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(54) **Title**: TRANSFORMING GROWTH FACTOR-RELATED ANTIBODIES AND USES THEREOF

(57) **Abstract**: Provided herein are proteins, antibodies, assays, compositions and methods useful for modulating growth factor levels and/or activities. In some embodiments, such growth factors are members of the TGF-β superfamily of proteins.

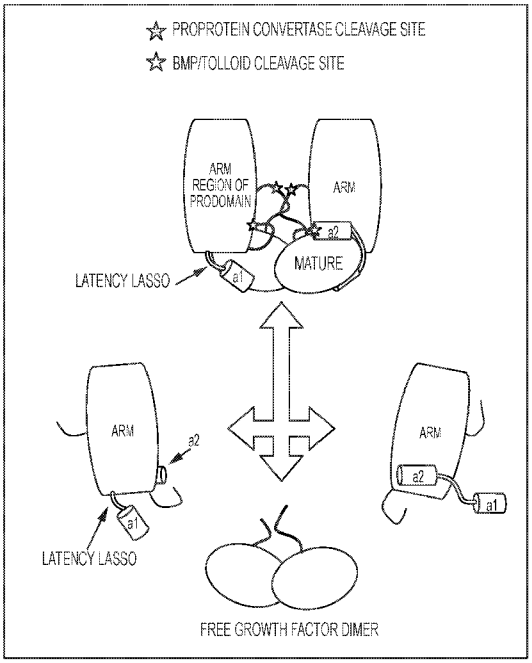


FIG. 4

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SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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TRANSFORMING GROWTH FACTOR-RELATED ANTIBODIES AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. § 119(e) of U.S. Provisional Patent Application No. 62/076,230, filed on November 6, 2014 and entitled "TRANSFORMING GROWTH FACTOR-RELATED ANTIBODIES AND USES THEREOF"; U.S. Provisional Patent Application No. 62/100,361, filed on January 6, 2015 and entitled "TRANSFORMING GROWTH FACTOR-RELATED ANTIBODIES AND USES THEREOF"; and U.S. Provisional Patent Application No. 62/187,348, filed on July 1, 2015 and entitled "TRANSFORMING GROWTH FACTOR-RELATED ANTIBODIES AND USES THEREOF". Each of these applications is incorporated herein by reference in its entirety for all purposes.

FIELD OF THE DISCLOSURE

[0002] Embodiments of the present disclosure may include modulators of growth factor activity. In some embodiments, such modulators may include antibodies and may modulate TGF-β family member activity and/or biology.

BACKGROUND OF THE DISCLOSURE

[0003] Cell signaling molecules stimulate a variety of cellular activities. Such signaling is often tightly regulated, often through interactions with other biomolecules, the extracellular and/or cellular matrix or within a particular cell environment or niche. Such interactions may be direct or indirect.

[0004] Cell signaling cascades are involved in a number of diverse biological pathways including, but not limited to modulation of cell growth, modulation of tissue homeostasis, extracellular matrix (ECM) dynamics, modulation of cell migration, invasion and immune modulation/suppression. In some cases, proteins involved in cell signaling are synthesized and/or are sequestered in latent form, requiring stimulus of some kind to participate in signaling events. There remains a need in the art for agents, tools and methods for modulating cell signaling and/or cellular activities.

SUMMARY OF THE DISCLOSURE

[0005] Aspects of the disclosure relate to a recognition that in some embodiments antibodies have selected binding profiles to TGFβ family member proteins and/or forms thereof. In some embodiments antibodies with selected binding profiles specifically bind to different forms of TGFβ family member proteins. For example, antibodies provided herein specifically bind to one or more of a pro-form, a latent-form, a primed-form, and/or a mature-form of a TGFβ family member protein, such as proMyostatin, latent Myostatin, primed Myostatin and/or mature Myostatin. In some embodiments, such antibodies inhibit Myostatin signaling. In some embodiments, inhibition of Myostatin signaling is useful for increasing muscle mass or preventing muscle atrophy. In some embodiments, antibodies provided herein bind to and prevent cleavage of Myostatin by a proprotein convertase and/or a tolloid protease. Preventing cleavage of proMyostatin or latent Myostatin, in some embodiments, prevents Myostatin activation. Further aspects of the disclosure relate to antibodies having selected binding profiles and an affinity to an antigen that is sensitive to pH. Furthermore, in some embodiments, antibodies provided herein are sweeping antibodies that can efficiently clear antigens (e.g., proMyostatin and/or latent Myostatin) from serum.

[0006] The present disclosure, in some aspects, includes an antibody that specifically binds human proMyostatin, human latent Myostatin, human GDF-8 prodomain, human GDF-11 ARM8 prodomain, and human proGDF11 ARM8, but does not specifically bind human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

[0007] Another aspect of the invention includes an antibody that specifically binds human proMyostatin, murine proMyostatin, human latent Myostatin, human GDF-8 prodomain, human GDF-11 ARM8 prodomain, and human proGDF11 ARM8, but does not specifically bind human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

[0008] In some embodiments, human proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 5. In some embodiments, murine proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 88. In some embodiments, human latent Myostatin has an amino acid sequence as set forth in SEQ ID NO: 5. In some embodiments, human GDF-8 prodomain has an amino acid sequence as set forth in SEQ ID NO: 38. In some embodiments, human GDF-11 ARM8 prodomain has an amino acid sequence as set forth in SEQ ID NO: 181. In some embodiments, human proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179. In some embodiments, an antibody specifically binds human latent proGDF11 ARM8, but does not specifically bind human proGDF11

having an amino acid sequence as set forth in SEQ ID NO: 4. In other embodiments, an antibody specifically binds murine latent myostatin and human latent proGDF11 ARM8, but does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4. In some embodiments, a murine latent myostatin has an amino acid sequence as set forth in SEQ ID NO: 88. In some embodiments, a human latent proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179.

[0009] In another embodiment, an antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 752, 780, 815, 772, 784, 770, 774, 756, 796, 785, 761, 788, 767, 765, 799, 749, 802, 809, 750, 803, 800, 806, 759, 805, 797, 787, or 766, 782, 967, 776, 755, 876, 891, 963, 996, 993, 970, 968 or 1008. In a further embodiment, an antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1367, 1394, 1660, 1387, 1397, 1385, 1388, 1371, 1409, 1398, 1376, 1401, 1382, 1380, 1656, 1364, 1413, 1418, 1365, 1658, 1657, 1415, 1374, 1659, 1410, 1400, 1381, 1395, 1582, 1390, 1370, 1670, 1485, 1578, 1611, 1608, 1585, 1583, or 1623.

[0010] In other embodiments, an antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP6a-1, BP6a-2, BP6a-3, BP6a-4, BP6a-5, BP6a-6, BP6a-7, BP6a-8, BP6a-9, BP6a-10, BP6a-11, BP6a-12, BP6a-13, BP6a-14, BP6a-15, BP6a-16, BP6a-17, BP6a-18, BP6a-19, BP6a-20, BP6a-21, BP6a-22, BP6a-23, BP6a-24, BP6a-25, BP6a-26, BP6a-27, BP6b-1, BP6b-2, BP6b-3, BP6b-4, BP6b-5, BP6b-6, BP6b-7, BP6b-8, BP6b-9, BP6b-10, BP6b-11 or BP6b-12 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP6a-1, BP6a-2, BP6a-3, BP6a-4, BP6a-5, BP6a-6, BP6a-7, BP6a-8, BP6a-9, BP6a-10, BP6a-11, BP6a-12, BP6a-13, BP6a-14, BP6a-15, BP6a-16, BP6a-17, BP6a-18, BP6a-19, BP6a-20, BP6a-21, BP6a-22, BP6a-23, BP6a-24, BP6a-25, BP6a-26, BP6a-27, BP6b-1, BP6b-2, BP6b-3, BP6b-4, BP6b-5, BP6b-6, BP6b-7, BP6b-8, BP6b-9, BP6b-10, BP6b-11 or BP6b-12 as set forth in Table 16.

[0011] In some embodiments, an antibody comprises a variable heavy chain amino acid sequence of clone BP6a-1, BP6a-2, BP6a-3, BP6a-4, BP6a-5, BP6a-6, BP6a-7, BP6a-8, BP6a-9, BP6a-10, BP6a-11, BP6a-12, BP6a-13, BP6a-14, BP6a-15, BP6a-16, BP6a-17, BP6a-18, BP6a-19, BP6a-20, BP6a-21, BP6a-22, BP6a-23, BP6a-24, BP6a-25, BP6a-26, BP6a-27, BP6b-1, BP6b-2, BP6b-3, BP6b-4, BP6b-5, BP6b-6, BP6b-7, BP6b-8, BP6b-9, BP6b-10, BP6b-11 or BP6b-12 as set forth in Table 14. In other embodiments, an antibody comprises the variable light chain amino acid sequence of clone BP6a-1, BP6a-2, BP6a-3, BP6a-4, BP6a-5, BP6a-6, BP6a-7, BP6a-8, BP6a-9, BP6a-10, BP6a-11, BP6a-12, BP6a-13,

BP6a-14, BP6a-15, BP6a-16, BP6a-17, BP6a-18, BP6a-19, BP6a-20, BP6a-21, BP6a-22, BP6a-23, BP6a-24, BP6a-25, BP6a-26, BP6a-27, BP6b-1, BP6b-2, BP6b-3, BP6b-4, BP6b-5, BP6b-6, BP6b-7, BP6b-8, BP6b-9, BP6b-10, BP6b-11 or BP6b-12 as set forth in Table 16.

[0012] Further aspects of the present disclosure include an antibody that specifically binds human proMyostatin, and human proGDF11 ARM8 but does not specifically bind human latent Myostatin having an amino acid sequence as set forth in SEQ ID NO: 5, human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

[0013] Another aspect of the present disclosure includes an antibody that specifically binds human proMyostatin, murine proMyostatin and human proGDF11 ARM8 but does not specifically bind human latent Myostatin having an amino acid sequence as set forth in SEQ ID NO: 5, human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

[0014] In some embodiments, the human proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 5. In other embodiments, the murine proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 88. In another embodiment, the human proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179. In some embodiments, the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 813. In other embodiments, the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1422. In another embodiment, the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP2a-1 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP2a-1 as set forth in Table 16. In some embodiments, the antibody comprises a variable heavy chain amino acid sequence of clone BP2a-1 as set forth in Table 14. In some embodiments, the antibody comprises the variable light chain amino acid sequence of clone BP2a-1 as set forth in Table 16.

[0015] The present disclosure, in some aspects, includes an antibody that specifically binds human proMyostatin, and human latent Myostatin, but does not specifically bind human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID

NO: 179, or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

[0016] Another aspect of the disclosure includes an antibody that specifically binds human proMyostatin, murine proMyostatin, and human latent Myostatin, but does not specifically bind human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179, or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

[0017] In some embodiments, a human proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 5. In other embodiments, a murine proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 88. In some embodiments, a human latent Myostatin has an amino acid sequence as set forth in SEQ ID NO: 5. In another embodiment, a antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 794, 804, or 751. In some embodiments, the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1407, 1414, or 1366. In other embodiments, the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP3a-1, BP3a-2 or BP3a-3 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP3a-1, BP3a-2 or BP3a-3 as set forth in Table 16. In some embodiments, the antibody comprises a variable heavy chain amino acid sequence of clone BP3a-1, BP3a-2 or BP3a-3 as set forth in Table 14. In some embodiments, the antibody comprises the variable light chain amino acid sequence of clone BP3a-1, BP3a-2 or BP3a-3 as set forth in Table 16.

[0018] Aspects of the present disclosure relate to an antibody that specifically binds human proMyostatin, human latent Myostatin and human GDF8 prodomain but does not specifically bind human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179 or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

[0019] Further aspects of the disclosure include an antibody that specifically binds human proMyostatin, murine proMyostatin, human latent Myostatin and human GDF8 prodomain but does not specifically bind human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino

acid sequence as set forth in SEQ ID NO: 179 or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

[0020] In some embodiments, the human proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 5. In another embodiment, the murine proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 88. In a further embodiment, the human latent Myostatin has an amino acid sequence as set forth in SEQ ID NO: 5. In some embodiments, the human GDF-8 prodomain has an amino acid sequence as set forth in SEQ ID NO: 38. In other embodiments, the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 768. In further embodiments, the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1383. In some embodiments, the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP4a-1 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP4a-1 as set forth in Table 16. In other embodiments, the antibody comprises a variable heavy chain amino acid sequence of clone BP4a-1 as set forth in Table 14. In another embodiment, the antibody comprises the variable light chain amino acid sequence of clone BP4a-1 as set forth in Table 16.

[0021] Aspects of the disclosure further relate to an antibody that specifically binds human proMyostatin, human latent Myostatin, and human proGDF11 ARM8, but does not specifically bind human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

[0022] Additional aspects of the disclosure include an antibody that specifically binds human proMyostatin, murine proMyostatin, human latent Myostatin, and human proGDF11 ARM8, but does not specifically bind human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

[0023] In some embodiments, the human proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 5. In other embodiments, the murine proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 88. In a further embodiment, the human latent Myostatin has an amino acid sequence as set forth in SEQ ID NO: 5. In another embodiment, the human proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179. In

some embodiments, the antibody specifically binds human latent proGDF11 ARM8, but does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4. In some embodiments, the antibody specifically binds murine latent myostatin and human latent proGDF11 ARM8, but does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4. In other embodiments, the murine latent myostatin has an amino acid sequence as set forth in SEQ ID NO: 88. In another embodiment, the human latent proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179. In other embodiments, the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 760, 798, 792, 789, 801, 790, 812, 758, 762, 775, 834, 974, 985, or 1002. In further embodiments, the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1375, 1411, 1405, 1402, 1412, 1403, 1421, 1373, 1377, 1389, 1661, 1589, 1600, or 1617.

[0024] In another embodiment, the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP5a-1, BP5a-2, BP5a-3, BP5a-4 or BP5a-5, BP5b-1, BP5b-2, BP5b-3, BP5b-4, BP5b-5, BP5b-6, BP5b-7, BP5b-8 or BP5b-9 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP5a-1, BP5a-2, BP5a-3, BP5a-4 or BP5a-5, BP5b-1, BP5b-2, BP5b-3, BP5b-4, BP5b-5, BP5b-6, BP5b-7, BP5b-8 or BP5b-9 as set forth in Table 16. In other embodiments, the antibody comprises a variable heavy chain amino acid sequence of clone BP5a-1, BP5a-2, BP5a-3, BP5a-4 or BP5a-5, BP5b-1, BP5b-2, BP5b-3, BP5b-4, BP5b-5, BP5b-6, BP5b-7, BP5b-8 or BP5b-9 as set forth in Table 14. In still other embodiments, the antibody comprises the variable light chain amino acid sequence of clone BP5a-1, BP5a-2, BP5a-3, BP5a-4 or BP5a-5, BP5b-1, BP5b-2, BP5b-3, BP5b-4, BP5b-5, BP5b-6, BP5b-7, BP5b-8 or BP5b-9 as set forth in Table 16.

[0025] Aspects of the present disclosure include an antibody that specifically binds human proMyostatin but does not specifically bind human latent Myostatin having an amino acid sequence as set forth in SEQ ID NO: 5, human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179,or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

[0026] Further aspects of the invention include an antibody that specifically binds human proMyostatin and murine proMyostatin but does not specifically bind human latent Myostatin having an amino acid sequence as set forth in SEQ ID NO: 5, human GDF-8

prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179,or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

[0027] In some embodiments, the human proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 5. In other embodiments, the murine proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 88). In another embodiment, the antibody does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4, or human latent proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179. In yet another embodiment, the antibody does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4, murine latent myostatin having an amino acid sequence as set forth in SEQ ID NO: 88 or human latent proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179. In some embodiments, the antibody comprises a CDR-H3 amino acid sequence as set forth in SEQ ID NO: 769 or 827. In other embodiments, the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1384 or 1435. In another embodiment, the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP1a-1 or BP1b-1 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP1a-1 or BP1b-1 as set forth in Table 16. In a further embodiment, the antibody comprises a variable heavy chain amino acid sequence of clone BP1a-1 or BP1b-1 as set forth in Table 14. In some embodiments, the antibody comprises the variable light chain amino acid sequence of clone BP1a-1 or BP1b-1 as set forth in Table 16.

[0028] Further aspects of the invention relate to an antibody that specifically binds human latent Myostatin but does not specifically bind human proMyostatin having an amino acid sequence as set forth in SEQ ID NO: 5, human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179, human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42 or human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4).

[0029] Additional aspects of the invention include an antibody that specifically binds human latent Myostatin but does not specifically bind murine proMyostatin having an amino acid sequence as set forth in SEQ ID NO: 88, human proMyostatin having an amino acid

sequence as set forth in SEQ ID NO: 5, human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179, human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42 or human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4).

[0030] In some embodiments, the human latent Myostatin has an amino acid sequence as set forth in SEQ ID NO: 5. In other embodiments, the antibody specifically binds human latent proGDF11 ARM8. In a further embodiment, the antibody specifically binds murine latent myostatin and human latent proGDF11 ARM8. In another embodiment, the murine latent myostatin has an amino acid sequence as set forth in SEQ ID NO: 88. In some embodiments, the human latent proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179. In other embodiments, the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 990. In some embodiments, the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1605. In other embodiments, the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP10b-1 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP10b-1 as set forth in Table 16. In further embodiments, the antibody comprises a variable heavy chain amino acid sequence of clone BP10b-1 as set forth in Table 14. In other embodiments, the antibody comprises the variable light chain amino acid sequence of clone BP10b-1as set forth in Table 16.

[0031] Some aspects of the present disclosure include an antibody that specifically binds human proMyostatin, human latent Myostatin, human proGDF11 ARM8 and human mature GDF-8 but does not specifically bind human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38 or human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181.

[0032] Another aspect of the present disclosure relates to an antibody that specifically binds human proMyostatin, murine proMyostatin, human latent Myostatin, human proGDF11 ARM8 and human mature GDF-8 but does not specifically bind human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38 or human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181.

[0033] In some embodiments, the human proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 5. In other embodiments, the murine proMyostatin has an amino

acid sequence as set forth in SEQ ID NO: 88. In another embodiment, the human latent Myostatin has an amino acid sequence as set forth in SEQ ID NO: 5. In some embodiments, the human proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179. In another embodiment, the human mature GDF-8 has an amino acid sequence as set forth in SEQ ID NO: 42. In other embodiments, the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 764. In some embodiments, the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1379. In other embodiments, the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP11a-1 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP11a-1 as set forth in Table 16. In another embodiment, the antibody comprises a variable heavy chain amino acid sequence of clone BP11a-1 as set forth in Table 14. In some embodiments, the antibody comprises the variable light chain amino acid sequence of clone BP11a-1 as set forth in Table 16.

[0034] Additional aspects of the present disclosure include an antibody that specifically binds human latent Myostatin and human mature GDF-8 but does not specifically bind human proMyostatin having an amino acid sequence as set forth in SEQ ID NO: 5, human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181 or human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179.

[0035] Further aspects of the present disclosure relate to an antibody that specifically binds human latent Myostatin and human mature GDF-8 but does not specifically bind murine proMyostatin having an amino acid sequence as set forth in SEQ ID NO: 88, human proMyostatin having an amino acid sequence as set forth in SEQ ID NO: 5, human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181 or human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179.

[0036] In some embodiments, the human latent Myostatin has an amino acid sequence as set forth in SEQ ID NO: 5. In other embodiments, the human mature GDF-8 has an amino acid sequence as set forth in SEQ ID NO: 42. In another embodiment, the antibody does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4 or human latent proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179. In some embodiments, the antibody specifically binds murine latent

myostatin but does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4 or human latent proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179. In other embodiments, the murine latent myostatin has an amino acid sequence as set forth in SEQ ID NO: 88. In another embodiment, the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 989. In some embodiments, the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1604. In other embodiments, the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP12b-1 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP12b-1as set forth in Table 16. In another embodiment, the antibody comprises a variable heavy chain amino acid sequence of clone BP12b-1 as set forth in Table 14. In some embodiments, the antibody comprises the variable light chain amino acid sequence of clone BP12b-1 as set forth in Table 16.

[0037] Further aspects of the present disclosure include an antibody that specifically binds human proMyostatin and human GDF-8 prodomain, but does not specifically bind human latent Myostatin having an amino acid sequence as set forth in SEQ ID NO: 5, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179 or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

[0038] Another aspect of the present disclosure relates to an antibody that specifically binds human proMyostatin and human GDF-8 prodomain, but does not specifically bind murine proMyostatin having an amino acid sequence as set forth in SEQ ID NO: 88, human latent Myostatin having an amino acid sequence as set forth in SEQ ID NO: 5, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179 or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

[0039] In some embodiments, the human proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 5. In other embodiments, the human GDF-8 prodomain has an amino acid sequence as set forth in SEQ ID NO: 38. In further embodiments, the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 786. In another embodiment, the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1399. In some embodiments, the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP15a-1 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable

light chain (VL) amino acid sequence of clone BP15a-1 as set forth in Table 16. In another embodiment, the antibody comprises a variable heavy chain amino acid sequence of clone BP15a-1 as set forth in Table 14. In other embodiments, the antibody comprises the variable light chain amino acid sequence of clone BP15a-1 as set forth in Table 16.

[0040] Another aspect of the present disclosure includes an antibody that specifically binds human proMyostatin and human latent Myostatin but does not specifically bind human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179 or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

[0041] An additional aspect of the present disclosure relates to an antibody that specifically binds human proMyostatin and human latent Myostatin but does not specifically bind murine proMyostatin having an amino acid sequence as set forth in SEQ ID NO: 88, human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179 or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

[0042] In some embodiments, the human proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 5. In other embodiments, the human latent Myostatin has an amino acid sequence as set forth in SEQ ID NO: 5. In further embodiments, the antibody does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4 or human latent proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179. In additional embodiments, the antibody does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4, murine latent myostatin having an amino acid sequence as set forth in SEQ ID NO: 88 or human latent proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179. In some embodiments, the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 810, 855, 971, 983, or 986. In other embodiments, the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1419, 1662, 1586, 1598, or 1601. In further embodiments, the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP16a-1, BP16b-1, BP16b-2, BP16b-3 or BP16b-4 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP16a-1, BP16b-

1, BP16b-2, BP16b-3 or BP16b-4 as set forth in Table 16. In another embodiment, the antibody comprises a variable heavy chain amino acid sequence of clone BP16a-1, BP16b-1, BP16b-2, BP16b-3 or BP16b-4 as set forth in Table 14. In some embodiments, the antibody comprises the variable light chain amino acid sequence of clone BP16a-1, BP16b-1, BP16b-2, BP16b-3 or BP16b-4 as set forth in Table 16.

[0043] Additional aspects of the present disclosure include an antibody that specifically binds human proMyostatin and human latent Myostatin but does not specifically bind human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179, human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42 or human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4.

[0044] Further aspects of the present disclosure relate to an antibody that specifically binds human proMyostatin and human latent Myostatin but does not specifically bind murine proMyostatin having an amino acid sequence as set forth in SEQ ID NO: 88, human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179, human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42, human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4 or murine latent myostatin having an amino acid sequence as set forth in SEQ ID NO: 88. In some embodiments, the human proMyostatin has amino acid sequence as set forth in SEQ ID NO: 5. In other embodiments, the human latent Myostatin has an amino acid sequence as set forth in SEQ ID NO: 5. In another embodiment, the antibody specifically binds human latent proGDF11 ARM8. In other embodiments, the human latent proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179. In some embodiments, the antibody does not specifically bind human latent proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179. In another embodiment, the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 982. In further embodiments, the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1597. In some embodiments, the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP17b-1 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP17b-1 as set forth in Table 16. In some embodiments, the antibody

comprises a variable heavy chain amino acid sequence of clone BP17b-1 as set forth in Table 14. In other embodiments, the antibody comprises the variable light chain amino acid sequence of clone BP17b-1 as set forth in Table 16.

[0045] Other aspects of the present disclosure relate to an antibody that specifically binds human proMyostatin, human latent Myostatin and human proGDF11 ARM8 but does not specifically bind human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181 or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

[0046] Another aspect of the present disclosure includes an antibody that specifically binds human proMyostatin, human latent Myostatin and human proGDF11 ARM8 but does not specifically bind murine proMyostatin having an amino acid sequence as set forth in SEQ ID NO: 88, human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181 or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42. In some embodiments, the human proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 5. In other embodiments, the human latent Myostatin has an amino acid sequence as set forth in SEQ ID NO: 5. In other embodiments, the human proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179. In another embodiment, the antibody specifically binds human latent proGDF11 ARM8 but does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4. In some embodiments, the antibody specifically binds human latent proGDF11 ARM8 but does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4 or murine latent myostatin having an amino acid sequence as set forth in SEQ ID NO: 88. In further embodiments, the human latent proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179. In another embodiment, the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 763, 814, 753, 777, 795, 969, 972, 976, or 981. In other embodiments, the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1378, 1423, 1368, 1391, 1408, 1584, 1587, 1591, or 1596.

[0047] In some embodiments, the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP18a-1 or BP18a-2, BP18b-1, BP18b-2, BP18b-3, BP18b-4, BP18b-5, BP18b-6 or BP18b-7 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain

(VL) amino acid sequence of clone BP18a-1 or BP18a-2, BP18b-1, BP18b-2, BP18b-3, BP18b-4, BP18b-5, BP18b-6 or BP18b-7as set forth in Table 16. In some embodiments, the antibody comprises a variable heavy chain amino acid sequence of clone BP18a-1 or BP18a-2, BP18b-1, BP18b-2, BP18b-3, BP18b-4, BP18b-5, BP18b-6 or BP18b-7 as set forth in Table 14. In some embodiments, the antibody comprises the variable light chain amino acid sequence of clone BP18a-1 or BP18a-2, BP18b-1, BP18b-2, BP18b-3, BP18b-4, BP18b-5, BP18b-6 or BP18b-7 as set forth in Table 16.

[0048] Further aspects of the present disclosure include an antibody that specifically binds human proMyostatin, human latent Myostatin, human GDF-8 prodomain, human GDF-11 ARM8 prodomain and human proGDF11 ARM8 but does not specifically bind human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

[0049] Additional aspects of the present disclosure relate to an antibody that specifically binds human proMyostatin, human latent Myostatin, human GDF-8 prodomain, human GDF-11 ARM8 prodomain and human proGDF11 ARM8 but does not specifically bind murine proMyostatin having an amino acid sequence as set forth in SEQ ID NO: 88 or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42. In some embodiments, the human proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 5. In other embodiments, the human latent Myostatin has an amino acid sequence as set forth in SEQ ID NO: 5. In further embodiments, the human GDF-8 prodomain has an amino acid sequence as set forth in SEQ ID NO: 38. In some embodiments, the human GDF-11 ARM8 prodomain has an amino acid sequence as set forth in SEQ ID NO: 181. In some embodiments, the human proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179. In other embodiments, the antibody specifically binds human latent proGDF11 ARM8 but does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4. In another embodiment, the antibody specifically binds human latent proGDF11 ARM8 but does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4 or murine latent myostatin having an amino acid sequence as set forth in SEQ ID NO: 88. In some embodiments, the human latent proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179. In another embodiment, the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 773, 807, 811, 754, 771, or 978. In other embodiments, the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1655, 1416, 1420, 1369, 1386, or 1593. In some embodiments, the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP19a-1, BP19a-2 or BP19a-3,

BP19b-1, BP19b-2 or BP19b-3 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP19a-1, BP19a-2 or BP19a-3, BP19b-1, BP19b-2 or BP19b-3 as set forth in Table 16. In some embodiments, the antibody comprises a variable heavy chain amino acid sequence of clone BP19a-1, BP19a-2 or BP19a-3, BP19b-1, BP19b-2 or BP19b-3 as set forth in Table 14. In other embodiments, the antibody comprises the variable light chain amino acid sequence of clone BP19a-1, BP19a-2 or BP19a-3, BP19b-1, BP19b-2 or BP19b-3 as set forth in Table 16.

[0050] Other aspects of present disclosure relate to an antibody that specifically binds human proMyostatin, human latent Myostatin, human proGDF11 ARM8, human proGDF11 or human latent proGDF11 ARM8 but does not specifically bind human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181 or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

[0051] Additional aspects of present disclosure include an antibody that specifically binds human proMyostatin, murine proMyostatin, human latent Myostatin, human proGDF11 ARM8, human proGDF11, murine latent myostatin or human latent proGDF11 ARM8 but does not specifically bind human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181 or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42. In some embodiments, the human proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 5. In other embodiments, the murine proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 88. In another embodiment, the human latent Myostatin has an amino acid sequence as set forth in SEQ ID NO: 5. In some embodiments, the human proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179. In other embodiments, the human proGDF11 has an amino acid sequence as set forth in SEQ ID NO: 4. In other embodiments, the murine latent myostatin has an amino acid sequence as set forth in SEQ ID NO: 88. In some embodiments, the human latent proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179. In another embodiment, the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 779. In other embodiments, the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1393. In some embodiments, the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP21b-1 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP21b-1 as set forth in Table 16.

In some embodiments, the antibody comprises a variable heavy chain amino acid sequence of clone BP21b-1 as set forth in Table 14. In other embodiments, the antibody comprises the variable light chain amino acid sequence of clone BP21b-1 as set forth in Table 16.

[0052] Additional aspects of the present disclosure relate to an antibody that specifically binds human proMyostatin, human latent Myostatin, human proGDF11, and human latent proGDF11 ARM8 but does not specifically bind human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179 or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

[0053] Further aspects of the present disclosure include an antibody that specifically binds human proMyostatin, murine proMyostatin, human latent Myostatin, human proGDF11, murine latent myostatin and human latent proGDF11 ARM8 but does not specifically bind human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179 or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42. In some embodiments, the human proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 5. In other embodiments, the murine proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 88. In another embodiment, the human latent Myostatin has an amino acid sequence as set forth in SEQ ID NO: 5. In some embodiments, the human proGDF11 has an amino acid sequence as set forth in SEQ ID NO: 4. In another embodiment, the murine latent myostatin has an amino acid sequence as set forth in SEQ ID NO: 88. In some embodiments, the human latent proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179. In other embodiments, the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 1006. In some embodiments, the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1621. In some embodiments, the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP22b-1 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP22b-1as set forth in Table 16. In some embodiments, the antibody comprises a variable heavy chain amino acid sequence of clone BP22b-1 as set forth in Table 14. In other embodiments, the antibody comprises the variable light chain amino acid sequence of clone BP22b-1 as set forth in Table 16.

[0054] Additional aspects of the present disclosure relate to an antibody that specifically binds proMyostatin and/or latent Myostatin, in which the antibody has an affinity to the proMyostatin and/or latent Myostatin that is pH sensitive.

[0055] Further aspects of the present disclosure include an antibody that specifically binds proMyostatin and/or latent Myostatin with a greater affinity at a pH in a range from 6.5 to 7.5 than it does at a pH in a range from 4.6 to 6.0. In some embodiments, the antibody has a Kd of binding to pro/latent-Myostatin in a range from10-3 M to 10-8 M under binding conditions having a pH in a range from 4.6 to 6.0. In other embodiments, the antibody has a Kd of binding to pro/latent-Myostatin in a range from10-6 M to 10-11 M, when the pH is in a range from 6.5 to 7.5. In another embodiment, the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 813, 804, 790, 762, 784, 770, 764, 986, 777, or 1006. In other embodiments, the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1422, 1414, 1403, 1377, 1397, 1385, 1379, 1601, 1391, or 1621. In some embodiments, the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP2a-1, BP3a-2, BP5b-1, BP5b-4, BP6a-5, BP6a-6, BP11a-1, BP16b-4, BP18b-2 or BP22b-1 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP2a-1, BP3a-2, BP5b-1, BP5b-4, BP6a-5, BP6a-6, BP11a-1, BP16b-4, BP18b-2 or BP22b-1 as set forth in Table 16. In some embodiments, the antibody comprises a variable heavy chain amino acid sequence of clone BP2a-1, BP3a-2, BP5b-1, BP5b-4, BP6a-5, BP6a-6, BP11a-1, BP16b-4, BP18b-2 or BP22b-1as set forth in Table 14. In other embodiments, the antibody comprises the variable light chain amino acid sequence of clone BP2a-1, BP3a-2, BP5b-1, BP5b-4, BP6a-5, BP6a-6, BP11a-1, BP16b-4, BP18b-2 or BP22b-1as set forth in Table 16.

[0056] Aspects of the present disclosure include an isolated antibody or antigen binding fragment thereof having at least one variable domain with an amino acid sequence having at least 95% sequence identity to one or more of those listed in Table 14 or 16. In some embodiments, the at least one variable domain comprises a variable domain pair, the variable domain pair comprising a heavy chain variable domain (VH) and a light chain variable domain (VL), in which the variable domain pair comprises at least 95% sequence identity to a variable domain pair present in an scFv selected from any of those listed in Table 13.

[0057] Additional aspects of the present disclosure include an isolated antibody or antigen binding fragment thereof comprising at least one variable domain, the at least one

variable domain comprising at least one complementarity determining region (CDR) sequence comprising at least 70% sequence identity to one or more of those listed in Table 15 or 17. In some embodiments, the at least one CDR sequence comprises at least 70% sequence identity to a heavy chain variable domain CDR (CDR-H) selected from any of those listed in Table 15. In some embodiments, the isolated antibody or antigen binding fragment thereof comprises at least one variable domain pair, the variable domain pair comprising a VH and a VL. In some embodiments, the VH comprises at least one CDR-H sequence with at least 70% sequence identity to a sequence selected from any of those listed in Table 15. In some embodiments, the VL comprises at least one CDR-L sequence with at least 70% sequence identity to a CDR-L sequence selected from any of those listed in Table 17.

[0058] Further aspects of the present disclosure include an isolated antibody or antigen binding fragment thereof that comprises: a VH sequence with at least 95% sequence identity to a sequence listed in Table 14, and a VL sequence with at least 95% sequence identity to a sequence listed in Table 16.

[0059] Further aspects of the present disclosure relate to an isolated antibody or antigen binding fragment thereof that comprises: a CDR-H1 sequence with at least 70% sequence identity to a sequence listed in Table 15, a CDR-H2 sequence with at least 70% sequence identity to a sequence listed in Table 15, a CDR-H3 sequence with at least 70% sequence identity to a sequence listed in Table 15, a CDR-L1 sequence with at least 70% sequence identity to a sequence listed in Table 17, a CDR-L2 sequence with at least 70% sequence identity to a sequence listed in Table 17, and a CDR-L3 sequence with at least 70% sequence identity to a sequence listed in Table 17. In some embodiments, the isolated antibody or antigen binding fragment thereof, comprising an antibody, in which the antibody is a monoclonal antibody. In some embodiments, the isolated antibody or antigen binding fragment thereof, comprising an antibody, in which the antibody comprises an IgG isotype. In other embodiments, the antibody comprises an IgG1 isotype. In another embodiment, the antibody binds to one or more recombinant antigens listed in Table 24 and/or one or more polypeptides comprising an amino acid sequence with at least 95% sequence identity to any of those listed in Tables 1, 2, 4, 5, 9, 10, 19, 20 or 25. In a further embodiment, the polypeptide comprises pro-growth differentiation factor (GDF)-8 (proGDF-8) (SEQ ID NO: 5). In some embodiments, the antibody binds to a latent GDF-8 growth factor prodomain complex (GPC).

[0060] Further aspects of the present disclosure include a method of modulating growth factor activity in a biological system comprising contacting the biological system with

the antibody or antigen binding fragment thereof. In some embodiments, the growth factor activity comprises GDF-8 activity. In other embodiments, the antibody is a stabilizing antibody and in which contacting the biological system with the stabilizing antibody results in inhibition of release of at least 5% of total GDF-8 mature growth factor in the biological system. In further embodiments, the stabilizing antibody comprises at least one variable domain comprising a VH and VL pair selected from the group consisting of the VH of SEQ ID NO: 462 and the VL of SEQ ID NO: 1037, the VH of SEQ ID NO: 472 and the VL of SEQ ID NO: 1047, the VH of SEQ ID NO: 448 and the VL of SEQ ID NO: 1023, the VH of SEQ ID NO: 502 and the VL of SEQ ID NO: 1077, the VH of SEQ ID NO: 581 and the VL of SEQ ID NO: 1153, the VH of SEQ ID NO: 442 and the VL of SEQ ID NO: 1017, the VH of SEQ ID NO: 464 and the VL of SEQ ID NO: 1039, the VH of SEQ ID NO: 593 and the VL of SEQ ID NO: 1166, the VH of SEQ ID NO: 598 and the VL of SEQ ID NO: 1171, the VH of SEQ ID NO: 626 and the VL of SEQ ID NO: 1199 and the VH of SEQ ID NO: 645 and the VL of SEQ ID NO: 1218. In some embodiments, the antibody is a releasing antibody and in which contacting the biological system with the releasing antibody results in release of at least 5% of total GDF-8 mature growth factor in the biological system.

[0061] Further aspects of the present disclosure include a method of treating a TGF-β-related indication in a subject comprising contacting the subject with the antibody or antigen binding fragment thereof of. In some embodiments, the TGF-β-related indication comprises a muscle disorder and/or injury. In other embodiments, the muscle disorder and/or injury comprises a muscle disorder selected from the group consisting of cachexia, inclusion body myositis (IBM) and sarcopenia. In another embodiment, the TGF-β-related indication comprises chronic obstructive pulmonary disease (COPD).

[0062] Further aspects of the present disclosure include a recombinant antigen comprising a growth differentiation factor (GDF) prodomain fused to an Fc-fusion protein. In some embodiments, the GDF is selected from the group consisting of GDF-8 and GDF-11. In other embodiments, the Fc-fusion protein comprises the sequence: DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG K (SEQ ID NO: 222). In some embodiments, the recombinant antigen comprises a sequence selected from any of those presented in Table 12.

[0063] Additional aspects of the present disclosure include a recombinant antigen comprising a chimeric protein selected from any of those in Tables 20 and 21.

[0064] Yet another aspect of the present disclosure relates to an isolated antibody or antigen binding fragment thereof that binds to a recombinant antigen described above. In some embodiments, the recombinant antigen comprises latent GDF-11 growth factor prodomain complex (GPC).

[0065] A further aspect of the present disclosure includes a method of modulating growth factor activity in a biological system comprising contacting the biological system with the antibody or antigen binding fragment thereof described above. In some embodiments, growth factor activity comprises GDF-11 activity. In some embodiments, an isolated antibody or antigen binding fragment thereof is a stabilizing antibody and in which contacting the biological system with the stabilizing antibody results in inhibition of release of at least 5% of total GDF-11 mature growth factor in the biological system. In some embodiments, an antibody is a releasing antibody and in which contacting the biological system with the releasing antibody results in release of at least 5% of total GDF-11 mature growth factor in the biological system.

[0066] A further aspect of the present disclosure includes a method of treating a TGF-β-related indication in a subject. In some embodiments, the methods involve administering to the subject any one or more of the antibodies, including antigen binding fragments, disclosed herein. In some embodiments, the TGF-β-related indication comprises a cardiovascular indication selected from the group consisting of cardiac hypertrophy, cardiac atrophy, atherosclerosis and restenosis. In some embodiments, the TGF-β-related indication comprises a GDF-11-related indication. In some embodiments, the GDF-11-related indication comprises anemia and/or β-thalassemia.

[0067] In some embodiments, method of enhancing skeletal muscle rejuvenation, cerebral circulation, neurogenesis and/or erythropoiesis are provided. In some embodiments, the methods involve administering to a subject any one or more of the antibodies, including antigen binding fragments, disclosed herein. In some embodiments, the antibody is a monoclonal antibody. In some embodiments, the antibody comprises an IgG isotype. In some embodiments, the IgG1 isotype. In some embodiments, the antibody is a bispecific antibody.

[0068] In some aspects, methods of increasing muscle mass in a subject are provided that comprise administering to the subject any one or more of the antibodies or antigen binding fragments disclosed herein. In some embodiments, the isolated antibody or antigen binding

fragment comprises at least one variable domain comprising a VH and VL pair selected from the group consisting of the VH of SEQ ID NO: 462 and the VL of SEQ ID NO: 1037, the VH of SEQ ID NO: 472 and the VL of SEQ ID NO: 1047, the VH of SEQ ID NO: 448 and the VL of SEQ ID NO: 1023, the VH of SEQ ID NO: 502 and the VL of SEQ ID NO: 1077, the VH of SEQ ID NO: 581 and the VL of SEQ ID NO: 1153, the VH of SEQ ID NO: 442 and the VL of SEQ ID NO: 1017, the VH of SEQ ID NO: 464 and the VL of SEQ ID NO: 1039, the VH of SEQ ID NO: 593 and the VL of SEQ ID NO: 1166, the VH of SEQ ID NO: 598 and the VL of SEQ ID NO: 1171, the VH of SEQ ID NO: 626 and the VL of SEQ ID NO: 1199 and the VH of SEQ ID NO: 645 and the VL of SEQ ID NO: 1218.

[0069] Assays involving the use of one or more of the recombinant antigens and/or one or more of the antibodies or antigen binding fragments thereof disclosed herein are also provided.

[0070] In some aspects, compositions are provided that comprise an antibody (or antigen binding fragment) and an excipient or carrier. In some embodiments, the composition is a pharmaceutical composition comprising (i) a therapeutically effective amount of an antibody and (ii) a pharmaceutically acceptable carrier. In some embodiments, the composition is for use in preventing muscle wasting or increasing muscle mass, and comprises a therapeutically effective amount of an antibody. In some embodiments, the carrier is a pharmaceutically acceptable carrier. In some embodiments, the antibody and carrier are in a lyophilized form. In some embodiments, the antibody and carrier are in solution. In some embodiments, the antibody and carrier are frozen. In some embodiments, the antibody and carrier are frozen at a temperature less than or equal to -65°C.

[0071] In some embodiments, nucleic acids are provided that encode an antibody (or antigen binding fragment) or recombinant antigen. Vectors and cells comprising such nucleic acids are also provided. Kits comprising any of the compositions disclosed herein are also provided.

[0072] Methods of developing an antibody are also provided. In some embodiments, the methods comprise: selecting a protein/antigen, subjecting the protein/antigen to structural analysis, identifying at least one epitope, and developing at least one antibody against the at least one epitope. In some embodiments, the protein is subjected to prodomain convertase cleavage prior to structural analysis. In some embodiments, the prodomain convertase cleaved protein is further subjected to cleavage with an enzyme selected from the group consisting of BMP-1, mammalian tolloid protein (mTLD), mammalian tolloid-like 1

(mTLL1) and mammalian tolloid-like 2 (mTLL2). In some embodiments, the protein comprises proGDF-8 (SEQ ID NO: 5) or proGDF-11 (SEQ ID NO: 4).

[0073] In some embodiments, an inhibitor of at least one BMP-1/Tolloid-like proteinase (B/TP) is provided. In some embodiments, the inhibitor comprises a polypeptide. In some embodiments, the inhibitor comprises an inhibiting antibody, *e.g.*, an anti-primed complex antibody. In some embodiments, the inhibitor prevents cleavage of a latent GPC. In some embodiments, the latent GPC is selected from the group consisting of latent GDF-8 and latent GDF-11. In some embodiments, the inhibitor prevents cleavage of a BMP/Tolloid cleavage site on the latent GPC. In some embodiments, the B/TP is selected from the group consisting of BMP-1, mammalian tolloid protein (mTLD), mammalian tolloid-like 1 (mTLL1), and mammalian tolloid-like 2 (mTLL2).

[0074] In some aspects, antibodies are provided that bind at or within 10 amino acid residues of a proprotein convertase cleavage site of proMyostatin or latent Myostatin. In some embodiments, the proprotein convertase cleavage site comprises the amino acid sequence (SEQ ID NO: 1667 or 1668). In some aspects, antibodies are provided that bind at or within 10 amino acid residues of a proprotein convertase docking site of proMyostatin or latent Myostatin. In some embodiments, the proprotein convertase docking site comprises the amino acid sequence (SEQ ID NO: 1667 or 1668). In some aspects, antibodies are provided that bind at or within 10 amino acid residues of a tolloid protease cleavage site of proMyostatin or latent Myostatin. In some embodiments, the tolloid protease cleavage site comprises the amino acid sequence (SEQ ID NO: 1665 or 1666). In some aspects, antibodies are provided that bind at or within 10 amino acid residues of a tolloid protease docking site of proMyostatin or latent Myostatin. In some embodiments, the tolloid protease docking site comprises the amino acid sequence (SEQ ID NO: 1665 or 1666). In some embodiments, binding of the antibody to the proMyostatin or the latent Myostatin inhibits proteolytic cleavage of the proMyostatin or the latent Myostatin by a proprotein convertase or a tolloid protease.

[0075] In some embodiments, the disclosure relates to antibodies that compete for binding to an epitope with any one of the antibodies disclosed herein. In some embodiments, the competing antibodies bind to an epitope of human proMyostatin or an epitope of human latent Myostatin. In some embodiments, the competing antibodies specifically bind to an epitope of human proMyostatin or human latent Myostatin. In some embodiments, the competing antibodies bind to the epitope with an equilibrium dissociation constant (Kd) between the antibody and the epitope of less than 10^{-6} M or in a range of 10^{-11} M to 10^{-6} M.

[0076] Aspects of the disclosure relate to sweeping antibodies or recycling antibodies. In some embodiments, the antibodies comprise an Fc portion. In some embodiments, the antibodies bind the neonatal Fc receptor FcRn. In some embodiments, the Fc portion binds the neonatal Fc receptor FcRn. In some embodiments, the antibodies bind FcRn at a pH greater than 6.0. In some embodiments, the antibodies bind FcRn at a pH in a range from 7.0 to 7.5. In some embodiments, the Kd of binding of the antibody to the FcRN is in a range from 10^{-3} M to 10^{-8} M. In some embodiments, the Kd of binding of the antibody to the FcRN is in a range from 10^{-4} M to 10^{-8} M. In some embodiments, the Kd of binding of the antibody to the FcRN is in a range from 10^{-5} M to 10^{-8} M. In some embodiments, the Kd of binding of the antibody to the FcRN is in a range from 10^{-6} M to 10^{-8} M. In some embodiments, the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 813, 804, 790, 762, 784, 770, 764, 986, 777, or 1006. In some embodiments, the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1422, 1414, 1403, 1377, 1397, 1385, 1379, 1601, 1391, or 1621. In some embodiments, the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP2a-1, BP3a-2, BP5b-1, BP5b-4, BP6a-5, BP6a-6, BP11a-1, BP16b-4, BP18b-2 or BP22b-1 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP2a-1, BP3a-2, BP5b-1, BP5b-4, BP6a-5, BP6a-6, BP11a-1, BP16b-4, BP18b-2 or BP22b-1 as set forth in Table 16. In some embodiments, the antibody comprises a variable heavy chain amino acid sequence of clone BP2a-1, BP3a-2, BP5b-1, BP5b-4, BP6a-5, BP6a-6, BP11a-1, BP16b-4, BP18b-2 or BP22b-1as set forth in Table 14. In some embodiments, the antibody comprises a variable light chain amino acid sequence of clone BP2a-1, BP3a-2, BP5b-1, BP5b-4, BP6a-5, BP6a-6, BP11a-1, BP16b-4, BP18b-2 or BP22b-1 as set forth in Table 16.

BRIEF DESCRIPTION OF THE FIGURES

[0077] The foregoing and other objects, features and advantages will be apparent from the following description of particular embodiments of the disclosure, as illustrated in the accompanying drawings. The drawings are not necessarily to scale, emphasis instead being placed upon illustrating the principles of various embodiments of the disclosure.

[0078] FIG. 1 is a diagram of the TGF-beta superfamily tree, where divergence is proportional to branch length.

[0079] FIG. 2 is a schematic of one embodiment of a linear representation of a translated growth factor monomer. In such embodiments, translated growth factors may comprise secretion signal peptides, prodomains and growth factor domains. In embodiments according to embodiment depicted here, translated growth factors may also comprise a cleavage site between prodomain and growth factor regions.

[0080] FIG. 3 is a schematic of one embodiment of a GDF growth factor-prodomain complex (GPC) made up of proGDF monomers as well as an embodiment of a free growth factor dimer and free prodomains, separated after proteolytic cleavage of the GPC.

[0081] FIG. 4 is a schematic of one embodiment of a GDF GPC as well as an embodiment of a free growth factor dimer and free prodomains, separated after proteolytic cleavage. Protein modules are indicated

[0082] FIG. 5 presents 3 tables showing the percent identity between amino acid sequences found in the TGF-β family. FIG. 5A demonstrates percent identity among pro-proteins (prodomain and growth factor). Percent identity among growth factor domains is presented in FIG. 5B while percent identity among prodomains is presented in FIG. 5C.

[0083] FIG. 6 shows structure-based alignment between TGF-β family member proteins [adapted from Shi et al (Shi, M. et al., *Latent TGF-β structure and activation*. Nature. 2011 Jun 15; 474(7351):343-9, the contents of which are herein incorporated by reference in their entirety)]. Cysteine residues required for interaction with LTBPs and/or GARPs are boxed. Residues mutated in Camurati-Engelmann syndrome are indicated with a star. Protease cleavage sites are indicated with an up arrow. Protein modules and secondary structural elements are indicated with solid bars. Residues underlined at the N-terminus of GDF-8 correspond to alternatively predicted signal peptide processing sites. "Chimeric module breakpoints" indicate regions where structural features are conserved and provide modules for chimeric protein construction (swapping of modules between family members) in all family members. N-terminal regions are shown in (A), internal regions are shown in (B) and C-terminal regions are shown in (C).

[0084] FIG. 7 is a schematic of an embodiment of a recombinant GPC.

[0085] FIG. 8 is a schematic of embodiments of mutant recombinant proteins of the disclosure.

[0086] FIG. 9 depicts the formation of a latent complex after furin cleavage of a pro-protein dimer. The latent complex retains the growth factor dimer until subjected to an activating cleavage [e.g. by members of the BMP-1/Tolloid-like proteinase (B/TP) family.]

[0087] FIG. 10 presents an alignment conducted between GDF-8 (myostatin), GDF-11, Inhibin A and a GDF-8 dimer. Arrows indicate cleavage sites. Regions involved in internal interactions are boxed. Solid rectangles appear above residues predicted to be involved in steric clashes in chimeric constructs. Stars denote important break points in protein modules.

[0088] FIG. 11 depicts recombinant histidine-tagged proGDF-8 (referred to in the figure as proMyostatin), separated by SDS-PAGE under reducing and non-reducing conditions, as visualized by colloidal blue staining.

[0089] FIG. 12 is a graph showing CAGA promoter-dependent luciferase activity is the presence of GDF-11 or proGDF-11 after treatment with proprotein convertase, Tolloid proteinase or a combination of proprotein convertase and Tolloid proteinase.

[0090] FIG. 13 is a stained gel showing separation of proteinase treated proGDF-11 under reducing and non-reducing conditions.

[0091] FIG. 14 presents results of a luciferase-based growth factor activity assay.

[0092] FIG. 15 is a schematic showing formation of the "primed" complex. The primed complex is an open, active conformation of GDF-8 GPCs or GDF-11 GPCs. Primed complexes are capable of receptor binding and inducing growth factor activity.

[0093] FIG. 16 is a graph showing that BP6a-5 dissociates rapidly at pH 5. The antibody blocks myostatin activation and promotes muscle growth *in vivo.*

[0094] FIG. 17 is a graph showing that BP6a-6 dissociates rapidly at pH 5. The antibody does not block Myostatin activation or signaling and is in the same epitope bin (by ELISA binding profile) as BP6a-5.

[0095] FIG. 18 displays eight antibodies that dissociate more rapidly at pH5 that at pH 7.4. The asterisk indicates some cross-reactivity with proGDF11 in ELISA and the bold indicates that the antibody inhibits GDF8 activation.

[0096] FIG. 19 shows CDR-H3 sequences of pH-sensitive antibodies. All listed antibodies have a histidine in the CDR-H3 sequence except for BP5b-1. The sequences, from top to bottom, correspond to SEQ ID NOs: 762, 764, 770, 777, 784, 986, 1006, and 790. Note that BP18b-2 only includes one histidine in the entire variable region, while BP5b-1 does not contain any histidines in the variable region. These two antibodies have the weakest pH sensitivity profiles.

[0097] FIG. 20 is a table of four antibodies for *in vivo* characterization of Myostatin sweeping. All antibodies will be produced both with and without the "sweeping" mutations in the constant region. Light grey indicates the antibody inhibits GDF8 activation.

[0098] FIG. 21 is a graph showing that BP11a-1 dissociates rapidly at pH5. The antibody does not block Myostatin activation or signaling, but does bind to proMyostatin, latent myostatin, and mature myostatin with equal affinity.

[0099] FIG. 22 is a graph showing that BP5b-4 dissociates rapidly at pH5. The antibody does not block Myostatin activation or signaling; however, it is a different epitope group from BP11a-1 and BP6a-5.

[00100] FIG. 23 shows an example of an antibody (BP6a-3) with no pH-sensitive binding.

[00101] FIGs. 24A-24L show the different pH sensitivities of specific antibodies: BP6a-3 (FIG. 24A), BP5a-1 (FIG. 24B), BP6a-11 (FIG. 24C), BP5b-4 (FIG. 24D), BP11a-1 (FIG. 24E), BP6a-6 (FIG. 24F), BP18b-2 (FIG. 24G), BP6a-2 (FIG. 24H), BP6a-5 (FIG. 24I), BP14a-1 (FIG. 24J), BP5b-2 (FIG. 24K), and BP18b-7 (FIG. 24L).

[00102] FIGs. 25A-25K show the different pH sensitivities of specific antibodies: BP16b-4 (FIG. 25A), BP6b-9 (FIG. 25B), BP22b-1 (FIG. 25C), BP3a-2 (FIG. 25D), BP5b-1 (FIG. 25E), BP6a-4 (FIG. 25F), BP6a-7 (FIG. 25G), BP1a-1 (FIG. 25H), BP2a-1 (FIG. 25I), BP5a-2 (FIG. 25J), and BP6a-1 (FIG. 25K).

DETAILED DESCRIPTION

[00103] Aspects of the disclosure relate to antibodies having particular binding profiles. In some embodiments, antibodies are selected for use (*e.g.*, in a particular assay) based on the fact that they have a known and/or desired binding profile (a selected binding profile). As used herein the term "binding profile" refers to a set of one or more parameters (*e.g.*, symbols, quantities, measurements, *etc.*) indicative of the extent to which an antibody specifically binds to one or more antigens. In some embodiments, a parameter indicative of the binding of an antibody for a target antigen is an IC50 or EC50 value. However, in some embodiments, a parameter indicative of the binding of an antibody for a target antigen is an equilibrium dissociation constant (Kd). In some embodiments, a parameter indicative of the binding is an equilibrium association constant (Ka). Other suitable parameters indicative of binding may be used in some embodiments. In some embodiments, the disclosure relates to antibodies having a selected myostatin-related binding profile, which comprises a set of one or more parameters indicative of the extent to which an antibody specifically binds to one or more antigens, at least one of which antigens is a myostatin-related protein (e.g., Myostatin, GDF11, *etc.*).

[00104] In some embodiments, a binding profile comprises one or more parameters indicative of whether or not an antibody exhibits a threshold level of binding (*e.g.*, specific binding) to one or more antigens. In some embodiments, a threshold level of binding is a level of binding that above (or below, depending on the parameter) a control or reference level of binding (*e.g.*, background or non-specific binding). In some embodiments, a threshold level of binding is a level of binding that is at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7 or more standard deviations greater than (or less than, depending on the assay and/or parameter) a control or reference level of binding (*e.g.*, background or non-specific binding), as measured by an appropriate immunoassay. In some embodiments, a threshold level of binding is a level of binding that is in a range of 1 to 10 standard deviations, 2 to 10 standard deviations , or 4 to 6 standard deviations greater than (or less than, depending on the assay and/or parameter) a control or reference level of binding (e.g., background or non-specific binding), as measured by an appropriate immunoassay.

[00105] In some embodiments, a threshold level of binding is determined through an appropriate immunoassay. In some embodiments, an appropriate immunoassay assesses the binding affinity of an antibody for a target antigen. In some embodiments, an appropriate immunoassay is an enzyme linked immune-sorbent assay. In some embodiments, an appropriate immunoassay is an assay that determines a kinetic measurement (e.g., on rate, off rate) indicative of binding between an antibody and antigen. In some embodiments, an appropriate immunoassay is an assay, such as an Octet assay, that determines one or more a kinetic parameters indicative of binding between an antibody and antigen. In some embodiments, an appropriate immunoassay is a cell-based assay that determines one or more a parameters indicative of specific binding between an antibody and antigen based on cellular activity, *e.g.*, growth factor signaling (such as SMAD signaling), cell growth, cell survival, gene expression, reporter expression, protein production, protein secretion, *etc*. In some embodiments, an appropriate immunoassay is an *in vivo* assay that determines one or more a parameters indicative of specific binding between an antibody and antigen based on cellular, tissue or other physiological activity.

[00106] In some embodiments, a binding profile comprises a set of one or more parameters indicative of the extent to which an antibody specifically binds to one or more one or more TGFβ family member proteins or forms thereof, one or more portions or domains of TGFβ family member proteins and/or one or more chimeras of TGFβ family member proteins. In some embodiments, a binding profile comprises a set of one or more parameters indicative of the extent to which an antibody specifically binds or does not specifically bind to one or more

different antigens. In some embodiments, a binding profile relates to the extent to which an antibody specifically binds or does not specifically bind to 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, or more different antigens. In some embodiments, a binding profile relates to the extent to which an antibody specifically binds or does not specifically bind to 5, 6, 7, 8, 9, 10 or 11 different antigens.

[00107] In some embodiments, a particular binding profile comprises a set of one or more parameters indicative of the extent to which an antibody specifically binds to one or more TGFβ family member proteins or forms thereof. In some embodiments, a TGFβ family member proteins is selected from the group consisting of AMH, ARTN, BMP10, BMP15, BMP2, BMP3, BMP4, BMP5, BMP6, BMP7, BMP8A, BMP8B, GDF1, GDF10, GDF11, GDF15, GDF2, GDF3, GDF3A, GDF5, GDF6, GDF7, GDF8, GDF9, GDNF, INHA, INHBA, INHBB, INHBC, INHBE, LEFTY1, LEFTY2, NODAL, NRTN, PSPN, TGFβ1, TGFβ2, and TGFβ3 protein. In some embodiments, TGFβ family member proteins or forms thereof are from a vertebrate organism. In some embodiments, TGFβ family member proteins or forms thereof are from a human, a monkey, a mouse or a rat. In some embodiments, TGFβ family member proteins or forms thereof are from a human or a mouse. In some embodiments, TGFβ family member proteins or forms thereof are from a human. Examples of sequences of human and non-human TGFβ family member proteins are shown in Tables 1, 4 and 5, provided herein. In some embodiments, TGFβ family member proteins or forms thereof may include any naturally-occurring isoforms or variants of TGFβ family member proteins. In some embodiments, TGFβ family member proteins comprise an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% identical to any of the amino acid sequences as set forth in any one of SEQ ID NOs: 1-37 and 70-115. In some embodiments, TGFβ family member proteins comprise an amino acid sequence as set forth in any one of SEQ ID NOs: 1-37 and 70-115. In some embodiments, TGFβ family member proteins consist of an amino acid sequence as set forth in any one of SEQ ID NOs: 1-37 and 70-115.

[00108] In some embodiments, a particular binding profile may also comprise one or more parameters indicative of to the extent to which antibodies specifically bind to or do not specifically bind to a portion or domain of one or more TGFβ family member proteins. In some embodiments, the portion or domain of a TGFβ family member protein is a prodomain, a straight jacket region, a growth factor domain, a fastener region, a furin cleavage site region, a bmp/tolloid cleavage site, an arm region, a fingers region 1, a fingers region 2, a latency loop, an alpha 1 helical region, and/or a bowtie region. Exemplary portions or

domains of TGFβ family member proteins are shown in Tables 2, 3, 9 and 11, provided herein. In some embodiments, portions or domains of TGFβ family member proteins are portions or domains of GDF proteins. In some embodiments, portions or domains of TGFβ family member proteins are portions or domains of GDF8 and/or GDF11. In some embodiments, portions or domains of TGFβ family member proteins are portions or domains of Inhibin beta A. However, it should be appreciated that the portions or domains of TGFβ family member proteins may be from any TGFβ family member protein provided herein. In some embodiments, the portion or domain of a TGFβ family member protein comprises an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% identical to any of the amino acid sequences as set forth in any one of SEQ ID NOs: 38-65, 162-177 and 202-221. In some embodiments, portions or domains of TGFβ family member proteins comprise an amino acid sequence as set forth in any one of SEQ ID NOs: 38-65, 162-177 and 202-221. In some embodiments, portions or domains of TGFβ family member proteins consist of an amino acid sequence as set forth in any one of SEQ ID NOs: 38-65, 162-177 and 202-221.

[00109] In some embodiments, forms of TGFβ family member proteins refer to complexes of TGFβ family member proteins. For example, forms of TGFβ family member proteins may include pro-forms, latent-forms, primed-forms, or mature forms of dimeric TGFβ family member proteins, such as, for example, proMyostatin, proGDF11, latent Myostatin, latent GDF11, primed Myostatin, and primed GDF11. In some embodiments, TGFβ family member proteins form dimeric complexes. In some embodiments, TGFβ family member proteins form homodimeric complexes. In some embodiments, TGFβ family member proteins form heterodimeric complexes. Dimeric forms of TGFβ family member proteins may include TGFβ family member proteins that are full-length or TGFβ family member proteins that have been cleaved (*e.g.*, by a proprotein convertase and/or a tolloid protease). In some embodiments, forms of TGFβ family member proteins are pro forms of TGFβ family member proteins (*e.g.,* proMyostatin or proGDF11). In some embodiments, forms of TGFβ family member proteins include full-length TGFβ family member proteins. For example, pro forms of TGFβ family member proteins include, without limitation, proMyostatin and proGDF11 that have not been cleaved at a proprotein convertase cleavage site (*e.g.,* by a proprotein convertase such as furin) or a tolloid protease cleavage site (*e.g.,* by a tolloid protease such as BMP-1). In some embodiments, forms of TGFβ family member proteins are latent forms of TGFβ family member proteins (*e.g.,* latent Myostatin or latent GDF11). In some embodiments, forms of TGFβ family member proteins include TGFβ family member

proteins that have been cleaved (*e.g.,* by a proprotein convertase). For example, latent forms of TGFβ family member proteins include, without limitation, latent Myostatin and latent GDF11 that have been cleaved at a proprotein convertase cleavage site (*e.g.,* by a proprotein convertase such as furin) but not at a tolloid protease cleavage site. In some embodiments, forms of TGFβ family member proteins are primed forms of TGFβ family member proteins (*e.g.,* primed Myostatin or primed GDF11). In some embodiments, forms of TGFβ family member proteins include TGFβ family member proteins that have been cleaved (*e.g.,* by a proprotein convertase and/or a tolloid protease). For example, primed forms of TGFβ family member proteins include, without limitation, primed Myostatin and primed GDF11 that have been cleaved at a proprotein convertase cleavage site (*e.g.,* by a proprotein convertase such as furin) and a tolloid protease cleavage site (*e.g.,* by a tolloid protease such as BMP-1). In some embodiments, forms of TGFβ family member proteins are mature forms of TGFβ family member proteins (*e.g.,* mature Myostatin or mature GDF11). In some embodiments, forms of TGFβ family member proteins include TGFβ family member proteins that have been cleaved (*e.g.,* by a proprotein convertase and/or a tolloid protease) and are not in complex with one or more portions of a prodomain of a TGFβ family member protein. For example, mature forms of TGFβ family member proteins include, without limitation, mature Myostatin and mature GDF11 that have been cleaved at a proprotein convertase cleavage site (*e.g.,* by a proprotein convertase such as furin), a tolloid protease cleavage site (*e.g.,* by a tolloid protease such as BMP-1), and are not in complex with a prodomain of a TGFβ family member protein.

[00110] In some embodiments, a particular binding profile comprises a set of one or more parameters indicative of the extent to which antibodies specifically bind to or do not specifically bind to chimeras of TGFβ family member proteins. In some embodiments, chimeras of TGFβ family member proteins can be used to provide information relating to particular epitopes to which any of the antibodies provided herein specifically bind or do not specifically bind. In some embodiments, chimeric TGFβ family member proteins comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 portions or domains of different TGFβ family member protein. For example, a chimeric TGFβ family member protein may comprise a prodomain, a straight jacket region, a growth factor domain, a fastener region, a furin cleavage site region, a bmp/tolloid cleavage site, an arm region, a fingers region 1, a fingers region 2, a latency loop, an alpha 1 helical region, and/or a bowtie region of one TGFβ family member protein and at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 of a prodomain, a straight jacket region, a growth factor domain, a fastener region, a furin

cleavage site region, a bmp/tolloid cleavage site, an arm region, a fingers region 1, a fingers region 2, a latency loop, an alpha 1 helical region, and/or a bowtie region from one or more different TGFβ family member proteins. Exemplary chimeras of TGFβ family member proteins are shown in Table 10, provided herein. In some embodiments, chimeras of TGFβ family member proteins comprise an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% identical to any of the amino acid sequences as set forth in any one of SEQ ID NOs: 178-201. In some embodiments, chimeras of TGFβ family member proteins comprise an amino acid sequence as set forth in any one of SEQ ID NOs: 178-201. In some embodiments, chimeras of TGFβ family member proteins consist of an amino acid sequence as set forth in any one of SEQ ID NOs: 178-201.

[00111] In some embodiments, TGFβ family member proteins include Fc fusion proteins to any of the TGFβ family member proteins or forms or domains or portions thereof. Exemplary TGFβ family member Fc fusion proteins are shown in Table 12, provided herein. In some embodiments, TGFβ family member Fc fusion proteins comprise an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% identical to any of the amino acid sequences as set forth in any one of SEQ ID NOs: 223-226. In some embodiments, TGFβ family member Fc fusion proteins comprise an amino acid sequence as set forth in any one of SEQ ID NOs: 223-226. In some embodiments, TGFβ family member Fc fusion proteins consist of an amino acid sequence as set forth in any one of SEQ ID NOs: 223-226.

[00112] In some embodiments, a particular binding profile comprises a set of one or more parameters indicative of the extent to which antibodies specifically bind to or do not specifically bind to one or more of a human proMyostatin, a murine proMyostatin, a human latent Myostatin, a human GDF-8 prodomain, a human GDF-11 ARM8 prodomain, a human proGDF11 ARM8, a human mature GDF-8, a human proGDF11, a murine latent myostatin and/or a human latent proGDF11 ARM8. However, in certain embodiments, parameters indicative of the extent of binding to one or more murine antigens can be removed from a binding profile. For example, in some embodiments, a particular binding profile comprises a set of one or more parameters indicative of the extent to which antibodies specifically bind to or do not specifically bind to one or more of a human proMyostatin, a human latent Myostatin, a human GDF-8 prodomain, a human GDF-11 ARM8 prodomain, a human proGDF11 ARM8, a human mature GDF-8, a human proGDF11, and/or a human latent proGDF11 ARM8. In some embodiments, a particular binding profile relates to an extent to which antibodies specifically bind to or do not specifically bind to one or more of a protein

that comprises an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% identical to a human proMyostatin, a murine proMyostatin, a human latent Myostatin, a human GDF-8 prodomain, a human GDF-11 ARM8 prodomain, a human proGDF11 ARM8, a human mature GDF-8, a human proGDF11, a murine latent myostatin and/or a human latent proGDF11 ARM8. In some embodiments, the human proMyostatin comprises an amino acid sequence as set forth in SEQ ID NO: 5. In some embodiments, the murine proMyostatin comprises an amino acid sequence as set forth in SEQ ID NO: 88. In some embodiments, the human latent Myostatin comprises an amino acid sequence as set forth in SEQ ID NO: 5. In some embodiments, the human GDF-8 prodomain comprises an amino acid sequence as set forth in SEQ ID NO: 38. In some embodiments, the human GDF-11 ARM8 prodomain comprises an amino acid sequence as set forth in SEQ ID NO: 181. In some embodiments, the human proGDF11 ARM8 comprises an amino acid sequence as set forth in SEQ ID NO: 179. In some embodiments, the human mature GDF-8 comprises an amino acid sequence as set forth in SEQ ID NO: 42. In some embodiments, the human proGDF11 comprises an amino acid sequence as set forth in SEQ ID NO: 4. In some embodiments, the murine latent myostatin comprises an amino acid sequence as set forth in SEQ ID NO: 88. In some embodiments, the human latent proGDF11 ARM8 comprises an amino acid sequence as set forth in SEQ ID NO: 179. In some embodiments, antibodies provided herein have a binding profile as set forth in Table 33.

[00113] In some embodiments, a binding profile may comprises one or more symbols (e.g., +, -, +/-) indicative of the extent to which an antibody binds to an antigen. For example, in some embodiments, binding of an antibody to an antigen at a level detectable beyond a threshold level (*e.g.*, 5 standard deviations beyond a reference level) may be indicated by a "+". In some embodiments, a "-" indicates that the antibody does not bind the antigen at level detectable beyond a threshold in a particular assay (*e.g.*, is less than 2, 3, 4 or 5 standard deviations beyond a reference level, *e.g.*, an assay background level). In some embodiments, a "+/-" indicates that an antibody is at or near a threshold of binding the antigen as determined by a particular assay (*e.g.*, within 2 to 5, 3 to 5, or 4 to 5 standard deviations of a reference level).

[00114] An antibody that "specifically binds" to a target antigen, binds to the target antigen with greater affinity, avidity, more readily, and/or with greater duration than it binds to non-target antigens. In some embodiments, antibodies provided herein have particular binding profiles, *e.g.*, based on whether they specifically bind or do not specifically bind to one or more TGFβ family member proteins or forms thereof, one or more portions or domains of

TGFβ family member proteins and/or one or more chimeras of TGFβ family member proteins. In some embodiments an antibody specifically binds an antigen if binding to that antigen is detected above a background level (*e.g.*, of a control antigen) using an *in vitro* binding assay (*e.g.,* an ELISA). In some embodiments, an antibody specifically binds an antigen if binding to that antigen is detected at least one, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, or at least 10 standard deviations above a background level (*e.g.*, of a control antigen) using an *in vitro* binding assay. In some embodiments an antibody specifically binds an antigen if binding to that antigen is detected at least one, at least 5 standard deviations above a background level (*e.g.*, of a control antigen) using an *in vitro* binding assay. In some embodiments, the *in vitro* binding assay is an enzyme linked immunosorbent assay (ELISA). In some embodiments, the ELISA is performed as described in Example 29, provided herein. However, it should be appreciated that additional methods for determining the binding affinity of a protein to an antigen are also within the scope of this disclosure

[00115] In some embodiments, an antibody specifically binds to an antigen (*e.g.,* proMyostatin) if it binds that antigen with a higher affinity as compared to another antigen (*e.g.,* latent Myostatin). In some embodiments, an antibody specifically binds to an antigen if it binds to that antigen by at least 2-fold, 5-fold, 10-fold, 50-fold, 100-fold, 200-fold, 500-fold, or 1,000-fold higher than another antigen.

[00116] In some embodiments, an antibody specifically binds to an antigen (*e.g.,* proMyostatin) if it binds that antigen with a higher affinity as compared to another antigen (*e.g.,* latent Myostatin). In some embodiments, an antibody specifically binds to an antigen if it binds to that antigen with a dissociation constant (Kd) that is less than 10^{-3} M, 10^{-4} M, 10^{-5} M, 10^{-6}M, 10^{-7} M, 10^{-8} M

Sweeping Antibodies

[00117] In some embodiments, antibodies bind an antigen but cannot effectively eliminate the antigen from the plasma. Thus, in some embodiments, the concentration of the antigen in the plasma may be increased by reducing the clearance of the antigen. However, in some embodiments, antibodies (*e.g.,* sweeping antibodies) provided herein have an affinity to an antigen that is sensitive to pH. Such pH sensitive antibodies may bind to the antigen in plasma at neutral pH and dissociate from the antigen in an acidic endosome, thus reducing antibody-mediated antigen accumulation and/or promoting antigen clearance from the plasma.

[00118] Aspects of the disclosure relate to sweeping antibodies. As used herein "sweeping antibodies" refer to antibodies having both pH-sensitive antigen binding and at least a threshold level of binding to cell surface neonatal Fc receptor (FcRn) at neutral or physiological pH. In some embodiments, sweeping antibodies bind to the neonatal Fc receptor FcRn at neutral pH. For example sweeping antibodies may bind to the FcRn at a pH ranging from 7.0 to 7.6. In some embodiments, sweeping antibodies can bind to an antigen at an antigen binding site and bind to a cellular FcRn via an Fc portion of the antibody. In some embodiments, sweeping antibodies may then be internalized, releasing antigen in an acidic endosome, which may be degraded. In some embodiments, a sweeping antibody, no longer bound to the antigen, may then be released (e.g., by exocytosis) by the cell back into the serum.

[00119] In some embodiments, FcRn in the vascular endothelia (*e.g.,* of a subject) extends the half-life of a sweeping antibody. In some embodiments, vascular endothelial cells internalize sweeping antibodies, which in some embodiments are bound to an antigen such as Myostatin (*e.g.,* proMyostatin, latent Myostatin or primed Myostatin). In some embodiments, a sweeping antibody is recycled back into the bloodstream. In some embodiments, a sweeping antibody has an increased half-life (*e.g.*, in the serum of a subject) as compared to its conventional counterpart. In some embodiments, a conventional counterpart of a sweeping antibody refers the antibody from which the sweeping antibody was derived (e.g., prior to engineering the Fc portion of the conventional antibody to bind FcRn with greater affinity at pH 7). In some embodiments, a sweeping antibody has a half-life in the serum of a subject that is at least 1%, 5%, 10%, 15%, 20%, 25%, 35%, 50%, 75%, 100%, 150%, 200% or 250% longer as compared to its conventional counterpart.

[00120] In some embodiments, an Fc portion of a sweeping antibody binds FcRn. In some embodiments, the Fc portion of a sweeping antibody binds to FcRn at a pH of 7.4 with a Kd ranging from 10^{-3} M to 10^{-8} M. In some embodiments, a sweeping antibody binds to FcRn at a pH of 7.4 with a Kd ranging from10^{-3} M to 10^{-7} M, from 10^{-3} M to 10^{-6} M, from 10^{-3} M to 10^{-5} M, from 10^{-3} M to 10^{-4} M, from 10^{-4} M to 10^{-8} M, from 10^{-4} M to 10^{-7} M, from 10^{-4} M to 10^{-6} M, from 10^{-4} M to 10^{-5} M, from 10^{-5} M to 10^{-8} M, from 10^{-5} M to 10^{-7} M, from 10^{-5} M to 10^{-6} M, from 10^{-6} M to 10^{-8} M, from 10^{-6} M to 10^{-7} M, or from 10^{-7} M to 10^{-8} M. In some embodiments, FcRn binds to the CH2-CH3 hinge region of a sweeping antibody. In some embodiments, FcRn binds to the same region as proteinA or protein G. In some embodiments, FcRn binds to a different binding site from FcγRs. In some embodiments, the amino acid residues AA of a sweeping antibody Fc region are required for binding to FcRn.

In some embodiments, the amino acid residues AA of a sweeping antibody Fc region affect binding to FcRn.

[00121] In some embodiments, any of the antibodies provided herein are engineered to bind FcRn with greater affinity. In some embodiments, any of the antibodies provided herein are engineered to bind FcRn with greater affinity at pH 7.4. In some embodiments, the affinity of sweeping antibodies to FcRn is increased to extend their pharmacokinetic (PK) properties as compared to their conventional counterparts. For example, in some embodiments, sweeping antibodies elicit less adverse reactions due to their efficacy at lower doses. In some embodiments, sweeping antibodies are administered less frequently. In some embodiments, transcytosis of sweeping antibodies to certain tissue types are increased. In some embodiments, sweeping antibodies enhance efficiency of trans-placental delivery. In some embodiments, sweeping antibodies are less costly to produce.

[00122] In some embodiments, any of the antibodies provided herein are engineered to bind FcRn with lower affinity. In some embodiments, any of the antibodies provided herein are engineered to bind FcRn with lower affinity at pH 7.4. In some embodiments, the affinity of sweeping antibodies to FcRn is decreased to shorten their pharmacokinetic (PK) properties as compared to their conventional counterparts. For example, in some embodiments, sweeping antibodies are more rapidly cleared for imaging and/or radioimmunotherapy. In some embodiments, sweeping antibodies promote clearance of endogenous pathogenic antibodies as a treatment for autoimmune diseases. In some embodiments, sweeping antibodies reduce the risk of adverse pregnancy outcome, which may be caused by trans-placental transport of material fetus-specific antibodies.

[00123] In some embodiments, sweeping antibodies have decreased affinity to an antigen at low pH as compared to a neutral or physiological pH (*e.g.,* pH 7.4). In some embodiments, sweeping antibodies have a decreased affinity to an antigen at an acidic pH (*e.g.* a pH ranging from 5.5 to 6.5) as compared to a physiological pH (*e.g.,* pH 7.4). It should be appreciated that any of the antibodies provided herein can be engineered to dissociate from the antigen depending on changes in pH (*e.g.,* pH sensitive antibodies). In some embodiments, sweeping antibodies provided herein are engineered to bind antigen dependent on pH. In some embodiments,, sweeping antibodies provided herein are engineered to bind FcRn dependent on pH. In some embodiments, sweeping antibodies provided herein are internalized by endocytosis. In some embodiments, sweeping antibodies provided here are internalized by FcRn binding. In some embodiments, endocytosed sweeping antibodies release antigen in an endosome. In some embodiments, sweeping antibodies are recycled back to the cell surface.

In some embodiments, sweeping antibodies remain attached to cells. In some embodiments, endocytosed sweeping antibodies are recycled back to the plasma. It should be appreciated that the Fc portion of any of the antibodies provided herein may be engineered to have different FcRn binding activity. In some embodiments, FcRn binding activity affects the clearance time of an antigen by a sweeping antibody. In some embodiments, sweeping antibodies may be long-acting or rapid-acting sweeping antibodies.

[00124] In some embodiments, converting a conventional therapeutic antibody into a sweeping antibody reduces the efficacious dose. In some embodiments, converting a conventional therapeutic antibody into a sweeping antibody reduces the efficacious dose by at least 1%, 2%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 99%. In some embodiments, converting a conventional therapeutic antibody into a sweeping antibody reduces the efficacious dose by at least 1.5 fold, 2 fold, 3 fold, 4 fold, 5 fold, 6 fold, 8 fold, 10 fold, 15 fold, 20 fold, 50 fold or 100 fold.

[00125] In some embodiments, selecting an appropriate dose of a sweeping antibody for therapy may be performed empirically. In some embodiments, a high dose of a sweeping antibody may saturate FcRn, resulting in antibodies which stabilize antigen in serum without being internalized. In some embodiments, a low dose of a sweeping antibody may not be therapeutically effective. In some embodiments, sweeping antibodies are administered once a day, once a week, once every two weeks, once every three weeks, once every four weeks, once every 6 weeks, once every 8 weeks, once every 10 weeks, once every 12 weeks, once every 16 weeks, once every 20 weeks, or once every 24 weeks.

[00126] In some embodiments, any of the antibodies provided herein may be modified or engineered to be sweeping antibodies. In some embodiments, any of the antibodies provided herein may be converted into a sweeping antibody using any suitable method. For example, suitable methods for making sweeping antibodies have been previously described in Igawa *et al.,* (2013) "Engineered Monoclonal Antibody with Novel Antigen-Sweeping Activity In Vivo," *PLoS ONE* 8(5): e63236; and Igawa *et al.*, "pH-dependent antigen-binding antibodies as a novel

[00127] therapeutic modality," *Biochimica et Biophysica Acta* 1844 (2014) 1943–1950; the contents of each of which are hereby incorporated by reference. It should be appreciated, however, that the methods for making sweeping antibodies as provided herein are not meant to be limiting. Thus, additional methods for making sweeping antibodies are within the scope of this disclosure.

Competing and Cross-Competing Antibodies

[00128] Aspects of the disclosure relate to antibodies that compete or cross-compete with any of the antibodies provided herein. The term "compete", as used herein with regard to an antibody, means that a first antibody binds to an epitope of a protein (*e.g.,* latentMyostatin) in a manner sufficiently similar to the binding of a second antibody, such that the result of binding of the first antibody with its epitope is detectably decreased in the presence of the second antibody compared to the binding of the first antibody in the absence of the second antibody. The alternative, where the binding of the second antibody to its epitope is also detectably decreased in the presence of the first antibody, can, but need not be the case. That is, a first antibody can inhibit the binding of a second antibody to its epitope without that second antibody inhibiting the binding of the first antibody to its respective epitope. However, where each antibody detectably inhibits the binding of the other antibody with its epitope or ligand, whether to the same, greater, or lesser extent, the antibodies are said to "cross-compete" with each other for binding of their respective epitope(s). Both competing and cross-competing antibodies are within the scope of this disclosure. Regardless of the mechanism by which such competition or cross-competition occurs (e.g., steric hindrance, conformational change, or binding to a common epitope, or portion thereof), the skilled artisan would appreciate that such competing and/or cross-competing antibodies are encompassed and can be useful for the methods and/or compositions provided herein.

[00129] Aspects of the disclosure relate to antibodies that compete or cross-compete with any of the antibodies provided herein. In some embodiments, an antibody binds at or near the same epitope as any of the antibodies provided herein. In some embodiments, an antibody binds near an epitope if it binds within 15 or fewer amino acid residues of the epitope. In some embodiments, any of the antibodies provided herein bind within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acid residues of an epitope that is bound by any of the antibodies provided herein. For example, in some embodiments any of the antibodies provided herein bind at or near a tolloid cleavage site or at or near a tolloid docking site of a TGFβ family member protein (*e.g.,* proMyostatin or latent Myostatin). In some embodiments, an antibody binds near a tolloid cleavage site or near a tolloid docking site if it binds within 15 or fewer amino acid residues of the tolloid cleavage site or tolloid docking site. In some embodiments, any of the antibodies provided herein bind within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acid residues of a tolloid cleavage site or tolloid docking site. In some embodiments, an antibody binds at or near a tolloid cleavage site of

GDF11. For example, an antibody may bind an amino acid sequence as set forth in SEQ ID NO: 1665. PKAPPLQQILDLHDFQGDALQPEDFLEEDEYHA (SEQ ID NO: 1665). In some embodiments, an antibody binds at or near a tolloid cleavage site of GDF8. For example, an antibody may bind an amino acid sequence as set forth in SEQ ID NO: 1666. PKAPPLRELIDQYDVQRDDSSDGSLEDDDYHAT (SEQ ID NO: 1666). In some embodiments, binding of an antibody at or near a tolloid cleavage site or at or near a tolloid docking site of a TGFβ family member protein inhibits cleavage of the TGFβ family member protein, for example, by a tolloid protease (e.g., BMP-1).

[00130] In other embodiments, any of the antibodies provided herein bind at or near a proprotein convertase cleavage site or at or near a proprotein convertase docking site of a TGFβ family member protein (*e.g.,* proMyostatin or latent Myostatin) In some embodiments, an antibody binds near a proprotein convertase cleavage site or near a proprotein convertase docking site if it binds within 15 or fewer amino acid residues of the proprotein convertase cleavage site or proprotein convertase docking site. In some embodiments, any of the antibodies provided herein bind within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acid residues of a proprotein convertase cleavage site or proprotein convertase docking site. In some embodiments, an antibody binds at or near a proprotein convertase cleavage site of GDF11. For example, an antibody may bind an amino acid sequence as set forth in SEQ ID NO: 1667. GLHPFMELRVLENTKRSRRNLGLDCDEHSSESRC (SEQ ID NO: 1667). In some embodiments, an antibody binds at or near a proprotein convertase cleavage site of GDF8. For example, an antibody may bind an amino acid sequence as set forth in SEQ ID NO: 1668. GLNPFLEVKVTDTPKRSRRDFGLDCDEHSTESRC (SEQ ID NO: 1668). In some embodiments, binding of an antibody at or near a proprotein convertase cleavage site or at or near a proprotein convertase docking site of a TGFβ family member protein inhibits cleavage of the TGFβ family member protein, for example, by a proprotein convertase (*e.g.,* furin).

[00131] In another embodiment, an antibody competes or cross-competes for binding to any of the antigens provided hererin (*e.g.,* one or more TGFβ family member proteins or forms thereof, one or more portions or domains of TGFβ family member proteins and/or one or more chimeras of TGFβ family member proteins) with an equilibrium dissociation constant, Kd, between the antibody and the protein of less than 10^{-6} M. In other embodiments, an antibody competes or cross-competes for binding to any of the antigens provided herein with a Kd in a range from 10^{-11} M to 10^{-6} M.

[00132] Any of the antibodies provided herein can be characterized using any suitable methods. For example, one method is to identify the epitope to which the antigen binds, or "epitope mapping." There are many suitable methods for mapping and characterizing the location of epitopes on proteins, including solving the crystal structure of an antibody-antigen complex, competition assays, gene fragment expression assays, and synthetic peptide-based assays, as described, for example, in Chapter 11 of Harlow and Lane, Using Antibodies, a Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1999. In an additional example, epitope mapping can be used to determine the sequence to which an antibody binds. The epitope can be a linear epitope, i.e., contained in a single stretch of amino acids, or a conformational epitope formed by a three-dimensional interaction of amino acids that may not necessarily be contained in a single stretch (primary structure linear sequence). Peptides of varying lengths (e.g., at least 4-6 amino acids long) can be isolated or synthesized (e.g., recombinantly) and used for binding assays with an antibody. In another example, the epitope to which the antibody binds can be determined in a systematic screen by using overlapping peptides derived from the target antigen sequence and determining binding by the antibody. According to the gene fragment expression assays, the open reading frame encoding the target antigen is fragmented either randomly or by specific genetic constructions and the reactivity of the expressed fragments of the antigen with the antibody to be tested is determined. The gene fragments may, for example, be produced by PCR and then transcribed and translated into protein in vitro, in the presence of radioactive amino acids. The binding of the antibody to the radioactively labeled antigen fragments is then determined by immunoprecipitation and gel electrophoresis. Certain epitopes can also be identified by using large libraries of random peptide sequences displayed on the surface of phage particles (phage libraries). Alternatively, a defined library of overlapping peptide fragments can be tested for binding to the test antibody in binding assays. In additional examples, mutagenesis of an antigen binding domain, domain swapping experiments and alanine scanning mutagenesis can be performed to identify residues required, sufficient, and/or necessary for epitope binding. For example, domain swapping experiments can be performed using a mutant of a target antigen in which various fragments of TGFβ family member proteins have been replaced (swapped) with sequences from related, but antigenically distinct proteins, such as another member of a TGFβ family member protein. By assessing a binding profile of an antigen, the importance of the particular antigen fragment to antibody binding can be assessed.

[00133] Alternatively, competition assays can be performed using other antibodies known to bind to the same antigen to determine whether an antibody binds to the same epitope as the other antibodies. Such competition assays would be apparent to the skilled artisan.

[00134] Any of the suitable methods, e.g., the epitope mapping methods as described herein, can be applied to determine whether any of the antibodies provided hererin binds one or more of the specific residues/segments of one or more TGFβ family member proteins as described herein. Further, the interaction of an antibody with one or more of those defined residues in TGFβ family member proteins can be determined by routine technology. For example, a crystal structure can be determined, and the distances between the residues in TGFβ family member proteins and one or more residues in an antibody can be determined accordingly. Based on such distance, whether a specific residue in a TGFβ family member protein interacts with one or more residues in an antibody can be determined. Further, suitable methods, such as competition assays and target mutagenesis assays can be applied to determine the preferential binding of a candidate antibody to a TGFβ family member protein as compared to another TGFβ family member protein.

Immunoassays and Related Binding Profiles

[00135] Aspects of the disclosure relate to methods for assessing a biological sample using one or more antibodies having a selected binding profile (e.g., a binding profile as outlined in Table 33). In some embodiments, antibodies are selected for use (e.g., in an immunoassay) based on the fact that they have a known and/or desired binding profile (a selected binding profile). For example, antibodies may have a selected binding profile to one or more TGFβ family member proteins or forms thereof, one or more portions or domains of TGFβ family member proteins and/or one or more chimeras of TGFβ family member proteins. In some embodiments, antibodies with selected binding profiles may be used as research and/or diagnostic tools. In some embodiments, antibodies with selected binding profiles may be used to assess a level of a protein, a localization pattern of a protein (*e.g.,* at the tissue, cellular, and/or sub-cellular level) and/or a ratio of a protein with respect to another protein. For example, antibodies with selected binding profiles may be used to assess the level of proMyostatin and the level of latent Myostatin, which may be used to determine a ratio of proMyostatin to latent Myostatin. In some embodiments, methods include obtaining one or more antibodies that have a selected binding profile and subjecting a biological sample to an immunoassay using the one or more antibodies with selected binding profiles. In some embodiments, at least 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 or more antibodies having a selected binding profile are used in an assay to assess a biological sample. In some embodiments, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 antibodies having a selected binding profile are used in an assay to assess a biological sample.

[00136] In some embodiments, a biological sample is subjected to an immunoassay using two or more antibodies having different selected binding profiles. In some embodiments, a biological sample is subjected to an immunoassay using 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 antibodies having different selected binding profiles. In some embodiments, antibodies have a selected binding profile to one or more of a human proMyostatin, a human latent Myostatin, a human GDF-8 prodomain, a human GDF-11 ARM8 prodomain, a human proGDF11 ARM8, a human mature GDF-8, a human proGDF11, and/or a human latent proGDF11 ARM8. In some embodiments, antibodies have a selected binding profile to one or more of a human proMyostatin, a murine proMyostatin, a human latent Myostatin, a human GDF-8 prodomain, a human GDF-11 ARM8 prodomain, a human proGDF11 ARM8, a human mature GDF-8, a human proGDF11, a murine latent Myostatin and/or a human latent proGDF11 ARM8. In some embodiments, In some embodiments, the human proMyostatin comprises an amino acid sequence as set forth in SEQ ID NO: 5. In some embodiments, the murine proMyostatin comprises an amino acid sequence as set forth in SEQ ID NO: 88. In some embodiments, the human latent Myostatin comprises an amino acid sequence as set forth in SEQ ID NO: 5. In some embodiments, the human GDF-8 prodomain comprises an amino acid sequence as set forth in SEQ ID NO: 38. In some embodiments, the human GDF-11 ARM8 prodomain comprises an amino acid sequence as set forth in SEQ ID NO: 181. In some embodiments, the human proGDF11 ARM8 comprises an amino acid sequence as set forth in SEQ ID NO: 179. In some embodiments, the human mature GDF-8 comprises an amino acid sequence as set forth in SEQ ID NO: 42. In some embodiments, the human proGDF11 comprises an amino acid sequence as set forth in SEQ ID NO: 4. In some embodiments, the murine latent Myostatin comprises an amino acid sequence as set forth in SEQ ID NO: 88. In some embodiments, the human latent proGDF11 ARM8 comprises an amino acid sequence as set forth in SEQ ID NO: 179.

[00137] In some embodiments, a biological sample is subjected to an immunoassay using two or more antibodies having different selected binding profiles. In some embodiments, antibodies have selected binding profiles as shown in Table 33. In some embodiments, antibodies have selected binding profiles of any one of the antibodies B1a-1, BP1b-1, BP2a-

1, BP3a-1, BP3a-2, BP3a-3, BP4a-1, BP5a-1, BP5b-1, BP5a-2, BP5a-3, BP5a-4, BP5a-5, BP5b-2, BP5b-3, BP5b-4, BP5b-5, BP5b-6, BP5b-7, BP5b-8, BP5b-9, BP6a-1, BP6a-2, BP6a-3, BP6a-4, BP6a-5, BP6a-6, BP6b-1, BP6b-2, BP6a-7, BP6a-8, BP6a-9, BP6a-10, BP6a-11, BP6a-12, BP6a-13, BP6a-14, BP6a-15, BP6a-16, BP6a-17, BP6a-18, BP6a-19, BP6a-20, BP6a-21, BP6a-22, BP6a-23, BP6a-24, BP6a-25, BP6a-26, BP6a-27, BP6b-3, BP6b-4, BP6b-5, BP6b-6, BP6b-7, BP6b-8, BP6b-9, BP6b-10, BP6b-11, BP6b-12, BP7b-1, BP8b-1, BP9b-1, BP10b-1, BP11a-1, BP12b-1, BP13a-1, BP14a-1, BP15a-1, BP16b-1, BP16b-2, BP16b-3, BP16b-4, BP16a-1, BP17b-1, BP18b-1, BP18b-2, BP18b-3, BP18b-4, BP18b-5, BP18b-6, BP18b-7, BP18a-1, BP18a-2, BP19b-1, BP19b-2, BP19b-3, BP19a-1, BP19a-2, BP19a-3, BP20b-1, BP21b-1 or BP22b-1.

