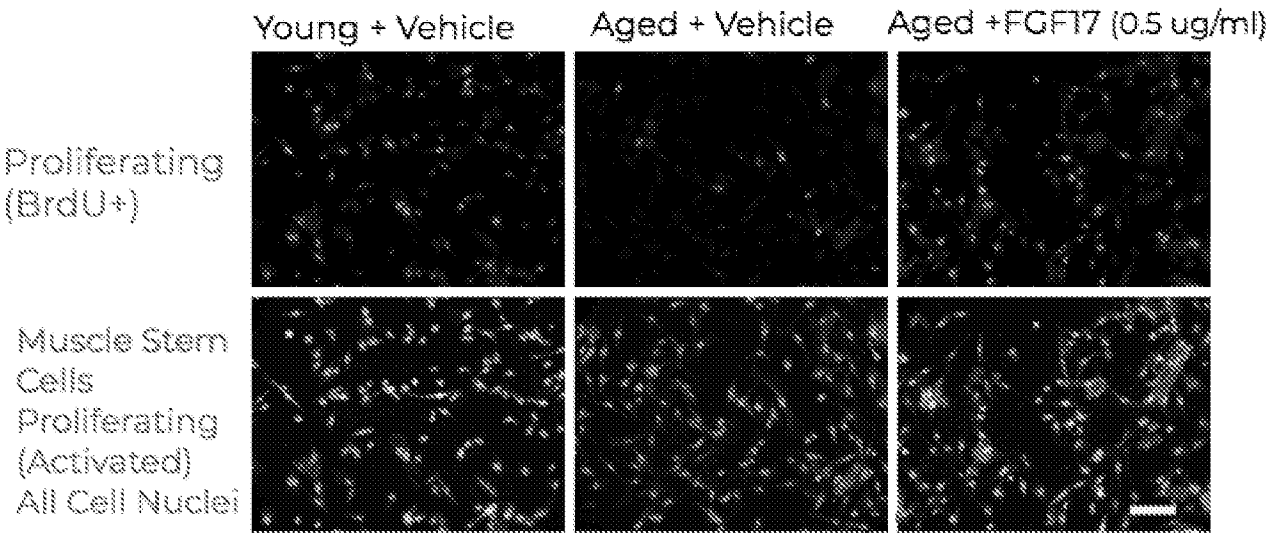


FIG. 10C

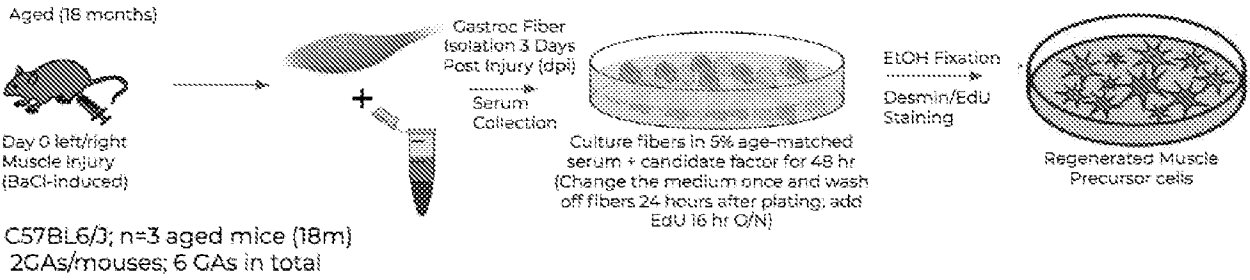


FIG. 11A

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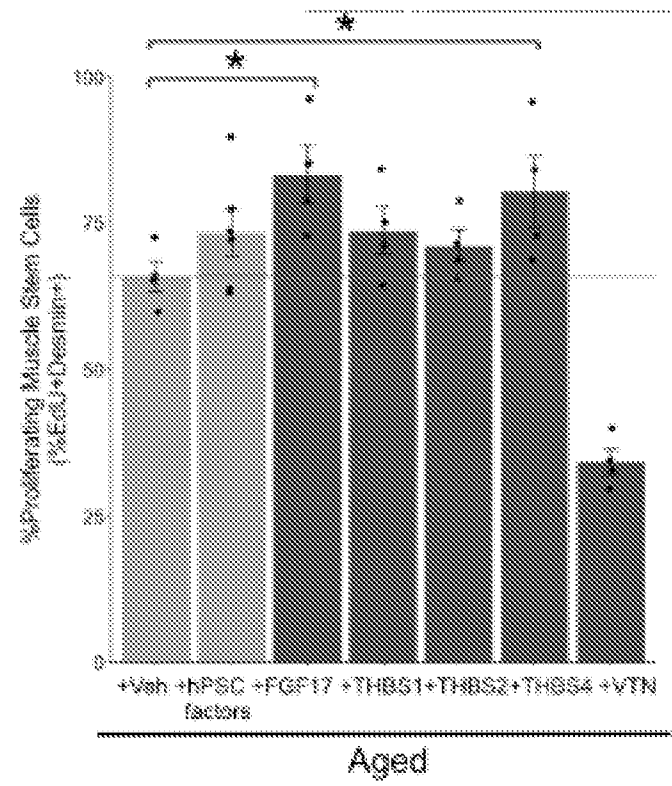