[00138] In some embodiments, a biological sample is subjected to one or more immunoassays using a set of two or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) antibodies, in which the set comprises two antibodies having binding profiles, as outlined in Table 33, selected from the following pairs: {BP1a, BP1b}, {BP1a, BP2a}, {BP1a, BP3a}, {BP1a, BP4a}, {BP1a, BP5a}, {BP1a, BP5b}, {BP1a, BP6a}, {BP1a, BP6b}, {BP1a, BP7b}, {BP1a, BP8b}, {BP1a, BP9b}, {BP1a, BP10b}, {BP1a, BP11a}, {BP1a, BP12b}, {BP1a, BP13a}, {BP1a, BP14a}, {BP1a, BP15a}, {BP1a, BP16b}, {BP1a, BP16a}, {BP1a, BP17b}, {BP1a, BP18b}, {BP1a, BP18a}, {BP1a, BP19b}, {BP1a, BP19a}, {BP1a, BP20b}, {BP1a, BP21b}, {BP1a, BP22b}, {BP1b, BP2a}, {BP1b, BP3a}, {BP1b, BP4a}, {BP1b, BP5a}, {BP1b, BP5b}, {BP1b, BP6a}, {BP1b, BP6b}, {BP1b, BP7b}, {BP1b, BP8b}, {BP1b, BP9b}, {BP1b, BP10b}, {BP1b, BP11a}, {BP1b, BP12b}, {BP1b, BP13a}, {BP1b, BP14a}, {BP1b, BP15a}, {BP1b, BP16b}, {BP1b, BP16a}, {BP1b, BP17b}, {BP1b, BP18b}, {BP1b, BP18a}, {BP1b, BP19b}, {BP1b, BP19a}, {BP1b, BP20b}, {BP1b, BP21b}, {BP1b, BP22b}, {BP2a, BP3a}, {BP2a, BP4a}, {BP2a, BP5a}, {BP2a, BP5b}, {BP2a, BP6a}, {BP2a, BP6b}, {BP2a, BP7b}, {BP2a, BP8b}, {BP2a, BP9b}, {BP2a, BP10b}, {BP2a, BP11a}, {BP2a, BP12b}, {BP2a, BP13a}, {BP2a, BP14a}, {BP2a, BP15a}, {BP2a, BP16b}, {BP2a, BP16a}, {BP2a, BP17b}, {BP2a, BP18b}, {BP2a, BP18a}, {BP2a, BP19b}, {BP2a, BP19a}, {BP2a, BP20b}, {BP2a, BP21b}, {BP2a, BP22b}, {BP3a, BP4a}, {BP3a, BP5a}, {BP3a, BP5b}, {BP3a, BP6a}, {BP3a, BP6b}, {BP3a, BP7b}, {BP3a, BP8b}, {BP3a, BP9b}, {BP3a, BP10b}, {BP3a, BP11a}, {BP3a, BP12b}, {BP3a, BP13a}, {BP3a, BP14a}, {BP3a, BP15a}, {BP3a, BP16b}, {BP3a, BP16a}, {BP3a, BP17b}, {BP3a, BP18b}, {BP3a, BP18a}, {BP3a, BP19b}, {BP3a, BP19a}, {BP3a, BP20b}, {BP3a, BP21b}, {BP3a, BP22b}, {BP4a, BP5a}, {BP4a, BP5b}, {BP4a, BP6a}, {BP4a, BP6b}, {BP4a, BP7b}, {BP4a, BP8b}, {BP4a, BP9b}, {BP4a, BP10b}, {BP4a, BP11a}, {BP4a, BP12b}, {BP4a, BP13a},

{BP4a, BP14a}, {BP4a, BP15a}, {BP4a, BP16b}, {BP4a, BP16a}, {BP4a, BP17b}, {BP4a, BP18b}, {BP4a, BP18a}, {BP4a, BP19b}, {BP4a, BP19a}, {BP4a, BP20b}, {BP4a, BP21b}, {BP4a, BP22b}, {BP5a, BP5b}, {BP5a, BP6a}, {BP5a, BP6b}, {BP5a, BP7b}, {BP5a, BP8b}, {BP5a, BP9b}, {BP5a, BP10b}, {BP5a, BP11a}, {BP5a, BP12b}, {BP5a, BP13a}, {BP5a, BP14a}, {BP5a, BP15a}, {BP5a, BP16b}, {BP5a, BP16a}, {BP5a, BP17b}, {BP5a, BP18b}, {BP5a, BP18a}, {BP5a, BP19b}, {BP5a, BP19a}, {BP5a, BP20b}, {BP5a, BP21b}, {BP5a, BP22b}, {BP5b, BP6a}, {BP5b, BP6b}, {BP5b, BP7b}, {BP5b, BP8b}, {BP5b, BP9b}, {BP5b, BP10b}, {BP5b, BP11a}, {BP5b, BP12b}, {BP5b, BP13a}, {BP5b, BP14a}, {BP5b, BP15a}, {BP5b, BP16b}, {BP5b, BP16a}, {BP5b, BP17b}, {BP5b, BP18b}, {BP5b, BP18a}, {BP5b, BP19b}, {BP5b, BP19a}, {BP5b, BP20b}, {BP5b, BP21b}, {BP5b, BP22b}, {BP6a, BP6b}, {BP6a, BP7b}, {BP6a, BP8b}, {BP6a, BP9b}, {BP6a, BP10b}, {BP6a, BP11a}, {BP6a, BP12b}, {BP6a, BP13a}, {BP6a, BP14a}, {BP6a, BP15a}, {BP6a, BP16b}, {BP6a, BP16a}, {BP6a, BP17b}, {BP6a, BP18b}, {BP6a, BP18a}, {BP6a, BP19b}, {BP6a, BP19a}, {BP6a, BP20b}, {BP6a, BP21b}, {BP6a, BP22b}, {BP6b, BP7b}, {BP6b, BP8b}, {BP6b, BP9b}, {BP6b, BP10b}, {BP6b, BP11a}, {BP6b, BP12b}, {BP6b, BP13a}, {BP6b, BP14a}, {BP6b, BP15a}, {BP6b, BP16b}, {BP6b, BP16a}, {BP6b, BP17b}, {BP6b, BP18b}, {BP6b, BP18a}, {BP6b, BP19b}, {BP6b, BP19a}, {BP6b, BP20b}, {BP6b, BP21b}, {BP6b, BP22b}, {BP7b, BP8b}, {BP7b, BP9b}, {BP7b, BP10b}, {BP7b, BP11a}, {BP7b, BP12b}, {BP7b, BP13a}, {BP7b, BP14a}, {BP7b, BP15a}, {BP7b, BP16b}, {BP7b, BP16a}, {BP7b, BP17b}, {BP7b, BP18b}, {BP7b, BP18a}, {BP7b, BP19b}, {BP7b, BP19a}, {BP7b, BP20b}, {BP7b, BP21b}, {BP7b, BP22b}, {BP8b, BP9b}, {BP8b, BP10b}, {BP8b, BP11a}, {BP8b, BP12b}, {BP8b, BP13a}, {BP8b, BP14a}, {BP8b, BP15a}, {BP8b, BP16b}, {BP8b, BP16a}, {BP8b, BP17b}, {BP8b, BP18b}, {BP8b, BP18a}, {BP8b, BP19b}, {BP8b, BP19a}, {BP8b, BP20b}, {BP8b, BP21b}, {BP8b, BP22b}, {BP9b, BP10b}, {BP9b, BP11a}, {BP9b, BP12b}, {BP9b, BP13a}, {BP9b, BP14a}, {BP9b, BP15a}, {BP9b, BP16b}, {BP9b, BP16a}, {BP9b, BP17b}, {BP9b, BP18b}, {BP9b, BP18a}, {BP9b, BP19b}, {BP9b, BP19a}, {BP9b, BP20b}, {BP9b, BP21b}, {BP9b, BP22b}, {BP10b, BP11a}, {BP10b, BP12b}, {BP10b, BP13a}, {BP10b, BP14a}, {BP10b, BP15a}, {BP10b, BP16b}, {BP10b, BP16a}, {BP10b, BP17b}, {BP10b, BP18b}, {BP10b, BP18a}, {BP10b, BP19b}, {BP10b, BP19a}, {BP10b, BP20b}, {BP10b, BP21b}, {BP10b, BP22b}, {BP11a, BP12b}, {BP11a, BP13a}, {BP11a, BP14a}, {BP11a, BP15a}, {BP11a, BP16b}, {BP11a, BP16a}, {BP11a, BP17b}, {BP11a, BP18b}, {BP11a, BP18a}, {BP11a, BP19b}, {BP11a, BP19a}, {BP11a, BP20b}, {BP11a, BP21b}, {BP11a, BP22b}, {BP12b, BP13a}, {BP12b, BP14a}, {BP12b, BP15a}, {BP12b, BP16b}, {BP12b, BP16a}, {BP12b,

BP17b}, {BP12b, BP18b}, {BP12b, BP18a}, {BP12b, BP19b}, {BP12b, BP19a}, {BP12b, BP20b}, {BP12b, BP21b}, {BP12b, BP22b}, {BP13a, BP14a}, {BP13a, BP15a}, {BP13a, BP16b}, {BP13a, BP16a}, {BP13a, BP17b}, {BP13a, BP18b}, {BP13a, BP18a}, {BP13a, BP19b}, {BP13a, BP19a}, {BP13a, BP20b}, {BP13a, BP21b}, {BP13a, BP22b}, {BP14a, BP15a}, {BP14a, BP16b}, {BP14a, BP16a}, {BP14a, BP17b}, {BP14a, BP18b}, {BP14a, BP18a}, {BP14a, BP19b}, {BP14a, BP19a}, {BP14a, BP20b}, {BP14a, BP21b}, {BP14a, BP22b}, {BP15a, BP16b}, {BP15a, BP16a}, {BP15a, BP17b}, {BP15a, BP18b}, {BP15a, BP18a}, {BP15a, BP19b}, {BP15a, BP19a}, {BP15a, BP20b}, {BP15a, BP21b}, {BP15a, BP22b}, {BP16b, BP16a}, {BP16b, BP17b}, {BP16b, BP18b}, {BP16b, BP18a}, {BP16b, BP19b}, {BP16b, BP19a}, {BP16b, BP20b}, {BP16b, BP21b}, {BP16b, BP22b}, {BP16a, BP17b}, {BP16a, BP18b}, {BP16a, BP18a}, {BP16a, BP19b}, {BP16a, BP19a}, {BP16a, BP20b}, {BP16a, BP21b}, {BP16a, BP22b}, {BP17b, BP18b}, {BP17b, BP18a}, {BP17b, BP19b}, {BP17b, BP19a}, {BP17b, BP20b}, {BP17b, BP21b}, {BP17b, BP22b}, {BP18b, BP18a}, {BP18b, BP19b}, {BP18b, BP19a}, {BP18b, BP20b}, {BP18b, BP21b}, {BP18b, BP22b}, {BP18a, BP19b}, {BP18a, BP19a}, {BP18a, BP20b}, {BP18a, BP21b}, {BP18a, BP22b}, {BP19b, BP19a}, {BP19b, BP20b}, {BP19b, BP21b}, {BP19b, BP22b}, {BP19a, BP20b}, {BP19a, BP21b}, {BP19a, BP22b}, {BP20b, BP21b}, {BP20b, BP22b}, and {BP21b, BP22b}. In some embodiments, a biological sample is subjected to an immunoassay using a set of one or more antibodies comprising any two of the antibodies of Table 33. In some embodiments, a biological sample is subjected to an immunoassay using a set of one or more antibodies comprising of any three, four , five, six, seven, eight, nine, ten or more of the antibodies of Table 33.

[00139] In some embodiments, a biological sample is subjected to an immunoassay using three or more antibodies having different selected binding profiles. In some embodiments, antibodies have selected binding profiles as shown in Table 33. In some embodiments, antibodies have selected binding profiles of any one of the antibodies B1a-1, BP1b-1, BP2a-1, BP3a-1, BP3a-2, BP3a-3, BP4a-1, BP5a-1, BP5b-1, BP5a-2, BP5a-3, BP5a-4, BP5a-5, BP5b-2, BP5b-3, BP5b-4, BP5b-5, BP5b-6, BP5b-7, BP5b-8, BP5b-9, BP6a-1, BP6a-2, BP6a-3, BP6a-4, BP6a-5, BP6a-6, BP6b-1, BP6b-2, BP6a-7, BP6a-8, BP6a-9, BP6a-10, BP6a-11, BP6a-12, BP6a-13, BP6a-14, BP6a-15, BP6a-16, BP6a-17, BP6a-18, BP6a-19, BP6a-20, BP6a-21, BP6a-22, BP6a-23, BP6a-24, BP6a-25, BP6a-26, BP6a-27, BP6b-3, BP6b-4, BP6b-5, BP6b-6, BP6b-7, BP6b-8, BP6b-9, BP6b-10, BP6b-11, BP6b-12, BP7b-1, BP8b-1, BP9b-1, BP10b-1, BP11a-1, BP12b-1, BP13a-1, BP14a-1, BP15a-1, BP16b-1, BP16b-2, BP16b-3, BP16b-4, BP16a-1, BP17b-1, BP18b-1, BP18b-2, BP18b-3, BP18b-4,

BP18b-5, BP18b-6, BP18b-7, BP18a-1, BP18a-2, BP19b-1, BP19b-2, BP19b-3, BP19a-1, BP19a-2, BP19a-3, BP20b-1, BP21b-1 or BP22b-1. In some embodiments, methods provided herein relate to methods for detecting one or more TGFβ family member proteins or forms thereof, one or more portions or domains of TGFβ family member proteins and/or one or more chimeras of TGFβ family member proteins in a sample obtained from a subject. In some embodiments, a subject refers to an individual organism, for example, an individual mammal. In some embodiments, the subject is a human. In some embodiments, the subject is a non-human mammal. In some embodiments, the subject is a non-human primate. In some embodiments, the subject is a rodent (*e.g.*, a mouse or rat). In some embodiments, the subject is a sheep, a goat, a cattle, a cat, or a dog. In some embodiments, the subject is a vertebrate, an amphibian, a reptile, a fish, an insect, a fly, or a nematode. In some embodiments, the subject is a research animal. In some embodiments, the subject is genetically engineered, *e.g.*, a genetically engineered non-human subject. The subject may be of either sex and at any stage of development. In some embodiments, the subject is a patient or a healthy volunteer.

[00140] In some embodiments, a method for detecting one or more TGFβ family member proteins or forms thereof, one or more portions or domains of TGFβ family member proteins and/or one or more chimeras of TGFβ family member proteins in a sample obtained from a subject involves (a) contacting the sample with an antibody having a selected binding profile under conditions suitable for binding of the antibody to the antigen, if the antigen is present in the sample, thereby forming binding complexes; and (b) determining the level of the antibody or antigen binding fragment bound to the antigen (*e.g.*, determining the level of the binding complexes).

[00141] As used herein a binding complex refers to a biomolecular complex of antibody bound to antigen (*e.g.*, one or more TGFβ family member proteins or forms thereof, one or more portions or domains of TGFβ family member proteins and/or one or more chimeras of TGFβ family member proteins). Binding complexes may comprise antibodies with a single specificity or two or more antibodies or antigen binding fragments with different specificities. In one embodiment, a binding complex comprises two or more antibodies recognizing different antigenic sites on the same antigen. In some instances, an antibody may be bound to an antigen, having bound to it other biomolecules such as RNA, DNA, polysaccharides or proteins. In one embodiment, a binding complex comprises two or more antibodies recognizing different antigens. In some embodiments, an antibody in a binding complex (*e.g.*, an immobilized antibody bound to antigen), may itself by bound, as an antigen, to an

antibody (*e.g.*, a detectably labeled antibody). Thus, binding complexes may, in some instances, comprise multiple antigens and multiple antibodies or antigen binding fragments.

[00142] Antigens present in binding complexes may or may not be in their native *in situ* conformation. In some embodiments, a binding complex is formed between an antibody and a purified protein antigen, or isolated proteins comprising antigen, in which the antigen is not in its native *in situ* conformation. In some embodiments, a binding complex is formed between an antibody and a purified protein antigen, in which the antigen is not in its native *in situ* conformation and is immobilized on solid support (*e.g.*, a PVDF membrane). In some embodiments, a binding complex is formed with an antibody and, for example, a cell surface protein that is present *in situ* in a native confirmation (*e.g.*, on the surface of a cell).

[00143] Antibodies in binding complexes may or may not be detectably labeled. In some embodiments, binding complexes comprise detectably labeled antibodies and non-labeled antibodies. In some embodiments, binding complexes comprise detectably labeled antigen. In some embodiments, antibodies, in binding complexes, are immobilized to one or more solid supports. In some embodiments, antigens, in binding complexes, are immobilized to one or more solid supports. Exemplary solid supports are disclosed herein and will be apparent to one of ordinary skill in the art. The foregoing examples of binding complexes are not intended to be limiting. Other examples of binding complexes will be apparent to one or ordinary skill in the art.

[00144] In any of the detection, diagnostic, and monitoring methods, antibody or antigen may be conjugated to a solid support surface, either directly or indirectly. Methods for conjugation to solid supports are standard and can be accomplished via covalent and non-covalent interactions. Non-limiting examples of conjugation methods include: adsorption, cross-linking, protein A/G - antibody interactions, and streptavidin-biotin interactions. Other methods of conjugation will be readily apparent to one of ordinary skill in the art.

[00145] In some aspects, detection, diagnosis, and monitoring methods include comparing the level of the antibody (including antigen binding fragments) bound to the antigen (*e.g.*, one or more TGFβ family member proteins or forms thereof, one or more portions or domains of TGFβ family member proteins and/or one or more chimeras of TGFβ family member proteins) to one or more reference standards. The reference standard may be, for example, the level of a corresponding TGFβ family member protein in a subject that does or does not have the TGFβ family member protein. In one embodiment, the reference standard is the level of a TGFβ family member protein detected in a sample that does not contain the TGFβ family member protein (*e.g.*, a background level). Alternatively, a background level can be

determined from a sample that contains a particular pro/latent-Myostatin, by contacting the sample with non-specific antibodies (*e.g.*, antibodies obtained from non-immune serum). Then again, the reference standard may be the level of a TGFβ family member protein detected in a sample that does contain the TGFβ family member protein (*e.g.*, a positive control). In some cases, the reference standard may be a series of levels associated with varying concentrations of a TGFβ family member protein in a sample and useful for quantifying the concentration of the TGFβ family member protein in the test sample. The foregoing examples of reference standards are not limiting and other suitable reference standard will be readily apparent to one of ordinary skill in the art.

[00146] The level of one or more TGFβ family member proteins or forms thereof, one or more portions or domains of TGFβ family member proteins and/or one or more chimeras of TGFβ family member proteins may be measured, as provided herein, from a biological sample using any of the antibodies having a selected binding profile. A biological sample refers to any biological material which may be obtained from a subject or cell. For example, a biological sample may be whole blood, plasma, serum, saliva, cerebrospinal fluid, urine, cells (or cell lysate) or tissue (*e.g.*, normal tissue or diseased tissue). In some embodiments, a biological sample is a fluid sample. In some embodiments, a biological sample is a solid tissue sample. For example, a tissue sample may include, without limitation skeletal muscle, cardiac muscle, adipose tissue as well as tissue from other organs. In some embodiments, a biological sample is a biopsy sample. In some embodiments, a solid tissue sample may be made into a fluid sample using routine methods in the art.

[00147] A biological sample may also include one or more cells of a cell line. In some embodiments, a cell line includes human cells, primate cells (*e.g.*, vero cells), rat cells (*e.g.*, GH3 cells, OC23 cells) or mouse cells (*e.g.*, MC3T3 cells). There are a variety of human cell lines, including, without limitation, human embryonic kidney (HEK) cells, HeLa cells, cancer cells from the National Cancer Institute's 60 cancer cell lines (NCI60), DU145 (prostate cancer) cells, Lncap (prostate cancer) cells, MCF-7 (breast cancer) cells, MDA-MB-438 (breast cancer) cells, PC3 (prostate cancer) cells, T47D (breast cancer) cells, THP-1 (acute myeloid leukemia) cells, U87 (glioblastoma) cells, SHSY5Y human neuroblastoma cells (cloned from a myeloma) and Saos-2 (bone cancer) cells.

[00148] A further embodiment relates to a method for monitoring a disease, a condition, or any treatment thereof (e.g., myopathy or myopathy treatment) in a subject having, or at risk of having, the disease or condition comprising: (a) obtaining a biological sample from the subject, (b) determining the level of one or more TGFβ family member proteins or forms

thereof, one or more portions or domains of TGFβ family member proteins and/or one or more chimeras of TGFβ family member proteins in the biological sample using an antibody having a selected binding profile and (c) repeating steps (a) and (b) on one or more occasions.

[00149] Biomarkers such as Myostatin may be used as for assessing disease conditions, however, available commercial reagents (*e.g.,* antibodies for ELISAs and Western Blots) are often either not specific for Myostatin, detect only mature Myostatin or do not detect Myostatin at all. Thus, provided herein are methods and reagents (*e.g.,* antibodies with selected binding profiles) for detecting one or more TGFβ family member proteins or forms thereof, in the context of diseases and/or conditions (*e.g.,* muscle atrophy) for diagnostic purposes. As one example, the level of proMyostatin or latent Myostatin may be measured in a subject, or biological sample therefrom, to detect or monitor the progression of a disease or condition. As another example, the level of proMyostatin or latent Myostatin may be measured in a subject, or biological sample therefrom, to monitor the response to a treatment for a disease or condition. It should be appreciated that the level of proMyostatin or latent Myostatin may be monitored over any suitable period of time, which may differ depending on the disease or condition, the subject has or any treatment regimen that the subject may be subject to.

[00150] Another embodiment relates to a diagnostic composition comprising any one of the above described antibodies, antigen binding fragments, polynucleotides, vectors or cells and optionally suitable means for detection. The antibodies are, for example, suited for use in immunoassays in which they can be utilized in liquid phase or bound to a solid phase carrier. Examples of immunoassays which can utilize the antibody are competitive and non-competitive immunoassays in either a direct or indirect format. Examples of such immunoassays are the Enzyme Linked Immunoassay (ELISA), radioimmunoassay (RIA), the sandwich (immunometric assay), flow cytometry, the western blot assay, immunoprecipitation assays, immunohistochemistry, immuno-microscopy, lateral flow immuno-chromatographic assays, and proteomics arrays. The antigens and antibodies can be bound to many different solid supports (*e.g.*, carriers, membrane, columns, proteomics array, etc.). Examples of solid support materials include glass, polystyrene, polyvinyl chloride, polyvinylidene difluoride, polypropylene, polyethylene, polycarbonate, dextran, nylon, amyloses, natural and modified celluloses, such as nitrocellulose, polyacrylamides, agaroses, and magnetite. The nature of the support can be either fixed or suspended in a solution (*e.g.*, beads).

[00151] By a further embodiment, antibodies (including antigen binding fragments) provided herein may also be used in a method for evaluating expression of one or more TGFβ family member proteins or forms thereof in a subject by obtaining a biological sample from the subject which may be a tissue sample, a blood sample or any other appropriate body fluid sample. The procedure may comprise contacting the blood sample (whole blood, serum, plasma), a tissue sample, or protein sample isolated therefrom, with an antibody having a selected binding profile, under conditions enabling the formation of binding complexes between antibody and antigen. The level of such binding complexes may then be determined by any suitable method. In some embodiments, the biological sample is contacted with the antibody under conditions suitable for binding of the antibody to one or more TGFβ family member proteins or forms thereof, if the antigen is present in the sample, and formation of binding complexes consisting of antibody, bound to the antigen. In some embodiments, this contacting step is performed in a reaction chamber, such as a tube, plate well, membrane bath, cell culture dish, microscope slide, and the like. In some embodiments, an antibody having a selected binding profile is immobilized on a solid support. In some embodiments, the antigen is immobilized on a solid support. In some embodiments, the solid support is the surface of a the reaction chamber. In some embodiments, the solid support is of a polymeric membrane (*e.g.*, nitrocellulose strip, Polyvinylidene Difluoride (PVDF) membrane, etc.). Other appropriate solid supports may be used.

[00152] In some embodiments, an antibody having a selected binding profile is immobilized on the solid support prior to contacting with the antigen. In other embodiments, immobilization of the antibody is performed after formation of binding complexes. In still other embodiments, antigen is immobilized on a solid support prior to formation of binding complexes. A detection reagent is added to the reaction chamber to detect immobilized binding complexes. In some embodiments, the detection reagent comprises a detectably labeled secondary antibody directed against the antigen. In some embodiments, the primary antibody is itself detectable labeled, and is thereby the detection reagent.

[00153] In one aspect, detection methods comprise the steps of immobilizing antibodies to a solid support; applying a sample (*e.g.*, a biological sample or isolated protein sample) to the solid support under conditions that permit binding of antigen to the antibodies, if present in the sample; removing the excess sample from the solid support; applying detectably labeled antibodies under conditions that permit binding of the detectably labeled antibodies to the antigen-bound immobilized antibodies; washing the solid support and assaying for the presence of label on the solid support.

[00154] In some embodiments, the antigen is immobilized on the solid support, such as a PVDF membrane, prior to contacting with the antibody in a reaction chamber (*e.g.*, a membrane bath). A detection reagent is added to the reaction chamber to detect immobilized binding complexes. In some embodiments, the detection reagent comprises a detectably labeled secondary antibody directed against the antigen. In some embodiments, the detection reagent comprises a detectably labeled secondary antibody directed against the primary antibody. As disclosed herein, the detectable label may be, for example, a radioisotope, a fluorophore, a luminescent molecule, an enzyme, a biotin-moiety, an epitope tag, or a dye molecule. In some embodiments, the primary antibody is itself detectable labeled, and is thereby the detection reagent. Suitable detectable labels are described herein, and will be readily apparent to one of ordinary skill in the art.

[00155] Accordingly, diagnostic kits, suitable for home or clinical use (point of care service), are provided that comprise (a) detectably labeled and/or non-labeled antibodies having a selected binding profile, as antigen binding reagents (*e.g.*, reagents that bind one or more TGFβ family member proteins or forms thereof); (b) a detection reagent; and, optionally, (c) complete instructions for using the reagents to detect antigens in a sample. In some embodiments, the diagnostic kit includes the antibody having a selected binding profile, and/or one or more TGFβ family member proteins or forms thereof immobilized on a solid support. Any of the solid supports described herein are suitable for incorporation in the diagnostic kits. In a preferred embodiment, the solid support is the surface of a reaction chamber of a plate well. Typically, the plate well is in a multi-well plate having a number of wells selected from: 6, 12, 24, 96, 384, and 1536, but it is not so limited. In other embodiments, the diagnostic kits provide a detectably labeled antibody. Diagnostic kits are not limited to these embodiments and other variations in kit composition will be readily apparent to one of ordinary skill in the art.

[00156] In some embodiments, Myostatin protein is present in muscle tissue. In some embodiments, Myostatin protein is present in circulation. In some embodiments, Myostatin protein is present in muscle tissue and in circulation. In some embodiments, Myostatin expression is altered in diseases or conditions involving muscle atrophy. Exemplary diseases or conditions involving muscle atrophy include, without limitation, muscular dystrophy, cachexia, sarcopenia, spinal chord injury and atrophy associated with muscle disuse. Thus, Myostatin in tissues or circulating Myostatin, can be a biomarker for muscular atrophic disease. Without wishing to be bound by any particular theory, development of Myostatin as biomarker has been hampered by the paucity of available antibodies to Myostatin, which,

because of the high homology between mature Myostatin growth factor and other members of the TGFβ family, are not highly selective for Myostatin. Furthermore, many Myostatin antibodies cannot distinguish between the pro-, latent, and mature forms of Myostatin. Thus, detecting the location and expression levels of various Myostatin forms (*e.g.,* proMyostatin, latent Myostatin, primed Myostatin, and mature Myostatin) may provide significant insight into Myostatin biology in normal and disease states. In addition to their therapeutic potential, antibodies to pro-, latent, and mature Myostatin may be useful in biomarker assays for muscle atrophy. Thus, in some embodiments, antibodies provided herein can be incorporated into assays for MSD, ELISA, RIA, quantitative western blotting (capillary western, Odyssey or similar technology), immunohistochemistry, and any other technology requiring specific binding of antibodies. In some embodiments, assays (*e.g.,* any of the immunoassays provided herein) are be applied to analysis of Myostatin levels and isoform distribution in muscle or other tissue, blood and blood derivatives (*e.g.,* serum, plasma, exosome-like vesicles (ELVs) from blood), and urine and derivatives (*e.g.,* urinary ELVs).

[00157] In some embodiments, any of the antibodies provided herein can be used in an immunohistochemistry (IHC) assay. In some embodiments, an immunohistochemistry assay is performed on a tissue sample (*e.g.,* a muscle biopsy) to identify a level or localization of one or more TGFβ family member proteins or forms thereof (e.g., proMyostatin, latent Myostatin , primed Myostatin, and/or mature Myostatin). In some embodiments, an IHC assay begins with antigen retrieval, which may vary in terms of reagents and methods. The antigen retrieval process may involve pressure cooking, protease treatment, microwaving, or heating histologic sections in baths of appropriate buffers, with the standard goal of unmasking antigens hidden by formalin crosslinks or other fixation. See, e.g., Leong et al. Appl. Immnunohistochem. 4(3):201 (1996).

[00158] In some embodiments, an IHC assay is a direct assay. In some embodiments, an IHC assay is an indirect assay. In a direct IHC assay, binding of antibody to the target antigen can be determined directly. A direct assay may use a labeled reagent, such as a fluorescent tag or an enzyme-labeled primary antibody, which can be visualized without further antibody interaction. In a typical indirect assay, unconjugated primary antibody binds to the antigen and then a labeled secondary antibody binds to the primary antibody. Where the secondary antibody is conjugated to an enzymatic label, a chromagenic or fluorogenic substrate is added to provide visualization of the antigen. Signal amplification may occur because several secondary antibodies may react with different epitopes on the primary antibody.

[00159] In some embodiments, a primary and/or secondary antibody used for IHC is labeled with a detectable moiety. Numerous labels are available and include, without limitation, radioisotopes, colloidal gold particles, fluorescent or chemiluminescent labels. In some embodiments, a primary and/or secondary antibody used for IHC is labeled with a, radioisotope (*e.g.*, S, C, I or H) using the techniques described in Current Protocols in Immunology, Volumes 1 and 2, Coligen et al, Ed. Wiley-Interscience, New York, N.Y., Pubs. (1991) for example and radioactivity can be measured using scintillation counting. Other radionuclides include, without limitation, 99Tc,90Y, mIn, 32P, UC, 150, 13N, 18F, 51Cr, 57To, 225Ra, 60Co, 59Fe, 57Se, 152Eu, 67CU, 217Ci, 211At, 212Pb, 47Sc, 109Pd, 234Th, and 40K, 157Gd, 55Mn, 52Tr, and 56Fe. In some embodiments, a primary and/or secondary antibody used for IHC is labeled with Colloidal gold particles. In some embodiments, a primary and/or secondary antibody used for IHC is labeled with fluorescent or chemiluminescent labels including, but not limited to, rare earth chelates (europium chelates), fluorescein and its derivatives, rhodamine and its derivatives, isothiocyanate, phycoerythrin, phycocyanin, allophycocyanin, o-phthaladehyde, fluorescamine, dansyl, umbelliferone, luciferin, luminal label, isoluminal label, an aromatic acridinium ester label, an imidazole label, an acridimium salt label, an oxalate ester label, an aequorin label, 2,3-dihydrophthalazinediones, Texas Red, dansyl, Lissamine, umbelliferone, phycocrytherin, phycocyanin, or commercially available fluorophores such SPECTRUM ORANGE® and SPECTRUM GREEN® and/or derivatives of any one or more of the above. In some embodiments, fluorescence can be quantified using a fluorimeter.

[00160] In some embodiments, a primary and/or secondary antibody used for IHC is labeled with an enzyme. In some embodiments, an enzyme catalyzes a chemical alteration of a chromogenic substrate that can be measured using various techniques. For example, an enzyme may catalyze a color change in a substrate, which can be measured spectrophotometrically. Alternatively, an enzyme may alter the fluorescence or chemiluminescence of the substrate. Techniques for quantifying a change in fluorescence would be apparent to the skilled artisan. In some embodiments, a chemiluminescent substrate becomes electronically excited by a chemical reaction and may then emit light which can be measured (*e.g.,* using a chemiluminometer) or donates energy to a fluorescent acceptor.

[00161] In some embodiments, enzymatic labels include luciferases (e.g. firefly luciferase and bacterial luciferase; U.S. Pat. No. 4,737,456), luciferin, 2,3-dihydrophthalazinediones, malate dehydrogenase, urease, peroxidase such as horseradish peroxidase (HRPO), alkaline phosphatase, β-galactosidase, glucoamylase, lysozyme, saccharide oxidases (e.g., glucose

oxidase, galactose oxidase, and glucose-6-phosphate dehydrogenase), heterocyclic oxidases (such as uricase and xanthine oxidase), lactoperoxidase, microperoxidase, and the like. Techniques for conjugating enzymes to antibodies are described in O'Sullivan et al, Methods for the Preparation of Enzyme- Antibody Conjugates for use in Enzyme Immunoassay, in Methods in Enzym. (ed J. Langbne & H. Van Vunakis), Academic press, New York, 73:147-166 (1981).

[00162] In some embodiments, a label is indirectly conjugated to any of the antibodies with a selected binding profile provided herein. For example, in some embodiments, an antibody can be conjugated with biotin and any suitable label can be conjugated with avidin, or vice versa. Biotin binds selectively to avidin and thus, the label can be conjugated with the antibody in this indirect manner.

[00163] In some embodiments, after antigen retrieval and an optional blocking step, a tissue section (*e.g.,* an FFPE section or a frozen section) is exposed to one or more of the antibodies provided herein as primary antibodies for a sufficient period of time and under suitable conditions to allow one or more primary antibody to bind to one or more TGFβ family member proteins or forms thereof of the tissue section. In some embodiments, appropriate conditions for achieving suitable binding can be determined by routine experimentation, In some embodiments, a slide containing a biological sample is subjected to a wash step to remove unbound and excess amounts of primary antibody.

[00164] In some embodiments, primary antibody is linked to a detectable label, such as paramagnetic ions, radioactive isotopes, fluorochromes, and NM -detectable substances, and the slide is evaluated for staining of one or more TGFβ family member proteins or forms thereof using an appropriate imaging apparatus.

[00165] In some embodiments, a tissue sample used to prepare stained tissue sections for evaluating expression of one or more TGFβ family member proteins or forms thereof can be collected from a subject before and/or after exposure of the subject to one or more therapeutic agents, *e.g.,* an anti-latent Myostatin antibody. Accordingly, tissue samples may be collected from a subject over a period of time. In some embodiments, a tissues sample (*e.g.*, a muscle tissue sample) is obtained by any suitable procedure, which includes, but not limited to, surgical excision, aspiration or biopsy. In some embodiments, a tissue sample is sectioned and examined for one or more TGFβ family member proteins or forms thereof as a fresh specimen. In other embodiments, a tissue sample is frozen for further sectioning. In other embodiments, a tissue sample is preserved by fixing and embedding in paraffin (FFPE) or the like.

[00166] In some embodiments, a tissue sample may be fixed by conventional methodology, with the length of fixation depending on the size of the tissue sample and the fixative used. Exemplary fixatives include, but are not limited to neutral buffered formalin, glutaraldehyde, Bouin's or paraformaldehyde. In some embodiments, a tissue sample is fixed with formalin. In some embodiments, a fixed tissue sample is also embedded in paraffin to prepare a formalin-fixed and paraffin- embedded (FFPE) tissue sample. Examples of paraffin include, but are not limited to, Paraplast, Broloid and Tissuemay.

[00167] In some embodiments, a tissue sample is fixed and dehydrated through an ascending series of alcohols, infiltrated and embedded with paraffin or other sectioning media so that the tissue sample may be sectioned. Alternatively, a tissue sample is first sectioned and then the individual sections are fixed.

TGF-β family of growth factors

[00168] Growth factors are cell signaling molecules that stimulate a variety of cellular activities. Due to their broad-reaching influence within biological systems, growth factor signaling is tightly regulated, often through interactions with other biomolecules, the extracellular and/or cellular matrix or within a particular cell environment or niche. These interactions may be direct or indirect.

[00169] Growth factors of the transforming growth factor beta (TGF-β) family are involved in a variety of cellular processes. Growth factor binding to type II receptors leads to type I receptor phosphorylation and activation (Denicourt, C. et al., Another twist in the transforming growth factor β-induced cell-cycle arrest chronicle. PNAS. 2003. 100(26):15290-1). Activated type I receptors may in turn phosphorylate receptor-associated SMADs (R-SMADs) promoting co-SMAD (e.g. SMAD4) dimer/trimer formation and nuclear translocation. SMAD complexes collaborate with cofactors to modulate expression of TGF-β family member target genes.

[00170] TGF-β family member signaling cascades are involved in a number of diverse biological pathways including, but not limited to inhibition of cell growth, tissue homeostasis, extracellular matrix (ECM) remodeling, endothelial to mesenchymal transition (EMT) in cell migration and invasion and immune modulation/suppression as well as in mesenchymal to epithelial transition. TGF-β signaling related to growth inhibition and tissue homeostasis may affect epithelial, endothelial, hematopoietic and immune cells through the activation of p21 and $p15^{INK}$ to mediate cell cycle arrest and repress myc. In relation to ECM remodeling, TGF-β signaling may increase fibroblast populations and ECM deposition (e.g.

collagen). TGF-β signaling related to cell migration and invasion may affect epithelial and/or endothelial cells, inducing stem cell-like phenotypes. This aspect of signaling may play a role in smooth muscle cell proliferation following vascular surgery and/or stenting. In the immune system, TGF-β ligand is necessary for T regulatory cell function and maintenance of immune precursor cell growth and homeostasis. Nearly all immune cells comprise receptors for TGF-β and TGF-β knockout mice die postnataly due in part to inflammatory pathologies. Finally, TGF-β suppresses interferon gamma-induced activation of natural killer cells (Wi, J. et al., 2011. Hepatology. 53(4):1342-51, the contents of which are herein incorporated by reference in their entirety).

[00171] The solution of the crystal structure of the latent form of TGF-beta is a first for the entire TGF-beta family and offers deep insights into these complexes (Shi, M. et al., *Latent TGF-β structure and activation*. Nature. 2011 Jun 15; 474(7351):343-9). Almost all signaling in the TGF-beta family goes through a common pathway whereby a dimeric ligand is recognized by a heterotetrameric receptor complex containing two type I and two type II receptors. Each receptor has a serine-threonine kinase domain. Type II receptors phosphorylate type I receptors, which in turn phosphorylate receptor-regulated Smads that translocate to and accumulate in the nucleus and regulate transcription.

[00172] There are 33 different members of the TGF-beta family in humans (FIG. 1). Members include the bone morphogenetic proteins (BMP), inhibin, activin, growth and differentiation factor (GDF), myostatin, nodal, anti-Mullerian hormone, and lefty proteins. A review of TGF-β family members, related signaling molecules as well as their relationships can be found in Massague., 2000. Nature Reviews Molecular Cell Biology. 1:169-78, the contents of which are herein incorporated by reference in their entirety. In some embodiments, mature growth factors are synthesized along with their prodomains as single polypeptide chains (see FIG. 2). In some embodiments, such polypeptide chains may comprise cleavage sites for separation of prodomains from mature growth factors. In some embodiments, such cleavage sites are furin cleavage sites recognized and cleaved by proprotein convertases.

[00173] In general, homology among TGF-β family member growth factor domains is relatively high. Interestingly, prodomain homology is much lower. This lack of homology may be an important factor in altered growth factor regulation among family members. In some cases, prodomains may guide proper folding and/or dimerization of growth factor domains. Prodomains have very recently been recognized, in some cases, to have important functions in directing growth factors (after secretion) to specific locations in the extracellular

matrix (ECM) and/or cellular matrix, until other signals are received that cause growth factor release from latency. Release from latency may occur in highly localized environments whereby growth factors may act over short distances (e.g. from about 1 cell diameter to about a few cell diameters, from about 2 cell diameters to about 100 cell diameters and/or from about 10 cell diameters to about 10,000 cell diameters) and cleared once they reach the circulation. Some growth factor-prodomain complexes are secreted as homodimers. In some embodiments, prodomain-growth factor complexes may be secreted as heterodimers.

[00174] As used herein, the term "TGF-β-related protein" refers to a TGF-β isoform, a TGF-β family member or a TGF-β family member-related protein. TGF-β family members may include, but are not limited to any of those shown in in FIG. 1 and/or listed in Table 1. These include, but are not limited to TGF-β proteins, BMPs, myostatin, GDFs and inhibins. Aspects of the present disclosure provide tools and/or methods for characterizing and/or modulating cellular activities related to growth factor signaling. In other embodiments, tools of the present disclosure may comprise antigens comprising one or more components of one or more TGF-β-related proteins. Some tools may comprise antibodies directed toward antigens of the present disclosure. In additional embodiments, tools of the present disclosure may comprise assays for the detection and/or characterization of TGF-β-related proteins, the detection and/or characterization of antibodies directed toward TGF-β-related proteins and/or the detection and/or characterization of cellular activities and/or their cellular signaling related to TGF-β-related proteins.

[00175] Described herein are compounds for the modulation of growth factor activity and/or levels. Such growth factors include growth differentiation factor (GDF) proteins which are TGF-β family member proteins involved in a number of cellular and developmental activities. Part of the disclosure provides GDF-modulatory antibodies as well as methods for generating, optimizing and using such antibodies. Further antibodies include GDF-modulatory antibodies that are capable of distinguishing between various growth factor complexes allowing for growth factor activity modulation that occurs only at sites of specific complex formations.

Proteins of interest

[00176] TGF-β-related proteins are involved in a number of cellular processes. In embryogenesis, the 33 members of the TGF-β family of proteins are involved in regulating major developmental processes and the details of the formation of many organs. Much of this regulation occurs before birth; however, the family continues to regulate many processes

after birth, including, but not limited to immune responses, wound healing, bone growth, endocrine functions and muscle mass. TGF-β-related proteins are listed and described in International Patent Application No. WO2014074532, the contents of which are herein incorporated by reference in their entirety.

[00177] A list of exemplary TGF-β family pro-proteins, i.e. the protein after removal of the secretion signal sequence, is shown in Table 1. The pro-protein contains, and is the precursor of, the prodomain and the growth factor. Shown in the Table are the names of the originating TGF-β family member and the pro-protein sequence. Also identified in "**bold**" and "underlined" are proprotein convertase cleavage sites. Upon cleavage, the resulting prodomain retains this site, whereas the mature growth factor begins following the cleavage site. It is noted that Lefty1 and Lefty2 are not cleaved by proprotein convertases just prior to the start of the mature growth factor.

Table 1. Pro-proteins of the TGF-beta family

TGF Member	Prodomain and growth factor Sequence	SEQ ID NO
TGF-β1	LSTCKTIDMELVKRKRIEAIRGQILSKLRLASPPSQGEVPPGPL PEAVLALYNSTRDRVAGESAEPEPEPEADYYAKEVTRVLMV ETHNEIYDKFKQSTHSIYMFFNTSELREAVPEPVLLSRAELRL LRLKLKVEQHVELYQKYSNNSWRYLSNRLLAPSDSPEWLSF DVTGVVRQWLSRGGEIEGFRLSAHCSCDSRDNTLQVDINGFT TGRRGDLATIHGMNRPFLLLMATPLERAQHLQSS**RHRR**ALD TNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFC LGPCPYIWSLDTQYSKVLALYNQHNPGASAAPCCVPQALEPL PIVYYVGRKPKVEQLSNMIVRSCKCS	1
TGF-β2	SLSTCSTLDMDQFMRKRIEAIRGQILSKLKLTSPPEDYPEPEEV PPEVISIYNSTRDLLQEKASRRAAACERERSDEEYYAKEVYKI DMPPFFPSENAIPPTFYRPYFRIVRFDVSAMEKNASNLVKAEF RVFRLQNPKARVPEQRIELYQILKSKDLTSPTQRYIDSKVVKT RAEGEWLSFDVTDAVHEWLHHKDRNLGFKISLHCPCCTFVP SNNYIIPNKSEELEARFAGIDGTSTYTSGDQKTIKSTRKKNSG KTPHLLLMLLPSYRLESQQTNR**RKKR**ALDAAYCFRNVQDN CCLRPLYIDFKRDLGWKWIHEPKGYNANFCAGACPYLWSSD TQHSRVLSLYNTINPEASASPCCVSQDLEPLTILYYIGKTPKIE QLSNMIVKSCKCS	2
TGF-β3	SLSLSTCTTLDFGHIKKKRVEAIRGQILSKLRLTSPPEPTVMTH VPYQVLALYNSTRELLEEMHGEREEGCTQENTESEYYAKEIH KFDMIQGLAEHNELAVCPKGITSKVFRFNVSSVEKNRTNLFR AEFRVLRVPNPSSKRNEQRIELFQILRPDEHIAKQRYIGGKNL PTRGTAEWLSFDVTDTVREWLLRRESNLGLEISIHCPCHTFQP NGDILENIHEVMEIKFKGVDNEDDHGRGDLGRLKKQKDHHN PHLILMMIPPHRLDNPGQGGQ**RKKR**ALDTNYCFRNLEENCC VRPLYIDFRQDLGWKWVHEPKGYYANFCSGPCPYLRSADTT HSTVLGLYNTLNPEASASPCCVPQDLEPLTILYYVGRTPKVE QLSNMVVKSCKCS	3

GDF-11	AEGPAAAAAAAAAAAAAGVGGE**RSSR**PAPSVAPEPDGCPV CVWRQHSRELRLESIKSQILSKLRLKEAPNISREVVKQLLPKA PPLQQILDLHDFQGDALQPEDFLEEDEYHATTETVISMAQET DPAVQTDGSPLCCHFHFSPKVMFTKVLKAQLWVYLRPVPRP ATVYLQILRLKPLTGEGTAGGGGGGRRHIRIRSLKIELHSRSG HWQSIDFKQVLHSWFRQPQSNWGIEINAFDPSGTDLAVTSLG PGAEGLHPFMELRVLENTK**RSRR**NLGLDCDEHSSESRCCRYP LTVDFEAFGWDWIIAPKRYKANYCSGQCEYMFMQKYPHTH LVQQANPRGSAGPCCTPTKMSPINMLYFNDKQQIIYGKIPGM VVDRCGCS	4
GDF-8 (myostatin)	NENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKIQILSKLRL ETAPNISKDVIRQLLPKAPPLRELIDQYDVQRDDSSDGSLEDD DYHATTETIITMPTESDFLMQVDGKPKCCFFKFSSKIQYNKV VKAQLWIYLRPVETPTTVFVQILRLIKPMKDGTRYTGIRSLKL DMNPGTGIWQSIDVKTVLQNWLKQPESNLGIEIKALDENGH DLAVTFPGPGEDGLNPFLEVKVTDTPK**RSRR**DFGLDCDEHST ESRCCRYPLTVDFEAFGWDWIIAPKRYKANYCSGECEFVFLQ KYPHTHLVHQANPRGSAGPCCTPTKMSPINMLYFNGKEQIIY GKIPAMVVDRCGCS	5
Inhibin-beta A	SPTPGSEGHSAAPDCPSCALAALPKDVPNSQPEMVEAVKKHI LNMLHLKKRPDVTQPVPKAALLNAIRKLHVGKVGENGYVEI EDDIGRRAEMNELMEQTSEIITFAESGTARKTLHFEISKEGSD LSVVERAEVWLFLKVPKANRTRTKVTIRLFQQQKHPQGSLD TGEEAEEVGLKGERSELLLSEKVVDARKSTWHVFPVSSSIQR LLDQGKSSLDVRIACEQCQESGASLVLLGKKKKKEEEGEGK KKGGGEGGAGADEEKEQSHRPFLMLQARQSEDHPHR**RRRR** GLECDGKVNICCKKQFFVSFKDIGWNDWIIAPSGYHANYCE GECPSHIAGTSGSSLSFHSTVINHYRMRGHSPFANLKSCCVPT KLRPMSMLYYDDGQNIIKKDIQNMIVEECGCS	6
Inhibin-beta B	SPTPPPTPAAPPPPPPPGSPGGSQDTCTSCGGFRRPEELGRVDG DFLEAVKRHILSRLQMRGRPNITHAVPKAAMVTALRKLHAG KVREDGRVEIPHLDGHASPGADGQERVSEIISFAETDGLASSR VRLYFFISNEGNQNLFVVQASLWLYLKLLPYVLEKGSRRKV RVKVYFQEQGHGDRWNMVEKRVDLKRSGWHTFPLTEAIQA LFERGERRLNLDVQCDSCQELAVVPVFVDPGEESHRPFVVV QARLGDSRHR**IRKR**GLECDGRTNLCCRQQFFIDFRLIGWND WIIAPTGYYGNYCEGSCPAYLAGVPGSASSFHTAVVNQYRM RGLNPGTVNSCCIPTKLSTMSMLYFDDEYNIVKRDVPNMIVE ECGCA	7
Inhibin-beta C	TPRAGGQCPACGGPTLELESQRELLLDLAKRSILDKLHLTQR PTLNRPVSRAALRTALQHLHGVPQGALLEDNREQECEIISFAE TGLSTINQTRLDFHFSSDRTAGDREVQQASLMFFVQLPSNTT WTLKVRVLVLGPHNTNLTLATQYLLEVDASGWHQLPLGPE AQAACSQGHLTLELVLEGQVAQSSVILGGAAHRPFVAARVR VGGKHQ**IHRR**GIDCQGGSRMCCRQEFFVDFREIGWHDWIIQ PEGYAMNFCIGQCPLHIAGMPGIAASFHTAVLNLLKANTAAG TTGGGSCCVPTARRPLSLLYYDRDSNIVKTDIPDMVVEACGC S	8
Inhibin-beta E	QGTGSVCPSCGGSKLAPQAERALVLELAKQQILDGLHLTSRP RITHPPPQAALTRALRRLQPGSVAPGNGEEVISFATVTDSTSA YSSLLTFHLSTPRSHHLYHARLWLHVLPTLPGTLCLRIFRWGP RRRRQGSRTLLAEHHITNLGWHTLTLPSSGLRGEKSGVLKLQ LDCRPLEGNSTVTGQPRRLLDTAGHQQPFLELKIRANEPGAG **RARR**RTPTCEPATPLCCRRDHYVDFQELGWRDWILQPEGYQ	9

	LNYCSGQCPPHLAGSPGIAASFHSAVFSLLKANNPWPASTSC CVPTARRPLSLLYLDHNGNVVKTDVPDMVVEACGCS	
Lefty1	LTGEQLLGSLLRQLQLKEVPTLDRADMEELVIPTHVRAQYV ALLQRSHGDRS**RGKR**FSQSFREVAGRFLALEASTHLLVFGM EQRLPPNSELVQAVLRLFQEPVPKAALH**RHGR**LSPRSARAR VTVEWLRVRDDGSNRTSLIDSRLVSVHESGWKAFDVTEAVN FWQQLSRPRQPLLLQVSVQREHLGPLASGAHKLVRFASQGA PAGLGEPQLELHTLDLGDYGAQGDCDPEAPMTEGTRCCRQE MYIDLQGMKWAENWVLEPPGFLAYECVGTCRQPPEALAFK WPFLGPRQCIASETDSLPMIVSIKEGGRTRPQVVSLPNMRVQ KCSCASDGALVPRRLQP	10
Lefty2	LTEEQLLGSLLRQLQLSEVPVLDRADMEKLVIPAHVRAQYV VLLRRSHGDRS**RGKR**FSQSFREVAGRFLASEASTHLLVFGM EQRLPPNSELVQAVLRLFQEPVPKAALH**RHGR**LSPRSAQAR VTVEWLRVRDDGSNRTSLIDSRLVSVHESGWKAFDVTEAVN FWQQLSRPRQPLLLQVSVQREHLGPLASGAHKLVRFASQGA PAGLGEPQLELHTLDLRDYGAQGDCDPEAPMTEGTRCCRQE MYIDLQGMKWAKNWVLEPPGFLAYECVGTCQQPPEALAFN WPFLGPRQCIASETASLPMIVSIKEGGRTRPQVVSLPNMRVQ KCSCASDGALVPRRLQP	11
GDF-15	LSLAEASRASFPGPSELHSEDSRFRELRKRYEDLLTRLRANQS WEDSNTDLVPAPAVRILTPEVRLGSGGHLHLRISRAALPEGLP EASRLHRALFRLSPTASRSWDVTRPLRRQLSLARPQAPALHL RLSPPPSQSDQLLAESSSARPQLELHLRPQAARGR**RRAR**ARN GDHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQVTM CIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPASYNP MVLIQKTDTGVSLQTYDDLLAKDCHCI	12
Anti-Mullerian hormone	LLGTEALRAEEPAVGTSGLIFREDLDWPPGIPQEPLCLVALGG DSNGSSSPLRVVGALSAYEQAFLGAVQRARWGPRDLATFGV CNTGDRQAALPSLRRLGAWLRDPGGQRLVVLHLEEVTWEPT PSLRFQEPPPGGAGPPELALLVLYPGPGPEVTVTRAGLPGAQS LCPSRDTRYLVLAVDRPAGAWRGSGLALTLQPRGEDSRLST ARLQALLFGDDHRCFTRMTPALLLLPRSEPAPLPAHGQLDTV PFPPPRPSAELEESPPSADPFLETLTRLVRALRVPPARASAPRL ALDPDALAGFPQGLVNLSDPAALERLLDGEEPLLLLLRPTAA TTGDPAPLHDPTSAPWATALARRVAAELQAAAAAELRSLPGL PPATAPLLARLLALCPGGPGGLGDPLRALLLLKALQGLRVE WRGRDPRGPG**RAQR**SAGATAADGPCALRELSVDLRAERSV LIPETYQANNCQGVCGWPQSDRNPRYGNHVVLLLKMQVRG AALARPPCCVPTAYAGKLLISLSEERISAHHVPNMVATECGC R	13
Inhibin-alpha	CQGLELARELVLAKVRALFLDALGPPAVTREGGDPGVRRLP RRHALGGFTHRGSEPEEEEDVSQAILFPATDASCEDKSAARG LAQEAEEGLFRYMFRPSQHTRSRQVTSAQLWFHTGLDRQGT AASNSSEPLLGLLALSPGGPVAVPMSLGHAPPHWAVLHLATS ALSLLTHPVLVLLLRCPLCTCSARPEATPFLVAHTRTRPPSGG E**RARR**STPLMSWPWSPSALRLLQRPPEEPAAHANCHRVALN ISFQELGWERWIVYPPSFIFHYCHGGCGLHIPPNLSLPVPGAPP TPAQPYSLLPGAQPCCAALPGTMRPLHVRTTSDGGYSFKYET VPNLLTQHCACI	14
GDF-1	PVPPGPAAALLQALGLRDEPQGAPRLRPVPPVMWRLFRRRD PQETRSGSRRTSPGVTLQPCHVEELGVAGNIVRHIPDRGAPTR ASEPASAAGHCPEWTVVFDLSAVEPAERPSRARLELRFAAAA AAAPEGGWELSVAQAGQGAGADPGPVLLRQLVPALGPPVR	15

	AELLGAAWARNASWPRSLRLALALRPRAPAACARLAEASLL LVTLDPRLCHPLA**RPRR**DAEPVLGGGPGGAC**RARR**LYVSFR EVGWHRWVIAPRGFLANYCQGQCALPVALSGSGGPPALNH AVLRALMHAAAPGAADLPCCVPARLSPISVLFFDNSDNVVL RQYEDMVVDECGCR	
GDF-3	QEYVFLQFLGLDKAPSPQKFQPVPYILKKIFQDREAAATTGV SRDLCYVKELGVRGNVLRFLPDQGFFLYPKKISQASSCLQKL LYFNLSAIKEREQLTLAQLGLDLGPNSYYNLGPELELALFLV QEPHVWGQTTPKPGKMFVLRSVPWPQGAVHFNLLDVAKD WNDNPRKNFGLFLEILVKEDRDSGVNFQPEDTCARLRCSLH ASLLVVTLNPDQCHPS**RKRR**AAIPVPKLSCKNLCHRHQLFIN FRDLGWHKWIIAPKGFMANYCHGECPFSLTISLNSSNYAFMQ ALMHAVDPEIPQAVCIPTKLSPISMLYQDNNDNVILRHYEDM VVDECGCG	16
GDF-5	APDLGQRPQGTRPGLAKAEAKERPPLARNVFRPGGHSYGGG ATNANARAKGGTGQTGGLTQPKKDEPKKLPPRPGGPEPKPG HPPQTRQATARTVTPKGQLPGGKAPPKAGSVPSSFLLKKARE PGPPREPKEPFRPPPITPHEYMLSLYRTLSDADRKGGNSSVKL EAGLANTITSFIDKGQDDRGPVVRKQRYVFDISALEKDGLLG AELRILRKKPSDTAKPAAPGGGRAAQLKLSSCPSGRQPASLL DVRSVPGLDGSGWEVFDIWKLFRNFKNSAQLCLELEAWERG RAVDLRGLGFDRAARQVHEKALFLVFGRTKKRDLFFNEIKA RSGQDDKTVYEYLFSQR**RKRR**APLATRQGKRPSKNLKARCS RKALHVNFKDMGWDDWIIAPLEYEAFHCEGLCEFPLRSHLE PTNHAVIQTLMNSMDPESTPPTCCVPTRLSPISILFIDSANNVV YKQYEDMVVESCGCR	17
GDF-6	FQQASISSSSSSAELGSTKGMRSRKEGKMQRAPRDSDAGREG QEPQPRPQDEPRAQQPRAQEPPGRGPRVVPHEYMLSIYRTYSI AEKLGINASFFQSSKSANTITSFVDRGLDDLSHTPLRRQKYLF DVSMLSDKEELVGAELRLFRQAPSAPWGPPAGPLHVQLFPCL SPLLLDARTLDPQGAPPAGWEVFDVWQGLRHQPWKQLCLE LRAAWGELDAGEAEARARGPQQPPPPDLRSLGFGRRVRPPQ ERALLVVFTRSQRKNLFAEMREQLGSAEAAGPGAGAEGSWP PPSGAPDARPWLPSPGR**RRRR**TAFASR**HGKR**HG**KKSR**LRCS KKPLHVNFKELGWDDWIIAPLEYEAYHCEGVCDFPLRSHLEP TNHAIIQTLMNSMDPGSTPPSCCVPTKLTPISILYIDAGNNVV YKQYEDMVVESCGCR	18
GDF-7	RDGLEAAAVLRAAGAGPVRSPGGGGGGGGGGRTLAQAAGA AAVPAAAVPRARAARRAAGSGFRNGSVVPHHFMMSLYRSL AGRAPAGAAAVSASGHGRADTITGFTDQATQDESAAETGQS FLFDVSSLNDADEVVGAELRVLRRGSPESGPGSWTSPPLLLLS TCPGAARAPRLLYSRAAEPLVGQRWEAFDVADAMRRHRRE PRPPRAFCLLLRAVAGPVPSPLALRRLGFGWPGGGGSAAEER AVLVVSSRTQRKESLFREIRAQARALGAALASEPLPDPGTGT ASPRAVIGGR**RRRR**TALAGTRTAQGSGGGAGRGHG**RRGR**S RCSRKPLHVDFKELGWDDWIIAPLDYEAYHCEGLCDFPLRSH LEPTNHAIIQTLLNSMAPDAAPASCCVPARLSPISILYIDAANN VVYKQYEDMVVEACGCR	19
BMP-10	SPIMNLEQSPLEEDMSLFGDVFSEQDGVDFNTLLQSMKDEFL KTLNLSDIPTQDSAKVDPPEYMLELYNKFATDRTSMPSANIIR SFKNEDLFSQPVSFNGLRKYPLLFNVSIPHHEEVIMAELRLYT LVQRDRMIYDGVDRKITIFEVLESKGDNEGERNMLVLVSGEI YGTNSEWETFDVTDAIRRWQKSGSSTHQLEVHIESKHDEAE DASSGRLEIDTSAQNKHNPLLIVFSDDQSSDKERKEELNEMIS	20

	HEQLPELDNLGLDSFSSGPGEEALLQMRSNIIYDSTA**RIRR**NA KGNYCKRTPLYIDFKEIGWDSWIIAPPGYEAYECRGVCNYPL AEHLTPTKHAIIQALVHLKNSQKASKACCVPTKLEPISILYLD KGVVTYKFKYEGMAVSECGCR	
BMP-9 (GDF-2)	KPLQSWGRGSAGGNAHSPLGVPGGGLPEHTFNLKMFLENVK VDFLRSLNLSGVPSQDKTRVEPPQYMIDLYNRYTSDKSTTPA SNIVRSFSMEDAISITATEDFPFQKHILLFNISIPRHEQITRAELR LYVSCQNHVDPSHDLKGSVVIYDVLDGTDAWDSATETKTFL VSQDIQDEGWETLEVSSAVKRWVRSDSTKSKNKLEVTVESH RKGCDTLDISVPPGSRNLPFFVVFSNDHSSGTKETRLELREMI SHEQESVLKKLSKDGSTEAGESSHEEDTDGHVAAGSTLA**RR KR**SAGAGSHCQKTSLRVNFEDIGWDSWIIAPKEYEAYECKG GCFFPLADDVTPTKHAIVQTLVHLKFPTKVGKACCVPTKLSPI SVLYKDDMGVPTLKYHYEGMSVAECGCR	21
Nodal	TVATALLRTRGQPSSPSPLAYMLSLYRDPLPRADIIRSLQAED VAVDGQNWTFAFDFSFLSQQEDLAWAELRLQLSSPVDLPTE GSLAIEIFHQPKPDTEQASDSCLERFQMDLFTVTLSQVTFSLG SMVLEVTRPLSKWLKRPGALEKQMSRVAGECWPRPPTPPAT NVLLMLYSNLSQEQRQLGGSTLLWEAESSWRAQEGQLSWE WGK**RHRR**HHLPDRSQLCRKVKFQVDFNLIGWGSWIIYPKQ YNAYRCEGECPNPVGEEFHPTNHAYIQSLLKRYQPHRVPSTC CAPVKTKPLSMLYVDNGRVLLDHHKDMIVEECGCL	22
BMP-2	LVPELGRRKFAAASSGRPSSQPSDEVLSEFELRLLSMFGLKQR PTPSRDAVVPPYMLDLYRRHSGQPGSPAPDHRLERAASRAN TVRSFHHEESLEELPETSGKTTRRFFFNLSSIPTEEFITSAELQV FREQMQDALGNNSSFHHRINIYEIIKPATANSKFPVTRLLDTR LVNQNASRWESFDVTPAVMRWTAQGHANHGFVVEVAHLE EKQGVSKRHV**RISR**SLHQDEHSWSQIRPLLVTFGHDGKGHPL HK**REKR**QAKHKQRKRLKSSCKRHPLYVDFSDVGWNDWIV APPGYHAFYCHGECPFPLADHLNSTNHAIVQTLVNSVNSKIP KACCVPTELSAISMLYLDENEKVVLKNYQDMVVEGCGCR	23
BMP-4	GASHASLIPETGKKKVAEIQGHAGGRRSGQSHELLRDFEATL LQMFGLRRRPQPSKSAVIPDYMRDLYRLQSGEEEEEQIHSTG LEYPERPASRANTVRSFHHEEHLENIPGTSENSAFRFLFNLSSI PENEVISSAELRLFREQVDQGPDWERGFHRINIYEVMKPPAE VVPGHLITRLLDTRLVHHNVTRWETFDVSPAVLRWTREKQP NYGLAIEVTHLHQTRTHQGQHV**RISR**SLPQGSGNWAQLRPL LVTFGHDGRGHALTRRR**RAKR**SPKHHSQRARKKNKNCRRH SLYVDFSDVGWNDWIVAPPGYQAFYCHGDCPFPLADHLNST NHAIVQTLVNSVNSSIPKACCVPTELSAISMLYLDEYDKVVL KNYQEMVVEGCGCR	24
BMP-5	DNHVHSSFIYRRLRNHERREIQREILSILGLPHRPRPFSPGKQA SSAPLFMLDLYNAMTNEENPEESEYSVRASLAEETRGARKG YPASPNGYPRRIQLSRTTPLTTQSPPLASLHDTNFLNDADMV MSFVNLVERDKDFSHQRRHYKEFRFDLTQIPHGEAVTAAEFR IYKDRSNNRFENETIKISIYQIIKEYTNRDADLFLLDTRKAQAL DVGWLVFDITVTSNHWVINPQNNLGLQLCAETGDGRSINVK SAGLVGRQGPQSKQPFMVAFFKASEVLL**RSVR**AANKRKNQ NRNKSSSHQDSSRMSSVGDYNTSEQKQACKKHELYVSFRDL GWQDWIIAPEGYAAFYCDGECSFPLNAHMNATNHAIVQTLV HLMFPDHVPKPCCAPTKLNAISVLYFDDSSNVILKKYRNMV VRSCGCH	25
BMP-6	CCGPPPLRPPLPAAAAAAAGGQLLGDGGSPGRTEQPPPSPQS SSGFLYRRLKTQEKREMQKEILSVLGLPHRPRPLHGLQQPQP	26

	PALRQQEEQQQQQQLPRGEPPPGRLKSAPLFMLDLYNALSA DNDEDGASEGERQQSWPHEAASSSQRRQPPPGAAHPLNRKS LLAPGSGSGGASPLTSAQDSAFLNDADMVMSFVNLVEYDKE FSPRQRHHKEFKFNLSQIPEGEVVTAAEFRIYKDCVMGSFKN QTFLISIYQVLQEHQHRDSDLFLLDTRVVWASEEGWLEFDIT ATSNLWVVTPQHNMGLQLSVVTRDGVHVHPRAAGLVGRD GPYDKQPFMVAFFKVSEVHV**RTTR**SAS**SRRR**QQSRNRSTQS QDVARVSSASDYNSSELKTACRKHELYVSFQDLGWQDWIIA PKGYAANYCDGECSFPLNAHMNATNHAIVQTLVHLMNPEY VPKPCCAPTKLNAISVLYFDDNSNVILKKYRNMVVRACGCH	
BMP-7	DFSLDNEVHSSFIHRRLRSQERREMQREILSILGLPHRPRPHLQ GKHNSAPMFMLDLYNAMAVEEGGGPGGQGFSYPYKAVFST QGPPLASLQDSHFLTDADMVMSFVNLVEHDKEFFHPRYHHR EFRFDLSKIPEGEAVTAAEFRIYKDYIRERFDNETFRISVYQVL QEHLGRESDLFLLDSRTLWASEEGWLVFDITATSNHWVVNP RHNLGLQLSVETLDGQSINPKLAGLIGRHGPQNKQPFMVAFF KATEVHF**RSIR**STGSKQRSQNRSKTPKNQEALRMANVAENS SSDQRQACKKHELYVSFRDLGWQDWIIAPEGYAAYYCEGEC AFPLNSYMNATNHAIVQTLVHFINPETVPKPCCAPTQLNAISV LYFDDSSNVILKKYRNMVVRACGCH	27
BMP-8A	GGGPGLRPPPGCPQRRLGA**RERR**DVQREILAVLGLPGRPRPR APPAASRLPASAPLFMLDLYHAMAGDDDEDGAPAEQRLGR ADLVMSFVNMVERDRALGHQEPHWKEFRFDLTQIPAGEAVT AAEFRIYKVPSIHLLNRTLHVSMFQVVQEQSNRESDLFFLDL QTLRAGDEGWLVLDVTAASDCWLLKRHKDLGLRLYVETED GHSVDPGLAGLLGQRAPRSQQPFVVTFFRASPSPI**RTPR**AVR PLRRRQPKKSNELPQANRLPGIFDDVRGSHGRQVCRRHELYV SFQDLGWLDWVIAPQGYSAYYCEGECSFPLDSCMNATNHAI LQSLVHLMKPNAVPKACCAPTKLSATSVLYYDSSNNVILRK HRNMVVKACGCH	28
BMP-8B	GGGPGLRPPPGCPQRRLGA**RERR**DVQREILAVLGLPGRPRPR APPAASRLPASAPLFMLDLYHAMAGDDDEDGAPAERRLGRA DLVMSFVNMVERDRALGHQEPHWKEFRFDLTQIPAGEAVTA AEFRIYKVPSIHLLNRTLHVSMFQVVQEQSNRESDLFFLDLQT LRAGDEGWLVLDVTAASDCWLLKRHKDLGLRLYVETEDGH SVDPGLAGLLGQRAPRSQQPFVVTFFRASPSPI**RTPR**AVRPLR RRQPKKSNELPQANRLPGIFDDVHGSHGRQVCRRHELYVSF QDLGWLDWVIAPQGYSAYYCEGECSFPLDSCMNATNHAILQ SLVHLMMPDAVPKACCAPTKLSATSVLYYDSSNNVILRKHR NMVVKACGCH	29
BMP-15	MEHRAQMAEGGQSSIALLAEAPTLPLIEELLEESPGEQPRKPR LLGHSLRYMLELYRRSADSHGHPRENRTIGATMVRLVKPLTS VARPHRGTWHIQILGFPLRPNRGLYQLVRATVVYRHHLQLT RFNLSCHVEPWVQKNPTNHFPSSEGDSSKPSLMSNAWKEMD ITQLVQQRFWNNKGHRILRLRFMCQQQKDSGGLELWHGTSS LDIAFLLLYFNDTHKSIRKAKFLPRGMEEFMERESLL**RRTR**Q ADGISAEVTASSSKHSGPENNQCSLHPFQISFRQLGWDHWIIA PPFYTPNYCKGTCLRVLRDGLNSPNHAIIQNLINQLVDQSVPR PSCVPYKYVPISVLMIEANGSILYKEYEGMIAESCTCR	30
GDF-9	SQASGGEAQIAASAELESGAMPWSLLQHIDERDRAGLLPALF KVLSVGRGGSPRLQPDSRALHYMKKLYKTYATKEGIPKSNR SHLYNTVRLFTPCTRHKQAPGDQVTGILPSVELLFNLDRITTV EHLLKSVLLYNINNSVSFSSAVKCVCNLMIKEPKSSSRTLGRA PYSFTFNSQFEFGKKHKWIQIDVTSLLQPLVASNKRSIHMSIN	31

	FTCMKDQLEHPSAQNGLFNMTLVSPSLILYLNDTSAQAYHS WYSLHYKRRPSQGPDQERSLSAYPVGEEAAEDGRSSHH**RHR R**GQETVSSELKKPLGPASFNLSEYFRQFLLPQNECELHDFRLS FSQLKWDNWIVAPHRYNPRYCKGDCPRAVGHRYGSPVHTM VQNIIYEKLDSSVPRPSCVPAKYSPLSVLTIEPDGSIAYKEYED MIATKCTCR	
BMP-3	ERPKPPFPELRKAVPGDRTAGGGPDSELQPQDKVSEHMLRLY DRYSTVQAARTPGSLEGGSQPWRPRLLREGNTVRSFRAAAA ETLERKGLYIFNLTSLTKSENILSATLYFCIGELGNISLSCPVSG GCSHHAQRKHIQIDLSAWTLKFSRNQSQLLGHLSVDMAKSH RDIMSWLSKDITQLLRKAKENEEFLIGFNITSKGRQLPKRRLP FPEPYILVYANDAAISEPESVVSSLQGHRNFPTGTVPKWDSHI RAALSIERRKKRSTGVLLPLQNNELPGAEYQYKKDEVWEER KPYKTLQAQAPEKSKNK**KKQR**KGPHRKSQTLQFDEQTLK**K ARR**KQWIEPRNCARRYLKVDFADIGWSEWIISPKSFDAYYCS GACQFPMPKSLKPSNHATIQSIVRAVGVVPGIPEPCCVPEKMS SLSILFFDENKNVVLKVYPNMTVESCACR	32
GDF-10	SHRAPAWSALPAAADGLQGDRDLQRHPGDAAATLGPSAQD MVAVHMHRLYEKYSRQGARPGGGNTVRSFRARLEVVDQK AVYFFNLTSMQDSEMILTATFHFYSEPPRWPRALEVLCKPRA KNASGRPLPLGPPTRQHLLFRSLSQNTATQGLLRGAMALAPP PRGLWQAKDISPIVKAARRDGELLLSAQLDSEERDPGVPRPS PYAPYILVYANDLAISEPNSVAVTLQRYDPFPAGDPEPRAAP NNSADPRVRRAAQATGPLQDNELPGLDERPPRAHAQHFHKH QLWPSPFRALKPRPGRKDRRKKGQEVFMAASQVLDFDEKT MQ**KARR**KQWDEPRVCSRRYLKVDFADIGWNEWIISPKSFDA YYCAGACEFPMPKIVRPSNHATIQSIVRAVGIIPGIPEPCCVPD KMNSLGVLFLDENRNVVLKVYPNMSVDTCACR	33
GDNF	FPLPAGKRPPEAPAEDRSLGRRRAPFALSSDSNMPEDYPDQF DDVMDFIQATIK**RLKR**SPDKQMAVLPRRERNRQAAAANPE NSRGKGRRGQRGKNRGCVLTAIHLNVTDLGLGYETKEELIFR YCSGSCDAAETTYDKILKNLSRNRRLVSDKVGQACCRPIAFD DDLSFLDDNLVYHILRKHSAKRCGCI	34
NRTN	IWMCREGLLLSHRLGPALVPLHRLPRTLDARIARLAQYRALL QGAPDAMELRELTPWAGRPPGPRRRAGP**RRRR**ARARLGAR PCGLRELEVRVSELGLGYASDETVLFRYCAGACEAAARVYD LGLRRLRQRRRLRRERVRAQPCCRPTAYEDEVSFLDAHSRY HTVHELSARECACV	35
PSPN	WGPDARGVPVADGEFSSEQVAKAGGTWLGTHRPLA**RLRR**A LSGPCQLWSLTLSVAELGLGYASEEKVIFRYCAGSCPRGART QHGLALARLQGQGRAHGGPCCRPTRYTDVAFLDDRHRWQR LPQLSAAACGCGG	36
ARTN	SLGSAPRSPAPREGPPPVLASPAGHLPGGRTARWCSG**RARR**P PPQPSRPAPPPPAPPSALP**RGGRAAR**AGGPGSRARAAGARGC RLRSQLVPVRALGLGHRSDELVRFRFCSGSCRRARSPHDLSL ASLLGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRT VDRLSATACGCLG	37

[00178] It is noted that some prodomains may be cleaved by proprotein convertase enzymes. As used herein, the term "proprotein convertase" refers to an enzyme that cleaves a prodomain from a translated protein to facilitate protein maturation. Some proprotein convertases of the present disclosure include the subtilisin-like proprotein convertase (SPC)

family member enzymes. The SPC family comprises calcium-dependent serine endoproteases that include, but are not limited to furin/PACE, PC1/3, PC2, PC4, PC5/6, PACE4 and PC7 (Fuller et al., 2009. Invest Ophthalmol Vis Sci. 50(12):5759-68, the contents of which are herein incorporated by reference in their entirety). GDF-11 may in some cases, be cleaved by PC5/6. In some cases, proprotein convertases may cleave proproteins at additional sites, other than those indicated in Table 1. In some embodiments, pro-proteins may be cleaved at a first cleavage site (the first site being the site closest to the N-terminus). In other embodiments, pro-proteins may be cleaved at a cleavage site other than a first cleavage site. In some cases, proprotein convertase cleavage may occur intracellularly. In some cases, proprotein convertase cleavage may occur extracellularly.

[00179] Many TGF-β family member proteins are synthesized in conjunction with prodomains. Some prodomains may remain associated with growth factors after cleavage. Such associations may form latent growth factor-prodomain complexes (GPCs) that modulate the availability of growth factors for cell signaling. Growth factors may be released from latency in GPCs through associations with one or more extracellular proteins. In some cases, growth factor release may rely on force applied to GPCs through extracellular protein interactions. Such forces may pull from C-terminal and/or N-terminal regions of GPCs resulting in the release of associated growth factors.

[00180] In some TGF-β family members, the prodomain portion of the GPC is responsible for growth factor retention and blocking the interaction of retained growth factors with their receptors. Such GPCs, where the bound growth factor is unable to promote signaling activity, are also referred to herein as "latent complexes." Prodomain portions of GPCs that function to block growth factor signaling activity are referred to as latency associated peptides (LAPs). TGF-β1, 2 and 3 are know to comprise LAPs. GDF prodomains also function to block growth factor activity. Some prodomains may comprise LAP-like domains. As used herein, the term "LAP-like domain" refers to prodomain portions of GPCs and/or free prodomains that may be structurally similar or synthesized in a similar manner to LAPs, but that may not function to prevent growth factor/receptor interactions.

[00181] FIG. 3 is a schematic depicting an embodiment of a GPC before and after growth factor release. According to such embodiments, growth factor dimers may associate with prodomain modules to form a GPC. In some embodiments, GPCs comprise protein modules necessary for different aspects of growth factor signaling, secretion, latency and/or release from latent GPCs. As used herein, the term "protein module" refers to any component, region and/or feature of a protein. Protein modules may vary in length, comprising one or more

amino acids. Protein modules may be from about 2 amino acid residues in length to about 50 amino acid residues in length, from about 5 amino acid residues in length to about 75 amino acid residues in length, from about 10 amino acid residues in length to about 100 amino acid residues in length, from about 25 amino acid residues in length to about 150 amino acid residues in length, from about 125 amino acid residues in length to about 250 amino acid residues in length, from about 175 amino acid residues in length to about 400 amino acid residues in length, from about 200 amino acid residues in length to about 500 amino acid residues in length and/or at least 500 amino acid residues in length.

[00182] In some embodiments, protein modules comprise one or more regions with known functional features (e.g. protein binding domain, nucleic acid binding domain, hydrophobic pocket, etc). Protein modules may comprise functional protein domains necessary for different aspects of growth factor signaling, secretion, latency and/or release from latent conformations.

[00183] In some embodiments, protein modules may be derived from TGF-β-related proteins. Such protein modules may include, but are not limited to prodomains (e.g. latency-associated peptides (LAPs) or LAP-like domains), growth factor domains, fastener regions, proprotein convertase cleavage sites (e.g. furin cleavage sites), B/TP cleavage sites, arm regions, finger regions, residues (such as cysteine residues for example) for extracellular protein associations, latency loops (also referred to herein as latency lassos), alpha 1 helical regions, alpha 2 helical regions, RGD sequences and bowtie regions. FIG. 4 is a schematic diagram showing some of the protein modules present in a GPC as well as in the prodomains and growth factor dimer after activating cleavage of the GPC.

[00184] In some embodiments, prodomains may associate with growth factors in GPCs. Some prodomains may sterically prevent growth factor association with one or more cellular receptors. Prodomains may comprise arm regions and/or straight jacket regions. Some prodomains may comprise C-terminal regions referred to herein as "bowtie regions." In some prodomain dimers, bowtie regions of each monomer may associate and/or interact. Such associations may comprise disulfide bond formation, as is found between monomers of TGF-β isoform LAPs.

[00185] In some embodiments, arm regions may comprise trigger loop regions. Trigger loops may comprise regions that associate with integrins. Such regions may comprise amino acid sequences comprising RGD (Arg-Gly-Asp). Regions comprising RGD sequences are referred to herein as RGD sequence regions. In some embodiments, prodomains comprise latency loops (also referred to herein as latency lassos). Some latency loops may maintain

associations between prodomains and growth factors present within GPCs. Prodomains may also comprise fastener regions. Such fastener regions may promote associations between prodomains and growth factors present within GPCs by maintaining prodomain conformations that promote growth factor retention.

[00186] In some cases, GPCs may require enzymatic cleavage to promote dissociation of bound growth factors and growth factor activity. Such enzymatic cleavage events are referred to herein as "activating cleavage" events. Activating cleavage of GPCs may be carried out in some instances by members of the BMP-1/Tolloid-like proteinase (B/TP) family (Muir et al., 2011. J Biol Chem. 286(49):41905-11, the contents of which are herein incorporated by reference in their entirety). These metaloproteinases may include, but are not limited to BMP-1, mammalian tolloid protein (mTLD), mammalian tolloid-like 1 (mTLL1) and mammalian tolloid-like 2 (mTLL2). Exemplary GPCs that may be subjected to activating cleavage by such metalloproteinases may include, but are not limited to GDF-8 and GDF-11. In some cases, GDF-8 may be cleaved by mTLL2. In some cases, activating cleavages may occur intracellularly. In some cases, activating cleavages may occur extracellularly.

[00187] Growth factor release from GPCs may require cleavage by a proprotein convertase enzyme followed by an activating cleavage [e.g. by one or more members of the BMP-1/Tolloid-like proteinase (B/TP) family.] In one example, GDF-8 and GDF-11 GPCs may be transformed by furin cleavage into a latent complex that further requires cleavage by BMP/Tolloid proteases for growth factor release.

[00188] In some embodiments, the present disclosure provides polypeptide inhibitors (e.g., antibodies) that inhibit one or more members of the B/TP family. Such inhibitors may block cleavage of BMP-1/Tolloid cleavage sites, including, but not limited to BMP/Tolloid cleavage sites on one or more latent complexes (e.g., GDF-8 latent complexes and/or GDF-11 latent complexes).

[00189] In some cases, activating cleavage may not lead to dissociation of bound growth factor, but instead may promote an active conformation of the GPC. As used herein when referring to a GPC, the term "active conformation" refers to a GPC protein confirmation that allows the growth factor to engage in receptor interaction. Such scenarios have been predicted with proBMP-7 and proBMP-9 (Sengle, G. et al., 2008. JMB. 381: 1025-39 and Mi et al., 2015. PNAS. 112(12): 3710-5, the contents of each of which are herein incorporated by reference in their entirety). In some embodiments, the present disclosure provides antibodies that specifically target active conformations to modulate growth factor activity.

[00190] Active conformations of GDF-8 GPCs or GDF-11 GPCs are referred to herein as "primed" complexes, and can be produced by the sequential cleavage of GPCs at the furin cleavage site and the BMP/Tolloid cleavage site. Primed complexes (either the entire complex or portions of the complex) may bind receptors resulting in receptor signaling. In some cases, prodomains may be dissociated from growth factors upon receptor binding and/or signaling activity. In some cases, prodomains may remain associated with growth factors upon receptor binding and/or signaling activity. In some cases, prodomains may become partially dissociated from growth factors during receptor binding and/or signaling activity.

[00191] In some cases, primed complexes may bind preferentially to one or more receptors over one or more other receptors. In some cases, receptor activity resulting from primed complex interactions may be quenched or competed for by excess prodomain or fragments thereof.

[00192] In some embodiments, the present disclosure provides polypeptide inhibitors (e.g., inhibiting antibodies) that block the formation of primed complexes from latent complexes. In some cases, such inhibitors bind BMP/Tolloid cleavage sites on latent GPCs (e.g., latent GDF-8 or latent GDF-11). In some embodiments, such inhibitors prevent cleavage of the BMP/Tolloid cleavage site.

[00193] Straight jacket regions may comprise alpha 1 helical regions. In some embodiments, alpha 1 helical regions may be positioned between growth factor monomers. Some alpha 1 helical regions comprise N-terminal regions of prodomains. Alpha 1 helical regions may also comprise N-terminal regions for extracellular associations. Such extracellular associations may comprise extracellular matrix proteins and/or proteins associated with the extracellular matrix. Some extracellular associations may comprise associations with proteins that may include, but are not limited to LTBPs (e.g. LTBP1, LTBP2, LTBP3 and/or LTBP4), fibrillins (e.g. fibrillin-1, fibrillin-2, fibrillin-3 and/or fibrillin-4), perlecan, decorin and/or GASPs. N-terminal extracellular associations may comprise disulfide bonds between cysteine residues. In some cases, extracellular matrix proteins and/or proteins associated with the extraceullar matrix may comprise bonds or interactions with one or more regions of prodomains other than N-terminal regions.

[00194] In some embodiments, growth factor domains comprise one or more growth factor monomers. Some growth factor domains comprise growth factor dimers. Such growth factor domains may comprise growth factor homodimers or heterodimers (comprising growth factor monomers from different TGF-β-related proteins). Some growth factor domains may

comprise fingers regions. Such fingers regions may comprise β-pleated sheets. Fingers regions may associate with prodomains. Some fingers regions may maintain association between growth factor domains and prodomains.

[00195] In some embodiments, recombinant proteins of the present disclosure may comprise protein modules from growth differentiation factor (GDF) proteins. Such GDF protein modules may comprise the protein modules and/or amino acid sequences listed in Table 2. In some embodiments, protein modules of the present disclosure may comprise amino acid sequences similar to those in Table 2, but comprise additional or fewer amino acids than those listed. Some such amino acid sequences may comprise about 1 more or fewer amino acids, about 2 more or fewer amino acids, about 3 more or fewer amino acids, about 4 more or fewer amino acids, about 5 more or fewer amino acids, about 6 more or fewer amino acids, about 7 more or fewer amino acids, about 8 more or fewer amino acids, about 9 more or fewer amino acids, about 10 more or fewer amino acids or greater than 10 more or fewer amino acids on N-terminal and/or C-terminal ends.

Table 2. GDF protein modules

TGF-β Family Member	Protein Module	Prodomain and growth factor Sequence	SEQ ID NO
GDF-8	prodomain	NENSEQKENVEKEGLCNACTWRQNTKSSRIEA IKIQILSKLRLETAPNISKDVIRQLLPKAPPLREL IDQYDVQRDDSSDGSLEDDDYHATTETIITMPT ESDFLMQVDGKPKCCFFKFSSKIQYNKVVKAQ LWIYLRPVETPTTVFVQILRLIKPMKDGTRYTG IRSLKLDMNPGTGIWQSIDVKTVLQNWLKQPE SNLGIEIKALDENGHDLAVTFPGPGEDGLNPFL EVKVTDTPKRSRR	38
GDF-11	prodomain	AEGPAAAAAAAAAAAAAGVGGERSSRPAPSV APEPDGCPVCVWRQHSRELRLESIKSQILSKLR LKEAPNISREVVKQLLPKAPPLQQILDLHDFQG DALQPEDFLEEDEYHATTETVISMAQETDPAV QTDGSPLCCHFHFSPKVMFTKVLKAQLWVYL RPVPRPATVYLQILRLKPLTGEGTAGGGGGGR RHIRIRSLKIELHSRSGHWQSIDFKQVLHSWFR QPQSNWGIEINAFDPSGTDLAVTSLGPGAEGLH PFMELRVLENTKRSRR	39
GDF-8	straight jacket region	NENSEQKENVEKEGLCNACTWRQNTKSSRIEA IKIQILSKLRLETAPNISKDVIRQLLPKAPPL	40
GDF-11	straight jacket region	AEGPAAAAAAAAAAAAAGVGGERSSRPAPSV APEPDGCPVCVWRQHSRELRLESIKSQILSKLR LKEAPNISREVVKQLLPKAPPL	41
GDF-8	growth factor domain	DFGLDCDEHSTESRCCRYPLTVDFEAFGWDWI IAPKRYKANYCSGECEFVFLQKYPHTHLVHQA NPRGSAGPCCTPTKMSPINMLYFNGKEQIIYGK IPAMVVDRCGCS	42

GDF-11	growth factor domain	NLGLDCDEHSSESRCCRYPLTVDFEAFGWDWI IAPKRYKANYCSGQCEYMFMQKYPHTHLVQQ ANPRGSAGPCCTPTKMSPINMLYFNDKQQIIYG KIPGMVVDRCGCS	43
GDF-8	fastener region	residues 87-89, DYH	--
GDF-11	fastener region	residues 110-112, EYH	--
GDF-8 and GDF-11	furin cleavage site region	RSRR	44
GDF-8	BMP/Tolloid cleavage site	between residues R75 and D76	--
GDF-11	BMP/Tolloid cleavage site	between residues G97 and D98	--
GDF-8	arm region	RELIDQYDVQRDDSSDGSLEDDDYHATTETIIT MPTESDFLMQVDGKPKCCFFKFSSKIQYNKVV KAQLWIYLRPVETPTTVFVQILRLIKPMKDGTR YTGIRSLKLDMNPGTGIWQSIDVKTVLQNWLK QPESNLGIEIKALDENGHDLAVTFPGPGEDGLN PFLEVKVTDTPKRSRR	45
GDF-11	arm region	QQILDLHDFQGDALQPEDFLEEDEYHATTETVI SMAQETDPAVQTDGSPLCCHFHFSPKVMFTKV LKAQLWVYLRPVPRPATVYLQILRLKPLTGEG TAGGGGGGRRHIRIRSLKIELHSRSGHWQSIDF KQVLHSWFRQPQSNWGIEINAFDPSGTDLAVT SLGPGAEGLHPFMELRVLENTKRSRR	46
GDF-8 and GDF-11	fingers region 1	CRYPLTVDFEAFGWDWIIAPKRYKANYCS	47
GDF-8	fingers region 2	CTPTKMSPINMLYFNGKEQIIYGKIPAMVVDRC GCS	48
GDF-11	fingers region 2	CTPTKMSPINMLYFNDKQQIIYGKIPGMVVDR CGCS	49
GDF-8	latency loop	RLETAPNISKDVIRQLLPKAPPL	50
GDF-11	latency loop	RLKEAPNISREVVKQLLPKAPP	51
GDF-8	alpha 1 helical region	GLCNACTWRQNTKSSRIEAIKIQILSK	52
GDF-11	alpha 1 helical region	DGCPVCVWRQHSRELRLESIKSQILSKL	53
GDF-8	bowtie region	DENGHDLAVTFPGP	54
GDF-11	bowtie region	DPSGTDLAVTSLG	55

[00196] Some recombinant proteins of the present disclosure may comprise GDF-15, GDF-15 signaling pathway-related proteins and/or modules and/or portions thereof. GDF-15 is a TGF-β family protein that is highly expressed in liver. Expression of GDF-15 is dramatically upregulated following liver injury (Hsiao et al. 2000. Mol Cell Biol. 20(10):3742-51). Additionally, its expression in macrophages may serve a protective function in the context of atherosclerosis, possibly through regulation of adhesion molecule expression (Preusch et al., 2013. Eur J Med Res. 18:19). While a member of the TGF-β family, GDF-15 comprises less than 30% homology with other members, making it the most divergent member of the family

(Tanno et al., 2010. Curr Opin Hematol. 17(3):184-90, the contents of which are incorporated herein by reference in their entirety). The mature form is soluble and can be found in the blood stream. Interestingly, GDF-15 levels in circulation have been found to negatively correlate with hepcidin levels, suggesting a role for GDF-15 in iron load and/or metabolism (Finkenstedt et al., 2008. British Journal of Haematology. 144:789-93). Elevated GDF-15 in the blood is also associated with ineffective and/or apoptotic erythropoiesis, such as in subjects suffering from beta-thalassemia or dyserythropoietic anemias.

[00197] In some embodiments, recombinant proteins of the present disclosure may comprise protein modules from activin subunits. Such protein modules may comprise the protein modules and/or amino acid sequences of the activin subunit inhibin beta A, listed in Table 3. In some embodiments, protein modules of the present disclosure may comprise amino acid sequences similar to those in Table 3, but comprise additional or fewer amino acids than those listed. Some such amino acid sequences may comprise about 1 more or fewer amino acids, about 2 more or fewer amino acids, about 3 more or fewer amino acids, about 4 more or fewer amino acids, about 5 more or fewer amino acids, about 6 more or fewer amino acids, about 7 more or fewer amino acids, about 8 more or fewer amino acids, about 9 more or fewer amino acids, about 10 more or fewer amino acids or greater than 10 more or fewer amino acids on N-terminal and/or C-terminal ends.

Table 3. Inhibin beta A protein modules

Protein Module	Prodomain and growth factor Sequence	SEQ ID NO
prodomain	SPTPGSEGHSAAPDCPSCALAALPKDVPNSQPE MVEAVKKHILNMLHLKKRPDVTQPVPKAALL NAIRKLHVGKVGENGYVEIEDDIGRRAEMNEL MEQTSEIITFAESGTARKTLHFEISKEGSDLSVV ERAEVWLFLKVPKANRTRTKVTIRLFQQQKHP QGSLDTGEEAEEVGLKGERSELLLSEKVVDAR KSTWHVFPVSSSIQRLLDQGKSSLDVRIACEQC QESGASLVLLGKKKKKEEEGEGKKKGGGEGG AGADEEKEQSHRPFLMLQARQSEDHPHRRRR R	56
straight jacket region	SPTPGSEGHSAAPDCPSCALAALPKDVPNSQPE MVEAVKKHILNMLHLKKRPDVTQPVPKAALL N	57
growth factor domain	RGLECDGKVNICCKKQFFVSFKDIGWNDWIIA PSGYHANYCEGECPSHIAGTSGSSLSFHSTVIN HYRMRGHSPFANLKSCCVPTKLRPMSMLYYD DGQNIIKKDIQNMIVEECGCS	58
fastener region	residues 89-91, RRA	--
furin cleavage site	RRRR	59

region		
arm region	LNAIRKLHVGKVGENGYVEIEDDIGRRAEMNE LMEQTSEIITFAESGTARKTLHFEISKEGSDLSV VERAEVWLFLKVPKANRTRTKVTIRLFQQQKH PQGSLDTGEEAEEVGLKGERSELLLSEKVVDA RKSTWHVFPVSSSIQRLLDQGKSSLDVRIACEQ CQESGASLVLLGKKKKKEEEGEGKKKGGGEG GAGADEEKEQSHRPFLMLQARQSEDHPHRRR RR	60
fingers region 1	KKQFFVSFKDIGWNDWIIAPSGYHANYC	61
fingers region 2	CVPTKLRPMSMLYYDDGQNIIKKDIQNMIVEE CGCS	62
latency loop	LKKRPDVTQPVPKAALL	63
alpha 1 helical region	ALAALPKDVPNSQPEMVEAVKKHILNML	64
bowtie region	QESGASLVLLGKKKKKEEEGEGKKKGGGEGG AG	65

[00198] Growth factor domains among TGF-β family members are more highly conserved while prodomains comprise a much lower percent identity among family members (FIG. 5). Prodomains may vary in length from about 50 to about 200, from about 100 to about 400 or from about 300 to about 500 amino acids residues. In some embodiments, prodomains range from about 169 to about 433 residues. Prodomains may be unrelated in sequence and/or low in homology. Some prodomains may have similar folds and/or three dimensional structures. Prodomains of TGF-β family members may comprise latency loops. Such loops may be proline-rich. Latency loop length may determine the ability of such loops to encircle growth factor finger regions.

[00199] In some embodiments, protein modules from some TGF-β family members comprise low sequence identity with protein modules from other TGF-β family members. Such low sequence identity may indicate specialized roles for such family members with distinct protein modules.

[00200] Association of GPCs with extracellular proteins may strengthen prodomain-growth factor interactions. In some embodiments, such extracellular proteins may include, but are not limited to LTBPs, fibrillins, GASPs, perlecan and/or decorin. In some cases, extracellular protein associations are required to keep growth factors latent in GPCs.

[00201] GARP expression has been shown to be required for surface expression of GPCs on the surface of cells of hematopoietic origin (Tran, D.Q. et al., GARP (LRRC32) is essential for the surface expression of latent TGF-β on platelets and activated FOXP3+ regulatory T cells. PNAS. 2009, Jun 2. 106(32):13445-50). GARP may act as a tether to hold

GPCs in place on the surface of these cells, including, but not limited to regulatory T-cells and/or platelets.

[00202] In some embodiments, recombinant proteins of the present disclosure may comprise bone morphogenetic proteins (BMPs), a family of TGF-β-related proteins. Protein modules comprising sequences from BMPs may comprise sequences from any of those BMP modules disclosed in FIG. 6. While related to other TGF-β family member proteins, BMPs generally signal through SMAD1, 5 and 8 proteins while TGF-β isoforms (e.g. TGF-β1, TGF-β2 and TGF-β3) signal through SMAD2 and SMAD3.

[00203] Some BMP receptors and/or co-receptors are also distinct from other TGF-β family member proteins. Among these is the repulsive guidance molecule (RGM) family of proteins. RGM proteins act as co-receptors for BMP signaling. There are three RGM family members, RGMA, RGMB and RGMC [also known as hemojuvelin (Hjv)]. Recombinant proteins of the present disclosure comprising one or more BMP protein module may be useful for the development of antibodies and/or assays to study, enhance and/or perturb BMP interactions with RGM proteins.

[00204] Another family of GDF/BMP interacting proteins is C-terminal cysteine knot-like (CTCK) domain-containing proteins. In some cases, CTCK domain-containing proteins may act antagonistically with regard to GDF/BMP signal transduction. CTCK domain-containing proteins include, but are not limited to Cerberus, Connective tissue growth factor (CTGF), DAN domain family member 5 (DAND5), Gremlin-1 (GREM1), Gremlin-2 (GREM2), Mucin-19 (MUC19), Mucin-2 (MUC2), Mucin-5AC (MUC5AC), Mucin-5B (MUC5B), Mucin-6 (MUC6), Neuroblastoma suppressor of tumorigenicity 1 (NBL1), Norrin (NDP), Otogelin (OTOG), Otogelin-like protein (OTOGL), Protein CYR61 (CYR61), Protein NOV homolog (NOV), Sclerostin (SOST), Sclerostin domain-containing protein 1 (SOSTDC1), SCO-spondin (SSPO), Slit homolog 1 protein (SLIT1), Slit homolog 2 protein (SLIT2), Slit homolog 3 protein (SLIT3), von Willebrand factor (VWF), WNT1-inducible-signaling pathway protein 1 (WISP1) and WNT1-inducible-signaling pathway protein 3 (WISP3).

Recombinant proteins

[00205] In some embodiments, the present disclosure provides recombinant proteins. As used herein, the term "recombinant protein" refers to a protein produced by an artificial gene and/or process (e.g. genetic engineering). Such recombinant proteins may comprise one or more protein modules from one or more TGF-β-related proteins. Some recombinant proteins disclosed herein may be useful as recombinant antigens. As used herein, the term

"recombinant antigen" refers to a recombinant protein that may be used to immunize one or more hosts for the production of antibodies directed toward one or more epitopes present on such recombinant antigens. Some recombinant antigens may be cell-based antigens. As used herein, the term "cell-based antigen" refers to recombinant antigens that are expressed in cells for presentation of such antigens on the cell surface. Such cells may be used to immunize hosts for the production of antibodies directed to such cell-based antigens.

[00206] In some embodiments, recombinant proteins disclosed herein may be used as therapeutics. Recombinant proteins disclosed herein may modulate growth factor (e.g. growth factors comprising TGF-β-related proteins) levels and/or activity (e.g. signaling) upon administration and/or introduction to one or more subjects and/or niches.

[00207] In some embodiments, recombinant proteins disclosed herein may be used to assay growth factor (e.g. growth factors comprising TGF-β-related proteins) levels and/or activity (e.g. signaling). Some recombinant proteins disclosed herein may be used in the isolation of antibodies directed to TGF-β-related proteins. Recombinant proteins of the present disclosure may also be used as recombinant antigens in the development of stabilizing [reducing or preventing dissociation between two agents, (e.g. growth-factor release from GPCs, GPC release from one or more protein interactions)] and/or releasing [enhancing the dissociation between two agents (e.g. growth-factor release from GPCs, GPC release from one or more protein interactions)] antibodies. Recombinant proteins of the present disclosure may include TGF-β family member proteins as well as components and/or protein modules thereof. Some recombinant proteins of the present disclosure may comprise prodomains without associated growth factors, furin cleavage-deficient mutants, mutants deficient in extracellular protein associations and/or combinations thereof.

[00208] In some embodiments, recombinant proteins may comprise detectable labels. Detectable labels may be used to allow for detection and/or isolation of recombinant proteins. Some detectable labels may comprise biotin labels, polyhistidine tags and/or flag tags. Such tags may be used to isolate tagged proteins. Proteins produced may comprise additional amino acids encoding one or more 3C protease cleavage site. Such sites allow for cleavage at the 3C protease cleavage site upon treatment with 3C protease, including, but not limited to rhinovirus 3C protease. Such cleavage sites are introduced to allow for removal of detectable labels from recombinant proteins.

Recombinant GPCs

[00209] FIG. 7 is a schematic depicting an embodiment of a recombinant GPC. Recombinant proteins according to FIG. 7 comprising TGF-β-family member proteins may comprise features including, but not limited to C-terminal regions of the mature growth factor, N-terminal regions of the prodomain and/or proprotein cleavage sites. The proprotein cleavage site of recombinant GPCs may, for example, comprise the furin consensus sequences RXXR, or RXR wherein R is arginine and X indicates amino acid residues that may vary among TGF-β family members. Furin cleavage site sequences (although not limited to cleavage by furin alone and may include cleavage by other proprotein convertase enzymes) for each TGF-β family member are indicated in Table 1. In some cases, prodomains of GPCs may comprise one or more cysteine residues within and/or near the N-terminal region of the prodomain. Such cysteine residues may be from about 1 to about 10 amino acids, from about 4 to about 15 amino acids, from about 5 to about 20 amino acids and/or from about 7 to about 50 amino acids from the N-terminus of the prodomain. In some cases, recombinant GPCs may also be expressed with detectable labels. Such detectable labels may be useful for detection and/or isolation of recombinant GPCs. Detectable labels may comprise 2 or more histidine (His) residues. Such detectable labels may also be referred to herein as polyhistidine tags. Polyhistidine tags may include hexa histidine tags or HIS-TAG™ (EMD Biosciences, Darmstadt, Germany) comprising a chain of six histidine residues. Some polyhistidine tags may be present at the N-terminus of recombinant proteins disclosed herein. Some polyhistidine tags may be present at the C-terminus of recombinant proteins disclosed herein. Proteins produced may comprise additional amino acids encoding one or more 3C protease cleavage site. Such sites allow for cleavage at the 3C protease cleavage site upon treatment with 3C protease, including, but not limited to rhinovirus 3C protease. Some cleavage sites may be introduced to allow for removal of detectable labels from recombinant proteins.

[00210] In some embodiments of the present disclosure, recombinant GPCs may comprise mutations in one or more amino acids as compared to wild type sequences. In some cases, one or more regions of proteolytic processing may be mutated (see FIG. 8). Such regions may comprise proprotein convertase cleavage sites. Proprotein convertase (e.g. furin) cleavage site mutations prevent enzymatic cleavage at that site and/or prevent enzymatic cleavage of growth factors from their prodomains. Some proprotein convertase cleavage sites comprising RXXR sequences may be mutated to RXG (wherein X indicates a site where amino acid residues may be variable). Such mutations are herein abbreviated as "D2G" mutations and may be resistant to enzymatic cleavage. In some embodiments, furin cleavage sites

comprising RXXR sequences are mutated to AXXA. Such AXXA sequences may also be resistant to enzymatic cleavage.

[00211] In some embodiments, regions of proteolytic processing by tolloid and/or tolloid-like proteins may be mutated to prevent such proteolytic processing. In some embodiments, tolloid processing regions on GDF-8 and/or GDF-11 may be mutated. In some embodiments, mutation of aspartic acid residues to alanine residues within tolloid processing regions prevents tolloid processing. Mutation of aspartic acid residue 76 (D76) of the GDF-8 (myostatin) proprotein has been shown to prevent proteolytic activation of latent GDF-8 (Wolfman, N.M. et al.,PNAS. 2003, Oct 6. 100(26):15842-6). In some embodiments, Asp 120 (D120, residue number counted from the translated protein, D98 from the proprotein of SEQ ID NO: 4) in GDF-11 may be mutated to prevent tolloid processing (Ge et al., 2005. Mol Cell Biol. 25(14):5846-58, the contents of which are herein incorporated by reference in their entirety).

[00212] In some embodiments, one or more amino acids may be mutated in order to form recombinant GPCs with reduced latency. Such mutations are referred to herein as "activating mutations." These mutations may introduce one or more regions of steric clash between complex prodomains and growth factor domains. As used herein, the term "steric clash," when referring to the interaction between two proteins or between two domains and/or epitopes within the same protein, refers to a repulsive interaction between such proteins, domains and/or epitopes due to overlapping position in three-dimensional space. Steric clash within GPCs may reduce the affinity between prodomains and growth factor domains, resulting in elevated ratios of free growth factor to latent growth factor. In some embodiments, one or more amino acids may be mutated in order to form recombinant GPCs with increased latency. Such mutations are referred to herein as "stabilizing mutations." These mutations may increase the affinity between prodomains and growth factor domains, resulting in decreased ratios of free growth factor to latent growth factor.

Recombinant growth differentiation factors (GDFs), activins and inhibins

[00213] Growth differentiation factors (GDFs), activins and inhibins are TGF-β family member proteins involved in a number of cellular and/or developmental activities. In some embodiments of the present disclosure, recombinant proteins may comprise one or more protein modules from one or more GDFs, activins and/or inhibins. In further embodiments, GDF protein modules may comprise GDF-8 and/or GDF-11 protein modules.

[00214] GDF-8 and GDF-11, which are secreted as latent complexes (Sengle et al., 2011. J Biol Chem. 286(7):5087-99; Ge et al., 2005. Mol Cel Biol. 25(14):5846-58), show conservation of the fastener residues (Lys 27 and Tyr 75 of TGF-β1). GDF-8 (also referred to herein as myostatin) is involved in regulating muscle mass, and its deficiency increases muscle mass in multiple species, including humans (Rodino-Klapac, L.R. et al., 2009. Muscle Nerve. 39(3):283-96). GDF-8 may be found in the circulation in latent form, but may also be stored in the extracellular matrix, bound to LTBP3 (Anderson et al., 2007. J Biol Chem. 283(11):7027-35) or perlecan (Sengle et al., 2011. J Biol Chem. 286(7):5087-99). While complexed with its prodomain, GDF-8 is unable to participate in receptor binding with the type II receptor, ActRIIB (Sengle et al., 2008. J Mol Biol. 381(4):1025-39). While GDF-8 is expressed primarily in muscle, GDF-11 expression is more systemic and its activity is thought to be involved in multiple processes (Lee et al., 2013. PNAS. 110(39):E3713-22). It is believed to be involved in development of multiple tissues, including, but not limited to the retina, kidney, pancreas and olfactory system. It is also believed to be a circulating factor in the blood. Recent studies indicate that GDF-11 may rejuvenate skeletal muscle, improve cerebral circulation and promote neurogenesis (Sinha, M. et al., 2014. Science. 344(6184):649-52 and Katsimpardi, L. et al., 2014. Science. 344(6184):630-4, the contents of each of which are herein incorporated by reference in their entirety). In some cases, antibodies of the disclosure may promote skeletal muscle rejuvenation, improve cerebral circulation and promote neurogenesis by promoting the release of GDF-11 growth factor from latent complexes. GDF-11 has also been identified as a regulator of erythropoiesis. In some cases, antibodies of the invation that inhibit GDF-11 may restore the ability of erythroid progenitors to differentiate and hence alleviate anemia (Paulson, RF. 2014. Nature Medicine. 20:334-5, the contents of which are herein incorporated by reference in their entirety).

[00215] GDF-8 and GDF-11 also share considerable homology. While the prodomains only share 48% homology, GDF-8 and GDF-11 growth factor domains share 90% homology (60% homology when prodomains and growth factors are taken together). Given the high degree of sequence similarity, it is not surprising that GDF-11 and 8 growth factors bind and signal through the same receptors consisting of a Type I receptor (ALK4/5) in association with a type II receptor (ACTRIIA/B). The high degree of conservation in the mature growth factors has made it challenging to identify reagents and monoclonal antibodies that can differentiate between mature GDF-11 and 8. Consequently, there are no therapies in clinical trials today that are specific for GDF-11.

[00216] Expressed proGDF proteins require furin cleavage in order to form latent complexes (see FIG. 9). In some cases, furin cleavage is carried out by cells in which proGDF proteins are expressed. In some cases, furin cleavage may be carried out through furin addition to cultures or solutions comprising proGDF proteins. Furin cleavage of recombinant proteins of the disclosure may in some cases occur intracellularly. In some cases furin cleavage of recombinant proteins of the disclosure may occur extracellularly. Release of GDF-8 and GDF-11 from latent GPCs requires activating cleavage of latent complexes. An activating cleavage refers to a proteolytic cleavage of a latent complex that leads to growth factor release and/or activation. Activating cleavage may include prodomain cleavage at a BMP/tolloid/tolloid-like proteinase cleavage site. Such sites may include the site located between Arg 75 and Asp 76 in GDF-8 and between Gly 97 and Asp 98 in GDF-11. This cleavage is between the 2 helix and the fastener.

[00217] In some embodiments, recombinant proteins of the present disclosure comprising GDFs may comprise sequences listed in Table 4 or fragments thereof. In some cases, these sequences are expressed in association with N- and/or C-terminal secretion signal sequences [e.g. human Ig kappa chains with amino acid sequence MDMRVPAQLLGLLLLWFSGVLG (SEQ ID NO: 66)], flag tag sequences [e.g. DYKDDDDK (SEQ ID NO: 67)], one or more 3C protease cleavage site [e.g. LEVLFQGP (SEQ ID NO: 68)], one or more biotinylation site and/or His-tag sequences [e.g. HHHHHH (SEQ ID NO: 69)].

Table 4. Recombinant GDFs

Protein	Sequence	SEQ ID NO
proGDF-8	NENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKIQILSKLRLE TAPNISKDVIRQLLPKAPPLRELIDQYDVQRDDSSDGSLEDDDY HATTETIITMPTESDFLMQVDGKPKCCFFKFSSKIQYNKVVKA QLWIYLRPVETPTTVFVQILRLIKPMKDGTRYTGIRSLKLDMNP GTGIWQSIDVKTVLQNWLKQPESNLGIEIKALDENGHDLAVTF PGPGEDGLNPFLEVKVTDTPKRSRRDFGLDCDEHSTESRCCRY PLTVDFEAFGWDWIIAPKRYKANYCSGECEFVFLQKYPHTHL VHQANPRGSAGPCCTPTKMSPINMLYFNGKEQIIYGKIPAMVV DRCGCS	5
GDF-8 prodomain	NENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKIQILSKLRLE TAPNISKDVIRQLLPKAPPLRELIDQYDVQRDDSSDGSLEDDDY HATTETIITMPTESDFLMQVDGKPKCCFFKFSSKIQYNKVVKA QLWIYLRPVETPTTVFVQILRLIKPMKDGTRYTGIRSLKLDMNP GTGIWQSIDVKTVLQNWLKQPESNLGIEIKALDENGHDLAVTF PGPGEDGLNPFLEVKVTDTPKRSRR	38
GDF-8 prodomain D76A	NENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKIQILSKLRLE TAPNISKDVIRQLLPKAPPLRELIDQYDVQRADSSDGSLEDDDY HATTETIITMPTESDFLMQVDGKPKCCFFKFSSKIQYNKVVKA	70

	QLWIYLRPVETPTTVFVQILRLIKPMKDGTRYTGIRSLKLDMNP GTGIWQSIDVKTVLQNWLKQPESNLGIEIKALDENGHDLAVTF PGPGEDGLNPFLEVKVTDTPKRSRR	
proGDF-8 AXXA	NENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKIQILSKLRLE TAPNISKDVIRQLLPKAPPLRELIDQYDVQRDDSSDGSLEDDDY HATTETIITMPTESDFLMQVDGKPKCCFFKFSSKIQYNKVVKA QLWIYLRPVETPTTVFVQILRLIKPMKDGTRYTGIRSLKLDMNP GTGIWQSIDVKTVLQNWLKQPESNLGIEIKALDENGHDLAVTF PGPGEDGLNPFLEVKVTDTPKASRADFGLDCDEHSTESRCCRY PLTVDFEAFGWDWIIAPKRYKANYCSGECEFVFLQKYPHTHL VHQANPRGSAGPCCTPTKMSPINMLYFNGKEQIIYGKIPAMVV DRCGCS	71
proGDF-8 D76A	NENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKIQILSKLRLE TAPNISKDVIRQLLPKAPPLRELIDQYDVQRADSSDGSLEDDDY HATTETIITMPTESDFLMQVDGKPKCCFFKFSSKIQYNKVVKA QLWIYLRPVETPTTVFVQILRLIKPMKDGTRYTGIRSLKLDMNP GTGIWQSIDVKTVLQNWLKQPESNLGIEIKALDENGHDLAVTF PGPGEDGLNPFLEVKVTDTPKRSRRDFGLDCDEHSTESRCCRY PLTVDFEAFGWDWIIAPKRYKANYCSGECEFVFLQKYPHTHL VHQANPRGSAGPCCTPTKMSPINMLYFNGKEQIIYGKIPAMVV DRCGCS	72
proGDF-8 AXXA D76A	NENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKIQILSKLRLE TAPNISKDVIRQLLPKAPPLRELIDQYDVQRADSSDGSLEDDDY HATTETIITMPTESDFLMQVDGKPKCCFFKFSSKIQYNKVVKA QLWIYLRPVETPTTVFVQILRLIKPMKDGTRYTGIRSLKLDMNP GTGIWQSIDVKTVLQNWLKQPESNLGIEIKALDENGHDLAVTF PGPGEDGLNPFLEVKVTDTPKASRADFGLDCDEHSTESRCCRY PLTVDFEAFGWDWIIAPKRYKANYCSGECEFVFLQKYPHTHL VHQANPRGSAGPCCTPTKMSPINMLYFNGKEQIIYGKIPAMVV DRCGCS	73
proGDF-11	AEGPAAAAAAAAAAAAAGVGGERSSRPAPSVAPEPDGCPVC VWRQHSRELRLESIKSQILSKLRLKEAPNISREVVKQLLPKAPP LQQILDLHDFQGDALQPEDFLEEDEYHATTETVISMAQETDPA VQTDGSPLCCHFHFSPKVMFTKVLKAQLWVYLRPVPRPATVY LQILRLKPLTGEGTAGGGGGGRRHIRIRSLKIELHSRSGHWQSI DFKQVLHSWFRQPQSNWGIEINAFDPSGTDLAVTSLGPGAEGL HPFMELRVLENTKRSRRNLGLDCDEHSSESRCCRYPLTVDFEA FGWDWIIAPKRYKANYCSGQCEYMFMQKYPHTHLVQQANPR GSAGPCCTPTKMSPINMLYFNDKQQIIYGKIPGMVVDRCGCS	4
proGDF-11 D98A	AEGPAAAAAAAAAAAAAGVGGERSSRPAPSVAPEPDGCPVC VWRQHSRELRLESIKSQILSKLRLKEAPNISREVVKQLLPKAPP LQQILDLHDFQGAALQPEDFLEEDEYHATTETVISMAQETDPA VQTDGSPLCCHFHFSPKVMFTKVLKAQLWVYLRPVPRPATVY LQILRLKPLTGEGTAGGGGGGRRHIRIRSLKIELHSRSGHWQSI DFKQVLHSWFRQPQSNWGIEINAFDPSGTDLAVTSLGPGAEGL HPFMELRVLENTKRSRRNLGLDCDEHSSESRCCRYPLTVDFEA FGWDWIIAPKRYKANYCSGQCEYMFMQKYPHTHLVQQANPR GSAGPCCTPTKMSPINMLYFNDKQQIIYGKIPGMVVDRCGCS	74
proGDF-11 D2G	AEGPAAAAAAAAAAAAAGVGGERSSRPAPSVAPEPDGCPVC VWRQHSRELRLESIKSQILSKLRLKEAPNISREVVKQLLPKAPP LQQILDLHDFQGDALQPEDFLEEDEYHATTETVISMAQETDPA VQTDGSPLCCHFHFSPKVMFTKVLKAQLWVYLRPVPRPATVY LQILRLKPLTGEGTAGGGGGGRRHIRIRSLKIELHSRSGHWQSI DFKQVLHSWFRQPQSNWGIEINAFDPSGTDLAVTSLGPGAEGL	75

	HPFMELRVLENTKRSGNLGLDCDEHSSESRCCRYPLTVDFEAF GWDWIIAPKRYKANYCSGQCEYMFMQKYPHTHLVQQANPRG SAGPCCTPTKMSPINMLYFNDKQQIIYGKIPGMVVDRCGCS	
proGDF-11 AxxA	AEGPAAAAAAAAAAAAAGVGGERSSRPAPSVAPEPDGCPVC VWRQHSRELRLESIKSQILSKLRLKEAPNISREVVKQLLPKAPP LQQILDLHDFQGDALQPEDFLEEDEYHATTETVISMAQETDPA VQTDGSPLCCHFHFSPKVMFTKVLKAQLWVYLRPVPRPATVY LQILRLKPLTGEGTAGGGGGGRRHIRIRSLKIELHSRSGHWQSI DFKQVLHSWFRQPQSNWGIEINAFDPSGTDLAVTSLGPGAEGL HPFMELRVLENTKASRANLGLDCDEHSSESRCCRYPLTVDFEA FGWDWIIAPKRYKANYCSGQCEYMFMQKYPHTHLVQQANPR GSAGPCCTPTKMSPINMLYFNDKQQIIYGKIPGMVVDRCGCS	76
proGDF-11 AxxA D98A	AEGPAAAAAAAAAAAAAGVGGERSSRPAPSVAPEPDGCPVC VWRQHSRELRLESIKSQILSKLRLKEAPNISREVVKQLLPKAPP LQQILDLHDFQGAALQPEDFLEEDEYHATTETVISMAQETDPA VQTDGSPLCCHFHFSPKVMFTKVLKAQLWVYLRPVPRPATVY LQILRLKPLTGEGTAGGGGGGRRHIRIRSLKIELHSRSGHWQSI DFKQVLHSWFRQPQSNWGIEINAFDPSGTDLAVTSLGPGAEGL HPFMELRVLENTKASRANLGLDCDEHSSESRCCRYPLTVDFEA FGWDWIIAPKRYKANYCSGQCEYMFMQKYPHTHLVQQANPR GSAGPCCTPTKMSPINMLYFNDKQQIIYGKIPGMVVDRCGCS	77
GDF-11 prodomain D98A	AEGPAAAAAAAAAAAAAGVGGERSSRPAPSVAPEPDGCPVC VWRQHSRELRLESIKSQILSKLRLKEAPNISREVVKQLLPKAPP LQQILDLHDFQGAALQPEDFLEEDEYHATTETVISMAQETDPA VQTDGSPLCCHFHFSPKVMFTKVLKAQLWVYLRPVPRPATVY LQILRLKPLTGEGTAGGGGGGRRHIRIRSLKIELHSRSGHWQSI DFKQVLHSWFRQPQSNWGIEINAFDPSGTDLAVTSLGPGAEGL HPFMELRVLENTKRSRR	78
GDF-11 prodomain	AEGPAAAAAAAAAAAAAGVGGERSSRPAPSVAPEPDGCPVC VWRQHSRELRLESIKSQILSKLRLKEAPNISREVVKQLLPKAPP LQQILDLHDFQGDALQPEDFLEEDEYHATTETVISMAQETDPA VQTDGSPLCCHFHFSPKVMFTKVLKAQLWVYLRPVPRPATVY LQILRLKPLTGEGTAGGGGGGRRHIRIRSLKIELHSRSGHWQSI DFKQVLHSWFRQPQSNWGIEINAFDPSGTDLAVTSLGPGAEGL HPFMELRVLENTKRSRR	39

[00218] Activins and inhibins are TGF-β family member proteins, the activity of each of which often results in opposing functions (Bilezikjian, L.M. et al., 2012. Mol Cell Endocrinol. 359(1-2): 43-52). Like other family members, these proteins occur physiologically as dimers. Activins and inhibins are constructed in part from the same β-subunits, that may include inhibin-beta A, inhibin-beta B, inhibin-beta C and inhibin-beta E (referred to herein as β-subunit A, B, C and E, respectively). The difference between activins and inhibins, structurally, is that activins are β-subunit dimers while inhibins are heterodimers, wherein the second subunit is inhibin-α. Activins are named for their subunit pairs, such that activin A comprises a homodimer of two A subunits, activin AB comprises a dimer of A and B subunits, B comprises a dimer of B subunits, etc. (Muenster, U. et al., 2011. Vitam Horm. 85: 105-28). Activins are involved in a variety of functions that may include,

but are not limited to cell growth, differentiation, programmed cell death, endocrine functions, cellular metabolism, bone growth, etc. They are especially recognized for their control of reproductive hormone cycles. Activin and inhibin signaling often functions antagonistically in this regard.

[00219] In some embodiments, recombinant proteins of the present disclosure may comprise integrins. Integrins are cell surface heterodimers formed by alpha and beta subunits, each of which has a transmembrane domain and in the N-terminal portion of the extracellular domain come together to form the ligand binding site. Recombinant proteins of the present disclosure may comprise integrins and/or integrin subunits. Such integrins and/or integrin subunits may comprise any of those disclosed in International Patent Application No. WO2014074532, the contents of which are herein incorporated by reference in their entirety.

[00220] Recombinant proteins of the disclosure may include intercellular adhesion molecule 1 (ICAM-1). In some cases, ICAM-1 proteins of the present disclosure may be used as control proteins during antibody development and/or antibody testing. In some cases, ICAM-1 may be used as a control during selection of binding molecules using phage display technologies. In some cases, ICAM-1 proteins of the disclosure comprise one or more detectable label. Detectable labels may include, for example, histidine tags.

[00221] In some embodiments, recombinant GPCs of the present disclosure may comprise mutations in one or more N-terminal regions for extracellular associations. As used herein, the term "N-terminal region for extracellular association" refers to regions at or near protein N-termini that may be necessary for extracellular associations with one or more N-terminal regions. Such regions may comprise at least the first N-terminal residue, at least the first 5 N-terminal residues, at least the first 10 N-terminal residues, at least the first 20 amino acid residues and/or at least the first 50 amino acid residues. Some mutations may comprise from about 1 amino acid residue to about 30 amino acid residues, from about 5 amino acid residues to about 40 amino acid residues and/or from about 10 amino acid residues to about 50 amino acid residues at or near protein N-termini. Such regions may comprise residues for association with extracellular proteins (e.g. LTBPs, fibrillins, GASPs, perlecan and/or decorin). In some cases, one or more cysteine residues present within and/or near N-terminal regions for extracellular associations may be necessary for such associations. In some embodiments, cysteine residues present within and/or near N-terminal regions for extracellular associations are present within about the first 5 N-terminal residues, about the first 10 N-terminal residues, about the first 20 N-terminal residues, about the first 50 N-terminal residues, about the first 60 N-terminal residues, about the first 70 N-terminal

residues and/or at least the first 100 N-terminal residues. Some mutations in one or more N-terminal regions for extracellular associations comprise substitution and/or deletion of such cysteine residues. Such mutations may modulate the association of GPCs and/or prodomains with one or more extracellular proteins, including, but not limited to LTBPs, fibrillins, GASPs, perlecan and/or decorin. These mutations may also comprise substitution of one or more cysteine with another amino acid. Cysteine residue substitutions are abbreviated herein as "C#X" wherein # represents the residue number [counting from the N-terminus of the pro-protein (without the signal peptide)] of the original cysteine residue and X represents the one letter amino acid code for the amino acid that is used for substitution. Any amino acid may be used for such substitutions. In some cases, serine (S) residues are used to substitute cysteine residues. Nonlimiting examples of such mutations in GDF-8 may include C16S, C19S, C38S and/or C41S.

[00222] In some cases, one or more cysteine in one or more other region of GPCs may be substituted or deleted. In some embodiments, such GPC modifications may promote the release of mature growth factor from prodomains. In some cases, such cysteines or other residues may include those present in one or more of mature growth factors, alpha 2 helices, fasteners, latency lassos and/or bow-tie regions.

[00223] In some embodiments, recombinant proteins of the present disclosure may comprise protein modules derived from one or more species, including mammals, including, but not limited to mice, rats, rabbits, pigs, monkeys and/or humans. Recombinant proteins may comprise one or more amino acids from one or more amino acid sequences derived from one or more non-human protein sequences listed in Table 5. In some cases, recombinant proteins of the present disclosure may comprise such sequences with or without the native signal peptide. In some cases, these sequences are expressed in association with N- and/or C-terminal secretion signal sequences [e.g. human Ig kappa chains with amino acid sequence MDMRVPAQLLGLLLLWFSGVLG (SEQ ID NO: 66)], flag tag sequences [e.g. DYKDDDDK (SEQ ID NO: 67)], one or more 3C protease cleavage site [e.g. LEVLFQGP (SEQ ID NO: 68)], one or more biotinylation site and/or His-tag sequences [e.g. HHHHHH (SEQ ID NO: 69)].

Table 5. Non-human proteins

Protein	Species	Sequence	SEQ ID NO
proTGF-β1	Mouse	LSTCKTIDMELVKRKRIEAIRGQILSKLRLASPPSQGEVPP GPLPEAVLALYNSTRDRVAGESADPEPEPEADYYAKEV	79

		TRVLMVDRNNAIYEKTKDISHSIYMFFNTSDIREAVPEPP LLSRAELRLQRLKSSVEQHVELYQKYSNNSWRYLGNRL LTPTDTPEWLSFDVTGVVRQWLNQGDGIQGFRFSAHCS CDSKDNKLHVEINGISPKRRGDLGTIHDMNRPFLLLMAT PLERAQHLHSSRHRRALDTNYCFSSTEKNCCVRQLYIDF RKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVL ALYNQHNPGASASPCCVPQALEPLPIVYYVGRKPKVEQ LSNMIVRSCKCS	
proTGF-β1	Cyno	LSTCKTIDMELVKRKRIEAIRGQILSKLRLASPPSQGEVPP GPLPEAVLALYNSTRDRVAGESAEPEPEPEADYYAKEVT RVLMVETHNEIYDKFKQSTHSIYMFFNTSELREAVPEPV LLSRAELRLLRLKLKVEQHVELYQKYSNNSWRYLSNRL LAPSDSPEWLSFDVTGVVRQWLSRGGEIEGFRLSAHCSC DSKDNTLQVDINGFTTGRRGDLATIHGMNRPFLLLMAT PLERAQHLQSSRHRRALDTNYCFSSTEKNCCVRQLYIDF RKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVL ALYNQHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQ LSNMIVRSCKCS	80
TGF-β1 LAP C4S	Mouse	LSTSKTIDMELVKRKRIEAIRGQILSKLRLASPPSQGEVPP GPLPEAVLALYNSTRDRVAGESADPEPEPEADYYAKEV TRVLMVDRNNAIYEKTKDISHSIYMFFNTSDIREAVPEPP LLSRAELRLQRLKSSVEQHVELYQKYSNNSWRYLGNRL LTPTDTPEWLSFDVTGVVRQWLNQGDGIQGFRFSAHCS CDSKDNKLHVEINGISPKRRGDLGTIHDMNRPFLLLMAT PLERAQHLHSSRHRR	81
TGF-β1 LAP C4S	Cyno	LSTSKTIDMELVKRKRIEAIRGQILSKLRLASPPSQGEVPP GPLPEAVLALYNSTRDRVAGESAEPEPEPEADYYAKEVT RVLMVETHNEIYDKFKQSTHSIYMFFNTSELREAVPEPV LLSRAELRLLRLKLKVEQHVELYQKYSNNSWRYLSNRL LAPSDSPEWLSFDVTGVVRQWLSRGGEIEGFRLSAHCSC DSKDNTLQVDINGFTTGRRGDLATIHGMNRPFLLLMAT PLERAQHLQSSRHRR	82
proTGF-β1 C4S D2G	Mouse	LSTSKTIDMELVKRKRIEAIRGQILSKLRLASPPSQGEVPP GPLPEAVLALYNSTRDRVAGESADPEPEPEADYYAKEV TRVLMVDRNNAIYEKTKDISHSIYMFFNTSDIREAVPEPP LLSRAELRLQRLKSSVEQHVELYQKYSNNSWRYLGNRL LTPTDTPEWLSFDVTGVVRQWLNQGDGIQGFRFSAHCS CDSKDNKLHVEINGISPKRRGDLGTIHDMNRPFLLLMAT PLERAQHLHSSRHGALDTNYCFSSTEKNCCVRQLYIDFR KDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLA LYNQHNPGASASPCCVPQALEPLPIVYYVGRKPKVEQLS NMIVRSCKCS	83
proTGF-β1 C4S	Mouse	LSTSKTIDMELVKRKRIEAIRGQILSKLRLASPPSQGEVPP GPLPEAVLALYNSTRDRVAGESADPEPEPEADYYAKEV TRVLMVDRNNAIYEKTKDISHSIYMFFNTSDIREAVPEPP LLSRAELRLQRLKSSVEQHVELYQKYSNNSWRYLGNRL LTPTDTPEWLSFDVTGVVRQWLNQGDGIQGFRFSAHCS CDSKDNKLHVEINGISPKRRGDLGTIHDMNRPFLLLMAT PLERAQHLHSSRHRRALDTNYCFSSTEKNCCVRQLYIDF RKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVL ALYNQHNPGASASPCCVPQALEPLPIVYYVGRKPKVEQ LSNMIVRSCKCS	84
proTGF-β1 C4S	Cyno	LSTSKTIDMELVKRKRIEAIRGQILSKLRLASPPSQGEVPP GPLPEAVLALYNSTRDRVAGESAEPEPEPEADYYAKEVT	85

		RVLMVETHNEIYDKFKQSTHSIYMFFNTSELREAVPEPV LLSRAELRLLRLKLKVEQHVELYQKYSNNSWRYLSNRL LAPSDSPEWLSFDVTGVVRQWLSRGGEIEGFRLSAHCSC DSKDNTLQVDINGFTTGRRGDLATIHGMNRPFLLLMAT PLERAQHLQSSRHRRALDTNYCFSSTEKNCCVRQLYIDF RKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVL ALYNQHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQ LSNMIVRSCKCS	
proTGF-β1 C4S D2G	Cyno	LSTSKTIDMELVKRKRIEAIRGQILSKLRLASPPSQGEVPP GPLPEAVLALYNSTRDRVAGESAEPEPEPEADYYAKEVT RVLMVETHNEIYDKFKQSTHSIYMFFNTSELREAVPEPV LLSRAELRLLRLKLKVEQHVELYQKYSNNSWRYLSNRL LAPSDSPEWLSFDVTGVVRQWLSRGGEIEGFRLSAHCSC DSKDNTLQVDINGFTTGRRGDLATIHGMNRPFLLLMAT PLERAQHLQSSRHGALDTNYCFSSTEKNCCVRQLYIDFR KDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLA LYNQHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQL SNMIVRSCKCS	86
LRRC32	Cyno	AQHQDKVACKMVDKKVSCQGLGLLQVPLVLPPDTETL DLSGNQLRSILASPLGFYTALRHLDLSTNEINFLQPGAFQ ALTHLEHLSLAHNRLAMATALSAGGLGPLPRVTSLDLS GNSLYSGLLERLLGEAPSLHTLSLAENSLTRLTRHTFRD MPALEQLDLHSNVLMDIEDGAFEGLPHLTHLNLSRNSLT CISDFSLQQLRVLDLSCNSIEAFQTASQPQAEFQLTWLDL RENKLLHFPDLAALPRLIYLNLSNNLIRLPTGPPQDSKGI HAPSEGWSALPLSTPNGNVSARPLSQLLNLDLSYNEIELI PDSFLEHLTSLCFLNLSRNCLRTFEARRSGSLPCLMLLDL SHNALETLELGARALGSLRTLLLQGNALRDLPPYTFANL ASLQRLNLQGNRVSPCGGPNEPGPASCVAFSGIASLRSLS LVDNEIELLRAGAFLHTPLTELDLSSNPGLEVATGALTGL EASLEVLALQGNGLTVLQVDLPCFICLKRLNLAENRLSH LPAWTQAVSLEVLDLRNNSFSLLPGSAMGGLETSLRRL YLQGNPLSCCGNGWLAAQLHQGRVDVDATQDLICRFSS QEEVSLSHVRPEDCEKGGLKNINLIIILTFILVSAILLTTLA TCCCVRRQKFNQQYKA	87
proGDF-8	Mouse	NEGSEREENVEKEGLCNACAWRQNTRYSRIEAIKIQILS KLRLETAPNISKDAIRQLLPRAPPLRELIDQYDVQRDDSS DGSLEDDDYHATTETIITMPTESDFLMQADGKPKCCFFK FSSKIQYNKVVKAQLWIYLRPVKTPTTVFVQILRLIKPM KDGTRYTGIRSLKLDMSPGTGIWQSIDVKTVLQNWLKQ PESNLGIEIKALDENGHDLAVTFPGPGEDGLNPFLEVKV TDTPKRSRRDFGLDCDEHSTESRCCRYPLTVDFEAFGW DWIIAPKRYKANYCSGECEFVFLQKYPHTHLVHQANPR GSAGPCCTPTKMSPINMLYFNGKEQIIYGKIPAMVVDRC GCS	88
proGDF-8 AxxA	Mouse	NEGSEREENVEKEGLCNACAWRQNTRYSRIEAIKIQILS KLRLETAPNISKDAIRQLLPRAPPLRELIDQYDVQRDDSS DGSLEDDDYHATTETIITMPTESDFLMQADGKPKCCFFK FSSKIQYNKVVKAQLWIYLRPVKTPTTVFVQILRLIKPM KDGTRYTGIRSLKLDMSPGTGIWQSIDVKTVLQNWLKQ PESNLGIEIKALDENGHDLAVTFPGPGEDGLNPFLEVKV TDTPKASRADFGLDCDEHSTESRCCRYPLTVDFEAFGW DWIIAPKRYKANYCSGECEFVFLQKYPHTHLVHQANPR GSAGPCCTPTKMSPINMLYFNGKEQIIYGKIPAMVVDRC	89

		GCS	
proGDF-8 D76A	Mouse	NEGSEREENVEKEGLCNACAWRQNTRYSRIEAIKIQILS KLRLETAPNISKDAIRQLLPRAPPLRELIDQYDVQRADSS DGSLEDDDYHATTETIITMPTESDFLMQADGKPKCCFFK FSSKIQYNKVVKAQLWIYLRPVKTPTTVFVQILRLIKPM KDGTRYTGIRSLKLDMSPGTGIWQSIDVKTVLQNWLKQ PESNLGIEIKALDENGHDLAVTFPGPGEDGLNPFLEVKV TDTPKRSRRDFGLDCDEHSTESRCCRYPLTVDFEAFGW DWIIAPKRYKANYCSGECEFVFLQKYPHTHLVHQANPR GSAGPCCTPTKMSPINMLYFNGKEQIIYGKIPAMVVDRC GCS	90
proGDF-8 AxxA D76A	Mouse	NEGSEREENVEKEGLCNACAWRQNTRYSRIEAIKIQILS KLRLETAPNISKDAIRQLLPRAPPLRELIDQYDVQRADSS DGSLEDDDYHATTETIITMPTESDFLMQADGKPKCCFFK FSSKIQYNKVVKAQLWIYLRPVKTPTTVFVQILRLIKPM KDGTRYTGIRSLKLDMSPGTGIWQSIDVKTVLQNWLKQ PESNLGIEIKALDENGHDLAVTFPGPGEDGLNPFLEVKV TDTPKASRADFGLDCDEHSTESRCCRYPLTVDFEAFGW DWIIAPKRYKANYCSGECEFVFLQKYPHTHLVHQANPR GSAGPCCTPTKMSPINMLYFNGKEQIIYGKIPAMVVDRC GCS	91
GDF-8 prodomain	Mouse	NEGSEREENVEKEGLCNACAWRQNTRYSRIEAIKIQILS KLRLETAPNISKDAIRQLLPRAPPLRELIDQYDVQRDDSS DGSLEDDDYHATTETIITMPTESDFLMQADGKPKCCFFK FSSKIQYNKVVKAQLWIYLRPVKTPTTVFVQILRLIKPM KDGTRYTGIRSLKLDMSPGTGIWQSIDVKTVLQNWLKQ PESNLGIEIKALDENGHDLAVTFPGPGEDGLNPFLEVKV TDTPKRSRR	92
GDF-8 prodomain D76A	Mouse	NEGSEREENVEKEGLCNACAWRQNTRYSRIEAIKIQILS KLRLETAPNISKDAIRQLLPRAPPLRELIDQYDVQRADSS DGSLEDDDYHATTETIITMPTESDFLMQADGKPKCCFFK FSSKIQYNKVVKAQLWIYLRPVKTPTTVFVQILRLIKPM KDGTRYTGIRSLKLDMSPGTGIWQSIDVKTVLQNWLKQ PESNLGIEIKALDENGHDLAVTFPGPGEDGLNPFLEVKV TDTPKRSRR	93
proGDF-8	Cyno	NENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKIQILSK LRLETAPNISKDAIRQLLPKAPPLRELIDQYDVQRDDSSD GSLEDDDYHATTETIITMPTESDFLMQVDGKPKCCFFKF SSKIQYNKVVKAQLWIYLRPVETPTTVFVQILRLIKPMK DGTRYTGIRSLKLDMNPGTGIWQSIDVKTVLQNWLKQP ESNLGIEIKALDENGHDLAVTFPGPGEDGLNPFLEVKVT DTPKRSRRDFGLDCDEHSTESRCCRYPLTVDFEAFGWD WIIAPKRYKANYCSGECEFVFLQKYPHTHLVHQANPRG SAGPCCTPTKMSPINMLYFNGKEQIIYGKIPAMVVDRCG CS	94
proGDF-8 AxxA	Cyno	NENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKIQILSK LRLETAPNISKDAIRQLLPKAPPLRELIDQYDVQRDDSSD GSLEDDDYHATTETIITMPTESDFLMQVDGKPKCCFFKF SSKIQYNKVVKAQLWIYLRPVETPTTVFVQILRLIKPMK DGTRYTGIRSLKLDMNPGTGIWQSIDVKTVLQNWLKQP ESNLGIEIKALDENGHDLAVTFPGPGEDGLNPFLEVKVT DTPKASRADFGLDCDEHSTESRCCRYPLTVDFEAFGWD WIIAPKRYKANYCSGECEFVFLQKYPHTHLVHQANPRG SAGPCCTPTKMSPINMLYFNGKEQIIYGKIPAMVVDRCG	95

		CS	
proGDF-8 D76A	Cyno	NENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKIQILSK LRLETAPNISKDAIRQLLPKAPPLRELIDQYDVQRADSSD GSLEDDDYHATTETIITMPTESDFLMQVDGKPKCCFFKF SSKIQYNKVVKAQLWIYLRPVETPTTVFVQILRLIKPMK DGTRYTGIRSLKLDMNPGTGIWQSIDVKTVLQNWLKQP ESNLGIEIKALDENGHDLAVTFPGPGEDGLNPFLEVKVT DTPKRSRRDFGLDCDEHSTESRCCRYPLTVDFEAFGWD WIIAPKRYKANYCSGECEFVFLQKYPHTHLVHQANPRG SAGPCCTPTKMSPINMLYFNGKEQIIYGKIPAMVVDRCG CS	96
proGDF-8 AxxA D76A	Cyno	NENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKIQILSK LRLETAPNISKDAIRQLLPKAPPLRELIDQYDVQRADSSD GSLEDDDYHATTETIITMPTESDFLMQVDGKPKCCFFKF SSKIQYNKVVKAQLWIYLRPVETPTTVFVQILRLIKPMK DGTRYTGIRSLKLDMNPGTGIWQSIDVKTVLQNWLKQP ESNLGIEIKALDENGHDLAVTFPGPGEDGLNPFLEVKVT DTPKASRADFGLDCDEHSTESRCCRYPLTVDFEAFGWD WIIAPKRYKANYCSGECEFVFLQKYPHTHLVHQANPRG SAGPCCTPTKMSPINMLYFNGKEQIIYGKIPAMVVDRCG CS	97
GDF-8 prodomain	Cyno	NENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKIQILSK LRLETAPNISKDAIRQLLPKAPPLRELIDQYDVQRDDSSD GSLEDDDYHATTETIITMPTESDFLMQVDGKPKCCFFKF SSKIQYNKVVKAQLWIYLRPVETPTTVFVQILRLIKPMK DGTRYTGIRSLKLDMNPGTGIWQSIDVKTVLQNWLKQP ESNLGIEIKALDENGHDLAVTFPGPGEDGLNPFLEVKVT DTPKRSRR	98
GDF-8 prodomain D76A	Cyno	NENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKIQILSK LRLETAPNISKDAIRQLLPKAPPLRELIDQYDVQRADSSD GSLEDDDYHATTETIITMPTESDFLMQVDGKPKCCFFKF SSKIQYNKVVKAQLWIYLRPVETPTTVFVQILRLIKPMK DGTRYTGIRSLKLDMNPGTGIWQSIDVKTVLQNWLKQP ESNLGIEIKALDENGHDLAVTFPGPGEDGLNPFLEVKVT DTPKRSRR	99
proGDF-11	Mouse	AEGPAAAAAAAAAAAGVGGERSSRPAPSAPPEPDGCPV CVWRQHSRELRLESIKSQILSKLRLKEAPNISREVVKQLL PKAPPLQQILDLHDFQGDALQPEDFLEEDEYHATTETVIS MAQETDPAVQTDGSPLCCHFHFSPKVMFTKVLKAQLW VYLRPVPRPATVYLQILRLKPLTGEGTAGGGGGGRRHIR IRSLKIELHSRSGHWQSIDFKQVLHSWFRQPQSNWGIEIN AFDPSGTDLAVTSLGPGAEGLHPFMELRVLENTKRSRRN LGLDCDEHSSESRCCRYPLTVDFEAFGWDWIIAPKRYKA NYCSGQCEYMFMQKYPHTHLVQQANPRGSAGPCCTPT KMSPINMLYFNDKQQIIYGKIPGMVVDRCGCS	100
proGDF-11 AxxA	Mouse	AEGPAAAAAAAAAAAGVGGERSSRPAPSAPPEPDGCPV CVWRQHSRELRLESIKSQILSKLRLKEAPNISREVVKQLL PKAPPLQQILDLHDFQGDALQPEDFLEEDEYHATTETVIS MAQETDPAVQTDGSPLCCHFHFSPKVMFTKVLKAQLW VYLRPVPRPATVYLQILRLKPLTGEGTAGGGGGGRRHIR IRSLKIELHSRSGHWQSIDFKQVLHSWFRQPQSNWGIEIN AFDPSGTDLAVTSLGPGAEGLHPFMELRVLENTKASRA NLGLDCDEHSSESRCCRYPLTVDFEAFGWDWIIAPKRYK ANYCSGQCEYMFMQKYPHTHLVQQANPRGSAGPCCTP	101

		TKMSPINMLYFNDKQQIIYGKIPGMVVDRCGCS	
proGDF-11 AxxA D96A	Mouse	AEGPAAAAAAAAAAAGVGGERSSRPAPSAPPEPDGCPV CVWRQHSRELRLESIKSQILSKLRLKEAPNISREVVKQLL PKAPPLQQILDLHDFQGAALQPEDFLEEDEYHATTETVIS MAQETDPAVQTDGSPLCCHFHFSPKVMFTKVLKAQLW VYLRPVPRPATVYLQILRLKPLTGEGTAGGGGGGRRHIR IRSLKIELHSRSGHWQSIDFKQVLHSWFRQPQSNWGIEIN AFDPSGTDLAVTSLGPGAEGLHPFMELRVLENTKASRA NLGLDCDEHSSESRCCRYPLTVDFEAFGWDWIIAPKRYK ANYCSGQCEYMFMQKYPHTHLVQQANPRGSAGPCCTP TKMSPINMLYFNDKQQIIYGKIPGMVVDRCGCS	102
proGDF-11 D96A	Mouse	AEGPAAAAAAAAAAAGVGGERSSRPAPSAPPEPDGCPV CVWRQHSRELRLESIKSQILSKLRLKEAPNISREVVKQLL PKAPPLQQILDLHDFQGDALQPEDFLEEDEYHATTETVIS MAQETDPAVQTDGSPLCCHFHFSPKVMFTKVLKAQLW VYLRPVPRPATVYLQILRLKPLTGEGTAGGGGGGRRHIR IRSLKIELHSRSGHWQSIDFKQVLHSWFRQPQSNWGIEIN AFDPSGTDLAVTSLGPGAEGLHPFMELRVLENTKRSRRN LGLDCDEHSSESRCCRYPLTVDFEAFGWDWIIAPKRYKA NYCSGQCEYMFMQKYPHTHLVQQANPRGSAGPCCTPT KMSPINMLYFNDKQQIIYGKIPGMVVDRCGCS	103
GDF-11 prodomain	Mouse	AEGPAAAAAAAAAAAGVGGERSSRPAPSAPPEPDGCPV CVWRQHSRELRLESIKSQILSKLRLKEAPNISREVVKQLL PKAPPLQQILDLHDFQGDALQPEDFLEEDEYHATTETVIS MAQETDPAVQTDGSPLCCHFHFSPKVMFTKVLKAQLW VYLRPVPRPATVYLQILRLKPLTGEGTAGGGGGGRRHIR IRSLKIELHSRSGHWQSIDFKQVLHSWFRQPQSNWGIEIN AFDPSGTDLAVTSLGPGAEGLHPFMELRVLENTKRSRR	104
GDF-11 prodomain D96A	Mouse	AEGPAAAAAAAAAAAGVGGERSSRPAPSAPPEPDGCPV CVWRQHSRELRLESIKSQILSKLRLKEAPNISREVVKQLL PKAPPLQQILDLHDFQGAALQPEDFLEEDEYHATTETVIS MAQETDPAVQTDGSPLCCHFHFSPKVMFTKVLKAQLW VYLRPVPRPATVYLQILRLKPLTGEGTAGGGGGGRRHIR IRSLKIELHSRSGHWQSIDFKQVLHSWFRQPQSNWGIEIN AFDPSGTDLAVTSLGPGAEGLHPFMELRVLENTKRSRR	105
LTBP3	CYNO	GPAGERGAGGGGALARERFKVVFAPVICKRTCLKGQCR DSCQQGSNMTLIGENGHSTDTLTGSGFRVVVCPLPCMN GGQCSSRNQCLCPPDFTGRFCQVPAGGAGGGTGGSGPG LSRAGALSTGALPPLAPEGDSVASKHAIYAVQVIADPPG PGEGPPAQHAAFLVPLGPGQISAEVQAPPPVVNVRVHHP PEASVQVHRIESSNAEGAAPSQHLLPHPKPSHPRPPTQKP LGRCFQDTLPKQPCGSNPLPGLTKQEDCCGSIGTAWGQS KCHKCPQLQYTGVQKPGPVRGEVGADCPQGYKRLNST HCQDINECAMPGVCRHGDCLNNPGSYRCVCPPGHSLGP SRTQCIADKPEEKSLCFRLVSPEHQCQHPLTTRLTRQLCC CSVGKAWGARCQRCPADGTAAFKEICPAGKGYHILTSH QTLTIQGESDFSLFLHPDGPPKPQQLPESPSQAPPPEDTEE ERGVTTDSPVSEERSVQQSHPTATTSPARPYPELISRPSPP TMRWFLPDLPPSRSAVEIAPTQVTETDECRLNQNICGHG ECVPGPPDYSCHCNPGYRSHPQHRYCVDVNECEAEPCG PGRGICMNTGGSYNCHCNRGYRLHVGAGGRSCVDLNE CAKPHLCGDGGFCINFPGHYKCNCYPGYRLKASRPPVC EDIDECRDPSSCPDGKCENKPGSFKCIACQPGYRSQGGG ACRDVNECAEGSPCSPGWCENLPGSFRCTCAQGYAPAP	106

		DGRSCVDVDECEAGDVCDNGICTNTPGSFQCQCLSGYH LSRDRSHCEDIDECDFPAACIGGDCINTNGSYRCLCPQG HRLVGGRKCQDIDECTQDPGLCLPHGACKNLQGSYVCV CDEGFTPTQDQHGCEEVEQPHHKKECYLNFDDTVFCDS VLATNVTQQECCCSLGAGWGDHCEIYPCPVYSSAEFHS LCPDGKGYTQDNNIVNYGIPAHRDIDECMLFGAEICKEG KCVNTQPGYECYCKQGFYYDGNLLECVDVDECLDESN CRNGVCENTRGGYRCACTPPAEYSPAQRQCLSPEEMDV DECQDPAACRPGRCVNLPGSYRCECRPPWVPGPSGRDC QLPESPAERAPERRDVCWSQRGEDGMCAGPQAGPALTF DDCCCRQGRGWGAQCRPCPPRGAGSQCPTSQSESNSFW DTSPLLLGKPRRDEDSSEEDSDECRCVSGRCVPRPGGAV CECPGGFQLDASRARCVDIDECRELNQRGLLCKSERCV NTSGSFRCVCKAGFARSRPHGACVPQRRR	
LTBP3	Mouse	GPAGERGTGGGGALARERFKVVFAPVICKRTCLKGQCR DSCQQGSNMTLIGENGHSTDTLTGSAFRVVVCPLPCMN GGQCSSRNQCLCPPDFTGRFCQVPAAGTGAGTGSSGPG LARTGAMSTGPLPPLAPEGESVASKHAIYAVQVIADPPG PGEGPPAQHAAFLVPLGPGQISAEVQAPPPVVNVRVHHP PEASVQVHRIEGPNAEGPASSQHLLPHPKPPHPRPPTQKP LGRCFQDTLPKQPCGSNPLPGLTKQEDCCGSIGTAWGQS KCHKCPQLQYTGVQKPVPVRGEVGADCPQGYKRLNST HCQDINECAMPGNVCHGDCLNNPGSYRCVCPPGHSLGP LAAQCIADKPEEKSLCFRLVSTEHQCQHPLTTRLTRQLC CCSVGKAWGARCQRCPADGTAAFKEICPGKGYHILTSH QTLTIQGESDFSLFLHPDGPPKPQQLPESPSRAPPLEDTEE ERGVTMDPPVSEERSVQQSHPTTTTSPPRPYPELISRPSPP TFHRFLPDLPPSRSAVEIAPTQVTETDECRLNQNICGHGQ CVPGPSDYSCHCNAGYRSHPQHRYCVDVNECEAEPCGP GKGICMNTGGSYNCHCNRGYRLHVGAGGRSCVDLNEC AKPHLCGDGGFCINFPGHYKCNCYPGYRLKASRPPICED IDECRDPSTCPDGKCENKPGSFKCIACQPGYRSQGGGAC RDVNECSEGTPCSPGWCENLPGSYRCTCAQYEPAQDGL SCIDVDECEAGKVCQDGICTNTPGSFQCQCLSGYHLSRD RSRCEDIDECDFPAACIGGDCINTNGSYRCLCPLGHRLV GGRKCKKDIDECSQDPGLCLPHACENLQGSYVCVCDEG FTLTQDQHGCEEVEQPHHKKECYLNFDDTVFCDSVLAT NVTQQECCCSLGAGWGDHCEIYPCPVYSSAEFHSLVPD GKRLHSGQQHCELCIPAHRDIDECILFGAEICKEGKCVNT QPGYECYCKQGFYYDGNLLECVDVDECLDESNCRNGV CENTRGGYRCACTPPAEYSPAQAQCLIPERWSTPQRDV KCAGASEERTACVWGPWAGPALTFDDCCCRQPRLGTQ CRPCPPRGTGSQCPTSQSESNSFWDTSPLLLGKSPRDEDS SEEDSDECRCVSGRCVPRPGGAVCECPGGFQLDASRAR CVDIDECRELNQRGLLCKSERCVNTSGSFRCVCKAGFTR SRPHGPACLSAAADDAAIAHTSVIDHRGYFH	107
LTBP1S	Cyno	NHTGRIKVVFTPSICKVTCTKGSCQNSCEKGNTTTLISEN GHAADTLTATNFRVVLCHLPCMNGGQCSSRDKCQCPPN FTGKLCQIPVHGASVPKLYQHSQQPGKALGTHVIHSTHT LPLTVTSQQGVKVKFPPNIVNIHVKHPPEASVQIHQVSRI DGPTGQKTKEAQPGQSQVSYQGLPVQKTQTIHSTYSHQ QVIPHVYPVAAKTQLGRCFQETIGSQCGKALPGLSKQED CCGTVGTSWGFNKCQKCPKKPSYHGYNQMMECLPGYK RVNNTFCQDINECQLQGVCPNGECLNTMGSYRCTCKIG FGPDPTFSSCVPDPPVISEEKGPCYRLVSSGRQCMHPLSV	108

		HLTKQLCCCSVGKAWGPHCEKCPLPGTAAFKEICPGGM GYTVSGVHRRRPIHHHVGKGPVFVKPKNTQPVAKSTHP PPLPAKEEPVEALTFSREHGPGVAEPEVATAPPEKEIPSL DQEKTKLEPGQPQLSPGISTIHLHPQFPVVIEKTSPPVPVE VAPEASTSSASQVIAPTQVTEINECTVNPDICGAGHCINL PVRYTCICYEGYKFSEQQRKCVDIDECTQVQHLCSQGRC ENTEGSFLCICPAGFMASEEGTNCIDVDECLRPDVCGEG HCVNTVGAFRCEYCDSGYRMTQRGRCEDIDECLNPSTC PDEQCVNSPGSYQCVPCTEGFRGWNGQCLDVDECLEPN VCTNGDCSNLEGSYMCSCHKGYTRTPDHKHCKDIDECQ QGNLCVNGQCKNTEGSFRCTCGQGYQLSAAKDQCEDID ECQHHHLCAHGQCRNTEGSFQCVCDQGYRASGLGDHC EDINECLEDKSVCQRGDCINTAGSYDCTCPDGFQLDDN KTCQDINECEHPGLCGPQGECLNTEGSFHCVCQQGFSIS ADGRTCEDIDECVNNTVCDSHGFCDNTAGSFRCLCYQG FQAPQDGQGCVDVNECELLSGVCGEAFCENVEGSFLCV CADENQEYSPMTGQCRSRTSTDLDVEQPKEEKKECYYN LNDASLCDNVLAPNVTKQECCCTSGAGWGDNCEIFPCP VLGTAEFTEMCPKGKGFVPAGESSSEAGGENYKDADEC LLFGQEICKNGFCLNTRPGYECYCKQGTYYDPVKLQCF DMDECQDPSSCIDGQCVNTEGSYNCFCTHPMVLDASEK RCIRPAESNEQIEETDVYQDLCWEHLSDEYVCSRPLVGK QTTYTECCCLYGEAWGMQCALCPMKDSDDYAQLCNIP VTGRRQPYGRDALVDFSEQYAPEADPYFIQDRFLNSFEE LQAEECGILNGCENGRCVRVQEGYTCDCFDGYHLDTAK MTCVDVNECDELNNRMSLCKNAKCINTEGSYKCLCLPG YVPSDKPNYCTPLNTALNLEKDSDLE	
LTBP1S	mouse	NHTGRIKVVFTPSICKVTCTKGNCQNSCQKGNTTTLISE NGHAADTLTATNFRVVICHLPCMNGGQCSSRDKCQCPP NFTGKLCQIPVLGASMPKLYQHAQQQGKALGSHVIHST HTLPLTMTSQQGVKVKFPPNIVNIHVKHPPEASVQIHQV SRIDSPGGQKVKEAQPGQSQVSYQGLPVQKTQTVHSTY SHQQLIPHVYPVAAKTQLGRCFQETIGSQCGKALPGLSK QEDCCGTVGTSWGFNKCQKCPKKQSYHGYTQMMECL QGYKRVNNTFCQDINECQLQGVCPNGECLNTMGSYRCS CKMGFGPDPTFSSCVPDPPVISEEKGPCYRLVSPGRHCM HPLSVHLTKQICCCSVGKAWGPHCEKCPLPGTAAFKEIC PGGMGYTVSGVHRRRPIHQHIGKEAVYVKPKNTQPVAK STHPPPLPAKEEPVEALTSSWEHGPRGAEPEVVTAPPEK EIPSLDQEKTRLEPGQPQLSPGVSTIHLHPQFPVVVEKTSP PVPVEVAPEASTSSASQVIAPTQVTEINECTVNPDICGAG HCINLPVRYTCICYEGYKFSEQLRKCVDIDECAQVRHLC SQGRCENTEGSFLCVCPAGFMASEEGTNCIDVDECLRPD MCRDGRCINTAGAFRCEYCDSGYRMSRRGYCEDIDECL KPSTCPEEQCVNTPGSYQCVPCTEGFRGWNGQCLDVDE CLQPKVCTNGSCTNLEGSYMCSCHRGYSPTPDHRHCQD IDECQQGNLCMNGQCRNTDGSFRCTCGQGYQLSAAKD QCEDIDECEHHHLCSHGQCRNTEGSFQCVCNQGYRASV LGDHCEDINECLEDSSVCQGGDCINTAGSYDCTCPDGFQ LNDNKGCQDINECAQPGLCGSHGECLNTQGSFHCVCEQ GFSISADGRTCEDIDECVNNTVCDSHGFCDNTAGSFRCL CYQGFQAPQDGQGCVDVNECELLSGVCGEAFCENVEGS FLCVCADENQEYSPMTGQCRSRVTEDSGVDRQPREEKK ECYYNLNDASLCDNVLAPNVTKQECCCTSGAGWGDNC EIFPCPVQGTAEFTEMCPRGKGLVPAGESSYDTGGENYK	109

		DADECLLFGEEICKNGYCLNTQPGYECYCKQGTYYDPV KLQCFDMDECQDPNSCIDGQCVNTEGSYNCFCTHPMVL DASEKRCVQPTESNEQIEETDVYQDLCWEHLSEEYVCSR PLVGKQTTYTECCCLYGEAWGMQCALCPMKDSDDYA QLCNIPVTGRRRPYGRDALVDFSEQYGPETDPYFIQDRF LNSFEELQAEECGILNGCENGRCVRVQEGYTCDCFDGY HLDMAKMTCVDVNECSELNNRMSLCKNAKCINTEGSY KCLCLPGYIPSDKPNYCTPLNSALNLDKESDLE	
GARP	mouse	ISQRREQVPCRTVNKEALCHGLGLLQVPSVLSLDIQALY LSGNQLQSILVSPLGFYTALRHLDLSDNQISFLQAGVFQA LPYLEHLNLAHNRLATGMALNSGGLGRLPLLVSLDLSG NSLHGNLVERLLGETPRLRTLSLAENSLTRLARHTFWG MPAVEQLDLHSNVLMDIEDGAFEALPHLTHLNLSRNSL TCISDFSLQQLQVLDLSCNSIEAFQTAPEPQAQFQLAWL DLRENKLLHFPDLAVFPRLIYLNVSNNLIQLPAGLPRGSE DLHAPSEGWSASPLSNPSRNASTHPLSQLLNLDLSYNEIE LVPASFLEHLTSLRFLNLSRNCLRSFEARQVDSLPCLVLL DLSHNVLEALELGTKVLGSLQTLLLQDNALQELPPYTFA SLASLQRLNLQGNQVSPCGGPAEPGPPGCVDFSGIPTLH VLNMAGNSMGMLRAGSFLHTPLTELDLSTNPGLDVATG ALVGLEASLEVLELQGNGLTVLRVDLPCFLRLKRLNLAE NQLSHLPAWTRAVSLEVLDLRNNSFSLLPGNAMGGLET SLRRLYLQGNPLSCCGNGWLAAQLHQGRVDVDATQDL ICRFGSQEELSLSLVRPEDCEKGGLKNVNLILLLSFTLVS AIVLTTLATICFLRRQKLSQQYKA	110
sGARP	mouse	ISQRREQVPCRTVNKEALCHGLGLLQVPSVLSLDIQALY LSGNQLQSILVSPLGFYTALRHLDLSDNQISFLQAGVFQA LPYLEHLNLAHNRLATGMALNSGGLGRLPLLVSLDLSG NSLHGNLVERLLGETPRLRTLSLAENSLTRLARHTFWG MPAVEQLDLHSNVLMDIEDGAFEALPHLTHLNLSRNSL TCISDFSLQQLQVLDLSCNSIEAFQTAPEPQAQFQLAWL DLRENKLLHFPDLAVFPRLIYLNVSNNLIQLPAGLPRGSE DLHAPSEGWSASPLSNPSRNASTHPLSQLLNLDLSYNEIE LVPASFLEHLTSLRFLNLSRNCLRSFEARQVDSLPCLVLL DLSHNVLEALELGTKVLGSLQTLLLQDNALQELPPYTFA SLASLQRLNLQGNQVSPCGGPAEPGPPGCVDFSGIPTLH VLNMAGNSMGMLRAGSFLHTPLTELDLSTNPGLDVATG ALVGLEASLEVLELQGNGLTVLRVDLPCFLRLKRLNLAE NQLSHLPAWTRAVSLEVLDLRNNSFSLLPGNAMGGLET SLRRLYLQGNPLSCCGNGWLAAQLHQGRVDVDATQDL ICRFGSQEELSLSLVRPEDCEKGGLKNVN	111
LRRC33	mouse	WRSGPGTATAASQGGCKVVDGVADCRGLNLASVPSSLP PHSRMLILDANPLKDLWNHSLQAYPRLENLSLHSCHLD RISHYAFREQGHLRNLVLADNRLSENYKESAAALHTLL GLRRLDLSGNSLTEDMAALMLQNLSSLEVVSLARNTLM RLDDSIFEGLEHLVELDLQRNYIFEIEGGAFDGLTELRRL NLAYNNLPCIVDFSLTQLRFLNVSYNILEWFLAAREEVA FELEILDLSHNQLLFFPLLPQCGKLHTLLLQDNNMGFYR ELYNTSSPQEMVAQFLLVDGNVTNITTVNLWEEFSSSDL SALRFLDMSQNQFRHLPDGFLKKTPSLSHLNLNQNCLK MLHIREHEPPGALTELDLSHNQLAELHLAPGLTGSLRNL RVFNLSSNQLLGVPTGLFDNASSITTIDMSHNQISLCPQM VPVDWEGPPSCVDFRNMGSLRSLSLDGCGLKALQDCPF QGTSLTHLDLSSNWGVLNGSISPLWAVAPTLQVLSLRD	112

		VGLGSGAAEMDFSAFGNLRALDLSGNSLTSFPKFKGSLA LRTLDLRRNSLTALPQRVVSEQPLRGLQTIYLSQNPYDC CGVEGWGALQQHFKTVADLSMVTCNLSSKIVRVVELPE GLPQGCKWEQVDTGLFYLVLILPSCLTLLVACTVVFLTF KKPLLQVIKSRCHWSSIY	
sLRRC33	mouse	WRSGPGTATAASQGGCKVVDGVADCRGLNLASVPSSLP PHSRMLILDANPLKDLWNHSLQAYPRLENLSLHSCHLD RISHYAFREQGHLRNLVLADNRLSENYKESAAALHTLL GLRRLDLSGNSLTEDMAALMLQNLSSLEVVSLARNTLM RLDDSIFEGLEHLVELDLQRNYIFEIEGGAFDGLTELRRL NLAYNNLPCIVDFSLTQLRFLNVSYNILEWFLAAREEVA FELEILDLSHNQLLFFPLLPQCGKLHTLLLQDNNMGFYR ELYNTSSPQEMVAQFLLVDGNVTNITTVNLWEEFSSSDL SALRFLDMSQNQFRHLPDGFLKKTPSLSHLNLNQNCLK MLHIREHEPPGALTELDLSHNQLAELHLAPGLTGSLRNL RVFNLSSNQLLGVPTGLFDNASSITTIDMSHNQISLCPQM VPVDWEGPPSCVDFRNMGSLRSLSLDGCGLKALQDCPF QGTSLTHLDLSSNWGVLNGSISPLWAVAPTLQVLSLRD VGLGSGAAEMDFSAFGNLRALDLSGNSLTSFPKFKGSLA LRTLDLRRNSLTALPQRVVSEQPLRGLQTIYLSQNPYDC CGVEGWGALQQHFKTVADLSMVTCNLSSKIVRVVELPE GLPQGCKWEQVDTGL	113
LRRC33	Cyno	WRDRSVTATAASQRGCKLVGGDTDCRGQSLASVPSSLP PHARTLILDANPLKALWNHSLQPYPLLESLSLHSCHLERI GRGAFQEQGHLRSLVLGDNCLSENYKETAAALHTLPGL QTLDLSGNSLTEDMAALMLQNLSSLQSVSLARNTIMRL DDSVFEGLERLRELDLQRNYIFEIEGGAFDGLTELRHLNL AYNNLPCIVDFGLTQLRSLNVSYNVLEWFLAAGGEAAF ELETLDLSHNQLLFFPLLPQYSKLHTLLLRDNNMGFYRD LYNTSSPREMVAQFLLVDGNVTNITTVNLWEEFSSSDLA DLRFLDMSQNQFQYLPDGFLRKMPSLSHLNLNQNCLMT LHIREHEPPGALTELDLSHNQLSELHLTPGLASCLGSLRL FNLSSNQLLGVPPGLFANARNITTLDMSHNQISLCPLPAA SDRVGPPSCVDFRNMASLRSLSLEGCGLGALPDCPFQGT SLTSLDLSSNWGVLNGSLAPLRDVAPMLQVLSLRNMGL HSNFMALDFSGFGNLRDLDLSGNCLTTFPRFGGSLALET LDLRRNSLTALPQKAVSEQLSRGLRTIYLSQNPYDCCGV DGWGALQQGQTVADWATVTCNLSSKIIRLAELPGGVPR DCKWERLDLGLLYLVLILPSCLTLLVACTLIVLTFKKPLL QVIKSRCHWSSVY	114
sLRRC33	Cyno	WRDRSVTATAASQRGCKLVGGDTDCRGQSLASVPSSLP PHARTLILDANPLKALWNHSLQPYPLLESLSLHSCHLERI GRGAFQEQGHLRSLVLGDNCLSENYKETAAALHTLPGL QTLDLSGNSLTEDMAALMLQNLSSLQSVSLARNTIMRL DDSVFEGLERLRELDLQRNYIFEIEGGAFDGLTELRHLNL AYNNLPCIVDFGLTQLRSLNVSYNVLEWFLAAGGEAAF ELETLDLSHNQLLFFPLLPQYSKLHTLLLRDNNMGFYRD LYNTSSPREMVAQFLLVDGNVTNITTVNLWEEFSSSDLA DLRFLDMSQNQFQYLPDGFLRKMPSLSHLNLNQNCLMT LHIREHEPPGALTELDLSHNQLSELHLTPGLASCLGSLRL FNLSSNQLLGVPPGLFANARNITTLDMSHNQISLCPLPAA SDRVGPPSCVDFRNMASLRSLSLEGCGLGALPDCPFQGT SLTSLDLSSNWGVLNGSLAPLRDVAPMLQVLSLRNMGL HSNFMALDFSGFGNLRDLDLSGNCLTTFPRFGGSLALET	115

		LDLRRNSLTALPQKAVSEQLSRGLRTIYLSQNPYDCCGV DGWGALQQGQTVADWATVTCNLSSKIIRLAELPGGVPR DCKWERLDLGL	

[00224] In some embodiments, recombinant proteins may be combined and/or complexed with one or more additional recombinant components. Such components may include extracellular proteins known to associate with GPCs including, but not limited to LTBPs, fibrillins, perlecan, GASP1/2 proteins, follistatin, follistatin-related gene (FLRG), decorin and/or GARP (including, but not limited to recombinant forms of such proteins). Some recombinant GPCs of the present disclosure must be co-expressed with one or more of such extracellular proteins for proper expression and/or folding.

[00225] In some embodiments, complexed LTBPs may include, but are not limited to LTBP1, LTBP2, LTBP3 and/or LTBP4 with or without detectable labels. Complexed LTBPs may comprise LTBP fragments and/or mutations. Some recombinant forms of LTBPs complexed with recombinant GPCs may comprise alternatively spliced variants of LTBPs. Some such variants of LTBP1 are shortened at the N-terminus, referred to herein as LTBP1S. Some recombinant proteins of the present disclosure may comprise LTBPs, fragments or mutants thereof comprising the amino acid sequences listed in the Table below. In some cases, these sequences are expressed in association with N- and/or C-terminal secretion signal sequences [e.g. human Ig kappa chains with amino acid sequence MDMRVPAQLLGLLLLWFSGVLG (SEQ ID NO: 66)], flag tag sequences [e.g. DYKDDDDK (SEQ ID NO: 67)], one or more 3C protease cleavage site [e.g. LEVLFQGP (SEQ ID NO: 68)], one or more biotinylation site and/or His-tag sequences [e.g. HHHHHH (SEQ ID NO: 69)].

Table 6. LTBP sequences

Protein	Sequence	SEQ ID NO
LTBP1 1265-1443	NECELLSGVCGEAFCENVEGSFLCVCADENQEYSPMTGQC RSRTSTDLDVDVDQPKEEKKECYYNLNDASLCDNVLAPNV TKQECCCTSGVGWGDNCEIFPCPVLGTAEFTEMCPKGKGF VPAGESSSEAGGENYKDADECLLFGQEICKNGFCLNTRPGY ECYCKQGTYYDPVKLQCF	116
LTBP1 1265-1698	NECELLSGVCGEAFCENVEGSFLCVCADENQEYSPMTGQC RSRTSTDLDVDVDQPKEEKKECYYNLNDASLCDNVLAPNV TKQECCCTSGVGWGDNCEIFPCPVLGTAEFTEMCPKGKGF VPAGESSSEAGGENYKDADECLLFGQEICKNGFCLNTRPGY ECYCKQGTYYDPVKLQCFDMDECQDPSSCIDGQCVNTEGS YNCFCTHPMVLDASEKRCIRPAESNEQIEETDVYQDLCWE HLSDEYVCSRPLVGKQTTYTECCCLYGEAWGMQCALCPL	117

	KDSDDYAQLCNIPVTGRRQPYGRDALVDFSEQYTPEADPY FIQDRFLNSFEELQAEECGILNGCENGRCVRVQEGYTCDCF DGYHLDTAKMTCVDVNECDELNNRMSLCKNAKCINTDGS YKCLCLPGYVPSDKPNYCTPLNTALNLEKDSDLE	
LTBP1 809-1698	PSLDQEKTKLEPGQPQLSPGISTIHLHPQFPVVIEKTSPPVPV EVAPEASTSSASQVIAPTQVTEINECTVNPDICGAGHCINLP VRYTCICYEGYRFSEQQRKCVDIDECTQVQHLCSQGRCEN TEGSFLCICPAGFMASEEGTNCIDVDECLRPDVCGEGHCVN TVGAFRCEYCDSGYRMTQRGRCEDIDECLNPSTCPDEQCV NSPGSYQCVPCTEGFRGWNGQCLDVDECLEPNVCANGDC SNLEGSYMCSCHKGYTRTPDHKHCRDIDECQQGNLCVNG QCKNTEGSFRCTCGQGYQLSAAKDQCEDIDECQHRHLCAH GQCRNTEGSFQCVCDQGYRASGLGDHCEDINECLEDKSVC QRGDCINTAGSYDCTCPDGFQLDDNKTCQDINECEHPGLC GPQGECLNTEGSFHCVCQQGFSISADGRTCEDIDECVNNTV CDSHGFCDNTAGSFRCLCYQGFQAPQDGQGCVDVNECEL LSGVCGEAFCENVEGSFLCVCADENQEYSPMTGQCRSRTS TDLDVDVDQPKEEKKECYYNLNDASLCDNVLAPNVTKQE CCCTSGVGWGDNCEIFPCPVLGTAEFTEMCPKGKGFVPAG ESSSEAGGENYKDADECLLFGQEICKNGFCLNTRPGYECYC KQGTYYDPVKLQCFDMDECQDPSSCIDGQCVNTEGSYNCF CTHPMVLDASEKRCIRPAESNEQIEETDVYQDLCWEHLSDE YVCSRPLVGKQTTYTECCCLYGEAWGMQCALCPLKDSDD YAQLCNIPVTGRRQPYGRDALVDFSEQYTPEADPYFIQDRF LNSFEELQAEECGILNGCENGRCVRVQEGYTCDCFDGYHL DTAKMTCVDVNECDELNNRMSLCKNAKCINTDGSYKCLC LPGYVPSDKPNYCTPLNTALNLEKDSDLE	118
LTBP1S	NHTGRIKVVFTPSICKVTCTKGSCQNSCEKGNTTTLISENGH AADTLTATNFRVVICHLPCMNGGQCSSRDKCQCPPNFTGK LCQIPVHGASVPKLYQHSQQPGKALGTHVIHSTHTLPLTVT SQQGVKVKFPPNIVNIHVKHPPEASVQIHQVSRIDGPTGQK TKEAQPGQSQVSYQGLPVQKTQTIHSTYSHQQVIPHVYPVA AKTQLGRCFQETIGSQCGKALPGLSKQEDCCGTVGTSWGF NKCQKCPKKPSYHGYNQMMECLPGYKRVNNTFCQDINEC QLQGVCPNGECLNTMGSYRCTCKIGFGPDPTFSSCVPDPPV ISEEKGPCYRLVSSGRQCMHPLSVHLTKQLCCCSVGKAWG PHCEKCPLPGTAAFKEICPGGMGYTVSGVHRRRPIHHHVG KGPVFVKPKNTQPVAKSTHPPPLPAKEEPVEALTFSREHGP GVAEPEVATAPPEKEIPSLDQEKTKLEPGQPQLSPGISTIHLH PQFPVVIEKTSPPVPVEVAPEASTSSASQVIAPTQVTEINECT VNPDICGAGHCINLPVRYTCICYEGYRFSEQQRKCVDIDEC TQVQHLCSQGRCENTEGSFLCICPAGFMASEEGTNCIDVDE CLRPDVCGEGHCVNTVGAFRCEYCDSGYRMTQRGRCEDI DECLNPSTCPDEQCVNSPGSYQCVPCTEGFRGWNGQCLDV DECLEPNVCANGDCSNLEGSYMCSCHKGYTRTPDHKHCR DIDECQQGNLCVNGQCKNTEGSFRCTCGQGYQLSAAKDQ CEDIDECQHRHLCAHGQCRNTEGSFQCVCDQGYRASGLGD HCEDINECLEDKSVCQRGDCINTAGSYDCTCPDGFQLDDN KTCQDINECEHPGLCGPQGECLNTEGSFHCVCQQGFSISAD GRTCEDIDECVNNTVCDSHGFCDNTAGSFRCLCYQGFQAP QDGQGCVDVNECELLSGVCGEAFCENVEGSFLCVCADEN QEYSPMTGQCRSRTSTDLDVDVDQPKEEKKECYYNLNDAS LCDNVLAPNVTKQECCCTSGVGWGDNCEIFPCPVLGTAEF TEMCPKGKGFVPAGESSSEAGGENYKDADECLLFGQEICK NGFCLNTRPGYECYCKQGTYYDPVKLQCFDMDECQDPSS	119

	CIDGQCVNTEGSYNCFCTHPMVLDASEKRCIRPAESNEQIE ETDVYQDLCWEHLSDEYVCSRPLVGKQTTYTECCCLYGEA WGMQCALCPLKDSDDYAQLCNIPVTGRRQPYGRDALVDF SEQYTPEADPYFIQDRFLNSFEELQAEECGILNGCENGRCVR VQEGYTCDCFDGYHLDTAKMTCVDVNECDELNNRMSLCK NAKCINTDGSYKCLCLPGYVPSDKPNYCTPLNTALNLEKDS DLE	
LTBP3	GPAGERGAGGGGALARERFKVVFAPVICKRTCLKGQCRDS CQQGSNMTLIGENGHSTDTLTGSGFRVVVCPLPCMNGGQC SSRNQCLCPPDFTGRFCQVPAGGAGGGTGGSGPGLSRTGA LSTGALPPLAPEGDSVASKHAIYAVQVIADPPGPGEGPPAQ HAAFLVPLGPGQISAEVQAPPPVVNVRVHHPPEASVQVHRI ESSNAESAAPSQHLLPHPKPSHPRPPTQKPLGRCFQDTLPKQ PCGSNPLPGLTKQEDCCGSIGTAWGQSKCHKCPQLQYTGV QKPGPVRGEVGADCPQGYKRLNSTHCQDINECAMPGVCR HGDCLNNPGSYRCVCPPGHSLGPSRTQCIADKPEEKSLCFR LVSPEHQCQHPLTTRLTRQLCCCSVGKAWGARCQRCPTDG TAAFKEICPAGKGYHILTSHQTLTIQGESDFSLFLHPDGPPK PQQLPESPSQAPPPEDTEEERGVTTDSPVSEERSVQQSHPTA TTTPARPYPELISRPSPPTMRWFLPDLPPSRSAVEIAPTQVTE TDECRLNQNICGHGECVPGPPDYSCHCNPGYRSHPQHRYC VDVNECEAEPCGPGRGICMNTGGSYNCHCNRGYRLHVGA GGRSCVDLNECAKPHLCGDGGFCINFPGHYKCNCYPGYRL KASRPPVCEDIDECRDPSSCPDGKCENKPGSFKCIACQPGY RSQGGGACRDVNECAEGSPCSPGWCENLPGSFRCTCAQGY APAPDGRSCLDVDECEAGDVCDNGICSNTPGSFQCQCLSG YHLSRDRSHCEDIDECDFPAACIGGDCINTNGSYRCLCPQG HRLVGGRKCQDIDECSQDPSLCLPHGACKNLQGSYVCVCD EGFTPTQDQHGCEEVEQPHHKKECYLNFDDTVFCDSVLAT NVTQQECCCSLGAGWGDHCEIYPCPVYSSAEFHSLCPDGK GYTQDNNIVNYGIPAHRDIDECMLFGSEICKEGKCVNTQPG YECYCKQGFYYDGNLLECVDVDECLDESNCRNGVCENTR GGYRCACTPPAEYSPAQRQCLSPEEMDVDECQDPAACRPG RCVNLPGSYRCECRPPWVPGPSGRDCQLPESPAERAPERRD VCWSQRGEDGMCAGPLAGPALTFDDCCCRQGRGWGAQC RPCPPRGAGSHCPTSQSESNSFWDTSPLLLGKPPRDEDSSEE DSDECRCVSGRCVPRPGGAVCECPGGFQLDASRARCVDID ECRELNQRGLLCKSERCVNTSGSFRCVCKAGFARSRPHGA CVPQRRR	120
LTBP3 EGF-like domain, module 1	DIDECMLFGSEICKEGKCVNTQPGYECYCKQGFYYDGNLL ECVDVDECLDESNCRNGVCENTRGGYRCACTPPAEYSPAQ RQCLSP	121
LTBP3 EGF-like domain, module 2	DVDECQDPAACRPGRCVNLPGSYRCECRPPWVPGPSGRDC QLP	122
LTBP3 EGF-like domain, module 3	DIDECSQDPSLCLPHGACKNLQGSYVCVCDEGFTPTQDQH GCE	123
LTBP3 EGF-like domain, module 4	DIDECMLFGSEICKEGKCVNTQPGYECYCKQGFYYDGNLL ECV	124
TB domain, module 1	KKECYLNFDDTVFCDSVLATNVTQQECCCSLGAGWGDHC EIYPCPVYSSAEFHSLCP	125
TB domain, module 2	DVCWSQRGEDGMCAGPLAGPALTFDDCCCRQGRGWGAQ CRPCPPRGAGSHCP	126
L3-TB3TB4 isoform 1	KKECYLNFDDTVFCDSVLATNVTQQECCCSLGAGWGDHC EIYPCPVYSSAEFHSLCPDGKGYTQDNNIVNYGIPAHRDIDE	127

	CMLFGSEICKEGKCVNTQPGYECYCKQGFYYDGNLLECVD VDECLDESNCRNGVCENTRGGYRCACTPPAEYSPAQRQCL SPEEMDVDECQDPAACRPGRCVNLPGSYRCECRPPWVPGP SGRDCQLPESPAERAPERRDVCWSQRGEDGMCAGPLAGP ALTFDDCCCRQGRGWGAQCRPCPPRGAGSHCPTSQSE	
L3-TB3TB4 isoform 2	KKECYLNFDDTVFCDSVLATNVTQQECCCSLGAGWGDHC EIYPCPVYSSAEFHSLCPDGKGYTQDNNIVNYGIPAHRDIDE CMLFGSEICKEGKCVNTQPGYECYCKQGFYYDGNLLECVD VDECLDESNCRNGVCENTRGGYRCACTPPAEYSPAQRQCL SPEEMERAPERRDVCWSQRGEDGMCAGPLAGPALTFDDC CCRQGRGWGAQCRPCPPRGAGSHCPTSQSE	128
L3-ETB3E, type 1	DIDECSQDPSLCLPHGACKNLQGSYVCVCDEGFTPTQDQH GCEEVEQPHHKKECYLNFDDTVFCDSVLATNVTQQECCCS LGAGWGDHCEIYPCPVYSSAEFHSLCPDGKGYTQDNNIVN YGIPAHRDIDECMLFGSEICKEGKCVNTQPGYECYCKQGFY YDGNLLECVDVDE	129
L3-ETB3E, type 2	QDIDECSQDPSLCLPHGACKNLQGSYVCVCDEGFTPTQDQ HGCEEVEQPHHKKECYLNFDDTVFCDSVLATNVTQQECCC SLGAGWGDHCEIYPCPVYSSAEFHSLCPDGKGYTQDNNIV NYGIPAHRDIDECMLFGSEICKEGKCVNTQPGYECYCKQGF YYDGNLLECVDVDE	130
L3-ETB3E, type 3	DIDECSQDPSLCLPHGACKNLQGSYVCVCDEGFTPTQDQH GCEEVEQPHHKKECYLNFDDTVFCDSVLATNVTQQECCCS LGAGWGDHCEIYPCPVYSSAEFHSLCPDGKGYTQDNNIVN YGIPAHRDIDECMLFGSEICKEGKCVNTQPGYECYCKQGFY YDGNLLECV	131
L3-ETB3E, type 4	QDIDECSQDPSLCLPHGACKNLQGSYVCVCDEGFTPTQDQ HGCEEVEQPHHKKECYLNFDDTVFCDSVLATNVTQQECCC SLGAGWGDHCEIYPCPVYSSAEFHSLCPDGKGYTQDNNIV NYGIPAHRDIDECMLFGSEICKEGKCVNTQPGYECYCKQGF YYDGNLLECV	132
L3-ETB3E, type 1N	SSGDIDECSQDPSLCLPHGACKNLQGSYVCVCDEGFTPTQD QHGCEEVEQPHHKKECYLNFDDTVFCDSVLATNVTQQECC CSLGAGWGDHCEIYPCPVYSSAEFHSLCPDGKGYTQDNNI VNYGIPAHRDIDECMLFGSEICKEGKCVNTQPGYECYCKQ GFYYDGNLLECVDVDE	133
L3-ETB3E, type 2N	SSGQDIDECSQDPSLCLPHGACKNLQGSYVCVCDEGFTPTQ DQHGCEEVEQPHHKKECYLNFDDTVFCDSVLATNVTQQE CCCSLGAGWGDHCEIYPCPVYSSAEFHSLCPDGKGYTQDN NIVNYGIPAHRDIDECMLFGSEICKEGKCVNTQPGYECYCK QGFYYDGNLLECVDVDE	134
L3-ETB3E, type 3N	SSGDIDECSQDPSLCLPHGACKNLQGSYVCVCDEGFTPTQD QHGCEEVEQPHHKKECYLNFDDTVFCDSVLATNVTQQECC CSLGAGWGDHCEIYPCPVYSSAEFHSLCPDGKGYTQDNNI VNYGIPAHRDIDECMLFGSEICKEGKCVNTQPGYECYCKQ GFYYDGNLLECV	135
L3-ETB3E, type 4N	SSGQDIDECSQDPSLCLPHGACKNLQGSYVCVCDEGFTPTQ DQHGCEEVEQPHHKKECYLNFDDTVFCDSVLATNVTQQE CCCSLGAGWGDHCEIYPCPVYSSAEFHSLCPDGKGYTQDN NIVNYGIPAHRDIDECMLFGSEICKEGKCVNTQPGYECYCK QGFYYDGNLLECV	136
L1-ETB3E, type 1	GQGCVDVNECELLSGVCGEAFCENVEGSFLCVCADENQEY SPMTGQCRSRTSTDLDVDVDQPKEEKKECYYNLNDASLCD NVLAPNVTKQECCCTSGVGWGDNCEIFPCPVLGTAEFTEM	137

	CPKGKGFVPAGESSSEAGGENYKDADECLLFGQEICKNGF CLNTRPGYECYCKQGTYYDPVKLQCF	
L1-ETB3-C-term, type 1	GQGCVDVNECELLSGVCGEAFCENVEGSFLCVCADENQEY SPMTGQCRSRTSTDLDVDVDQPKEEKKECYYNLNDASLCD NVLAPNVTKQECCCTSGVGWGDNCEIFPCPVLGTAEFTEM CPKGKGFVPAGESSSEAGGENYKDADECLLFGQEICKNGF CLNTRPGYECYCKQGTYYDPVKLQCFDMDECQDPSSCIDG QCVNTEGSYNCFCTHPMVLDASEKRCIRPAESNEQIEETDV YQDLCWEHLSDEYVCSRPLVGKQTTYTECCCLYGEAWGM QCALCPLKDSDDYAQLCNIPVTGRRQPYGRDALVDFSEQY TPEADPYFIQDRFLNSFEELQAEECGILNGCENGRCVRVQE GYTCDCFDGYHLDTAKMTCVDVNECDELNNRMSLCKNA KCINTDGSYKCLCLPGYVPSDKPNYCTPLNTALNLEKDSDL E	138
L1-ETB3E, type 2	NECELLSGVCGEAFCENVEGSFLCVCADENQEYSPMTGQC RSRTSTDLDVDVDQPKEEKKECYYNLNDASLCDNVLAPNV TKQECCCTSGVGWGDNCEIFPCPVLGTAEFTEMCPKGKGF VPAGESSSEAGGENYKDADECLLFGQEICKNGFCLNTRPGY ECYCKQGTYYDPVKLQCF	139
L1-ETB3-C-term, type 2	NECELLSGVCGEAFCENVEGSFLCVCADENQEYSPMTGQC RSRTSTDLDVDVDQPKEEKKECYYNLNDASLCDNVLAPNV TKQECCCTSGVGWGDNCEIFPCPVLGTAEFTEMCPKGKGF VPAGESSSEAGGENYKDADECLLFGQEICKNGFCLNTRPGY ECYCKQGTYYDPVKLQCFDMDECQDPSSCIDGQCVNTEGS YNCFCTHPMVLDASEKRCIRPAESNEQIEETDVYQDLCWE HLSDEYVCSRPLVGKQTTYTECCCLYGEAWGMQCALCPL KDSDDYAQLCNIPVTGRRQPYGRDALVDFSEQYTPEADPY FIQDRFLNSFEELQAEECGILNGCENGRCVRVQEGYTCDCF DGYHLDTAKMTCVDVNECDELNNRMSLCKNAKCINTDGS YKCLCLPGYVPSDKPNYCTPLNTALNLEKDSDLE	140
L1-ETB3E, type 3	DVNECELLSGVCGEAFCENVEGSFLCVCADENQEYSPMTG QCRSRTSTDLDVDVDQPKEEKKECYYNLNDASLCDNVLAP NVTKQECCCTSGVGWGDNCEIFPCPVLGTAEFTEMCPKGK GFVPAGESSSEAGGENYKDADECLLFGQEICKNGFCLNTRP GYECYCKQGTYYDPVKLQCF	141
L1-EETB3EE	DIDECVNNTVCDSHGFCDNTAGSFRCLCYQGFQAPQDGQG CVDVNECELLSGVCGEAFCENVEGSFLCVCADENQEYSPM TGQCRSRTSTDLDVDVDQPKEEKKECYYNLNDASLCDNVL APNVTKQECCCTSGVGWGDNCEIFPCPVLGTAEFTEMCPK GKGFVPAGESSSEAGGENYKDADECLLFGQEICKNGFCLN TRPGYECYCKQGTYYDPVKLQCFDMDECQDPSSCIDGQCV NTEGSYNCFCTHPMVLDASEKRCI	142
L1-E11-TB3	EINECTVNPDICGAGHCINLPVRYTCICYEGYRFSEQQRKCV DIDECTQVQHLCSQGRCENTEGSFLCICPAGFMASEEGTNCI DVDECLRPDVCGEGHCVNTVGAFRCEYCDSGYRMTQRGR CEDIDECLNPSTCPDEQCVNSPGSYQCVPCTEGFRGWNGQ CLDVDECLEPNVCANGDCSNLEGSYMCSCHKGYTRTPDH KHCRDIDECQQGNLCVNGQCKNTEGSFRCTCGQGYQLSA AKDQCEDIDECQHRHLCAHGQCRNTEGSFQCVCDQGYRA SGLGDHCEDINECLEDKSVCQRGDCINTAGSYDCTCPDGFQ LDDNKTCQDINECEHPGLCGPQGECLNTEGSFHCVCQQGF SISADGRTCEDIDECVNNTVCDSHGFCDNTAGSFRCLCYQG FQAPQDGQGCVDVNECELLSGVCGEAFCENVEGSFLCVCA DENQEYSPMTGQCRSRTSTDLDVDVDQPKEEKKECYYNL	143

	NDASLCDNVLAPNVTKQECCCTSGVGWGDNCEIFPCPVLG TAEFTEMCPKGKGFVPAGESSSEAGGENYKDA	
L1-E11-TB3EE	EINECTVNPDICGAGHCINLPVRYTCICYEGYRFSEQQRKCV DIDECTQVQHLCSQGRCENTEGSFLCICPAGFMASEEGTNCI DVDECLRPDVCGEGHCVNTVGAFRCEYCDSGYRMTQRGR CEDIDECLNPSTCPDEQCVNSPGSYQCVPCTEGFRGWNGQ CLDVDECLEPNVCANGDCSNLEGSYMCSCHKGYTRTPDH KHCRDIDECQQGNLCVNGQCKNTEGSFRCTCGQGYQLSA AKDQCEDIDECQHRHLCAHGQCRNTEGSFQCVCDQGYRA SGLGDHCEDINECLEDKSVCQRGDCINTAGSYDCTCPDGFQ LDDNKTCQDINECEHPGLCGPQGECLNTEGSFHCVCQQGF SISADGRTCEDIDECVNNTVCDSHGFCDNTAGSFRCLCYQG FQAPQDGQGCVDVNECELLSGVCGEAFCENVEGSFLCVCA DENQEYSPMTGQCRSRTSTDLDVDVDQPKEEKKECYYNL NDASLCDNVLAPNVTKQECCCTSGVGWGDNCEIFPCPVLG TAEFTEMCPKGKGFVPAGESSSEAGGENYKDADECLLFGQ EICKNGFCLNTRPGYECYCKQGTYYDPVKLQCFDMDECQD PSSCIDGQCVNTEGSYNCFCTHPMVLDASEKRCI	144
L1-ΔN441	STHPPPLPAKEEPVEALTFSREHGPGVAEPEVATAPPEKEIP SLDQEKTKLEPGQPQLSPGISTIHLHPQFPVVIEKTSPPVPVE VAPEASTSSASQVIAPTQVTEINECTVNPDICGAGHCINLPV RYTCICYEGYRFSEQQRKCVDIDECTQVQHLCSQGRCENTE GSFLCICPAGFMASEEGTNCIDVDECLRPDVCGEGHCVNTV GAFRCEYCDSGYRMTQRGRCEDIDECLNPSTCPDEQCVNS PGSYQCVPCTEGFRGWNGQCLDVDECLEPNVCANGDCSN LEGSYMCSCHKGYTRTPDHKHCRDIDECQQGNLCVNGQC KNTEGSFRCTCGQGYQLSAAKDQCEDIDECQHRHLCAHGQ CRNTEGSFQCVCDQGYRASGLGDHCEDINECLEDKSVCQR GDCINTAGSYDCTCPDGFQLDDNKTCQDINECEHPGLCGP QGECLNTEGSFHCVCQQGFSISADGRTCEDIDECVNNTVCD SHGFCDNTAGSFRCLCYQGFQAPQDGQGCVDVNECELLSG VCGEAFCENVEGSFLCVCADENQEYSPMTGQCRSRTSTDL DVDVDQPKEEKKECYYNLNDASLCDNVLAPNVTKQECCC TSGVGWGDNCEIFPCPVLGTAEFTEMCPKGKGFVPAGESSS EAGGENYKDADECLLFGQEICKNGFCLNTRPGYECYCKQG TYYDPVKLQCFDMDECQDPSSCIDGQCVNTEGSYNCFCTH PMVLDASEKRCIRPAESNEQIEETDVYQDLCWEHLSDEYV CSRPLVGKQTTYTECCCLYGEAWGMQCALCPLKDSDDYA QLCNIPVTGRRQPYGRDALVDFSEQYTPEADPYFIQDRFLN SFEELQAEECGILNGCENGRCVRVQEGYTCDCFDGYHLDT AKMTCVDVNECDELNNRMSLCKNAKCINTDGSYKCLCLP GYVPSDKPNYCTPLNTALNLEKDSDLE	145

[00226] In some embodiments, LTBPs may comprise detectable labels. Detectable labels may be used to allow for detection and/or isolation of recombinant proteins comprising LTBPs. Some detectable labels may comprise biotin labels, polyhistidine tags and/or flag tags. Such tags may be used to isolate tagged proteins. Proteins produced may comprise additional amino acids encoding one or more 3C protease cleavage site. Such sites allow for cleavage at the 3C protease cleavage site upon treatment with 3C protease, including, but not

limited to rhinovirus 3C protease. Such cleavage sites may be introduced to allow for removal of detectable labels from recombinant proteins.