FIG. 11B

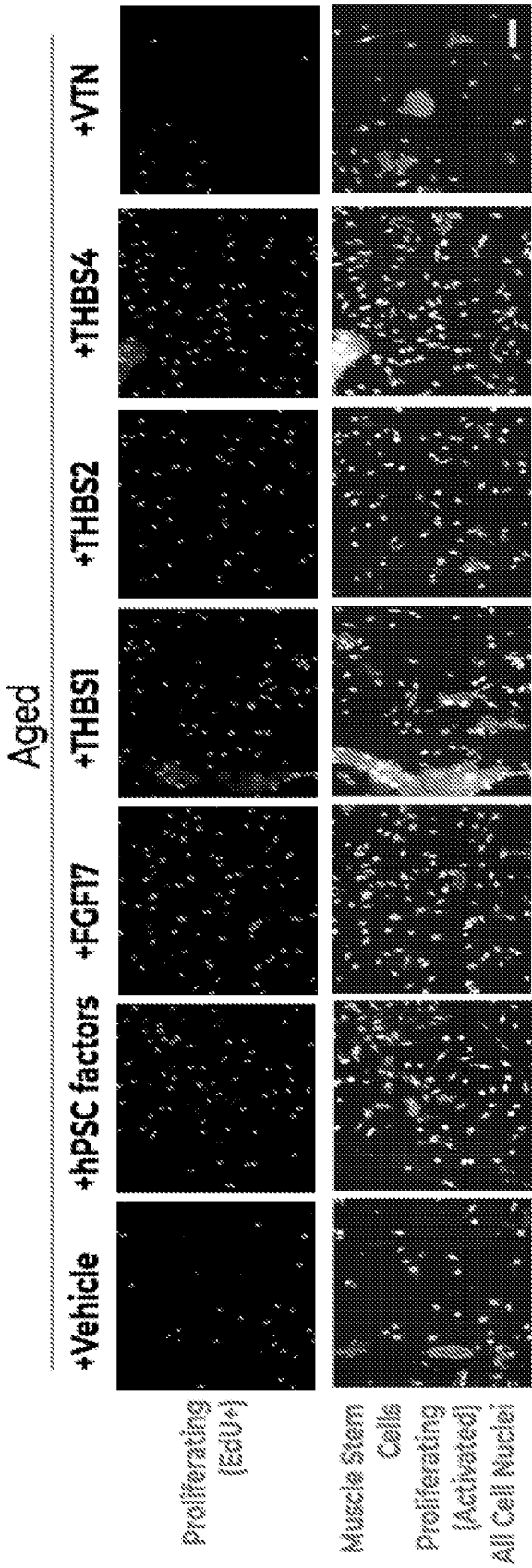


FIG. 11C

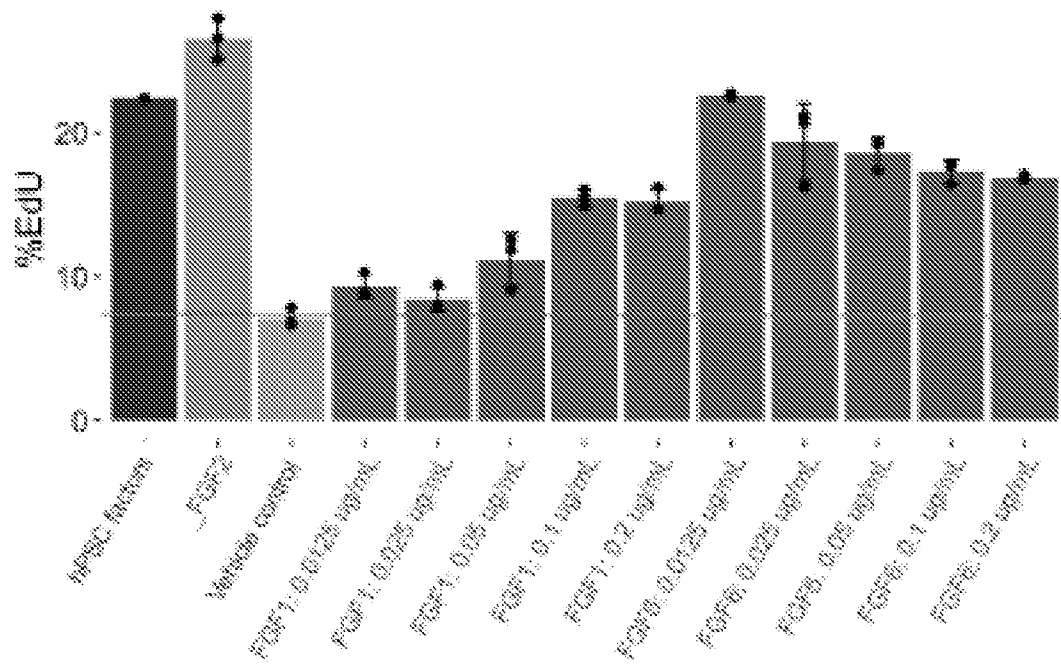


FIG. 12A

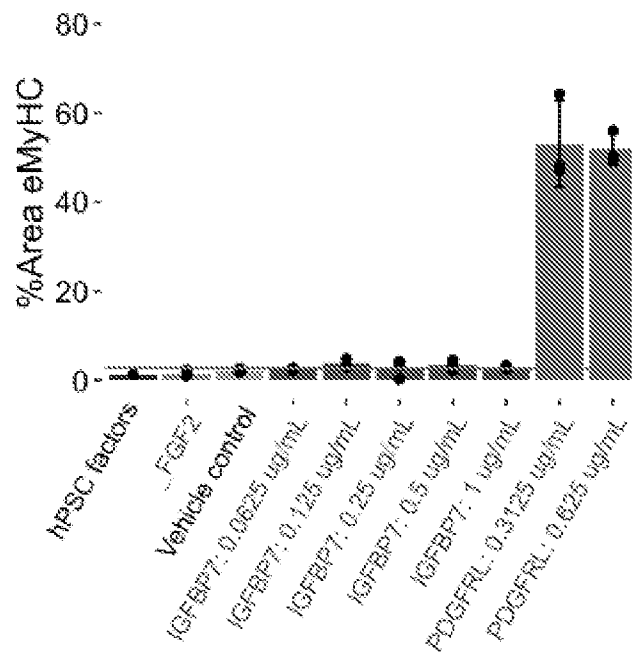


FIG. 12B

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 19/39567

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 38/10, A61K 38/17, A61K 47/48 (2019.01)

CPC - A61K 38/00, C07K 14/81, A61K 31/337, A61K 31/704, A61K 38/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 1997/040072 A2 (THE UNIVERSITY OF SHEFFIELD) 30 October 1997 (30.10.1997) Especially abstract, pg 28, para 2; pg 22, para 3	1, 2, 42
A	WO 2012/037687 A1 (ANGIOCHEM INC.) 29 March 2012 (29.03.2012) claim 16; p. 25, ln 8-12	1

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

14 October 2019

Date of mailing of the international search report

06 NOV 2019

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 19/39567

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 4-41, 45-62
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I+, claims 1-3 and 42-44, directed to composition comprising a first and second therapeutic polypeptide. The composition will be searched to the extent that the first and second therapeutic polypeptide encompass A1BG and A2M (the first and second polypeptides listed in Table 2). It is believed that claims 1, 2 and 42 encompass this first named invention, and thus these claims will be searched without fee to the extent that the first and second polypeptides encompass A1BG and A2M. Additional first and second polypeptide(s) will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected first and second polypeptide(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. An exemplary election would be first and second polypeptides comprising A1Bg and ABCFI (the first and third polypeptides listed in Table 2), (claims 1, 2 and 42).

-----Please see continuation in first extra sheet-----

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 2, 42 limited to A1BG and A2M