[00227] Recombinant proteins of the present disclosure may be coexpressed with GDF-associated serum protein (GASP) 1 and/or GASP-2. Such recombinant proteins may include, but are not limited to GDF-8 and/or GDF-11. GASPs are circulating proteins that bind and prevent activity of GDF-8 and GDF-11 (Hill, J.J. et al., 2003. Mol Endocrinology. 17(6):1144-54 and Hill, J.J. et al., 2002. JBC. 277(43):40735-41, the contents of each of which are herein incorporated by reference in their entirety). Interestingly, GDF-8 and GDF-11 growth factors are not found free in serum. About 70% are in GPCs with the remaining 30% associated with GASPs as well as other proteins (e.g. follistatin, follistatin-like related gene and decorin). Studies using mice lacking expression of GASP-1 (also known as WFIKKNRP or WFIKKN2) and/or GASP-2 (also known as WFIKKN or WFIKKN1) display phenotypes indicative of myostatin and/or GDF-11 overactivity (Lee et al., 2013. PNAS. 110(39):E3713-22). GASP bound GDF-8 and/or GDF-11 are unable to bind type II receptors and transmit related cellular signals. In some cases, recombinant proteins of the present disclosure may comprise one or more of the GASP sequences listed in Table 7. In some cases, these sequences are expressed in association with N- and/or C-terminal secretion signal sequences [e.g. human Ig kappa chains with amino acid sequence MDMRVPAQLLGLLLLWFSGVLG (SEQ ID NO: 66)], flag tag sequences [e.g. DYKDDDDK (SEQ ID NO: 67)], one or more 3C protease cleavage site [e.g. LEVLFQGP (SEQ ID NO: 68)], one or more biotinylation site and/or His-tag sequences [e.g. HHHHHH (SEQ ID NO: 69)].

Table 7. GASP Sequences

Protein	Sequence	SEQ ID NO
GASP1, NP_783165.1	MWAPRCRRFWSRWEQVAALLLLLLLLGVPPRSL ALPPIRYSHAGICPNDMNPNLWVDAQSTCRRECE TDQECETYEKCCPNVCGTKSCVAARYMDVKGKK GPVGMPKEATCDHFMCLQQGSECDIWDGQPVCK CKDRCEKEPSFTCASDGLTYYNRCYMDAEACSK GITLAVVTCRYHFTWPNTSPPPPETTMHPTTASPE TPELDMAAPALLNNPVHQSVTMGETVSFLCDVV GRPRPEITWEKQLEDRENVVMRPNHVRGNVVVT NIAQLVIYNAQLQDAGIYTCTARNVAGVLRADFP LSVVRGHQAAATSESSPNGTAFPAAECLKPPDSED CGEEQTRWHFDAQANNCLTFTFGHCHRNLNHFE TYEACMLACMSGPLAACSLPALQGPCKAYAPRW AYNSQTGQCQSFVYGGCEGNGNNFESREACEESC	150

	PFPRGNQRCRACKPRQKLVTSFCRSDFVILGRVSE LTEEPDSGRALVTVDEVLKDEKMGLKFLGQEPLE VTLLHVDWACPCPNVTVSEMPLIIMGEVDGGMA MLRPDSFVGASSARRVRKLREVMHKKTCDVLKE FLGLH	
GASP1, residue 303-576 of NP_783165.1	SVVRGHQAAATSESSPNGTAFPAAECLKPPDSED CGEEQTRWHFDAQANNCLTFTFGHCHRNLNHFE TYEACMLACMSGPLAACSLPALQGPCKAYAPRW AYNSQTGQCQSFVYGGCEGNGNNFESREACEESC PFPRGNQRCRACKPRQKLVTSFCRSDFVILGRVSE LTEEPDSGRALVTVDEVLKDEKMGLKFLGQEPLE VTLLHVDWACPCPNVTVSEMPLIIMGEVDGGMA MLRPDSFVGASSARRVRKLREVMHKKTCDVLKE FLGLH	151
GASP1, residue 35-576 of NP_783165.1	LPPIRYSHAGICPNDMNPNLWVDAQSTCRRECET DQECETYEKCCPNVCGTKSCVAARYMDVKGKK GPVGMPKEATCDHFMCLQQGSECDIWDGQPVCK CKDRCEKEPSFTCASDGLTYYNRCYMDAEACSK GITLAVVTCRYHFTWPNTSPPPPETTMHPTTASPE TPELDMAAPALLNNPVHQSVTMGETVSFLCDVV GRPRPEITWEKQLEDRENVVMRPNHVRGNVVVT NIAQLVIYNAQLQDAGIYTCTARNVAGVLRADFP LSVVRGHQAAATSESSPNGTAFPAAECLKPPDSED CGEEQTRWHFDAQANNCLTFTFGHCHRNLNHFE TYEACMLACMSGPLAACSLPALQGPCKAYAPRW AYNSQTGQCQSFVYGGCEGNGNNFESREACEESC PFPRGNQRCRACKPRQKLVTSFCRSDFVILGRVSE LTEEPDSGRALVTVDEVLKDEKMGLKFLGQEPLE VTLLHVDWACPCPNVTVSEMPLIIMGEVDGGMA MLRPDSFVGASSARRVRKLREVMHKKTCDVLKE FLGLH	152
GASP1, residue 384-576 of NP_783165.1	AACSLPALQGPCKAYAPRWAYNSQTGQCQSFVY GGCEGNGNNFESREACEESCPFPRGNQRCRACKP RQKLVTSFCRSDFVILGRVSELTEEPDSGRALVTV DEVLKDEKMGLKFLGQEPLEVTLLHVDWACPCP NVTVSEMPLIIMGEVDGGMAMLRPDSFVGASSAR RVRKLREVMHKKTCDVLKEFLGLH	153
GASP1, residue 438-576 of NP_783165.1	FPRGNQRCRACKPRQKLVTSFCRSDFVILGRVSEL TEEPDSGRALVTVDEVLKDEKMGLKFLGQEPLEV TLLHVDWACPCPNVTVSEMPLIIMGEVDGGMAM LRPDSFVGASSARRVRKLREVMHKKTCDVLKEFL GLH	154
GASP, NP_444514.1	MPALRPLLPLLLLLRLTSGAGLLPGLGSHPGVCPN QLSPNLWVDAQSTCERECSRDQDCAAAEKCCINV CGLHSCVAARFPGSPAAPTTAASCEGFVCPQQGS DCDIWDGQPVCRCRDRCEKEPSFTCASDGLTYYN RCYMDAEACLRGLHLHIVPCKHVLSWPPSSPGPP ETTARPTPGAAPVPPALYSSPSPQAVQVGGTASLH CDVSGRPPPAVTWEKQSHQRENLIMRPDQMYGN VVVTSIGQLVLYNARPEDAGLYTCTARNAAGLLR ADFPLSVVQREPARDAAPSIPAPAECLPDVQACTG PTSPHLVLWHYDPQRGGCMTFPARGCDGAARGF ETYEACQQACARGPGDACVLPAVQGPCRGWEPR WAYSPLLQQCHPFVYGGCEGNGNNFHSRESCED	155

	ACPVPRTPPCRACRLRSKLALSLCRSDFAIVGRLT EVLEEPEAAGGIARVALEDVLKDDKMGLKFLGTK YLEVTLSGMDWACPCPNMTAGDGPLVIMGEVRD GVAVLDAGSYVRAASEKRVKKILELLEKQACELL NRFQD	
GASP, residue 279-548 of NP_444514.1	SVVQREPARDAAPSIPAPAECLPDVQACTGPTSPH LVLWHYDPQRGGCMTFPARGCDGAARGFETYEA CQQACARGPGDACVLPAVQGPCRGWEPRWAYSP LLQQCHPFVYGGCEGNGNNFHSRESCEDACPVPR TPPCRACRLRSKLALSLCRSDFAIVGRLTEVLEEPE AAGGIARVALEDVLKDDKMGLKFLGTKYLEVTL SGMDWACPCPNMTAGDGPLVIMGEVRDGVAVL DAGSYVRAASEKRVKKILELLEKQACELLNRFQD	156
GASP, residue 20-548 of NP_444514.1	AGLLPGLGSHPGVCPNQLSPNLWVDAQSTCEREC SRDQDCAAAEKCCINVCGLHSCVAARFPGSPAAP TTAASCEGFVCPQQGSDCDIWDGQPVCRCRDRCE KEPSFTCASDGLTYYNRCYMDAEACLRGLHLHIV PCKHVLSWPPSSPGPPETTARPTPGAAPVPPALYS SPSPQAVQVGGTASLHCDVSGRPPPAVTWEKQSH QRENLIMRPDQMYGNVVVTSIGQLVLYNARPED AGLYTCTARNAAGLLRADFPLSVVQREPARDAAP SIPAPAECLPDVQACTGPTSPHLVLWHYDPQRGG CMTFPARGCDGAARGFETYEACQQACARGPGDA CVLPAVQGPCRGWEPRWAYSPLLQQCHPFVYGG CEGNGNNFHSRESCEDACPVPRTPPCRACRLRSKL ALSLCRSDFAIVGRLTEVLEEPEAAGGIARVALED VLKDDKMGLKFLGTKYLEVTLSGMDWACPCPN MTAGDGPLVIMGEVRDGVAVLDAGSYVRAASEK RVKKILELLEKQACELLNRFQD	157
GASP, residue 357-548 of NP_444514.1	DACVLPAVQGPCRGWEPRWAYSPLLQQCHPFVY GGCEGNGNNFHSRESCEDACPVPRTPPCRACRLR SKLALSLCRSDFAIVGRLTEVLEEPEAAGGIARVA LEDVLKDDKMGLKFLGTKYLEVTLSGMDWACPC PNMTAGDGPLVIMGEVRDGVAVLDAGSYVRAAS EKRVKKILELLEKQACELLNRFQD	158
GASP, residue 411-548 of NP_444514.1	VPRTPPCRACRLRSKLALSLCRSDFAIVGRLTEVL EEPEAAGGIARVALEDVLKDDKMGLKFLGTKYLE VTLSGMDWACPCPNMTAGDGPLVIMGEVRDGV AVLDAGSYVRAASEKRVKKILELLEKQACELLNR FQD	159

[00228] Some recombinant proteins may be coexpressed with perlecan. Such recombinant proteins may include, but are not limited to GDF-8. Studies by Sengle et al (Sengle et al., 2011. J Biol Chem. 286(7):5087-99, the contents of which are herein incorporated by reference in their entirety) found that the GDF-8 prodomain associates with perlecan. Further studies indicate that perlecan knockout leads to muscular hypertrophy, suggesting that the interaction between GDF-8 and perlecan may contribute to GDF-8 activity (Xu et al. 2010. Matrix Biol. 29(6):461-70). In some cases, recombinant proteins may comprise one or more of the perlecan sequences presented in Table 8. In some cases, these sequences are expressed

in association with N- and/or C-terminal secretion signal sequences [e.g. human Ig kappa chains with amino acid sequence MDMRVPAQLLGLLLLWFSGVLG (SEQ ID NO: 66)], flag tag sequences [e.g. DYKDDDDK (SEQ ID NO: 67)], one or more 3C protease cleavage site [e.g. LEVLFQGP (SEQ ID NO: 68)], one or more biotinylation site and/or His-tag sequences [e.g. HHHHHH (SEQ ID NO: 69)].

Table 8. Perlecan sequences

Protein	Sequence	SEQ ID NO
Perlecan, NP_001278789.1	MGWRAAGALLLALLLHGRLLAVTHGLRAYDGLSLPEDIETVTA SQMRWTHSYLSDDEDMLADSISGDDLGSGDLGSGDFQMVYFR ALVNFTRSIEYSPQLEDAGSREFREVSEAVVDTLESEYLKIPGDQ VVSVVFIKELDGWVFVELDVGSEGNADGAQIQEMLLRVISSGSV ASYVTSPQGFQFRRLGTVPQFPRACTEAEFACHSYNECVALEYR CDRRPDCRDMSDELNCEEPVLGISPTFSLLVETTSLPPRPETTIMR QPPVTHAPQPLLPGSVRPLPCGPQEAACRNGHCIPRDYLCDGQE DCEDGSDELDCGPPPPCEPNEFPCGNGHCALKLWRCDGDFDCE DRTDEANCPTKRPEEVCGPTQFRCVSTNMCIPASFHCDEESDCP DRSDEFGCMPPQVVTPPRESIQASRGQTVTFTCVAIGVPTPIINW RLNWGHIPSHPRVTVTSEGGRGTLIIRDVKESDQGAYTCEAMNA RGMVFGIPDGVLELVPQRAGPCPDGHFYLEHSAACLPCFCFGITS VCQSTRRFRDQIRLRFDQPDDFKGVNVTMPAQPGTPPLSSTQLQI DPSLHEFQLVDLSRRFLVHDSFWALPEQFLGNKVDSYGGSLRYN VRYELARGMLEPVQRPDVVLMGAGYRLLSRGHTPTQPGALNQ RQVQFSEEHWVHESGRPVQRAELLQVLQSLEAVLIQTVYNTKM ASVGLSDIAMDTTVTHATSHGRAHSVEECRCPIGYSGLSCESCD AHFTRVPGGPYLGTCSGCNCNGHASSCDPVYGHCLNCQHNTEG PQCNKCKAGFFGDAMKATATSCRPCPCPYIDASRRFSDTCFLDT DGQATCDACAPGYTGRRCESCAPGYEGNPIQPGGKCRPVNQEIV RCDERGSMGTSGEACRCKNNVVGRLCNECADGSFHLSTRNPDG CLKCFCMGVSRHCTSSSWSRAQLHGASEEPGHFSLTNAASTHTT NEGIFSPTPGELGFSSFHRLLSGPYFWSLPSRFLGDKVTSYGGELR FTVTQRSQPGSTPLHGQPLVVLQGNNIILEHHVAQEPSPGQPSTFI VPFREQAWQRPDGQPATREHLLMALAGIDTLLIRASYAQQPAES RVSGISMDVAVPEETGQDPALEVEQCSCPPGYRGPSCQDCDTGY TRTPSGLYLGTCERCSCHGHSEACEPETGACQGCQHHTEGPRCE QCQPGYYGDAQRGTPQDCQLCPCYGDPAAGQAAHTCFLDTDG HPTCDACSPGHSGRHCERCAPGYYGNPSQGQPCQRDSQVPGPIG CNCDPQGSVSSQCDAAGQCQCKAQVEGLTCSHCRPHHFHLSAS NPDGCLPCFCMGITQQCASSAYTRHLISTHFAPGDFQGFALVNP QRNSRLTGEFTVEPVPEGAQLSFGNFAQLGHESFYWQLPETYQG DKVAAYGGKLRYTLSYTAGPQGSPLSDPDVQITGNNIMLVASQP ALQGPERRSYEIMFREEFWRRPDGQPATREHLLMALADLDELLI RATFSSVPLAASISAVSLEVAQPGPSNRPRALEVEECRCPPGYIGL SCQDCAPGYTRTGSGLYLGHCELCECNGHSDLCHPETGACSQC QHNAAGEFCELCAPGYYGDATAGTPEDCQPCACPLTNPENMFS RTCESLGAGGYRCTACEPGYTGQYCEQCGPGYVGNPSVQGGQC LPETNQAPLVVEVHPARSIVPQGGSHSLRCQVSGSPPHYFYWSR EDGRPVPSGTQQRHQGSELHFPSVQPSDAGVYICTCRNLHQSNT SRAELLVTEAPSKPITVTVEEQRSQSVRPGADVTFICTAKSKSPA	160

	YTLVWTRLHNGKLPTRAMDFNGILTIRNVQLSDAGTYVCTGSN MFAMDQGTATLHVQASGTLSAPVVSIHPPQLTVQPGQLAEFRCS ATGSPTPTLEWTGGPGGQLPAKAQIHGGILRLPAVEPTDQAQYL CRAHSSAGQQVARAVLHVHGGGGPRVQVSPERTQVHAGRTVR LYCRAAGVPSATITWRKEGGSLPPQARSERTDIATLLIPAITTAD AGFYLCVATSPAGTAQARIQVVVLSASDASPPPVKIESSSPSVTE GQTLDLNCVVAGSAHAQVTWYRRGGSLPPHTQVHGSRLRLPQ VSPADSGEYVCRVENGSGPKEASITVSVLHGTHSGPSYTPVPGST RPIRIEPSSSHVAEGQTLDLNCVVPGQAHAQVTWHKRGGSLPAR HQTHGSLLRLHQVTPADSGEYVCHVVGTSGPLEASVLVTIEASV IPGPIPPVRIESSSSTVAEGQTLDLSCVVAGQAHAQVTWYKRGGS LPARHQVRGSRLYIFQASPADAGQYVCRASNGMEASITVTVTGT QGANLAYPAGSTQPIRIEPSSSQVAEGQTLDLNCVVPGQSHAQV TWHKRGGSLPVRHQTHGSLLRLYQASPADSGEYVCRVLGSSVP LEASVLVTIEPAGSVPALGVTPTVRIESSSSQVAEGQTLDLNCLV AGQAHAQVTWHKRGGSLPARHQVHGSRLRLLQVTPADSGEYV CRVVGSSGTQEASVLVTIQQRLSGSHSQGVAYPVRIESSSASLAN GHTLDLNCLVASQAPHTITWYKRGGSLPSRHQIVGSRLRIPQVTP ADSGEYVCHVSNGAGSRETSLIVTIQGSGSSHVPSVSPPIRIESSSP TVVEGQTLDLNCVVARQPQAIITWYKRGGSLPSRHQTHGSHLRL HQMSVADSGEYVCRANNNIDALEASIVISVSPSAGSPSAPGSSMP IRIESSSSHVAEGETLDLNCVVPGQAHAQVTWHKRGGSLPSHHQ TRGSRLRLHHVSPADSGEYVCRVMGSSGPLEASVLVTIEASGSS AVHVPAPGGAPPIRIEPSSSRVAEGQTLDLKCVVPGQAHAQVTW HKRGGNLPARHQVHGPLLRLNQVSPADSGEYSCQVTGSSGTLE ASVLVTIEPSSPGPIPAPGLAQPIYIEASSSHVTEGQTLDLNCVVPG QAHAQVTWYKRGGSLPARHQTHGSQLRLHLVSPADSGEYVCR AASGPGPEQEASFTVTVPPSEGSSYRLRSPVISIDPPSSTVQQGQD ASFKCLIHDGAAPISLEWKTRNQELEDNVHISPNGSIITIVGTRPS NHGTYRCVASNAYGVAQSVVNLSVHGPPTVSVLPEGPVWVKV GKAVTLECVSAGEPRSSARWTRISSTPAKLEQRTYGLMDSHAVL QISSAKPSDAGTYVCLAQNALGTAQKQVEVIVDTGAMAPGAPQ VQAEEAELTVEAGHTATLRCSATGSPAPTIHWSKLRSPLPWQHR LEGDTLIIPRVAQQDSGQYICNATSPAGHAEATIILHVESPPYATT VPEHASVQAGETVQLQCLAHGTPPLTFQWSRVGSSLPGRATAR NELLHFERAAPEDSGRYRCRVTNKVGSAEAFAQLLVQGPPGSLP ATSIPAGSTPTVQVTPQLETKSIGASVEFHCAVPSDRGTQLRWFK EGGQLPPGHSVQDGVLRIQNLDQSCQGTYICQAHGPWGKAQAS AQLVIQALPSVLINIRTSVQTVVVGHAVEFECLALGDPKPQVTW SKVGGHLRPGIVQSGGVVRIAHVELADAGQYRCTATNAAGTTQ SHVLLLVQALPQISMPQEVRVPAGSAAVFPCIASGYPTPDISWSK LDGSLPPDSRLENNMLMLPSVRPQDAGTYVCTATNRQGKVKAF AHLQVPERVVPYFTQTPYSFLPLPTIKDAYRKFEIKITFRPDSADG MLLYNGQKRVPGSPTNLANRQPDFISFGLVGGRPEFRFDAGSGM ATIRHPTPLALGHFHTVTLLRSLTQGSLIVGDLAPVNGTSQGKFQ GLDLNEELYLGGYPDYGAIPKAGLSSGFIGCVRELRIQGEEIVFH DLNLTAHGISHCPTCRDRPCQNGGQCHDSESSSYVCVCPAGFTG SRCEHSQALHCHPEACGPDATCVNRPDGRGYTCRCHLGRSGLR CEEGVTVTTPSLSGAGSYLALPALTNTHHELRLDVEFKPLAPDG VLLFSGGKSGPVEDFVSLAMVGGHLEFRYELGSGLAVLRSAEPL ALGRWHRVSAERLNKDGSLRVNGGRPVLRSSPGKSQGLNLHTL LYLGGVEPSVPLSPATNMSAHFRGCVGEVSVNGKRLDLTYSFLG SQGIGQCYDSSPCERQPCQHGATCMPAGEYEFQCLCRDGFKGD LCEHEENPCQLREPCLHGGTCQGTRCLCLPGFSGPRCQQGSGHG IAESDWHLEGSGGNDAPGQYGAYFHDDGFLAFPGHVFSRSLPEV	

	PETIELEVRTSTASGLLLWQGVEVGEAGQGKDFISLGLQDGHLV FRYQLGSGEARLVSEDPINDGEWHRVTALREGRRGSIQVDGEEL VSGRSPGPNVAVNAKGSVYIGGAPDVATLTGGRFSSGITGCVKN LVLHSARPGAPPPQPLDLQHRAQAGANTRPCPS	
Perlecan, residues 3653-4392 of NP_001278 789.1	AFAHLQVPERVVPYFTQTPYSFLPLPTIKDAYRKFEIKITFRPDSA DGMLLYNGQKRVPGSPTNLANRQPDFISFGLVGGRPEFRFDAGS GMATIRHPTPLALGHFHTVTLLRSLTQGSLIVGDLAPVNGTSQG KFQGLDLNEELYLGGYPDYGAIPKAGLSSGFIGCVRELRIQGEEI VFHDLNLTAHGISHCPTCRDRPCQNGGQCHDSESSSYVCVCPAG FTGSRCEHSQALHCHPEACGPDATCVNRPDGRGYTCRCHLGRS GLRCEEGVTVTTPSLSGAGSYLALPALTNTHHELRLDVEFKPLA PDGVLLFSGGKSGPVEDFVSLAMVGGHLEFRYELGSGLAVLRSA EPLALGRWHRVSAERLNKDGSLRVNGGRPVLRSSPGKSQGLNL HTLLYLGGVEPSVPLSPATNMSAHFRGCVGEVSVNGKRLDLTYS FLGSQGIGQCYDSSPCERQPCQHGATCMPAGEYEFQCLCRDGFK GDLCEHEENPCQLREPCLHGGTCQGTRCLCLPGFSGPRCQQGSG HGIAESDWHLEGSGGNDAPGQYGAYFHDDGFLAFPGHVFSRSL PEVPETIELEVRTSTASGLLLWQGVEVGEAGQGKDFISLGLQDG HLVFRYQLGSGEARLVSEDPINDGEWHRVTALREGRRGSIQVDG EELVSGRSPGPNVAVNAKGSVYIGGAPDVATLTGGRFSSGITGC VKNLVLHSARPGAPPPQPLDLQHRAQAGANTRPCPS	161

[00229] In some cases, recombinant proteins of the disclosure may be coexpressed with follistatin and/or FLRG. Such recombinant proteins may include, but are not limited to GDF-8. Both follistatin and FLRG are known to antagonize some TGF-β family member proteins, including, but not limited to GDF-8 (Lee, S-J. et al., 2010. Mol Endocrinol. 24(10):1998-2008, Takehara-Kasamatsu, Y. et al., 2007. J Med Invest. 54(3-4):276-88, the contents of each of which are herein incorporated by reference in their entirety). Follistatin has been shown to block GDF-8 activity by binding to the free growth factor and preventing receptor binding. Both follistatin and FLRG are implicated in modulating growth factor activity during development.

[00230] In some embodiments, recombinant proteins of the disclosure may be coexpressed with decorin. Such recombinant proteins may include, but are not limited to TGF-β and GDF-8. Decorin is a known antagonist of TGF-β activity (Zhu, J. et al., 2007. J Biol Chem. 282:25852-63, the cotents of which are herein incorporated by reference in their entirety) and may also antagonize other TGF-β family members, including, but not limited to GDF-8. Decorin-dependent inhibition of TGF-β and GDF-8 activity has been shown to reduce fibrosis in various tissues. Decorin expression has also been shown to increase the expression of follistatin, a known inhibitor of free GDF-8.

[00231] In some embodiments, recombinant proteins of the present disclosure may comprise those depicted in FIG. 8. Some recombinant proteins of the present disclosure may

comprise one or more features and/or combinations of protein modules from the embodiments depicted in FIG. 8.

Chimeric proteins

[00232] In some embodiments, recombinant proteins of the present disclosure may comprise chimeric proteins. As used herein, the term "chimeric protein" refers to a protein comprising one or more protein modules from at least two different proteins [formed from the same gene (e.g. variants arising from alternative splicing) or from different genes]. Chimeric proteins may comprise protein modules from two or more TGF-β family member proteins. Such chimeric proteins may comprise protein modules from TGF-β1, TGF-β2 and/or TGF-β3. Some chimeric proteins of the present disclosure may comprise protein modules including, but not limited to the protein modules and/or amino acid sequences listed in Table 9 (residue numbers correspond to the pro-protein sequences listed in Table 1). Some chimeric proteins of the present disclosure may comprise protein modules comprising amino acid sequences similar to those in Table 9, but comprising additional or fewer amino acids than those listed. Such modules may comprise about 1 more or fewer amino acids, about 2 more or fewer amino acids, about 3 more or fewer amino acids, about 4 more or fewer amino acids, about 5 more or fewer amino acids, about 6 more or fewer amino acids, about 7 more or fewer amino acids, about 8 more or fewer amino acids, about 9 more or fewer amino acids, about 10 more or fewer amino acids or greater than 10 more or fewer amino acids on N-terminal and/or C-terminal ends.

Table 9. Protein modules

Protein	Residues	Sequence	SEQ ID NO
GDF-8	1-75	NENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKIQIL SKLRLETAPNISKDVIRQLLPKAPPLRELIDQYDVQR	162
GDF-8	1-64	NENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKIQIL SKLRLETAPNISKDVIRQLLPKAPPL	40
GDF-8	75 – end	RDDSSDGSLEDDDYHATTETIITMPTESDFLMQVDGK PKCCFFKFSSKIQYNKVVKAQLWIYLRPVETPTTVFV QILRLIKPMKDGTRYTGIRSLKLDMNPGTGIWQSIDVK TVLQNWLKQPESNLGIEIKALDENGHDLAVTFPGPGE DGLNPFLEVKVTDTPKRSRRDFGLDCDEHSTESRCCR YPLTVDFEAFGWDWIIAPKRYKANYCSGECEFVFLQK YPHTHLVHQANPRGSAGPCCTPTKMSPINMLYFNGK EQIIYGKIPAMVVDRCGCS	163
GDF8	65-end	RELIDQYDVQRDDSSDGSLEDDDYHATTETIITMPTES DFLMQVDGKPKCCFFKFSSKIQYNKVVKAQLWIYLR PVETPTTVFVQILRLIKPMKDGTRYTGIRSLKLDMNPG TGIWQSIDVKTVLQNWLKQPESNLGIEIKALDENGHD	164

		LAVTFPGPGEDGLNPFLEVKVTDTPKRSRRDFGLDCD EHSTESRCCRYPLTVDFEAFGWDWIIAPKRYKANYCS GECEFVFLQKYPHTHLVHQANPRGSAGPCCTPTKMSP INMLYFNGKEQIIYGKIPAMVVDRCGCS	
GDF8	65-243	RELIDQYDVQRDDSSDGSLEDDDYHATTETIITMPTES DFLMQVDGKPKCCFFKFSSKIQYNKVVKAQLWIYLR PVETPTTVFVQILRLIKPMKDGTRYTGIRSLKLDMNPG TGIWQSIDVKTVLQNWLKQPESNLGIEIKALDENGHD LAVTFPGPGEDGLNPFLEVKVTDTPKRSRR	45
GDF-8	76-243	DDSSDGSLEDDDYHATTETIITMPTESDFLMQVDGKP KCCFFKFSSKIQYNKVVKAQLWIYLRPVETPTTVFVQI LRLIKPMKDGTRYTGIRSLKLDMNPGTGIWQSIDVKT VLQNWLKQPESNLGIEIKALDENGHDLAVTFPGPGED GLNPFLEVKVTDTPKRSRR	165
GDF-8	244-352	DFGLDCDEHSTESRCCRYPLTVDFEAFGWDWIIAPKR YKANYCSGECEFVFLQKYPHTHLVHQANPRGSAGPC CTPTKMSPINMLYFNGKEQIIYGKIPAMVVDRCGCS	42
GDF-11	1-86	AEGPAAAAAAAAAAAAAGVGGERSSRPAPSVAPEPD GCPVCVWRQHSRELRLESIKSQILSKLRLKEAPNISRE VVKQLLPKAPPL	41
GDF-11	1-96	AEGPAAAAAAAAAAAAAGVGGERSSRPAPSVAPEPD GCPVCVWRQHSRELRLESIKSQILSKLRLKEAPNISRE VVKQLLPKAPPLQQILDLHDFQ	166
GDF-11	1-108	AEGPAAAAAAAAAAAAAGVGGERSSRPAPSVAPEPD GCPVCVWRQHSRELRLESIKSQILSKLRLKEAPNISRE VVKQLLPKAPPLQQILDLHDFQGDALQPEDFLEE	167
GDF-11	97-274	GDALQPEDFLEEDEYHATTETVISMAQETDPAVQTDG SPLCCHFHFSPKVMFTKVLKAQLWVYLRPVPRPATV YLQILRLKPLTGEGTAGGGGGGRRHIRIRSLKIELHSR SGHWQSIDFKQVLHSWFRQPQSNWGIEINAFDPSGTD LAVTSLGPGAEGLHPFMELRVLENTKRSRR	168
GDF-11	87-274	QQILDLHDFQGDALQPEDFLEEDEYHATTETVISMAQ ETDPAVQTDGSPLCCHFHFSPKVMFTKVLKAQLWVY LRPVPRPATVYLQILRLKPLTGEGTAGGGGGGRRHIRI RSLKIELHSRSGHWQSIDFKQVLHSWFRQPQSNWGIEI NAFDPSGTDLAVTSLGPGAEGLHPFMELRVLENTKRS RR	46
GDF-11	275-383	NLGLDCDEHSSESRCCRYPLTVDFEAFGWDWIIAPKR YKANYCSGQCEYMFMQKYPHTHLVQQANPRGSAGP CCTPTKMSPINMLYFNDKQQIIYGKIPGMVVDRCGCS	43
Inhibin Beta A	1-64	SPTPGSEGHSAAPDCPSCALAALPKDVPNSQPEMVEA VKKHILNMLHLKKRPDVTQPVPKAALL	169
Inhibin Beta A	1-76	SPTPGSEGHSAAPDCPSCALAALPKDVPNSQPEMVEA VKKHILNMLHLKKRPDVTQPVPKAALLNAIRKLHVG KVG	170
Inhibin Beta A	65-288	NAIRKLHVGKVGENGYVEIEDDIGRRAEMNELMEQT SEIITFAESGTARKTLHFEISKEGSDLSVVERAEVWLFL KVPKANRTRTKVTIRLFQQQKHPQGSLDTGEEAEEVG LKGERSELLLSEKVVDARKSTWHVFPVSSSIQRLLDQ GKSSLDVRIACEQCQESGASLVLLGKKKKKEEEGEGK KKGGGEGGAGADEEKEQSHRPFLMLQARQSEDHPHR RR	171
Inhibin Beta A	65-289	NAIRKLHVGKVGENGYVEIEDDIGRRAEMNELMEQT SEIITFAESGTARKTLHFEISKEGSDLSVVERAEVWLFL	172

		KVPKANRTRTKVTIRLFQQQKHPQGSLDTGEEAEEVG LKGERSELLLSEKVVDARKSTWHVFPVSSSIQRLLDQ GKSSLDVRIACEQCQESGASLVLLGKKKKKEEEGEGK KKGGGEGGAGADEEKEQSHRPFLMLQARQSEDHPHR RRR	
Inhibin Beta A	65-290	NAIRKLHVGKVGENGYVEIEDDIGRRAEMNELMEQT SEIITFAESGTARKTLHFEISKEGSDLSVVERAEVWLFL KVPKANRTRTKVTIRLFQQQKHPQGSLDTGEEAEEVG LKGERSELLLSEKVVDARKSTWHVFPVSSSIQRLLDQ GKSSLDVRIACEQCQESGASLVLLGKKKKKEEEGEGK KKGGGEGGAGADEEKEQSHRPFLMLQARQSEDHPHR RRRR	173
Inhibin Beta A	77-289	ENGYVEIEDDIGRRAEMNELMEQTSEIITFAESGTARK TLHFEISKEGSDLSVVERAEVWLFLKVPKANRTRTKV TIRLFQQQKHPQGSLDTGEEAEEVGLKGERSELLLSEK VVDARKSTWHVFPVSSSIQRLLDQGKSSLDVRIACEQ CQESGASLVLLGKKKKKEEEGEGKKKGGGEGGAGA DEEKEQSHRPFLMLQARQSEDHPHRRRR	174
Inhibin Beta A	77-290	ENGYVEIEDDIGRRAEMNELMEQTSEIITFAESGTARK TLHFEISKEGSDLSVVERAEVWLFLKVPKANRTRTKV TIRLFQQQKHPQGSLDTGEEAEEVGLKGERSELLLSEK VVDARKSTWHVFPVSSSIQRLLDQGKSSLDVRIACEQ CQESGASLVLLGKKKKKEEEGEGKKKGGGEGGAGA DEEKEQSHRPFLMLQARQSEDHPHRRRRR	175
Inhibin Beta A	77-end	ENGYVEIEDDIGRRAEMNELMEQTSEIITFAESGTARK TLHFEISKEGSDLSVVERAEVWLFLKVPKANRTRTKV TIRLFQQQKHPQGSLDTGEEAEEVGLKGERSELLLSEK VVDARKSTWHVFPVSSSIQRLLDQGKSSLDVRIACEQ CQESGASLVLLGKKKKKEEEGEGKKKGGGEGGAGA DEEKEQSHRPFLMLQARQSEDHPHRRRRRGLECDGK VNICCKKQFFVSFKDIGWNDWIIAPSGYHANYCEGEC PSHIAGTSGSSLSFHSTVINHYRMRGHSPFANLKSCCV PTKLRPMSMLYYDDGQNIIKKDIQNMIVEECGCS	176
Inhibin Beta A	291-406	GLECDGKVNICCKKQFFVSFKDIGWNDWIIAPSGYHA NYCEGECPSHIAGTSGSSLSFHSTVINHYRMRGHSPFA NLKSCCVPTKLRPMSMLYYDDGQNIIKKDIQNMIVEE CGCS	177

[00233] In some embodiments, chimeric proteins of the present disclosure may comprise combinations of any of the protein modules listed in Table 9. Some chimeric proteins comprising GPCs may comprise protein modules that have been substituted with any of the protein modules listed in Table 9.

[00234] In some embodiments, chimeric proteins may comprise protein modules from GDFs and/or inhibins. Such GDFs may include GDF-11 and/or GDF-8. Some such chimeric proteins may comprise a prodomain from GDF-11 and a growth factor from GDF-8. In such embodiments, chimeric proteins may comprise substituted N-terminal regions between GDF-11 and GDF-8. In other embodiments, chimeric proteins may comprise a prodomain from GDF-8 and a growth factor from GDF-11. Such chimeric proteins may comprise amino acid

residues 1-108 from GDF-11 and amino acid residues 90-the end of the protein from GDF-8. Some chimeric proteins may comprise an arm region from GDF-11.

[00235] Some chimerics of the present disclosure may comprise GDF-8 comprising an arm region of GDF-11. Such chimerics may be unstable due to steric clash between residue F95 from the GDF-11 arm and the α2 helix of the chimeric GPC. Therefore, in some cases, GDF8/GDF11/Activin chimeras may be designed so that the ARM region of such chimeric proteins contains the 2 helix. Furthermore, F95 may be an important residue in conferring latency for GDF11. This residue is in a similar position as a Camurati-Engelmann mutation found in TGF- 1, Y81H (see FIG. 6), thus, mutation of this residue to a smaller amino acid, such as an Alanine, may be carried out to promote dissociation of the mature GDF11 growth factor from the GPC. Such mutants may be useful as positive control molecules in designing assays to screen for GDF11 activating antibodies.

[00236] In some embodiments, chimeric proteins of the present disclosure may comprise protein module combinations including, but not limited to the combinations of protein modules and/or amino acid sequences listed in Table 10. Some chimeric proteins of the present disclosure may comprise protein modules comprising amino acid sequences similar to those in Table 10, but comprising additional or fewer amino acids than those listed. Such amino acid sequences may comprise about 1 more or fewer amino acids, about 2 more or fewer amino acids, about 3 more or fewer amino acids, about 4 more or fewer amino acids, about 5 more or fewer amino acids, about 6 more or fewer amino acids, about 7 more or fewer amino acids, about 8 more or fewer amino acids, about 9 more or fewer amino acids, about 10 more or fewer amino acids or greater than 10 more or fewer amino acids on N-terminal and/or C-terminal ends. In some cases, these sequences are expressed in association with N- and/or C-terminal secretion signal sequences [e.g. human Ig kappa chains with amino acid sequence MDMRVPAQLLGLLLLWFSGVLG (SEQ ID NO: 66)], flag tag sequences [e.g. DYKDDDDK (SEQ ID NO: 67)], one or more 3C protease cleavage site [e.g. LEVLFQGP (SEQ ID NO: 68)], one or more biotinylation site and/or His-tag sequences [e.g. HHHHHH (SEQ ID NO: 69)].

Table 10. Protein module combinations

Protein module 1	Protein module 2	Protein module 3	Chimeric Sequence	SEQ ID NO
GDF-11 (1-96)	GDF-8 (76-243)	GDF-11 (275-383)	AEGPAAAAAAAAAAAAAGVGGERSSRPAPSVAP EPDGCPVCVWRQHSRELRLESIKSQILSKLRLKEA PNISREVVKQLLPKAPPLQQILDLHDFQDDSSDGS	178

			LEDDDYHATTETIITMPTESDFLMQVDGKPKCCFF KFSSKIQYNKVVKAQLWIYLRPVETPTTVFVQILR LIKPMKDGTRYTGIRSLKLDMNPGTGIWQSIDVKT VLQNWLKQPESNLGIEIKALDENGHDLAVTFPGP GEDGLNPFLEVKVTDTPKRSRRNLGLDCDEHSSE SRCCRYPLTVDFEAFGWDWIIAPKRYKANYCSGQ CEYMFMQKYPHTHLVQQANPRGSAGPCCTPTKM SPINMLYFNDKQQIIYGKIPGMVVDRCGCS	
GDF-11 (1-86)	GDF-8 (65-243)	GDF-11 (275-383)	AEGPAAAAAAAAAAAAAGVGGERSSRPAPSVAP EPDGCPVCVWRQHSRELRLESIKSQILSKLRLKEA PNISREVVKQLLPKAPPLRELIDQYDVQRDDSSDG SLEDDDYHATTETIITMPTESDFLMQVDGKPKCCF FKFSSKIQYNKVVKAQLWIYLRPVETPTTVFVQIL RLIKPMKDGTRYTGIRSLKLDMNPGTGIWQSIDV KTVLQNWLKQPESNLGIEIKALDENGHDLAVTFP GPGEDGLNPFLEVKVTDTPKRSRRNLGLDCDEHS SESRCCRYPLTVDFEAFGWDWIIAPKRYKANYCS GQCEYMFMQKYPHTHLVQQANPRGSAGPCCTPT KMSPINMLYFNDKQQIIYGKIPGMVVDRCGCS	179
GDF-11 (1-96)	GDF-8 (76-243)	N/A	AEGPAAAAAAAAAAAAAGVGGERSSRPAPSVAP EPDGCPVCVWRQHSRELRLESIKSQILSKLRLKEA PNISREVVKQLLPKAPPLQQILDLHDFQDDSSDGS LEDDDYHATTETIITMPTESDFLMQVDGKPKCCFF KFSSKIQYNKVVKAQLWIYLRPVETPTTVFVQILR LIKPMKDGTRYTGIRSLKLDMNPGTGIWQSIDVKT VLQNWLKQPESNLGIEIKALDENGHDLAVTFPGP GEDGLNPFLEVKVTDTPKRSRR	180
GDF-11 (1-86)	GDF-8 (65-243)	NA	AEGPAAAAAAAAAAAAAGVGGERSSRPAPSVAP EPDGCPVCVWRQHSRELRLESIKSQILSKLRLKEA PNISREVVKQLLPKAPPLRELIDQYDVQRDDSSDG SLEDDDYHATTETIITMPTESDFLMQVDGKPKCCF FKFSSKIQYNKVVKAQLWIYLRPVETPTTVFVQIL RLIKPMKDGTRYTGIRSLKLDMNPGTGIWQSIDV KTVLQNWLKQPESNLGIEIKALDENGHDLAVTFP GPGEDGLNPFLEVKVTDTPKRSRR	181
GDF-11 (1-96)	Inhibin Beta A (77-290)	GDF-11 (275-383)	AEGPAAAAAAAAAAAAAGVGGERSSRPAPSVAP EPDGCPVCVWRQHSRELRLESIKSQILSKLRLKEA PNISREVVKQLLPKAPPLQQILDLHDFQENGYVEI EDDIGRRAEMNELMEQTSEIITFAESGTARKTLHF EISKEGSDLSVVERAEVWLFLKVPKANRTRTKVTI RLFQQQKHPQGSLDTGEEAEEVGLKGERSELLLS EKVVDARKSTWHVFPVSSSIQRLLDQGKSSLDVRI ACEQCQESGASLVLLGKKKKKEEEGEGKKKGGG EGGAGADEEKEQSHRPFLMLQARQSEDHPHRRR RRNLGLDCDEHSSESRCCRYPLTVDFEAFGWDWI IAPKRYKANYCSGQCEYMFMQKYPHTHLVQQAN PRGSAGPCCTPTKMSPINMLYFNDKQQIIYGKIPG MVVDRCGCS	182
GDF-11 (1-86)	Inhibin Beta A (65-290)	GDF-11 (275-383)	AEGPAAAAAAAAAAAAAGVGGERSSRPAPSVAP EPDGCPVCVWRQHSRELRLESIKSQILSKLRLKEA PNISREVVKQLLPKAPPLNAIRKLHVGKVGENGY VEIEDDIGRRAEMNELMEQTSEIITFAESGTARKTL HFEISKEGSDLSVVERAEVWLFLKVPKANRTRTK VTIRLFQQQKHPQGSLDTGEEAEEVGLKGERSELL	183

			LSEKVVDARKSTWHVFPVSSSIQRLLDQGKSSLD VRIACEQCQESGASLVLLGKKKKKEEEGEGKKKG GGEGGAGADEEKEQSHRPFLMLQARQSEDHPHR RRRRNLGLDCDEHSSESRCCRYPLTVDFEAFGWD WIIAPKRYKANYCSGQCEYMFMQKYPHTHLVQQ ANPRGSAGPCCTPTKMSPINMLYFNDKQQIIYGKI PGMVVDRCGCS	
GDF-11 (1-96)	Inhibin Beta A (77-290)	N/A	AEGPAAAAAAAAAAAAAGVGGERSSRPAPSVAP EPDGCPVCVWRQHSRELRLESIKSQILSKLRLKEA PNISREVVKQLLPKAPPLQQILDLHDFQENGYVEI EDDIGRRAEMNELMEQTSEIITFAESGTARKTLHF EISKEGSDLSVVERAEVWLFLKVPKANRTRTKVTI RLFQQQKHPQGSLDTGEEAEEVGLKGERSELLLS EKVVDARKSTWHVFPVSSSIQRLLDQGKSSLDVRI ACEQCQESGASLVLLGKKKKKEEEGEGKKKGGG EGGAGADEEKEQSHRPFLMLQARQSEDHPHRRR RR	184
GDF-11 (1-86)	Inhibin Beta A (65-290)	NA	AEGPAAAAAAAAAAAAAGVGGERSSRPAPSVAP EPDGCPVCVWRQHSRELRLESIKSQILSKLRLKEA PNISREVVKQLLPKAPPLNAIRKLHVGKVGENGY VEIEDDIGRRAEMNELMEQTSEIITFAESGTARKTL HFEISKEGSDLSVVERAEVWLFLKVPKANRTRTK VTIRLFQQQKHPQGSLDTGEEAEEVGLKGERSELL LSEKVVDARKSTWHVFPVSSSIQRLLDQGKSSLD VRIACEQCQESGASLVLLGKKKKKEEEGEGKKKG GGEGGAGADEEKEQSHRPFLMLQARQSEDHPHR RRRR	185
GDF-8 (1-75)	GDF-11 (97-274)	GDF-8 (244-352)	NENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKI QILSKLRLETAPNISKDVIRQLLPKAPPLRELIDQY DVQRGDALQPEDFLEEDEYHATTETVISMAQETD PAVQTDGSPLCCHFHFSPKVMFTKVLKAQLWVY LRPVPRPATVYLQILRLKPLTGEGTAGGGGGRR HIRIRSLKIELHSRSGHWQSIDFKQVLHSWFRQPQS NWGIEINAFDPSGTDLAVTSLGPGAEGLHPFMELR VLENTKRSRRDFGLDCDEHSTESRCCRYPLTVDFE AFGWDWIIAPKRYKANYCSGECEFVFLQKYPHTH LVHQANPRGSAGPCCTPTKMSPINMLYFNGKEQII YGKIPAMVVDRCGCS	186
GDF-8 (1-64)	GDF-11 (87-274)	GDF-8 (244-352)	NENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKI QILSKLRLETAPNISKDVIRQLLPKAPPLQQILDLH DFQGDALQPEDFLEEDEYHATTETVISMAQETDP AVQTDGSPLCCHFHFSPKVMFTKVLKAQLWVYL RPVPRPATVYLQILRLKPLTGEGTAGGGGGRRHI RIRSLKIELHSRSGHWQSIDFKQVLHSWFRQPQSN WGIEINAFDPSGTDLAVTSLGPGAEGLHPFMELRV LENTKRSRRDFGLDCDEHSTESRCCRYPLTVDFEA FGWDWIIAPKRYKANYCSGECEFVFLQKYPHTHL VHQANPRGSAGPCCTPTKMSPINMLYFNGKEQIIY GKIPAMVVDRCGCS	187
GDF-8 (1-75)	GDF-11 (97-274)	N/A	NENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKI QILSKLRLETAPNISKDVIRQLLPKAPPLRELIDQY DVQRGDALQPEDFLEEDEYHATTETVISMAQETD PAVQTDGSPLCCHFHFSPKVMFTKVLKAQLWVY LRPVPRPATVYLQILRLKPLTGEGTAGGGGGRR	188

			HIRIRSLKIELHSRSGHWQSIDFKQVLHSWFRQPQS NWGIEINAFDPSGTDLAVTSLGPGAEGLHPFMELR VLENTKRSRR	
GDF-8 (1-64)	GDF-11 (87-274)	GDF-8 (244-352)	NENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKI QILSKLRLETAPNISKDVIRQLLPKAPPLQQILDLH DFQGDALQPEDFLEEDEYHATTETVISMAQETDP AVQTDGSPLCCHFHFSPKVMFTKVLKAQLWVYL RPVPRPATVYLQILRLKPLTGEGTAGGGGGGRRHI RIRSLKIELHSRSGHWQSIDFKQVLHSWFRQPQSN WGIEINAFDPSGTDLAVTSLGPGAEGLHPFMELRV LENTKRSRRDFGLDCDEHSTESRCCRYPLTVDFEA FGWDWIIAPKRYKANYCSGECEFVFLQKYPHTHL VHQANPRGSAGPCCTPTKMSPINMLYFNGKEQIIY GKIPAMVVDRCGCS	189
GDF-8 (1-75)	Inhibin Beta A (77-289)	GDF-8 (244-352)	NENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKI QILSKLRLETAPNISKDVIRQLLPKAPPLRELIDQY DVQRENGYVEIEDDIGRRAEMNELMEQTSEIITFA ESGTARKTLHFEISKEGSDLSVVERAEVWLFLKVP KANRTRTKVTIRLFQQQKHPQGSLDTGEEAEEVG LKGERSELLLSEKVVDARKSTWHVFPVSSSIQRLL DQGKSSLDVRIACEQCQESGASLVLLGKKKKKEE EGEGKKKGGGEGGAGADEEKEQSHRPFLMLQAR QSEDHPHRRRRDFGLDCDEHSTESRCCRYPLTVD FEAFGWDWIIAPKRYKANYCSGECEFVFLQKYPH THLVHQANPRGSAGPCCTPTKMSPINMLYFNGKE QIIYGKIPAMVVDRCGCS	190
GDF-8 (1-64)	Inhibin Beta A (65-290)	GDF-8 (244-352)	NENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKI QILSKLRLETAPNISKDVIRQLLPKAPPLNAIRKLH VGKVGENGYVEIEDDIGRRAEMNELMEQTSEIITF AESGTARKTLHFEISKEGSDLSVVERAEVWLFLK VPKANRTRTKVTIRLFQQQKHPQGSLDTGEEAEE VGLKGERSELLLSEKVVDARKSTWHVFPVSSSIQR LLDQGKSSLDVRIACEQCQESGASLVLLGKKKKK EEEGEGKKKGGGEGGAGADEEKEQSHRPFLMLQ ARQSEDHPHRRRRRDFGLDCDEHSTESRCCRYPL TVDFEAFGWDWIIAPKRYKANYCSGECEFVFLQK YPHTHLVHQANPRGSAGPCCTPTKMSPINMLYFN GKEQIIYGKIPAMVVDRCGCS	191
GDF-8 (1-75)	Inhibin Beta A (77-290)	N/A	NENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKI QILSKLRLETAPNISKDVIRQLLPKAPPLRELIDQY DVQRENGYVEIEDDIGRRAEMNELMEQTSEIITFA ESGTARKTLHFEISKEGSDLSVVERAEVWLFLKVP KANRTRTKVTIRLFQQQKHPQGSLDTGEEAEEVG LKGERSELLLSEKVVDARKSTWHVFPVSSSIQRLL DQGKSSLDVRIACEQCQESGASLVLLGKKKKKEE EGEGKKKGGGEGGAGADEEKEQSHRPFLMLQAR QSEDHPHRRRRR	192
GDF-8 (1-64)	Inhibin Beta A (65-290)	NA	NENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKI QILSKLRLETAPNISKDVIRQLLPKAPPLNAIRKLH VGKVGENGYVEIEDDIGRRAEMNELMEQTSEIITF AESGTARKTLHFEISKEGSDLSVVERAEVWLFLK VPKANRTRTKVTIRLFQQQKHPQGSLDTGEEAEE VGLKGERSELLLSEKVVDARKSTWHVFPVSSSIQR LLDQGKSSLDVRIACEQCQESGASLVLLGKKKKK	193

			EEEGEGKKKGGGEGGAGADEEKEQSHRPFLMLQ ARQSEDHPHRRRRR	
Inhibin Beta A (1-76)	GDF-8 (76-243)	Inhibin Beta A (291-406)	SPTPGSEGHSAAPDCPSCALAALPKDVPNSQPEM VEAVKKHILNMLHLKKRPDVTQPVPKAALLNAIR KLHVGKVGDDSSDGSLEDDDYHATTETIITMPTES DFLMQVDGKPKCCFFKFSSKIQYNKVVKAQLWIY LRPVETPTTVFVQILRLIKPMKDGTRYTGIRSLKLD MNPGTGIWQSIDVKTVLQNWLKQPESNLGIEIKA LDENGHDLAVTFPGPGEDGLNPFLEVKVTDTPKR SRRGLECDGKVNICCKKQFFVSFKDIGWNDWIIAP SGYHANYCEGECPSHIAGTSGSSLSFHSTVINHYR MRGHSPFANLKSCCVPTKLRPMSMLYYDDGQNII KKDIQNMIVEECGCS	194
Inhibin Beta A (1-64)	GDF-8 (65-243)	Inhibin Beta A (291-406)	SPTPGSEGHSAAPDCPSCALAALPKDVPNSQPEM VEAVKKHILNMLHLKKRPDVTQPVPKAALLRELI DQYDVQRDDSSDGSLEDDDYHATTETIITMPTES DFLMQVDGKPKCCFFKFSSKIQYNKVVKAQLWIY LRPVETPTTVFVQILRLIKPMKDGTRYTGIRSLKLD MNPGTGIWQSIDVKTVLQNWLKQPESNLGIEIKA LDENGHDLAVTFPGPGEDGLNPFLEVKVTDTPKR SRRGLECDGKVNICCKKQFFVSFKDIGWNDWIIAP SGYHANYCEGECPSHIAGTSGSSLSFHSTVINHYR MRGHSPFANLKSCCVPTKLRPMSMLYYDDGQNII KKDIQNMIVEECGCS	195
Inhibin Beta A (1-76)	GDF-8 (76-243)	N/A	SPTPGSEGHSAAPDCPSCALAALPKDVPNSQPEM VEAVKKHILNMLHLKKRPDVTQPVPKAALLNAIR KLHVGKVGDDSSDGSLEDDDYHATTETIITMPTES DFLMQVDGKPKCCFFKFSSKIQYNKVVKAQLWIY LRPVETPTTVFVQILRLIKPMKDGTRYTGIRSLKLD MNPGTGIWQSIDVKTVLQNWLKQPESNLGIEIKA LDENGHDLAVTFPGPGEDGLNPFLEVKVTDTPKR SRR	196
Inhibin Beta A (1-64)	GDF-8 (65-243)	NA	SPTPGSEGHSAAPDCPSCALAALPKDVPNSQPEM VEAVKKHILNMLHLKKRPDVTQPVPKAALLRELI DQYDVQRDDSSDGSLEDDDYHATTETIITMPTES DFLMQVDGKPKCCFFKFSSKIQYNKVVKAQLWIY LRPVETPTTVFVQILRLIKPMKDGTRYTGIRSLKLD MNPGTGIWQSIDVKTVLQNWLKQPESNLGIEIKA LDENGHDLAVTFPGPGEDGLNPFLEVKVTDTPKR SRR	197
Inhibin Beta A (1-76)	GDF-11 (97-274)	Inhibin Beta A (291-406)	SPTPGSEGHSAAPDCPSCALAALPKDVPNSQPEM VEAVKKHILNMLHLKKRPDVTQPVPKAALLNAIR KLHVGKVGGDALQPEDFLEEDEYHATTETVISMA QETDPAVQTDGSPLCCHFHFSPKVMFTKVLKAQL WVYLRPVPRPATVYLQILRLKPLTGEGTAGGGGG GRRHIRIRSLKIELHSRSGHWQSIDFKQVLHSWFR QPQSNWGIEINAFDPSGTDLAVTSLGPGAEGLHPF MELRVLENTKRSRRGLECDGKVNICCKKQFFVSF KDIGWNDWIIAPSGYHANYCEGECPSHIAGTSGSS LSFHSTVINHYRMRGHSPFANLKSCCVPTKLRPMS MLYYDDGQNIIKKDIQNMIVEECGCS	198
Inhibin Beta A (1-64)	GDF-11 (87-274)	Inhibin Beta A (291-	SPTPGSEGHSAAPDCPSCALAALPKDVPNSQPEM VEAVKKHILNMLHLKKRPDVTQPVPKAALLQQIL DLHDFQGDALQPEDFLEEDEYHATTETVISMAQE	199

		406)	TDPAVQTDGSPLCCHFHFSPKVMFTKVLKAQLW VYLRPVPRPATVYLQILRLKPLTGEGTAGGGGGG RRHIRIRSLKIELHSRSGHWQSIDFKQVLHSWFRQ PQSNWGIEINAFDPSGTDLAVTSLGPGAEGLHPFM ELRVLENTKRSRRGLECDGKVNICCKKQFFVSFK DIGWNDWIIAPSGYHANYCEGECPSHIAGTSGSSL SFHSTVINHYRMRGHSPFANLKSCCVPTKLRPMS MLYYDDGQNIIKKDIQNMIVEECGCS	
Inhibin Beta A (1-76)	GDF-11 (97-274)	N/A	SPTPGSEGHSAAPDCPSCALAALPKDVPNSQPEM VEAVKKHILNMLHLKKRPDVTQPVPKAALLNAIR KLHVGKVGGDALQPEDFLEEDEYHATTETVISMA QETDPAVQTDGSPLCCHFHFSPKVMFTKVLKAQL WVYLRPVPRPATVYLQILRLKPLTGEGTAGGGGG GRRHIRIRSLKIELHSRSGHWQSIDFKQVLHSWFR QPQSNWGIEINAFDPSGTDLAVTSLGPGAEGLHPF MELRVLENTKRSRR	200
Inhibin Beta A (1-64)	GDF-11 (87-274)	NA	SPTPGSEGHSAAPDCPSCALAALPKDVPNSQPEM VEAVKKHILNMLHLKKRPDVTQPVPKAALLQQIL DLHDFQGDALQPEDFLEEDEYHATTETVISMAQE TDPAVQTDGSPLCCHFHFSPKVMFTKVLKAQLW VYLRPVPRPATVYLQILRLKPLTGEGTAGGGGGG RRHIRIRSLKIELHSRSGHWQSIDFKQVLHSWFRQ PQSNWGIEINAFDPSGTDLAVTSLGPGAEGLHPFM ELRVLENTKRSRR	201

[00237] Chimeric proteins may be used to characterize and/or map epitopes associated with GPCs. As used herein, the terms "map" or "mapping" refer to the identification, characterization and/or determination of one or more functional regions of one or more proteins. Such characterizations may be necessary for determining interactions between one or more protein modules and another agent (e.g. another protein and/or protein module). Some chimeric proteins may be used to characterize functions associated with one or more proteins and/or protein modules.

[00238] In some embodiments, chimeric proteins of the disclosure may comprise GPCs with trigger loops from alternative TGF-β family member proteins. Such chimeric proteins may have altered properties with regard to integrin-dependent activation. According to mouse tissue staining, integrin subunit α_9 is widely expressed in skeletal and cardiac muscle, visceral smooth muscle, hepatocytes, airway epithelium, squamous epithelium, choroid plexus epithelium and also on neutrophils (Palmer, E.L. et al., Sequence and tissue distribution of the integrin α_9 subunit, a novel partner of β1 that is widely distributed in epithelia and muscle. Journal of Cell Biology. 1993. 123(5):1289-97). Expression of α_9 is not detected earlier than E12.5, suggesting that it does not play a major role in the earliest tissue morphogenesis (Wang, A. et al., Expression of the integrin subunit α_9 in the murine embryo. Developmental Dynamics. 1995. 204:421-31). In vivo functions of α_9 are unclear.

Phenotypes observed in knockout mice suggest a role in lymphatic valve development (Bazigou, E. et al., Integrin- α_9 is required for fibronectin matrix assembly during lymphatic valve morphogenesis. Dev Cell. 2009 August. 17(2):175-86). Reported interaction partners of integrin $\alpha_9\beta_1$ include VCAM-1, the third FnIII domain on tenascin C, osteopontin, polydom/SVEP1, VEGF-A and NGF (Yokasaki, Y. et al., Identification of the ligand binding site for the integrin $\alpha_9\beta_1$ in the third fibronectin type III repeat of tenascin C. The Journal of Biological Chemistry. 1998. 273(19):11423-8; Marcinkiewicz, C. et al., Inhibitory effects of MLDG-containing heterodimeric disintegrins reveal distinct structural requirements for interaction of the integrin $\alpha_9\beta_1$ with VCAM-1, tenascin-C, and osteopontin. JBC. 2000. 275(41):31930-7; Oommen, S. et al., Vacular endothelial growth factor A (VEGF-A) induces endothelial and cancer cell migration through direct binding to integrin $\alpha_9\beta_1$. JBC. 2011. 286(2):1083-92; Sato-Nishiuchi, R. et al., Polydom/SVEP1 is a ligand for integrin $\alpha_9\beta_1$. JBC. 2012. 287(30):25615-30; Staniszewska, I. et al., Integrin $\alpha_9\beta_1$ is a receptor for nerve growth factor and other neurotrophins. Journal of Cell Science. 2007. 121(Pt 4):504-13; Yokosaki, Y. et al., The integrin $\alpha_9\beta_1$ binds to a novel recognition sequence (SVVYGLR; SEQ ID NO: 202) in the thrombin-cleaved amino-terminal fragment of osteopontin. JBC. 1999. 274(51):36328-34).

[00239] Binding sites on proteins that interact with $\alpha_9\beta_1$ have been mapped using linear peptides. These sites include binding sites on tenascin C (AEIDGIEL; SEQ ID NO: 203), osteopontin (SVVYGLR; SEQ ID NO: 202), polydom/SVEP1 (EDDMMEVPY; SEQ ID NO: 204) and VEGF-A (EYP). Unlike $\alpha_4\beta_1$ and $\alpha_5\beta_1$, $\alpha_9\beta_1$ does not require a canonical RGD sequence motif. Some, but not all reported targets have an acidic residue/hydrophobic residue/proline motif. Some also comprise a tyrosine residue.

[00240] The trigger loop of TGF-β1 and TGF-β3 carries an RGD sequence where $\alpha_v\beta_6$ and/or $\alpha_v\beta_8$ bind to enable growth factor release. The TGF-β2 trigger loop region is different from those of TGF-β1 and TGF-β3, comprising the sequence FAGIDGTSTYTSGDQKTIKSTRKKNSGKTP (SEQ ID NO: 205), without an RGD trimer. Of this region, residues AGIDGTST (SEQ ID NO: 206) align with the peptide on the third FnIII domain of tenascin-C that has been mapped as an $\alpha_9\beta_1$ binding site. Also, the tyrosine following this region may play a role in potential $\alpha_9\beta_1$ binding. Therefore, $\alpha_9\beta_1$ binding to TGF-β2 could be physiologically relevant. In some embodiments, chimeric proteins of the present disclosure may comprise trigger loop sequences comprising any of the sequences listed in Table 11.

Table 11. Trigger loop sequences

Source protein	Trigger loop sequence	SEQ ID NO
TGF-β2	FAGIDGTSTYTSGDQKTIKSTRKKNSGKTP	205
TGF-β2	AGIDGTST	206
TGF-β2 (short)	GTSTYTSGDQKTIKSTRKK	207
TGF-β1	INGFTTGRRGDLATIHGMNRP	208
TGF-β1	SGRRGDLATI	209
TGF-β1	TGRRGDLATI	210
TGF-β3	FKGVDNEDDHGRGDLGRLKKQKDHHNP	211
GDF-8	PGEDGLNP	212
GDF-11	PGAEGLHP	213
Inhibin A	RPEATP	214
BMP-9	SHRKGCDTLDISVPPGSRNLP	215
BMP-2	RHVRISRSLHQDEHSWSQIRP	216
BMP-4	QHVRISRSLPQGSGNWAQLRP	217
BMP-7	IGRHGPQNKQP	218
BMP-6	VGRDGPYDKQP	219
BMP-8	LGQRAPRSQQP	220
Lefty1	RFASQGAPAGLGEP	221
osteopontin	SVVYGLR	202
tenascin C	AEIDGIEL	203
polydom/SVEP1	EDDMMEVPY	204
VEGF-A	EYP	--

[00241] In some embodiments, chimeric proteins of the present disclosure may comprise one or more TGF-β2 trigger loops. Such chimeric proteins may exhibit activation (e.g. growth factor release) regulated in a manner similar to that of TGF-β2. Some chimeric proteins of the present disclosure may comprise TGF-β-related proteins wherein one or more protein modules are substituted with one or more protein modules comprising one or more TGF-β2 trigger loops. Some chimeric proteins comprise TGF-β-related proteins wherein one or more protein modules comprising at least one RGD sequence are substituted with one or more protein modules comprising one or more TGF-β2 trigger loops. In other embodiments, chimeric proteins may comprise TGF-β1 and/or TGF-β3 proteins wherein one or more protein modules comprising at least one RGD sequence are substituted with one or more protein modules comprising one or more TGF-β2 trigger loops. Such chimeric proteins may exhibit TGF-β1 activity.

[00242] In some embodiments, chimeric proteins of the present disclosure may comprise one or more protein modules from BMPs. Protein modules comprising sequences from BMPs

may comprise sequences from any of those BMP modules disclosed in FIG. 6. Chimeric proteins of the present disclosure comprising one or more BMP protein module may be useful for the development of antibodies and/or assays to study, enhance and/or perturb BMP interactions with other proteins, including, but not limited to RGM proteins.

[00243] Chimeric proteins may comprise detectable labels. Detectable labels may be used to allow for detection and/or isolation of chimeric proteins. Such detectable labels may comprise biotin labels, polyhistidine tags and/or flag tags. Tags may be used to identify and/or isolate tagged proteins. Proteins produced may comprise additional amino acids encoding one or more 3C protease cleavage site. Such sites allow for cleavage at the 3C protease cleavage site upon treatment with 3C protease, including, but not limited to rhinovirus 3C protease. 3C protease cleavage sites may be introduced to allow for removal of detectable labels from chimeric proteins.

Protein expression

[00244] In some embodiments, synthesis of recombinant proteins of the present disclosure may be carried out according to any method known in the art. Some protein synthesis may be carried out *in vitro*. Some protein synthesis may be carried out using cells. Such cells may be bacterial and/or eukaryotic. In some embodiments, eukaryotic cells may be used for protein synthesis. Some such cells may be mammalian. Some mammalian cells used for protein expression may include, but are not limited to mouse cells, rabbit cells, rat cells, monkey cells, hamster cells and human cells. Such cells may be derived from a cell line. In other embodiments, human cells may be used. In further embodiments, cell lines may include, but are not limited to HEK293 cells, CHO cells, HeLa cells, Sw-480 cells, EL4 T lymphoma cells, TMLC cells, 293T/17 cells, Hs68 cells, CCD1112sk cells, HFF-1 cells, Keloid fibroblasts, A204 cells, L17 RIB cells, C_2C_{12} cells and HepG2 cells.

[00245] In some embodiments, 293 cells are used for synthesis of recombinant proteins of the present disclosure. These cells are human cells that post-translationally modify proteins with human-like structures (e.g. glycans). Such cells are easily transfectable and scalable and are able to grow to high densities in suspension culture. 293 cells may include 293E cells. 293E cells are HEK293 cells stably expressing EBNA1 (Epstein-Barr virus nuclear antigen-1). In some cases, 293E cells may be grown in serum-free medium to simplify down-stream purification. In some cases, 293-6E cells (NRC Canada, Ottawa, CA) may be used. Such cells express truncated EBNA1 (EBNA1t) and may comprise enhanced production of recombinant proteins and may be optimized for growth and/or protein expression in serum-free medium to

simplify down-stream purification. In some cases, insect cells may be used to express recombinant proteins of the disclosure. In some cases, insect cell expression may be carried out using Spodoptera frugiperda cells including, but not limited to Sf9 and/or Sf-21 cells. In some cases, insect cell cultures may comprise Trichoplusia ni cells, including, but not limited to Tn-368 and/or HIGH-FIVE™ BTI-TN-5B1-4 cells. A further list of exemplary insect cell lines can be found in US Patent No. 5,024,947, the contents of which are herein incorporated by reference in their entirety.

[00246] In some embodiments, recombinant proteins of the disclosure may comprise an antibody Fc domain to create an Fc fusion protein. The formation of an Fc fusion protein with any of the recombinant proteins described herein may be carried out according to any method known in the art, including as described in Czajkowsky, D.M. et al., 2012. EMBO Mol Med. 4(10):1015-28 and US Patent Nos. 5,116,964, 5,541,087 and 8,637,637, the contents of each of which are herein incorporated by reference in their entirety. In some cases, proteins that may be difficult to express may be expressed as Fc fusion proteins to enhance protein stability and allow for expression and, in some cases, subsequent use as antigens. Fc fusion proteins of the disclosure may be linked to the hinge region of an IgG Fc via cysteine residues in the Fc hinge region. Resulting Fc fusion proteins may comprise an antibody-like structure, but without C_{H1} domains or light chains. In some cases, Fc fusion proteins may comprise pharmacokinetic profiles comparable to native antibodies. In some cases, Fc fusion proteins of the disclosure may comprise an extended half-life in circulation and/or altered biological activity. In some cases, Fc fusion proteins of the disclosure may be prepared using any of the TGF-β family proteins or TGF-β-related proteins described herein. In some cases, Fc fusion proteins may comprise TGF-β, GDF-8 and/or GDF-11.

[00247] In some embodiments, Fc domains may comprise the amino acid sequence DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG K (SEQ ID NO: 222). Some examples of Fc fusion proteins of the disclosure are presented in Table 12 below. Included in the Table, is an Fc fusion protein comprising a mutated GDF-11 prodomain sequence. The mutation is in a site that may, in some cases, be subjected to cleavage (e.g. by furin or similar enzyme). Fusion proteins with the mutation indicated may be resistant to such cleavage and thereby retain association with the Fc domain. Further, the

fusion proteins listed comprise an N-terminal secretion signal and and C-terminal histidine tag; however, variants without such elements are also contemplated.

Table 12. Fc fusion proteins

Protein	Amino Acid Sequence	SEQ ID NO
GDF-8 prodomain Fc-fusion protein	MDMRVPAQLLGLLLLWFSGVLGNENSEQKENVEKEGLCNACT WRQNTKSSRIEAIKIQILSKLRLETAPNISKDVIRQLLPKAPPLRELI DQYDVQRDDSSDGSLEDDDYHATTETIITMPTESDFLMQVDGKP KCCFFKFSSKIQYNKVVKAQLWIYLRPVETPTTVFVQILRLIKPM KDGTRYTGIRSLKLDMNPGTGIWQSIDVKTVLQNWLKQPESNLG IEIKALDENGHDLAVTFPGPGEDGLNPFLEVKVTDTPKRSDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEM TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG KHHHHHH	223
GDF-8 prodomain D76A Fc-fusion protein	MDMRVPAQLLGLLLLWFSGVLGNENSEQKENVEKEGLCNACT WRQNTKSSRIEAIKIQILSKLRLETAPNISKDVIRQLLPKAPPLRELI DQYDVQRADSSDGSLEDDDYHATTETIITMPTESDFLMQVDGKP KCCFFKFSSKIQYNKVVKAQLWIYLRPVETPTTVFVQILRLIKPM KDGTRYTGIRSLKLDMNPGTGIWQSIDVKTVLQNWLKQPESNLG IEIKALDENGHDLAVTFPGPGEDGLNPFLEVKVTDTPKRSDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEM TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG KHHHHHH	224
mutant GDF-11 prodomain Fc-fusion protein	MDMRVPAQLLGLLLLWFSGVLGAEGPAAAAAAAAAAAAAGVG GEASSAPAPSVAPEPDGCPVCVWRQHSRELRLESIKSQILSKLRL KEAPNISREVVKQLLPKAPPLQQILDLHDFQGDALQPEDFLEEDE YHATTETVISMAQETDPAVQTDGSPLCCHFHFSPKVMFTKVLKA QLWVYLRPVPRPATVYLQILRLKPLTGEGTAGGGGGGRRHIRIRS LKIELHSRSGHWQSIDFKQVLHSWFRQPQSNWGIEINAFDPSGTD LAVTSLGPGAEGLHPFMELRVLENTKRSDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKHHHHHH	225
GDF-11 prodomain Fc-fusion protein	MDMRVPAQLLGLLLLWFSGVLGAEGPAAAAAAAAAAAAAGVG GERSSRPAPSVAPEPDGCPVCVWRQHSRELRLESIKSQILSKLRLK EAPNISREVVKQLLPKAPPLQQILDLHDFQGDALQPEDFLEEDEY HATTETVISMAQETDPAVQTDGSPLCCHFHFSPKVMFTKVLKAQ LWVYLRPVPRPATVYLQILRLKPLTGEGTAGGGGGGRRHIRIRSL KIELHSRSGHWQSIDFKQVLHSWFRQPQSNWGIEINAFDPSGTDL AVTSLGPGAEGLHPFMELRVLENTKRSDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS	226

	NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKHHHHHH	

[00248] Sequences encoding recombinant proteins of the present disclosure may be inserted into any number of DNA vectors known in the art for expression. Such vectors may include plasmids. In some embodiments, sequences encoding recombinant proteins of the present disclosure are cloned into pTT5 vectors (NRC Biotechnology Research Institute, Montréal, Québec). In other embodiments pTT22, pTT28, pYD5, pYD7, pYD11(NRC Biotechnology Institute, Montréal, Québec) and/or pMA vectors (Life Technologies, Carlsbad, CA) may be used. Vectors may comprise promoter sequences to modulate expression of sequences encoding recombinant proteins of the present disclosure. Such promoters may be constitutively active and/or may be regulated by extrinsic and/or intrinsic factors. Some extrinsic factors may be used to enhance or suppress expression of sequences encoding recombinant proteins of the present disclosure. Some vectors may encode nuclear localization signals that may be incorporated into recombinant proteins of the present disclosure upon translation. Some vectors may produce mRNA transcripts that comprise nuclear export signals. RNA transcribed from a modified pTT5 vector (pTT5-WPRE) contains an element that facilitates nuclear export of the transcripts. Some vectors may be modified by insertion of one or more ligation-independent cloning (LIC) cassettes to provide for simpler cloning.

[00249] Vectors encoding recombinant proteins of the present disclosure may be delivered to cells according to any method known in the art, including, but not limited to transfection, electroporation and/or transduction. In some embodiments, vectors may comprise one or more elements to enhance vector replication in host cells. In some embodiments, vectors may comprise oriP sites for episomal replication in cells that express EBNA-1.

[00250] In some cases, cells are stably transfected to produce recombinant proteins of the present disclosure. Stably transfected cells pass transfected genes to daughter cells during cell division, thus eliminating the need for repeated transfection. In some cases, the transfected genes are stably inserted into the genome of the transfected cells. Transfected genes may comprise genes for cell selection, such as genes that confer resistance to one or more toxic or repressive compounds. Such genes may be used to support the growth of only cells with stable incorporation of the transfected genes when grown in the presence of such one or more toxic or repressive compounds (e.g. puromycin, kanamycin, etc.). Cell selection may also comprise selecting cells based on overall recombinant protein expression levels.

Determination of such levels may be carried out, for example, by Western Blot and/or ELISA.

[00251] In some embodiments, nucleotide sequences encoding recombinant proteins of the present disclosure may comprise one or more woodchuck hepatitis virus posttranscriptional regulatory element (WPRE). RNA nucleic acids comprising such elements may comprise the sequence GCCACGGCGGAACUCAUCGCCGCCUGCCUUGCCCGCUGCUGGACAGGGGCUCG GCUGUUGGGCACUGACAAUUCCGUGGU (SEQ ID NO: 227). RNA comprising WPREs may be transcribed from DNA comprising the sequence AATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACTATG TTGCTCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATT GCTTCCCGTATGGCTTTCATTTTCTCCTCCTTGTATAAATCCTGGTTGCTGTCTCTT TATGAGGAGTTGTGGCCCGTTGTCAGGCAACGTGGCGTGGTGTGCACTGTGTTTG CTGACGCAACCCCCACTGGTTGGGGCATTGCCACCACCTGTCAGCTCCTTTCCGG GACTTTCGCTTTCCCCCTCCCTATTGCCACGGCGGAACTCATCGCCGCCTGCCTTG CCCGCTGCTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGGTGTTGTC GGGGAAGCTGACGTCCTTTCCATGGCTGCTCGCCTGTGTTGCCACCTGGATTCTG CGCGGGACGTCCTTCTGCTACGTCCCTTCGGCCCTCAATCCAGCGGACCTTCCTTC CCGCGGCCTGCTGCCGGCTCTGCGGCCTCTTCCGCGTCTTCGCCTTCGCCCTCAGA CGAGTCGGATCTCCCTTTGGGCCGCCTCCCCGCCTG (SEQ ID NO: 228). WPREs may enhance translation of nucleic acids comprising WPREs. Such enhanced translation may be due to increased cytoplasmic export of newly transcribed mRNA.

[00252] In some embodiments, recombinant proteins may comprise one or more secretion signal sequences. As used herein, the term "secretion signal sequence" refers to a chain of amino acids (or nucleotides that encode them at the nucleic acid level) that when part of a protein, modulate secretion of such proteins from cells. Some secretion signal sequences may be located at protein termini. In other embodiments, secretion signal sequences may be N-terminal amino acid sequences. Other secretions signal sequences may comprise the secretion signal of the Ig kappa chains. Such Ig kappa chains may be human Ig kappa chains. In some embodiments, secretion signal sequences may comprise the amino acid sequence MDMRVPAQLLGLLLLWFSGVLG (SEQ ID NO: 66).

[00253] In some embodiments, recombinant proteins of the present disclosure may require coexpression with one or more other proteins for proper expression, folding, secretion,

activity and/or function. Some recombinant GPCs of the present disclosure may be coexpressed with LTBPs, fibrillins, GASPs, perlecan and/or decorin.

[00254] In some embodiments, recombinant proteins of the present disclosure may be biotinylated. As used herein, the term "biotinylating" refers to the attaching of one or more biotin labels. Such biotin labels may facilitate interactions of biotinylated recombinant proteins with avidin and/or streptavidin coated surfaces and/or proteins. As used herein, a "biotin label" refers to a detectable label comprising one or more biotin molecules. The term "biotinylated" refers to a molecule or protein that comprises one or more biotin labels. Biotin molecules bind with high affinity to avidin and streptavidin molecules. This property may be used to capture biotinylated proteins using avidin and/or stretavidin coated materials. Some recombinant GPCs of the present disclosure may be biotinylated near the N-terminus. Such recombinant GPCs may be introduced to avidin/streptavidin coated cell culture surfaces, allowing biotinylated recombinant GPCs to adhere to the surface in a manner such that the orientation and bonding of such bound GPCs mimics the orientation and bonding of GPCs to extracellular proteins (e.g. LTBPs, fibrillins, GASPs, perlecan and/or decorin).

[00255] In some embodiments, recombinant proteins produced may be analyzed for quality control purposes to assess both biophysical properties as well as bioactive properties. Biophysical characterization may include assessing protein migration patterns after reducing and/or non-reducing SDS PAGE. Biophysical characterization may also comprise gel filtration, mass spectrometric analysis and/or analysis of association/dissociation between LAPs or LAP-like domains and growth factor domains. Bioactive properties may be analyzed by assessing reactivity with antibodies and/or signaling activity of dissociated growth factors and/or latent GPCs.

[00256] Some proteins produced may comprise additional amino acids encoding one or more detectable labels for purification [e.g. polyhistidine tag, flag tag, etc.] In some embodiments, proteins are N-terminally labeled. In some embodiments, proteins are C-terminally labeled. In some embodiments, proteins are biotinylated. In some embodiments, recombinant proteins of the present disclosure are N-terminally biotinylated.

[00257] Proteins produced may comprise additional amino acids encoding one or more 3C protease cleavage site. Such sites allow for cleavage between residues Q and G of the 3C protease cleavage site upon treatment with 3C protease, including, but not limited to rhinovirus 3C protease. In some embodiments, such cleavage sites are introduced to allow for removal of detectable labels from recombinant proteins.

[00258] In some embodiments, modification of expressed growth factor proproteins may be carried out by enzymatic cleavage. In some cases, proprotein convertases may be used. Such proprotein convertases may include, but are not limited to furin/PACE3, PC1/3, PC2, PC4, PC5/6, PACE4 and PC7. Proprotein convertase cleavage may be carried out in solution or in tissue culture. In some cases, proprotein convertases are expressed in cells expressing proproteins to be cleaved. In some cases, proprotein convertases are added to tissue cultures of cells expressing proproteins to be cleaved.

Antibodies

[00259] In some embodiments, compounds and/or compositions of the present disclosure may comprise antibodies or fragments thereof. As used herein, the term "antibody" is referred to in the broadest sense and specifically covers various embodiments including, but not limited to monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g. bispecific antibodies formed from at least two intact antibodies), and antibody fragments such as diabodies so long as they exhibit a desired biological activity. Antibodies are primarily amino-acid based molecules but may also comprise one or more modifications (including, but not limited to the addition of sugar moieties, fluorescent moieties, chemical tags, etc.).

Recombinant and chimeric protein use in antibody generation

[00260] In some embodiments, recombinant and/or chimeric proteins described herein may be used as antigens (referred to herein as antigenic proteins) to generate antibodies. Such antigenic proteins may comprise epitopes that may be less accessible for antibody generation in similar wild type proteins. Some antibodies directed to antigenic proteins of the present disclosure may modulate the release of one or more growth factors from one or more GPCs). Some such antibodies may be stabilizing [reducing or preventing dissociation between two agents, (e.g. growth-factor release from GPCs, GPC release from one or more protein interactions)] and/or releasing [enhancing the dissociation between two agents (e.g. growth-factor release from GPCs, GPC release from one or more protein interactions)] antibodies. Antigenic proteins of the present disclosure may comprise TGF-β-related proteins as well as components and/or protein modules thereof. In some cases, antigenic proteins of the present disclosure may comprise prodomains without associated growth factors, furin cleavage-deficient mutants, mutants deficient in extracellular protein associations and/or combinations thereof.

[00261] In some embodiments, antigenic proteins may comprise TGF-β-related proteins and/or modules thereof. Such antigenic proteins may comprise epitopes from regions where growth factors associate with or comprise stereological proximity with prodomain regions. Antibodies of the present disclosure directed to such epitopes may bind overlapping regions between growth factors and prodomains. Such antibodies may stereologically inhibit the dissociation of growth factors from GPCs.

[00262] In some embodiments, antigenic proteins comprise only the prodomain or only the growth factor from a particular GPC. Epitopes present on such antigenic proteins may be shielded or unexposed in intact GPCs. Some antibodies of the present disclosure may be directed to such epitopes. Such antibodies may be releasing antibodies, promoting growth factor dissociation from GPCs. Further antibodies may compete with free growth factor for prodomain binding, thereby promoting growth factor dissociation from GPCs.

[00263] In some embodiments, antigenic proteins may comprise proprotein convertase (e.g. furin) cleavage site mutations. Such mutations may prevent enzymatic cleavage of growth factors from their prodomains. Some antibodies of the present disclosure may be directed to epitopes present on such mutant proteins. Such antibodies may stabilize the association between prodomains and growth factors. In some embodiments, furin cleavage site mutants comprise D2G mutants as described herein.

[00264] In some embodiments, antigenic proteins comprising prodomains may comprise N-terminal mutations that lead to decreased prodomain association with extracellular proteins and therefore may present epitopes in the N-terminal region that may otherwise be shielded by those associations. Some antibodies of the present disclosure may be directed to such epitopes.

[00265] In some embodiments, antigenic proteins may comprise one or more recombinant LTBP. Such recombinant LTBPs may comprise LTBP1, LTBP2, LTBP3, LTBP4, alternatively spliced variants and/or fragments thereof. Recombinant LTBPs may also be modified to comprise one or more detectable labels. Such detectable labels may include, but are not limited to biotin labels, polyhistidine tags, myc tags, HA tags and/or fluorescent tags.

[00266] In some embodiments, antigenic proteins may comprise one or more recombinant protein and/or chimeric protein complexed with one or more recombinant LTBP. Some antigenic proteins may comprise proprotein convertase cleavage site mutants (e.g. D2G mutants, AXXA mutants) complexed with one or more recombinant LTBP. Some such recombinant LTBPs may comprise LTBP1S. Some recombinant LTBPs may comprise one or

more detectable labels, including, but not limited to biotin labels, polyhistidine tags and/or flag tags.

[00267] In some embodiments, antigenic proteins of the present disclosure may comprise one or more protein modules from GDFs (e.g. GDF-11 and/or GDF-8). In some embodiments, antibodies of the present disclosure may be directed toward antigenic proteins comprising GDF-8 protein modules. In some embodiments, such antibodies may modulate GDF-8 levels and/or activity in one or more niches. In some embodiments, antibodies of the present disclosure may prevent the release of GDF-8 growth factors from GPCs. In some embodiments, antibodies of the present disclosure may be used to repair and/or enhance muscle tissues.

[00268] In some embodiments, recombinant proteins (including, but not limited to chimeric proteins) described herein may be used in studies to identify and map epitopes that may be important targets for antibody development. Such studies may be used to identify epitopes that may promote growth factor release or stabilization of GPCs upon antibody binding.

[00269] In some cases, recombinant proteins of the disclosure may comprise recombinant binding proteins, including, but not limited to antibodies, antibody fragments and fusion proteins comprising one or more antibodies or antibody fragments. Such recombinant binding proteins may comprise one or more regions from one or more antibodies developed using one or more recombinant antigens described herein.

Releasing antibodies

[00270] As used herein, the term "releasing antibody" refers to an antibody that increases the ratio of active and/or free growth factor relative to inactive and/or prodomain-associated growth factor upon the introduction of the antibody to a GPC, cell, niche, natural depot or any other site of growth factor sequestration. In this context, releasing antibodies may be characterized as agonists. As used herein, the term "natural depot" refers to a location within a cell, tissue or organ where increased levels of a biomolecule or ion are stored. For example, the extracellular matrix may act as a natural depot for one or more growth factors.

[00271] The contact necessary for growth-factor release may be defined as direct or indirect contact of antibody with a GPC or a component thereof or with a cellular structure such as an extracellular and/or cellular matrix protein and/or protein associated with the extracellular and/or cellular matrix [e.g. LTBPs (e.g. LTBP1, LTBP2, LTBP3 and/or LTBP4), fibrillins (e.g. fibrillin-1, fibrillin-2, fibrillin-3 and/or fibrillin-4), perlecan, decorin, elastin, collagen, GASPs and/or GARPs (e.g. GARP and/or LRRC33)] for release of growth

factor. Release of at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more of growth factor is sufficient to characterize antibodies of the present disclosure as releasing antibodies. It is understood that growth factor release after antibody administration may be local and may occur over a sustained period of time and may include peaks or spikes of release. Antibodies of the present disclosure may act to release one or more growth factor over minutes, hours, days or longer.

[00272] Release profiles may have an initial peak or burst within from about 4 hours to about 7 days of contacting in vivo or shorter periods in vitro. For example, initial peak or burst may occur from about 4 hours to about 5 hours, or from about 4 hours to about 6 hours, or from about 4 hours to about 7 hours, or from about 4 hours to about 8 hours, or from about 4 hours to about 9 hours, or from about 4 hours to about 10 hours, or from about 4 hours to about 11 hours, or from about 4 hours to about 12 hours, or from about 4 hours to about 24 hours, or from about 4 hours to about 36 hours, or from about 4 hours to about 48 hours, or from about 1 day to about 7 days, or from about 1 day to about 2 days, or from about 1 day to about 3 days, or from about 1 day to about 4 days, or from about 4 days to about 5 days, or from about 4 days to about 6 days, or from about 4 days to about 7 days. Compounds and/or compositions of the present disclosure may stimulate the release of 5 to 100% of the growth factor present. For example, the percent of growth factor release may be from about 5% to about 10%, or from about 5% to about 15%, or from about 5% to about 20%, or from about 5% to about 25%, or from about 10% to about 30%, or from about 10% to about 40%, or from about 10% to about 50%, or from about 10% to about 60%, or from about 20% to about 70%, or from about 20% to about 80%, or from about 40% to about 90%, or from about 40% to about 100%.

[00273] Releasing antibodies generated according to methods described herein may be generated to release growth factors from GPCs comprising any of the pro-proteins listed in Table 1. In some cases, releasing antibodies are directed to GPCs comprising GDFs and/or one or more modules from GDFs.

Stabilizing antibodies

[00274] As used herein, the term "stabilizing antibody" refers to an antibody that decreases the ratio of active and/or free growth factor relative to inactive and/or prodomain-associated growth factor upon the introduction of the antibody to one or more GPC, cell, niche, natural depot and/or any other site of growth factor sequestration. In this context, antibodies may be characterized as antagonists. As used herein, an "antagonist" is one which interferes with or

inhibits the physiological action of another. Antagonist action may even result in stimulation or activation of signaling downstream and hence may act agonistically relative to another pathway, separate from the one being antagonized. Pathways are interrelated, so, in one nonlimiting example, a TGF-β antagonist could act as a BMP agonist and vice versa. In the context of cellular events, as used herein, the term "downstream" refers to any signaling or cellular event that happens after the action, binding or targeting by compounds and/or compositions of the present disclosure.

[00275] Contact necessary for inhibition or stabilization may be direct or indirect contact between antibody and GPC or components thereof or with cellular structures such as an extracellular and/or cellular matrix protein and/or protein associated with the extracellular and/or cellular matrix [e.g. LTBPs (e.g. LTBP1, LTBP2, LTBP3 and/or LTBP4), fibrillins (e.g. fibrillin-1, fibrillin-2, fibrillin-3 and/or fibrillin-4), perlecan, decorin, elastin, collagen, GASPs and/or GARPs (e.g. GARP and/or LRRC33)] whereby release of growth factor is inhibited. Inhibition of release of at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more of growth factors may be sufficient, in some cases, to characterize antibodies of the present disclosure as inhibitory or stabilizing. Inhibitory antibodies may stabilize GPCs and trap them as heterodimers.

[00276] It is understood that inhibition of growth factor release after contact with one or more antibodies of the present disclosure may be local and may occur over a sustained period of time and may include peaks, troughs or spikes. Inhibitory antibodies which may also function to stabilize GPCs may be defined by their release kinetics. Release of growth factor and corresponding release kinetics, even locally, may be directly measured or inferred by downstream signaling events. In some embodiments, changes in protein or nucleic acid concentrations or phenotypic responses may be indicative of the effects of compounds and/or compositions of the present disclosure.

[00277] Antibodies of the present disclosure may act to inhibit release of a growth factor over minutes, hours or days. Inhibition and/or stabilization profiles may have an initial trough within from about 4 hours to about 7 days of introduction in vivo or shorter periods in vitro. For example, initial trough of inhibition or stabilization may occur from about 4 hours to about 5 hours, or from about 4 hours to about 6 hours, or from about 4 hours to about 7 hours, or from about 4 hours to about 8 hours, or from about 4 hours to about 9 hours, or from about 4 hours to about 10 hours, or from about 4 hours to about 11 hours, or from about 4 hours to about 12 hours, or from about 4 hours to about 24 hours, or from about 4 hours to about 36 hours, or from about 4 hours to about 48 hours, or from about 1 day to about 7 days, or from

about 1 day to about 2 days, or from about 1 day to about 3 days, or from about 1 day to about 4 days, or from about 4 days to about 5 days, or from about 4 days to about 6 days, or from about 4 days to about 7 days. Introduction of compounds and/or compositions of the present disclosure may lead to inhibition and/or stabilization of 5% to 100% of growth factor present. For example, the percent of growth factor inhibition or stabilization may be from about 5% to about 10%, from about 5% to about 15%, from about 5% to about 20%, from about 5% to about 25%, from about 10% to about 30%, from about 10% to about 40%, from about 10% to about 50%, from about 10% to about 60%, from about 20% to about 70%, from about 20% to about 80%, from about 40% to about 90% or from about 40% to about 100%.

[00278] Stabilizing antibodies generated according to methods described herein may be generated to block the release of growth factors from GPCs comprising any of the pro-proteins listed in Table 1. Such antibodies may physically interact with GPC protease cleavage sites and/or block the interaction of proteolytic enzymes that may target such cleavage sites. In some cases, stabilizing antibodies are directed to GPCs comprising GDFs and/or one or more modules from GDFs.

[00279] Stabilizing antibodies directed to GPCs comprising GDF-8 may block metalloproteinase cleavage of such complexes. Such agents may bind to GPCs comprising GDF-8 in such a way as to physically prevent interactions between such GPCs and metalloproteinases targeting such GPCs. Agents that actually target metalloproteinases themselves have been described previously (see US Patent No. US 7,572,599, the contents of which are herein incorporated by reference in their entirety).

Antibody selection

[00280] A desired antibody may be selected from a larger pool of two or more candidate antibodies based on the desired antibody's ability to associate with desired antigens and/or epitopes. Such antigens and/or epitopes may include, but are not limited to any of those described herein, including, but not limited to recombinant proteins, chimeric proteins, GPCs, prodomains (e.g. LAPs or LAP-like domains), growth factors, protein modules, LTBPs, fibrillins, GASPs, TGF-β-related proteins and/or mutants and/or variants and/or complexes and/or combinations thereof. Selection of desired antibodies may be carried out using an antibody binding assay, such as a surface Plasmon resonance-based assay, an enzyme-linked immunosorbent assay (ELISA) or fluorescence flow cytometry-based assay. Such assays may utilize a desired antigen to bind a desired antibody and then use one or more detection methods to detect binding.

[00281] In some embodiments, antibodies of the present disclosure may be selected from a larger pool of two or more candidate antibodies based on their ability to associate with desired antigens and/or epitopes from multiple species (referred to herein as "positive selection.")

[00282] In some embodiments, such species may comprise vertebrate species. In some embodiments, such species may comprise mammalian species. In some embodiments, such species may include, but are not limited to mice, rats, rabbits, goats, sheep, pigs, horses, cows and/or humans.

[00283] In some embodiments, negative selection is used to remove antibodies from a larger pool of two or more candidate antibodies. As used herein the term "negative selection" refers to the elimination of one or more factors from a group based on their ability to bind to one or more undesired antigens and/or epitopes. In some embodiments, undesired antigens and/or epitopes may include, but are not limited to any of those described herein, including, but not limited to recombinant proteins, chimeric proteins, GPCs, prodomains (e.g. LAPs or LAP-like domains), growth factors, protein modules, LTBPs, fibrillins, GASPs, TGF-β-related proteins and/or mutants and/or variants and/or combinations and/or complexes thereof.

[00284] In some embodiments, antibodies of the present disclosure may be directed to prodomains (e.g. the prodomain portion of a GPC and/or free LAP or LAP-like domains) that decrease growth factor signaling and/or levels (e.g. GDF growth factor signaling and/or levels) in a given niche. In some embodiments, antibodies of the present disclosure directed to prodomains may increase growth factor signaling and/or levels in a given niche. In some embodiments, antibodies of the present disclosure may be directed to prodomains (e.g. LAPs or LAP-like domains) and/or GPCs only when complexed with one or more extracellular protein, such as LTBPs, fibrillins, perlican, decorin and/or GASPs.

[00285] In some embodiments, antibodies of the present disclosure may be selected from a larger pool of two or more candidate antibodies based on their ability to modulate growth factor levels and/or activity. In some cases, growth factor activity assays may be used to test the ability of candidate antibodies to modulate growth factor activity. Growth factor activity assays may include, cell-based assays as described hereinbelow. Additional assays that may be used to determine the effect of candidate antibodies on growth factor activity may include, but are not limited to enzyme-linked immunosorbent assay (ELISA), Western blotting, reporter assays (e.g. luciferase-based reporter assays or other enzyme-based reporter assays), PCR analysis, RT-PCR analysis and/or other methods known in the art including any of the

methods described in International Patent Application No. WO2014074532, the contents of which are herein incorporated by reference in their entirety.

[00286] In some embodiments, one or more recombinant proteins or antibodies disclosed herein may be used in assays to test, develop and/or select antibodies. Recombinant GPCs may be expressed to test releasing and/or stabilizing abilities of one or more antibodies being assayed. In some embodiments, recombinant proteins may be expressed as positive or negative control components of assays. In some embodiments, multiple recombinant proteins may be expressed at once to modulate growth factor release and/or activity, wherein such recombinant proteins may act synergistically or antagonistically in such modulation.

Antibody development

[00287] In some embodiments, compounds and/or compositions of the present disclosure comprising antibodies, antibody fragments, their variants or derivatives as described above are specifically immunoreactive with antigenic proteins as described herein.

[00288] Antibodies of the present disclosure may be characterized by their target molecule(s), by the antigens used to generate them, by their function (whether as agonists, antagonists, growth-factor releasing, GPC stabilizing, activating and/or inhibitory) and/or by the cell niche in which they function.

[00289] As used herein the term, “antibody fragment" refers to any portion of an intact antibody. In some embodiments, antibody fragments comprise antigen binding regions from intact antibodies. Examples of antibody fragments may include, but are not limited to Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules; and multispecific antibodies formed from antibody fragments. Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site. Also produced is a residual "Fc" fragment, whose name reflects its ability to crystallize readily. Pepsin treatment yields an $F(ab')_2$ fragment that has two antigen-binding sites and is still capable of cross-linking antigen. Compounds and/or compositions of the present disclosure may comprise one or more of these fragments. For the purposes herein, an "antibody" may comprise a heavy and light variable domain as well as an Fc region.

[00290] As used herein, the term "native antibody" refers to a usually heterotetrameric glycoprotein of about 150,000 daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Genes encoding antibody heavy and light chains are known and segments making up each have been well characterized and described (Matsuda, F. et al.,

1998. The Journal of Experimental Medicine. 188(11); 2151-62 and Li, A. et al., 2004. Blood. 103(12: 4602-9, the content of each of which are herein incorporated by reference in their entirety). Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies among the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain (V_H) followed by a number of constant domains. Each light chain has a variable domain at one end (V_L) and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain.

[00291] As used herein, the term "variable domain" refers to specific antibody domains found on both the antibody heavy and light chains that differ extensively in sequence among antibodies and are used in the binding and specificity of each particular antibody for its particular antigen. Variable domains comprise hypervariable regions. As used herein, the term "hypervariable region" refers to a region within a variable domain comprising amino acid residues responsible for antigen binding. The amino acids present within the hypervariable regions determine the structure of the complementarity determining regions (CDRs) that become part of the antigen-binding site of the antibody. As used herein, the term “CDR” refers to a region of an antibody comprising a structure that is complimentary to its target antigen or epitope. Other portions of the variable domain, not interacting with the antigen, are referred to as framework (FW) regions. The antigen-binding site (also known as the antigen combining site or paratope) comprises the amino acid residues necessary to interact with a particular antigen. The exact residues making up the antigen-binding site are typically elucidated by co-crystallography with bound antigen, however computational assessments can also be used based on comparisons with other antibodies (Strohl, W.R. Therapeutic Antibody Engineering. Woodhead Publishing, Philadelphia PA. 2012. Ch. 3, p47-54, the contents of which are herein incorporated by reference in their entirety).

[00292] V_H and V_L domains have three CDRs each. V_L CDRs are referred to herein as CDR-L1, CDR-L2 and CDR-L3, in order of occurance when moving from N- to C- terminus along the variable domain polypeptide. V_H CDRs are referred to herein as CDR-H1, CDR-H2 and CDR-H3, in order of occurance when moving from N- to C- terminus along the variable domain polypeptide. Each of CDRs have favored canonical structures with the exception of the CDR-H3, which comprises amino acid sequences that may be highly variable in sequence and length between antibodies resulting in a variety of three-dimensional

structures in antigen-binding domains (Nikoloudis, D. et al., 2014. PeerJ. 2:e456). In some cases, CDR-H3s may be analyzed among a panel of related antibodies to assess antibody diversity. Various methods of determining CDR sequences are known in the art and may be applied to known antibody sequences (Strohl, W.R. Therapeutic Antibody Engineering. Woodhead Publishing, Philadelphia PA. 2012. Ch. 3, p47-54, the contents of which are herein incorporated by reference in their entirety).

[00293] As used herein, the term "Fv" refers to an antibody fragment comprising the minimum fragment on an antibody needed to form a complete antigen-binding site. These regions consist of a dimer of one heavy chain and one light chain variable domain in tight, non-covalent association. Fv fragments can be generated by proteolytic cleavage, but are largely unstable. Recombinant methods are known in the art for generating stable Fv fragments, typically through insertion of a flexible linker between the light chain variable domain and the heavy chain variable domain [to form a single chain Fv (scFv)] or through the introduction of a disulfide bridge between heavy and light chain variable domains (Strohl, W.R. Therapeutic Antibody Engineering. Woodhead Publishing, Philadelphia PA. 2012. Ch. 3, p46-47, the contents of which are herein incorporated by reference in their entirety).

[00294] As used herein, the term "light chain" refers to a component of an antibody from any vertebrate species assigned to one of two clearly distinct types, called kappa and lambda based on amino acid sequences of constant domains. Depending on the amino acid sequence of the constant domain of their heavy chains, antibodies can be assigned to different classes. There are five major classes of intact antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA, and IgA2.

[00295] As used herein, the term "single chain Fv" or "scFv" refers to a fusion protein of V_H and V_L antibody domains, wherein these domains are linked together into a single polypeptide chain by a flexible peptide linker. In some embodiments, the Fv polypeptide linker enables the scFv to form the desired structure for antigen binding.

[00296] As used herein, the term "bispecific antibody" refers to an antibody capable of binding two different antigens. Such antibodies typically comprise regions from at least two different antibodies. Bispecific antibodies may include any of those described in Riethmuller, G. 2012. Cancer Immunity. 12:12-18, Marvin, J.S. et al., 2005. Acta Pharmacologica Sinica. 26(6):649-58 and Schaefer, W. et al., 2011. PNAS. 108(27):11187-92, the contents of each of which are herein incorporated by reference in their entirety.

[00297] As used herein, the term "diabody" refers to a small antibody fragment with two antigen-binding sites. Diabodies comprise a heavy chain variable domain V_H connected to a light chain variable domain V_L in the same polypeptide chain. By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al. (Hollinger, P. et al., "Diabodies":Small bivalent and bispecific antibody fragments. PNAS. 1993. 90:6444-8) the contents of each of which are incorporated herein by reference in their entirety.

[00298] As used herein, the term "monoclonal antibody" refers to an antibody obtained from a population of substantially homogeneous cells (or clones), i.e., the individual antibodies comprising the population are identical and/or bind the same epitope, except for possible variants that may arise during production of the monoclonal antibodies, such variants generally being present in minor amounts. In contrast to polyclonal antibody preparations that typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen

[00299] The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. The monoclonal antibodies herein include "chimeric" antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies.

[00300] As used herein, the term "humanized antibody" refers to a chimeric antibody comprising a minimal portion from one or more non-human (e.g., murine) antibody source with the remainder derived from one or more human immunoglobulin sources. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from the hypervariable region from an antibody of the recipient are replaced by residues from the hypervariable region from an antibody of a non-human species (donor antibody) such as mouse, rat, rabbit or nonhuman primate having the desired specificity, affinity, and/or capacity.

[00301] In some embodiments, compounds and/or compositions of the present disclosure may be antibody mimetics. As used herein, the term "antibody mimetic" refers to any molecule which mimics the function or effect of an antibody and which binds specifically and with high affinity to their molecular targets. In some embodiments, antibody mimetics may be monobodies, designed to incorporate the fibronectin type III domain (Fn3) as a protein scaffold (US 6,673,901; US 6,348,584). In some embodiments, antibody mimetics may be those known in the art including, but are not limited to affibody molecules, affilins, affitins, anticalins, avimers, Centyrins, DARPINS™, Fynomers and Kunitz and domain peptides. In other embodiments, antibody mimetics may include one or more non-peptide region.

[00302] As used herein, the term "antibody variant" refers to a biomolecule resembling an antibody in structure and/or function comprising some differences in their amino acid sequence, composition or structure as compared to a native antibody.

[00303] The preparation of antibodies, whether monoclonal or polyclonal, is known in the art. Techniques for the production of antibodies are well known in the art and described, e.g. in Harlow and Lane "Antibodies, A Laboratory Manual", Cold Spring Harbor Laboratory Press, 1988; Harlow and Lane "Using Antibodies: A Laboratory Manual" Cold Spring Harbor Laboratory Press, 1999 and "Therapeutic Antibody Engineering: Current and Future Advances Driving the Strongest Growth Area in the Pharmaceutical Industry" Woodhead Publishing, 2012.

Standard monoclonal antibody generation

[00304] In some embodiments, antibodies are generated in knockout mice, lacking the gene that encodes for desired target antigens. Such mice may not be tolerized to target antigens and therefore may be better suited for generating antibodies against such antigens that may cross react with human and mouse forms of the antigen. For the production of monoclonal antibodies, host mice may be immunized with recombinant proteins to elicit lymphocytes that specifically bind such proteins. Resulting lymphocytes may be collected and fused with immortalized cell lines. Resulting hybridoma cells may be cultured in suitable culture medium with selection agents to support the growth of only fused cells.

[00305] Desired hybridoma cell lines may be identified through binding specificity analysis of secreted antibodies for target peptides and clones of such cells may be subcloned through limiting dilution procedures and grown by standard methods. Antibodies produced by subcloned hybridoma cells may be isolated and purified from culture medium by standard immunoglobulin purification procedures

Recombinant antibodies

[00306] Recombinant antibodies of the present disclosure may be generated according to any of the methods disclosed in International Patent Application No. WO2014074532, the contents of which are herein incorporated by reference in their entirety. In some embodiments, recombinant antibodies may be produced using variable domains obtained from hybridoma cell-derived antibodies produced according to methods described herein. Heavy and light chain variable region cDNA sequences of antibodies may be determined using standard biochemical techniques. Total RNA may be extracted from antibody-producing hybridoma cells and converted to cDNA by reverse transcriptase (RT) polymerase chain reaction (PCR). PCR amplification may be carried out on resulting cDNA to amplify variable region genes. Such amplification may comprise the use of primers specific for amplification of heavy and light chain sequences. In other embodiments, recombinant antibodies may be produced using variable domains obtained from other sources. This includes the use of variable domains selected from one or more antibody fragment library, such as an scFv library used in antigen panning. Resulting PCR products may then be subcloned into plasmids for sequence analysis. Once sequenced, antibody coding sequences may be placed into expression vectors. For humanization, coding sequences for human heavy and light chain constant domains may be used to substitute for homologous murine sequences. The resulting constructs may then be transfected into mammalian cells for large scale translation.

GDF-8-modulatory antibodies

[00307] Some antibodies, presented herein, are GDF-8-modulatory antibodies. Such antibodies may bind GDF-8, a GDF-8 fragment or one or more protein complex comprising GDF-8. In some cases, these antibodies may be releasing antibodies or stabilizing antibodies with regard to GDF-8 growth factor release and/or activity. GDF-8-modulating antibodies of the disclosure may comprise or be developed using any of the scFv sequences listed in Table 13 or fragments thereof. The scFv sequences listed comprise a VH domain joined to a VL domain via a linker comprising the sequence ASAPTLGGGGSGGGGSAAA (SEQ ID NO: 229). Some recombinant GDF-modulating antibodies of the disclosure may be designed to include at least one variable domain pair (VH and VL) present in any of the scFvs listed in Table 13 or variants thereof with at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least

about 98%, at least about 99%, at least about 99.5% or at least about 99.9% sequence identity to any of the scFv sequences listed. Recombinant GDF-8-modulatory antibodies may, in some cases, comprise alternative combinantions of the VH and VL domains present in the scFvs presented. Further recombinant GDF-8-modulatory antibodies may, in some cases, comprise VH and/or VL domains presented, but with different combinations of CDRs. Some recombinant GDF-modulating antibodies of the disclosure may comprise or be developed using scFv sequences that comprise at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 99.5% or at least about 99.9% sequence identity to any of the scFv sequences listed in Table 13. In some cases, GDF-8-modulatory antibodies constructed using one or more of the scFv sequences presented in Table 13 may interact with one or more of the recombinant proteins listed in Tables 4, 9 or 10.

Table 13. scFv antibody fragments

Clone ID	scFv sequence	SEQ ID NO
BP6a-16	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEWL GRTYYRSKWSNDYAVAVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCA RGFSGMGVWGQGTTVTVSSGSASAPTLGGGGSGGGGSAAASSELTQDPA VSVALGQTASITCSGDKLGDKYASWYQQKPGQSPVMVIHQDSKRPSGIPE RFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTVVFGGGTKLTVLGQP KAAPSVTLFPPSS	230
BP6a-19	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDQ AGDYGGNSGYFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIQ MTQSPSTLSASAGDRVTITCRASQSISRWLAWYQQKPGKPPKLLIYGASSL QSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQTYTTPWTFGQGTKVEI KRTVAAPSVF	231
BP3a-3	EVQLVQSGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWV SGISWNSGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK GQVPNYYDSRDPFDPWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAEIV LTQSPGTLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYGASNR ATGIPARFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYTTPFTFGPGTKVDI KRTVAAPSVF	232
BP6a-1	QIQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARITD DFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADVVMTQTPLSLPV TLGQPASISCRSSQSLVYSDGNTYLNWFQQRPGQSPRRLIYKVSNRDSGVP DRFSGSGSGTDFTLKISRVEAEDVGVYYCMQSTRWPWVFGQGTKVEIKRT VAAPSVF	233
BP18b-1	QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARGV AGYSSGWSDWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIVMTQSP LSLPVTPGEPASISCRSSQTLLHSNGFNYLDWYLQKPGQSPQLLMYLGSKR	234

	ASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPFTFGPGTKV DIKRTVAAPSVF	
BP19b-1	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYI YYSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARLRRG YFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSALTQPASVSGSP GQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGVSNRFS GSKSGNTASLTISGLQAEDEADYYCSSYTSSSTFVVFGGGTKLTVLGQPKA APSVTLFPPSS	235
BP6b-4	QVQLVQSGAEVKKPGESLKISCAASGFTFSSYGMHWVRQAPGKGLEWVA VIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAT RGYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSALTQPPSASGSPG QSVTISCSGTSSDIGGYDYVSWYQQHPGKAPKLMIYDVSERPSGVSNRFSG SKSGNTASLTISGLQAEDEADYYCSSFTSSSTLVFGGGTKLTVLRQPKAAPS VTLFPPSS	236
BP6a-8	QVQLQQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEW MGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCA REGGDYNNWFDPWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSVLT QPPSVSGAPGQKVTISCSGSSSNIGNNYVSWYQQRPGTAPKLLIYDNNKRP SGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDSSLSAVFGGGTKLT VLRQPKAAPSVTLFPPSS	237
BP13a-1	QVQLVQSGSEVKKPGASVKVSCKLSGYTLTELSMHWVRQAPGKGLEWM GGFDPEDDEAIYAQKFQGRVTMTEDTSTDTAYMELSSLRSEDTAVYYCAT DRVTGTTMAAFDIWGQGTMVAVSSGSASAPTLGGGGSGGGGSAAASSEL TQDPAVSVALGQTVKITCQGDSLRSYFASWYQQKPGQAPVLVLFGKNSRP SGIPGRFSGSGSGNTAVLTITGAQAEDEADYYCDSRHSSGNYVIFGGGTKV TVLSQPKAAPSVTLFPPSS	238
BP5b-3	EVQLVQSGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVS YISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCARDN WYYFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSALTQPPSAS GSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYEVSKRPSGVP DRFSGSKSGNTASLTVSGLQAEDEADYYCSSYAGSNSWVFGGGTKLTVLG QPKAAPSVTLFPPSS	239
BP6a-23	QVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVS SISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDL GGYFGNYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQPVLTQPPSV SLSPGQTASITCSGDDLGDKFASWYQQKPGQSPILVIYQDSKRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQAWDGTKVVFGGGTKLTVLGQPKA APSVTLFPPSS	240
BP5a-1	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCANHG LMDDSSGYYLSNAFDIWGQGTMVTVSSGSASAPTLGGGGSGGGGSAAAQ PVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVEWYQQLPGTAPKLLIHSNN QRPSGVPDRFSGSRSGTSASLAISGLQSEDEADYFCATWDDSLTGVVFGGG TTLTVLGQPKAAPSVTLFPPSS	241
BP6a-11	QIQLVQSGGVVVQPGGSLRLSCAASGFTFDDYTMHWVRQAPGKGLEWVS LISWDGGSTYYADSVKGRFTISRDNSKNSLYLQMNSLRTEDTALYYCAAG SYHTWWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQPVLTQPPSASG TPGQRVTISCSGSSSNIGSSTVNWYQQLPGTAPRLLIYSINQRPSGVPDRFSG SKSGTSASLAISGLQSDDEADYYCAAWDDSLNGWVFGGGTKLTVLRQPK ANPTVTLFPPSS	242
BP5b-4	QVQLQQSGGGLVQPGGSLRLSCAASGFTFSSYAMTWVRQAPGKGLEWVS AISGGGGATYYADSVEGRFTISRDNSKNTLYLQMNSLRAEDTAIYYCASPA GHICSGGSCQYYYYGMDVWGQGTTVTVSSGSASAPTLGGGGSGGGGSAA ADIQMTQSPSFLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKLLIYA	243

	ASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGT RVDMARTVAAPSVF	
BP18a-1	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARQP YYYGSGSGMDVWGQGTTVTVSSGSASAPTLGGGGSGGGGSAAAEIVMTQ SPLSLPVTLGQPASISCGSSQSLVYSDGNTYVNWFQQRPGQSPRRLIYKVS NRDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGTHWPYTFGQG TKLEIKRTVAAPSVF	244
BP11a-1	EVQLVQSGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWV SGISWNSGSIGYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK VDGLEYSSGHNFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSA LTQPPSVSGSPGQSVTISCTGSSSDVGYYDHVSWYQHHPGRAPKVIIYDVT KRPSGVPDRFSGSKSGNTASLTISGLQAEDEADYYCSSYAGSYTWVFGGG TELTVLGQPKAAPSVTLFPPSS	245
BP6a-14	EVQLVESGGGVVQPGRSLRLSCAASGFSFSSYGMHWVRQAPGKGLEWVA VTSYDGSNKYYGDSVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCAK DEYTYGSGIMDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAEIVLTQ SPGTLSLSPGEGATLSCRASQTVNSNDLAWYQQRPGQAPRLLIYDASTRAT GIPDRFSGSGSGTDFTLTISRLEPEDFAVYFCQQYHGSQTFGQGTRVEIKRT VAAPSVF	246
BP6a-27	QMQLVQSGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWV ALISYDGSYEYYADSVKGRFTISRDISKNTLYLQMNSLRAEDTAVYYCAR DSGARGYNYGLFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIQ MTQSPSSLSASVGDRVTITCRASQSINRHLNWYQQKPGKAPKFLISAASNL QSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPYTFGGGTKVEI KRTVAAPSVF	247
BP6a-13	EVQLVESGGGVVQPGRSLRLSCAASGFRFSNYGMHWVRQAPGKGLEWVS AISGSGGLTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARE DLWRMGELLGGEGFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAA DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYKA SSLGSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPWTFGQGTK VEIKRTVAAPSVF	248
BP4a-1	EVQLVQSGAEVKKPGASVKVSCKASGYTFSSYGITWVRQAPGQGLEWMG WSSAYNGNTNYAQKLQGRISMTTDTSTSTAYMELRSLRSDDTAVYYCAR GIYGDYEYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSALTQPAS VSGSPGQSITISCTGTSSDISIYNYVSWFQQHPGKAPKLMIYDVNNRPSGVS SRFSGSKSANTASLTISGLQAEDEADYYCSSYTYSNTLLFGGGTKLTVLGQ PKAAPSVTLFPPSS	249
BP1a-1	EVQLVQSGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWV SGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAK DTSNGGYSSSSFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSAL TQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGTAPKLMIYDVSY RPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTLVFGTGTKV TVLGQPKANPTVTLFPPSS	250
BP6a-6	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDR HLYRRGYSSVDGMDVWGQGTTVTVSSGSASAPTLGGGGSGGGGSAAAEI VMTQSPGTLSLSPGERATLSCRASQSVSSGYLAWYQQKAGQAPRLLIYGG SARAPGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSIWPLTFGGGTK VEIKRTVAAPSVF	251
BP19b-2	QLQLQQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWV AVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA KPRGRYYFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSALTQP PSASGSRGQSVSISCSGSRSDIGYYNYVSWYQQHPGKAPKLIIFDVNKRPSG	252

	VPDRFSGSKSGNTASLTVSGLQAEDVADYYCSSSVGSNNLVFGGGTKLTV LGQPKAAPSVTLFPPSS	
BP6a-4	QVQLQESGPGLVKPSETLSLTCTVSGDSITSYYWSWIRQPPGKGLEWIGYI HYSGSTYYNPSLKSRVTISVDRSKNQFSLKLSSVTAADTAVYYCARGPSRG LFDPWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSALTQPASVSGSP GQSITLSCTGTSSDVGDYNYVSWYQQYPGKAPKLMIYDVTKRPSGVSNRF SGSKSGNTASLTISGLQAEDEADYYCSSYTSSTTWVFGGGTKLTVLGQPK AAPSVTLFPPSS	253
BP19a-1	QVQLQESGGVVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGKGLEWVSSI SNSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASLSR GYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSVLTQPPSASGTPGQ RVSISCSGRMSNIGKNTVNWYQQVPGTAPKLLIYSNNQRPSGVPDRFSGSK SGTSASLAISGLQSEDEADYYCAAWDDSLNGWVFGGGTKLTVLGQPKAA PSVTLFPPSS	254
BP6a-7	QVQLQQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEW MGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCA RESLIRFLEDPQQGGMDVWGQGTTVTVSSGSASAPTLGGGGSGGGGSAA AQSALTQPASVSGSPGQSLTISCTGTSSDIGGYNYVSWYQQHPGKAPKLIIY DVTDRPSGVSGRFSGSKSGNTASLTISGLQTEDEAEYFCNSWTRSNNYIFG GGTKLTVLGQPKAAPSVTLFPPSS	255
BP5b-5	QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCATPYS SSSGTDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADVVMTQSPLS LPVTLGQPASISCRSSQSLVYSDGNTYLNWFQQRPGQSPRRLIYKVSNRDS GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGTHWPLTFGQGTKVEI TRTVVAPSVF	256
BP6b-3	QIQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG WINPNSGGTNYAQKFQGWVTMTRDTSISTAYMELSRLRSDDTAVYYCAR PRTLRGDAFDIWGRGTMVTVSSGSASAPTLGGGGSGGGGSAAASSELTQA PSVSVSPGQTASITCSGNKLGDKFASWYQQKPGQSPVMVMYEDRKRPSGI PERFSGSNSGNTATLTISGTQALDEADYYCQTWDSRTVVFGGGTKLTVLG QPKAAPSVTLFPPSS	257
BP18b-2	QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARHPI GSGYDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIVMTQSPVSL PVTLGQPASISCRSSQSVVYRDGNTYLSWFLQRPGQSPRRLIYKVSNRDSG VPDRFSGSGSATDFTLKISRVEAEDVGVYYCMQGSSWPYTFGQGTKLEIK RTVAAPSVF	258
BPx-1	QVQLVQSGAEVKKPGSSVKVSCKASGGAFSIYSINWVRQAPGQGLEWMG GIIPIFETANSAQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCARAGE NSDSNYAFDIWGRGTVVTVSSGSASAPTLGGGGSGGGGSAAADIVMTQSP LSLPVTPGEPASISCRSSQSLLHSDGNNYLDWYLQKPGQSPQLLIYLGSNRA SGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGLHTPTTFGQGTKVEI KRTVAAPSVF	259
BP21b-1	QLQLQQSGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWIG SIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARGRY SYGYFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAANFMLTQPHSV SESPGKTVTISCTRSSGSIASNYVQWYQQRPGSSPTTVIYEDNQRPSGVPDR FSGSIDSSSNSASLTISGLRTEDEADYYCQSYDHMYNWVIGGGTKLTVLGQ PKAAPSVTLFPPSS	260
BP6a-2	QVQLVQSGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVS SISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGI RVVGDEDYYYYYGMDVWGQGTTVTVSSGSASAPTLGGGGSGGGGSAAA QSVLTQPPSVSGAPGQKVTISCSGSSSNIGNNYVSWYQQLPGTAPKLLIYD	261

	NNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYHCAAWDDDLNGPVF GGGTKLTVLGQPKAAPSVTLFPPSS	
BPx-2	EVQLLQSGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVS YISSSSSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCARDS SGWLGMGDFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIQMT QSPSSLSASVGDRVTISCRASHSISRFLNWYQQKPGRAPKLLIYSTSSLQSG VPSRFSGSGSARDFTLTISGLQPEDFATYFCQQSYSTPWTFGQGTKVELKR TVAAPSVF	262
BP6b-1	QVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVS SISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREE YYGGNTDWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAASSELTQPPSVS VSPGQTATITCSGDKLGDKYASWYQQKPGQSPVLVIYQDTKRPSGIPARFS GSNSGNTATLTISGTQAMDEAAYYCQAWDSTTVVFGGGTKLTVLGQPKA APSVTLFPPSS	263
BPx-3	EVQLVQSGGGLVQPGGSLRLSCVTSGFSFSNYGMSWVRQAPGKGLEWVS EISGSGGSAYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARD ISHYDILTGQLDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIQMT QSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSG VPSRFSGSGYETDFTLTISSLQAEDVAVYYCQQYYSSPWTFGQGTRVEIKR TVAAPSVF	264
BP6a-5	QIQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVA VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARD LLVRFLEWSHYYGMDVWGQGTTVTVSSGSASAPTLGGGGSGGGGSAAA QPVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVHWYQQLPGTAPKLLIYSD NQRPSGVPDRFSGSKSGTSASLVISGLQSDDEADYYCAAWDDSLNGVFGG GTKLTVLgQPKAAPSVTLFSPSS	265
BP6a-10	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVA NIKQDGSEKYYVDSVKGRFTISRDNSENTLYLQMNSLRAEDTAVYYCAKE TDCSGGICYGVDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQPVL TQPPSVSVSPGQTASITCSGDKLGDKYASWYQQKPGQSPVMVIYQDRKRP SGIPERFSGSNSGNTATLTISGTQAMDEADYYCAAWDDSLSGRVFGGGTK LTVLGQPKAAPSVTLFPPSS	266
BP15a-1	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWM GWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCA RDAPYDILTGYLSYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAEIVM TQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSR ATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPYTFGQGTKLEI KRTVAAPSVF	267
BP6a-26	QIQLVQSGGGVVQPGRSLRLSCAASGFSFSTYAMHWLRQAPGKGPEWVA AISYDGTIKYYADSVKGRFTISRDSSKNTLYLQMNNLGPEDTALYYCARA GGAGSDGYNYWGYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAEIV LTQSPATLSLSPGDRATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNR ATGIPARFSGSGSGTDFSLTISRLEPEDFAVYYCQQSGSSPWTFGQGTKVEI KRTVAAPSVF	268
BP6a-12	QVQLVQSGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVS SISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDP GGKLGGAFDIWGQGTMVTVSSGSASAPTLGGGGSGGGGSAAADIVMTQS PATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLFIYGASTRATGIP DRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYSTPYTFGQGTKLEIKRTV AAPSVF	269
BP5a-4	QVQLVQSGAEVKKPGSSVKVSCKASGGTLSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDRP GNNRYDILTGGGWFDPWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQ SVLTQPPSVSAAPGQKVTISCSGGSSNIGNNYLSWYQQLPGTAPKLLIYDN	270

	NKRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDSSLSAGVFGG GTKLTVLGQPKAAPSVTLFPPSS	
BP5b-1	QVQLVQSGGGVVRPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWV SGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAK EISDTAMGFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSALTQP ASVSGSPGQSITISCTGTSSDVGGYNYISWYQQYPGKAPKLMIYDVSKRPS GVSNRFSGSKSGNTASLTISGLQAEDEADYYCNSYTSSRTVVFGGGTKLTV LGQPKAAPSVTLFPPSS	271
BPx-4	EVQLVESRGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVA VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARA YIPRLYYYGSGLDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAASSEL TQPPSVSVSPGQTASITCSGDQLGDKFVSWYQQKPGRSPVLVISEDNKRHS GTPERISGSNSGNTATLTISGTQSMDEADYFCQTWDSSAVVFGGGTKLTVL GQPKAAPSVTLFPPSS	272
BP5a-3	QVQLQESGPGLVKPSETLSLTCTVSGYSITNGYYWGWIRQSPGKGLEWIG NIFQSGSTYYNPSFKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARRVD YYDSSGYGEGYFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAASSE LTQDPAVSVALGQTVRITCQGDSLKKYYASWYQQKPGQAPVLVIYGKNL RPSGIPERFSGSSSGDTASLTITGTQAEDEADYYCQAWDSSTAVFGGGTKL TVLGQPKAAPSVTLFPPSS	273
BP14a-1	QVQLVQFGAEVKKPGESLKISCKGSGYNFNSYWIGWVRQMPGKGLEWM GIIYPGDSDIRYNPSFQGQVTISADKSISTAYLQWSSLKASDSAMYYCARH VSGSLDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADVVMTQSPLS LSVTPGQPASISCRSSQSLVHSDGNTYLNWFHQRPGQSPRRLIYKVSNRDP GVPDRFSGSGSGTDFTLKISRVEAEDAGVYYCMQGTHWPRLTFGGGTKVE IKRTVAAPSVF	274
BP3a-1	EVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKT AYYDSSGYYPDAFDIWGQGTMVTVSSGSASAPTLGGGGSGGGGSAAADI QMTQSPSSFSASTGDRVTITCRASQGISSYLAWYQQKPGKAPKLLIYAAST LQSGVPSRFSGSGSGTDFTLTISSLRLDDVATYYCQQYQSYPITFGQGTRLE IKRTVAAPSVF	275
BP18b-3	QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARGQ GGVLGAFDIWGQGTMVTVSSGSASAPTLGGGGSGGGGSAAAEIVLTQSPD SLAVSLGERATINCKSSQNLLYSSNNKNYLAWYQQKPGQPPKLLINWAST RVSGVPDRFSGSGSGTDFTLTINSLQAEDVAVYYCHQYYSSPYTFGPGTKV EIKRTVAAPSVF	276
BP6a-9	EVQLVESGAEVKKPGEPLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARQG RGEAFDIWGQGTMVTVSSGSASAPTLGGGGSGGGGSAAAQPVLTQPPSVS VSPGQTASITCSGDNLGDKYASWYQQKPGQSPVLVIFRDTKRPSGIPERFS GSNSGDTATLTISGTQAMDEADYYCQAWDSSAGGVFGGGTRLTVLGQPK AAPSVTLFPPSS	277
BP6a-25	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNTEAWNWIRQSPSRGLEWL GRTYYRSKWYHDYAPSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCA RTVFDSQVYWFDPWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADVV MTQSPLSLPVTPGEPASISCRSSQTLLHSNGFNYLDWYLQKPGQSPQLLMY LGSSRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGTHWPPTFG QGTKLEIRRTVAAPSVF	278
BPx-5	EVQLVESRGGLVKPGGSLRLSCAASGFTFSSYGMSWVRQAPGKGLEWVS SISNSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASLS RGYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQAVLTQPPSVSGTP GQTVIISCSGSNSNLGRNSANWYQQLPGTAPKLLIHSNHMRPSGVPDRFSG	279

	SKSGTSASLAISGLQSEDEADYYCAAWDDSLNGWVFGGGTKLTVLGQPK AAPSVTLFPPSS	
BP5a-2	QVQLVQSGGGLIQPGGSLRLSCAASGFTVSSYSMNWVRQAPGKGLEWVS YISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKVG TAAAGDAFDIWGQGTMVTVSSGSASAPTLGGGGSGGGGSAAAQPVLTQP PSASGTPGQRVTISCFGSSSNIGSNYVYWYQQLPGTAPKLLIYRNNQRPSG VPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLSGWVFGGGTKLT VLGQPKAAPSVTLFPPSS	280
BP6a-15	QVQLQESGPGLVKSSGTLSLTCAISGVSIASSNWWSWVRQPPGKGLEWVG EIYHSGSTFYNPSLQSRVTISVDKSKNQFSLTLNSVTAADTAVYYCASSSG WPYPTNWFDAWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIQMTQS PSTLSASVGDRVSITCRASQSVSSWLAWYQQKPGKAPKLLIYAASSLQSGV PSRFSGSGSGTDFTLTISNLQPEDSATYFCQQSYSTPWTFGQGTKVELKRTV AAPSVF	281
BP6a-21	EVQLLESRGSLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSG ISDSGGTTYYADSVKGQFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDA HNWNYGVFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIQMTQ SPSSLSASVGDRVTITCQASHDISNYLNWYQQKPGKAPKLLIYDASNLETG VPSTFSGSGSGTDFTLTISSLQPEDIATYYCQQSYSTPYTFGQGTKVEIKRTV AAPSVF	282
BP5a-5	QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRRAPGKGLEWVS YISSSSSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCASAL GATGAFDIWGQGTMVTVSSGSASAPTLGGGGSGGGGSAAAQSALTQPAS VSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSG VSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTTSSTLVFGGGTKVTVL GQPKAAPSVTLFPPSS	283
BP6a-17	QMQLVQSGGGLVKPGGSLRLSCAASGFTFSDYYMTWIRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKD ISGYEPLYYFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAASSELTQ DPSVSVSPGQTASITCSGDKLGDKYVGWYQQKPGQSPVLIIYRDYKRPSGT PERFSGSNSGNTATLTISGVEAGDEADYYCQVWDMSSDPLVFGGGTKLTV LGQPKAAPSVTLFPPSS	284
BP6a-20	EVQLVESRGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVA VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARD PGKQWRVRGYFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIV MTQSPSTLSVSVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSL ESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPYTFGQGTKLEIK RTVAAPSVF	285
BP3a-2	EVQLVQSGGDLEQPGGSLRLSCGTSGFTFSDYDMSWVRQAPGKGLEWVS GISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARE SDMAAAGSFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSALTQ PRSVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRP SGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTYVFGTGTKVT VLGQPKADPTVTLFPPSS	286
BP6a-24	EVQLVESRGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVS SISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREG NSGYDVWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQPVLTQPPSVS VSPGQTASITCSGDDLGDKFASWYQQKPGQSPILVIYQDSKRPSGIPERFSG SNSGNTATLTISGTQAMDEADYYCQAWDGTKVVFGGGTKVTVLGQPKA APSVTLFPPSSKARG	287
BP6a-22	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWM GWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCA RDSLWFGELSALDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIV MTQSPSSVSASVGDRVTITCRASQDISSWLAWYQQKPGKAPKLLIYAASSL	288

	QSGVPSRFSGSGSGTDFTLTISSLQPEDFASYYCQQANSFPQTFGGGTKVEI KRTVAAPSVF	
BP19a-2	QVQLVQSGGGVVLPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWV AVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR DVSSWAAFWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAANFMLTQPHS VSESPGKTVTISCTRSSGRIVSTYVQWYQHRPGSPPRLIMYDDVQRPSGVS ARFSGSIDISSNSASLTISGLLAEDEADYYCQSYNTSNLVFGGGTKLTVLSQ PKAAPSVTLFPPSS	289
BPx-6	QIQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMG WISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR GGRGGVITWFDPWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSALT QPPSASASPGQSVTISCTGTSSDVGGYDFVSWYQQHPGQAPKLMIYEVNK RPSGVPDRFSGSKSGNTASLTVSGLQADDEADYYCCAYAGSNILLFGGGT KLTVLGQPKAAPSVTLFPPSSKPRG	290
BP6a-18	QIQLVQSGGGLIQPGGSLRLSCAASGFTFSSFAMSWVRQAPGKGLEWVSSI TSRGDTTYYADSVRGRFTISRDNSKNTLYLQMNSLRADDTAVYYCARDRP QVPYDSSGNFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAAIQLT QSPSSLSASVGDRVTITCRASQSISTYLNWYQQKPGKAPKLLIYDTSSLHSG VPSRFSGSGSGTDFTLTISSLQPEDFATYHCQQSFITPYTFGQGTKLEIKRTV AAPSVF	291
BP16a-1	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTADYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCAREEA GYSSGWVEDAFDIWGQGTMVTVSSRSASAPTLGGGGSGGGGSAAAQSAL TQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMISDVSK RPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSNYTLVFGGGTK LTVLGQPKAAPSVTLFPPSS	292
BP19a-3	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWV AVISYDGSNKYYADSVKGRFTISRDNAENSLYLQMNSLRAEDTAVYYCAR MVGGYRFDYWGQGTTVTVSSGSASAPTLGGGGSGGGGSAAADIVMTQSP ATLSVSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIP ARFSGSGSGTDFTLTISSLEPEDFAVYYCQHRGSWPHTFGPGTKLEMKRTV AAPSVF	293
BP5b-2	EVQPLETGGGLVQPGGSLRLSCVTSGFSFSNYGMSWVRQAPGKGLEWVS EISGSGGSAYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKH GDYGGTFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAEIVMTQSP ATLSLSPGDRATLSCRASQNVGSYLGWYQQKVGQAPRLLIYDASNRATG VPGRFSGSGSGTDFTLTISSLEPEDFAVYYCQQYGSSPLFTFGPGTKVDIKR TVAAPSVF	294
BP2a-1	QIQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMG WISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELSSLRSEDTAVYYCAR VGFYDYVWGSYPYDAFDIWGQGTMVTVSSGSASAPTLGGGGSGGGGSA AAEIVMTQSPGTLSLSPGERATLSCRASQSVSSNYLAWYQQKPGQAPRLLI YDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFALYYCQQYGTSPLTFGG GTKLEIKRTVAAPSVF	295
BP18a-2	QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYWIAWVRQMPGKGLEWM GIIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWTSLKASDTAMYYCARR SSSSGSFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIVMTQSPL SLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRAS GVPDRFSGSESGTDFTLKISRVEAEDVGVYYCMQATHWPPRLTFGPGTKV DIKRTVAAPSVF	296
BP6a-3	QLQLQQSGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVS SISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCVRDR HSLGDFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAASSELTQPPSV SVSPGQTATITCSGDKLGDKYASWYQQKPGQSPVLVIYQDTKRPSGIPARF	297

	SGSNSGNTATLTISGTQAMDEAAYYCQAWDSTTVVFGGGTKLTVLGQPK AAPSVTLFPPSS	
BPx-7	QIQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVA VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARR FTMDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSALTQPASVSG SPGQSITISCTGTSSDVGGYNYVSWYQQRPGKAPKLMIYDVSNRPSGVSNR FSGSKSGNTASLTISGLQAEDEADYYCSSYTTSSTVVFGGGTKLTVLGQPK AAPSVTLFPPSS	298
BPx-8	QVQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWIG SIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARYSSS WELFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAARSALTQPASVS GSPGQSITISCTGSSNDVGGYKFVSWYQHHPGKAPKLLIYGVTQRPSGVSN RFSGSQSGNTASLTISGLQAEDEADYFCTSYTRSTTPIFGGGTKLTVLGQPK AAPSVTLFPPSS	299
BPx-9	QIQLVQSGAEVRKPGDSVKVSCRTSGYTFNDYHIHWVRQAPGQGLEWMG WISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLKSDDTAVYYCAR RNGSGSAPGYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSALTQP PSASGSPGQSVTVSCTGSSSDIGSYNYVSWFQRHPGQAPKLIIHDVTERPSG VPHRFSGSKSGNTASLTISGLQTEDEADYFCCSYSGDHTLPFIFAPATQVTV LGQPKANPTVTLFPPSS	300
BPx-10	EVQLVESGAEVKKPGESLRISCKGSGYSFTSYWIGWVRQMPGKGLEWMGI IYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARVGQ YYGMDVWGQGTTVTVSSGSASAPTLGGGGSGGGGSAAADIVMTQSPLSL PVTLGQPASISCRSSQGLVYSDGNTYLNWFQQRPGQSPRRLIYKVSNRDSG VPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQATHWPWTFGQGTKVEIK	301
BPx-11	QVQLQESGPGLVKPSETLSLACTVSGGSISSSSYYWGWIRQPPGKGLEWIA SINYSGNTYYNPSLKSRVIIPIDTSKNQFSLKLSSVTAADTAVYYCARRVLG YGYFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSVLTQPPSAS GTPGQRVTISCSGSSSNIGSNYVYWYQQLPGTAPKLLIYRNNQRPSGVPDR FSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLSGPVFGGGTKLTVLGQP KAAPSVTLFPPSS	302
BPx-12	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTGGG NVDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADVVMTQSPLSLPV TLGQPASISCRSSQSLVHGNGITYLNWFQQRPGQSPRRLIYKVSNRDSGVP DRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPSFGQGTRLEIKRTVA APSVF	303
BPx-13	EVQLLESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVS GISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKD KAGNYYYGMDVWGQGTTVTVSSGSASAPTLGGGGSGGGGSAAAQSALT QPPSASGSPGESVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLLIYDVTKR PSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTVVFGGGTKL TVPGQPKAAPSVTLFPPSS	304
BPx-14	QVQLVQSGGGVVQPGRSLRLSCAASGFTFGHYGMHWVRQAPGKGLEWV AVISYDGTNKYYADSVKGRFTISRDNSKNTLYLQMNSLRVDDTAVYYCA KGSRLDPWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSALTQPRSVS GSPGQSVTISCTGTSSDVGGYNYVSWYQHHPGKAPKLMIYDVNKRPSGVP DRFSGSKSANTASLTVSGLQAEDEADYYCSSYTAGGNWVFGGGTKLTVL GQPKAAPSVTLFPPSS	305
BPx-15	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEWL GRTYYRSKWYNDYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCV GQGYDSSGYYGMDVWGQGTTVTVSSGSASAPTLGGGGSGGGGSAAADV VMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYVQKPGQSPQHLI YLGSIRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGLQTPPTFG	306

	PGTKMDIKRTVAAPSVF	
BPx-16	QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARQY YDTSYFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADVVMTQSPL SLPVTLGQPASISCRSSQSLVYSDGNTYLSWFHQRPGQSPRRLIYKVSNRDS GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGTHWPWTFGQGTKVEI KRTVAAPSVF	307
BPx-17	EVQLVQSGGGLVQPGRSLRLSCAASGFTFGDYAMHWVRQAPGKGLEWV SGINWNSGGVGYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA KDSGYSYGINFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSAL TQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSK RPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTWVFGGGTK	308
BP1b-1	QIQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMG WISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR GDWFDPWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSALTQPPSAS GSPGQSVTISCSGTSSDIGGYDYVSWYQQHPGKAPKLIIYEVSKRPSGVPDR FSGSKSGNTASLTVSGLQADDGAHYYCSAYAGRNNMVFGGGTKVTVVG QPKAAPSVTLFPPSS	309
BPx-18	QVTLKESGPTLVKPTQTLTLTCTFSGFSLSTSGVGVGWIRQSPGKALEWLA LIYWDDDKRYSPSLKSRLTITKDTSKNQVVLTMTNMDPVDTATYYCAHM RWGYYFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSVLTQPPS ASGTPGQRVIISCSGSRSNNGSNYIYWYQHLPGTAPKLLIYRNNQRPSGVP DRFSGSKSGTSASLAISGLQSEDEADYYCAAWDRSLNAWVFGGGTKLTVL SQPKAAPSVTLFPPSS	310
BPx-19	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARRE MGAKGSGGIDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIVMTQ TPLSLPVTLGQPASISCRSSQSLVYSDGKTYLNWFQQRPGQSPRRLIYKVSN RDSGVPDRFSGSGSGTDFTLKITRVEAEDVGVYYCMQGTHWPHTFGQGT KLEIKRTVAAPSVF	311
BPx-20	EVQLVQSGGGLVKPGRSLRLSCTASGFTFGDYAMSWFRQAPGKGLEWVS YISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRVEDTAVYYCAREG WGSLLDYWGQGILVTVSSGSASAPTLGGGGSGGGGSAAAEIVMTQSPATL SLSPGERATLSCRASQSVNSSYFAWYHRRPGQAPRLLISRTSTRAAGIPDRF SGSGSGTDFTLKISRVEAEDVGVYYCMQGTYWPYTFGQGTKLEIKRTVAA PSVF	312
BPx-21	QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWV AVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA KDGDLGRYFDWLPLYYYYGMDVWGQGTTVTVSSGSASAPTLGGGGSGG GGSAAAQSALTQPPSASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGK APKLMIYDVSNRPSGVSNRFSASKSGNTASLTISGLQAEDEADYYCSSYTS SSTLDVVFGGGTKLTVLGQPKAAPSVTLFPPSS	313
BPx-22	EVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWISS ITGSSSTIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGGA RADYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSALTQPASMSGS PGQSITISCTGTSSDLGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGVSNRF SGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTPWVFGGGTKLTVLGQPK AAPSVTLFPPSS	314
BPx-23	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWV AVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAT PGPYYYYGMDVWGQGTTVTASSGSASAPTLGGGGSGGGGSAAANFMLT QPHSVSESPGKTVTISCTRSSGSIASNYVQWYQQRPGSSPTTVIYEDNQRPS GVPGRFSGSIDSSSNSASLTISGLQTEDEADYYCQSYDGSDVVFGGGTKLT VLSQPKAAPSVTLFPPSS	315

BP5b-6	EVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEW MGWINPNSGGTNYAQKFQGRVTVTRNTSISTAYMELSSLRSEDTAVYYCA RGIGDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSALTQPASVSG SPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGVSNR FSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTWVFGGGTKLTVLGQPK AAPSVTLFPPSS	316
BPx-24	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWV AGISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYHCA KDAGRWLEIPYYFDFWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAANF MLTQPHSVSESPGKTVTISCTGSSGSIASNYVQWYQQRPGSSPTTLIYEHNQ RPSGVPDRFSGSVDSSSNSASLTISGLKTEDEADYYCQSYDDNNVVFGGGT KLTVLGQPKAAPSVTLFPPSS	317
BPx-25	QVQLQESGPGLVKPSETLSLTCTVSGGSTSSSSYYWGWIRQPPGKGLEWIG SIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARVVW FGEPLFDPWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSALTQPPSA SGSPGQSVTISCTGTSSDIGGYNYVSWYQVHPGKAPKLIIYDVSKRPSGIPD RFSGSKSGNAASLTVSGLRTEDEADYYCSSYAGNNNLIFGGGTKVTVLSQ PKAAPSVTLFPPSS	318
BPx-26	QVQLVQSGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWV SGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAK DLSGYDQAIDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSALTQ PASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRP SGVSNRFSGSKSGNTASLTISGLQAEDEADYYCASYTSSTSVVFGGGTKLA VLGQPKAAPSVTLFPPSS	319
BPx-27	QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCVRSGS GWAIDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADVVMTQTPLSL PVTPGQPASISCRSSQSLVYSNGNTYLTWFQQRPGQSPRRLLHEVSKRDSG VPDRFVGSGSGTDFTLKISRVEPEDVGIYYCMQGSQWPPTFGQGTKLEIKR TVAAPSVF	320
BPx-28	QVQLVQSGAEVKKPGASMKASCKASGYTFTSYYIQWVRQAPGQGLEWV GVIHPGDGGTTYAQKFQGRVTMTTDTSTSTVYMELSSLRSEDTAVYYCAR GDLDNWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIVMTQTPVSLP VTLGQPASISCRSSQSLVHSDGNTYLNWFQQRPGQSPRRLIYKVSTRDSGV PDRFSGSGSATDFTLKISGVEAEDVGVYYCMQGTHWPKTFGQGTKVEIKR TVAAPSVF	321
BPx-29	QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARRY SSGWGFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAEIVMTQSPLS LPVTPGEPASISCRSSQSLLHKNGNNYLDWYLQKPGQSPQLLIYMASKRAS GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPPTFGGGTKVEIK RTVAAPSVF	322
BPx-30	QVTLKESGPTLVKPTQTLTLTCTFSGFSLSTSGVGVGWFRQPPGKALEWLA LIYWDDDKRYSPSLKSRLTITKDTSKNQVVLTMTNMDPVDTATYYCAHG EMDLFGYSSGWFPDFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAA EIVLTQSPATLSLSPGERATLSCRASQSITSNYLAWYQQKPGQAPRLLIVGA SSRATGIPDRFSGSGSGTDFTLTISRLEPEDSAVYYCQQYGNSPRTFGQGTK LEIKRTVAAPSVF	323
BPx-31	EVQLLETRAEVKKSGESLKISCQGSGYSFTAHWIAWVRQMPGKGLEWMG SIYPADSTTVYSPSFQGQVTISADKSFTTAYLQWTSLKASDTAMYYCVRQT SGWSDWGQGTLVTVSAGSASAPTLGGGGSGGGGSAAADIQMTQSPSTLS ASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSLESGVPSRFS GSGSGTEFTLTISSLQPEDFATYYCQQYQSYPITFGQGTRLEIKRTVAAPSV F	324

BPx-32	QVQLVQSGGGVVQPGGSLSLSCAVSGFTFSSYGMHWVRQAPGKGLEWV AVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR GDGYNHPLYYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAEIVLTQSP LSLPVTPGEPASISCRSSESLLHSIGYNYVDWYVQKPGQSPQLLIYLGSNRA SGVPDRFSGSTSGTDFTLKISRVEAEDVGVYYCMQALQTSITFGQGTRLEI KRTMAAPSVF	325
BPx-33	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWV AVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR G TLWFGELSVDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSALTQ PASVSGSPGQSITISCTGTSSDVGTYNYVSWYQQHPGKAPKLMIYDVNNRP SGVSNRFSGSKSGSTASLTISGLQAEDEADYYCSSYTSTSTPYVFGTGTKVT VLRQPKANPTVTLFPPSS	326
BPx-34	QVTLKESGPTLVKPTQTLTLTCTFSGFSLSTSGMGVSWIRQPPGKALEWLA LIDWDDDKYYSTSLKTRLTISKDTSKNQVVLTMTNMDPVDTATYYCARM YSYGATEFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSALTQP PSASGSPGQSVTISCTGTSSDIGGYNYVSWYQQHPGKAPKLMIYEVSERPS GVPDRFSGSKSGNTASLTIAGLQGEDEADYYCSSYRSSSTVVFGGGTKLTV LGQPKAAPSVTLFPPSS	327
BPx-35	QVQLVQSGGGLVQPGRSLRLSCAASGFTFGDYAMHWVRQAPGKGLEWV SGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAK DISSGWYSVGYFDLWGRGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSA LTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVS NRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTLVFGTGTK VTVLGQPKANPTVTLFPPSS	328
BPx-36	EVQLVESRAEVKKPGASVKVSCKASGYTFSDYYIHWVRQAPGQGLEWM GRISPNSGGTNYAQKFQGRVTMTRDTSMNTAYMELSRLNSDDTAVYYCA RGFFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIQMTQSPSFLS ASVGDRVTITCRASQGISSHLAWYQQKPGKAPKLLIYATSTLQSGVPSRFS GSGSGTDFTLTISSLQPEDFATYYCQQFDDLPVTFGPGTKVEIKRTVAAPSV F	329
BPx-37	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWV AVISYDGTNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA RGQTSYFYDSSGPEIPNFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSA AADIVMTQSPLSLPVTPGEPASISCRSSQTLLHANGFNYLDWYLQKPGQSP QLLMYLGSSRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQTLQT PPWTFGQGTKVEIKRTVAAPSVF	330
BPx-38	QMQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARGG GYYDSSGYPYYYYGMDVWGQGTTVTVSSGSASAPTLGGGGSGGGGSAA ADIVLTQSPATLSVSPGDRATLSCRASQSVNRNLAWYQQRPGQAPRILIYD ASTRATGIPTRFRGSGSGTEFTLTISSLQSEDFGIYYCQQYNNWLSFGGGTK VEVKRTVAAPSVF	331
BPx-39	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWM GWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCA RSTGYSSSSDWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQPVLTQPP SVSVSPGQTASITCSGDKLGDKYASWYQQKPGQSPVMVIYQDRKRPSGIPE RFSGSNSGNTATLTISGTQAMDEADYYCAAWDDSLSGRVFGGGTKLTVL GQPKAAPSVTLFPPSS	332
BPx-40	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWM GWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCA RDVGASGLLWFGELSFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAA ANFMLTQPHSVSESPGKTVTISCTRSSGTIVSTYVQWYQQRPGSSPTTVIYE DNQRPSGVPDRFSGSIDSSSNSASLTISGLKTEDEADYYCQSYDSSNRKVFG	333

	GGTKLTVLSQPKAAPSVTLFPPSS	
BPx-41	QIQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDRP HAGLYYYYYGMDVWGQGTTVTVSSGSASAPTLGGGGSGGGGSAAAQSA LTQPASVSGSPGQSITISCTGTSSDVETYNLVSWYQQHPGKAPKLMIYDVT KRPSGVPDRFSGSKSGNTASLTISGLQADDEADYYCSSYADSIAFVIFGGGT KVTVLGQPKAAPSVTLFPPSS	334
BPx-42	EVQLVQSGGGLVKPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVA VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK DLLYYYDSSGPVDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIV MTQSPATLSLSPGERATLSCRASQSFSSNLAWYQQKPGQAPRLLIYDASNG ATGVPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPRTFGQGTKLEI K	335
BPx-43	QVQLVQSGGVVVQPGGSLRLSCAASGFTFDDYTMHWVRQAPGKGLEWV SSISSSSSYIYHADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVDSS GYFDAFDIWGQGTMVTVSSGSASAPTLGGGGSGGGGSAAAQSVLTQPPSV SGAPGQRVTISCTGSSSNVGAGYDVHWYQQLPGTAPKLLIYGNTNRPSGV PERFTGSKSGTSASLAISGLRSEDEADYYCATWDDSLNGPVFGGGTKLTVL GQPKAAP	336
BP16b-1	QVQLVQSGGGVVRPGGSLRLSCAVSGFTFDDYGMSWVRQAPGKGLEWV SGINWNGGSTGYADSVKGRFTISRDNSKNTLYLQMNSPRAEDTAVYYCA REDYGDSEYYFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSVL TQPPSVSGAPGQRVTISCTGSTSNIGAGYDVHWYQQLPGTAPKLLIYGNTN RPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYCAAWDDSLNGWVFGGG TKLTVLGQPKAAPSVTLFPPSS	337
BPx-44	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARKG GYYGSGSYFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQAVLTQ PPSASGTPGQRVTISCSGSSSNIGSNYVYWYQQLPGTAPKLLIYRNNQRPSG VPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLSGWVFGGGTKLT VLGQPKAAPSVTLFPPSS	338
BPx-45	QVQLVESGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCAVEED YGGSFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSVLTQPPSAS GTPGQRVTISCSGSNSNIGSNHVYWYQQLPGTAPKLLIYSNNQRPSGVPDR FSGSKSGTSASLAISGLQSEDEADYYCAAWDDNVNGWVFGGGTKLTVLG QPKAAPSVTLFPPSS	339
BPx-46	EVQLVESGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARSRS GSYYGTDAFDIWGQGTMVTVSSGSASAPTLGGGGSGGGGSAAAQSALTQ PASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMISDVSKRP SGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSNYTLVFGGGTKLT VLGQPKAAPSVTLFPPSS	340
BPx-47	EVQLVESGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMG WISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR VDFYDYVWGSYLLDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQ AVLTQPPSASGTPGQRVTISCSGSSSNIGTNAVNWYQQLPGTAPKHLIYSN NQRPSGVPDRFSASKSGTSASLAISGLQSDDESDYYCAAWDDSLNGVVFG GGTKLTVL	341
BPx-48	QMQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDLV YSSGGPDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQPVLTQSPSA SGTPGQRVTISCSGSSSNIGSNYVYWYQQLPGTAPKLLIYRNSQRPSGVPD RFSGSKSGTSTSLAISDLRSEDEADYYCAAWDDSLSGWVFGGGTKLTVLG	342

	QPKAAPSVTLFPPSS	
BPx-49	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEW MGRISPNSGGTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYC ARRWDYDSSGYQNDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADI VMTQSPATLSLPPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDAS NRATGIPARFSGSGSGTDFTLTISSLQAEDVAVYFCQQYYSTPLTFGGGTK VEIKRTVAAPSVF	343
BPx-50	QVQLVQSGGGLVQPGGSLRLSCVTSGFSFSNYGMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARD QWIQLWIDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQPVLTQPPS ASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYINNQRPSGVPD RFSGSKSGTSASLAISGLQSEDEANYYCAAWDDSLSGPVFGGGTKLTVLG QPKAAPSVTLFPPSS	344
BPx-51	QIQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITRDMSTSTAYMELSSLRSEDTAVYYCAAEV PAAKLYYYYYGMDAWGQGTTVTVSSGSASAPTLGGGGSGGGGSAAAQA VLTQPPSASGAPGQTVTISCSGSSSNIGSKTVNWYQQVPGTVPKLLIYNNN QRPSGVPDRFSGSKSGTSASLAITGLRSEDEADYYCAAWDDSLSGPMFGG GTKLTVLGQPKAAPSVTLFPPSS	345
BPx-52	QIQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCARDH LYYYDSSGYYDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIVMT QSPSALSASVGDRVTITCRASQSIGSWLAWFQQKPGKAPNLLIYKASSVES GVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQSYSTPYTFGQGTKLEIKRT VAAPSVF	346
BPx-53	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTADYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCATYY DSSGYYPYYFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQAVLT QPPSVSVAPGKTAKITCGGLNIGSKSVHWYQQKAGQAPVLVMSYDSDRPS GIPERFSGSNSGSTATLSISRVAAGDEADYYCQVSDSDTDHPVFGGGTKLT VL	347
BPx-54	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWM GWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCA RDFKIAARGMDVWGQGTTVTVSSGSASAPTLGGGGSGGGGSAAADIVMT QSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGS NRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPYTFGQGT KLEIKRTVAAPSVF	348
BPx-55	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWV AVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA RGPHYFSDYGDYDSIGYYYYGMDVWGQGTAVTVSSGSASAPTLGGGGSG GGGSAAASSELTQDPAVSVALGQTVRITCQGDSLRTYYASWYQQKPGQA PKLLIYGKNNRPSGIPERFSGSSSRNSASLTITGTQAEDEADYYCDSRDSSTS QWVFGGGTKVTVLGQ	349
BPx-56	QVQLVQSGAEVKKPGASVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDK GSSGYYNFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQPVLTQP PSASGTPGQRVTISCSGTSSNIGSNTVSWYHHLPGTAPKLLIYSNNQRPSGV PDRFSGSRSGTSAALAISGLESEDEADYYCATWDDSLNGWVFGGGTKLTV LGQPKAAPSVTLFPPSS	350
BPx-57	QIQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWM GIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARE VLGDYYYGMDVWGQGTTVTVSSGSASAPTLGGGGSGGGGSAAADIVMT QSPDSLAVSLGERATIKCQSSQSVLYSFSNKNYLAWYQQKPGQPPKLLIY WASTRKSGVPDRFSGSGSGTDFSLTISSLQAEDVAVYYCQQYYLLPITFGQ	351

	GTRLEIK	
BPx-58	QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARYY YGSGSYFDLLDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQPVLT QPPSVSVAPGKTARITCGGNNIGSKSVHWYQQKPGQAPVLVIYYDSDRPS GIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDHVVFGGGTKL TVLGQPKAAPSVTLFPPSS	352
BPx-59	QVQLVQSGGGLVQPGGSLRLSCAVSGFTFGTYAMTWVRQAPGKGLEWV SAISGGGDSTYYGDSVKGRFTVSRDNSKNTLYLQMSSLRVEDTALYYCAK ATREDVQHGSFDYWGQGTLVTVSSRSASAPTLGGGGSGGGGSAAAEVVL TQSPLSLPVTPGEPASISCRSSQSLLHSIGYNYVDWYVQKPGQSPRLLIYLG SNRASGVPDRFSGSGSGTDFTLKITRVEAEDVGVYYCMQALQTIFTFGPGT KVDIKRTVAAPSVF	353
BPx-60	QVQLVQSGAEVKKPGSSVKVSCRASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARGVL GGGFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQPGLTQPPSAS GTPGQRVTISCSGSSSNIGSNYVYWYQQLPGTAPKLLIYRNNQRPSGVPDR FSGSKSGTSASLAISGLRSEDEGDYYCASWDDSVHGWVFGGGTKLTVLGQ PKAAPSVTLFPPSS	354
BPx-61	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYGISWVRQAPGQGLEWM GWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMGLRSLRSDDTAVYYCA RDGGVLGDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSALTQPA SVSASPGQSITISCTGTSSDVGSYNYVSWYQQHPGKAPKLIIFDVNNRPSGV SNRFSGSKSGNTASLTISGLQAEDEADYYCSSDTSSSTLVFGGGTKLTVLG QPKAAPSVTLFPPSS	355
BPx-62	QVQLQESGGGVVQPGRSLRLSCAASGFTFSNYDMHWVRQAPGKGLEWV AVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR RTPFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIVMTQSPDSLA VSLGERATISCKSSQSVLYSSNNKNYLAWYQQKPGHPPKLLIYGASTRESG VPDRFSGSGSETDFTLTISSLQAEDAAVYYCMQAAQLPLTFGGGTRVEIRR TVAAPSVF	356
BPx-63	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWM GWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSEDTAVYYCA RDYGGINDAFDIWGQGTMVTVSSGSASAPTLGGGGSGGGGSAAAQSVLT QPPSVSAAPGQKVTISCSGSSSNIGNQYVSWYQHLPGTAPKLLIYDNNKRP SGIPDRFSGSKSGTSATLDITGLQTGDEADYYCGTWDTSLSGFLFAGGTKL TVLSQPKAAPSVTLFPPSS	357
BP6b-5	QIQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCARDQ WLGGLSNYYYYGMDVWGQGTTVTVSSGSASAPTLGGGGSGGGGSAAAQ SVLTQPPSVSGAPGQRVTISCTGSGSNIGRGYDVHWYQQLPGTAPKLLIYG NTKRPSGVPERFAASKSGTSATLDITGLQTGDEADYYCGTWDTSLSGFLFA GGTKLTVLSQPKAAPSVTLFPPSS	359
BPx-65	QVQLVESGGGLVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVA VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK DLLAGGSYYYYYYGMDVWGQGTTVTVSSGSASAPTLGGGGSGGGGSAA AQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIHT NNQRPSGVPDRFSGSKSGTSASLAISGLQSEDEADFYCAAWDDSLNGPVF GGGTKLTVLGQPKAAPSVTLFPPSS	360
BPx-66	QIQLVQSGGGLVKPGGSLRLSCAASGFPFSNAWMSWVRQAPGKGLEWVA	361

	NIEQDGSEKYYVDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKE EYGDHYYFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAANFMLTQP HSVSESPGKTVTISCTRSSGRIASTYVQWYQHRPGSAPNIVIYEDDQRPSGV PDRFSGYVDNSSNSASLTISGLKPEDEAEYYCQSYDGDNAVFGGGTKLTV LGQPKAAPSVTLFPPSS	
BPx-67	EVQLLETRGGLVQPGRSLRLSCATSGFTFGDYAMHWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKD LATYYDFWSGLFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSA LTQPASVSGSLGQSITISCTGTSGDVETYNLVSWYQQHPGKVPKLIIYEVSE RPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYAGSGTLRLFGGGT KVTVLGQPKAAPSVTLFPPSS	362
BPx-68	EVQLVQSGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWV AVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCSG GSYYGAFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSVLTQPP SVSAAPGQKVTISCTGSSSNIGAGYDVHWYQQVPGTAPKLLIYGNSYRPSG VSDRFSGSKSGTSASLAISDLQPEDEAYYYCATWDDSLRGDVVFGGGTKL TVLGQPKAAPSVTLFPPSS	363
BPx-69	QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARKSS SGWSIDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADVVMTQSPLS LPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLASNRAS GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPATFGQGTKLEI KRTVAAPSVF	364
BPx-70	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAGG SYESSAYHYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQPVLTQPPS MSVSPGQTASITCSGHKLGHKYVGWYQQRPGQSPVLVIYQDNKRPSGIPE RFSGSNSGNTATLTISETQAIDEADYYCQAWDSSSTAYVFGTGTKVTVLG QPKANPTVTLFPPSS	365
BPx-71	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWM GWINTYNGNTNYAQKFQGRVTMTTDTSTSTTYMELRSLRSDDTAVYYCA REGWVGAKGGFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSA LTQPPSASGSPGQSVTISCSGTSSDVGGYNYVSWYQQYPGKAPKLVISEVS KRPSGVPDRFSGSKSGNTASLTVSGLQAEDEAEYYCSSYVGGNIWVFGGG TKLTVLGQPKAAPSVTLFPPSS	366
BPx-72	EVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVS SISSTSSYIYYAESVKGRFTISRDNAENSLYLQMNSLRGEDTAVYYCARDR GGYAYGDFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIQMTQS PSTLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVP SRFSGSGSGTDFALTISSLQPEDFATYYCQQSYSTPWTFGQGTKVEIKRTVA APSVF	367
BPx-73	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYTISWVRQAPGQGLEWMG RIIPILGIANYAQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCARTNS GTLDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQPVLTQPPSASGT PGQRVTISCSGSSSNIGSNYVYWYQQLPGTAPKLLMYRNNQRPSGVPDRFS GSKSGTSASLAISGLRSEDEADYYCAAWDDSLSGWVFGGGTKLTVLGQPK AAPSVTLFPPSS	368
BPx-74	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYDINWVRQATGQGLEWM GWMNPNSGNTGYAQKFQGRVTMTRNTSISTAYMELSSLRSEDTAVYYCA RGDFWSGYYYYYYGMDVWGQGTTVTVSSGSASAPTLGGGGSGGGGSAA AEIVMTQSPGTLSLSPGERVTLSCRASQYITSGYLAWYQQKPGQAPRLLFY GASRRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPTYTFGQ GTKLEIKRTVAAPSVF	369
BP8b-1	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSVTWDWIRQSPSRGLEWLG	370

	RTYYRSKWYNDYAVSVKSRITINPDTSKNQFSLHLSSVTPEDTAVYYCAR QNGGYDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAEIVLTQSPGT LSLSPGERATLSCRASESISNNYLAWYQQKPGQAPRLLIYGASSRATGIPDR FSGRGSGIDFTLTISRLEPEDFAVYYCQQYGYSPTFGPGTKVDVKRTVAAP SVF	
BPx-75	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEW MGWINPNSGGTNYAQKFQGRVTITRDTSASTAYMELSSLRSEDTAVYYCA RDGGVEMATIPGGYGMDVWGQGTTVTVPSGSASAPTLGGGGSGGGGSA AADIQMTQSPSSLSASVGDRVTVTCRASQSISIFVNWYQQRPGKAPKLLIY AASSLQTGVPSRFSGSGSGTEFTLTISSLQPEDYATYYCQQSYSMLSWTFGP GTKVENKRTVAAPSVF	371
BPx-76	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWM GGIIPIFGTANYAQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCARG RIGSGYDSVWLRYFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQ AVLTQPPSASGTPGQRVTISCSGSSSNIGSNYVSWYQQLPGTAPKLLIFSNN QRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYCAAWDDSLNGWVFGG GTKLTVLGQPKAAPSVTLFPPSS	372
BPx-77	EVQLVQSGGGLVQPGRSLRLSCAASGFTFGDYAMHWVRQAPGKGLEWV SGISWNSGSIGYADSVKGRVTISRDNAKNSLYLQMNSLRDEDTAVYYCAR EDEGSGSYYWGPVDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQS ALTQPASVSGSPGQSITISCTGTSSDVGAYNYVSWYQQYPGKAPKLMIYD VSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCGSYTTSSTLVFGG GTKVTVLGQPKAAPSVTLFPPSS	373
BP6b-6	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWV ANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCA RGYSNYAYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAASSELTQAPS VSVSPGQTASITCSGDKLGDKYVSWYQQRPGQSPVVVIYQDIRRPSGIPER FSGSNSGNTATLTISGTQAMDEADYYCQAWDSSSWVFGGGTKLTVLSQP KAAPSVTLFPPSS	374
BPx-78	QVQVVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEW MGWINPNSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYC ARKSGTMVRGPMWGSFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSA AAEIVLTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQ LLIYLGSNRASGVPDRFSGSVSGTDFTLKISRVEAEDVGVYYCMQGTHWS YTFGQGTKLEIKRTVAAPSVF	375
BPx-79	QIQLVQSGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVSY ISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKDPG WLQLDYYFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSALTQP ASVSGSPGQSITISCTGTSSDIGTYNYLSWYQQHPGKAPKLMIYDVVYRPS GVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYAGSSTVVFGGGTKLTV LGQPKAAPSVTLFPPSS	376
BPx-80	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTADYAQKFQGRATITADESTSTAYMELSSLRSEDTAVYYCARDR YCSGGSCYIYYGMDVWGQGTTVTVSSGSASAPTLGGGGSGGGGSAAADI QMTQSPASLSVSIGDRVTITCQASQDIANHLNWYQQKPGDVPKLLIFDATH MERGVPSRFDGSRSGTDFTFTISSLQPEDVATYYCQQFDELPLTFGGGTKV RIKGTVAAPSVF	377
BPx-81	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWV AVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR RTVGLGMDVWGQGTTVTVSSGSASAPTLGGGGSGGGGSAAANFMLTQP HSVSESPGKTITISCTRNSGRIASNYVQWYQQRPGSPPTTLIYEDSLRPSGVP DRFSGSIDTSSNSASLTISGLETEDEADYYCQSYDSRVYVFGTGTKVTAL	378
BPx-82	EVQLLESRGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVA VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARG	379

	YGSGSSWYFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAASSELTQ DPAVSVALGQTVRITCQGDSLKKYYASWYQQKPGQAPVLVIYGKNLRPS GIPERFSGSSSGDTASLTISATQAEDEADYYCNSRDSSGNPIFGGGTKLTVL GQPKAAPSVTLFPPSS	
BPx-83	EVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWV AVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR ALDLDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADVVMTQSPLSL PVTLGQPASISCRSSQSLVYSDGNTFLNWFQQRPGQPPRRLIYKVSNRDFG VPDRFSGSGSGTDFTLKISRVEADDVGVYYCMQGTHWPFTFGPGTK	380
BPx-84	QMQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG IINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGV VWRWLQSGGSGYFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQ SVLTQPPSVSEAPRQRVTISCSGSSSNIGNNAVNWYRQLPGKAPKLLIYDN NKRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDSSLSAWVFG GGTKLTVLGQPKAAPSVTLFPPSS	381
BP6b-11	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWM GWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSEDTAVYYCA RGYYGSGAMDVWGQGTTVTVSSGSASAPTLGGGGSGGGGSAAASSELTQ DPAVSVALGQTVRITCQGDSLKKYYASWYQQKPGQAPVLVIYGRNLRPS GIPERFSGPYSGNTASLTITGAQAEDEADYYCNSRDSRGNLLVFGGGTRLI VLGQPKAAPSVTLFPPSSKASGA	382
BP18b-4	EVQLVQSGAEVKKPGESLKISCKGSGYSFTTYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARYS YGYTFLDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIVMTQSPD SLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWAST RESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYTIPHTFGQGTKL EIKRTVAAPSVFKASGA	383
BP6b-2	QVQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWIG SIYYSGSTYYNPSLKSRVTISVDTSKNQFSLLLTSMTAADTAVYYCARTGT TRGDYFDNWGQGAKVTVSSGSASAPTLGGGGSGGGGSAAAQPVLTQPPS VSVSPGQTASITCSGDKLGDKYASWYQQKPGQSPLLVIYQDNKRPSGIPER FSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTVMFGGGTKLTVLGQP KAAPSVTLFPPSSKASGA	384
BP6b-10	EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYDINWVRQAPGQGLEWM GIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARA FDSSGYSYGMDVWGQGTTVTVSSGSASAPTLGGGGSGGGGSAAADIVMT QSPLSLPVTPGEPASISCRSSQSLLHTNGYNFLDWYLQKPGQSPQLLIHLGS YRASGVPDRFSGSGSGTDFTLKISRVAAEDVGVYYCMQALHTPMYTFGQ GTKLEIKRTVAAPSVFKASGA	385
BP16b-2	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYYMHWVRQAPGQGLEWM GIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARD IDRATNWFDPWGQGTLVTVSSGSASVPTLGGGGSGGGGSAAANFMLTQP HSVSESPGKTVTISCTGSSGSIASYYVQWYQQRPGSSPTTVIYEDNQRPSGV PDRFSGSIDSSSNSASLTISGLKTEDEADYYCQSYDSSNRWVFGGGTKLTV LGQPKAAPSVTLFPPSSKASGA	386
BP18b-5	QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWV ANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCA RDKWWPEGYYYYYYGMDVWGQGTTVTVPSGSASAPTLGGGGSGGGGS AAAEIVMTQSPLSLPVTPGEPASISCRSSQSLVHSNGNTYLNWFHQRPGQS PRRLIYEVSNRDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGTH WPYTSGQGTKLEIYRTVAAPSVFKASGA	387
BP7b-1	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQDRVTITADESTSTAYMELSSLRSEDTAVYYCARDG YCSSTSCYVWGEFDPWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIQ	388

	MTQSPSSLSASVGDRVTITCRASQSISRHLNWYQQKPGKAPKLLIYAASTL QSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSASTPLTFGGGTKVEI KRTVAAPSVFKASGA	
BP5b-7	EVQLVQSGGGLVKPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVS YISSGSSTLYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARD FGWYGSFDYWGQGTTVTVSSGSASAPTLGGGGSGGGGSAAADIVMTQSP LSLPVTLGQSASISCRSSQGLVYSDGNTFLSWFHQRPGQSPRRLIYMVSNR DSGVPDRFSGSGSGTDFTLKISRVEAEDVGIFYCMQGTHWPWTFGQGTKV EIKRTVAAPSVFKASGA	389
BPx-85	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYALHWVRQAPGKGLEWVA VLSYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR AAHSGYDLNYYYGMDAWGQGTTVTVSSGSASAPTLGGGGSGGGGSAAA DIQMTQSPSSLSASVGDRVTITCRASQNIINYLNWYQQKPGKAPDLLIHTAS NLQSGVPSRFSGSGFGTDFSLTITSLQPEDFATYYCQHSFSSPYTFGQGTKL EIKRTVAAPSVFKASGA	390
BP18b-6	QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCAKLR VGYNFFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIVMTQSPL SLPVTPGEPASISCRSSQTLLHSNGFNYLDWYLQKPGQSPQLLMYLGSSRA SGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQIPRTFGQGTKLEI KRTVAAPSVFKASGA	391
BP20b-1	EVQLVESRGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVA VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVG VDYYDSSGYPADYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIQM TQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFSLTITNLQPEDIATYYCQQTYIYPRTFGQGTKVEIKR TVAAPSVFKASGA	392
BPx-86	QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISVDKSINTAYLQWNSLKASDTAMYYCARG WSSADYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAEVVMTQSPLSL PVTLGQPASISCRSSQSLVYSDGNTYLNWFQQRPGQSPRRLLYKVSNRDSG VPDRFSGTGSGTDFTLRISRVEAEDVGVYYCMQGSHWPLTFGGGTKVEIK RTVAAPSVFKASGA	393
BP19b-3	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVS VIYSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARD WAFGGSYKLGDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSALT QPASVSGSPGQSITISCTGTSNDIGRYDYVSWYQQHPGKAPKLIIYAVKARP SGVSSRFSGSKSGNMASLTISGLQAEDEADYYCGSYTRSSTARFGTGTRVT VLGQPKANPTVTLFPPSSKASGA	394
BPx-87	QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVS SISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKDR FFTYYYDTSGRGGLDSWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAASS ELTQDPSVSVSPGQTATITCSGSKLGDKYVSWYQQKPGQSPVLVIYEDDK RPSGSSERFSGSNSGNTATLTISGTQAMDEADYYCQAWDSITAVFGGGTK LTVLGQPKAAPSVTLFPPSSKASGA	395
BPx-88	EVQLVQSGGGLVQPGGSLRLSCAASGFTFSGSSMNWVRQAPGKGLEWVS YISSSGNTIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGS EEMRGWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAASSELTQAPSVSVS PGQTASIPCSGDNLRSKYVSWYQQKPGQSPVMLIYQDDKRPSGIPEGFFGA TSGNTATLIIAETQPLDEGDYYCQTWDGNHVVFGGGTKLTVLGQPKAAPS VTLFPPSSKASGA	396
BP18b-7	QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARHD GNSRPGDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAEIVMTQSPLS	397

	LPVTLGQPASISCRSSQGLVYSDGNTYLNWFHQRPGQSPRRLIYKVSNRDS GVPDRFSGSGSGTDFTLKISRVEAEDVGIYYCMQGTQWPYTFGQGTRLDI KRTVAAPSVFKASGA	
BP17b-1	QVQLQQSGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKT VAGTRLYYYYYGMDVWGQGTTVTVSSGSASAPTLGGGGSGGGGSAAAQ SALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYD VSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTLVFGG GTKLTVLGQPKAAPSVTLFPPSSKASGA	398
BP16b-3	EVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWM GGFDPEDGETIYAQKFQGRVTMTEDTSTDTAYMELSSLRSEDTAVYYCAT DFYCSGGSCYSRGDAFDIWGQGTMVTVSSGSASAPTLGGGGSGGGGSAA AEIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLVYD ASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSGWPPKVTFGG GTKVEIKRTVAAPSVFKASGA	399
BPx-89	QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVS SISSSNSYIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTALYYCARDW SIYPASVDFFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIQMTQ SPSSLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSLESGV PSRFSGSGSGTEFTLTITSLQPEDFATYYCQQSYSTPFTFGPGTKVDIKRTVA APSVFKASGA	400
BPx-90	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVS SISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKDG RLGELSHWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQPVLTQPPSVS VSPGQTTNITCSGHELGDKYVSWYQQRPGQSPVVVIYQDNKRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQAWDSSTVVFGGGTKLTVLGQPKA APSVTLFPPSSKASG	401
BP5b-8	EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVA VISYDGSNQYYADSVKGRFTISRDNSKNTLYVQMNSLRAEDTAVYYCAR GNYYGSGSYPLLDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAASSE LTQAPSVSVAPGRTARITCGGNNIGNKSVHWYQQQPGQAPVLVIYYDIDR PSGIPERFSGSNSGNTATLTISRVEADDEADYYCQVWDSNSDHVVFGGGT KLTVLGQPKAAPSVTLFPPSSKASGA	402
BP16b-4	QVQLVQSGGGLVQPGGSLRLSCAASGFTFSNYWMYWVRQAPGKGLVWV SNINSDGSSTSYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCAR EGYNAHYFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSALTQP ASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLLIYDVTKRPS GVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTVVFGGGTKLTV LGQPKAAPSVTLFPPSSKASGA	403
BP9b-1	QVQLQQSGPRQVEPSQTLSLTCAISGDSVSSKSAAWNWIRQSPSRGLEWL GRTYYRSKWYYDYAVSVKSRIIVNPDTSRNQFSLHLNSVTPEDTAFYYCA RGEDSGYGSFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAANFMLT QPPSASGTPGQRVTISCSGSSSNIGNNAVNWYQQLPGTAPKLLIYSNNQRPS GVPDRFSGSKSGTSASLAISGLQSEDEADYYCATWDDSLNGWVFGGGTKL TVLGQPKAAPSVTLFPPSSKASGA	404
BPx-91	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWM GWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCA RDMKWLPRGVDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIVLT QSPLSLPVTPGEPASISCRSSQSLLHSNGFNYLDWYLQKPGQSPQLLIYLGS NRASGVPDRFSGSGSGTDFTLQISRVEAEDVGVYYCMQGLQTPYTFGQGT KLEIKRTVAAPSVFKASGA	405
BPx-92	QIQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGI IYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARLGF REIDYWGQGTLVTVSPGSASAPTLGGGGSGGGGSAAAQSVLTQPPSVSAA	406

	PGQTVTISCSGSTSNIGNNYVSWYEQLPGTAPKLLIYDNNRRPSGIPDRFSG SKSGTSAALGITGLQTGDEANYYCGTWDSSLSAWVFGGGTKLTVLGQPK AAPSVTLFPPSSKASGA	
BP12b-1	EVQLLESRAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGPEWMGI IYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARLVY GGYDEPGYYFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSVLT QPPSASGTPGQRVTISCSGSSSNIRSNTVNWYQQLPGTAPKLLIYSNNQRPS GVPDRFSGSKSGTSASLAISGLQSEDEADYYCAAWDDSLNGWVFGGGTK LTVLGQPKAAPSVTLFPPSSKASGA	407
BPx-93	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSHGMHWVRQAPGKGPEWV AVISYDGSNKYYPDSVRGRFTISRDNSKNTLYLQMNSLTTDDTAVYYCAK GGGYGDYAPGYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAANFMLT QPHSVSGSPGKTVTISCTRSSGSISSKYVQWYQQRPGSSPTTVMYEDKQRP SGVPARFSGSVDSSSNSATLTISGLKTEDEADYYCQSYDNTNVVFGGGTKL TVLGQPKAAPSVTLFPPSSKASGA	408
BPx-94	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GFDPEDGETIYAQKFQGRVTMTEDTSTDTAYMELSSLRSEDTAVYYCATG FWELEAGGFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAEVVLTQ SPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYMGSN RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPFTFGPGTK VDIKRTVAAPSVFKASGA	409
BPx-95	QVQLQQSGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWIG SIYYSGSTYYNPSLKSRVTISVDTSRKQVSLELSSVTAADTAVYYCARLWL GERPPDYWGQGMLVTVSSGSASAPTLGGGGSGGGGSAAANFMLTQPHSV SGSPGKTVTISCTGSNGAIASNYVQWYQQRPGGAPVTLIYEDNHRPPGVPD RFSGSIDTSSNSASLTISGLKTEDEADYYCQSYDSVYNWVFGGGTKLTVLG QPKAAPSVTLFPPSSKASGA	410
BPx-96	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEW MGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCA RDRGSGWYGGAFDIWGQGTMVTVSSGSASAPTLGGGGSGGGGSAAAQS ALTQPASVSGSPGQSITISCSGTSSDVGVYESVSWYQHHPGEAPKLMIYDV TKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYSTSSTFEVFGGG TRLTVLSQPKAAPSVTLFPPSSKASGA	411
BP6b-9	QIQLVQSGGGVVQPGRSLRLSCAASGFTFSSYAIHWVRQAPGKGLEWVAV ISYDGSIKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDT HEWELFVGTFDIWGQGTMVTVSSGSASAPTLGGGGSGGGGSAAADIQMT QSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPWTFGQGTKVQIKR TVAAPSVFKASGA	412
BPx-97	QVQLVQSGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVS SISSNSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDP DYYYGSGTREDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIQMT QSPSTLSASVGDRVTITCRASQSISRWLAWYQQKPGEAPKLLIYKASTLEG GVPSRFSGSGSGTEFTLTISSLQPEDSATYYCLQDYTTPYTFGQGTKLEIKR TVAAPSVFKASGA	413
BPx-98	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWV AVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR VEWADGAFDIWGQGTMVTVSSGSASAPTLGGGGSGGGGSAAAQSVLTQP PSTSGTPGQRVTISCSGSSSNIGSNTVDWYQQLPGTAPNLLIHSNNRRPSGV PDRFSGSKSATSASLAISGLQSEDEADYYCEAWDDSLSAVVFGGGTRVTV LGQPKAAPSVTLFPPSSKASGA	414
BPx-99	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVA NIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR GLIGDWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIVMTQTPDSLAV	415

	SLGERATISCKSSQSILYDSNLKNYLAWYQHKPGHPPKLLISWASTRESGV PDRFSGSGSDTDFTLTISSLQAEDVAVYSCQQFYTTPYTFGQGTKLEIKRTV AAPSVFKASGA	
BP6b-7	EVQLVQSGGGVVQSGRSLRLSCVASGFSFSNYGMHWVRQAPGKGLEWL AFIWYDGSNKWYADSVKGRFTISRDNSKNALYLQMNSLRAEDTAVYYCA RDRYSSSWGGGFDYWGQGTVLTVSSGSASAPTLGGGGSGGGGSAAANF MLTQPHSVSESPGRTVTIPCSGRGGSIASDSVQWYQQRPGSAPTTIIYEDNQ RPSGVPDRFSGSVDSSSNSASLTISGLRTEDEADYYCQSYDASSLWVFGGK TKLTVLGQPKAAPSVTLFPPSSKASGA	416
BPx-100	QIQLVQSGGGVVQPGRSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVG RIKSKTDGGTTDYAAPVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCT TDRVTMVRGVTPPFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQ SALTQPPSASGSPGQSVTISCTGTSRDVGRYNYVSWYQQHPGKAPKLMISE VSKRPSGVPDCFSGSKSGNTASLTISGLQAEDEADYYCCSYSGGYNWVFG GGTKLTVLGQPKAAPSVTLFPPSSKASGA	417
BP6b-8	QLQLQQSGGGLVQPGGSLRLSCAASGFTFSSYWMHWVRQAPGKGLVWV SRINSDGSSTSYADSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCAR DGWGSYRYVPGYYYYYGMDVWGQGTTVTVSSGSASAPTLGGGGSGGG GSAAAQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPK LLIYSNNQRPSGVPDRFSGSKSGTSATLDITGLQTGDEADYHCQSYDSSLS DSVVFGGGTKLTVLGQPKAAPSVTLFPPSSKASGA	418
BPx-101	QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARGS GWTNILDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAEVVLTQSPD SLAVSLGERATINCKSSQSILSNSNNKNYLTWYQQKPGQPPQLIISWASTRE SGVPDRFSGSGSGTDFTLTINSLQAEDVAVYYCQQYYSTPLTFGGGTKVEI KRTVAAPSVFKASGA	419
BPx-102	QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYWIGWVRQMPGKGLEWM GIIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCATQ PHDRGVWGQGTTVTVSSGSASAPTLGGGGSGGGGSAAADIVMTQSPPSLP VAPGEPASISCRSSQSLLHSDGKNYVDWYLQKPGQSPQLLIFLGSKRASGV PDRFSGSGSGTDFTLKISRVEAEDVGVYFCMQGTRWPYTFGQGTKLEIKRT VAAPSVFKASGA	420
BPx-103	QLQLQQFGPGLVKPSETLSLTCTVSGDSSSSYYWSWIRQPPGKGLEWIGSI YYSGSTYYNPSLKSRVTISVDTSKNQLSLKLNSVTAADTAVYYCARGAYG DKDLGVFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAANFMLTQPH SVSESPGKTVTISCTGTGDSIASNYVQWYQQRPGSAPTTVIYEDNQRPSGV PDRFSGSIDSSSNSASLTISGLRTEDEADYYCQSYDSVYNWIFGGGTRLTVL GQPKAAPSVTLFPPSSKASGA	421
BPx-104	QVQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWIG SIYYSGSTDYSPSLKSRVTISIDTSKNQFSLKVSSVTAADTAVYYCARERGN GDYDNWGLGTLVTVSAGSASAPTLGGGGSGGGGSAAAQSVLTQPPSVSA APGQKVTISCSGSSSNIGNNYVSWYQQLPGTAPKLLIYDNNKRPSGIPDRFS GSKSGTSASLAISGLQPEDEADYYCAVWDDSLNGWVFGGGTKLTVLRQP KAAPSVTLFPPSSKASGA	422
BPx-105	EVQLVQSGGGVVRPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWV SGINWNGGSTGYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA RQYVPEYNSGWPYYYYGMDVWGQGTTVTVSSGSASAPTLGGGGSGGGG SAAASSELTQDPSVSVSPGQTASITCSQTKLGDKYVSWYQQKPGQSPVLVI YEDDKRPSGISERFSGSNSGNTATLTISGTQAVDEADYYCQVYDSSTVVFG GGTKLTVLGQPKAAPSVTLFPPSSKASGA	423
BPx-106	EVQLVESGPGLVKPSGTLSLTCAVFGGSISSSDNWWGWVRQPPGEGLEWI GDISHSGNTIYNPSLKSRVTISVDKSKNQFSLKLGSVTAADTAVYYCARYD SRGYYYPTDAFDIWGQGAMVTVSSGSASAPTLGGGGSGGGGSAAADIQM	424

	TQSPSTLSASVGDRVTITCRASQSISRRLAWYQQKPGKAPKLLISGASNLEF GVPATFSGTGSGTEFTLTISSLQPDDFATYYCQQYESYQPPTFGGGTKVEM KRTVAAPSVFKASGA	
BP5b-9	EVQLVESGGGLEKPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVS AVNKGGDAAYSADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR GVWAVDAFDIWGQGTMVTVSSGSASAPTLGGGGSGGGGSAAADIQMTQ SPSSVSASVGDRVTITCRASQGISNWLAWYQQKPGKAPKLLIYGASSLQSG VPSRFSGSGSGTDFTLTISSLQFEDFATYYCQQSQSTPVTFGQGTRLEIKRT VAAPSVFKASGA	425
BPx-107	EVQLVQSGGGVVQPGRSLRLSCAASGFSFRNYAMHWVRQAPGKGLEWV AVISYDGSNKYYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCA RDNGYDSSGYYFLDHYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAE IVMTQSPATLSLSPGDRAALSCRASHSVGSHVDWFQQKPGQAPRLLIYDAS NRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQRSNWPRALSFGGG TKVEIKRTVAAPSVFKASGP	426
BPx-108	QVTLKESGPTLVKPTQTLTLTCTFSGFSLSTYGVGVGWIRQPPGKAPEWLA RIDWDDDEYYSTSLKTRLTISKDTSKNQVVLTMTDMDPVDTATYYCTRFV GAKADYWGQGILVTVSSGSASAPTLGGGGSGGGGSAAAQSALTQPASVS GSPGQSITISCTGTSSDVGAYNHVSWYQQYPGKAPKLMIYDVSNRPSGVS DRFSGSKSDNTASLTISGLQAEDEADYYCSSYTSSNTWVFGGGTKLTVLG QPKAAPSVTLFPPSSKASGA	427
BPx-109	EVQLVESRGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVA VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQLNSLRAEDTAVYYCARA RSPIAVAPNWFDPWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIVMT QSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIY WASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYSTPYTFGQ GTKLEIKRTVAAPSVFKASGA	428
BP22b-1	QIQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVA VIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK GLGYHPLFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIVMTQS PDSLAVSLGERATINCKSSQSVLYSSDNKNYLAWYQQKPGQPPKLLIYWA STRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYSTPSFGPGTK VDIKRTVAAPSVFKASGA	429
BPx-110	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWV AVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA KDLYSGSGGGDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAANFMLT QPHSVSESPGKTVTISCTRSSGSIASNYVQWYQQRPGSSPTTVIYEDNQRPS GVPARFSGSIDISSNSASLTISGLLTEDEADYYCQSYNTSNLVFGTGTKVTV LRQPKANPTVTLFPPSSKASGA	430
BP6b-12	EVQLVQSGGGLVQPGGSLRLSCAGSGFTFSDYDMSWVRQAPGKGLEWVS GISGSGGSTYYVDSVQGRFTISRDNSKNTLYLQMNGLRAEDTAVYYCAKD SSSGWYGLWDYWGQGTLVSVSSGSASAPTLGGGGSGGGGSAAADIQMT QSPSSVFASVGDRVTITCRASQDISTWLAWYQQKPGKGPKLLIYGASSLQS GVPSRFSGSGSGTDFTLTISSLQPDDFATYYCQQYQESPWTFGQGTKVEIK RTVAAPSVFKASGA	431
BPx-111	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYI YYSGSTNYNPSLKSRVTMSVDTSKNQLSLNLTSVTAADTAVYYCAREFPM GRPFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQSALTQPPSASG SRGQSVSISCSGSRSDIGYYNYVSWYQQHPGKAPKLIIFDVNKRPSGVSNR FSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTWVFGGGTKLTVLGQPK AAPSVTLFPPSSKASGA	432
BPx-112	EVQLVESGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMG WISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR DGMFAPGYFDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAAQPVLTQ	433

	PPSVSVAPGKTARITCGGNNIGSKSVHWYQQKPGQAPVLVVYDDSDRPSG IPERFSGSNSGNTATLTISRVEAGDEADYYCQVWESSSDEWDTTSDQWVF GGGTKVTVLGQPKAAPSVTLFPPSSKASGA	
BPx-113	QVTLKESGPVLVKPTETLTLTCAVSGFSLSNPRMGVSWIRQPPGKALEWL ALIYWDDDKRYSPSLKSRLTITKDTSKNQVVLTMTNMDPVDTATYYCAL WDDYSNYEIARGAFDIWGQGTMVTVSSGSASAPTLGGGGSGGGGSAAAN FMLTQPHSVSESPGKTVTLSCTGSGGSIARNYVQWYQQRPGSAPSAVIYED DRRPSGVPHRFSGSIDTSSNSATLTISGLKTEDEADYYCQSYDSAHHWVFG GGTKLTVLSQPKAAPSVTLFPPSSKASGA	434
BP10b-1	QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYDMHWVRQATGKGLEWVS AIGTAGDTYYPGSVKGRFTISRENAKNSLYLQMNSLRAGDTAVYYCARG KPLLSGYLINDAFDIWGQGTMVTVSSGSASAPTLGGGGSGGGGSAAAQSV LTQPPSVSAAPGQKVTISCSGSSSNIGDNYVSWYQQLPGTAPKLLIYDNNK RPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDDRLSGVVFGGGT KLTVLSQPKAAPSVTLFPPSSKASGA	435
BPx-114	EVQLLETGGGVVQPGRSLRLSCAASGFSFNNYGMHWVRQAPGKGLEWVS VIYSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDG GSGYHDYWGQGTLVTVSSGSASAPTLGGGGSGGGGSAAADIVMTQSPDS LAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWASTR ESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYFCQQYYGIPTFGGGTKVEIK RTVAAPSVFKASGA	436

[00308] Recombinant GDF-modulating antibodies of the disclosure may comprise or be developed using any of the VH sequences listed in Table 14. Some recombinant GDF-modulating antibodies of the disclosure may comprise or be developed using VH sequences that comprise at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 99.5% or at least about 99.9% sequence identity to any of the VH sequences listed in Table 14. Recombinant GDF-modulating antibodies may, in some cases, comprise VH domains presented, but with different combinations of CDRs (e.g. CDR-H1, CDR-H2 or CDR-H3). In some cases, such antibodies may interact with one or more of the recombinant proteins listed in Table 4, 9 or 10.