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 19/39567

Continuation of Box No. III. Observations where unity of invention is lacking

The inventions listed as Group I+ do not relate to a single special technical feature under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special technical features

The inventions of Group I+ each include the special technical feature of a unique polypeptide(s), and is considered a distinct technical feature.

Common technical features

The inventions of Group I+ share the common technical feature of a composition comprising a first therapeutic polypeptide a second therapeutic polypeptide, and a pharmaceutically acceptable excipient. However, this shared technical feature is previously taught by WO 2012/037687 A1 to Angiochem Inc. (hereinafter Angiochem).

Angiochem teaches a composition comprising a first therapeutic polypeptide a second therapeutic polypeptide, and a pharmaceutically acceptable excipient (claim 16 "A composition comprising: (c) a therapeutic polypeptide not conjugated to a therapeutic agent and (d) a therapeutic conjugate comprising a second polypeptide conjugated to a second therapeutic agent or a transport vector, wherein said therapeutic polypeptide and said therapeutic conjugate are together present in an effective amount"; p. 25, ln 8-12 "pharmaceutical compositions that contain a therapeutically effective amount of a therapeutic polypeptide and/or a conjugate of the invention...One or more physiologically acceptable excipients or carriers can also be included in the composition for proper formulation").

As the technical features were known in the art at the time of the invention, they cannot be considered special technical features that would otherwise unify the groups.

Therefore, Group I+ inventions lack unity under PCT Rule 13 because they do not share the same or corresponding special technical feature.

NOTE, continuation of Item 4 above: claims 4-41, 45-62 are held unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).