Table 14. VH domains

Clone ID	**scFv sequence**	**SEQ ID NO**
BP6a-16	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEWL GRTYYRSKWSNDYAVAVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCA RGFSGMGVWGQGTTVTVSSGS	437
BP6a-19	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDQ AGDYGGNSGYFDYWGQGTLVTVSSGS	438
BP3a-3	EVQLVQSGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWV SGISWNSGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK GQVPNYYDSRDPFDPWGQGTLVTVSSGS	439

BP6a-1	QIQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARITD DFDYWGQGTLVTVSSGS	440
BP18b-1	QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARGV AGYSSGWSDWGQGTLVTVSSGS	441
BP19b-1	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYIY YSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARLRRGYF DYWGQGTLVTVSSGS	442
BP6b-4	QVQLVQSGAEVKKPGESLKISCAASGFTFSSYGMHWVRQAPGKGLEWVA VIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAT RGYWGQGTLVTVSSGS	443
BP6a-8	QVQLQQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWM GIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARE GGDYNNWFDPWGQGTLVTVSSGS	444
BP13a-1	QVQLVQSGSEVKKPGASVKVSCKLSGYTLTELSMHWVRQAPGKGLEWM GGFDPEDDEAIYAQKFQGRVTMTEDTSTDTAYMELSSLRSEDTAVYYCAT DRVTGTTMAAFDIWGQGTMVAVSSGS	445
BP5b-3	EVQLVQSGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVS YISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCARDN WYYFDYWGQGTLVTVSSGS	446
BP6a-23	QVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVS SISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDL GGYFGNYWGQGTLVTVSSGS	447
BP5a-1	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCANHGL MDDSSGYYLSNAFDIWGQGTMVTVSSGS	448
BP6a-11	QIQLVQSGGVVVQPGGSLRLSCAASGFTFDDYTMHWVRQAPGKGLEWVS LISWDGGSTYYADSVKGRFTISRDNSKNSLYLQMNSLRTEDTALYYCAAG SYHTWWGQGTLVTVSSGS	449
BP5b-4	QVQLQQSGGGLVQPGGSLRLSCAASGFTFSSYAMTWVRQAPGKGLEWVS AISGGGGATYYADSVEGRFTISRDNSKNTLYLQMNSLRAEDTAIYYCASPA GHICSGGSCQYYYYGMDVWGQGTTVTVSSGS	450
BP18a-1	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARQP YYYGSGSGMDVWGQGTTVTVSSGS	451
BP11a-1	EVQLVQSGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWV SGISWNSGSIGYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK VDGLEYSSGHNFDYWGQGTLVTVSSGS	452
BP6a-14	EVQLVESGGGVVQPGRSLRLSCAASGFSFSSYGMHWVRQAPGKGLEWVA VTSYDGSNKYYGDSVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCAK DEYTYGSGIMDYWGQGTLVTVSSGS	453
BP6a-27	QMQLVQSGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWV ALISYDGSYEYYADSVKGRFTISRDISKNTLYLQMNSLRAEDTAVYYCAR DSGARGYNYGLFDYWGQGTLVTVSSGS	454
BP6a-13	EVQLVESGGGVVQPGRSLRLSCAASGFRFSNYGMHWVRQAPGKGLEWVS AISGSGGLTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARE DLWRMGELLGGEGFDYWGQGTLVTVSSGS	455
BP4a-1	EVQLVQSGAEVKKPGASVKVSCKASGYTFSSYGITWVRQAPGQGLEWMG WSSAYNGNTNYAQKLQGRISMTTDTSTSTAYMELRSLRSDDTAVYYCAR GIYGDYEYWGQGTLVTVSSGS	456
BP1a-1	EVQLVQSGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWV SGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAK DTSNGGYSSSSFDYWGQGTLVTVSSGS	457

BP6a-6	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDRH LYRRGYSSVDGMDVWGQGTTVTVSSGS	458
BP19b-2	QLQLQQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVA VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKP RGRYYFDYWGQGTLVTVSSGS	459
BP6a-4	QVQLQESGPGLVKPSETLSLTCTVSGDSITSYYWSWIRQPPGKGLEWIGYI HYSGSTYYNPSLKSRVTISVDRSKNQFSLKLSSVTAADTAVYYCARGPSRG LFDPWGQGTLVTVSSGS	460
BP19a-1	QVQLQESGGVVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGKGLEWVSSI SNSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASLSR GYWGQGTLVTVSSGS	461
BP6a-7	QVQLQQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWM GIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARE SLIRFLEDPQQGGMDVWGQGTTVTVSSGS	462
BP5b-5	QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCATPYS SSSGTDYWGQGTLVTVSSGS	463
BP6b-3	QIQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG WINPNSGGTNYAQKFQGWVTMTRDTSISTAYMELSRLRSDDTAVYYCAR PRTLRGDAFDIWGRGTMVTVSSGS	464
BP18b-2	QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARHPI GSGYDYWGQGTLVTVSSGS	465
BPx-1	QVQLVQSGAEVKKPGSSVKVSCKASGGAFSIYSINWVRQAPGQGLEWMG GIIPIFETANSAQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCARAGE NSDSNYAFDIWGRGTVVTVSSGS	466
BP21a	QLQLQQSGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWIG SIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARGRY SYGYFDYWGQGTLVTVSSGS	467
BP6a-2	QVQLVQSGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVS SISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGIR VVGDEDYYYYYGMDVWGQGTTVTVSSGS	468
BPx-2	EVQLLQSGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVS YISSSSSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCARDS SGWLGMGDFDYWGQGTLVTVSSGS	469
BP6b-1	QVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVS SISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREE YYGGNTDWGQGTLVTVSSGS	470
BPx-3	EVQLVQSGGGLVQPGGSLRLSCVTSGFSFSNYGMSWVRQAPGKGLEWVS EISGSGGSAYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDI SHYDILTGQLDYWGQGTLVTVSSGS	471
BP6a-5	QIQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVA VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARD LLVRFLEWSHYYGMDVWGQGTTVTVSSGS	472
BP6a-10	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVA NIKQDGSEKYYVDSVKGRFTISRDNSENTLYLQMNSLRAEDTAVYYCAKE TDCSGGICYGVDYWGQGTLVTVSSGS	473
BP15a-1	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMG WISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR DAPYDILTGYLSYWGQGTLVTVSSGS	474
BP6a-26	QIQLVQSGGGVVQPGRSLRLSCAASGFSFSTYAMHWLRQAPGKGPEWVA AISYDGTIKYYADSVKGRFTISRDSSKNTLYLQMNNLGPEDTALYYCARA GGAGSDGYNYWGYWGQGTLVTVSSGS	475

BP6a-12	QVQLVQSGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDPGGKLGGAFDIWGQGTMVTVSSGS	476
BP5a-4	QVQLVQSGAEVKKPGSSVKVSCKASGGTLSSYAISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDRPGNNRYDILTGGGWFDPWGQGTLVTVSSGS	477
BP5b-1	QVQLVQSGGGVVRPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKEISDTAMGFDYWGQGTLVTVSSGS	478
BPx-4	EVQLVESRGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARAYIPRLYYYGSGLDYWGQGTLVTVSSGS	479
BP5a-3	QVQLQESGPGLVKPSETLSLTCTVSGYSITNGYYWGWIRQSPGKGLEWIGNIFQSGSTYYNPSFKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARRVDYYDSSGYGEGYFDYWGQGTLVTVSSGS	480
BP14a-1	QVQLVQFGAEVKKPGESLKISCKGSGYNFNSYWIGWVRQMPGKGLEWMGIIYPGDSDIRYNPSFQGQVTISADKSISTAYLQWSSLKASDSAMYYCARHVSGSLDYWGQGTLVTVSSGS	481
BP3a-1	EVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKTAYYDSSGYYPDAFDIWGQGTMVTVSSGS	482
BP18b-3	QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARGQGGVLGAFDIWGQGTMVTVSSGS	483
BP6a-9	EVQLVESGAEVKKPGEPLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARQGRGEAFDIWGQGTMVTVSSGS	484
BP6a-25	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNTEAWNWIRQSPSRGLEWLGRTYYRSKWYHDYAPSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCARTVFDSQVYWFDPWGQGTLVTVSSGS	485
BPx-5	EVQLVESRGGLVKPGGSLRLSCAASGFTFSSYGMSWVRQAPGKGLEWVSSISNSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASLSRGYWGQGTLVTVSSGS	486
BP5a-2	QVQLVQSGGGLIQPGGSLRLSCAASGFTVSSYSMNWVRQAPGKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKVGTAAAGDAFDIWGQGTMVTVSSGS	487
BP6a-15	QVQLQESGPGLVKSSGTLSLTCAISGVSIASSNWWSWVRQPPGKGLEWVGEIYHSGSTFYNPSLQSRVTISVDKSKNQFSLTLNSVTAADTAVYYCASSSGWPYPTNWFDAWGQGTLVTVSSGS	488
BP6a-21	EVQLLESRGSLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSGISDSGGTTYYADSVKGQFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDAHNWNYGVFDYWGQGTLVTVSSGS	489
BP5a-5	QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRRAPGKGLEWVSYISSSSSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCASALGATGAFDIWGQGTMVTVSSGS	490
BP6a-17	QMQLVQSGGGLVKPGGSLRLSCAASGFTFSDYYMTWIRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDISGYEPLYYFDYWGQGTLVTVSSGS	491
BP6a-20	EVQLVESRGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDPGKQWRVRGYFDYWGQGTLVTVSSGS	492
BP3a-2	EVQLVQSGGDLEQPGGSLRLSCGTSGFTFSDYDMSWVRQAPGKGLEWVSGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARESDMAAAGSFDYWGQGTLVTVSSGS	493

BP6a-24	EVQLVESRGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSS ISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGN SGYDVWGQGTLVTVSSGS	494
BP6a-22	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMG WISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR DSLWFGELSALDYWGQGTLVTVSSGS	495
BP19a-2	QVQLVQSGGGVVLPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVA VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARD VSSWAAFWGQGTLVTVSSGS	496
BPx-6	QIQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMG WISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR GGRGGVITWFDPWGQGTLVTVSSGS	497
BP6a-18	QIQLVQSGGGLIQPGGSLRLSCAASGFTFSSFAMSWVRQAPGKGLEWVSSI TSRGDTTYYADSVRGRFTISRDNSKNTLYLQMNSLRADDTAVYYCARDRP QVPYDSSGNFDYWGQGTLVTVSSGS	498
BP16a-1	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTADYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCAREEA GYSSGWVEDAFDIWGQGTMVTVSSRS	499
BP19a-3	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWV AVISYDGSNKYYADSVKGRFTISRDNAENSLYLQMNSLRAEDTAVYYCAR MVGGYRFDYWGQGTTVTVSSGS	500
BP5b-2	EVQPLETGGGLVQPGGSLRLSCVTSGFSFSNYGMSWVRQAPGKGLEWVSE ISGSGGSAYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKHG DYGGTFDYWGQGTLVTVSSGS	501
BP2a-1	QIQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMG WISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELSSLRSEDTAVYYCAR VGFYDYVWGSYPYDAFDIWGQGTMVTVSSGS	502
BP18a-2	QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYWIAWVRQMPGKGLEWM GIIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWTSLKASDTAMYYCARR SSSSGSFDYWGQGTLVTVSSGS	503
BP6a-3	QLQLQQSGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVS SISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCVRDR HSLGDFDYWGQGTLVTVSSGS	504
BPx-7	QIQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVA VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARR FTMDYWGQGTLVTVSSGS	505
BPx-8	QVQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWIG SIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARYSSS WELFDYWGQGTLVTVSSGS	506
BPx-9	QIQLVQSGAEVRKPGDSVKVSCRTSGYTFNDYHIHWVRQAPGQGLEWMG WISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLKSDDTAVYYCAR RNGSGSAPGYWGQGTLVTVSSGS	507
BPx-10	EVQLVESGAEVKKPGESLRISCKGSGYSFTSYWIGWVRQMPGKGLEWMGI IYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARVGQ YYGMDVWGQGTTVTVSSGS	508
BPx-11	QVQLQESGPGLVKPSETLSLACTVSGGSISSSSYYWGWIRQPPGKGLEWIA SINYSGNTYYNPSLKSRVIIPIDTSKNQFSLKLSSVTAADTAVYYCARRVLG YGYFDYWGQGTLVTVSSGS	509
BPx-12	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTGGGN VDYWGQGTLVTVSSGS	510
BPx-13	EVQLLESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVS GISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKD KAGNYYYGMDVWGQGTTVTVSSGS	511

BPx-14	QVQLVQSGGGVVQPGRSLRLSCAASGFTFGHYGMHWVRQAPGKGLEWV AVISYDGTNKYYADSVKGRFTISRDNSKNTLYLQMNSLRVDDTAVYYCA KGSRLDPWGQGTLVTVSSGS	512
BPx-15	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEWL GRTYYRSKWYNDYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCV GQGYDSSGYYGMDVWGQGTTVTVSSGS	513
BPx-16	QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARQY YDTSYFDYWGQGTLVTVSSGS	514
BPx-17	EVQLVQSGGGLVQPGRSLRLSCAASGFTFGDYAMHWVRQAPGKGLEWV SGINWNSGGVGYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA KDSGYSYGINFDYWGQGTLVTVSSGS	515
BP1b-1	QIQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMG WISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR GDWFDPWGQGTLVTVSSGS	516
BPx-18	QVTLKESGPTLVKPTQTLTLTCTFSGFSLSTSGVGVGWIRQSPGKALEWLA LIYWDDDKRYSPSLKSRLTITKDTSKNQVVLTMTNMDPVDTATYYCAHM RWGYYFDYWGQGTLVTVSSGS	517
BPx-19	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARRE MGAKGSGGIDYWGQGTLVTVSSGS	518
BPx-20	EVQLVQSGGGLVKPGRSLRLSCTASGFTFGDYAMSWFRQAPGKGLEWVS YISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRVEDTAVYYCAREG WGSLLDYWGQGILVTVSSGS	519
BPx-21	QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWV AVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK DGDLGRYFDWLPLYYYYGMDVWGQGTTVTVSSGS	520
BPx-22	EVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWISS ITGSSSTIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGGA RADYWGQGTLVTVSSGS	521
BPx-23	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWV AVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAT PGPYYYYGMDVWGQGTTVTASSGS	522
BP5b-6	EVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEW MGWINPNSGGTNYAQKFQGRVTVTRNTSISTAYMELSSLRSEDTAVYYCA RGIGDYWGQGTLVTVSSGS	523
BPx-24	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWV AGISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYHCAK DAGRWLEIPYYFDFWGQGTLVTVSSGS	524
BPx-25	QVQLQESGPGLVKPSETLSLTCTVSGGSTSSSSYYWGWIRQPPGKGLEWIG SIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARVVW FGEPLFDPWGQGTLVTVSSGS	525
BPx-26	QVQLVQSGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWV SGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAK DLSGYDQAIDYWGQGTLVTVSSGS	526
BPx-27	QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCVRSGS GWAIDYWGQGTLVTVSSGS	527
BPx-28	QVQLVQSGAEVKKPGASMKASCKASGYTFTSYYIQWVRQAPGQGLEWV GVIHPGDGGTTYAQKFQGRVTMTTDTSTSTVYMELSSLRSEDTAVYYCAR GDLDNWGQGTLVTVSSGS	528
BPx-29	QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARRYS SGWGFDYWGQGTLVTVSSGS	529

BPx-30	QVTLKESGPTLVKPTQTLTLTCTFSGFSLSTSGVGVGWFRQPPGKALEWLA LIYWDDDKRYSPSLKSRLTITKDTSKNQVVLTMTNMDPVDTATYYCAHG EMDLFGYSSGWFPDFDYWGQGTLVTVSSGS	530
BPx-31	EVQLLETRAEVKKSGESLKISCQGSGYSFTAHWIAWVRQMPGKGLEWMG SIYPADSTTVYSPSFQGQVTISADKSFTTAYLQWTSLKASDTAMYYCVRQT SGWSDWGQGTLVTVSAGS	531
BPx-32	QVQLVQSGGGVVQPGGSLSLSCAVSGFTFSSYGMHWVRQAPGKGLEWV AVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR GDGYNHPLYYWGQGTLVTVSSGS	532
BPx-33	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWV AVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR GTLWFGELSVDYWGQGTLVTVSSGS	533
BPx-34	QVTLKESGPTLVKPTQTLTLTCTFSGFSLSTSGMGVSWIRQPPGKALEWLA LIDWDDDKYYSTSLKTRLTISKDTSKNQVVLTMTNMDPVDTATYYCARM YSYGATEFDYWGQGTLVTVSSGS	534
BPx-35	QVQLVQSGGGLVQPGRSLRLSCAASGFTFGDYAMHWVRQAPGKGLEWV SGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAK DISSGWYSVGYFDLWGRGTLVTVSSGS	535
BPx-36	EVQLVESRAEVKKPGASVKVSCKASGYTFSDYYIHWVRQAPGQGLEWMG RISPNSGGTNYAQKFQGRVTMTRDTSMNTAYMELSRLNSDDTAVYYCAR GFFDYWGQGTLVTVSSGS	536
BPx-37	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWV AVISYDGTNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR GQTSYFYDSSGPEIPNFDYWGQGTLVTVSSGS	537
BPx-38	QMQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARGG GYYDSSGYPYYYYGMDVWGQGTTVTVSSGS	538
BPx-39	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMG WISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR STGYSSSSDWGQGTLVTVSSGS	539
BPx-40	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMG WISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR DVGASGLLWFGELSFDYWGQGTLVTVSSGS	540
BPx-41	QIQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDRP HAGLYYYYYGMDVWGQGTTVTVSSGS	541
BPx-42	EVQLVQSGGGLVKPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVA VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKD LLYYYDSSGPVDYWGQGTLVTVSSGS	542
BPx-43	QVQLVQSGGVVVQPGGSLRLSCAASGFTFDDYTMHWVRQAPGKGLEWV SSISSSSSYIYHADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVDSS GYFDAFDIWGQGTMVTVSSGS	543
BP16b-1	QVQLVQSGGGVVRPGGSLRLSCAVSGFTFDDYGMSWVRQAPGKGLEWV SGINWNGGSTGYADSVKGRFTISRDNSKNTLYLQMNSPRAEDTAVYYCAR EDYGDSEYYFDYWGQGTLVTVSSGS	544
BPx-44	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARKG GYYGSGSYFDYWGQGTLVTVSSGS	545
BPx-45	QVQLVESGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCAVEED YGGSFDYWGQGTLVTVSSGS	546
BPx-46	EVQLVESGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGI IYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARSRS GSYYGTDAFDIWGQGTMVTVSSGS	547

BPx-47	EVQLVESGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMG WISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR VDFYDYVWGSYLLDYWGQGTLVTVSSGS	548
BPx-48	QMQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDLV YSSGGPDYWGQGTLVTVSSGS	549
BPx-49	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEW MGRISPNSGGTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYC ARRWDYDSSGYQNDYWGQGTLVTVSSGS	550
BPx-50	QVQLVQSGGGLVQPGGSLRLSCVTSGFSFSNYGMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARD QWIQLWIDYWGQGTLVTVSSGS	551
BPx-51	QIQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITRDMSTSTAYMELSSLRSEDTAVYYCAAEV PAAKLYYYYYGMDAWGQGTTVTVSSGS	552
BPx-52	QIQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCARDH LYYYDSSGYYDYWGQGTLVTVSSGS	553
BPx-53	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTADYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCATYYD SSGYYPYYFDYWGQGTLVTVSSGS	554
BPx-54	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMG WISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR DFKIAARGMDVWGQGTTVTVSSGS	555
BPx-55	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWV AVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA RGPHYFSDYGDYDSIGYYYYGMDVWGQGTAVTVSSGS	556
BPx-56	QVQLVQSGAEVKKPGASVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDK GSSGYYNFDYWGQGTLVTVSSGS	557
BPx-57	QIQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWM GIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARE VLGDYYYGMDVWGQGTTVTVSSGS	558
BPx-58	QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARYY YGSGSYFDLLDYWGQGTLVTVSSGS	559
BPx-59	QVQLVQSGGGLVQPGGSLRLSCAVSGFTFGTYAMTWVRQAPGKGLEWVS AISGGGDSTYYGDSVKGRFTVSRDNSKNTLYLQMSSLRVEDTALYYCAKA TREDVQHGSFDYWGQGTLVTVSSRS	560
BPx-60	QVQLVQSGAEVKKPGSSVKVSCRASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARGVL GGGFDYWGQGTLVTVSSGS	561
BPx-61	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYGISWVRQAPGQGLEWM GWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMGLRSLRSDDTAVYYCA RDGGVLGDYWGQGTLVTVSSGS	562
BPx-62	QVQLQESGGGVVQPGRSLRLSCAASGFTFSNYDMHWVRQAPGKGLEWV AVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR RTPFDYWGQGTLVTVSSGS	563
BPx-63	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMG WISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSEDTAVYYCAR DYGGINDAFDIWGQGTMVTVSSGS	564
BPx-64	QVQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWIG SIYHSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAAADD AFDIWGQGTMVTVSSGS	565

BP6b-5	QIQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCARDQ WLGGLSNYYYYGMDVWGQGTTVTVSSGS	566
BPx-65	QVQLVESGGGLVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVA VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKD LLAGGSYYYYYYGMDVWGQGTTVTVSSGS	567
BPx-66	QIQLVQSGGGLVKPGGSLRLSCAASGFPFSNAWMSWVRQAPGKGLEWVA NIEQDGSEKYYVDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKE EYGDHYYFDYWGQGTLVTVSSGS	568
BPx-67	EVQLLETRGGLVQPGRSLRLSCATSGFTFGDYAMHWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKD LATYYDFWSGLFDYWGQGTLVTVSSGS	569
BPx-68	EVQLVQSGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWV AVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCSG GSYYGAFDYWGQGTLVTVSSGS	570
BPx-69	QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARKSS SGWSIDYWGQGTLVTVSSGS	571
BPx-70	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAGG SYESSAYHYWGQGTLVTVSSGS	572
BPx-71	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMG WINTYNGNTNYAQKFQGRVTMTTDTSTSTTYMELRSLRSDDTAVYYCAR EGWVGAKGGFDYWGQGTLVTVSSGS	573
BPx-72	EVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVS SISSTSSYIYYAESVKGRFTISRDNAENSLYLQMNSLRGEDTAVYYCARDR GGYAYGDFDYWGQGTLVTVSSGS	574
BPx-73	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYTISWVRQAPGQGLEWMG RIIPILGIANYAQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCARTNS GTLDYWGQGTLVTVSSGS	575
BPx-74	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYDINWVRQATGQGLEWM GWMNPNSGNTGYAQKFQGRVTMTRNTSISTAYMELSSLRSEDTAVYYCA RGDFWSGYYYYYYGMDVWGQGTTVTVSSGS	576
BP8b-1	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSVTWDWIRQSPSRGLEWLG RTYYRSKWYNDYAVSVKSRITINPDTSKNQFSLHLSSVTPEDTAVYYCAR QNGGYDYWGQGTLVTVSSGS	577
BPx-75	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEW MGWINPNSGGTNYAQKFQGRVTITRDTSASTAYMELSSLRSEDTAVYYCA RDGGVEMATIPGGYGMDVWGQGTTVTVPSGS	578
BPx-76	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCARGRI GSGYDSVWLRYFDYWGQGTLVTVSSGS	579
BPx-77	EVQLVQSGGGLVQPGRSLRLSCAASGFTFGDYAMHWVRQAPGKGLEWV SGISWNSGSIGYADSVKGRVTISRDNAKNSLYLQMNSLRDEDTAVYYCAR EDEGSGSYYWGPVDYWGQGTLVTVSSGS	580
BP6b-6	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVA NIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR GYSNYAYWGQGTLVTVSSGS	581
BPx-78	QVQVVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEW MGWINPNSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYC ARKSGTMVRGPMWGSFDYWGQGTLVTVSSGS	582
BPx-79	QIQLVQSGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVSY ISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKDPG WLQLDYYFDYWGQGTLVTVSSGS	583

BPx-80	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTADYAQKFQGRATITADESTSTAYMELSSLRSEDTAVYYCARDRY CSGGSCYIYYGMDVWGQGTTVTVSSGS	584
BPx-81	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWV AVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR RTVGLGMDVWGQGTTVTVSSGS	585
BPx-82	EVQLLESRGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVA VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARG YGSGSSWYFDYWGQGTLVTVSSGS	586
BPx-83	EVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVA VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARA LDLDYWGQGTLVTVSSGS	587
BPx-84	QMQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG IINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGV VWRWLQSGGSGYFDYWGQGTLVTVSSGS	588
BPx-119	QVQLVQSGGGLVKPGTSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVA VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMSSLRAEDTAVYYCVKA RSGWYSSDAFDIWGQGTMVTVSSGS	589
BPx-120	EVQLVQSGGGLEQPGGSLRLSCATSGFTFTSHALSWIRQTPGKGLEWISSIS ANSDTIFYADSVKGRFTISRDNSTRMVYLQMNSLRAEDTAVYYCARDRYN WNYGYFDYWGQGTLVTVSSGS	590
BPx-121	QIQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMG WISAYNGNTNYAQNLQGRVTMTTNTSTNTAYMELSSLRSEDTAVYYCAK VGFYDYVWGSYPYDAFDIWGQGTMVTISSGS	591
BP6b-11	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMG WISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSEDTAVYYCAR GYYGSGAMDVWGQGTTVTVSSGS	592
BP18b-4	EVQLVQSGAEVKKPGESLKISCKGSGYSFTTYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARYS YGYTFLDYWGQGTLVTVSSGS	593
BP6b-2	QVQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWIG SIYYSGSTYYNPSLKSRVTISVDTSKNQFSLLLTSMTAADTAVYYCARTGT TRGDYFDNWGQGAKVTVSSGS	594
BP6b-10	EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYDINWVRQAPGQGLEWM GIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARA FDSSGYSYGMDVWGQGTTVTVSSGS	595
BP16b-2	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYYMHWVRQAPGQGLEWM GIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARD IDRATNWFDPWGQGTLVTVSSGS	596
BP18b-5	QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWV ANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCA RDKWWPEGYYYYYYGMDVWGQGTTVTVPSGS	597
BP7b-1	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQDRVTITADESTSTAYMELSSLRSEDTAVYYCARDG YCSSTSCYVWGEFDPWGQGTLVTVSSGS	598
BP5b-7	EVQLVQSGGGLVKPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVS YISSGSSTLYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARD FGWYGSFDYWGQGTTVTVSSGS	599
BPx-85	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYALHWVRQAPGKGLEWVA VLSYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR AAHSGYDLNYYYGMDAWGQGTTVTVSSGS	600
BP18b-6	QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCAKLR VGYNFFDYWGQGTLVTVSSGS	601

BP20b-1	EVQLVESRGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVA VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVGV DYYDSSGYPADYWGQGTLVTVSSGS	602
BPx-86	QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISVDKSINTAYLQWNSLKASDTAMYYCARG WSSADYWGQGTLVTVSSGS	603
BP19b-3	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVS VIYSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARD WAFGGSYKLGDYWGQGTLVTVSSGS	604
BPx-87	QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVS SISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKDR FFTYYYDTSGRGGLDSWGQGTLVTVSSGS	605
BPx-88	EVQLVQSGGGLVQPGGSLRLSCAASGFTFSGSSMNWVRQAPGKGLEWVS YISSSGNTIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGS EEMRGWGQGTLVTVSSGS	606
BP18b-7	QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARHD GNSRPGDYWGQGTLVTVSSGS	607
BP17b-1	QVQLQQSGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKT VAGTRLYYYYYGMDVWGQGTTVTVSSGS	608
BP16b-3	EVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWM GGFDPEDGETIYAQKFQGRVTMTEDTSTDTAYMELSSLRSEDTAVYYCAT DFYCSGGSCYSRGDAFDIWGQGTMVTVSSGS	609
BPx-89	QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVS SISSSNSYIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTALYYCARDW SIYPASVDFFDYWGQGTLVTVSSGS	610
BPx-90	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVS SISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKDG RLGELSHWGQGTLVTVSSGS	611
BP5b-8	EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVA VISYDGSNQYYADSVKGRFTISRDNSKNTLYVQMNSLRAEDTAVYYCAR GNYYGSGSYPLLDYWGQGTLVTVSSGS	612
BP16b-4	QVQLVQSGGGLVQPGGSLRLSCAASGFTFSNYWMYWVRQAPGKGLVWV SNINSDGSSTSYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCAR EGYNAHYFDYWGQGTLVTVSSGS	613
BP9b-1	QVQLQQSGPRQVEPSQTLSLTCAISGDSVSSKSAAWNWIRQSPSRGLEWLG RTYYRSKWYYDYAVSVKSRIIVNPDTSRNQFSLHLNSVTPEDTAFYYCAR GEDSGYGSFDYWGQGTLVTVSSGS	614
BPx-91	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMG WISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR DMKWLPRGVDYWGQGTLVTVSSGS	615
BPx-92	QIQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGI IYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARLGF REIDYWGQGTLVTVSPGS	616
BP12b-1	EVQLLESRAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGPEWMGI IYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARLVY GGGYDEPGYYFDYWGQGTLVTVSSGS	617
BPx-93	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSHGMHWVRQAPGKGPEWV AVISYDGSNKYYPDSVRGRFTISRDNSKNTLYLQMNSLTTDDTAVYYCAK GGGYGDYAPGYWGQGTLVTVSSGS	618
BPx-94	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GFDPEDGETIYAQKFQGRVTMTEDTSTDTAYMELSSLRSEDTAVYYCATG FWELEAGGFDYWGQGTLVTVSSGS	619

BPx-95	QVQLQQSGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWIG SIYYSGSTYYNPSLKSRVTISVDTSRKQVSLELSSVTAADTAVYYCARLWL GERPPDYWGQGMLVTVSSGS	620
BPx-96	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWM GIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARD RGSGWYGGAFDIWGQGTMVTVSSGS	621
BP6b-9	QIQLVQSGGGVVQPGRSLRLSCAASGFTFSSYAIHWVRQAPGKGLEWVAV ISYDGSIKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDT HEWELFVGTFDIWGQGTMVTVSSGS	622
BPx-97	QVQLVQSGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVS SISSNSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDP DYYYGSGTREDYWGQGTLVTVSSGS	623
BPx-98	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVA VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARV EWADGAFDIWGQGTMVTVSSGS	624
BPx-99	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVA NIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR GLIGDWGQGTLVTVSSGS	625
BP6b-7	EVQLVQSGGGVVQSGRSLRLSCVASGFSFSNYGMHWVRQAPGKGLEWLA FIWYDGSNKWYADSVKGRFTISRDNSKNALYLQMNSLRAEDTAVYYCAR DRYSSSWGGGFDYWGQGTVLTVSSGS	626
BPx-100	QIQLVQSGGGVVQPGRSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVG RIKSKTDGGTTDYAAPVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCT TDRVTMVRGVTPPFDYWGQGTLVTVSSGS	627
BP6b-8	QLQLQQSGGGLVQPGGSLRLSCAASGFTFSSYWMHWVRQAPGKGLVWV SRINSDGSSTSYADSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCAR DGWGSYRYVPGYYYYYGMDVWGQGTTVTVSSGS	628
BPx-101	QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMG IIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARGS GWTNILDYWGQGTLVTVSSGS	629
BPx-102	QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYWIGWVRQMPGKGLEWM GIIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCATQP HDRGVWGQGTTVTVSSGS	630
BPx-103	QLQLQQFGPGLVKPSETLSLTCTVSGDSSSSYYWSWIRQPPGKGLEWIGSI YYSGSTYYNPSLKSRVTISVDTSKNQLSLKLNSVTAADTAVYYCARGAYG DKDLGVFDYWGQGTLVTVSSGS	631
BPx-104	QVQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWIG SIYYSGSTDYSPSLKSRVTISIDTSKNQFSLKVSSVTAADTAVYYCARERGN GDYDNWGLGTLVTVSAGS	632
BPx-105	EVQLVQSGGGVVRPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVS GINWNGGSTGYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR QYVPEYNSGWPYYYYGMDVWGQGTTVTVSSGS	633
BPx-106	EVQLVESGPGLVKPSGTLSLTCAVFGGSISSSDNWWGWVRQPPGEGLEWI GDISHSGNTIYNPSLKSRVTISVDKSKNQFSLKLGSVTAADTAVYYCARYD SRGYYYPTDAFDIWGQGAMVTVSSGS	634
BP5b-9	EVQLVESGGGLEKPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVS AVNKGGDAAYSADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR GVWAVDAFDIWGQGTMVTVSSGS	635
BPx-107	EVQLVQSGGGVVQPGRSLRLSCAASGFSFRNYAMHWVRQAPGKGLEWV AVISYDGSNKYYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCA RDNGYDSSGYYFLDHYWGQGTLVTVSSGS	636
BPx-108	QVTLKESGPTLVKPTQTLTLTCTFSGFSLSTYGVGVGWIRQPPGKAPEWLA RIDWDDDEYYSTSLKTRLTISKDTSKNQVVLTMTDMDPVDTATYYCTRFV GAKADYWGQGILVTVSSGS	637

BPx-109	EVQLVESRGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVA VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQLNSLRAEDTAVYYCARA RSPIAVAPNWFDPWGQGTLVTVSSGS	638
BP22b-1	QIQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVA VIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK GLGYHPLFDYWGQGTLVTVSSGS	639
BPx-110	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVA VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKD LYSGSGGGDYWGQGTLVTVSSGS	640
BP6b-12	EVQLVQSGGGLVQPGGSLRLSCAGSGFTFSDYDMSWVRQAPGKGLEWVS GISGSGGSTYYVDSVQGRFTISRDNSKNTLYLQMNGLRAEDTAVYYCAKD SSSGWYGLWDYWGQGTLVSVSSGS	641
BPx-111	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYIY YSGSTNYNPSLKSRVTMSVDTSKNQLSLNLTSVTAADTAVYYCAREFPMG RPFDYWGQGTLVTVSSGS	642
BPx-112	EVQLVESGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMG WISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR DGMFAPGYFDYWGQGTLVTVSSGS	643
BPx-113	QVTLKESGPVLVKPTETLTLTCAVSGFSLSNPRMGVSWIRQPPGKALEWL ALIYWDDDKRYSPSLKSRLTITKDTSKNQVVLTMTNMDPVDTATYYCAL WDDYSNYEIARGAFDIWGQGTMVTVSSGS	644
BP10b-1	QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYDMHWVRQATGKGLEWVS AIGTAGDTYYPGSVKGRFTISRENAKNSLYLQMNSLRAGDTAVYYCARGK PLLSGYLINDAFDIWGQGTMVTVSSGS	645
BPx-114	EVQLLETGGGVVQPGRSLRLSCAASGFSFNNYGMHWVRQAPGKGLEWVS VIYSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDG GSGYHDYWGQGTLVTVSSGS	646

[00309] Recombinant GDF-modulating antibodies of the disclosure may comprise or be developed using any of the CDR-H sequences (CDR-H1, CDR-H2 and/or CDR-H3) listed in Table 15. Some recombinant GDF-modulating antibodies of the disclosure may comprise or be developed using CDR-H sequences that comprise at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 99.5% or at least about 99.9% sequence identity to any of the CDR-H sequences listed in Table 15. Recombinant GDF-modulating antibodies may, in some cases, comprise CDR-H domains presented, but with different combinations of CDRs from other clones listed. In some cases, such antibodies may interact with one or more of the recombinant proteins listed in Table 4, 9 or 10.

Table 15. CDR-H domains

CDR Region	Clone ID	CDR amino acid sequence	SEQ ID NO
CDR-H1	BP6a-16	GDSVSSNSAA	647
CDR-H1	BP6a-19	GGTFSSYA	648

CDR-H1	BP3a-3	GFTFDDYA	649
CDR-H1	BP18b-1	GYSFTSYW	650
CDR-H1	BP19b-1	GGSISSYY	651
CDR-H1	BP6b-4	GFTFSSYG	652
CDR-H1	BP6a-8	GYTFTSYY	653
CDR-H1	BP13a-1	GYTLTELS	654
CDR-H1	BP5b-3	GFTFSDYY	655
CDR-H1	BP6a-23	GFTFSSYS	656
CDR-H1	BP6a-11	GFTFDDYT	657
CDR-H1	BP5b-4	GFTFSSYA	658
CDR-H1	BP6a-14	GFSFSSYG	659
CDR-H1	BP6a-13	GFRFSNYG	660
CDR-H1	BP4a-1	GYTFSSYG	661
CDR-H1	BP6a-4	GDSITSYY	662
CDR-H1	BPx-1	GGAFSIYS	663
CDR-H1	BP21-a	GGSISSSSYY	664
CDR-H1	BPx-3	GFSFSNYG	665
CDR-H1	BP6a-10	GFTFSSYW	666
CDR-H1	BP15a-1	GYTFTSYG	667
CDR-H1	BP6a-26	GFSFSTYA	668
CDR-H1	BP5a-4	GGTLSSYA	669
CDR-H1	BP5b	GFTFDDYG	670
CDR-H1	BP5a-3	GYSITNGYY	671
CDR-H1	BP14a-1	GYNFNSYW	672
CDR-H1	BP6a-25	GDSVSSNTEA	673
CDR-H1	BP5a-2	GFTVSSYS	674
CDR-H1	BP6a-15	GVSIASSNW	675
CDR-H1	BP3a-2	GFTFSDYD	676
CDR-H1	BP6a-18	GFTFSSFA	677
CDR-H1	BP18a-2	GYSFTNYW	678
CDR-H1	BPx-9	GYTFNDYH	679
CDR-H1	BPx-14	GFTFGHYG	680
CDR-H1	BPx-17	GFTFGDYA	681
CDR-H1	BPx-18	GFSLSTSGVG	682
CDR-H1	BP5b-6	GYTFTGYY	683
CDR-H1	BPx-24	GFTFSDYG	684
CDR-H1	BPx-25	GGSTSSSSYY	685
CDR-H1	BPx-31	GYSFTAHW	686
CDR-H1	BPx-34	GFSLSTSGMG	687
CDR-H1	BPx-36	GYTFSDYY	688
CDR-H1	BPx-59	GFTFGTYA	689
CDR-H1	BPx-61	GYAFTSYG	690
CDR-H1	BPx-62	GFTFSNYD	691
CDR-H1	BPx-66	GFPFSNAW	692
CDR-H1	BPx-73	GGTFSSYT	693
CDR-H1	BPx-74	GYTFTSYD	694
CDR-H1	BP8b-1	GDSVSSNSVT	695
CDR-H2	BP6a-16	TYYRSKWSN	696

CDR-H2	BP6a-19	IIPIFGTA	697
CDR-H2	BP3a-3	ISWNSGST	698
CDR-H2	BP18b-1	IYPGDSDT	699
CDR-H2	BP19b-1	IYYSGSTN	700
CDR-H2	BP6b-4	IWYDGSNK	701
CDR-H2	BP6a-8	INPSGGST	702
CDR-H2	BP13a-1	FDPEDDEA	703
CDR-H2	BP5b-3	ISSSGSTI	704
CDR-H2	BP6a-23	ISSSSSYI	705
CDR-H2	BP6a-11	ISWDGGST	706
CDR-H2	BP5b-4	ISGGGGAT	707
CDR-H2	BP11a-1	ISWNSGSI	708
CDR-H2	BP6a-14	TSYDGSNK	709
CDR-H2	BP6a-27	ISYDGSYE	710
CDR-H2	BP6a-13	ISGSGGLT	711
CDR-H2	BP4a-1	SSAYNGNT	712
CDR-H2	BP19b-2	ISYDGSNK	713
CDR-H2	BP6a-4	IHYSGSTY	714
CDR-H2	BP19a-1	ISNSGGST	715
CDR-H2	BP6b-3	INPNSGGT	716
CDR-H2	BPx-1	IIPIFETA	717
CDR-H2	BP21b-1	IYYSGSTY	718
CDR-H2	BPx-2	ISSSSSTI	719
CDR-H2	BPx-3	ISGSGGSA	720
CDR-H2	BP6a-10	IKQDGSEK	721
CDR-H2	BP15a-1	ISAYNGNT	722
CDR-H2	BP6a-26	ISYDGTIK	723
CDR-H2	BP5a-3	IFQSGSTY	724
CDR-H2	BP14a-1	IYPGDSDIR	725
CDR-H2	BP3a-1	ISGSGGST	726
CDR-H2	BP6a-25	TYYRSKWYH	727
CDR-H2	BP6a-15	IYHSGSTF	728
CDR-H2	BP6a-21	ISDSGGTT	729
CDR-H2	BP6a-18	ITSRGDTT	730
CDR-H2	BPx-11	INYSGNTY	731
CDR-H2	BPx-14	ISYDGTNK	732
CDR-H2	BPx-15	TYYRSKWYN	733
CDR-H2	BPx-17	INWNSGGV	734
CDR-H2	BPx-18	IYWDDDKR	735
CDR-H2	BPx-22	ITGSSSTI	736
CDR-H2	BPx-28	IHPGDGGT	737
CDR-H2	BPx-31	IYPADSTT	738
CDR-H2	BPx-34	IDWDDDKY	739
CDR-H2	BPx-36	ISPNSGGT	740
CDR-H2	BP16b-1	INWNGGST	741
CDR-H2	BPx-59	ISGGGDST	742
CDR-H2	BPx-66	IEQDGSEK	743
CDR-H2	BPx-71	INTYNGNT	744

CDR-H2	BPx-72	ISSTSSYI	745
CDR-H2	BPx-73	IIPILGIA	746
CDR-H2	BPx-74	MNPNSGNT	747
CDR-H2	BPx-64	IYHSGSTY	748
CDR-H3	BP6a-16	ARGFSGMGV	749
CDR-H3	BP6a-19	ARDQAGDYGGNSGYFDY	750
CDR-H3	BP3a-3	AKGQVPNYYDSRDPFDP	751
CDR-H3	BP6a-1	ARITDDFDY	752
CDR-H3	BP18b-1	ARGVAGYSSGWSD	753
CDR-H3	BP19b-1	ARLRRGYFDY	754
CDR-H3	BP6b-4	ATRGY	755
CDR-H3	BP6a-8	AREGGDYNNWFDP	756
CDR-H3	BP13a-1	ATDRVTGTTMAAFDI	757
CDR-H3	BP5b-3	ARDNWYYFDY	758
CDR-H3	BP6a-23	ARDLGGYFGNY	759
CDR-H3	BP5a-1	ANHGLMDDSSGYYLSNAFDI	760
CDR-H3	BP6a-11	AAGSYHTW	761
CDR-H3	BP5b-4	ASPAGHICSGGSCQYYYYGMDV	762
CDR-H3	BP18a-1	ARQPYYYGSGSGMDV	763
CDR-H3	BP11a-1	AKVDGLEYSSGHNFDY	764
CDR-H3	BP6a-14	AKDEYTYGSGIMDY	765
CDR-H3	BP6a-27	ARDSGARGYNYGLFDY	766
CDR-H3	BP6a-13	AREDLWRMGELLGGEGFDY	767
CDR-H3	BP4a-1	ARGIYGDYEY	768
CDR-H3	BP1a-1	AKDTSNGGYSSSSFDY	769
CDR-H3	BP6a-6	ARDRHLYRRGYSSVDGMDV	770
CDR-H3	BP19b-2	AKPRGRYYFDY	771
CDR-H3	BP6a-4	ARGPSRGLFDP	772
CDR-H3	BP19a-1	ASLSRGY	773
CDR-H3	BP6a-7	ARESLIRFLEDPQQGGMDV	774
CDR-H3	BP5b-5	ATPYSSSSGTDY	775
CDR-H3	BP6b-3	ARPRTLRGDAFDI	776
CDR-H3	BP18b-2	ARHPIGSGYDY	777
CDR-H3	BPx-1	ARAGENSDSNYAFDI	778
CDR-H3	BP21b-1	ARGRYSYGYFDY	779
CDR-H3	BP6a-2	ARGIRVVGDEDYYYYYGMDV	780
CDR-H3	BPx-2	ARDSSGWLGMGDFDY	781
CDR-H3	BP6b-1	AREEYYGGNTD	782
CDR-H3	BPx-3	ARDISHYDILTGQLDY	783
CDR-H3	BP6a-5	ARDLLVRFLEWSHYYGMDV	784
CDR-H3	BP6a-10	AKETDCSGGICYGVDY	785
CDR-H3	BP15a-1	ARDAPYDILTGYLSY	786
CDR-H3	BP6a-26	ARAGGAGSDGYNYWGY	787
CDR-H3	BP6a-12	ARDPGGKLGGAFDI	788
CDR-H3	BP5a-4	ARDRPGNNRYDILTGGGWFDP	789
CDR-H3	BP5b-1	AKEISDTAMGFDY	790
CDR-H3	BPx-4	ARAYIPRLYYYGSGLDY	791
CDR-H3	BP5a-3	ARRVDYYDSSGYGEGYFDY	792

CDR-H3	BP14a-1	ARHVSGSLDY	793
CDR-H3	BP3a-1	AKTAYYDSSGYYPDAFDI	794
CDR-H3	BP18b-3	ARGQGGVLGAFDI	795
CDR-H3	BP6a-9	ARQGRGEAFDI	796
CDR-H3	BP6a-25	ARTVFDSQVYWFDP	797
CDR-H3	BP5a-2	AKVGTAAAGDAFDI	798
CDR-H3	BP6a-15	ASSSGWPYPTNWFDA	799
CDR-H3	BP6a-21	AKDAHNWNYGVFDY	800
CDR-H3	BP5a-5	ASALGATGAFDI	801
CDR-H3	BP6a-17	AKDISGYEPLYYFDY	802
CDR-H3	BP6a-20	ARDPGKQWRVRGYFDY	803
CDR-H3	BP3a-2	ARESDMAAAGSFDY	804
CDR-H3	BP6a-24	AREGNSGYDV	805
CDR-H3	BP6a-22	ARDSLWFGELSALDY	806
CDR-H3	BP19a-2	ARDVSSWAAF	807
CDR-H3	BPx-6	ARGGRGGVITWFDP	808
CDR-H3	BP6a-18	ARDRPQVPYDSSGNFDY	809
CDR-H3	BP16a-1	AREEAGYSSGWVEDAFDI	810
CDR-H3	BP19a-3	ARMVGGYRFDY	811
CDR-H3	BP5b-2	AKHGDYGGTFDY	812
CDR-H3	BP2a-1	ARVGFYDYVWGSYPYDAFDI	813
CDR-H3	BP18a-2	ARRSSSSGSFDY	814
CDR-H3	BP6a-3	VRDRHSLGDFDY	815
CDR-H3	BPx-7	ARRFTMDY	816
CDR-H3	BPx-8	ARYSSSWELFDY	817
CDR-H3	BPx-9	ARRNGSGSAPGY	818
CDR-H3	BPx-10	ARVGQYYGMDV	819
CDR-H3	BPx-11	ARRVLGYGYFDY	820
CDR-H3	BPx-12	TGGGNVDY	821
CDR-H3	BPx-13	AKDKAGNYYYGMDV	822
CDR-H3	BPx-14	AKGSRLDP	823
CDR-H3	BPx-15	VGQGYDSSGYYGMDV	824
CDR-H3	BPx-16	ARQYYDTSYFDY	825
CDR-H3	BPx-17	AKDSGYSYGINFDY	826
CDR-H3	BP1b-1	ARGDWFDP	827
CDR-H3	BPx-18	AHMRWGYYFDY	828
CDR-H3	BPx-19	ARREMGAKGSGGIDY	829
CDR-H3	BPx-20	AREGWGSLLDY	830
CDR-H3	BPx-21	AKDGDLGRYFDWLPLYYYYGMDV	831
CDR-H3	BPx-22	ARGGARADY	832
CDR-H3	BPx-23	ATPGPYYYYGMDV	833
CDR-H3	BP5b-6	ARGIGDY	834
CDR-H3	BPx-24	AKDAGRWLEIPYYFDF	835
CDR-H3	BPx-25	ARVVWFGEPLFDP	836
CDR-H3	BPx-26	AKDLSGYDQAIDY	837
CDR-H3	BPx-27	VRSGSGWAIDY	838
CDR-H3	BPx-28	ARGDLDN	839
CDR-H3	BPx-29	ARRYSSGWGFDY	840

CDR-H3	BPx-30	AHGEMDLFGYSSGWFPDFDY	841
CDR-H3	BPx-31	VRQTSGWSD	842
CDR-H3	BPx-32	ARGDGYNHPLYY	843
CDR-H3	BPx-33	ARGTLWFGELSVDY	844
CDR-H3	BPx-34	ARMYSYGATEFDY	845
CDR-H3	BPx-35	AKDISSGWYSVGYFDL	846
CDR-H3	BPx-36	ARGFFDY	847
CDR-H3	BPx-37	ARGQTSYFYDSSGPEIPNFDY	848
CDR-H3	BPx-38	ARGGGYYDSSGYPYYYYGMDV	849
CDR-H3	BPx-39	ARSTGYSSSSD	850
CDR-H3	BPx-40	ARDVGASGLLWFGELSFDY	851
CDR-H3	BPx-41	ARDRPHAGLYYYYYGMDV	852
CDR-H3	BPx-42	AKDLLYYYDSSGPVDY	853
CDR-H3	BPx-43	VDSSGYFDAFDI	854
CDR-H3	BP16b-1	AREDYGDSEYYFDY	855
CDR-H3	BPx-44	ARKGGYYGSGSYFDY	856
CDR-H3	BPx-45	AVEEDYGGSFDY	857
CDR-H3	BPx-46	ARSRSGSYYGTDAFDI	858
CDR-H3	BPx-47	ARVDFYDYVWGSYLLDY	859
CDR-H3	BPx-48	ARDLVYSSGGPDY	860
CDR-H3	BPx-49	ARRWDYDSSGYQNDY	861
CDR-H3	BPx-50	ARDQWIQLWIDY	862
CDR-H3	BPx-51	AAEVPAAKLYYYYYGMDA	863
CDR-H3	BPx-52	ARDHLYYYDSSGYYDY	864
CDR-H3	BPx-53	ATYYDSSGYYPYYFDY	865
CDR-H3	BPx-54	ARDFKIAARGMDV	866
CDR-H3	BPx-55	ARGPHYFSDYGDYDSIGYYYYGMDV	867
CDR-H3	BPx-56	ARDKGSSGYYNFDY	868
CDR-H3	BPx-57	AREVLGDYYYGMDV	869
CDR-H3	BPx-58	ARYYYGSGSYFDLLDY	870
CDR-H3	BPx-59	AKATREDVQHGSFDY	871
CDR-H3	BPx-60	ARGVLGGGFDY	872
CDR-H3	BPx-61	ARDGGVLGDY	873
CDR-H3	BPx-62	ARRTPFDY	874
CDR-H3	BPx-63	ARDYGGINDAFDI	875
CDR-H3	BP6b-5	ARDQWLGGLSNYYYYGMDV	876
CDR-H3	BPx-65	AKDLLAGGSYYYYYYGMDV	877
CDR-H3	BPx-66	AKEEYGDHYYFDY	878
CDR-H3	BPx-67	AKDLATYYDFWSGLFDY	879
CDR-H3	BPx-68	SGGSYYGAFDY	880
CDR-H3	BPx-69	ARKSSSGWSIDY	881
CDR-H3	BPx-70	AGGSYESSAYHY	882
CDR-H3	BPx-71	AREGWVGAKGGFDY	883
CDR-H3	BPx-72	ARDRGGYAYGDFDY	884
CDR-H3	BPx-73	ARTNSGTLDY	885
CDR-H3	BPx-74	ARGDFWSGYYYYYYGMDV	886
CDR-H3	BP8b-1	ARQNGGYDY	887
CDR-H3	BPx-75	ARDGGVEMATIPGGYGMDV	888

CDR-H3	BPx-76	ARGRIGSGYDSVWLRYFDY	889
CDR-H3	BPx-77	AREDEGSGSYYWGPVDY	890
CDR-H3	BP6b-6	ARGYSNYAY	891
CDR-H3	BPx-78	ARKSGTMVRGPMWGSFDY	892
CDR-H3	BPx-79	AKDPGWLQLDYYFDY	893
CDR-H3	BPx-80	ARDRYCSGGSCYIYYGMDV	894
CDR-H3	BPx-81	ARRTVGLGMDV	895
CDR-H3	BPx-82	ARGYGSGSSWYFDY	896
CDR-H3	BPx-83	ARALDLDY	897
CDR-H3	BPx-84	ARGVVWRWLQSGGSGYFDY	898
CDR-H3	BPx-64	AAADDAFDI	899
CDR-H1	BP20b-1	GFTFSSYA	900
CDR-H1	BPx-89	GFTFSSYS	901
CDR-H1	BPx-105	GFTFDDYG	902
CDR-H1	BPx-99	GFTFSSYW	903
CDR-H1	BPx-93	GFTFSSHG	904
CDR-H1	BPx-92	GYSFTSYW	905
CDR-H1	BP6b-7	GFSFSNYG	906
CDR-H1	BPx-100	GFTFSNAW	907
CDR-H1	BPx-95	GGSISSSSYY	908
CDR-H1	BPx-111	GGSISSYY	909
CDR-H1	BP6b-11	GYTFTSYG	910
CDR-H1	BP18b-4	GYSFTTYW	911
CDR-H1	BP6b-10	GYTFTSYD	912
CDR-H1	BP16b-2	GYTFTSYY	913
CDR-H1	BP7b-1	GGTFSSYA	914
CDR-H1	BP5b-7	GFTFSSYG	915
CDR-H1	BPx-88	GFTFSGSS	916
CDR-H1	BP16b-3	GYTLTELS	917
CDR-H1	BP16b-4	GFTFSNYW	918
CDR-H1	BP9b-1	GDSVSSKSAA	919
CDR-H1	BP10b-1	GFTFSSYD	920
CDR-H1	BPx-102	GYSFTNYW	921
CDR-H1	BPx-103	GDSSSSYY	922
CDR-H1	BPx-106	GGSISSSDNW	923
CDR-H1	BP5b-9	GFTFSNYA	924
CDR-H1	BPx-107	GFSFRNYA	925
CDR-H1	BPx-108	GFSLSTYGVG	926
CDR-H1	BP6b-12	GFTFSDYD	927
CDR-H1	BPx-114	GFSFNNYG	928
CDR-H1	BPx-113	GFSLSNPRMG	929
CDR-H2	BP20b-1	ISYDGSNK	930
CDR-H2	BPx-89	ISSSNSYI	931
CDR-H2	BPx-105	INWNGGST	932
CDR-H2	BPx-99	IKQDGSEK	933
CDR-H2	BPx-92	IYPGDSDT	934
CDR-H2	BP6b-7	IWYDGSNK	935
CDR-H2	BPx-100	IKSKTDGGTT	936

CDR-H2	BPx-95	IYYSGST	937
CDR-H2	BP6b-11	ISAYNGNT	938
CDR-H2	BP6b-10	INPSGGST	939
CDR-H2	BP7b-1	IIPIFGTA	940
CDR-H2	BP5b-7	ISSGSSTL	941
CDR-H2	BPx-85	LSYDGSNK	942
CDR-H2	BP19b-3	IYSGGST	943
CDR-H2	BPx-87	ISSSSSYI	944
CDR-H2	BPx-88	ISSSGNTI	945
CDR-H2	BP16b-3	FDPEDGET	946
CDR-H2	BP5b-8	ISYDGSNQ	947
CDR-H2	BP16b-4	INSDGSST	948
CDR-H2	BP9b-1	TYYRSKWYY	949
CDR-H2	BP10b-1	IGTAGDT	950
CDR-H2	BP6b-9	ISYDGSIK	951
CDR-H2	BPx-97	ISSNSSYI	952
CDR-H2	BPx-106	ISHSGNTI	953
CDR-H2	BP5b-9	VNKGGDAA	954
CDR-H2	BPx-108	IDWDDDE	955
CDR-H2	BPx-113	IYWDDDK	956
CDR-H3	BP20b-1	VGVDYYDSSGYPADY	957
CDR-H3	BPx-89	ARDWSIYPASVDFFDY	958
CDR-H3	BPx-105	ARQYVPEYNSGWPYYYYGMDV	959
CDR-H3	BPx-99	ARGLIGD	960
CDR-H3	BPx-93	AKGGGYGDYAPGY	961
CDR-H3	BPx-92	ARLGFREIDY	962
CDR-H3	BP6b-7	ARDRYSSSWGGGFDY	963
CDR-H3	BPx-100	TTDRVTMVRGVTPPFDY	964
CDR-H3	BPx-95	ARLWLGERPPDY	965
CDR-H3	BPx-111	AREFPMGRPFDY	966
CDR-H3	BP6b-2	ARTGTTRGDYFDN	967
CDR-H3	BP6b-11	ARGYYGSGAMDV	968
CDR-H3	BP18b-4	ARYSYGYTFLDY	969
CDR-H3	BP6b-10	ARAFDSSGYSYGMDV	970
CDR-H3	BP16b-2	ARDIDRATNWFDP	971
CDR-H3	BP18b-5	ARDKWWPEGYYYYYYGMDV	972
CDR-H3	BP7b-1	ARDGYCSSTSCYVWGEFDP	973
CDR-H3	BP5b-7	ARDFGWYGSFDY	974
CDR-H3	BPx-85	ARAAHSGYDLNYYYGMDA	975
CDR-H3	BP18b-6	AKLRVGYNFFDY	976
CDR-H3	BPx-86	ARGWSSADY	977
CDR-H3	BP19b-3	ARDWAFGGSYKLGDY	978
CDR-H3	BPx-87	AKDRFFTYYYDTSGRGGLDS	979
CDR-H3	BPx-88	AKGSEEMRG	980
CDR-H3	BP18b-7	ARHDGNSRPGDY	981
CDR-H3	BP17b-1	AKTVAGTRLYYYYYGMDV	982
CDR-H3	BP16b-3	ATDFYCSGGSCYSRGDAFDI	983
CDR-H3	BPx-90	AKDGRLGELSH	984

CDR-H3	BP5b-8	ARGNYYGSGSYPLLDY	985
CDR-H3	BP16b-4	AREGYNAHYFDY	986
CDR-H3	BP9b-1	ARGEDSGYGSFDY	987
CDR-H3	BPx-91	ARDMKWLPRGVDY	988
CDR-H3	BP12b-1	ARLVYGGYDEPGYYFDY	989
CDR-H3	BP10b-1	ARGKPLLSGYLINDAFDI	990
CDR-H3	BPx-94	ATGFWELEAGGFDY	991
CDR-H3	BPx-96	ARDRGSGWYGGAFDI	992
CDR-H3	BP6b-9	ARDTHEWELFVGTFDI	993
CDR-H3	BPx-97	ARDPDYYYGSGTREDY	994
CDR-H3	BPx-98	ARVEWADGAFDI	995
CDR-H3	BP6b-8	ARDGWGSYRYVPGYYYYYGMDV	996
CDR-H3	BPx-101	ARGSGWTNILDY	997
CDR-H3	BPx-102	ATQPHDRGV	998
CDR-H3	BPx-103	ARGAYGDKDLGVFDY	999
CDR-H3	BPx-104	ARERGNGDYDN	1000
CDR-H3	BPx-106	ARYDSRGYYYPTDAFDI	1001
CDR-H3	BP5b-9	ARGVWAVDAFDI	1002
CDR-H3	BPx-107	ARDNGYDSSGYYFLDHY	1003
CDR-H3	BPx-108	TRFVGAKADY	1004
CDR-H3	BPx-109	ARARSPIAVAPNWFDP	1005
CDR-H3	BP22b-1	AKGLGYHPLFDY	1006
CDR-H3	BPx-110	AKDLYSGSGGGDY	1007
CDR-H3	BP6b-12	AKDSSSGWYGLWDY	1008
CDR-H3	BPx-112	ARDGMFAPGYFDY	1009
CDR-H3	BPx-114	ARDGGSGYHDY	1010
CDR-H3	BPx-113	ALWDDYSNYEIARGAFDI	1011

[00310] Recombinant GDF-modulating antibodies of the disclosure may comprise or be developed using any of the VL sequences listed in Table 16. Some recombinant GDF-modulating antibodies of the disclosure may comprise or be developed using VL sequences that comprise at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 99.5% or at least about 99.9% sequence identity to any of the VL sequences listed in Table 16. Recombinant GDF-modulating antibodies may, in some cases, comprise VL domains presented, but with different combinations of CDRs (e.g. CDR-L1, CDR-L2 or CDR-L3). In some cases, such antibodies may interact with one or more of the recombinant proteins listed in Table 4, 9 or 10.

Table 16. VL domains

Clone ID	VL amino acid sequence	SEQ ID

		NO
BP6a-16	SSELTQDPAVSVALGQTASITCSGDKLGDKYASWYQQKPGQSPVMVIHQDSKRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTVVFGGGTKLTVLGQPKAAPSVTLFPPSS	1012
BP6a-19	DIQMTQSPSTLSASAGDRVTITCRASQSISRWLAWYQQKPGKPPKLLIYGASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQTYTTPWTFGQGTKVEIKRTVAAPSVF	1013
BP3a-3	EIVLTQSPGTLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYGASNRATGIPARFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYTTPFTFGPGTKVDIKRTVAAPSVF	1014
BP6a-1	DVVMTQTPLSLPVTLGQPASISCRSSQSLVYSDGNTYLNWFQQRPGQSPRRLIYKVSNRDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQSTRWPWVFGQGTKVEIKRTVAAPSVF	1015
BP18b-1	DIVMTQSPLSLPVTPGEPASISCRSSQTLLHSNGFNYLDWYLQKPGQSPQLLMYLGSKRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPFTFGPGTKVDIKRTVAAPSVF	1016
BP19b-1	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTFVVFGGGTKLTVLGQPKAAPSVTLFPPSS	1017
BP6b-4	QSALTQPPSASGSPGQSVTISCSGTSSDIGGYDYVSWYQQHPGKAPKLMIYDVSERPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSFTSSSTLVFGGGTKLTVLRQPKAAPSVTLFPPSS	1018
BP6a-8	QSVLTQPPSVSGAPGQKVTISCSGSSSNIGNNYVSWYQQRPGTAPKLLIYDNNKRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDSSLSAVFGGGTKLTVLRQPKAAPSVTLFPPSS	1019
BP13a-1	SSELTQDPAVSVALGQTVKITCQGDSLRSYFASWYQQKPGQAPVLVLFGKNSRPSGIPGRFSGSGSGNTAVLTITGAQAEDEADYYCDSRHSSGNYVIFGGGTKVTVLSQPKAAPSVTLFPPSS	1020
BP5b-3	QSALTQPPSASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYEVSKRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYYCSSYAGSNSWVFGGGTKLTVLGQPKAAPSVTLFPPSS	1021
BP6a-23	QPVLTQPPSVSLSPGQTASITCSGDDLGDKFASWYQQKPGQSPILVIYQDSKRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWDGTKVVFGGGTKLTVLGQPKAAPSVTLFPPSS	1022
BP5a-1	QPVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVEWYQQLPGTAPKLLIHSNNQRPSGVPDRFSGSRSGTSASLAISGLQSEDEADYFCATWDDSLTGVVFGGGTTLTVLGQPKAAPSVTLFPPSS	1023
BP6a-11	QPVLTQPPSASGTPGQRVTISCSGSSSNIGSSTVNWYQQLPGTAPRLLIYSINQRPSGVPDRFSGSKSGTSASLAISGLQSDDEADYYCAAWDDSLNGWVFGGGTKLTVLRQPKANPTVTLFPPSS	1024
BP5b-4	DIQMTQSPSFLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTRVDMARTVAAPSVF	1025
BP18a-1	EIVMTQSPLSLPVTLGQPASISCGSSQSLVYSDGNTYVNWFQQRPGQSPRRLIYKVSNRDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGTHWPYTFGQGTKLEIKRTVAAPSVF	1026
BP11a-1	QSALTQPPSVSGSPGQSVTISCTGSSSDVGYYDHVSWYQHHPGRAPKVIIYDVTKRPSGVPDRFSGSKSGNTASLTISGLQAEDEADYYCSSYAGSYTWVFGGGTELTVLGQPKAAPSVTLFPPSS	1027

BP6a-14	EIVLTQSPGTLSLSPGEGATLSCRASQTVNSNDLAWYQQRPGQAPRLLIYDASTRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYFCQQYHGSQTFGQGTRVEIKRTVAAPSVF	1028
BP6a-27	DIQMTQSPSSLSASVGDRVTITCRASQSINRHLNWYQQKPGKAPKFLISAASNLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPYTFGGGTKVEIKRTVAAPSVF	1029
BP6a-13	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSLGSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPWTFGQGTKVEIKRTVAAPSVF	1030
BP4a-1	QSALTQPASVSGSPGQSITISCTGTSSDISIYNYVSWFQQHPGKAPKLMIYDVNNRPSGVSSRFSGSKSANTASLTISGLQAEDEADYYCSSYTYSNTLLFGGGTKLTVLGQPKAAPSVTLFPPSS	1031
BP1a-1	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGTAPKLMIYDVSYRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTLVFGTGTKVTVLGQPKANPTVTLFPPSS	1032
BP6a-6	EIVMTQSPGTLSLSPGERATLSCRASQSVSSGYLAWYQQKAGQAPRLLIYGGSARAPGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSIWPLTFGGGTKVEIKRTVAAPSVF	1033
BP19b-2	QSALTQPPSASGSRGQSVSISCSGSRSDIGYYNYVSWYQQHPGKAPKLIIFDVNKRPSGVPDRFSGSKSGNTASLTVSGLQAEDVADYYCSSSVGSNNLVFGGGTKLTVLGQPKAAPSVTLFPPSS	1034
BP6a-4	QSALTQPASVSGSPGQSITLSCTGTSSDVGDYNYVSWYQQYPGKAPKLMIYDVTKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSTTWVFGGGTKLTVLGQPKAAPSVTLFPPSS	1035
BP19a-1	QSVLTQPPSASGTPGQRVSISCSGRMSNIGKNTVNWYQQVPGTAPKLLIYSNNQRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYCAAWDDSLNGWVFGGGTKLTVLGQPKAAPSVTLFPPSS	1036
BP6a-7	QSALTQPASVSGSPGQSLTISCTGTSSDIGGYNYVSWYQQHPGKAPKLIIYDVTDRPSGVSGRFSGSKSGNTASLTISGLQTEDEAEYFCNSWTRSNNYIFGGGTKLTVLGQPKAAPSVTLFPPSS	1037
BP5b-5	DVVMTQSPLSLPVTLGQPASISCRSSQSLVYSDGNTYLNWFQQRPGQSPRRLIYKVSNRDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGTHWPLTFGQGTKVEITRTVVAPSVF	1038
BP6b-3	SSELTQAPSVSVSPGQTASITCSGNKLGDKFASWYQQKPGQSPVMVMYEDRKRPSGIPERFSGSNSGNTATLTISGTQALDEADYYCQTWDSRTVVFGGGTKLTVLGQPKAAPSVTLFPPSS	1039
BP18b-2	DIVMTQSPVSLPVTLGQPASISCRSSQSVVYRDGNTYLSWFLQRPGQSPRRLIYKVSNRDSGVPDRFSGSGSATDFTLKISRVEAEDVGVYYCMQGSSWPYTFGQGTKLEIKRTVAAPSVF	1040
BPx-1	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSDGNNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGLHTPTTFGQGTKVEIKRTVAAPSVF	1041
BP21b-1	NFMLTQPHSVSESPGKTVTISCTRSSGSIASNYVQWYQQRPGSSPTTVIYEDNQRPSGVPDRFSGSIDSSSNSASLTISGLRTEDEADYYCQSYDHMYNWVIGGGTKLTVLGQPKAAPSVTLFPPSS	1042
BP6a-2	QSVLTQPPSVSGAPGQKVTISCSGSSSNIGNNYVSWYQQLPGTAPKLLIYDNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYHCAAWDDDLNGPVFGGGTKLTVLGQPKAAPSVTLFPPSS	1043
BPx-2	DIQMTQSPSSLSASVGDRVTISCRASHSISRFLNWYQQKPGRAPKLLI	1044

	YSTSSLQSGVPSRFSGSGSARDFTLTISGLQPEDFATYFCQQSYSTPW TFGQGTKVELKRTVAAPSVF	
BP6b-1	SSELTQPPSVSVSPGQTATITCSGDKLGDKYASWYQQKPGQSPVLVI YQDTKRPSGIPARFSGSNSGNTATLTISGTQAMDEAAYYCQAWDST TVVFGGGTKLTVLGQPKAAPSVTLFPPSS	1045
BPx-3	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGYETDFTLTISSLQAEDVAVYYCQQYYSSP WTFGQGTRVEIKRTVAAPSVF	1046
BP6a-5	QPVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVHWYQQLPGTAPKL LIYSDNQRPSGVPDRFSGSKSGTSASLVISGLQSDDEADYYCAAWD DSLNGVFGGGTKLTVLgQPKAAPSVTLFSPSS	1047
BP6a-10	QPVLTQPPSVSVSPGQTASITCSGDKLGDKYASWYQQKPGQSPVMV IYQDRKRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCAAWDD SLSGRVFGGGTKLTVLGQPKAAPSVTLFPPSS	1048
BP15a-1	EIVMTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRL LIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSS PYTFGQGTKLEIKRTVAAPSVF	1049
BP6a-26	EIVLTQSPATLSLSPGDRATLSCRASQSVSSYLAWYQQKPGQAPRLL IYDASNRATGIPARFSGSGSGTDFSLTISRLEPEDFAVYYCQQSGSSP WTFGQGTKVEIKRTVAAPSVF	1050
BP6a-12	DIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLF IYGASTRATGIPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYSTP YTFGQGTKLEIKRTVAAPSVF	1051
BP5a-4	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNNYLSWYQQLPGTAPKL LIYDNNKRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDS SLSAGVFGGGTKLTVLGQPKAAPSVTLFPPSS	1052
BP5b-1	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYISWYQQYPGKAPK LMIYDVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCNSYT SSRTVVFGGGTKLTVLGQPKAAPSVTLFPPSS	1053
BPx-4	SSELTQPPSVSVSPGQTASITCSGDQLGDKFVSWYQQKPGRSPVLVIS EDNKRHSGTPERISGSNSGNTATLTISGTQSMDEADYFCQTWDSSA VVFGGGTKLTVLGQPKAAPSVTLFPPSS	1054
BP5a-3	SSELTQDPAVSVALGQTVRITCQGDSLKKYYASWYQQKPGQAPVL VIYGKNLRPSGIPERFSGSSSGDTASLTITGTQAEDEADYYCQAWDS STAVFGGGTKLTVLGQPKAAPSVTLFPPSS	1055
BP14a-1	DVVMTQSPLSLSVTPGQPASISCRSSQSLVHSDGNTYLNWFHQRPG QSPRRLIYKVSNRDPGVPDRFSGSGSGTDFTLKISRVEAEDAGVYYC MQGTHWPRLTFGGGTKVEIKRTVAAPSVF	1056
BP3a-1	DIQMTQSPSSFSASTGDRVTITCRASQGISSYLAWYQQKPGKAPKLLI YAASTLQSGVPSRFSGSGSGTDFTLTISSLRLDDVATYYCQQYQSYPI TFGQGTRLEIKRTVAAPSVF	1057
BP18b-3	EIVLTQSPDSLAVSLGERATINCKSSQNLLYSSNNKNYLAWYQQKP GQPPKLLINWASTRVSGVPDRFSGSGSGTDFTLTINSLQAEDVAVYY CHQYYSSPYTFGPGTKVEIKRTVAAPSVF	1058
BP6a-9	QPVLTQPPSVSVSPGQTASITCSGDNLGDKYASWYQQKPGQSPVLVI FRDTKRPSGIPERFSGSNSGDTATLTISGTQAMDEADYYCQAWDSS AGGVFGGGTRLTVLGQPKAAPSVTLFPPSS	1059
BP6a-25	DVVMTQSPLSLPVTPGEPASISCRSSQTLLHSNGFNYLDWYLQKPGQ SPQLLMYLGSSRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	1060

	MQGTHWPPTFGQGTKLEIRRTVAAPSVF	
BPx-5	QAVLTQPPSVSGTPGQTVIISCSGSNSNLGRNSANWYQQLPGTAPKL LIHSNHMRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYCAAWD DSLNGWVFGGGTKLTVLGQPKAAPSVTLFPPSS	1061
BP5a-2	QPVLTQPPSASGTPGQRVTISCFGSSSNIGSNYVYWYQQLPGTAPKL LIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWD DSLSGWVFGGGTKLTVLGQPKAAPSVTLFPPSS	1062
BP6a-15	DIQMTQSPSTLSASVGDRVSITCRASQSVSSWLAWYQQKPGKAPKL LIYAASSLQSGVPSRFSGSGSGTDFTLTISNLQPEDSATYFCQQSYSTP WTFGQGTKVELKRTVAAPSVF	1063
BP6a-21	DIQMTQSPSSLSASVGDRVTITCQASHDISNYLNWYQQKPGKAPKL LIYDASNLETGVPSTFSGSGSGTDFTLTISSLQPEDIATYYCQQSYSTP YTFGQGTKVEIKRTVAAPSVF	1064
BP5a-5	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAP KLMIYDVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSY TTSSTLVFGGGTKVTVLGQPKAAPSVTLFPPSS	1065
BP6a-17	SSELTQDPSVSVSPGQTASITCSGDKLGDKYVGWYQQKPGQSPVLII YRDYKRPSGTPERFSGSNSGNTATLTISGVEAGDEADYYCQVWDM SSDPLVFGGGTKLTVLGQPKAAPSVTLFPPSS	1066
BP6a-20	DIVMTQSPSTLSVSVGDRVTITCRASQSISSWLAWYQQKPGKAPKLL IYKASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPY TFGQGTKLEIKRTVAAPSVF	1067
BP3a-2	QSALTQPRSVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPK LMIYDVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYT SSSTYVFGTGTKVTVLGQPKADPTVTLFPPSS	1068
BP6a-24	QPVLTQPPSVSVSPGQTASITCSGDDLGDKFASWYQQKPGQSPILVI YQDSKRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWDGT KVVFGGGTKVTVLGQPKAAPSVTLFPPSSKARG	1069
BP6a-22	DIVMTQSPSSVSASVGDRVTITCRASQDISSWLAWYQQKPGKAPKL LIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFASYYCQQANSF PQTFGGGTKVEIKRTVAAPSVF	1070
BP19a-2	NFMLTQPHSVSESPGKTVTISCTRSSGRIVSTYVQWYQHRPGSPPRLI MYDDVQRPSGVSARFSGSIDISSNSASLTISGLLAEDEADYYCQSYN TSNLVFGGGTKLTVLSQPKAAPSVTLFPPSS	1071
BPx-6	QSALTQPPSASASPGQSVTISCTGTSSDVGGYDFVSWYQQHPGQAP KLMIYEVNKRPSGVPDRFSGSKSGNTASLTVSGLQADDEADYYCCA YAGSNILLFGGGTKLTVLGQPKAAPSVTLFPPSSKPRG	1072
BP6a-18	AIQLTQSPSSLSASVGDRVTITCRASQSISTYLNWYQQKPGKAPKLLI YDTSSLHSGVPSRFSGSGSGTDFTLTISSLQPEDFATYHCQQSFITPYT FGQGTKLEIKRTVAAPSVF	1073
BP16a-1	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAP KLMISDVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSY TSNYTLVFGGGTKLTVLGQPKAAPSVTLFPPSS	1074
BP19a-3	DIVMTQSPATLSVSPGERATLSCRASQSVSSYLAWYQQKPGQAPRL LIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQHRGSW PHTFGPGTKLEMKRTVAAPSVF	1075
BP5b-2	EIVMTQSPATLSLSPGDRATLSCRASQNVGSYLGWYQQKVGQAPRL LIYDASNRATGVPGRFSGSGSGTDFTLTISSLEPEDFAVYYCQQYGSS PLFTFGPGTKVDIKRTVAAPSVF	1076

BP2a-1	EIVMTQSPGTLSLSPGERATLSCRASQSVSSNYLAWYQQKPGQAPR LLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFALYYCQQYGT SPLTFGGGTKLEIKRTVAAPSVF	1077
BP18a-2	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQ SPQLLIYLGSNRASGVPDRFSGSESGTDFTLKISRVEAEDVGVYYCM QATHWPPRLTFGPGTKVDIKRTVAAPSVF	1078
BPx-7	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQRPGKAPK LMIYDVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYT TSSTVVFGGGTKLTVLGQPKAAPSVTLFPPSS	1079
BPx-8	RSALTQPASVSGSPGQSITISCTGSSNDVGGYKFVSWYQHHPGKAPK LLIYGVTQRPSGVSNRFSGSQSGNTASLTISGLQAEDEADYFCTSYT RSTTPIFGGGTKLTVLGQPKAAPSVTLFPPSS	1080
BPx-9	QSALTQPPSASGSPGQSVTVSCTGSSSDIGSYNYVSWFQRHPGQAPK LIIHDVTERPSGVPHRFSGSKSGNTASLTISGLQTEDEADYFCCSYSG DHTLPFIFAPATQVTVLGQPKANPTVTLFPPSS	1081
BPx-10	DIVMTQSPLSLPVTLGQPASISCRSSQGLVYSDGNTYLNWFQQRPGQ SPRRLIYKVSNRDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCM QATHWPWTFGQGTKVEIK	1082
BPx-11	QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNYVYWYQQLPGTAPKL LIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWD DSLSGPVFGGGTKLTVLGQPKAAPSVTLFPPSS	1083
BPx-12	DVVMTQSPLSLPVTLGQPASISCRSSQSLVHGNGITYLNWFQQRPGQ SPRRLIYKVSNRDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCM QALQTPSFGQGTRLEIKRTVAAPSVF	1084
BPx-13	QSALTQPPSASGSPGESVTISCTGTSSDVGGYNYVSWYQQHPGKAP KLLIYDVTKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSY TSSSTVVFGGGTKLTVPGQPKAAPSVTLFPPSS	1085
BPx-14	QSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQHHPGKAP KLMIYDVNKRPSGVPDRFSGSKSANTASLTVSGLQAEDEADYYCSS YTAGGNWVFGGGTKLTVLGQPKAAPSVTLFPPSS	1086
BPx-15	DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYVQKPG QSPQHLIYLGSIRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC MQGLQTPPTFGPGTKMDIKRTVAAPSVF	1087
BPx-16	DVVMTQSPLSLPVTLGQPASISCRSSQSLVYSDGNTYLSWFHQRPGQ SPRRLIYKVSNRDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCM QGTHWPWTFGQGTKVEIKRTVAAPSVF	1088
BPx-17	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAP KLMIYDVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSY TSSSTWVFGGGTK	1089
BP1b-1	QSALTQPPSASGSPGQSVTISCSGTSSDIGGYDYVSWYQQHPGKAPK LIIYEVSKRPSGVPDRFSGSKSGNTASLTVSGLQADDGAHYYCSAYA GRNNMVFGGGTKVTVVGQPKAAPSVTLFPPSS	1090
BPx-18	QSVLTQPPSASGTPGQRVIISCSGSRSNNGSNYIYWYQHLPGTAPKL LIYRNNQRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYCAAWD RSLNAWVFGGGTKLTVLSQPKAAPSVTLFPPSS	1091
BPx-19	DIVMTQTPLSLPVTLGQPASISCRSSQSLVYSDGKTYLNWFQQRPGQ SPRRLIYKVSNRDSGVPDRFSGSGSGTDFTLKITRVEAEDVGVYYCM QGTHWPHTFGQGTKLEIKRTVAAPSVF	1092
BPx-	EIVMTQSPATLSLSPGERATLSCRASQSVNSSYFAWYHRRPGQAPRL	1093

20	LISRTSTRAAGIPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGTY WPYTFGQGTKLEIKRTVAAPSVF	
BPx-21	QSALTQPPSASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAP KLMIYDVSNRPSGVSNRFSASKSGNTASLTISGLQAEDEADYYCSSY TSSSTLDVVFGGGTKLTVLGQPKAAPSVTLFPPSS	1094
BPx-22	QSALTQPASMSGSPGQSITISCTGTSSDLGGYNYVSWYQQHPGKAP KLMIYDVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSY TSSSTPWVFGGGTKLTVLGQPKAAPSVTLFPPSS	1095
BPx-23	NFMLTQPHSVSESPGKTVTISCTRSSGSIASNYVQWYQQRPGSSPTT VIYEDNQRPSGVPGRFSGSIDSSSNSASLTISGLQTEDEADYYCQSYD GSDVVFGGGTKLTVLSQPKAAPSVTLFPPSS	1096
BP5b-6	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAP KLMIYDVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSY TSSSTWVFGGGTKLTVLGQPKAAPSVTLFPPSS	1097
BPx-24	NFMLTQPHSVSESPGKTVTISCTGSSGSIASNYVQWYQQRPGSSPTT LIYEHNQRPSGVPDRFSGSVDSSSNSASLTISGLKTEDEADYYCQSY DDNNVVFGGGTKLTVLGQPKAAPSVTLFPPSS	1098
BPx-25	QSALTQPPSASGSPGQSVTISCTGTSSDIGGYNYVSWYQVHPGKAPK LIIYDVSKRPSGIPDRFSGSKSGNAASLTVSGLRTEDEADYYCSSYAG NNNLIFGGGTKVTVLSQPKAAPSVTLFPPSS	1099
BPx-26	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAP KLMIYDVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCASY TSSTSVVFGGGTKLAVLGQPKAAPSVTLFPPSS	1100
BPx-27	DVVMTQTPLSLPVTPGQPASISCRSSQSLVYSNGNTYLTWFQQRPG QSPRRLLHEVSKRDSGVPDRFVGSGSGTDFTLKISRVEPEDVGIYYC MQGSQWPPTFGQGTKLEIKRTVAAPSVF	1101
BPx-28	DIVMTQTPVSLPVTLGQPASISCRSSQSLVHSDGNTYLNWFQQRPGQ SPRRLIYKVSTRDSGVPDRFSGSGSATDFTLKISGVEAEDVGVYYCM QGTHWPKTFGQGTKVEIKRTVAAPSVF	1102
BPx-29	EIVMTQSPLSLPVTPGEPASISCRSSQSLLHKNGNNYLDWYLQKPGQ SPQLLIYMASKRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC MQALQTPPTFGGGTKVEIKRTVAAPSVF	1103
BPx-30	EIVLTQSPATLSLSPGERATLSCRASQSITSNYLAWYQQKPGQAPRL LIVGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDSAVYYCQQYGNS PRTFGQGTKLEIKRTVAAPSVF	1104
BPx-31	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLL IYKASSLESGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQYQSYPI TFGQGTRLEIKRTVAAPSVF	1105
BPx-32	EIVLTQSPLSLPVTPGEPASISCRSSESLLHSIGYNYVDWYVQKPGQS PQLLIYLGSNRASGVPDRFSGSTSGTDFTLKISRVEAEDVGVYYCMQ ALQTSITFGQGTRLEIKRTMAAPSVF	1106
BPx-33	QSALTQPASVSGSPGQSITISCTGTSSDVGTYNYVSWYQQHPGKAPK LMIYDVNNRPSGVSNRFSGSKSGSTASLTISGLQAEDEADYYCSSYT STSTPYVFGTGTKVTVLRQPKANPTVTLFPPSS	1107
BPx-34	QSALTQPPSASGSPGQSVTISCTGTSSDIGGYNYVSWYQQHPGKAPK LMIYEVSERPSGVPDRFSGSKSGNTASLTIAGLQGEDEADYYCSSYR SSSTVVFGGGTKLTVLGQPKAAPSVTLFPPSS	1108
BPx-35	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAP KLMIYDVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSY	1109

	TSSSTLVFGTGTKVTVLGQPKANPTVTLFPPSS	
BPx-36	DIQMTQSPSFLSASVGDRVTITCRASQGISSHLAWYQQKPGKAPKLL IYATSTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFDDLP VTFGPGTKVEIKRTVAAPSVF	1110
BPx-37	DIVMTQSPLSLPVTPGEPASISCRSSQTLLHANGFNYLDWYLQKPGQ SPQLLMYLGSSRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC MQTLQTPPWTFGQGTKVEIKRTVAAPSVF	1111
BPx-38	DIVLTQSPATLSVSPGDRATLSCRASQSVNRNLAWYQQRPGQAPRIL IYDASTRATGIPTRFRGSGSGTEFTLTISSLQSEDFGIYYCQQYNNWL SFGGGTKVEVKRTVAAPSVF	1112
BPx-40	NFMLTQPHSVSESPGKTVTISCTRSSGTIVSTYVQWYQQRPGSSPTT VIYEDNQRPSGVPDRFSGSIDSSSNSASLTISGLKTEDEADYYCQSYD SSNRKVFGGGTKLTVLSQPKAAPSVTLFPPSS	1113
BPx-41	QSALTQPASVSGSPGQSITISCTGTSSDVETYNLVSWYQQHPGKAPK LMIYDVTKRPSGVPDRFSGSKSGNTASLTISGLQADDEADYYCSSYA DSIAFVIFGGGTKVTVLGQPKAAPSVTLFPPSS	1114
BPx-42	DIVMTQSPATLSLSPGERATLSCRASQSFSSNLAWYQQKPGQAPRLL IYDASNGATGVPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSS PRTFGQGTKLEIK	1115
BPx-43	QSVLTQPPSVSGAPGQRVTISCTGSSSNVGAGYDVHWYQQLPGTAP KLLIYGNTNRPSGVPERFTGSKSGTSASLAISGLRSEDEADYYCATW DDSLNGPVFGGGTKLTVLGQPKAAP	1116
BP16b-1	QSVLTQPPSVSGAPGQRVTISCTGSTSNIGAGYDVHWYQQLPGTAP KLLIYGNTNRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYCAAW DDSLNGWVFGGGTKLTVLGQPKAAPSVTLFPPSS	1117
BPx-44	QAVLTQPPSASGTPGQRVTISCSGSSSNIGSNYVYWYQQLPGTAPKL LIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWD DSLSGWVFGGGTKLTVLGQPKAAPSVTLFPPSS	1118
BPx-45	QSVLTQPPSASGTPGQRVTISCSGSNSNIGSNHVYWYQQLPGTAPKL LIYSNNQRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYCAAWDD NVNGWVFGGGTKLTVLGQPKAAPSVTLFPPSS	1119
BPx-47	QAVLTQPPSASGTPGQRVTISCSGSSSNIGTNAVNWYQQLPGTAPKH LIYSNNQRPSGVPDRFSASKSGTSASLAISGLQSDDESDYYCAAWDD SLNGVVFGGGTKLTVL	1120
BPx-48	QPVLTQSPSASGTPGQRVTISCSGSSSNIGSNYVYWYQQLPGTAPKL LIYRNSQRPSGVPDRFSGSKSGTSTSLAISDLRSEDEADYYCAAWDD SLSGWVFGGGTKLTVLGQPKAAPSVTLFPPSS	1121
BPx-49	DIVMTQSPATLSLPPGERATLSCRASQSVSSYLAWYQQKPGQAPRL LIYDASNRATGIPARFSGSGSGTDFTLTISSLQAEDVAVYFCQQYYST PLTFGGGTKVEIKRTVAAPSVF	1122
BPx-50	QPVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKL LIYINNQRPSGVPDRFSGSKSGTSASLAISGLQSEDEANYYCAAWDD SLSGPVFGGGTKLTVLGQPKAAPSVTLFPPSS	1123
BPx-51	QAVLTQPPSASGAPGQTVTISCSGSSSNIGSKTVNWYQQVPGTVPKL LIYNNNQRPSGVPDRFSGSKSGTSASLAITGLRSEDEADYYCAAWD DSLSGPMFGGGTKLTVLGQPKAAPSVTLFPPSS	1124
BPx-52	DIVMTQSPSALSASVGDRVTITCRASQSIGSWLAWFQQKPGKAPNL LIYKASSVESGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQSYSTP YTFGQGTKLEIKRTVAAPSVF	1125

BPx-53	QAVLTQPPSVSVAPGKTAKITCGGLNIGSKSVHWYQQKAGQAPVL VMSYDSDRPSGIPERFSGSNSGSTATLSISRVAAGDEADYYCQVSDS DTDHPVFGGGTKLTVL	1126
BPx-54	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQ SPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCM QALQTPYTFGQGTKLEIKRTVAAPSVF	1127
BPx-55	SSELTQDPAVSVALGQTVRITCQGDSLRTYYASWYQQKPGQAPKLL IYGKNNRPSGIPERFSGSSSRNSASLTITGTQAEDEADYYCDSRDSST SQWVFGGGTKVTVLGQ	1128
BPx-56	QPVLTQPPSASGTPGQRVTISCSGTSSNIGSNTVSWYHHLPGTAPKLL IYSNNQRPSGVPDRFSGSRSGTSAALAISGLESEDEADYYCATWDDS LNGWVFGGGTKLTVLGQPKAAPSVTLFPPSS	1129
BPx-57	DIVMTQSPDSLAVSLGERATIKCQSSQSVLYSFSNKNYLAWYQQKP GQPPKLLIYWASTRKSGVPDRFSGSGSGTDFSLTISSLQAEDVAVYY CQQYYLLPITFGQGTRLEIK	1130
BPx-58	QPVLTQPPSVSVAPGKTARITCGGNNIGSKSVHWYQQKPGQAPVLV IYYDSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSS SDHVVFGGGTKLTVLGQPKAAPSVTLFPPSS	1131
BPx-59	EVVLTQSPLSLPVTPGEPASISCRSSQSLLHSIGYNYVDWYVQKPGQ SPRLLIYLGSNRASGVPDRFSGSGSGTDFTLKITRVEAEDVGVYYCM QALQTIFTFGPGTKVDIKRTVAAPSVF	1132
BPx-60	QPGLTQPPSASGTPGQRVTISCSGSSSNIGSNYVYWYQQLPGTAPKL LIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEGDYYCASWDD SVHGWVFGGGTKLTVLGQPKAAPSVTLFPPSS	1133
BPx-61	QSALTQPASVSASPGQSITISCTGTSSDVGSYNYVSWYQQHPGKAPK LIIFDVNNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSDTS SSTLVFGGGTKLTVLGQPKAAPSVTLFPPSS	1134
BPx-62	DIVMTQSPDSLAVSLGERATISCKSSQSVLYSSNNKNYLAWYQQKP GHPPKLLIYGASTRESGVPDRFSGSGSETDFTLTISSLQAEDAAVYYC MQAAQLPLTFGGGTRVEIRRTVAAPSVF	1135
BPx-63	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNQYVSWYQHLPGTAPKL LIYDNNKRPSGIPDRFSGSKSGTSATLDITGLQTGDEADYYCGTWDT SLSGFLFAGGTKLTVLSQPKAAPSVTLFPPSS	1136
BPx-64	QSVLTQPPSSSASPGESARLTCTLPSDINVGQPKAAPSVTLFPPSS	1137
BP6b-5	QSVLTQPPSVSGAPGQRVTISCTGSGSNIGRGYDVHWYQQLPGTAP KLLIYGNTKRPSGVPERFAASKSGTSATLDITGLQTGDEADYYCGT WDTSLSGFLFAGGTKLTVLSQPKAAPSVTLFPPSS	1138
BPx-65	QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKL LIHTNNQRPSGVPDRFSGSKSGTSASLAISGLQSEDEADFYCAAWDD SLNGPVFGGGTKLTVLGQPKAAPSVTLFPPSS	1139
BPx-66	NFMLTQPHSVSESPGKTVTISCTRSSGRIASTYVQWYQHRPGSAPNI VIYEDDQRPSGVPDRFSGYVDNSSNSASLTISGLKPEDEAEYYCQSY DGDNAVFGGGTKLTVLGQPKAAPSVTLFPPSS	1140
BPx-67	QSALTQPASVSGSLGQSITISCTGTSGDVETYNLVSWYQQHPGKVPK LIIYEVSERPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYAG SGTLRLFGGGTKVTVLGQPKAAPSVTLFPPSS	1141
BPx-68	QSVLTQPPSVSAAPGQKVTISCTGSSSNIGAGYDVHWYQQVPGTAP KLLIYGNSYRPSGVSDRFSGSKSGTSASLAISDLQPEDEAYYYCATW	1142

	DDSLRGDVVFGGGTKLTVLGQPKAAPSVTLFPPSS	
BPx-69	DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPG QSPQLLIYLASNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC MQALQTPATFGQGTKLEIKRTVAAPSVF	1143
BPx-70	QPVLTQPPSMSVSPGQTASITCSGHKLGHKYVGWYQQRPGQSPVLV IYQDNKRPSGIPERFSGSNSGNTATLTISETQAIDEADYYCQAWDSSS TAYVFGTGTKVTVLGQPKANPTVTLFPPSS	1144
BPx-71	QSALTQPPSASGSPGQSVTISCSGTSSDVGGYNYVSWYQQYPGKAP KLVISEVSKRPSGVPDRFSGSKSGNTASLTVSGLQAEDEAEYYCSSY VGGNIWVFGGGTKLTVLGQPKAAPSVTLFPPSS	1145
BPx-72	DIQMTQSPSTLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLL IYAASSLQSGVPSRFSGSGSGTDFALTISSLQPEDFATYYCQQSYSTP WTFGQGTKVEIKRTVAAPSVF	1146
BPx-73	QPVLTQPPSASGTPGQRVTISCSGSSSNIGSNYVYWYQQLPGTAPKL LMYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWD DSLSGWVFGGGTKLTVLGQPKAAPSVTLFPPSS	1147
BPx-74	EIVMTQSPGTLSLSPGERVTLSCRASQYITSGYLAWYQQKPGQAPRL LFYGASRRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSS PTYTFGQGTKLEIKRTVAAPSVF	1148
BP8b-1	EIVLTQSPGTLSLSPGERATLSCRASESISNNYLAWYQQKPGQAPRL LIYGASSRATGIPDRFSGRGSGIDFTLTISRLEPEDFAVYYCQQYGYS PTFGPGTKVDVKRTVAAPSVF	1149
BPx-75	DIQMTQSPSSLSASVGDRVTVTCRASQSISIFVNWYQQRPGKAPKLL IYAASSLQTGVPSRFSGSGSGTEFTLTISSLQPEDYATYYCQQSYSML SWTFGPGTKVENKRTVAAPSVF	1150
BPx-76	QAVLTQPPSASGTPGQRVTISCSGSSSNIGSNYVSWYQQLPGTAPKL LIFSNNQRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYCAAWDD SLNGWVFGGGTKLTVLGQPKAAPSVTLFPPSS	1151
BPx-77	QSALTQPASVSGSPGQSITISCTGTSSDVGAYNYVSWYQQYPGKAP KLMIYDVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCGSY TTSSTLVFGGGTKVTVLGQPKAAPSVTLFPPSS	1152
BP6b-6	SSELTQAPSVSVSPGQTASITCSGDKLGDKYVSWYQQRPGQSPVVVI YQDIRRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSS WVFGGGTKLTVLSQPKAAPSVTLFPPSS	1153
BPx-78	EIVLTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQS PQLLIYLGSNRASGVPDRFSGSVSGTDFTLKISRVEAEDVGVYYCMQ GTHWSYTFGQGTKLEIKRTVAAPSVF	1154
BPx-79	QSALTQPASVSGSPGQSITISCTGTSSDIGTYNYLSWYQQHPGKAPK LMIYDVVYRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYA GSSTVVFGGGTKLTVLGQPKAAPSVTLFPPSS	1155
BPx-80	DIQMTQSPASLSVSIGDRVTITCQASQDIANHLNWYQQKPGDVPKLL IFDATHMERGVPSRFDGSRSGTDFTFTISSLQPEDVATYYCQQFDELP LTFGGGTKVRIKGTVAAPSVF	1156
BPx-81	NFMLTQPHSVSESPGKTITISCTRNSGRIASNYVQWYQQRPGSPPTTL IYEDSLRPSGVPDRFSGSIDTSSNSASLTISGLETEDEADYYCQSYDSR VYVFGTGTKVTAL	1157
BPx-82	SSELTQDPAVSVALGQTVRITCQGDSLKKYYASWYQQKPGQAPVL VIYGKNLRPSGIPERFSGSSSGDTASLTISATQAEDEADYYCNSRDSS GNPIFGGGTKLTVLGQPKAAPSVTLFPPSS	1158

BPx-83	DVVMTQSPLSLPVTLGQPASISCRSSQSLVYSDGNTFLNWFQQRPGQPPRRLIYKVSNRDFGVPDRFSGSGSGTDFTLKISRVEADDVGVYYCMQGTHWPFTFGPGTK	1159
BPx-84	QSVLTQPPSVSEAPRQRVTISCSGSSSNIGNNAVNWYRQLPGKAPKLLIYDNNKRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDSSLSAWVFGGGTKLTVLGQPKAAPSVTLFPPSS	1160
BPx-115	DVVMTQSPDSLAVSLGERATINCKSSQNILYSSTNKNYLAWYQQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYSTPVTFGQGTKVEIKRTVAAPSVF	1161
BPx-116	QSALTQPASVSGSPGQSITISCTGTSSDITIYNYVSWFQQHPGKVPKLMIYDVNDRPAGVSSRFSGSKSGNTASLTISGLQAEDEADYYCSSYTYSNTLVFGGGTKVTVLGQPKAAPSVTLFPPSS	1162
BPx-117	EIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLMYLGSKRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQARQTPVTFGQGTRLETKRTVAAPSV	1163
BPx-118	NFMLTQPHSVSESPGKTVTISCTGSSGSIASNYVQWYQQRPGSAPTTVIYEDNQRPSGVPDRFSGSIDSSSNSASLTISGLKTEDEADYYCQSYDSSILVVFGGGTKLTVL	1164
BP6b-11	SSELTQDPAVSVALGQTVRITCQGDSLKKYYASWYQQKPGQAPVLVIYGRNLRPSGIPERFSGPYSGNTASLTITGAQAEDEADYYCNSRDSRGNLLVFGGGTRLIVLGQPKAAPSVTLFPPSSKASGA	1165
BP18b-4	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYTIPHTFGQGTKLEIKRTVAAPSVFKASGA	1166
BP6b-2	QPVLTQPPSVSVSPGQTASITCSGDKLGDKYASWYQQKPGQSPLLVIYQDNKRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTVMFGGGTKLTVLGQPKAAPSVTLFPPSSKASGA	1167
BP6b-10	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHTNGYNFLDWYLQKPGQSPQLLIHLGSYRASGVPDRFSGSGSGTDFTLKISRVAAEDVGVYYCMQALHTPMYTFGQGTKLEIKRTVAAPSVFKASGA	1168
BP16b-2	NFMLTQPHSVSESPGKTVTISCTGSSGSIASYYVQWYQQRPGSSPTTVIYEDNQRPSGVPDRFSGSIDSSSNSASLTISGLKTEDEADYYCQSYDSSNRWVFGGGTKLTVLGQPKAAPSVTLFPPSSKASGA	1169
BP18b-5	EIVMTQSPLSLPVTPGEPASISCRSSQSLVHSNGNTYLNWFHQRPGQSPRRLIYEVSNRDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGTHWPYTSGQGTKLEIYRTVAAPSVFKASGA	1170
BP7b-1	DIQMTQSPSSLSASVGDRVTITCRASQSISRHLNWYQQKPGKAPKLLIYAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSASTPLTFGGGTKVEIKRTVAAPSVFKASGA	1171
BP5b-7	DIVMTQSPLSLPVTLGQSASISCRSSQGLVYSDGNTFLSWFHQRPGQSPRRLIYMVSNRDSGVPDRFSGSGSGTDFTLKISRVEAEDVGIFYCMQGTHWPWTFGQGTKVEIKRTVAAPSVFKASGA	1172
BPx-85	DIQMTQSPSSLSASVGDRVTITCRASQNIINYLNWYQQKPGKAPDLLIHTASNLQSGVPSRFSGSGFGTDFSLTITSLQPEDFATYYCQHSFSSPYTFGQGTKLEIKRTVAAPSVFKASGA	1173
BP18b-6	DIVMTQSPLSLPVTPGEPASISCRSSQTLLHSNGFNYLDWYLQKPGQSPQLLMYLGSSRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQIPRTFGQGTKLEIKRTVAAPSVFKASGA	1174
BP20b	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLI	1175

-1	YAASSLQSGVPSRFSGSGSGTDFSLTITNLQPEDIATYYCQQTYIYPR TFGQGTKVEIKRTVAAPSVFKASGA	
BPx-86	EVVMTQSPLSLPVTLGQPASISCRSSQSLVYSDGNTYLNWFQQRPG QSPRRLLYKVSNRDSGVPDRFSGTGSGTDFTLRISRVEAEDVGVYY CMQGSHWPLTFGGGTKVEIKRTVAAPSVFKASGA	1176
BP19b-3	QSALTQPASVSGSPGQSITISCTGTSNDIGRYDYVSWYQQHPGKAPK LIIYAVKARPSGVSSRFSGSKSGNMASLTISGLQAEDEADYYCGSYT RSSTARFGTGTRVTVLGQPKANPTVTLFPPSSKASGA	1177
BPx-87	SSELTQDPSVSVSPGQTATITCSGSKLGDKYVSWYQQKPGQSPVLVI YEDDKRPSGSSERFSGSNSGNTATLTISGTQAMDEADYYCQAWDSI TAVFGGGTKLTVLGQPKAAPSVTLFPPSSKASGA	1178
BPx-88	SSELTQAPSVSVSPGQTASIPCSGDNLRSKYVSWYQQKPGQSPVMLI YQDDKRPSGIPEGFFGATSGNTATLIIAETQPLDEGDYYCQTWDGN HVVFGGGTKLTVLGQPKAAPSVTLFPPSSKASGA	1179
BP18b-7	EIVMTQSPLSLPVTLGQPASISCRSSQGLVYSDGNTYLNWFHQRPGQ SPRRLIYKVSNRDSGVPDRFSGSGSGTDFTLKISRVEAEDVGIYYCM QGTQWPYTFGQGTRLDIKRTVAAPSVFKASGA	1180
BP17b-1	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAP KLMIYDVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSY TSSSTLVFGGGTKLTVLGQPKAAPSVTLFPPSSKASGA	1181
BP16b-3	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLL VYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSGW PPKVTFGGGTKVEIKRTVAAPSVFKASGA	1182
BPx-89	DIQMTQSPSSLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLL IYKASSLESGVPSRFSGSGSGTEFTLTITSLQPEDFATYYCQQSYSTPF TFGPGTKVDIKRTVAAPSVFKASGA	1183
BPx-90	QPVLTQPPSVSVSPGQTTNITCSGHELGDKYVSWYQQRPGQSPVVVI YQDNKRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWDSS TVVFGGGTKLTVLGQPKAAPSVTLFPPSSKASG	1184
BP5b-8	SSELTQAPSVSVAPGRTARITCGGNNIGNKSVHWYQQQPGQAPVLV IYYDIDRPSGIPERFSGSNSGNTATLTISRVEADDEADYYCQVWDSN SDHVVFGGGTKLTVLGQPKAAPSVTLFPPSSKASGA	1185
BP16b-4	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAP KLLIYDVTKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSY TSSSTVVFGGGTKLTVLGQPKAAPSVTLFPPSSKASGA	1186
BP9b-1	NFMLTQPPSASGTPGQRVTISCSGSSSNIGNNAVNWYQQLPGTAPKL LIYSNNQRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYCATWDD SLNGWVFGGGTKLTVLGQPKAAPSVTLFPPSSKASGA	1187
BPx-91	DIVLTQSPLSLPVTPGEPASISCRSSQSLLHSNGFNYLDWYLQKPGQS PQLLIYLGSNRASGVPDRFSGSGSGTDFTLQISRVEAEDVGVYYCMQ GLQTPYTFGQGTKLEIKRTVAAPSVFKASGA	1188
BPx-92	QSVLTQPPSVSAAPGQTVTISCSGSTSNIGNNYVSWYEQLPGTAPKL LIYDNNRRPSGIPDRFSGSKSGTSAALGITGLQTGDEANYYCGTWDS SLSAWVFGGGTKLTVLGQPKAAPSVTLFPPSSKASGA	1189
BP12b-1	QSVLTQPPSASGTPGQRVTISCSGSSSNIRSNTVNWYQQLPGTAPKL LIYSNNQRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYCAAWDD SLNGWVFGGGTKLTVLGQPKAAPSVTLFPPSSKASGA	1190
BPx-93	NFMLTQPHSVSGSPGKTVTISCTRSSGSISSKYVQWYQQRPGSSPTT VMYEDKQRPSGVPARFSGSVDSSSNSATLTISGLKTEDEADYYCQS	1191

	YDNTNVVFGGGTKLTVLGQPKAAPSVTLFPPSSKASGA	
BPx-94	EVVLTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYMGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPFTFGPGTKVDIKRTVAAPSVFKASGA	1192
BPx-95	NFMLTQPHSVSGSPGKTVTISCTGSNGAIASNYVQWYQQRPGGAPVTLIYEDNHRPPGVPDRFSGSIDTSSNSASLTISGLKTEDEADYYCQSYDSVYNWVFGGGTKLTVLGQPKAAPSVTLFPPSSKASGA	1193
BPx-96	QSALTQPASVSGSPGQSITISCSGTSSDVGVYESVSWYQHHPGEAPKLMIYDVTKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYSTSSTFEVFGGGTRLTVLSQPKAAPSVTLFPPSSKASGA	1194
BP6b-9	DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPWTFGQGTKVQIKRTVAAPSVFKASGA	1195
BPx-97	DIQMTQSPSTLSASVGDRVTITCRASQSISRWLAWYQQKPGEAPKLLIYKASTLEGGVPSRFSGSGSGTEFTLTISSLQPEDSATYYCLQDYTTPYTFGQGTKLEIKRTVAAPSVFKASGA	1196
BPx-98	QSVLTQPPSTSGTPGQRVTISCSGSSSNIGSNTVDWYQQLPGTAPNLLIHSNNRRPSGVPDRFSGSKSATSASLAISGLQSEDEADYYCEAWDDSLSAVVFGGGTRVTVLGQPKAAPSVTLFPPSSKASGA	1197
BPx-99	DIVMTQTPDSLAVSLGERATISCKSSQSILYDSNLKNYLAWYQHKPGHPPKLLISWASTRESGVPDRFSGSGSDTDFTLTISSLQAEDVAVYSCQQFYTTPYTFGQGTKLEIKRTVAAPSVFKASGA	1198
BP6b-7	NFMLTQPHSVSESPGRTVTIPCSGRGGSIASDSVQWYQQRPGSAPTTIIYEDNQRPSGVPDRFSGSVDSSSNSASLTISGLRTEDEADYYCQSYDASSLWVFGGKTKLTVLGQPKAAPSVTLFPPSSKASGA	1199
BPx-100	QSALTQPPSASGSPGQSVTISCTGTSRDVGRYNYVSWYQQHPGKAPKLMISEVSKRPSGVPDCFSGSKSGNTASLTISGLQAEDEADYYCCSYSGGYNWVFGGGTKLTVLGQPKAAPSVTLFPPSSKASGA	1200
BP6b-8	QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYSNNQRPSGVPDRFSGSKSGTSATLDITGLQTGDEADYHCQSYDSSLSDSVVFGGGTKLTVLGQPKAAPSVTLFPPSSKASGA	1201
BPx-101	EVVLTQSPDSLAVSLGERATINCKSSQSILSNSNNKNYLTWYQQKPGQPPQLIISWASTRESGVPDRFSGSGSGTDFTLTINSLQAEDVAVYYCQQYYSTPLTFGGGTKVEIKRTVAAPSVFKASGA	1202
BPx-102	DIVMTQSPPSLPVAPGEPASISCRSSQSLLHSDGKNYVDWYLQKPGQSPQLLIFLGSKRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYFCMQGTRWPYTFGQGTKLEIKRTVAAPSVFKASGA	1203
BPx-103	NFMLTQPHSVSESPGKTVTISCTGTGDSIASNYVQWYQQRPGSAPTTVIYEDNQRPSGVPDRFSGSIDSSSNSASLTISGLRTEDEADYYCQSYDSVYNWIFGGGTRLTVLGQPKAAPSVTLFPPSSKASGA	1204
BPx-104	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNYVSWYQQLPGTAPKLLIYDNNKRPSGIPDRFSGSKSGTSASLAISGLQPEDEADYYCAVWDDSLNGWVFGGGTKLTVLRQPKAAPSVTLFPPSSKASGA	1205
BPx-105	SSELTQDPSVSVSPGQTASITCSQTKLGDKYVSWYQQKPGQSPVLVIYEDDKRPSGISERFSGSNSGNTATLTISGTQAVDEADYYCQVYDSSTVVFGGGTKLTVLGQPKAAPSVTLFPPSSKASGA	1206
BPx-106	DIQMTQSPSTLSASVGDRVTITCRASQSISRRLAWYQQKPGKAPKLLISGASNLEFGVPATFSGTGSGTEFTLTISSLQPDDFATYYCQQYESYQPPTFGGGTKVEMKRTVAAPSVFKASGA	1207

BP5b-9	DIQMTQSPSSVSASVGDRVTITCRASQGISNWLAWYQQKPGKAPKL LIYGASSLQSGVPSRFSGSGSGTDFTLTISSLQFEDFATYYCQQSQSTP VTFGQGTRLEIKRTVAAPSVFKASGA	1208
BPx-107	EIVMTQSPATLSLSPGDRAALSCRASHSVGSHVDWFQQKPGQAPRL LIYDASNRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQRSN WPRALSFGGGTKVEIKRTVAAPSVFKASGP	1209
BPx-108	QSALTQPASVSGSPGQSITISCTGTSSDVGAYNHVSWYQQYPGKAP KLMIYDVSNRPSGVSDRFSGSKSDNTASLTISGLQAEDEADYYCSSY TSSNTWVFGGGTKLTVLGQPKAAPSVTLFPPSSKASGA	1210
BPx-109	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKP GQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYY CQQYYSTPYTFGQGTKLEIKRTVAAPSVFKASGA	1211
BP22b-1	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSDNKNYLAWYQQKP GQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYY CQQYYSTPSFGPGTKVDIKRTVAAPSVFKASGA	1212
BPx-110	NFMLTQPHSVSESPGKTVTISCTRSSGSIASNYVQWYQQRPGSSPTT VIYEDNQRPSGVPARFSGSIDISSNSASLTISGLLTEDEADYYCQSYN TSNLVFGTGTKVTVLRQPKANPTVTLFPPSSKASGA	1213
BP6b-12	DIQMTQSPSSVFASVGDRVTITCRASQDISTWLAWYQQKPGKGPKL LIYGASSLQSGVPSRFSGSGSGTDFTLTISSLQPDDFATYYCQQYQES PWTFGQGTKVEIKRTVAAPSVFKASGA	1214
BPx-111	QSALTQPPSASGSRGQSVSISCSGSRSDIGYYNYVSWYQQHPGKAPK LIIFDVNKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTS SSTWVFGGGTKLTVLGQPKAAPSVTLFPPSSKASGA	1215
BPx-112	QPVLTQPPSVSVAPGKTARITCGGNNIGSKSVHWYQQKPGQAPVLV VYDDSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWESS SDEWDTTSDQWVFGGGTKVTVLGQPKAAPSVTLFPPSSKASGA	1216
BPx-113	NFMLTQPHSVSESPGKTVTLSCTGSGGSIARNYVQWYQQRPGSAPS AVIYEDDRRPSGVPHRFSGSIDTSSNSATLTISGLKTEDEADYYCQSY DSAHHWVFGGGTKLTVLSQPKAAPSVTLFPPSSKASGA	1217
BP10b-1	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGDNYVSWYQQLPGTAPKL LIYDNNKRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDD RLSGVVFGGGTKLTVLSQPKAAPSVTLFPPSSKASGA	1218
BPx-114	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKP GQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYF CQQYYGIPTFGGGTKVEIKRTVAAPSVFKASGA	1219
BP6a-3	SSELTQPSVSVSPGQTATITCSGDKLGDKYASWYQQKPGQSPVLVIY QDTKRPSGIPARFSGSNSGNTATLTISGTQAMDEAAYYCQAWDSTT VVFGGGTKLTVLGQPKAAPSVTLFPPSS	1664

[00311] Recombinant GDF-modulating antibodies of the disclosure may comprise or be developed using any of the CDR-L sequences (CDR-L1, CDR-L2 and/or CDR-L3) listed in Table 17. Some recombinant GDF-modulating antibodies of the disclosure may comprise or be developed using CDR-L sequences that comprise at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 99.5% or at least about

99.9% sequence identity to any of the CDR-L sequences listed in Table 17. Recombinant GDF-modulating antibodies may, in some cases, comprise CDR-L domains presented, but with different combinations of CDRs from other clones listed. In some cases, such antibodies may interact with one or more of the recombinant proteins listed in Table 4, 9 or 10.

Table 17. CDR-L domains

CDR Region	Clone ID	CDR amino acid sequence	SEQ ID NO
CDR-L1	BP6a-16	DKLGDKY	1220
CDR-L1	BP6a-19	QSISRW	1221
CDR-L1	BP3a-3	QSVSSY	1222
CDR-L1	BP6a-1	QSLVYSDGNTY	1223
CDR-L1	BP18b-1	QTLLHSNGFNY	1224
CDR-L1	BP19b-1	SSDVGGYNY	1225
CDR-L1	BP6b-4	SSDIGGYDY	1226
CDR-L1	BP6a-8	SSNIGNNY	1227
CDR-L1	BP13a-1	DSLRSYF	1228
CDR-L1	BP6a-23	DDLGDKF	1229
CDR-L1	BP5a-1	SSNIGSNT	1230
CDR-L1	BP6a-11	SSNIGSST	1231
CDR-L1	BP5b-4	QGISSY	1232
CDR-L1	BP11a-1	SSDVGYYDH	1233
CDR-L1	BP6a-14	QTVNSND	1234
CDR-L1	BP6a-27	QSINRH	1235
CDR-L1	BP6a-13	QSISSW	1236
CDR-L1	BP4a-1	SSDISIYNY	1237
CDR-L1	BP6a-6	QSVSSGY	1238
CDR-L1	BP19b-2	RSDIGYYNY	1239
CDR-L1	BP6a-4	SSDVGDYNY	1240
CDR-L1	BP19a-1	MSNIGKNT	1241
CDR-L1	BP6a-7	SSDIGGYNY	1242
CDR-L1	BP6b-3	NKLGDKF	1243
CDR-L1	BP18b-2	QSVVYRDGNTY	1244
CDR-L1	BPx-1	QSLLHSDGNNY	1245
CDR-L1	BP21b-1	SGSIASNY	1246
CDR-L1	BPx-2	HSISRF	1247
CDR-L1	BPx-3	QSISSY	1248
CDR-L1	BP15a-1	QSVSSSY	1249
CDR-L1	BPx-4	DQLGDKF	1250
CDR-L1	BP5a-3	DSLKKYY	1251
CDR-L1	BP14a-1	QSLVHSDGNTY	1252
CDR-L1	BP18b-3	QNLLYSSNNKNY	1253
CDR-L1	BP6a-9	DNLGDKY	1254
CDR-L1	BPx-5	NSNLGRNS	1255
CDR-L1	BP5a-2	SSNIGSNY	1256
CDR-L1	BP6a-15	QSVSSW	1257

CDR-L1	BP6a-21	HDISNY	1258
CDR-L1	BP6a-22	QDISSW	1259
CDR-L1	BP19a-2	SGRIVSTY	1260
CDR-L1	BPx-6	SSDVGGYDF	1261
CDR-L1	BP6a-18	QSISTY	1262
CDR-L1	BP5b-2	QNVGSY	1263
CDR-L1	BP2a-1	QSVSSNY	1264
CDR-L1	BP18a-2	QSLLHSNGYNY	1265
CDR-L1	BPx-8	SNDVGGYKF	1266
CDR-L1	BPx-9	SSDIGSYNY	1267
CDR-L1	BPx-10	QGLVYSDGNTY	1268
CDR-L1	BPx-12	QSLVHGNGITY	1269
CDR-L1	BPx-18	RSNNGSNY	1270
CDR-L1	BPx-19	QSLVYSDGKTY	1271
CDR-L1	BPx-20	QSVNSSY	1272
CDR-L1	BPx-22	SSDLGGYNY	1273
CDR-L1	BPx-27	QSLVYSNGNTY	1274
CDR-L1	BPx-29	QSLLHKNGNNY	1275
CDR-L1	BPx-30	QSITSNY	1276
CDR-L1	BPx-32	ESLLHSIGYNY	1277
CDR-L1	BPx-33	SSDVGTYNY	1278
CDR-L1	BPx-36	QGISSH	1279
CDR-L1	BPx-37	QTLLHANGFNY	1280
CDR-L1	BPx-38	QSVNRN	1281
CDR-L1	BPx-40	SGTIVSTY	1282
CDR-L1	BPx-41	SSDVETYNL	1283
CDR-L1	BPx-42	QSFSSN	1284
CDR-L1	BPx-43	SSNVGAGYD	1285
CDR-L1	BP16b-1	TSNIGAGYD	1286
CDR-L1	BPx-45	NSNIGSNH	1287
CDR-L1	BPx-47	SSNIGTNA	1288
CDR-L1	BPx-51	SSNIGSKT	1289
CDR-L1	BPx-52	QSIGSW	1290
CDR-L1	BPx-53	LNIGSKS	1291
CDR-L1	BPx-55	DSLRTYY	1292
CDR-L1	BPx-57	QSVLYSFSNKNY	1293
CDR-L1	BPx-58	NNIGSKS	1294
CDR-L1	BPx-59	QSLLHSIGYNY	1295
CDR-L1	BPx-61	SSDVGSYNY	1296
CDR-L1	BPx-62	QSVLYSSNNKNY	1297
CDR-L1	BPx-63	SSNIGNQY	1298
CDR-L1	BP6b-5	GSNIGRGYD	1299
CDR-L1	BPx-66	SGRIASTY	1300
CDR-L1	BPx-67	SGDVETYNL	1301
CDR-L1	BPx-68	SSNIGAGYD	1302
CDR-L1	BPx-70	HKLGHKY	1303
CDR-L1	BPx-74	QYITSGY	1304
CDR-L1	BP8b-1	ESISNNY	1305

CDR-L1	BPx-75	QSISIF	1306
CDR-L1	BPx-77	SSDVGAYNY	1307
CDR-L1	BPx-79	SSDIGTYNY	1308
CDR-L1	BPx-80	QDIANH	1309
CDR-L1	BPx-81	SGRIASNY	1310
CDR-L1	BPx-83	QSLVYSDGNTF	1311
CDR-L1	BPx-84	SSNIGNNA	1312
CDR-L1	BPx-115	QNILYSSTNKNY	1313
CDR-L1	BPx-116	SSDITIYNY	1314
CDR-L2	BP6a-16	QDS	1315
CDR-L2	BP6a-19	GAS	1316
CDR-L2	BP6a-1	KVS	1317
CDR-L2	BP18b-1	LGS	1318
CDR-L2	BP19b-1	DVS	1319
CDR-L2	BP6a-8	DNN	1320
CDR-L2	BP13a-1	GKN	1321
CDR-L2	BP5b-3	EVS	1322
CDR-L2	BP5a-1	SNN	1323
CDR-L2	BP6a-11	SIN	1324
CDR-L2	BP5b-4	AAS	1325
CDR-L2	BP11a-1	DVT	1326
CDR-L2	BP6a-14	DAS	1327
CDR-L2	BP6a-13	KAS	1328
CDR-L2	BP4a-1	DVN	1329
CDR-L2	BP6a-6	GGS	1330
CDR-L2	BP6b-3	EDR	1331
CDR-L2	BP21b-1	EDN	1332
CDR-L2	BPx-2	STS	1333
CDR-L2	BP6b-1	QDT	1334
CDR-L2	BP6a-5	SDN	1335
CDR-L2	BP6a-10	QDR	1336
CDR-L2	BP18b-3	WAS	1337
CDR-L2	BP6a-9	RDT	1338
CDR-L2	BPx-5	SNH	1339
CDR-L2	BP5a-2	RNN	1340
CDR-L2	BP6a-17	RDY	1341
CDR-L2	BP19a-2	DDV	1342
CDR-L2	BPx-6	EVN	1343
CDR-L2	BP6a-18	DTS	1344
CDR-L2	BPx-8	GVT	1345
CDR-L2	BPx-20	RTS	1346
CDR-L2	BPx-24	EHN	1347
CDR-L2	BPx-29	MAS	1348
CDR-L2	BPx-36	ATS	1349
CDR-L2	BPx-43	GNT	1350
CDR-L2	BPx-48	RNS	1351
CDR-L2	BPx-50	INN	1352
CDR-L2	BPx-51	NNN	1353

CDR-L2	BPx-53	YDS	1354
CDR-L2	BPx-65	TNN	1355
CDR-L2	BPx-66	EDD	1356
CDR-L2	BPx-68	GNS	1357
CDR-L2	BPx-69	LAS	1358
CDR-L2	BPx-70	QDN	1359
CDR-L2	BP6b-6	QDI	1360
CDR-L2	BPx-79	DVV	1361
CDR-L2	BPx-80	DAT	1362
CDR-L2	BPx-81	EDS	1363
CDR-L3	BP6a-16	QAWDSSTVV	1364
CDR-L3	BP6a-19	QQTYTTPWT	1365
CDR-L3	BP3a-3	QQYYTTPFT	1366
CDR-L3	BP6a-1	MQSTRWPWV	1367
CDR-L3	BP18b-1	MQALQTPFT	1368
CDR-L3	BP19b-1	SSYTSSSTFVV	1369
CDR-L3	BP6b-4	SSFTSSSTLV	1370
CDR-L3	BP6a-8	GTWDSSLSAV	1371
CDR-L3	BP13a-1	DSRHSSGNYVI	1372
CDR-L3	BP5b-3	SSYAGSNSWV	1373
CDR-L3	BP6a-23	QAWDGTKVV	1374
CDR-L3	BP5a-1	ATWDDSLTGVV	1375
CDR-L3	BP6a-11	AAWDDSLNGWV	1376
CDR-L3	BP5b-4	QQSYSTPLT	1377
CDR-L3	BP18a-1	MQGTHWPYT	1378
CDR-L3	BP11a-1	SSYAGSYTWV	1379
CDR-L3	BP6a-14	QQYHGSQT	1380
CDR-L3	BP6a-27	QQSYSTPYT	1381
CDR-L3	BP6a-13	QQSYSTPWT	1382
CDR-L3	BP4a-1	SSYTYSNTLL	1383
CDR-L3	BP1a-1	SSYTSSSTLV	1384
CDR-L3	BP6a-6	QQRSIWPLT	1385
CDR-L3	BP19b-2	SSSVGSNNLV	1386
CDR-L3	BP6a-4	SSYTSSTTWV	1387
CDR-L3	BP6a-7	NSWTRSNNYI	1388
CDR-L3	BP5b-5	MQGTHWPLT	1389
CDR-L3	BP6b-3	QTWDSRTVV	1390
CDR-L3	BP18b-2	MQGSSWPYT	1391
CDR-L3	BPx-1	MQGLHTPTT	1392
CDR-L3	BP21b-1	QSYDHMYNWV	1393
CDR-L3	BP6a-2	AAWDDDLNGPV	1394
CDR-L3	BP6b-1	QAWDSTTVV	1395
CDR-L3	BPx-3	QQYYSSPWT	1396
CDR-L3	BP6a-5	AAWDDSLNGV	1397
CDR-L3	BP6a-10	AAWDDSLSGRV	1398
CDR-L3	BP15a-1	QQYGSSPYT	1399
CDR-L3	BP6a-26	QQSGSSPWT	1400
CDR-L3	BP6a-12	QQYYSTPYT	1401

CDR-L3	BP5a-4	GTWDSSLSAGV	1402
CDR-L3	BP5b-1	NSYTSSRTVV	1403
CDR-L3	BPx-4	QTWDSSAVV	1404
CDR-L3	BP5a-3	QAWDSSTAV	1405
CDR-L3	BP14a-1	MQGTHWPRLT	1406
CDR-L3	BP3a-1	QQYQSYPIT	1407
CDR-L3	BP18b-3	HQYYSSPYT	1408
CDR-L3	BP6a-9	QAWDSSAGGV	1409
CDR-L3	BP6a-25	MQGTHWPPT	1410
CDR-L3	BP5a-2	AAWDDSLSGWV	1411
CDR-L3	BP5a-5	SSYTTSSTLV	1412
CDR-L3	BP6a-17	QVWDMSSDPLV	1413
CDR-L3	BP3a-2	SSYTSSSTYV	1414
CDR-L3	BP6a-22	QQANSFPQT	1415
CDR-L3	BP19a-2	QSYNTSNLV	1416
CDR-L3	BPx-6	CAYAGSNILL	1417
CDR-L3	BP6a-18	QQSFITPYT	1418
CDR-L3	BP16a-1	SSYTSNYTLV	1419
CDR-L3	BP19a-3	QHRGSWPHT	1420
CDR-L3	BP5b-2	QQYGSSPLFT	1421
CDR-L3	BP2a-1	QQYGTSPLT	1422
CDR-L3	BP18a-2	MQATHWPPRLT	1423
CDR-L3	BPx-7	SSYTTSSTVV	1424
CDR-L3	BPx-8	TSYTRSTTPI	1425
CDR-L3	BPx-9	CSYSGDHTLPFI	1426
CDR-L3	BPx-10	MQATHWPWT	1427
CDR-L3	BPx-11	AAWDDSLSGPV	1428
CDR-L3	BPx-12	MQALQTPS	1429
CDR-L3	BPx-13	SSYTSSSTVV	1430
CDR-L3	BPx-14	SSYTAGGNWV	1431
CDR-L3	BPx-15	MQGLQTPPT	1432
CDR-L3	BPx-16	MQGTHWPWT	1433
CDR-L3	BPx-17	SSYTSSSTWV	1434
CDR-L3	BP1b-1	SAYAGRNNMV	1435
CDR-L3	BPx-18	AAWDRSLNAWV	1436
CDR-L3	BPx-19	MQGTHWPHT	1437
CDR-L3	BPx-20	MQGTYWPYT	1438
CDR-L3	BPx-21	SSYTSSSTLDVV	1439
CDR-L3	BPx-22	SSYTSSSTPWV	1440
CDR-L3	BPx-23	QSYDGSDVV	1441
CDR-L3	BPx-24	QSYDDNNVV	1442
CDR-L3	BPx-25	SSYAGNNNLI	1443
CDR-L3	BPx-26	ASYTSSTSVV	1444
CDR-L3	BPx-27	MQGSQWPPT	1445
CDR-L3	BPx-28	MQGTHWPKT	1446
CDR-L3	BPx-29	MQALQTPPT	1447
CDR-L3	BPx-30	QQYGNSPRT	1448
CDR-L3	BPx-32	MQALQTSIT	1449

CDR-L3	BPx-33	SSYTSTSTPYV	1450
CDR-L3	BPx-34	SSYRSSSTVV	1451
CDR-L3	BPx-36	QQFDDLPVT	1452
CDR-L3	BPx-37	MQTLQTPPWT	1453
CDR-L3	BPx-38	QQYNNWLS	1454
CDR-L3	BPx-40	QSYDSSNRKV	1455
CDR-L3	BPx-41	SSYADSIAFVI	1456
CDR-L3	BPx-42	QQYGSSPRT	1457
CDR-L3	BPx-43	ATWDDSLNGPV	1458
CDR-L3	BPx-45	AAWDDNVNGWV	1459
CDR-L3	BPx-47	AAWDDSLNGVV	1460
CDR-L3	BPx-49	QQYYSTPLT	1461
CDR-L3	BPx-51	AAWDDSLSGPM	1462
CDR-L3	BPx-53	QVSDSDTDHPV	1463
CDR-L3	BPx-54	MQALQTPYT	1464
CDR-L3	BPx-55	DSRDSSTSQWV	1465
CDR-L3	BPx-56	ATWDDSLNGWV	1466
CDR-L3	BPx-57	QQYYLLPIT	1467
CDR-L3	BPx-58	QVWDSSSDHVV	1468
CDR-L3	BPx-59	MQALQTIFT	1469
CDR-L3	BPx-60	ASWDDSVHGWV	1470
CDR-L3	BPx-61	SSDTSSSTLV	1471
CDR-L3	BPx-62	MQAAQLPLT	1472
CDR-L3	BPx-63	GTWDTSLSGFL	1473
CDR-L3	BPx-65	AAWDDSLNGPV	1474
CDR-L3	BPx-66	QSYDGDNAV	1475
CDR-L3	BPx-67	SSYAGSGTLRL	1476
CDR-L3	BPx-68	ATWDDSLRGDVV	1477
CDR-L3	BPx-69	MQALQTPAT	1478
CDR-L3	BPx-70	QAWDSSSTAYV	1479
CDR-L3	BPx-71	SSYVGGNIWV	1480
CDR-L3	BPx-74	QQYGSSPTYT	1481
CDR-L3	BP8b-1	QQYGYSPT	1482
CDR-L3	BPx-75	QQSYSMLSWT	1483
CDR-L3	BPx-77	GSYTTSSTLV	1484
CDR-L3	BP6b-6	QAWDSSSWV	1485
CDR-L3	BPx-78	MQGTHWSYT	1486
CDR-L3	BPx-79	SSYAGSSTVV	1487
CDR-L3	BPx-80	QQFDELPLT	1488
CDR-L3	BPx-81	QSYDSRVYV	1489
CDR-L3	BPx-82	NSRDSSGNPI	1490
CDR-L3	BPx-83	MQGTHWPFT	1491
CDR-L3	BPx-84	GTWDSSLSAWV	1492
CDR-L3	BPx-115	QQYYSTPVT	1493
CDR-L3	BPx-116	SSYTYSNTLV	1494
CDR-L3	BPx-117	MQARQTPVT	1495
CDR-L3	BPx-118	QSYDSSILVV	1496
CDR-L1	BP20b-1	QSISSY	1497

CDR-L1	BPx-89	QSISSW	1498
CDR-L1	BPx-105	KLGDKY	1499
CDR-L1	BPx-99	QSILYDSNLKNY	1500
CDR-L1	BPx-93	SGSISSKY	1501
CDR-L1	BPx-92	TSNIGNNY	1502
CDR-L1	BP6b-7	GGSIASDS	1503
CDR-L1	BPx-100	SRDVGRYNY	1504
CDR-L1	BPx-95	NGAIASNY	1505
CDR-L1	BPx-111	RSDIGYYNY	1506
CDR-L1	BP6b-11	SLKKYY	1507
CDR-L1	BP18b-4	QSVLYSSNNKNY	1508
CDR-L1	BP6b-10	QSLLHTNGYNF	1509
CDR-L1	BP16b-2	SGSIASYY	1510
CDR-L1	BP18b-5	QSLVHSNGNTY	1511
CDR-L1	BP7b-1	QSISRH	1512
CDR-L1	BP5b-7	QGLVYSDGNTF	1513
CDR-L1	BPx-85	QNIINY	1514
CDR-L1	BP18b-6	QTLLHSNGFNY	1515
CDR-L1	BPx-86	QSLVYSDGNTY	1516
CDR-L1	BP19b-3	SNDIGRYDY	1517
CDR-L1	BPx-88	NLRSKY	1518
CDR-L1	BP18b-7	QGLVYSDGNTY	1519
CDR-L1	BP17b-1	SSDVGGYNY	1520
CDR-L1	BP16b-3	QSVSSY	1521
CDR-L1	BPx-90	ELGDKY	1522
CDR-L1	BP5b-8	NIGNKS	1523
CDR-L1	BP9b-1	SSNIGNNA	1524
CDR-L1	BPx-91	QSLLHSNGFNY	1525
CDR-L1	BP12b-1	SSNIRSNT	1526
CDR-L1	BP10b-1	SSNIGDNY	1527
CDR-L1	BPx-94	QSLLHSNGYNY	1528
CDR-L1	BPx-96	SSDVGVYES	1529
CDR-L1	BP6b-9	QGISSW	1530
CDR-L1	BPx-97	QSISRW	1531
CDR-L1	BPx-98	SSNIGSNT	1532
CDR-L1	BPx-101	QSILSNSNNKNY	1533
CDR-L1	BPx-102	QSLLHSDGKNY	1534
CDR-L1	BPx-103	GDSIASNY	1535
CDR-L1	BPx-104	SSNIGNNY	1536
CDR-L1	BPx-106	QSISRR	1537
CDR-L1	BP5b-9	QGISNW	1538
CDR-L1	BPx-107	HSVGSH	1539
CDR-L1	BPx-108	SSDVGAYNH	1540
CDR-L1	BP22b-1	QSVLYSSDNKNY	1541
CDR-L1	BPx-110	SGSIASNY	1542
CDR-L1	BP6b-12	QDISTW	1543
CDR-L1	BPx-112	NIGSKS	1544
CDR-L1	BPx-113	GGSIARNY	1545

CDR-L2	BP20b-1	AAS	1546
CDR-L2	BPx-89	KAS	1547
CDR-L2	BPx-105	EDD	1548
CDR-L2	BPx-99	WAS	1549
CDR-L2	BPx-93	EDK	1550
CDR-L2	BPx-92	DNN	1551
CDR-L2	BP6b-7	EDN	1552
CDR-L2	BPx-100	EVS	1553
CDR-L2	BPx-111	DVN	1554
CDR-L2	BP6b-2	QDN	1555
CDR-L2	BP6b-11	GRN	1556
CDR-L2	BP6b-10	LGS	1557
CDR-L2	BP5b-7	MVS	1558
CDR-L2	BPx-85	TAS	1559
CDR-L2	BPx-86	KVS	1560
CDR-L2	BP19b-3	AVK	1561
CDR-L2	BPx-88	QDD	1562
CDR-L2	BP17b-1	DVS	1563
CDR-L2	BP16b-3	DAS	1564
CDR-L2	BP5b-8	YDI	1565
CDR-L2	BP16b-4	DVT	1566
CDR-L2	BP9b-1	SSN	1567
CDR-L2	BP12b-1	SNN	1568
CDR-L2	BPx-94	MGS	1569
CDR-L2	BPx-106	GAS	1570
CDR-L2	BPx-112	DDS	1571
CDR-L3	BP20b-1	QQTYIYPRT	1572
CDR-L3	BPx-89	QQSYSTPFT	1573
CDR-L3	BPx-105	QVYDSSTVV	1574
CDR-L3	BPx-99	QQFYTTPYT	1575
CDR-L3	BPx-93	QSYDNTNVV	1576
CDR-L3	BPx-92	GTWDSSLSAWV	1577
CDR-L3	BP6b-7	QSYDASSLWV	1578
CDR-L3	BPx-100	CSYSGGYNWV	1579
CDR-L3	BPx-95	QSYDSVYNWV	1580
CDR-L3	BPx-111	SSYTSSSTWV	1581
CDR-L3	BP6b-2	QAWDSSTVM	1582
CDR-L3	BP6b-11	NSRDSRGNLLV	1583
CDR-L3	BP18b-4	QQYYTIPHT	1584
CDR-L3	BP6b-10	MQALHTPMYT	1585
CDR-L3	BP16b-2	QSYDSSNRWV	1586
CDR-L3	BP18b-5	MQGTHWPYT	1587
CDR-L3	BP7b-1	QQSASTPLT	1588
CDR-L3	BP5b-7	MQGTHWPWT	1589
CDR-L3	BPx-85	QHSFSSPYT	1590
CDR-L3	BP18b-6	MQALQIPRT	1591
CDR-L3	BPx-86	MQGSHWPLT	1592
CDR-L3	BP19b-3	GSYTRSSTAR	1593

CDR-L3	BPx-87	QAWDSITAV	1594
CDR-L3	BPx-88	QTWDGNHVV	1595
CDR-L3	BP18b-7	MQGTQWPYT	1596
CDR-L3	BP17b-1	SSYTSSSTLV	1597
CDR-L3	BP16b-3	QQRSGWPPKVT	1598
CDR-L3	BPx-90	QAWDSSTVV	1599
CDR-L3	BP5b-8	QVWDSNSDHVV	1600
CDR-L3	BP16b-4	SSYTSSSTVV	1601
CDR-L3	BP9b-1	ATWDDSLNGW	1602
CDR-L3	BPx-91	MQGLQTPYT	1603
CDR-L3	BP12b-1	AAWDDSLNGWV	1604
CDR-L3	BP10b-1	GTWDDRLSGVV	1605
CDR-L3	BPx-94	MQALQTPFT	1606
CDR-L3	BPx-96	SSYSTSSTFEV	1607
CDR-L3	BP6b-9	QQSYSTPWT	1608
CDR-L3	BPx-97	LQDYTTPYT	1609
CDR-L3	BPx-98	EAWDDSLSAVV	1610
CDR-L3	BP6b-8	QSYDSSLSDSVV	1611
CDR-L3	BPx-101	QQYYSTPLT	1612
CDR-L3	BPx-102	MQGTRWPYT	1613
CDR-L3	BPx-103	QSYDSVYNWI	1614
CDR-L3	BPx-104	AVWDDSLNGWV	1615
CDR-L3	BPx-106	QQYESYQPPT	1616
CDR-L3	BP5b-9	QQSQSTPVT	1617
CDR-L3	BPx-107	QQRSNWPRALS	1618
CDR-L3	BPx-108	SSYTSSNTWV	1619
CDR-L3	BPx-109	QQYYSTPYT	1620
CDR-L3	BP22b-1	QQYYSTPS	1621
CDR-L3	BPx-110	QSYNTSNLV	1622
CDR-L3	BP6b-12	QQYQESPWT	1623
CDR-L3	BPx-112	QVWESSSDEWDTTSDQWV	1624
CDR-L3	BPx-114	QQYYGIPT	1625
CDR-L3	BPx-113	QSYDSAHHWV	1626
CDR-L3	BP19a-1	AAWDDSLNGWV	1655
CDR-L3	BP6a-15	QQSYSTPWT	1656
CDR-L3	BP6a-21	QQSYSTPYT	1657
CDR-L3	BP6a-20	QQSYSTPYT	1658
CDR-L3	BP6a-24	QAWDGTKVV	1659
CDR-L3	BP6a-3	QAWDSTTVV	1660
CDR-L3	BP5b-6	SYTSSSTWV	1661
CDR-L3	BP16b-1	AAWDDSLNGWV	1662
CDR-L3	BP8b-1;	GTWDTSLSGFL	1669
CDR-L3	BP6b-5	GTWDTSLSGFL	1670

GDF-11 modulatory antibodies

[00312] GDF-8 and GDF-11 share considerable homology. While the prodomains only share 48% homology, GDF-8 and GDF-11 growth factor domains share 90% homology (60%

homology when prodomains and growth factors are taken together). Given the high degree of sequence similarity, it is not surprising that GDF-11 and 8 bind and signal through the same receptors consisting of a Type I receptor (ALK4/5) in association with a type II receptor (ACTRIIA/B). The high degree of conservation in the mature growth factors has made it challenging to identify reagents and monoclonal antibodies that can differentiate between mature GDF-11 and 8. Consequently, there are no therapies in clinical trials today that are specific for GDF-11.

[00313] In some embodiments, the present disclosure provides GDF-11-modulatory antibodies as well as methods of developing and identifying such antibodies. In some cases, GDF-modulatory antibodies specifically recognize the prodomain of GDF-11, but do not cross-react with the GDF-8 prodomain. Such antibodies may be functionally assessed to determine if they block or activate the release of the GDF-11 mature growth factor and can be further characterized in animal models to evaluate the effects of modulating specific growth factor levels in disease-relevant models.

[00314] Like other members of the TGF-β superfamily, GDF-11 and 8 are both initially expressed as inactive precursor polypeptides (termed proGDF-8 and proGDF-11). For GDF-11 and 8, activation and release of the mature growth factor is accomplished by discrete protease cleavage events. The first cleavage step of proGDF-8 and proGDF-11 is carried out by a proprotein convertase, which cuts at a conserved RXXR site between the prodomain and mature growth factor. This cleavage produces a latent complex, in which the mature growth factor is shielded from binding to its receptors by the prodomain (see FIG. 9). Activation and release of the mature, active GDF-11 growth factor is accomplished after cleavage by an additional protease from the BMP/Tolloid family.

[00315] In contrast to myostatin that has a well-defined role as a negative regulator of skeletal muscle mass, much less is known about the physiological roles of GDF-11. During the last year, several groups have revealed exciting new biology for GDF-11. Using parabiotic surgical techniques, blood systems of old and young mice were connected to look at the effects of circulating factors (Loffredo et al., 2013. Cell. 153:828-39). After 4 weeks of shared blood circulation, old mice had dramatically improved reversal of age-related cardiac hypertrophy. Additional studies suggested GDF-11 was the factor that was responsible for the rejuvenating effects. Subsequently, follow up studies showed that GDF-11 levels decrease with age and if systemic levels are restored, functional impairments in skeletal muscle due to the aging process can be reversed (Sinha, M. et al., 2014. Science Express. 10.1126/science.1251152, p2-6). Additional improvements in the vasculature of the

neurogenic niche were improved by the addition of GDF-11 suggesting that increasing GDF-11 levels could be beneficial in treating neurodegenerative and neurovascular diseases. (Katsimpardi, L. et al., 2014. Science Express. 10.1126/science.1251141)

[00316] Other groups have recently published convincing data that GDF-11 is a novel negative regulator of late stage erythropoiesis (Carrancio, S. et al., 2014. Br J Haematol. 165(6):870-82 and Suragani, R.N.V.S. et al. 2014. Blood. 123(25): 3864-72, the contents of each of which are herein incorporated by reference in their entirety). These studies have led to the testing of two TGF-β superfamily ligand traps, ACE-011, an ACTRIIa-Fc fusion protein, and ACE-536, an ACTRIIb-Fc fusion protein, in the clinic for the treatment of anemias such as anemia associated with cancer and β-thalassemia. Although GDF-11 was shown to be the growth factor responsible for inhibiting late-stage erythropoiesis, neither of these fusion proteins is specific for GDF-11 as they bind to multiple other members of the TGF-β superfamily.

[00317] The new data implicating GDF-11 in reversing aging contradicts what has previously been established in the literature for GDF-8 and GDF-11. Moreover, the studies implicating GDF-11 in erythropoiesis are still in very early stages. None of the current experimental approaches differentiate GDF-11 from GDF-8 leaving the question how GDF-11 can be distinguished from GDF-8 at the level of receptor binding and downstream signaling unanswered. There are no molecular tools that can differentiate among different forms of circulating GDF-11 precursor, latent and mature forms so it is unknown what the relative circulating and tissue-bound levels of GDF-11 are in the body.

[00318] In some embodiments, GDF-11-modulatory antibodies of the disclosure may target the GDF-11 prodomain, and therefore the activation mechanism of GDF-11. Such antibodies may achieve specificity and safety that cannot be obtained by currently available methods. In some cases, GDF-11 modulatory antibodies may also be useful as specific tools to interrogate the role of GDF-11 in vivo and importantly allow for the development of therapeutic antibodies that may either block or activate GDF-11 release and that may be evaluated in clinical trials.

Development of cytotoxic antibodies

[00319] In some embodiments, antibodies of the present disclosure may be capable of inducing antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and/or antibody-dependent cell phagocytosis (ADCP). ADCC is an immune mechanism whereby cells are lysed as a result of immune cell attack. Such immune

cells may include CD56+ cells, CD3- natural killer (NK) cells, monocytes and neutrophils (Strohl, W.R. Therapeutic Antibody Engineering. Woodhead Publishing, Philadelphia PA. 2012. Ch. 8, p186, the contents of which are herein incorporated by reference in their entirety).

[00320] In some cases, antibodies of the present disclosure may be engineered to comprise a given isotype depending on whether or not ADCC or ADCP is desired upon antibody binding. Such antibodies, for example, may be engineered according to any of the methods disclosed by Alderson, K.L. et al., J Biomed Biotechnol. 2011. 2011:379123). In the case of mouse antibodies, different isotypes of antibodies are more effective at promoting ADCC. IgG2a, for example, is more effective at inducing ADCC than is IgG2b. Some antibodies of the present disclosure, comprising mouse IgG2b antibodies may be reengineered to comprise IgG2a antibodies. Such reengineered antibodies may be more effective at inducing ADCC upon binding cell-associated antigens.

[00321] In some embodiments, genes encoding variable regions of antibodies developed according to methods of the present disclosure may be cloned into mammalian expression vectors encoding human Fc regions. Such Fc regions may comprise Fc regions from human IgG1κ. IgG1κ Fc regions may comprise amino acid mutations known to enhance Fc-receptor binding and antibody-dependent cell-mediated cytotoxicity ADCC.

[00322] In some cases, antibodies may be engineered to reduce ADCC. Antibodies that do not activate ADCC or that are associated with reduced levels of ADCC may be desireable for antibody embodiments of the present disclosure, in some cases due to no or limited immune-mediated clearance, allowing longer half-lives in circulation.

Antibody fragment display library screening techniques

[00323] In some embodiments, antibodies of the present disclosure may be produced and/or optimized using high throughput methods of discovery. Such methods may include any of the display techniques (e.g. display library screening techniques) disclosed in International Patent Application No. WO2014074532, the contents of which are herein incorporated by reference in their entirety. In some embodiments, synthetic antibodies may be designed, selected or optimized by screening target antigens using display technologies (e.g. phage display technologies). Phage display libraries may comprise millions to billions of phage particles, each expressing unique antibody fragments on their viral coats. Such libraries may provide richly diverse resources that may be used to select potentially hundreds of antibody fragments with diverse levels of affinity for one or more antigens of interest (McCafferty, et al., 1990.

Nature. 348:552-4; Edwards, B.M. et al., 2003. JMB. 334: 103-18; Schofield, D. et al., 2007. Genome Biol. 8, R254 and Pershad, K. et al., 2010. Protein Engineering Design and Selection. 23:279-88; the contents of each of which are herein incorporated by reference in their entirety). Often, the antibody fragments present in such libraries comprise scFv antibody fragments, comprising a fusion protein of V_H and V_L antibody domains joined by a flexible linker (e.g. a Ser/Gly-rich linker). In some cases, scFvs may contain the same sequence with the exception of unique sequences encoding variable loops of the complementarity determining regions (CDRs). In some cases, scFvs are expressed as fusion proteins, linked to viral coat proteins (e.g. the N-terminus of the viral pIII coat protein). V_L chains may be expressed separately for assembly with V_H chains in the periplasm prior to complex incorporation into viral coats.

[00324] Phage selection according to the present disclosure may include the use of the antibody display library described in Schofield, D. et al., 2007. Genome Biol. 8, R254 and Pershad, K. et al., 2010. Protein Engineering Design and Selection. 23:279-88, the contents of which are herein incorporated by reference in their entirety. This library included over 10^{10} clones and has been validated through the successful generation of antibodies to over 300 antigens, producing more than 7,500 distinct antibody clones. Further, antibody production using this library may be carried out as described in Falk, R. et al., 2012. Methods. 58: 69-78 and/or Melidoni et al., 2013. PNAS 110(44): 17802-7, the contents of each of which are herein incorporated by reference in their entirety.

[00325] For selection, target antigens may be incubated, in vitro, with phage display library particles for precipitation of positive binding partners. This process is referred to herein as "phage enrichment." In some cases, phage enrichment comprises solid-phase phage enrichment. According to such enrichment, target antigens are bound to a substrate (e.g. by passive adsorption) and contacted with one or more solutions comprising phage particles. Phage particles with affinity for such target antigens are precipitated out of solution. In some cases, phage enrichment comprises solution-phase phage enrichment where target antigens are present in a solution that is combined with phage solutions. According to such methods, target antigens may comprise detectable labels (e.g. biotin labels) to facilitate retrieval from solution and recovery of bound phage. In other embodiments, solution-phase phage enrichment may comprise the use of antigens bound to beads (e.g. streptavidin beads). In some cases, such beads may be magnetic beads to facilitate precipitation.

[00326] In some embodiments, phage enrichment may comprise solid-phase enrichment where target antigens are immobilized on solid surface. According to such methods, phage

solutions may be used to contact the solid surface for enrichment with the immobilized antigens. Solid surfaces may include any surfaces capable of retaining antigens and may include, but are not limited to dishes, plates, flasks and tubes. In some cases, immunotubes may be used wherein the inner surface of such tubes may be coated with antigens. Phage enrichment with immunotubes may be carried out by passage of phage solution through the tubes to enrich bound antigens.

[00327] After selection, bound phage may be used to infect E. coli cultures that are co-infected with helper phage, to produce an amplified output library for the next round of enrichment. This process may be repeated producing narrower and narrower clone sets. In some embodiments, rounds of enrichment are limited to improve the diversity of selected phage.

[00328] Precipitated library members may be sequenced from the bound phage to obtain cDNA encoding desired scFvs. Such sequences may be directly incorporated into antibody sequences for recombinant antibody production, or mutated and utilized for further optimization through in vitro affinity maturation.

[00329] IgG antibodies comprising one or more variable domains from selected scFvs may be synthesized for further testing and/or product development. Such antibodies may be produced by insertion of one or more segments of scFv cDNA into expression vectors suited for IgG production. Expression vectors may comprise mammalian expression vectors suitable for IgG expression in mammalian cells. Mammalian expression of IgGs may be carried out to ensure that antibodies produced comprise modifications (e.g. glycosylation) characteristic of mammalian proteins and/or to ensure that antibody preparations lack endotoxin and/or other contaminants that may be present in protein preparations from bacterial expression systems.

[00330] In some embodiments, scFvs developed according to the disclosure may be expressed as scFv-Fc fusion proteins, comprising an antibody Fc domain. Such scFvs may be useful for further screening and analysis of scFv binding and affinity.

[00331] In some cases phage display screening may be used to generate broadly diverse panels of antibodies. Such diversity may be measured by diversity of antibody sequences and/or diversity of epitopes targeted.

[00332] Affinity binding estimates may be made using cross blocking experiments to bin antibodies. In some cases, affinity analysis instruments may be used. Such instruments may include, but are not limited surface plasmon resonance instrumentation, including, but not limited to Octet® (ForteBio, Menlo Park, CA).

[00333] In some cases, epitope binning may be carried out to identify groups of antibodies binding distinct epitopes present on the same antigen. Such binning may be informed by data obtained from affinity analysis using cross blocking experiments and/or affinity analysis instrumentation.

Affinity maturation techniques

[00334] Affinity maturation techniques of the present disclosure may comprise any of those disclosed in International Patent Application No. WO2014074532, the contents of which are herein incorporated by reference in their entirety. After antibody fragments capable of binding target antigens are identified (e.g. through the use of phage display libraries as described above), high affinity mutants may be derived from these through the process of affinity maturation. Affinity maturation technology is used to identify sequences encoding CDRs that have the highest affinity for target antigens. Using such technologies, select CDR sequences (e.g. ones that have been isolated or produced according to processes described herein) may be mutated randomly as a whole or at specific residues to create millions to billions of variants. Such variants may be subjected to repeated rounds of affinity screening (e.g. display library screening) for their ability to bind target antigens. Such repeated rounds of selection, mutation and expression may be carried out to identify antibody fragment sequences with the highest affinity for target antigens. Such sequences may be directly incorporated into antibody sequences for recombinant antibody production.

Antibody characterization

[00335] Compounds and/or compositions of the present disclosure comprising antibodies may act to decrease local concentration of one or more GPC through removal by phagocytosis, pinocytosis, or inhibiting assembly in the extracellular matrix and/or cellular matrix. Introduction of compounds and/or compositions of the present disclosure may lead to the removal of 5% to 100% of the growth factor present in a given area. For example, the percent of growth factor removal may be from about 5% to about 10%, from about 5% to about 15%, from about 5% to about 20%, from about 5% to about 25%, from about 10% to about 30%, from about 10% to about 40%, from about 10% to about 50%, from about 10% to about 60%, from about 20% to about 70%, from about 20% to about 80%, from about 40% to about 90% or from about 40% to about 100%.

[00336] Measures of release, inhibition or removal of one or more growth factors may be made relative to a standard or to the natural release or activity of growth factor under normal

physiologic conditions, *in vitro* or *in vivo*. Measurements may also be made relative to the presence or absence of antibodies. Such methods of measuring growth factor levels, release, inhibition or removal include standard measurement in tissue and/or fluids (e.g. serum or blood) such as Western blot, enzyme-linked immunosorbent assay (ELISA), activity assays, reporter assays, luciferase assays, polymerase chain reaction (PCR) arrays, gene arrays, Real Time reverse transcriptase (RT) PCR and the like.

[00337] Antibodies of the present disclosure may bind or interact with any number of epitopes on or along GPCs or their associated structures to either enhance or inhibit growth factor signaling. Such epitopes may include any and all possible sites for altering, enhancing or inhibiting GPC function. In some embodiments, such epitopes include, but are not limited to epitopes on or within growth factors, regulatory elements, GPCs, GPC modulatory factors, growth factor receiving cells or receptors, LAPs or LAP-like domains, fastener regions, furin cleavage sites, arm regions, fingers regions, LTBP binding domains, fibrillin binding domains, glycoprotein A repetitions predominant (GARP) binding domains, latency lassos, alpha 1 regions, RGD sequences, bowtie regions, extracellular matrix and/or cellular matrix components and/or epitopes formed by combining regions or portions of any of the foregoing.

[00338] Compounds and/or compositions of the present disclosure exert their effects via binding (reversibly or irreversibly) to one or more epitopes and/or regions of antibody recognition. While not wishing to be bound by theory, such binding sites for antibodies, are most often formed by proteins, protein domains or regions. Binding sites may; however, include biomolecules such as sugars, lipids, nucleic acid molecules or any other form of binding epitope.

[00339] In some embodiments, antagonist antibodies of the present disclosure may bind to GDF prodomains, stabilizing and preventing growth factor release, for example, by blocking an enzymatic cleavage site or by stabilizing the structure. Such antibodies would be useful in the treatment of GDF-related indications resulting from excessive GDF activity.

[00340] Alternatively or additionally, antibodies of the present disclosure may function as ligand mimetics which would induce internalization of GPCs. Such antibodies may act as nontraditional payload carriers, acting to deliver and/or ferry bound or conjugated drug payloads to specific GPC and/or GPC-related sites.

[00341] Changes elicited by antibodies of the present disclosure may result in neomorphic changes in the cell. As used herein, the term "neomorphic change" refers to a change or alteration that is new or different. For example, an antibody that elicits the release or

stabilization of one or more growth factor not typically associated with a particular GPC targeted by the antibody, would be a neomorphic antibody and the release would be a neomorphic change.

[00342] In some embodiments, compounds and/or compositions of the present disclosure may act to alter and/or control proteolytic events. In some embodiments, such proteolytic events may be intracellular or extracellular. In some embodiments, such proteolytic events may include the alteration of furin cleavage and/or other proteolytic processing events. In some embodiments, such proteolytic events may comprise proteolytic processing of growth factor signaling molecules or downstream cascades initiated by growth factor signaling molecules.

[00343] In some embodiments, compounds and/or compositions of the present disclosure may induce or inhibit dimerization or multimerization of growth factors (ligands) or their receptors. In some embodiments, such actions may be through stabilization of monomeric, dimeric or multimeric forms or through the disruption of dimeric or multimeric complexes.

[00344] In some embodiments, compounds and/or compositions of the present disclosure may act on homo and/or heterodimers of the monomeric units comprising either receptor groups or GPCs or other signaling molecule pairs.

[00345] Antibodies of the present disclosure may be internalized into cells prior to binding target antigens. Upon internalization, such antibodies may act to increase or decrease one or more signaling events, release or stabilize one or more GPCs, block or facilitate growth factor release and/or alter one or more cell niche.

[00346] In some embodiments, compounds and/or compositions of the present disclosure may also alter the residence time of one or more growth factor in one or more GPC and/or alter the residence time of one or more GPC in the extracellular matrix and/or cellular matrix. Such alterations may result in irreversible localization and/or transient localization.

[00347] Antibodies of the present disclosure may be designed, manufactured and/or selected using any methods known to one of skill in the art. In some embodiments, antibodies and/or antibody producing cells of the present disclosure are produced according to any of the methods listed in International Patent Application No. WO2014074532, the contents of which are herein incorporated by reference in their entirety.

Antibody generation in knockout mice

[00348] In some embodiments, antibodies of the current disclosure may be generated in knockout mice that lack a gene encoding one or more desired antigens. Such mice would not

be tolerized to such antigens and therefore may be able to generate antibodies against them that could cross react with human and mouse forms of the antigen. For the production of monoclonal antibodies, host mice are immunized with the target peptide to elicit lymphocytes that specifically bind that peptide. Lymphocytes are collected and fused with an immortalized cell line. The resulting hybridoma cells are cultured in a suitable culture medium with a selection agent to support the growth of only the fused cells.

[00349] In some embodiments, knocking out one or more growth factor gene may be lethal and/or produce a fetus or neonate that is non-viable. In some embodiments, neonatal animals may only survive for a matter of weeks (e.g. 1, 2, 3, 4 or 5 weeks). In such embodiments, immunizations may be carried out in neonatal animals shortly after birth. Oida et al (Oida, T. et al., TGF-β induces surface LAP expression on Murine CD4 T cells independent of FoxP3 induction. PLOS One. 2010. 5(11):e15523) demonstrate immunization of neonatal TGF-β knockout mice through the use of galectin-1 injections to prolong survival (typically 3-4 weeks after birth in these mice). Mice were immunized with cells expressing murine TGF-β every other day for 10 days beginning on the 8th day after birth and spleen cells were harvested on day 22 after birth. Harvested spleen cells were fused with myeloma cells and of the resulting hybridoma cells, many were found to successfully produce anti-LAP antibodies. In some embodiments of the present disclosure, these methods may be used to generate antibodies. In some embodiments, such methods may comprise the use of human antigens.

[00350] Methods of the present disclosure may also comprise one or more steps of the immunization methods described by Oida et al combined with one or more additional and/or modified steps. Modified steps may include, but are not limited to the use of alternate cell types for fusions, the pooling of varying number of spleen cells when performing fusions, altering the injection regimen, altering the date of spleen cell harvest, altering immunogen and/or altering immunogen dose. Additional steps may include the harvesting of other tissues (e.g. lymph nodes) from immunized mice.

Activating and inhibiting antibodies

[00351] Antibodies of the present disclosure may comprise activating or inhibiting antibodies. As used herein, the term "activating antibody" refers to an antibody that promotes growth factor activity. Activating antibodies include antibodies targeting any epitope that promotes growth factor activity. Such epitopes may lie on prodomains (e.g. LAPs and LAP-like domains), growth factors or other epitopes that when bound by antibody, lead to growth factor activity. Activating antibodies of the present disclosure may include, but are not

limited to GDF-activating antibodies such as GDF-8-activating antibodies and GDF-11-activating antibodies.

[00352] As used herein, the term "inhibiting antibody" refers to an antibody that reduces growth factor activity. Inhibiting antibodies include antibodies targeting any epitope that reduces growth factor activity when associated with such antibodies. Such epitopes may lie on prodomains (e.g. LAPs and LAP-like domains), growth factors or other epitopes that lead to reduced growth factor activity when bound by antibody. Inhibiting antibodies of the present disclosure may include, but are not limited to GDF-inhibiting antibodies such as GDF-8-inhibiting antibodies and GDF-11-inhibiting antibodies.

[00353] In some embodiments, inhibiting antibodies of the disclosure may include anti-primed complex antibodies. Such antibodies may target GDF-8 primed complexes and/or GDF-11 primed complexes and block resulting growth factor activity. In some cases, anti-primed complex antibodies may prevent dissociation of bound prodomain upon receptor binding. In some cases, anti-primed complex antibodies may prevent primed complexes from binding to receptors. In some cases, anti-primed complex antibodies may prevent primed complexes from associating with one or more other factors, leading to modulation of growth factor activity.

[00354] Embodiments of the present disclosure include methods of using activating and/or inhibiting antibodies in solution, in cell culture and/or in subjects to modify growth factor signaling.

Anti-prodomain antibodies

[00355] In some embodiments, compounds and/or compositions of the present disclosure may comprise one or more antibody targeting a prodomain, including LAP and/or LAP-like domains. Such antibodies may reduce or elevate growth factor signaling depending on the specific prodomain that is bound and/or depending on the specific epitope targeted by such antibodies. Anti-LAP and/or anti-LAP-like protein antibodies of the disclosure may promote dissociation of free growth factors from GPCs. Such dissociation may be induced upon antibody binding to a GPC or dissociation may be promoted by preventing the reassociation of free growth factor with LAP or LAP-like protein. In some cases, anti-GDF prodomain antibodies are provided. Anti-GDF prodomain antibodies may comprise GDF-activating antibodies. Such antibodies may increase GDF activity (e.g. GDF-8 or GDF-11 activity), in some cases by releasing GDF free growth factor from latent GPCs and/or preventing the reassociation of free growth factors with prodomains. In some cases, anti-GDF prodomain

antibodies may increase GDF activity more favorably when a proGDF is associated with an extracellular protein (e.g. LTBP, fibrillin or a GASP protein).

Multispecific antibodies

[00356] In some embodiments, antibodies of the disclosure may be capable of binding more than one epitope. As used herein, the terms "multibody" or "multispecific antibody" refer to an antibody wherein two or more variable regions bind to different epitopes. The epitopes may be on the same or different targets. In certain embodiments, a multi-specific antibody is a "bispecific antibody," which recognizes two different epitopes on the same or different antigens.

Bispecific antibodies

[00357] In some cases, antibodies of the present disclosure may be bispecific antibodies. Bispecific antibodies are capable of binding two different antigens. Such antibodies typically comprise antigen-binding regions from at least two different antibodies. For example, a bispecific monoclonal antibody (BsMAb, BsAb) is an artificial protein composed of fragments of two different monoclonal antibodies, thus allowing the BsAb to bind to two different types of antigen.

[00358] Bispecific antibodies may include any of those described in Riethmuller, G., 2012. *Cancer Immunity*. 12:12-18; Marvin, J.S. *et al*., 2005. *Acta Pharmacologica Sinica*. 26(6):649-58; and Schaefer, W. *et al*., 2011. *PNAS*. 108(27):11187-92, the contents of each of which are herein incorporated by reference in their entirety.

[00359] New generations of BsMAb, called "trifunctional bispecific" antibodies, have been developed. These consist of two heavy and two light chains, one each from two different antibodies, where the two Fab regions (the arms) are directed against two antigens, and the Fc region (the foot) comprises the two heavy chains and forms the third binding site.

[00360] Of the two paratopes that form the tops of the variable domains of a bispecific antibody, one can be directed against a target antigen and the other against a T-lymphocyte antigen like CD3. In the case of trifunctional antibodies, the Fc region may additionally binds to a cell that expresses Fc receptors, like a mactrophage, a natural killer (NK) cell or a dendritic cell. In sum, the targeted cell is connected to one or two cells of the immune system, which subsequently destroy it.

[00361] Other types of bispecific antibodies have been designed to overcome certain problems, such as short half-life, immunogenicity and side-effects caused by cytokine

liberation. They include chemically linked Fabs, consisting only of the Fab regions, and various types of bivalent and trivalent single-chain variable fragments (scFvs), fusion proteins mimicking the variable domains of two antibodies. The furthest developed of these newer formats are the bi-specific T-cell engagers (BiTEs) and mAb2's, antibodies engineered to contain an Fcab antigen-binding fragment instead of the Fc constant region.

[00362] A bispecific, single-chain antibody Fv fragment (Bs-scFv) was successfully used to kill cancer cells. Some human cancers are caused by functional defects in p53 that are restored by gene therapy with wild-type p53. Weisbart, *et al.*, describe the construction and expression of a bispecific single-chain antibody that penetrates living colon cancer cells, binds intracellular p53, and targets and restores its wild type function (Weisbart, *et al.*, *Int. J. Oncol.* 2004 Oct;25(4):1113-8; and Weisbart, *et al.*, *Int. J. Oncol.* 2004 Dec;25(6):1867-73). In these studies, a bispecific, single-chain antibody Fv fragment (Bs-scFv) was constructed from (i) a single-chain Fv fragment of mAb 3E10 that penetrates living cells and localizes in the nucleus, and (ii) a single-chain Fv fragment of a non-penetrating antibody, mAb PAb421 that binds the C-terminal of p53. PAb421 binding restores wild-type functions of some p53 mutants, including those of SW480 human colon cancer cells. The Bs-scFv penetrated SW480 cells and was cytotoxic, suggesting an ability to restore activity to mutant p53. COS-7 cells (monkey kidney cells with wild-type p53) served as a control since they are unresponsive to PAb421 due to the presence of SV40 large T antigen that inhibits binding of PAb421 to p53. Bs-scFv penetrated COS-7 cells but was not cytotoxic, thereby eliminating non-specific toxicity of Bs-scFv unrelated to binding p53. Fv fragments alone were not cytotoxic, indicating that killing was due to transduction of p53. A single mutation in CDR1 of PAb421 VH eliminated binding of the Bs-scFv to p53 and abrogated cytotoxicity for SW480 cells without altering cellular penetration, further supporting the requirement of PAb421 binding to p53 for cytotoxicity (Weisbart, *et al.*, *Int. J. Oncol.* 2004 Oct;25(4):1113-8; and Weisbart, *et al.*, *Int. J. Oncol.* 2004 Dec;25(6):1867-73).

[00363] In some embodiments, antibodies of the present disclosure may be diabodies. Diabodies are functional bispecific single-chain antibodies (bscAb). These bivalent antigen-binding molecules are composed of non-covalent dimers of scFvs, and can be produced in mammalian cells using recombinant methods. (*See, e.g.*, Mack *et al*, *Proc. Natl. Acad. Sci.*, 92: 7021-7025, 1995). Few diabodies have entered clinical development. An iodine-123-labeled diabody version of the anti-CEA chimeric antibody cT84.66 has been evaluated for pre-surgical immunoscintigraphic detection of colorectal cancer in a study sponsored by the

Beckman Research Institute of the City of Hope (Clinicaltrials.gov NCT00647153) (Nelson, A. L., *MAbs*.2010. Jan-Feb; 2(1):77–83).

[00364] Using molecular genetics, two scFvs can be engineered in tandem into a single polypeptide, separated by a linker domain, called a "tandem scFv" (tascFv). TascFvs have been found to be poorly soluble and require refolding when produced in bacteria, or they may be manufactured in mammalian cell culture systems, which avoids refolding requirements but may result in poor yields. Construction of a tascFv with genes for two different scFvs yields a "bispecific single-chain variable fragments" (bis-scFvs). Only two tascFvs have been developed clinically by commercial firms; both are bispecific agents in active early phase development by Micromet for oncologic indications, and are described as "Bispecific T-cell Engagers (BiTE)." Blinatumomab is an anti-CD19/anti-CD3 bispecific tascFv that potentiates T-cell responses to B-cell non-Hodgkin lymphoma in Phase 2. MT110 is an anti-EP-CAM/anti-CD3 bispecific tascFv that potentiates T-cell responses to solid tumors in Phase 1. Bispecific, tetravalent "TandAbs" are also being researched by Affimed (Nelson, A. L., *MAbs*.2010. Jan-Feb; 2(1):77–83).

[00365] Also included are maxibodies (bivalent scFV fused to the amino terminus of the Fc (CH2-CH3 domains) of IgG.

[00366] Bispecific T-cell-engager (BiTE) antibodies are designed to transiently engage cytotoxic T-cells for lysis of selected target cells. The clinical activity of BiTE antibodies corroborates findings that *ex vivo* expanded, autologous T-cells derived from tumor tissue, or transfected with specific T-cell receptors, have shown therapeutic potential in the treatment of solid tumors. While these personalized approaches prove that T-cells alone can have considerable therapeutic activity, even in late-stage cancer, they are cumbersome to perform on a broad basis. This is different for cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibodies, which facilitate generation of tumor-specific T-cell clones, and also for bi- and tri-specific antibodies that directly engage a large proportion of patients' T-cells for cancer cell lysis. The potential of global T-cell engagement for human cancer therapy by T-cell-engaging antibodies is under active investigation (Baeuerle PA, *et al.*, *Current Opinion in Molecular Therapeutics*. 2009, 11(1):22-30).

[00367] Third generation molecules include "miniaturized" antibodies. Among the best examples of mAb miniaturization are the small modular immunopharmaceuticals (SMIPs) from Trubion Pharmaceuticals. These molecules, which can be monovalent or bivalent, are recombinant single-chain molecules containing one V_L, one V_H antigen-binding domain, and one or two constant "effector" domains, all connected by linker domains. Presumably, such a

molecule might offer the advantages of increased tissue or tumor penetration claimed by fragments while retaining the immune effector functions conferred by constant domains. At least three "miniaturized" SMIPs have entered clinical development. TRU-015, an anti-CD20 SMIP developed in collaboration with Wyeth, is the most advanced project, having progressed to Phase 2 for rheumatoid arthritis (RA). Earlier attempts in systemic lupus erythrematosus (SLE) and B cell lymphomas were ultimately discontinued. Trubion and Facet Biotechnology are collaborating in the development of TRU-016, an anti-CD37 SMIP, for the treatment of CLL and other lymphoid neoplasias, a project that has reached Phase 2. Wyeth has licensed the anti-CD20 SMIP SBI-087 for the treatment of autoimmune diseases, including RA, SLE and possibly multiple sclerosis, although these projects remain in the earliest stages of clinical testing. (Nelson, A. L., *MAbs*.2010. Jan-Feb; 2(1):77–83).

[00368] Genmab is researching application of their "Unibody" technology, in which the hinge region has been removed from IgG4 molecules. While IgG4 molecules are unstable and can exchange light-heavy chain heterodimers with one another, deletion of the hinge region prevents heavy chain-heavy chain pairing entirely, leaving highly specific monovalent light/heavy heterodimers, while retaining the Fc region to ensure stability and half-life in vivo. This configuration may minimize the risk of immune activation or oncogenic growth, as IgG4 interacts poorly with FcRs and monovalent unibodies fail to promoteintracellular signaling complex formation. These contentions are, however, largely supported by laboratory, rather than clinical, evidence. Biotecnol is also developing a "miniaturized" mAb, CAB051, which is a "compacted" 100 kDa anti-HER2 antibody in preclinical research (Nelson, A. L., *MAbs*.2010. Jan-Feb; 2(1):77–83).

[00369] Recombinant therapeutics composed of single antigen-binding domains have also been developed, although they currently account for only 4% of the clinical pipeline. These molecules are extremely small, with molecular weights approximately one-tenth of those observed for full-sized mAbs. Arana and Domantis engineer molecules composed of antigen-binding domains of human immunoglobulin light or heavy chains, although only Arana has a candidate in clinical testing, ART-621, an anti-TNFα molecule in Phase 2 study for the treatment of psoriasis and rheumatoid arthritis. Ablynx produces "nanobodies" derived from the antigen-binding variable heavy chain regions (V_{HH}s) of heavy chain antibodies found in camels and llamas, which lack light chains. Two Ablynx anti-von Willebrand Factor nanobodies have advanced to clinical development, including ALX-0081, in Phase 2 development as an intravenous therapy to prevent thrombosis in patients undergoing percutaneous coronary intervention for acute coronary syndrome, and ALX-0681, a Phase 1

molecule for subcutaneous administration intended for both patients with acute coronary syndrome and thrombotic thrombocytopenic purpura (Nelson, A. L., *MAbs*.2010. Jan-Feb; 2(1):77–83).

Development of multispecific antibodies

[00370] In some embodiments, antibody sequences of the disclosure may be used to develop multispecific antibodies (*e.g.*, bispecific, trispecific, or of greater multispecificity). Multispecific antibodies can be specific for different epitopes of a target antigen of the present disclosure, or can be specific for both a target antigen of the present disclosure, and a heterologous epitope, such as a heterologous glycan, peptide or solid support material. (*See, e.g.*, WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, A. *et al.*, *Trispecific F(ab')3 derivatives that use cooperative signaling via the TCR/CD3 complex and CD2 to activate and redirect resting cytotoxic T cells. J. Immunol.* 1991 Jul 1;147(1):60-9; U.S. Pat. Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; and Kostelny, S.A. *et al.*, *Formation of a bispecific antibody by the use of leucine zippers. J. Immunol.* 1992 Mar 1;148(5):1547-53); U.S. Pat. No. 5,932,448.

[00371] Disclosed and claimed in PCT Publication WO2014144573 to Memorial Sloan-Kettering Cancer Center are multimerization technologies for making dimeric multispecific binding agents (*e.g.*, fusion proteins comprising antibody components) with improved properties over multispecific binding agents without the capability of dimerization.

[00372] Disclosed and claimed in PCT Publication WO2014144357 to Merck Patent GMBH are tetravalent bispecific antibodies (TetBiAbs), and methods of making and methods of using TetBiAbs for diagnostics and for the treatment of cancer or immune disorders. TetBiAbs feature a second pair of Fab fragments with a second antigen specificity attached to the C-terminus of an antibody, thus providing a molecule that is bivalent for each of the two antigen specificities. The tetravalent antibody is produced by genetic engineering methods, by linking an antibody heavy chain covalently to a Fab light chain, which associates with its cognate, co-expressed Fab heavy chain.

[00373] Disclosed and claimed in PCT Publication WO2014028560 to IBC Pharmaceuticals, Inc. are T cell redirecting bispecific antibodies (bsAb), with at least one binding site for a T-cell antigen and at least one binding site for an antigen on a diseased cell or pathogen, for treatment of disease. Preferably, this bsAb is an anti-CD3 x anti-CD19 bispecific antibody, although antibodies against other T-cell antigens and/or disease-associated antigens may be used. The complex is capable of targeting effector T cells to

induce T-cell-mediated cytotoxicity of cells associated with a disease, such as cancer, autoimmune disease or infectious disease. The cytotoxic immune response is enhanced by co-administration of interfon-based agents that comprise interferon-α, interferon-bgr; interferon-λ1, interferon-λ2 or interferon-λ3.

[00374] Disclosed and claimed in PCT Publication WO2013092001 to Synimmune GMBH is a bispecific antibody molecule, as well as a method for producing the same, its use and a nucleic acid molecule encoding the bispecific antibody molecule. In particular is provided an antibody molecule that is capable of mediating target cell restricted activation of immune cells.

[00375] Disclosed and claimed in PCT Publication WO2012007167 is a multispecific modular antibody specifically binding to at least a glycoepitope and a receptor of the erbB class on the surface of a tumor cell, thereby crosslinking the glycoepitope and the receptor, which antibody has apoptotic activity effecting cytolysis independent of NK cells.

[00376] Disclosed and claimed in PCT Publications WO2012048332 and WO2013055404 are meditopes, meditope-binding antibodies, meditope delivery systems, as well as a monoclonal antibody framework binding interface for meditopes, and methods for their use. Specifically, two antibody binding peptides, C-QFDLSTRRLK-C ("cQFD"; SEQ ID NO:1 therein) and C-QYNLSSRALK-C ("cQYN"; SEQ ID NO:2 therein) were shown to have novel mAb binding properties. Also called "meditopes," cQFD and cQYN were shown to bind to a region of the Fab framework of the anti-EGFR mAb cetuximab and not to bind the complementarity determining regions (CDRs) that bind antigen. The binding region on the Fab framework is distinct from other framework-binding antigens, such as the superantigens *Staphylococcal* protein A (SpA) (Graille *et al.*, 2000) and *Peptostreptococcus magnus* protein L (PpL) (Graille *et al.*, 2001). Accordingly, one embodiment disclosed is a framework binding interface comprising a framework region of a unique murine-human antibody or functional fragment thereof that binds a cyclic meditope.

[00377] Exemplary patents and patent publications of interest are: U.S. Patent Nos. 5,585,089; 5,693,761; and 5,693,762, all filed Jun 7, 1995 and U.S. Patent No. 6,180,370, all assigned to Protein Design Labs, Inc., describe methods for producing, and compositions of, humanized immunoglobulins having one or more complementarity determining regions (CDR's) and possible additional amino acids from a donor immunoglobulin and a framework region from an accepting human immunoglobulin. Each humanized immunoglobulin chain is said to usually comprise, in addition to the CDR's, amino acids from the donor immunoglobulin framework that are, *e.g.*, capable of interacting with the CDRs to effect

binding affinity, such as one or more amino acids which are immediately adjacent to a CDR in the donor immunoglobulin or those within about about 3 Å as predicted by molecular modeling. The heavy and light chains may each be designed by using any one or all of various position criteria. When combined into an intact antibody, the humanized immunoglobulins of the present disclosure is said to be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen, such as a protein or other compound containing an epitope.

[00378] U.S. Patent No. 5,951,983, assigned to Universite Catholique De Louvain and Bio Transplant, Inc., describes a humanized antibody against T-lymphocytes. Framework regions from a human V kappa gene designated as HUM5400 (EMBL accession X55400) and from the human antibody clone Amu 5-3 (GenBank accession number U00562) are set forth therein.

[00379] U.S. Patent No. 5,091,513, to Creative Biomolecules, Inc., describes a family of synthetic proteins having affinity for a preselected antigen. The proteins are characterized by one or more sequences of amino acids constituting a region which behaves as a biosynthetic antibody binding site (BABS). The sites comprise 1) non-covalently associated or disulfide bonded synthetic V_H and V_L dimers, 2) V_H-V_L or V_L-V_H single chains wherein the V_H and V_L are attached by a polypeptide linker, or 3) individuals V_H or V_L domains. The binding domains comprise linked CDR and FR regions, which may be derived from separate immunoglobulins. The proteins may also include other polypeptide sequences which function, *e.g.*, as an enzyme, toxin, binding site, or site of attachment to an immobilization media or radioactive atom. Methods are disclosed for producing the proteins, for designing BABS having any specificity that can be elicited by in vivo generation of antibody, and for producing analogs thereof.

[00380] U.S. Patent No. 8,399,625, to ESBATech, an Alcon Biomedical Research Unit, LLC, describes antibody acceptor frameworks and methods for grafting non-human antibodies, *e.g.*, rabbit antibodies, using a particularly well suited antibody acceptor framework.

Intrabodies

[00381] In some embodiments, antibodies of the present disclosure may be intrabodies. Intrabodies are a form of antibody that is not secreted from a cell in which it is produced, but instead targets one or more intracellular proteins. Intrabodies are expressed and function intracellularly, and may be used to affect a multitude of cellular processes including, but not

limited to intracellular trafficking, transcription, translation, metabolic processes, proliferative signaling and cell division. In some embodiments, methods described herein include intrabody-based therapies. In some such embodiments, variable domain sequences and/or CDR sequences disclosed herein are incorporated into one or more constructs for intrabody-based therapy. For example, intrabodies may target one or more glycated intracellular proteins or may modulate the interaction between one or more glycated intracellular proteins and an alternative protein.

[00382] More than two decades ago, intracellular antibodies against intracellular targets were first described (Biocca, Neuberger and Cattaneo *EMBO J.* 9: 101-108, 1990). The intracellular expression of intrabodies in different compartments of mammalian cells allows blocking or modulation of the function of endogenous molecules (Biocca, *et al.*, *EMBO J.* 9: 101-108, 1990; Colby *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 101 : 17616-21 , 2004). Intrabodies can alter protein folding, protein-protein, protein-DNA, protein-RNA interactions and protein modification. They can induce a phenotypic knockout and work as neutralizing agents by direct binding to the target antigen, by diverting its intracellular traffic or by inhibiting its association with binding partners. They have been largely employed as research tools and are emerging as therapeutic molecules for the treatment of human diseases as viral pathologies, cancer and misfolding diseases. The fast growing bio-market of recombinant antibodies provides intrabodies with enhanced binding specificity, stability and solubility, together with lower immunogenicity, for their use in therapy (Biocca, abstract in *Antibody Expression and Production Cell Engineering* Volume 7, 2011, pp. 179-195).

[00383] In some embodiments, intrabodies have advantages over interfering RNA (iRNA); for example, iRNA has been shown to exert multiple non-specific effects, whereas intrabodies have been shown to have high specificity and affinity of to target antigens. Furthermore, as proteins, intrabodies possess a much longer active half-life than iRNA. Thus, when the active half-life of the intracellular target molecule is long, gene silencing through iRNA may be slow to yield an effect, whereas the effects of intrabody expression can be almost instantaneous. Lastly, it is possible to design intrabodies to block certain binding interactions of a particular target molecule, while sparing others.

Development of intrabodies

[00384] Intrabodies are often single chain variable fragments (scFvs) expressed from a recombinant nucleic acid molecule and engineered to be retained intracellularly (*e.g.*, retained in the cytoplasm, endoplasmic reticulum, or periplasm). Intrabodies may be used, for

example, to ablate the function of a protein to which the intrabody binds. The expression of intrabodies may also be regulated through the use of inducible promoters in the nucleic acid expression vector comprising the intrabody. Intrabodies may be produced using methods known in the art, such as those disclosed and reviewed in: (Marasco *et al.*, 1993 *Proc. Natl. Acad. Sci. USA*, 90: 7889-7893; Chen *et al.*, 1994, *Hum. Gene Ther.* 5:595-601; Chen *et al.*, 1994, *Proc. Natl. Acad. Sci. USA*, 91: 5932-5936; Maciejewski *et al.*, 1995, *Nature Med.*, 1: 667-673; Marasco, 1995, *Immunotech*, 1: 1-19; Mhashilkar, *et al.*, 1995, *EMBO J.* 14: 1542-51; Chen *et al.*, 1996, *Hum. Gene Therap.*, 7: 1515-1525; Marasco, *Gene Ther.* 4:11-15, 1997; Rondon and Marasco, 1997, *Annu. Rev. Microbiol.* 51:257-283; Cohen, *et al.*, 1998, *Oncogene* 17:2445-56; Proba *et al.*, 1998, *J. Mol. Biol.* 275:245-253; Cohen *et al.*, 1998, *Oncogene* 17:2445-2456; Hassanzadeh, *et al.*, 1998, *FEBS Lett.* 437:81-6; Richardson *et al.*, 1998, *Gene Ther.* 5:635-44; Ohage and Steipe, 1999, *J. Mol. Biol.* 291:1119-1128; Ohage *et al.*, 1999, *J. Mol. Biol.* 291:1129-1134; Wirtz and Steipe, 1999, *Protein Sci.* 8:2245-2250; Zhu *et al.*, 1999, *J. Immunol. Methods* 231:207-222; Arafat *et al.*, 2000, *Cancer Gene Ther.* 7:1250-6; der Maur *et al.*, 2002, *J. Biol. Chem.* 277:45075-85; Mhashilkar *et al.*, 2002, *Gene Ther.* 9:307-19; and Wheeler *et al.*, 2003, *FASEB J.* 17: 1733-5; and references cited therein). In particular, a CCR5 intrabody has been produced by Steinberger *et al.*, 2000, *Proc. Natl. Acad. Sci. USA* 97:805-810). *See* generally Marasco, WA, 1998, "Intrabodies: Basic Research and Clinical Gene Therapy Applications" Springer:New York; and for a review of scFvs, *see* Pluckthun in "The Pharmacology of Monoclonal Antibodies," 1994, vol. 113, Rosenburg and Moore *eds*. Springer-Verlag, New York, pp. 269-315.

[00385] In some embodiments, antibody sequences disclosed herein may be used to develop intrabodies. Intrabodies are often recombinantly expressed as single domain fragments such as isolated VH and VL domains or as a single chain variable fragment (scFv) antibody within the cell. For example, intrabodies are often expressed as a single polypeptide to form a single chain antibody comprising the variable domains of the heavy and light chain joined by a flexible linker polypeptide. Intrabodies typically lack disulfide bonds and are capable of modulating the expression or activity of target genes through their specific binding activity. Single chain antibodies can also be expressed as a single chain variable region fragment joined to the light chain constant region.

[00386] As is known in the art, an intrabody can be engineered into recombinant polynucleotide vectors to encode sub-cellular trafficking signals at its N or C terminus to allow expression at high concentrations in the sub-cellular compartments where a target protein is located. For example, intrabodies targeted to the endoplasmic reticulum (ER) are

engineered to incorporate a leader peptide and, optionally, a C-terminal ER retention signal, such as the KDEL amino acid motif. Intrabodies intended to exert activity in the nucleus are engineered to include a nuclear localization signal. Lipid moieties are joined to intrabodies in order to tether the intrabody to the cytosolic side of the plasma membrane. Intrabodies can also be targeted to exert function in the cytosol. For example, cytosolic intrabodies are used to sequester factors within the cytosol, thereby preventing them from being transported to their natural cellular destination.

[00387] There are certain technical challenges with intrabody expression. In particular, protein conformational folding and structural stability of the newly-synthesized intrabody within the cell is affected by reducing conditions of the intracellular environment. In human clinical therapy, there are safety concerns surrounding the application of transfected recombinant DNA, which is used to achieve intrabody expression within the cell. Of particular concern are the various viral-based vectors commonly-used in genetic manipulation. Thus, one approach to circumvent these problems is to fuse protein transduction domains (PTD) to scFv antibodies, to create a 'cell-permeable' antibody or 'Transbody.' Transbodies are cell-permeable antibodies in which a protein transduction domain (PTD) is fused with single chain variable fragment (scFv) antibodies (Heng and Cao, 2005, *Med Hypotheses*. 64:1105-8).

[00388] Upon interaction with a target gene, an intrabody modulates target protein function and/or achieves phenotypic/functional knockout by mechanisms such as accelerating target protein degradation and sequestering the target protein in a non-physiological sub-cellular compartment. Other mechanisms of intrabody-mediated gene inactivation can depend on the epitope to which the intrabody is directed, such as binding to the catalytic site on a target protein or to epitopes that are involved in protein-protein, protein-DNA, or protein-RNA interactions.

[00389] In one embodiment, intrabodies are used to capture a target in the nucleus, thereby preventing its activity within the nucleus. Nuclear targeting signals are engineered into such intrabodies in order to achieve the desired targeting. Such intrabodies are designed to bind specifically to a particular target domain. In another embodiment, cytosolic intrabodies that specifically bind to a target protein are used to prevent the target from gaining access to the nucleus, thereby preventing it from exerting any biological activity within the nucleus (e.g., preventing the target from forming transcription complexes with other factors).

[00390] In order to specifically direct the expression of such intrabodies to particular cells, the transcription of the intrabody is placed under the regulatory control of an appropriate

tumor-specific promoter and/or enhancer. In order to target intrabody expression specifically to prostate, for example, the PSA promoter and/or promoter/enhancer can be utilized (See, for example, U.S. Patent No. 5,919,652 issued 6 July 1999).

[00391] Protein transduction domains (PTDs) are short peptide sequences that enable proteins to translocate across the cell membrane and be internalized within the cytosol, through atypical secretory and internalization pathways. There are a number of distinct advantages that a 'Transbody' would possess over conventional intrabodies expressed within the cell. For a start, 'correct' conformational folding and disulfide bond formation can take place prior to introduction into the target cell. More importantly, the use of cell-permeable antibodies or 'Transbodies' would avoid the overwhelming safety and ethical concerns surrounding the direct application of recombinant DNA technology in human clinical therapy, which is required for intrabody expression within the cell. 'Transbodies' introduced into the cell would possess only a limited active half-life, without resulting in any permanent genetic alteration. This would allay any safety concerns with regards to their application in human clinical therapy (Heng and Cao 2005, *Med Hypotheses*. 64:1105-8).

[00392] Intrabodies are promising therapeutic agents for the treatment of misfolding diseases, including Alzheimer's, Parkinson's, Huntington's and prion diseases, because of their virtually infinite ability to specifically recognize the different conformations of a protein, including pathological isoforms, and because they can be targeted to the potential sites of aggregation (both intra- and extracellular sites). These molecules can work as neutralizing agents against amyloidogenic proteins by preventing their aggregation, and/or as molecular shunters of intracellular traffic by rerouting the protein from its potential aggregation site (Cardinale, and Biocca, *Curr. Mol. Med.* 2008, 8:2-11).

[00393] Exemplary Patent Publications describing intracellular antibodies or intrabodies are set forth hereinbelow, each of which is incorporated by reference in its entirety.

[00394] PCT Publication WO03014960 and US Patent 7,608,453 granted to Cattaneo, *et al.*, describe an intracellular antibody capture technology method of identifying at least one consensus sequence for an intracellular antibody (ICS) comprising the steps of: creating a database comprising sequences of validated intracellular antibodies (VIDA database) and aligning the sequences of validated intracellular antibodies according to Kabat; determining the frequency with which a particular amino acid occurs in each of the positions of the aligned antibodies; selecting a frequency threshold value (LP or consensus threshold) in the range from 70% to 100%; identifying the positions of the alignment at which the frequency

of a particular amino acid is greater than or equal to the LP value; and identifying the most frequent amino acid, in the position of said alignment.

[00395] PCT Publications WO0054057; WO03077945; WO2004046185; WO2004046186; WO2004046187; WO2004046188; WO2004046189; US Patent Application Publications US2005272107; US2005276800; US2005288492; US2010143939; granted US Patents 7,569,390 and 7,897,347 and granted European Patents EP1560853; and EP1166121 all assigned to the Medical Research Council and including inventors Cattaneo, *et al.*, describe intracellular intracellular single domain immunoglobulins, and a method for determining the ability of a immunoglobulin single domain to bind to a target in an intracellular environment, as well as methods for generating intracellular antibodies.

[00396] PCT Publication WO0235237; US Patent Application Publication 2003235850 and granted European Patent EP1328814 naming Catteneo as an inventor and assigned to S.I.S.S.A. Scuola Internazionale Superiore describe a method for the *in vivo* identification of epitopes of an intracellular antigen.

[00397] PCT Publication WO2004046192 and European Patent EP1565558 assigned to Lay Line Genomics SPA and naming Catteneo as an inventor describe a method for isolating intracellular antibodies that disrupt and neutralize an interaction between a protein ligand x and a protein ligand y inside a cell. Also disclosed are a method to identify a protein ligand x able to bind to a known y ligand using intracellular antibodies able to the interaction between x and y; and a method for the isolation of a set of antibody fragments against a significant proportion of the protein-protein interactions of a given cell (interactome) or against the protein interactions that constitute an intracellular pathway or network.

[00398] US Patent Application Publication 2006034834 and PCT Publication WO9914353 entitled "Intrabody-mediated control of immune reactions" and assigned to Dana Farber Cancer Institute Inc. name inventors Marasco and Mhashilkar are directed to methods of altering the regulation of the immune system, *e.g.*, by selectively targeting individual or classes of immunomodulatory receptor molecules (IRMs) on cells comprising transducing the cells with an intracellularly expressed antibody, or intrabody, against the IRMs. In a preferred embodiment the intrabody comprises a single chain antibody against an IRM, *e.g*, MHC-1 molecules.

[00399] PCT Publication WO2013033420 assigned to Dana Farber Cancer Institute Inc. and Whitehead Biomedical Institute, and naming inventors Bradner, Rahl and Young describes methods and compositions useful for inhibiting interaction between a bromodomain protein and an immunoglobulin (Ig) regulatory element and downregulating expression of an

oncogene translocated with an Ig locus, as well as for treating a cancer (*e.g.*, hematological malignancy) characterized by increased expression of an oncogene which is translocated with an Ig locus. Intrabodies are generally described.

[00400] PCT Publication WO02086096 and US Patent Application Publication 2003104402 entitled "Methods of producing or identifying intrabodies in eukaryotic cells," assigned to University of Rochester Medical Center and naming inventors Zauderer, Wei and Smith describe a high efficiency method of expressing intracellular immunoglobulin molecules and intracellular immunoglobulin libraries in eukaryotic cells using a trimolecular recombination method. Further provided are methods of selecting and screening for intracellular immunoglobulin molecules and fragments thereof, and kits for producing, screening and selecting intracellular immunoglobulin molecules, as well as the intracellular immunoglobulin molecules and fragments produced using these methods.

[00401] PCT Publication WO2013023251 assigned to Affinity Biosciences PTY LTD and naming inventors Beasley, Niven and Kiefel describes polypeptides, such as antibody molecules and polynucleotides encoding such polypeptides, and libraries thereof, wherein the expressed polypeptides that demonstrate high stability and solubility. In particular, polypeptides comprising paired VL and VH domains that demonstrate soluble expression and folding in a reducing or intracellular environment are described, wherein a human scFv library was screened, resulting in the isolation of soluble scFv genes that have identical framework regions to the human germline sequence as well as remarkable thermostability and tolerance of CDR3 grafting onto the scFv scaffold.

[00402] European Patent Application EP2314622 and PCT Publications WO03008451 and WO03097697 assigned to Esbatech AG and University of Zuerich and naming inventors Ewert, Huber, Honneger and Plueckthun describe the modification of human variable domains and provide compositions useful as frameworks for the creation of very stable and soluble single-chain Fv antibody fragments. These frameworks have been selected for intracellular performance and are thus ideally suited for the creation of scFv antibody fragments or scFv antibody libraries for applications where stability and solubility are limiting factors for the performance of antibody fragments, such as in the reducing environment of a cell. Such frameworks can also be used to identify highly conserved residues and consensus sequences which demonstrate enhanced solubility and stability.

[00403] PCT Publication WO02067849 and US Patent Application Publication 2004047891 entitled "Systems devices and methods for intrabody targeted delivery and reloading of therapeutic agents" describe systems, devices and methods for intrabody targeted

delivery of molecules. More particularly, some embodiments relate to a reloadable drug delivery system, which enables targeted delivery of therapeutic agents to a tissue region of a subject, in a localized and timely manner.

[00404] PCT Publication WO2005063817 and US Patent 7,884,054 assigned to Amgen Inc. and naming inventors Zhou, Shen and Martin describe methods for identifying functional antibodies, including intrabodies. In particular, a homodimeric intrabody is described, wherein each polypeptide chain of the homodimer comprises an Fc region, an scFv, and an intracellular localization sequence. The intracellular localization sequence may cause the intrabody to be localized to the ER or the Golgi. Optionally, each polypeptide chain comprises not more than one scFv.

[00405] PCT Publication WO2013138795 by Vogan, *et al.* and assigned to Permeon Biologics Inc. describes cell penetrating compositions for delivery of intracellular antibodies and antibody-like moieties and methods for delivering them (referred to herein as "AAM moieties" or "an AAM moiety") into a cell. Without being bound by theory, the present disclosure is based, at least in part, on the discovery that an AAM moiety can be delivered into a cell by complexing the AAM moiety with a cell penetrating polypeptide having surface positive charge (referred to herein as a "Surf+ Penetrating Polypeptide") . Examples of some applications of intraphilin technology are also provided

[00406] PCT Publication WO2010004432 assigned to the Pasteur Institute describes immunoglobulins from camelidae (camels, dromedaries, llamas and alpacas), about 50% of which are antibodies devoid of light chain. These heavy-chain antibodies interact with the antigen by the virtue of only one single variable domain, referred to as VHH(s), VHH domain(s) or VHH antibody (ies). Despite the absence of light chain, these homodimeric antibodies exhibit a broad antigen-binding repertoire by enlarging their hypervariable regions, and can act as a transbody and/or intrabody *in vitro* as well as *in vivo*, when the VHH domain is directed against an intracellular target.

[00407] PCT Publication WO2014106639 describes a method for identifying a cellular target involved in a cell phenotype by identifying an intrabody that can modify a cell phenotype and identifying a direct or indirect cellular target of the intrabody. In particular, intrabodies 3H2-1, 3H2-VH and 5H4 are capable of inhibiting the degranulation reaction in mast cells triggered by an allergic stimulus; furthermore, intrabodies 3H2-1 and 5H4 directly or indirectly targeted a protein of the ABCF1 family and C120RF4 family, respectively. These ABCF1 and C120RF4 inhibitors are said to be useful in therapy, in particular for treating allergic and/or inflammatory conditions.

[00408] PCT Publication WO0140276 assigned to Urogenesis Inc. generally describes the possibility of inhibition of STEAP (Six Transmembrane Epithelial Antigen of the Prostate) proteins using intracellular antibodies (intrabodies).

[00409] PCT Publication WO02086505 assigned to University of Manchester and US Patent Application Publication US2004115740 naming inventors Simon and Benton describe a method for the intracelular analysis of a target molecule, wherein intrabodies are said to be preferred. In one embodiment, a vector (designated pScFv-ECFP) capable of expressing an anti-MUC1 intrabody coupled to CFP is described.

[00410] PCT Publication WO03095641 and WO0143778 assigned to Gene Therapy Systems Inc. describe compositions and methods for intracellular protein delivery, and intrabodies are generally described.

[00411] PCT Publication WO03086276 assigned to Selective Genetics Inc. describes a platform technology for the treatment of intracellular infections. Compositions and methods described therein include non-target specific vectors that target infectable cells via linked ligands that bind and internalize through cell surface receptors/moieties associated with infection. The vectors comprise exogenous nucleic acid sequences that are expressed upon internalization into a target cell. Vector associated ligands and nucleic acid molecules may be altered to target different infectious agents. In addition, the disclosure provides methods of identifying epitopes and ligands capable of directing internalization of a vector and capable of blocking viral entry.

[00412] PCT Publication WO03062415 assigned to Erasmus University describes a transgenic organism comprising a polynucleotide construct encoding an intracellular antibody which disrupts the catalysis of the production of the xenoantigen galactose alpha 1,3 galactose and/or a polynucleotide construct which encodes an intracellular antibody which binds specifically to a retrovirus protein, such as a PERV particle protein. Cells, tissues and organs of the transgenic organism may be used in xenotransplantation.

[00413] PCT Publication WO2004099775 entitled "Means for detecting protein conformation and applications thereof" describes the use of scFv fragments as conformation-specific antibodies for specifically detecting a conformational protein state, said to have applications as sensors for following in livings cells, upon intracellular expression, the behavior of endogeneous proteins.

[00414] PCT Publication WO2008070363 assigned to Imclone Systems Inc. describes a single domain intrabody that binds to an intracellular protein or to an intracellular domain of an intracellular protein, such as Etk, the endothelial and epithelial tyrosine kinase, which is a

member of the Tec family of non-receptor tyrosine kinases. Also provided is a method of inhibiting an intracellular enzyme, and treating a tumor in a patient by administering the intrabody or a nucleic acid expressing the intrabody.

[00415] PCT Publication WO2009018438 assigned to Cornell Research Foundation Inc. describes a method of identifying a protein that binds to a target molecule and has intracellular functionality, by providing a construct comprising a DNA molecule encoding the protein which binds to the target molecule, with the DNA molecule being coupled to a stall sequence. A host cell is transformed with the construct and then cultured under conditions effective to form, within the host cell, a complex of the protein whose translation has been stalled, the mRNA encoding the protein, and ribosomes. The protein in the complex is in a properly folded, active form and the complex is recovered from the cell. This method can be carried out with a cell-free extract preparation containing ribosomes instead of a host cell. The present disclosure also relates to a construct which includes a DNA molecule encoding a protein that binds to a target molecule and an SecM stalling sequence coupled to the DNA molecule. The DNA molecule and the SecM stalling sequence are coupled with sufficient distance between them to permit expression of their encoded protein, within the cell, in a properly folded, active form. The use of intrabodies is generally described.

[00416] PCT Publication WO2014030780 assigned to Mogam Biotech Research Institute describes a method named Tat-associated protein engineering (TAPE), for screening a target protein having higher solubility and excellent thermostability, in particular, an immunoglobulin variable domain (VH or VL) derived from human germ cells, by preparing a gene construct where the target protein and an antibiotic -resistant protein are linked to a Tat signal sequence, and then expressing this within *E. coli*. Also disclosed are human or engineered VH and VL domain antibodies and human or engineered VH and VL domain antibody scaffolds having solubility and excellent thermostability, which are screened by the TAPE method. Also provided is a library including random CDR sequences in the human or engineered VH or VL domain antibody scaffold screened by the TAPE method, a preparing method thereof, a VH or VL domain antibody having binding ability to the target protein screened by using the library, and a pharmaceutical composition including the domain antibody.

[00417] European Patent Application EP2422811 describes an antibody that binds to an intracellular epitope; such intrabodies comprise at least a portion of an antibody that is capable of specifically binding an antigen and preferably does not contain operable sequences coding for its secretion and thus remains within the cell. In one embodiment, the intrabody

comprises a scFv. The scFv polypeptide further comprises a polypeptide linker between the VH and VL domains which enables the scFv to form the desired structure for antigen binding. Also described is a specific embodiment in which the intrabody binds to the cytoplasmic domain of an Eph receptor and prevents its signaling (*e.g.*, autophosphorylation). In another specific embodiment, an intrabody binds to the cytoplasmic domain of a B-type Ephrin (*e.g.*, EphrinB1, EphrinB2 or EphrinB3).

[00418] PCT Publication WO2011003896 and European Patent Application EP2275442 describe intracellular functional PCNA-Chromobodies made using nucleic acid molecule encoding a polypeptide specifically binding to proliferating cell nuclear antigen (PCNA). Examples of such polypeptides comprising conservative substitutions of one or more amino acids in one or two framework regions are represented by SEQ ID NOs 16 and 18, including the framework region of the polypeptide. In the examples, the framework regions as well as the CDR regions involved in the binding of PCNA have been determined.

[00419] European Patent Application EP2703485 describes a method for selecting plasma cells or plasmablasts, as well as for producing target antigen specific antibodies, and novel monoclonal antibodies. In one embodiment, cells expressing intracellular immunoglobulin were identified.

Structural analysis

[00420] In some cases, recombinant proteins of the disclosure may be subjected to structural analysis using any methods available in the art to reveal one or more structural features (e.g. secondary, tertiary and/or quaternary structure). Methods of structural analysis may include, but are not limited to X-ray crystallography, nuclear magnetic resonance analysis, hydrogen/deuterium exchange mass spectrometry, and computer-based modeling. In some cases, structural analysis may be used to identify epitopes that may be desireable targets for inhibiting or activating antibodies. For instance, in some cases, structural analysis of a protein complex may reveal one or more epitopes where antibody binding may stabilize the complex. In some cases, structural analysis of a protein complex may reveal one or more epitopes where antibody binding may destabilize the complex. In some cases, structural analysis may be used to identify one or more epitopes where antibody binding may prevent complex formation.

[00421] In some embodiments, structural analysis may be used to assess interactions between antibodies of the disclosure and their targets. Such analysis may be used to provide insight into the exact epitope bound by a particular antibody and/or or provide insight into

how a particular antibody performs a specific function (e.g. inhibitory or activating functions).

[00422] In some cases, structural analysis may be used to help in the design of one or more recombinant proteins, for example, recombinant proteins to be used as antigens or to be used in selection of binding partners from a display library.

Variations

[00423] Compounds and/or compositions of the present disclosure may exist as a whole polypeptide, a plurality of polypeptides or fragments of polypeptides, which independently may be encoded by one or more nucleic acids, a plurality of nucleic acids, fragments of nucleic acids or variants of any of the aforementioned. As used herein, the term "polypeptide" refers to a polymer of amino acid residues (natural or unnatural) linked together most often by peptide bonds. The term, as used herein, refers to proteins, polypeptides, and peptides of any size, structure, or function. In some instances the polypeptide encoded is smaller than about 50 amino acids and the polypeptide is then termed a peptide. If the polypeptide is a peptide, it will be at least about 2, 3, 4, or at least 5 amino acid residues long. Thus, polypeptides include gene products, naturally occurring polypeptides, synthetic polypeptides, homologs, orthologs, paralogs, fragments and other equivalents, variants, and analogs of the foregoing. A polypeptide may be a single molecule or may be a multi-molecular complex such as a dimer, trimer or tetramer. They may also comprise single chain or multichain polypeptides and may be associated or linked. The term polypeptide may also apply to amino acid polymers in which one or more amino acid residues are an artificial chemical analogue of a corresponding naturally occurring amino acid.

[00424] As used herein, the term "polypeptide variant" refers to molecules which differ in their amino acid sequence from a native or reference sequence. The amino acid sequence variants may possess substitutions, deletions, and/or insertions at certain positions within the amino acid sequence, as compared to a native or reference sequence. Variants may possess at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 99.5% or at least about 99.9% identity (homology) to a native or reference sequence.

[00425] In some embodiments “variant mimics” are provided. As used herein, the term “variant mimic” refers to a variant which contains one or more amino acids which would mimic an activated sequence. For example, glutamate may serve as a mimic for phospho-threonine and/or phospho-serine. Alternatively, variant mimics may result in deactivation or in an inactivated product containing the mimic, e.g., phenylalanine may act as an inactivating substitution for tyrosine; or alanine may act as an inactivating substitution for serine.The amino acid sequences of the compounds and/or compositions of the disclosure may comprise naturally occurring amino acids and as such may be considered to be proteins, peptides, polypeptides, or fragments thereof. Alternatively, the compounds and/or compositions may comprise both naturally and non-naturally occurring amino acids.

[00426] As used herein, the term "amino acid sequence variant" refers to molecules with some differences in their amino acid sequences as compared to a native or starting sequence. The amino acid sequence variants may possess substitutions, deletions, and/or insertions at certain positions within the amino acid sequence. As used herein, the terms “native” or “starting” when referring to sequences are relative terms referring to an original molecule against which a comparison may be made. Native or starting sequences should not be confused with wild type sequences. Native sequences or molecules may represent the wild-type (that sequence found in nature) but do not have to be identical to the wild-type sequence.

[00427] Ordinarily, variants will possess at least about 70% homology to a native sequence, and preferably, they will be at least about 80%, more preferably at least about 90% homologous to a native sequence.

[00428] As used herein, the term "homology" as it applies to amino acid sequences is defined as the percentage of residues in the candidate amino acid sequence that are identical with the residues in the amino acid sequence of a second sequence after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent homology. Methods and computer programs for the alignment are well known in the art. It is understood that homology depends on a calculation of percent identity but may differ in value due to gaps and penalties introduced in the calculation.

[00429] As used herein, the term "homolog" as it applies to amino acid sequences is meant the corresponding sequence of other species having substantial identity to a second sequence of a second species.

[00430] As used herein, the term "analog" is meant to include polypeptide variants which differ by one or more amino acid alterations, e.g., substitutions, additions or deletions of amino acid residues that still maintain the properties of the parent polypeptide.

[00431] As used herein, the term "derivative" is used synonymously with the term "variant" and refers to a molecule that has been modified or changed in any way relative to a reference molecule or starting molecule.

[00432] The present disclosure contemplates several types of compounds and/or compositions which are amino acid based including variants and derivatives. These include substitutional, insertional, deletional and covalent variants and derivatives. As such, included within the scope of this disclosure are compounds and/or compositions comprising substitutions, insertions, additions, deletions and/or covalent modifications. For example, sequence tags or amino acids, such as one or more lysines, can be added to peptide sequences of the disclosure (e.g., at the N-terminal or C-terminal ends). Sequence tags can be used for peptide purification or localization. Lysines can be used to increase peptide solubility or to allow for biotinylation. In some cases, amino acid sequences may be included that are targets for biotinylation (e.g. via bacterial ligase). Such sequences may include any of those listed in US Patent No. 5,723,584, the contents of which are herein incorporated by reference in their entirety. For example, the amino acid sequence GLNDIFEAQKIEWHE (SEQ ID NO: 1627) may be used, where the biotin is joined via bacterial ligase to the embedded lysine residue. In addition, antibodies specific for GLNDIFEAQKIEWHE (SEQ ID NO: 1627) may be used to target proteins expressing that sequence. In some cases, these sequences are expressed in association with N- and/or C-terminal secretion signal sequences [e.g. human Ig kappa chains with amino acid sequence MDMRVPAQLLGLLLLWFSGVLG (SEQ ID NO: 66)], flag tag sequences [e.g. DYKDDDDK (SEQ ID NO: 67)], one or more 3C protease cleavage site [e.g. LEVLFQGP (SEQ ID NO: 68)], one or more biotinylation site and/or His-tag sequences [e.g. HHHHHH (SEQ ID NO: 69)].

[00433] Amino acid residues located at the carboxy and amino terminal regions of the amino acid sequence of a peptide or protein may optionally be deleted providing for truncated sequences. Certain amino acids (e.g., C-terminal or N-terminal residues) may alternatively be deleted depending on the use of the sequence, as for example, expression of the sequence as part of a larger sequence which is soluble, or linked to a solid support.

[00434] "Substitutional variants" when referring to proteins are those that have at least one amino acid residue in a native or starting sequence removed and a different amino acid inserted in its place at the same position. The substitutions may be single, where only one amino acid in the molecule has been substituted, or they may be multiple, where two or more amino acids have been substituted in the same molecule.

[00435] As used herein, the term "conservative amino acid substitution" refers to the substitution of an amino acid that is normally present in the sequence with a different amino acid of similar size, charge, or polarity. Examples of conservative substitutions include the substitution of a non-polar (hydrophobic) residue such as isoleucine, valine and leucine for another non-polar residue. Likewise, examples of conservative substitutions include the substitution of one polar (hydrophilic) residue for another such as between arginine and lysine, between glutamine and asparagine, and between glycine and serine. Additionally, the substitution of a basic residue such as lysine, arginine or histidine for another, or the substitution of one acidic residue such as aspartic acid or glutamic acid for another acidic residue are additional examples of conservative substitutions. Examples of non-conservative substitutions include the substitution of a non-polar (hydrophobic) amino acid residue such as isoleucine, valine, leucine, alanine, methionine for a polar (hydrophilic) residue such as cysteine, glutamine, glutamic acid or lysine and/or a polar residue for a non-polar residue.

[00436] As used herein, the term "insertional variants" when referring to proteins are those with one or more amino acids inserted immediately adjacent to an amino acid at a particular position in a native or starting sequence. As used herein, the term "immediately adjacent" refers to an adjacent amino acid that is connected to either the alpha-carboxy or alpha-amino functional group of a starting or reference amino acid.

[00437] As used herein, the term "deletional variants" when referring to proteins, are those with one or more amino acids in the native or starting amino acid sequence removed. Ordinarily, deletional variants will have one or more amino acids deleted in a particular region of the molecule.

[00438] As used herein, the term “derivatives," as referred to herein includes variants of a native or starting protein comprising one or more modifications with organic proteinaceous or non-proteinaceous derivatizing agents, and post-translational modifications. Covalent modifications are traditionally introduced by reacting targeted amino acid residues of the protein with an organic derivatizing agent that is capable of reacting with selected side-chains or terminal residues, or by harnessing mechanisms of post-translational modifications that function in selected recombinant host cells. The resultant covalent derivatives are useful in programs directed at identifying residues important for biological activity, for immunoassays, or for the preparation of anti-protein antibodies for immunoaffinity purification of the recombinant glycoprotein. Such modifications are within the ordinary skill in the art and are performed without undue experimentation.

[00439] Certain post-translational modifications are the result of the action of recombinant host cells on the expressed polypeptide. Glutaminyl and asparaginyl residues are frequently post-translationally deamidated to the corresponding glutamyl and aspartyl residues. Alternatively, these residues are deamidated under mildly acidic conditions. Either form of these residues may be present in the proteins used in accordance with the present disclosure.

[00440] Other post-translational modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the alpha-amino groups of lysine, arginine, and histidine side chains (T. E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)).

[00441] Covalent derivatives specifically include fusion molecules in which proteins of the disclosure are covalently bonded to a non-proteinaceous polymer. The non-proteinaceous polymer ordinarily is a hydrophilic synthetic polymer, i.e. a polymer not otherwise found in nature. However, polymers which exist in nature and are produced by recombinant or in vitro methods are useful, as are polymers which are isolated from nature. Hydrophilic polyvinyl polymers fall within the scope of this disclosure, e.g. polyvinylalcohol and polyvinylpyrrolidone. Particularly useful are polyvinylalkylene ethers such a polyethylene glycol, polypropylene glycol. The proteins may be linked to various non-proteinaceous polymers, such as polyethylene glycol, polypropylene glycol or polyoxyalkylenes, in the manner set forth in U.S. Pat. No. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337.

[00442] As used herein, the term "features" when referring to proteins are defined as distinct amino acid sequence-based components of a molecule. Features of the proteins of the present disclosure include surface manifestations, local conformational shape, folds, loops, half-loops, domains, half-domains, sites, termini or any combination thereof.

[00443] As used herein, the term "surface manifestation" when referring to proteins refers to a polypeptide based component of a protein appearing on an outermost surface.

[00444] As used herein, the term "local conformational shape" when referring to proteins refers to a polypeptide based structural manifestation of a protein which is located within a definable space of the protein.

[00445] As used herein, the term “fold”, when referring to proteins, refers to the resultant conformation of an amino acid sequence upon energy minimization. A fold may occur at the secondary or tertiary level of the folding process. Examples of secondary level folds include beta sheets and alpha helices. Examples of tertiary folds include domains and regions formed

due to aggregation or separation of energetic forces. Regions formed in this way include hydrophobic and hydrophilic pockets, and the like.

[00446] As used herein, the term "turn" as it relates to protein conformation, refers to a bend which alters the direction of the backbone of a peptide or polypeptide and may involve one, two, three or more amino acid residues.

[00447] As used herein, the term "loop," when referring to proteins, refers to a structural feature of a peptide or polypeptide which reverses the direction of the backbone of a peptide or polypeptide and comprises four or more amino acid residues. Oliva et al. have identified at least 5 classes of protein loops (Oliva, B. et al., An automated classification of the structure of protein loops. J Mol Biol. 1997. 266(4):814-30).

[00448] As used herein, the term "half-loop," when referring to proteins, refers to a portion of an identified loop having at least half the number of amino acid resides as the loop from which it is derived. It is understood that loops may not always contain an even number of amino acid residues. Therefore, in those cases where a loop contains or is identified to comprise an odd number of amino acids, a half-loop of the odd-numbered loop will comprise the whole number portion or next whole number portion of the loop (number of amino acids of the loop/2+/-0.5 amino acids). For example, a loop identified as a 7 amino acid loop could produce half-loops of 3 amino acids or 4 amino acids (7/2=3.5+/-0.5 being 3 or 4).

[00449] As used herein, the term "domain," when referring to proteins, refers to a motif of a polypeptide having one or more identifiable structural or functional characteristics or properties (e.g., binding capacity, serving as a site for protein-protein interactions).

[00450] As used herein, the term "half-domain," when referring to proteins, refers to a portion of an identified domain having at least half the number of amino acid resides as the domain from which it is derived. It is understood that domains may not always contain an even number of amino acid residues. Therefore, in those cases where a domain contains or is identified to comprise an odd number of amino acids, a half-domain of the odd-numbered domain will comprise the whole number portion or next whole number portion of the domain (number of amino acids of the domain/2+/-0.5 amino acids). For example, a domain identified as a 7 amino acid domain could produce half-domains of 3 amino acids or 4 amino acids (7/2=3.5+/-0.5 being 3 or 4). It is also understood that sub-domains may be identified within domains or half-domains, these subdomains possessing less than all of the structural or functional properties identified in the domains or half domains from which they were derived. It is also understood that the amino acids that comprise any of the domain types herein need

not be contiguous along the backbone of the polypeptide (i.e., nonadjacent amino acids may fold structurally to produce a domain, half-domain or subdomain).

[00451] As used herein, the terms "site," as it pertains to amino acid based embodiments is used synonymously with "amino acid residue" and "amino acid side chain". A site represents a position within a peptide or polypeptide that may be modified, manipulated, altered, derivatized or varied within the polypeptide based molecules of the present disclosure.

[00452] As used herein, the terms "termini" or "terminus," when referring to proteins refers to an extremity of a peptide or polypeptide. Such extremity is not limited only to the first or final site of the peptide or polypeptide but may include additional amino acids in the terminal regions. The polypeptide based molecules of the present disclosure may be characterized as having both an N-terminus (terminated by an amino acid with a free amino group (NH2)) and a C-terminus (terminated by an amino acid with a free carboxyl group (COOH)). Proteins of the disclosure are in some cases made up of multiple polypeptide chains brought together by disulfide bonds or by non-covalent forces (multimers, oligomers). These sorts of proteins will have multiple N- and C-termini. Alternatively, the termini of the polypeptides may be modified such that they begin or end, as the case may be, with a non-polypeptide based moiety such as an organic conjugate.

[00453] Once any of the features have been identified or defined as a component of a molecule of the disclosure, any of several manipulations and/or modifications of these features may be performed by moving, swapping, inverting, deleting, randomizing or duplicating. Furthermore, it is understood that manipulation of features may result in the same outcome as a modification to the molecules of the disclosure. For example, a manipulation which involved deleting a domain would result in the alteration of the length of a molecule just as modification of a nucleic acid to encode less than a full length molecule would.

[00454] Modifications and manipulations can be accomplished by methods known in the art such as site directed mutagenesis. The resulting modified molecules may then be tested for activity using in vitro or in vivo assays such as those described herein or any other suitable screening assay known in the art.

[00455] In some embodiments, compounds and/or compositions of the present disclosure may comprise one or more atoms that are isotopes. As used herein, the term "isotope" refers to a chemical element that has one or more additional neutrons. In some embodiments, compounds of the present disclosure may be deuterated. As used herein, the term "deuterate" refers to the process of replacing one or more hydrogen atoms in a substance with deuterium

isotopes. Deuterium isotopes are isotopes of hydrogen. The nucleus of hydrogen contains one proton while deuterium nuclei contain both a proton and a neutron. The compounds and/or compositions of the present disclosure may be deuterated in order to change one or more physical property, such as stability, or to allow compounds and/or compositions to be used in diagnostic and/or experimental applications.

Conjugates and Combinations

[00456] It is contemplated by the present disclosure that the compounds and/or compositions of the present disclosure may be complexed, conjugated or combined with one or more homologous or heterologous molecules. As used herein, the term "homologous molecule" refers to a molecule which is similar in at least one of structure or function relative to a starting molecule while a "heterologous molecule" is one that differs in at least one of structure or function relative to a starting molecule. Structural homologs are therefore molecules which may be substantially structurally similar. In some embodiments, such homologs may be identical. Functional homologs are molecules which may be substantially functionally similar. In some embodiments, such homologs may be identical.

[00457] Compounds and/or compositions of the present disclosure may comprise conjugates. Such conjugates of the disclosure may include naturally occurring substances or ligands, such as proteins (e.g., human serum albumin (HSA), low-density lipoprotein (LDL), high-density lipoprotein (HDL), or globulin); carbohydrates (e.g., a dextran, pullulan, chitin, chitosan, inulin, cyclodextrin or hyaluronic acid); or lipids. Conjugates may also be recombinant or synthetic molecules, such as synthetic polymers, e.g., synthetic polyamino acids, an oligonucleotide (e.g. an aptamer). Examples of polyamino acids may include polylysine (PLL), poly L-aspartic acid, poly L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolied) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacryllic acid), N-isopropylacrylamide polymers, or polyphosphazine. Example of polyamines include: polyethylenimine, polylysine (PLL), spermine, spermidine, polyamine, pseudopeptide-polyamine, peptidomimetic polyamine, dendrimer polyamine, arginine, amidine, protamine, cationic lipid, cationic porphyrin, quaternary salt of a polyamine, or an alpha helical peptide.

[00458] In some embodiments, conjugates may also include targeting groups. As used herein, the term "targeting group" refers to a functional group or moiety attached to an agent that facilitates localization of the agent to a desired region, tissue, cell and/or protein. Such

targeting groups may include, but are not limited to cell or tissue targeting agents or groups (e.g. lectins, glycoproteins, lipids, proteins, an antibody that binds to a specified cell type such as a kidney cell or other cell type). In some embodiments, targeting groups may comprise thyrotropins, melanotropins, lectins, glycoproteins, surfactant protein A, mucin carbohydrates, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-gulucosamine, multivalent mannose, multivalent fucose, glycosylated polyaminoacids, multivalent galactose, transferrin, bisphosphonate, polyglutamate, polyaspartate, lipids, cholesterol, steroids, bile acids, folates, vitamin B12, biotin, an RGD peptide, an RGD peptide mimetic or an aptamer.

[00459] In some embodiments, targeting groups may be proteins, e.g., glycoproteins, or peptides, e.g., molecules having a specific affinity for a co-ligand, or antibodies e.g., an antibody, that binds to a specified cell type such as a cancer cell, endothelial cell, or bone cell. Targeting groups may also comprise hormones and/or hormone receptors.

[00460] In some embodiments, targeting groups may be any ligand capable of targeting specific receptors. Examples include, without limitation, folate, GalNAc, galactose, mannose, mannose-6-phosphate, apatamers, integrin receptor ligands, chemokine receptor ligands, transferrin, biotin, serotonin receptor ligands, PSMA, endothelin, GCPII, somatostatin, LDL, and HDL ligands. In some embodiments, targeting groups are aptamers. Such aptamers may be unmodified or comprise any combination of modifications disclosed herein.

[00461] In still other embodiments, compounds and/or compositions of the present disclosure may be covalently conjugated to cell penetrating polypeptides. In some embodiments, cell-penetrating peptides may also include signal sequences. In some embodiments, conjugates of the disclosure may be designed to have increased stability, increased cell transfection and/or altered biodistribution (e.g., targeted to specific tissues or cell types).

[00462] In some embodiments, conjugating moieties may be added to compounds and/or compositions of the present disclosure such that they allow the attachment of detectable labels to targets for clearance. Such detectable labels include, but are not limited to biotin labels, ubiquitins, fluorescent molecules, human influenza hemaglutinin (HA), c-myc, histidine (His), flag, glutathione S-transferase (GST), V5 (a paramyxovirus of simian virus 5 epitope), biotin, avidin, streptavidin, horse radish peroxidase (HRP) and digoxigenin.

[00463] In some embodiments, compounds of the disclosure may be conjugated with an antibody Fc domain to create an Fc fusion protein. The formation of an Fc fusion protein with any of the compounds described herein may be carried out according to any method known in

the art, including as described in US Patent Nos. 5,116,964, 5,541,087 and 8,637,637, the contents of each of which are herein incorporated by reference in their entirety. Fc fusion proteins of the disclosure may comprise a compound of the disclosure linked to the hinge region of an IgG Fc via cysteine residues in the Fc hinge region. Resulting Fc fusion proteins may comprise an antibody-like structure, but without C_{H1} domains or light chains. In some cases, Fc fusion proteins may comprise pharmacokinetic profiles comparable to native antibodies. In some cases, Fc fusion proteins of the disclosure may comprise extended half-life in circulation and/or altered biological activity.

[00464] In some embodiments, compounds and/or compositions of the present disclosure may be combined with one another or other molecules in the treatment of diseases and/or conditions.

Nucleic acids

[00465] In some embodiments, compounds and/or compositions of the present disclosure may be encoded by nucleic acid molecules. Such nucleic acid molecules include, without limitation, DNA molecules, RNA molecules, polynucleotides, oligonucleotides, mRNA molecules, vectors, plasmids and the like. In some embodiments, the present disclosure may comprise cells programmed or generated to express nucleic acid molecules encoding compounds and/or compositions of the present disclosure. In some cases, nucleic acids of the disclosure include codon-optimized nucleic acids. Methods of generating codon-optimized nucleic acids are known in the art and may include, but are not limited to those described in US Patent Nos. 5,786,464 and 6,114,148, the contents of each of which are herein incorporated by reference in their entirety.

Methods of use

[00466] Methods of the present disclosure include methods of modifying growth factor activity in one or more biological system. Such methods may include contacting one or more biological system with a compound and/or composition of the disclosure. In some cases, these methods include modifying the level of free growth factor in a biological system (e.g. in a cell niche or subject). Compounds and/or compostions according to such methods may include, but are not limited to biomolecules, including, but not limited to recombinant proteins, protein complexes and/or antibodies described herein.

[00467] In some embodiments, methods of the present disclosure may be used to initiate or increase growth factor activity, termed “activating methods” herein. Some such methods may

comprise growth factor release from a GPC and/or inhibition of growth factor reassociation into a latent GPC. In some cases, activating methods may comprise the use of an antibody, a recombinant protein and/or a protein complex. According to some activating methods, one or more activating antibody is provided. In such methods, one or more growth factor may be released or prevented from being drawn back into a GPC. In one, non-limiting example, an anti-LAP antibody may be provided that enhances dissociation between a growth factor and a GPC and/or prevents reformation of a GPC.

[00468] Embodiments of the present disclosure include methods of using anti-prodomain antibodies to modify growth factor activity. In some cases, such methods may include the use of anti-GDF prodomain antibodies as GDF-activating antibodies.

[00469] In some embodiments, methods of the present disclosure may be used to reduce or eliminate growth factor activity, termed "inhibiting methods" herein. Some such methods may comprise growth factor retention in a GPC and/or promotion of reassociation of growth factor into a latent GPC. In some cases, inhibiting methods may comprise the use of an antibody, a recombinant protein and/or a protein complex. According to some inhibiting methods, one or more inhibiting antibody is provided. In some cases, inhibiting methods comprise the use of inhibiting recombinant proteins or inhibiting protein complexes capable of association with a growth factor, wherein the association prevents growth factor activity.

Targeting complexes

[00470] In some embodiments methods of the present disclosure may comprise the use of one or more targeting complex. As used herein, the term "targeting complex" refers to a protein complex wherein at least one protein component acts as a targeting agent. As used herein, the term "targeting agent" refers to an agent that directs cargo or other components complexed with the agent to a target site.

[00471] In some cases, targeting complexes may comprise one or more extracellular matrix proteins and/or proteins associated with the extracellular matrix. Such proteins may function as targeting agents in a targeting complex. According to such embodiments, the extracellular matrix component of a targeting complex may direct the complex to target sites comprising extracellular matrix and/or cellular matrix. Extracellular matrix components of targeting complexes may include, but are not limited to LTBPs (e.g. LTBP1, LTBP2, LTBP3 and/or LTBP4), fibrillins (e.g. fibrillin-1, fibrillin-2, fibrillin-3 and/or fibrillin-4), perlecan, decorin, elastin, collagen, GASPs and/or GARPs (e.g. GARP and/or LRRC33).

[00472] In some embodiments, LTBP isoforms may be used as targeting agents to direct targeting complexes to areas of extra cellular matrix surrounding different tissues. LTBP1, for example, has been shown to be expressed predominantly in the heart, lung, kidney, placenta, spleen and stomach. As such, targeting complexes may be directed to those organs by incorporation of LTBP1 as a targeting agent. Similarly, LTBP2 is found in the lung, skeletal muscle, liver and placenta while LTBP3 and LTBP4 are both known to be expressed in the skeletal muscle, heart, ovaries and small intestine (Ceco, E. 2013. FEBS J. 280(17):4198-209, the contents of which are herein incorporated by reference in their entirety). These differential regions of expression may be target sites for targeting complexes in which LTBP2, 3 or 4 isoforms may be used as targeting agents.

[00473] Some targeting complexes of the disclosure may comprise one or more prodomain component, such as a prodomain. In some cases, the portion of such targeting complexes may function to bind free growth factors to reduce free growth factor levels and/or activity. In some cases, GDF prodomains may be included in targeting complexes.

Therapeutics

[00474] In some embodiments, compositions and methods of the disclosure may be used to treat a wide variety of diseases, disorders and/or conditions. In some cases, such diseases, disorders and/or conditions may be TGF-β-related indications. As used herein, the term "TGF-β-related indication" refers to any disease, disorder and/or condition related to expression, activity and/or metabolism of a TGF-β family member protein or any disease, disorder and/or condition that may benefit from modulation of the activity and/or levels of one or more TGF-β family member protein. TGF-β-related indications may include, but are not limited to, fibrosis, anemia of the aging, cancer (including, but not limited to colon, renal, breast, malignant melanoma and glioblastoma), facilitation of rapid hematopoiesis following chemotherapy, bone healing, endothelial proliferation syndromes, asthma and allergy, gastrointestinal disorders, aortic aneurysm, orphan indications (such as Marfan's syndrome and Camurati-Engelmann disease), obesity, diabetes, arthritis, multiple sclerosis, muscular dystrophy, amyotrophic lateral sclerosis (ALS), Parkinson's disease, osteoporosis, osteoarthritis, osteopenia, metabolic syndromes, nutritional disorders, organ atrophy, chronic obstructive pulmonary disease (COPD), and anorexia. Additional indications may include any of those disclosed in US Pub. No. 2013/0122007, US Pat. No. 8,415,459 or International Pub. No. WO 2011/151432, the contents of each of which are herein incorporated by reference in their entirety.

[00475] Efficacy of treatment or amelioration of disease can be assessed, for example by measuring disease progression, disease remission, symptom severity, reduction in pain, quality of life, dose of a medication required to sustain a treatment effect, level of a disease marker or any other measurable parameter appropriate for a given disease being treated or targeted for prevention. It is well within the ability of one skilled in the art to monitor efficacy of treatment or prevention by measuring any one of such parameters, or any combination of parameters. In connection with the administration of compositions of the present disclosure, "effective against" for example a cancer, indicates that administration in a clinically appropriate manner results in a beneficial effect for at least a statistically significant fraction of patients, such as an improvement of symptoms, a cure, a reduction in disease load, reduction in tumor mass or cell numbers, extension of life, improvement in quality of life, or other effect generally recognized as positive by medical doctors familiar with treating the particular type of cancer.

[00476] A treatment or preventive effect is evident when there is a statistically significant improvement in one or more parameters of disease status, or by a failure to worsen or to develop symptoms where they would otherwise be anticipated. As an example, a favorable change of at least 10% in a measurable parameter of disease, and preferably at least 20%, 30%, 40%, 50% or more can be indicative of effective treatment. Efficacy for a given composition or formulation of the present disclosure can also be judged using an experimental animal model for the given disease as known in the art. When using an experimental animal model, efficacy of treatment is evidenced when a statistically significant change is observed.

Therapeutics for anemia, thrombocytopenia and neutropenia

[00477] During chemotherapy, cell division is temporarily halted to prevent the growth and spread of cancerous cells. An unfortunate side effect is the loss of red blood cells, platelets and white blood cells which depend on active cell division of bone marrow cells. In some embodiments, compounds and/or compositions of the present disclosure may be designed to treat patients suffering from anemia (the loss of red blood cells), thrombocytopenia (a decrease in the number of platelets) and/or neutropenia (a decrease in the number of neutrophils).

Therapeutics for cancer

[00478] Various cancers may be treated with compounds and/or compositions of the present disclosure. As used herein, the term "cancer" refers to any of various malignant neoplasms characterized by the proliferation of anaplastic cells that tend to invade surrounding tissue and metastasize to new body sites and also refers to the pathological condition characterized by such malignant neoplastic growths. Cancers may be tumors or hematological malignancies, and include but are not limited to, all types of lymphomas/leukemias, carcinomas and sarcomas, such as those cancers or tumors found in the anus, bladder, bile duct, bone, brain, breast, cervix, colon/rectum, endometrium, esophagus, eye, gallbladder, head and neck, liver, kidney, larynx, lung, mediastinum (chest), mouth, ovaries, pancreas, penis, prostate, skin, small intestine, stomach, spinal marrow, tailbone, testicles, thyroid and uterus.

[00479] In cancer, TGF-β may be either growth promoting or growth inhibitory. As an example, in pancreatic cancers, SMAD4 wild type tumors may experience inhibited growth in response to TGF-β, but as the disease progresses, constitutively activated type II receptor is typically present. Additionally, there are SMAD4-null pancreatic cancers. In some embodiments, compounds and/or compositions of the present disclosure are designed to selectively target components of TGF-β signaling pathways that function uniquely in one or more forms of cancer. Leukemias, or cancers of the blood or bone marrow that are characterized by an abnormal proliferation of white blood cells i.e., leukocytes, can be divided into four major classifications including Acute lymphoblastic leukemia (ALL), Chronic lymphocytic leukemia (CLL), Acute myelogenous leukemia or acute myeloid leukemia (AML) (AML with translocations between chromosome 10 and 11 [t(10, 11)], chromosome 8 and 21 [t(8;21)], chromosome 15 and 17 [t(15;17)], and inversions in chromosome 16 [inv(16)]; AML with multilineage dysplasia, which includes patients who have had a prior myelodysplastic syndrome (MDS) or myeloproliferative disease that transforms into AML; AML and myelodysplastic syndrome (MDS), therapy-related, which category includes patients who have had prior chemotherapy and/or radiation and subsequently develop AML or MDS; d) AML not otherwise categorized, which includes subtypes of AML that do not fall into the above categories; and e) Acute leukemias of ambiguous lineage, which occur when the leukemic cells cannot be classified as either myeloid or lymphoid cells, or where both types of cells are present); and Chronic myelogenous leukemia (CML).

[00480] The types of carcinomas include, but are not limited to, papilloma/carcinoma, choriocarcinoma, endodermal sinus tumor, teratoma, adenoma/adenocarcinoma, melanoma,

fibroma, lipoma, leiomyoma, rhabdomyoma, mesothelioma, angioma, osteoma, chondroma, glioma, lymphoma/leukemia, squamous cell carcinoma, small cell carcinoma, large cell undifferentiated carcinomas, basal cell carcinoma and sinonasal undifferentiated carcinoma.

[00481] The types of sarcomas include, but are not limited to, soft tissue sarcoma such as alveolar soft part sarcoma, angiosarcoma, dermatofibrosarcoma, desmoid tumor, desmoplastic small round cell tumor, extraskeletal chondrosarcoma, extraskeletal osteosarcoma, fibrosarcoma, hemangiopericytoma, hemangiosarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, lymphosarcoma, malignant fibrous histiocytoma, neurofibrosarcoma, rhabdomyosarcoma, synovial sarcoma, and Askin's tumor, Ewing's sarcoma (primitive neuroectodermal tumor), malignant hemangioendothelioma, malignant schwannoma, osteosarcoma, and chondrosarcoma.

[00482] In some embodiments, compositions and methods of the disclosure may be used to treat one or more types of cancer or cancer-related conditions that may include, but are not limited to colon cancer, renal cancer, breast cancer, malignant melanoma and glioblastomas (Schlingensiepen et al., 2008; Ouhtit et al., 2013).

[00483] High-grade gliomas (e.g. anaplastic astrocytomas and glioblastomas) make up around 60% of malignant brain tumors. TGF-β2 has been found to be overexpressed in over 90% of such gliomas and expression levels correlate with tumor progression. Further, studies using TGF-β2 reduction at the mRNA level in cancer patients showed significant improvement in tumor outcome (Bogdahn et al., 2010). In light of these studies, some compositions of the present disclosure may be used therapeutically to treat individuals with high-grade gliomas. Such compositions may act to lower the levels of free TGF-β2 and/or the levels of TGF-β2 activity.

[00484] In some cases, TGF-β2 activity may contribute to tumor development through modulation of metastasis, angiogenesis, proliferation and/or immunosuppressive functions that impair immunological tumor surveillance (Schlingensiepen et al., 2008). A study by Reed et al (Reed et al., 1994) demonstrated TGF-β2 mRNA expression in a large percentage of melanocytic lesions including primary invasive melanomas and metastatic melanomas. Some compounds and/or compositions of the present disclosure may be used to modulate TGF-β2 activity and/or levels in such lesions and or prevent lesion formation. Melanoma cell growth in the brain parenchyma has also been shown to be influenced by TGF-β2 activity (Zhang et al., 2009). Some compounds and/or compositions of the present disclosure may be used to prevent or control such cell growth through modulation of TGF-β2 activity and/or levels.

[00485] Among females worldwide, breast cancer is the most prevalent form of cancer. Breast cancer metastasis is mediated in part through interactions between cancer cells and extracellular matrix components, such as hyaluronic acid (HA). CD44 has been shown to be the major receptor for HA on cancer cells (Ouhtit et al., 2013). The interaction between CD44 and HA leads to modulation of cell motility, survival adhesion and proliferation. TGF-β2 transcription is also upregulated by CD44 signaling activity and is believe to contribute to resulting changes in cell motility. Unfortunately, current therapies have limited efficacy and many carry adverse effects due to a lack of specificity. In some cases, compounds and/or compositions of the present disclosure may be used to alter cellular activities induced by TGF-β2 upregulation.

[00486] The disclosure further relates to the use of compounds and/or compositions of the present disclosure for treating one or more forms of cancer, in combination with other pharmaceuticals and/or other therapeutic methods, *e.g.*, with known pharmaceuticals and/or known therapeutic methods, such as, for example, those which are currently employed for treating these disorders. For example, the compounds and/or compositions of the present disclosure can also be administered in conjunction with one or more additional anti-cancer treatments, such as biological, chemotherapy and radiotherapy. Accordingly, a treatment can include, for example, imatinib (Gleevac), all-trans-retinoic acid, a monoclonal antibody treatment (gemtuzumab, ozogamicin), chemotherapy (for example, chlorambucil, prednisone, prednisolone, vincristine, cytarabine, clofarabine, farnesyl transferase inhibitors, decitabine, inhibitors of MDR1), rituximab, interferon-α, anthracycline drugs (such as daunorubicin or idarubicin), L-asparaginase, doxorubicin, cyclophosphamide, doxorubicin, bleomycin, fludarabine, etoposide, pentostatin, or cladribine), bone marrow transplant, stem cell transplant, radiation therapy, anti-metabolite drugs (methotrexate and 6-mercaptopurine), or any combination thereof.

[00487] Radiation therapy (also called radiotherapy, X-ray therapy, or irradiation) is the use of ionizing radiation to kill cancer cells and shrink tumors. Radiation therapy can be administered externally via external beam radiotherapy (EBRT) or internally via brachytherapy. The effects of radiation therapy are localized and confined to the region being treated. Radiation therapy may be used to treat almost every type of solid tumor, including cancers of the brain, breast, cervix, larynx, lung, pancreas, prostate, skin, stomach, uterus, or soft tissue sarcomas. Radiation is also used to treat leukemia and lymphoma.

[00488] Chemotherapy is the treatment of cancer with drugs that can destroy cancer cells. In current usage, the term "chemotherapy" usually refers to cytotoxic drugs which affect

rapidly dividing cells in general, in contrast with targeted therapy. Chemotherapy drugs interfere with cell division in various possible ways, e.g. with the duplication of DNA or the separation of newly formed chromosomes. Most forms of chemotherapy target all rapidly dividing cells and are not specific to cancer cells, although some degree of specificity may come from the inability of many cancer cells to repair DNA damage, while normal cells generally can.

[00489] Most chemotherapy regimens are given in combination. Exemplary chemotherapeutic agents include , but are not limited to, 5-FU Enhancer, 9-AC, AG2037, AG3340, Aggrecanase Inhibitor, Aminoglutethimide, Amsacrine (m-AMSA), Asparaginase, Azacitidine, Batimastat (BB94), BAY 12-9566, BCH-4556, Bis-Naphtalimide, Busulfan, Capecitabine, Carboplatin, Carmustaine+Polifepr Osan, cdk4/cdk2 inhibitors, Chlorombucil, CI-994, Cisplatin, Cladribine, CS-682, Cytarabine HCl, D2163, Dactinomycin, Daunorubicin HCl, DepoCyt, Dexifosamide, Docetaxel, Dolastain, Doxifluridine, Doxorubicin, DX8951f, E 7070, EGFR, Epirubicin, Erythropoietin, Estramustine phosphate sodium, Etoposide (VP16-213), Farnesyl Transferase Inhibitor, FK 317, Flavopiridol, Floxuridine, Fludarabine, Fluorouracil (5-FU), Flutamide, Fragyline, Gemcitabine, Hexamethylmelamine (HMM), Hydroxyurea (hydroxycarbamide), Ifosfamide, Interferon Alfa-2a, Interferon Alfa-2b, Interleukin-2, Irinotecan, ISI 641, Krestin, Lemonal DP 2202, Leuprolide acetate (LHRH-releasing factor analogue), Levamisole, LiGLA (lithium-gamma linolenate), Lodine Seeds, Lometexol, Lomustine (CCNU), Marimistat, Mechlorethamine HCl (nitrogen mustard), Megestrol acetate, Meglamine GLA, Mercaptopurine, Mesna, Mitoguazone (methyl-GAG; methyl glyoxal bis-guanylhydrazone; MGBG), Mitotane (o.p'-DDD), Mitoxantrone, Mitoxantrone HCl, MMI 270, MMP, MTA/LY 231514, Octreotide, ODN 698, OK-432, Oral Platinum, Oral Taxoid, Paclitaxel (TAXOL.RTM.), PARP Inhibitors, PD 183805, Pentostatin (2' deoxycoformycin), PKC 412, Plicamycin, Procarbazine HCl, PSC 833, Ralitrexed, RAS Farnesyl Transferase Inhibitor, RAS Oncogene Inhibitor, Semustine (methyl-CCNU), Streptozocin, Suramin, Tamoxifen citrate, Taxane Analog, Temozolomide, Teniposide (VM-26), Thioguanine, Thiotepa, Topotecan, Tyrosine Kinase, UFT (Tegafur/Uracil), Valrubicin, Vinblastine sulfate, Vindesine sulfate, VX-710, VX-853, YM 116, ZD 0101, ZD 0473/Anormed, ZD 1839, ZD 9331.

[00490] Biological therapies use the body's immune system, either directly or indirectly, to fight cancer or to lessen the side effects that may be caused by some cancer treatments. In some embodiments, compounds and/or compositions of the present disclosure may be considered biological therapies in that they may stimulate immune system action against one

or more tumor, for example. However, this approach may also be considered with other such biological approaches, e.g., immune response modifying therapies such as the administration of interferons, interleukins, colony-stimulating factors, other monoclonal antibodies, vaccines, gene therapy, and nonspecific immunomodulating agents are also envisioned as anti-cancer therapies to be combined with the compounds and/or compositions of the present disclosure.

[00491] Small molecule targeted therapy drugs are generally inhibitors of enzymatic domains on mutated, overexpressed, or otherwise critical proteins within the cancer cell, such as tyrosine kinase inhibitors imatinib (Gleevec/Glivec) and gefitinib (Iressa). Examples of monoclonal antibody therapies that can be used with compounds and/or compositions of the present disclosure include, but are not limited to, the anti-HER2/neu antibody trastuzumab (Herceptin) used in breast cancer, and the anti-CD20 antibody rituximab, used in a variety of B-cell malignancies. The growth of some cancers can be inhibited by providing or blocking certain hormones. Common examples of hormone-sensitive tumors include certain types of breast and prostate cancers. Removing or blocking estrogen or testosterone is often an important additional treatment. In certain cancers, administration of hormone agonists, such as progestogens may be therapeutically beneficial.

[00492] Cancer immunotherapy refers to a diverse set of therapeutic strategies designed to induce the patient's own immune system to fight the tumor, and include, but are not limited to, intravesical BCG immunotherapy for superficial bladder cancer, vaccines to generate specific immune responses, such as for malignant melanoma and renal cell carcinoma, and the use of Sipuleucel-T for prostate cancer, in which dendritic cells from the patient are loaded with prostatic acid phosphatase peptides to induce a specific immune response against prostate-derived cells.

Therapeutics for angiogenic and endothelial proliferation conditions

[00493] The compounds and/or compositions of the present disclosure may be used to treat angiogenic and endothelial proliferation syndromes, diseases or disorders. The term “angiogenesis”, as used herein refers to the formation and/or reorganization of new blood vessels. Angiogenic disease involves the loss of control over angiogenesis in the body. In such cases, blood vessel growth, formation or reorganization may be overactive (including during tumor growth and cancer where uncontrolled cell growth requires increased blood supply) or insufficient to sustain healthy tissues. Such conditions may include, but are not limited to angiomas, angiosarcomas, telangiectasia, lymphangioma, congenital vascular

anomalies, tumor angiogenesis and vascular structures after surgery. Excessive angiogenesis is noted in cancer, macular degeneration, diabetic blindness, rheumatoid arthritis, psoriasis as well as many other conditions. Excessive angiogenesis is often promoted by excessive angiogenic growth factor expression. Compounds and/or compositions of the present disclosure may act to block growth factors involved in excessive angiogenesis. Alternatively, compounds and/or compositions of the present disclosure may be utilized to promote growth factor signaling to enhance angiogenesis in conditions where angiogenesis is inhibited. Such conditions include, but are not limited to coronary artery disease, stroke, diabetes and chronic wounds.

Therapeutics for cardiovascular indications

[00494] In some embodiments, compounds and/or compositions of the present disclosure may be used to treat one or more cardiovascular indications, including, but not limited to cardiac hypertrophy. Cardiac hypertrophy comprises enlargement of the heart due, typically due to increased cell volume of cardiac cells (Aurigemma 2006. N Engl J Med. 355(3):308-10). Age-related cardiac hypertrophy may be due, in part, to reduced circulating levels of GDF-11. A study by Loffredo et al (Loffredo et al., 2013. Cell. 153:828-39) found that fusion of the circulatory system between young and old mice had a protective effect with regard to cardiac hypertrophy. The study identified GDF-11 as a circulating factor that decreased with age in mice and was able to show that its administration could also reduce cardiac hypertrophy. Some compounds and/or compositions of the present disclosure may be used to treat and/or prevent cardiac atrophy. Such compounds and/or compositions may comprise GDF-11 agonists that elevate levels of circulating GDF-11, in some cases through enhancing the dissociation of GDF-11 growth factor from latent GPCs.

[00495] In some embodiments, animal models may be used to develop and test compounds and/or compositions of the present disclosure for use in the treatment of cardiovascular diseases, disorders and/or conditions. In some cases, vascular injury models may be used to test compounds in the treatment of atherosclerosis and/or restenosis. Such models may include balloon injury models. In some cases, these may be carried out as described in Smith et al., 1999. Circ Res. 84(10):1212-22, the contents of which are herein incorporated by reference in their entirety.

Therapeutics related to muscle disorders and/or injuries

[00496] In some embodiments, compounds and/or compositions of the present disclosure may be used to treat one or more muscle disorders and/or injuries. In some cases, such compounds and/or composition may include, but are not limited to antibodies that modulate GDF-8, GDF-11 and/or activin activity. Muscle comprises about 40-50% of total body weight, making it the largest organ in the body. Muscle disorders may include cachexia (e.g. muscle wasting). Muscle wasting may be associated with a variety of diseases and catabolic disorders (e.g. HIV/AIDS, cancer, cancer cachexia, renal failure, congestive heart failure, muscular dystrophy, disuse atrophy, chronic obstructive pulmonary disease, motor neuron disease, trauma, neurodegenerative disease, infection, rheumatoid arthritis, immobilization, diabetes, etc.). In such disorders, GDF-8 and/or activin signaling activity may contribute to muscle catabolism (Han et al., 2013. Int J Biochem Cell Biol. 45(10):2333-47; Lee., 2010. Immunol Endocr Metab Agents Med Chem. 10:183-94, the contents of each of which are herein incorporated by reference in their entirety). Other muscle disorders may comprise sarcopenia. Sarcopenia is the progressive loss of muscle and function associated with aging. In the elderly, sarcopenia can cause frailty, weakness, fatigue and loss of mobility (Morely. 2012. Family Practice. 29:i44-i48). With the aged population increasing in numbers, sarcopenia is progressively becoming a more serious public health concern. A study by Hamrick et al (Hamrick et al., 2010. 69(3):579-83) demonstrated that GDF-8 inhibition could repair muscle in a mouse model of fibula osteotomoy comprising lateral compartment muscle damage. Administration of GDF-8 propeptides was sufficient to increase muscle mass by nearly 20% as well as improve fracture healing. Some compounds and/or compositions of the present disclosure may be used to treat muscle diseases, disorders and/or injuries by modulating GDF-8 activity. In some cases, compounds of the present disclosure may be GDF-8 signaling antagonists, preventing or reducing GDF-8 signaling activity.

[00497] Inclusion body myositis (IBM) is a disease characterized by progressive muscle loss, typically occurring in mid- to late-life. The disease is thought to occur due to an autoimmune response to autoantigens in the muscle causing T-cell invasion of the muscle fiber and resulting in myofiber destruction (Greenberg 2012. Curr Opin Neurol. 25(5):630-9). Therapeutic compounds are being investigated, including Bimagrumab (BYM338; Novartis, Basel, Switzerland), an antibody that targets type II activin receptors, preventing GDF-8 and/or activin signal transduction, thereby stimulating muscle production and strengthening [see clinical trial number NCT01925209 entitled *Efficacy and Safety of Bimagrumab/BYM338 at 52 Weeks on Physical Function, Muscle Strength, Mobility in sIBM Patients (RESILIENT)*]. Some compounds and/or compositions of the present disclosure may

be used to treat subjects with IBM. In some cases, such compounds and/or compositions may block GDF-8 activity (e.g. through stabilization of GDF-8 GPCs). In addition to IBM, BYM338 is being investigated for treatment of chronic obstructive pulmonary disease (COPD). In some cases, compounds and/or compositions of the present disclosure utilized for IBM treatment, may be used to treat COPD as well. In some cases, compounds and/or compositions of the present disclosure may be administered in combination and/or coordination with BYM338.

Therapeutics for diabetes

[00498] Skeletal muscle uses and stores glucose for fuel. Due to this, skeletal muscle is an important regulator of circulating glucose levels. Uptake of glucose by muscle can be stimulated by either contraction or by insulin stimulation (McPherron et al., 2013. Adipocyte. 2(2):92-8, herein incorporated by reference in its entirety). A recent study by Guo et al (Guo, et al., 2012. Diabetes 61(10):2414-23) found that when GDF-8 receptor-deficient mice were crossed with A-ZIP/F1 mice (a lipodistrophic mouse strain, used as a diabetic model), hybrid off-spring showed reduced levels of blood glucose and improved sensitivity to insulin. Hyperphagia (excessive eating) was also reduced in these mice. In some embodiments, compound and/or compositions of the present disclosure may be used to treat diabetes and/or hyperphagia. Some such treatments may be used to reduce blood glucose and/or improve insulin sensitivity. In some cases, such treatments may comprise GDF-8 signaling antagosists, such as one or more antibodies that prevent dissociation of GDF-8 from its prodomain.

Therapeutics for GDF-11-related indications

[00499] In some embodiments, compounds of the disclosure may be used to treat TGF-β-related indications comprising GDF-11-related indications. As used herein, a GDF-11-related indication is a disease, disorder and/or condition related to GDF-11 activity. GDF-11 expression is systemic and its activity is thought to be involved in multiple processes (Lee et al., 2013. PNAS. 110(39):E3713-22, the contents of which are herein incorporated by reference in their entirety). It is believed to be involved in development of multiple tissues, including, but not limited to the retina, kidney, pancreas and olfactory system. It is also believed to be a circulating factor in the blood. Recent studies indicate that GDF-11 may rejuvenate skeletal muscle, improve cerebral circulation and promote neurogenesis (Sinha, M. et al., 2014. Science Express. 10.1126/science.1251152, p2-6 and Katsimpardi, L. et al.,

2014. Science Express. 10.1126/science.1251141, the contents of each of which are herein incorporated by reference in their entirety). In some cases, antibodies of the disclosure may promote skeletal muscle rejuvenation, improve cerebral circulation and promote neurogenesis by promoting the release of GDF-11 growth factor from latent complexes.

[00500] Although its role is somewhat controversial, GDF-11 is thought to be involved in the regulation of erythropoiesis with both positive and negative regulation being described in scientific literature. Carrancio et al and Suragani et al (Carrancio, S. et al., 2014. Br J Haematol. 165(6):870-82 and Suragani, R.N.V.S. et al. 2014. Blood. 123(25): 3864-72, the contents of each of which are herein incorporated by reference in their entirety) demonstrate that a GDF-11 ligand trap, comprising an activin receptor IIA extracellular domain (SOTATERCEPT®), enhances erythropoiesis. A similar agent shown to bind GDF-11 and modified to reduce affinity for activin, ACE-536, was also shown to stimulate erythropoiesis (Suragani, R.N.V.S. et al. 2014. Nature Medicine. 20(4): 408-17, the contents of which are herein incorporated by reference in their entirety). Further studies demonstrate short term increases in hemoglobin levels in patients receiving SOTATERCEPT® (El-Shahawy, M. et al., 2014. Poster #81, National Kidney Foundation (NKF) 2014 Spring Clinical Meeting). In some cases, GDF-11 inhibiting antibodies of the disclosure may be used according to the methods described in these studies to stimulate erythropoiesis and treat anemia and/or β-thalassemia.

Veterinary applications

[00501] In some embodiments, it is contemplated that compositions and methods of the disclosure will find utility in the area of veterinary care including the care and treatment of non-human vertebrates. As described herein, the term "vertebrate" includes all vertebrates including, but not limited to fish, amphibians, birds, reptiles and mammals (including, but not limited to alpaca, banteng, bison, camel, cat, cattle, deer, dog, donkey, gayal, goat, guinea pig, horse, llama, mice, monkeys, mule, pig, rabbit, rats, reindeer, sheep water buffalo, yak and humans). As used herein the term "non-human vertebrate" refers to any vertebrate with the exception of humans (i.e. Homo sapiens). Exemplary non-human vertebrates include wild and domesticated species such as companion animals and livestock. Livestock include domesticated animals raised in an agricultural setting to produce materials such as food, labor, and derived products such as fiber and chemicals. Generally, livestock includes all mammals, avians and fish having potential agricultural significance. In particular, four-legged slaughter animals include steers, heifers, cows, calves, bulls, cattle, swine and sheep.

Bioprocessing

[00502] In some embodiments, the present disclosure provides methods for producing one or more biological products in host cells by contacting such cells with compounds and/or compositions of the present disclosure capable of modulating expression of target genes, or altering the level of growth factor signaling molecules wherein such modulation or alteration enhances production of biological products. According to the present disclosure, bioprocessing methods may be improved by using one or more compounds and/or compositions of the present disclosure. They may also be improved by supplementing, replacing or adding one or more compounds and/or compositions.

Pharmaceutical compositions

[00503] The pharmaceutical compositions described herein may be characterized by one or more of bioavailability, therapeutic window and/or volume of distribution.

Bioavailability

[00504] In some embodiments, pharmaceutical compositions comprise complexes of compounds and/or compositions of the present disclosure with GPCs. In such embodiments, complexes may be implanted at desired therapeutic sites where steady dissociation of growth factors from complexes may occur over a desired period of time. In some embodiments, implantation complexes may be carried out in association with sponge and/or bone-like matrices. Such implantations may include, but are not limited to dental implant sites and/or sites of bone repair.

[00505] In some embodiments, compounds and/or compositions of the present disclosure are made in furin-deficient cells. GPCs produced in such cells may be useful for treatment in areas where release is slowed due to the fact that furin cleavage in vivo is rate-limiting during GPC processing. In some embodiments, one or more tolloid and/or furin sites in GPCs are mutated, slowing the action of endogenous tolloid and/or furin proteases. In such embodiments, growth factor release may be slowed (e.g. at sites of implantation).

[00506] Antibodies of the present disclosure, when formulated into compositions with delivery/formulation agents or vehicles as described herein, may exhibit increased bioavailability as compared to compositions lacking delivery agents as described herein. As used herein, the term "bioavailability" refers to the systemic availability of a given amount of a particular agent administered to a subject. Bioavailability may be assessed by measuring the area under the curve (AUC) or the maximum serum or plasma concentration (C_{max}) of the

unchanged form of a compound following administration of the compound to a mammal. AUC is a determination of the area under the curve plotting the serum or plasma concentration of a compound along the ordinate (Y-axis) against time along the abscissa (X-axis). Generally, the AUC for a particular compound may be calculated using methods known to those of ordinary skill in the art and as described in G. S. Banker, Modern Pharmaceutics, Drugs and the Pharmaceutical Sciences, v. 72, Marcel Dekker, New York, Inc., 1996, the contents of which are herein incorporated by reference in their entirety.

[00507] C_{max} values are maximum concentrations of compounds achieved in serum or plasma of a subject following administration of compounds to the subject. C_{max} values of particular compounds may be measured using methods known to those of ordinary skill in the art. As used herein, the phrases "increasing bioavailability" or "improving the pharmacokinetics," refer to actions that may increase the systemic availability of a compounds and/or compositions of the present disclosure (as measured by AUC, C_{max}, or C_{min}) in a subject. In some embodiments, such actions may comprise co-administration with one or more delivery agents as described herein. In some embodiments, the bioavailability of compounds and/or compositions may increase by at least about 2%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95% or about 100%.

Therapeutic window

[00508] Compounds and/or compositions of the present disclosure, when formulated with one or more delivery agents as described herein, may exhibit increases in the therapeutic window of compound and/or composition administration as compared to the therapeutic window of compounds and/or compositions administered without one or more delivery agents as described herein. As used herein, the term "therapeutic window" refers to the range of plasma concentrations, or the range of levels of therapeutically active substance at the site of action, with a high probability of eliciting a therapeutic effect. In some embodiments, therapeutic windows of compounds and/or compositions when co-administered with one or more delivery agent as described herein may increase by at least about 2%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least

about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95% or about 100%.

Volume of distribution

[00509] Compounds and/or compositions of the present disclosure, when formulated with one or more delivery agents as described herein, may exhibit an improved volume of distribution (V_{dist}), e.g., reduced or targeted, relative to formulations lacking one or more delivery agents as described herein. V_{dist} relates the amount of an agent in the body to the concentration of the same agent in the blood or plasma. As used herein, the term "volume of distribution" refers to the fluid volume that would be required to contain the total amount of an agent in the body at the same concentration as in the blood or plasma: V_{dist} equals the amount of an agent in the body/concentration of the agent in blood or plasma. For example, for a 10 mg dose of a given agent and a plasma concentration of 10 mg/L, the volume of distribution would be 1 liter. The volume of distribution reflects the extent to which an agent is present in the extravascular tissue. Large volumes of distribution reflect the tendency of agents to bind to the tissue components as compared with plasma proteins. In clinical settings, V_{dist} may be used to determine loading doses to achieve steady state concentrations. In some embodiments, volumes of distribution of compounds and/or compositions of the present disclosure when co-administered with one or more delivery agents as described herein may decrease at least about 2%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%.

Formulation, administration, delivery and dosing

[00510] In some embodiments, compounds and/or compositions of the present disclosure are pharmaceutical compositions. As used herein, the term "pharmaceutical composition" refers to a compound and/or composition of the present disclosure that has been formulated with one or more pharmaceutically acceptable excipients. In some embodiments, pharmaceutical compositions may optionally comprise one or more additional active substances, e.g. therapeutically and/or prophylactically active substances. General considerations in the formulation and/or manufacture of pharmaceutical agents may be found, for example, in *Remington: The Science and Practice of Pharmacy* 21st ed., Lippincott Williams & Wilkins, 2005 (incorporated herein by reference).

[00511] In some embodiments, compositions may be administered to humans, human patients or subjects. For the purposes of the present disclosure, the phrase "active ingredient" generally refers to compounds and/or compositions of the present disclosure to be delivered as described herein.

[00512] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to other subjects, *e.g.,* to non-human animals, e.g. non-human mammals. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with merely ordinary, if any, experimentation. Subjects to which administration of pharmaceutical compositions is contemplated include, but are not limited to, humans and/or other primates; mammals, including commercially relevant mammals such as cattle, pigs, horses, sheep, cats, dogs, mice, and/or rats; and/or birds, including commercially relevant birds such as poultry, chickens, ducks, geese, and/or turkeys.

[00513] In some embodiments, formulations of the pharmaceutical compositions described herein may be prepared by any method known or hereafter developed in the art of pharmacology. In general, such preparatory methods include the step of bringing active ingredients into association with excipients and/or one or more other accessory ingredients, and then, if necessary and/or desirable, dividing, shaping and/or packaging products into desired single- or multi-dose units.

[00514] In some embodiments, pharmaceutical compositions of the present disclosure may be prepared, packaged, and/or sold in bulk, as single unit doses, and/or as a plurality of single unit doses. As used herein, the term "unit dose" refers to a discrete amount of the pharmaceutical composition comprising a predetermined amount of active ingredient. Amounts of active ingredient are generally equal to the dosage of active ingredients which would be administered to subjects and/or convenient fractions of such a dosages such as, for example, one-half or one-third of such a dosages.

[00515] In some embodiments, relative amounts of active ingredients, pharmaceutically acceptable excipients, and/or any additional ingredients in pharmaceutical compositions of the present disclosure may vary, depending upon identity, size, and/or condition of subjects to be treated and further depending upon routes by which compositions are to be administered. By way of example, compositions may comprise between about 0.1% and 100%, e.g., from

about 0.5% to about 50%, from about 1% to about 30%, from about 5% to about 80% or at least 80% (w/w) active ingredient. In some embodiments, active ingredients are antibodies directed toward regulatory elements and/or GPCs.

Formulations

[00516] Compounds and/or compositions of the present disclosure may be formulated using one or more excipients to: (1) increase stability; (2) increase cell permeability; (3) permit the sustained or delayed release (e.g., of compounds and/or growth factors from such formulations); and/or (4) alter the biodistribution (e.g., target compounds to specific tissues or cell types). In addition to traditional excipients such as any and all solvents, dispersion media, diluents, liquid vehicles, dispersion aids, suspension aids, surface active agents, isotonic agents, thickening agents, emulsifying agents and preservatives, formulations of the present disclosure may comprise, without limitation, liposomes, lipid nanoparticles, polymers, lipoplexes, core-shell nanoparticles, peptides, proteins, cells transfected with the compounds and/or compositions of the present disclosure (e.g., for transplantation into subjects) and combinations thereof.

Excipients

[00517] Various excipients for formulating pharmaceutical compositions and techniques for preparing the composition are known in the art (see Remington: The Science and Practice of Pharmacy, 21st Edition, A. R. Gennaro, Lippincott, Williams & Wilkins, Baltimore, MD, 2006; incorporated herein by reference).

[00518] In some embodiments, the use of conventional excipient media are contemplated within the scope of the present disclosure, except insofar as any conventional excipient media may be incompatible with substances and/or their derivatives, such as by producing any undesirable biological effects or otherwise interacting in deleterious manners with any other component(s) of pharmaceutical compositions.

[00519] Formulations of pharmaceutical compositions described herein may be prepared by any method known or hereafter developed in the art of pharmacology. In general, such preparatory methods include steps of associating active ingredients with excipients and/or other accessory ingredients.

[00520] Pharmaceutical compositions, in accordance with the present disclosure, may be prepared, packaged, and/or sold in bulk, as single unit doses, and/or as a plurality of single unit doses.

[00521] Relative amounts of active ingredients, pharmaceutically acceptable excipients, and/or additional ingredients in pharmaceutical compositions of the present disclosure may vary, depending upon identity, size, and/or condition of subjects being treated and further depending upon routes by which pharmaceutical compositions may be administered.

[00522] In some embodiments, pharmaceutically acceptable excipient are at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or 100% pure. In some embodiments, excipients are approved for use in humans and/or for veterinary use. In some embodiments, excipients are approved by the United States Food and Drug Administration. In some embodiments, excipients are pharmaceutical grade. In some embodiments, excipients meet the standards of the United States Pharmacopoeia (USP), the European Pharmacopoeia (EP), the British Pharmacopoeia, and/or the International Pharmacopoeia.

[00523] In some embodiments, pharmaceutically acceptable excipients of the present disclosure may include, but are not limited to, inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Such excipients may optionally be included in pharmaceutical compositions.

[00524] Exemplary diluents include, but are not limited to, calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, *etc.*, and/or combinations thereof.

[00525] Exemplary granulating and/or dispersing agents include, but are not limited to, potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose and wood products, natural sponge, cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked poly(vinyl-pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (VEEGUM®), sodium lauryl sulfate, quaternary ammonium compounds, *etc.*, and/or combinations thereof.

[00526] Exemplary surface active agents and/or emulsifiers include, but are not limited to, natural emulsifiers (e.g. acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (e.g. bentonite [aluminum silicate] and VEEGUM® [magnesium

aluminum silicate]), long chain amino acid derivatives, high molecular weight alcohols (e.g. stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (e.g. carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (e.g. carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (e.g. polyoxyethylene sorbitan monolaurate [TWEEN®20], polyoxyethylene sorbitan [TWEENn®60], polyoxyethylene sorbitan monooleate [TWEEN®80], sorbitan monopalmitate [SPAN®40], sorbitan monostearate [Span®60], sorbitan tristearate [Span®65], glyceryl monooleate, sorbitan monooleate [SPAN®80]), polyoxyethylene esters (e.g. polyoxyethylene monostearate [MYRJ®45], polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and SOLUTOL®), sucrose fatty acid esters, polyethylene glycol fatty acid esters (e.g. CREMOPHOR®), polyoxyethylene ethers, (e.g. polyoxyethylene lauryl ether [BRIJ®30]), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, PLUORINC®F 68, POLOXAMER®188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, etc. and/or combinations thereof.

[00527] Exemplary binding agents include, but are not limited to, starch (*e.g.* cornstarch and starch paste); gelatin; sugars (*e.g.* sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol),; natural and synthetic gums (*e.g.* acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl-pyrrolidone), magnesium aluminum silicate (Veegum®), and larch arabogalactan); alginates; polyethylene oxide; polyethylene glycol; inorganic calcium salts; silicic acid; polymethacrylates; waxes; water; alcohol; *etc.*; and combinations thereof.

[00528] Exemplary preservatives may include, but are not limited to, antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and/or other preservatives. Exemplary antioxidants include, but are not limited to, alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and/or sodium sulfite. Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA), citric acid

monohydrate, disodium edetate, dipotassium edetate, edetic acid, fumaric acid, malic acid, phosphoric acid, sodium edetate, tartaric acid, and/or trisodium edetate. Exemplary antimicrobial preservatives include, but are not limited to, benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and/or thimerosal. Exemplary antifungal preservatives include, but are not limited to, butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and/or sorbic acid. Exemplary alcohol preservatives include, but are not limited to, ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and/or phenylethyl alcohol. Exemplary acidic preservatives include, but are not limited to, vitamin A, vitamin C, vitamin E, beta-carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and/or phytic acid. Other preservatives include, but are not limited to, tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, GLYDANT PLUS®, PHENONIP®, methylparaben, GERMALL®115, GERMABEN®II, NEOLONE™, KATHON™, and/or EUXYL®.

[00529] Exemplary buffering agents include, but are not limited to, citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium glubionate, calcium gluceptate, calcium gluconate, D-gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, *etc.*, and/or combinations thereof.

[00530] Exemplary lubricating agents include, but are not limited to, magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behanate, hydrogenated vegetable

oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, *etc.*, and combinations thereof.

[00531] Exemplary oils include, but are not limited to, almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and/or combinations thereof.

[00532] Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and/or perfuming agents can be present in the composition, according to the judgment of the formulator.

Formulation vehicles: liposomes, lipoplexes, and lipid nanoparticles

[00533] Compounds and/or compositions of the present disclosure may be formulated using one or more liposomes, lipoplexes and/or lipid nanoparticles. In some embodiments, pharmaceutical compositions comprise liposomes. Liposomes are artificially-prepared vesicles which may primarily be composed of a lipid bilayer and may be used as delivery vehicles for the administration of nutrients and pharmaceutical formulations. Liposomes may be of different sizes such as, but not limited to, multilamellar vesicles (MLVs) which may be hundreds of nanometers in diameter and may contain a series of concentric bilayers separated by narrow aqueous compartments, small unicellular vesicle (SUVs) which may be smaller than 50 nm in diameter and large unilamellar vesicle (LUVs) which may be between 50 and 500 nm in diameter. Liposome components may include, but are not limited to, opsonins or ligands in order to improve the attachment of liposomes to unhealthy tissue or to activate events such as, but not limited to, endocytosis. Liposomes may comprise low or high pH. In some embodiments, liposome pH may be varied in order to improve delivery of pharmaceutical formulations.

[00534] In some embodiments, liposome formation may depend on physicochemical characteristics such as, but not limited to, the pharmaceutical formulation entrapped, liposomal ingredients, the nature of the medium in which lipid vesicles are dispersed, the effective concentration of entrapped substances, potential toxicity of entrapped substances, additional processes involved during the application and/or delivery of vesicles, optimization size, polydispersity, shelf-life of vesicles for the intended application, batch-to-batch reproducibility and possibility of large-scale production of safe and efficient liposomal products.

[00535] In some embodiments, formulations may be assembled or compositions altered such that they are passively or actively directed to different cell types *in vivo*.

[00536] In some embodiments, formulations may be selectively targeted through expression of different ligands on formulation surfaces as exemplified by, but not limited by, folate, transferrin, N-acetylgalactosamine (GalNAc), and antibody targeted approaches.

[00537] In some embodiments, pharmaceutical compositions of the present disclosure may be formulated with liposomes, lipoplexes and/or lipid nanoparticles to improve efficacy of function. Such formulations may be able to increase cell transfection by pharmaceutical compositions. In some embodiments, liposomes, lipoplexes, or lipid nanoparticles may be used to increase pharmaceutical composition stability.

[00538] In some embodiments, liposomes are specifically formulated for pharmaceutical compositions comprising one or more antibodies. Such liposomes may be prepared according to techniques known in the art, such as those described by Eppstein et al. (Eppstein, D.A. et al., Biological activity of liposome-encapsulated murine interferon gamma is mediated by a cell membrane receptor. Proc Natl Acad Sci U S A. 1985 Jun;82(11):3688-92); Hwang et al. (Hwang, K.J. et al., Hepatic uptake and degradation of unilamellar sphingomyelin/cholesterol liposomes: a kinetic study. Proc Natl Acad Sci U S A. 1980 Jul;77(7):4030-4); US 4,485,045 and US 4,544,545. Production of liposomes with sustained circulation time are also described in US 5,013,556.

[00539] In some embodiments, liposomes of the present disclosure comprising antibodies may be generated using reverse phase evaporation utilizing lipids such as phosphatidylcholine, cholesterol as well as phosphatidylethanolamine that have been polyethylene glycol-derivatized. Filters with defined pore size are used to extrude liposomes of the desired diameter. In another embodiment, compounds and/or compositions of the present disclosure may be conjugated to external surfaces of liposomes by disulfide interchange reactions as is described by Martin et al. (Martin, F.J. et al., Irreversible coupling

of immunoglobulin fragments to preformed vesicles. An improved method for liposome targeting. J Biol Chem. 1982 Jan 10;257(1):286-8).

Formulation vehicles: polymers and nanoparticles

[00540] Compounds and/or compositions of the present disclosure may be formulated using natural and/or synthetic polymers. Non-limiting examples of polymers which may be used for delivery include, but are not limited to DMRI/DOPE, poloxamer, chitosan, cyclodextrin, and poly(lactic-co-glycolic acid) (PLGA) polymers. In some embodiments, polymers may be biodegradable.

[00541] In some embodiments, polymer formulation may permit sustained and/or delayed release of compounds and/or compositions (e.g., following intramuscular and/or subcutaneous injection). Altered release profile for compounds and/or compositions of the present disclosure may result in, for example, compound release over an extended period of time. Polymer formulations may also be used to increase the stability of compounds and/or compositions of the present disclosure.

[00542] In some embodiments, polymer formulations may be selectively targeted through expression of different ligands as exemplified by, but not limited by, folate, transferrin, and N-acetylgalactosamine (GalNAc) (Benoit, D.S. et al., Synthesis of folate-functionalized RAFT polymers for targeted siRNA delivery. Biomacromolecules. 2011 12:2708-14; Rozema, D.B. et al., Dynamic polyconjugates for targeted in vivo delivery of siRNA to hepatocytes. Proc Natl Acad Sci U S A. 2007 104:12982-12887; Davis, M.E. et al., The first targeted delivery of siRNA in humans via a self-assembling, cyclodextrin polymer-based nanoparticle: from concept to clinic. Mol Pharm. 2009 6:659-668; Davis, M.E. et al., Evidence of RNAi in humans from systemically administered siRNA via targeted nanoparticles. Nature. 2010. 464:1067-70; the contents of each of which are herein incorporated by reference in their entirety).

[00543] Compounds and/or compositions of the present disclosure may be formulated as nanoparticles using combinations of polymers, lipids, and/or other biodegradable agents, such as, but not limited to, calcium phosphates. In some embodiments, components may be combined in core-shells, hybrids, and/or layer-by-layer architectures, to allow for fine-tuning of nanoparticle structure, so delivery may be enhanced. For antibodies of the present disclosure, systems based on poly(2-(methacryloyloxy)ethyl phosphorylcholine)-block-(2-(diisopropylamino)ethyl methacrylate), (PMPC-PDPA), a pH sensitive diblock copolymer that self-assembles to form nanometer-sized vesicles, also known as polymersomes, at

physiological pH may be used. These polymersomes have been shown to successfully deliver relatively high antibody payloads within live cells. (Massignani, M. et al., Cellular delivery of antibodies: effective targeted subcellular imaging and new therapeutic tool. Nature Proceedings. 2010. p1-17).

[00544] In some embodiments, PEG-charge-conversional polymers (Pitella, F. et al., Enhanced endosomal escape of siRNA-incorporating hybrid nanoparticles from calcium phosphate and PEG-block charge-conversional polymer for efficient gene knockdown with negligible cytotoxicity. Biomaterials. 2011 32:3106-14) may be used to form nanoparticles for delivery of compounds and/or compositions of the present disclosure. In some embodiments, PEG-charge-conversional polymers may improve upon PEG-polyanion block copolymers by being cleaved into polycations at acidic pH, thus enhancing endosomal escape.

[00545] In some embodiments, complexation, delivery and/or internalization of polymeric nanoparticles may be precisely controlled by altering chemical compositions in both core and shell nanoparticle components (Siegwart, D.J. et al., Combinatorial synthesis of chemically diverse core-shell nanoparticles for intracellular delivery. Proc Natl Acad Sci U S A. 2011 108:12996-3001).

[00546] In some embodiments, matrices of poly(ethylene-co-vinyl acetate), are used to deliver compounds and/or compositions of the disclosure. Such matrices have bee described by others (Sherwood, J.K. et al., Controlled antibody delivery systems. Nature Biotechnology. 1992. 10:1446-9).

Antibody formulations

[00547] Antibodies of the present disclosure may be formulated for intravenous administration or extravascular administration (Daugherty, et al., Formulation and delivery issues for monoclonal antibody therapeutics. Adv Drug Deliv Rev. 2006 Aug 7;58(5-6):686-706 and US patent application publication number US2011/0135570, the contents of each of which are herein incorporated by reference in their entirety). Extravascular administration routes may include, but are not limited to subcutaneous administration, intraperitoneal administration, intracerebral administration, intraocular administration, intralesional administration, topical administration and intramuscular administration.

[00548] In some embodiments, antibody structures may be modified to improve effectiveness as therapeutics. Improvements may include, but are not limited to improved thermodynamic stability, reduced Fc receptor binding properties and/or imporved folding

efficiency. Modifications may include, but are not limited to amino acid substitutions, glycosylation, palmitoylation and/or protein conjugation.

[00549] In some embodiments, antibodies of the present disclosure may be formulated with antioxidants to reduce antibody oxidation. Antibodies of the present disclosure may also be formulated with additives to reduce protein aggregation. Such additives may include, but are not limited to albumin, amino acids, sugars, urea, guanidinium chloride, polyalchohols, polymers (such as polyethylene glycol and dextrans), surfactants (including, but not limited to polysorbate 20 and polysorbate 80) or even other antibodies.

[00550] In some embodiments, antibodies of the present disclosure may be formulated to reduce the impact of water on antibody structure and function. Antibody preparartions in such formulations may be may be lyophilized. Formulations subject to lyophilization may include carbohydrates or polyol compounds to protect and/or stabilize antibody structure. Such compounds may include, but are not limited to sucrose, trehalose and mannitol.

[00551] In some embodiments, antibodies of the present disclosure may be formulated with polymers. In some embodiments, polymer formulations may comprise hydrophobic polymers. Such polymers may be microspheres formulated with polylactide-co-glycolide through solid-in-oil-in-water encapsulation methods. In some embodiments, microspheres comprising ethylene-vinyl acetate copolymer may also be used for antibody delivery and/or to extend the time course of antibody release at sites of delivery. In some embodiments, polymers may be aqueous gels. Such gels may, for example, comprise carboxymethylcellulose. In some embodiments, aqueous gels may also comprise hyaluronic acid hydrogels. In some embodiments, antibodies may be covalently linked to such gels through hydrazone linkages that allow for sustained delivery in tissues, including but not limited to tissues of the central nervous system.

Formulation vehicles: peptides and proteins

[00552] Compounds and/or compositions of the present disclosure may be formulated with peptides and/or proteins. In some embodiments, peptides such as, but not limited to, cell penetrating peptides and/or proteins/peptides that enable intracellular delivery may be used to deliver pharmaceutical formulations. Non-limiting examples of a cell penetrating peptides which may be used with pharmaceutical formulations of the present disclosure include cell-penetrating peptide sequences attached to polycations that facilitates delivery to the intracellular space, e.g., HIV-derived TAT peptide, penetratins, transportans, or hCT derived cell-penetrating peptides (see, e.g. Caron, N.J. et al., Intracellular delivery of a Tat-eGFP

fusion protein into muscle cells. Mol Ther. 2001. 3(3):310-8; Langel, U., Cell-Penetrating Peptides: Processes and Applications, CRC Press, Boca Raton FL, 2002; El-Andaloussi, S. et al., Cell-penetrating peptides: mechanisms and applications. Curr Pharm Des. 2003. 11(28):3597-611; and Deshayes, S. et al., Cell-penetrating peptides: tools for intracellular delivery of therapeutics. Cell Mol Life Sci. 2005. 62(16):1839-49, the contents of each of which are herein incorporated by reference in their entirety). Compounds and/or compositions of the present disclosure may also be formulated to include cell penetrating agents, e.g., liposomes, which enhance delivery of the compositions to intracellular spaces. Compounds and/or compositions of the present disclosure may be complexed with peptides and/or proteins such as, but not limited to, peptides and/or proteins from Aileron Therapeutics (Cambridge, MA) and Permeon Biologics (Cambridge, MA) in order to enable intracellular delivery (Cronican, J.J. et al., Potent delivery of functional proteins into mammalian cells in vitro and in vivo using a supercharged protein. ACS Chem Biol. 2010. 5:747-52; McNaughton, B.R. et al., Mammalian cell penetration, siRNA transfection, and DNA transfection by supercharged proteins. Proc Natl Acad Sci, USA. 2009. 106:6111-6; Verdine, G.L. et al., Stapled peptides for intracellular drug targets. Methods Enzymol. 2012. 503:3-33; the contents of each of which are herein incorporated by reference in their entirety).

[00553] In some embodiments, the cell-penetrating polypeptides may comprise first and second domains. First domains may comprise supercharged polypeptides. Second domains may comprise protein-binding partner. As used herein, protein-binding partners may include, but are not limited to, antibodies and functional fragments thereof, scaffold proteins and/or peptides. Cell-penetrating polypeptides may further comprise intracellular binding partners for protein-binding partners. In some embodiments, cell-penetrating polypeptides may be capable of being secreted from cells where compounds and/or compositions of the present disclosure may be introduced.

[00554] Compositions of the present disclosure comprising peptides and/or proteins may be used to increase cell transfection and/or alter compound/composition biodistribution (e.g., by targeting specific tissues or cell types).

Formulation vehicles: cells

[00555] Cell-based formulations of compounds and/or compositions of the present disclosure may be used to ensure cell transfection (e.g., in cellular carriers) or to alter biodistribution (e.g., by targeting cell carriers to specific tissues or cell types).

Cell transfer methods

[00556] A variety of methods are known in the art and suitable for introduction of nucleic acids or proteins into cells, including viral and non-viral mediated techniques. Examples of typical non-viral mediated techniques include, but are not limited to, electroporation, calcium phosphate mediated transfer, nucleofection, sonoporation, heat shock, magnetofection, liposome mediated transfer, microinjection, microprojectile mediated transfer (nanoparticles), cationic polymer mediated transfer (DEAE-dextran, polyethylenimine, polyethylene glycol (PEG) and the like) or cell fusion.

[00557] The technique of sonoporation, or cellular sonication, is the use of sound (e.g., ultrasonic frequencies) for modifying the permeability of cell plasma membranes. Sonoporation methods are known to those in the art and are used to deliver nucleic acids *in vivo* (Yoon, C.S. et al., Ultrasound-mediated gene delivery. Expert Opin Drug Deliv. 2010 7:321-30; Postema, M. et al., Ultrasound-directed drug delivery. Curr Pharm Biotechnol. 2007 8:355-61; Newman, C.M. et al., Gene therapy progress and prospects: ultrasound for gene transfer. Gene Ther. 2007. 14(6):465-75; the contents of each of which are herein incorporated by reference in their entirety). Sonoporation methods are known in the art and are also taught for example as they relate to bacteria in US Patent application publication US2010/0196983 and as it relates to other cell types in, for example, US Patent application publication US2010/0009424, the contents of each of which are incorporated herein by reference in their entirety.

[00558] Electroporation techniques are also well known in the art and are used to deliver nucleic acids *in vivo* and clinically (Andre, F.M. et al., Nucleic acids electrotransfer in vivo: mechanisms and practical aspects. Curr Gene Ther. 2010 10:267-80; Chiarella, P. et al., Application of electroporation in DNA vaccination protocols. Curr Gene Ther. 2010. 10:281-6; Hojman, P., Basic principles and clinical advancements of muscle electrotransfer. Curr Gene Ther. 2010 10:128-38; the contents of each of which are herein incorporated by reference in their entirety). In some embodiments, compounds and/or compositions of the present disclosure may be delivered by electroporation.

Administration and delivery

[00559] Compounds and/or compositions of the present disclosure may be administered by any of the standard methods or routes known in the art. Such methods may include any route which results in a therapeutically effective outcome. These include, but are not limited to enteral, gastroenteral, epidural, oral, transdermal, epidural (peridural), intracerebral (into the

cerebrum), intracerebroventricular (into the cerebral ventricles), epicutaneous (application onto the skin), intradermal, (into the skin itself), subcutaneous (under the skin), nasal administration (through the nose), intravenous (into a vein), intraarterial (into an artery), intramuscular (into a muscle), intracardiac (into the heart), intraosseous infusion (into the bone marrow), intrathecal (into the spinal canal), intraperitoneal, (infusion or injection into the peritoneum), intravesical infusion, intravitreal, (through the eye), intracavernous injection, (into the base of the penis), intravaginal administration, intrauterine, extra-amniotic administration, transdermal (diffusion through the intact skin for systemic distribution), transmucosal (diffusion through a mucous membrane), insufflation (snorting), sublingual, sublabial, enema, eye drops (onto the conjunctiva), or in ear drops. In specific embodiments, compounds and/or compositions of the present disclosure may be administered in ways which allow them to cross the blood-brain barrier, vascular barriers, or other epithelial barriers. Methods of formulation and administration may include any of those disclosed in US Pub. No. 2013/0122007, US Pat. No. 8,415,459 or International Pub. No. WO 2011/151432, the contents of each of which are herein incorporated by reference in their entirety. Non-limiting routes of administration for compounds and/or compositions of the present disclosure are described below.

Parenteral and injectible administration

[00560] In some embodiments, compounds and/or compositions of the present disclosure may be administered parenterally. Liquid dosage forms for oral and parenteral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and/or elixirs. In addition to active ingredients, liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and/or perfuming agents. In certain embodiments for parenteral administration, compositions are mixed with solubilizing agents such as CREMOPHOR®, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and/or

combinations thereof. In other embodiments, surfactants are included such as hydroxypropylcellulose.

[00561] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing agents, wetting agents, and/or suspending agents. Sterile injectable preparations may be sterile injectable solutions, suspensions, and/or emulsions in nontoxic parenterally acceptable diluents and/or solvents, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P., and isotonic sodium chloride solution. Sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. Fatty acids such as oleic acid can be used in the preparation of injectables.

[00562] Injectable formulations may be sterilized, for example, by filtration through a bacterial-retaining filter, and/or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00563] In order to prolong the effect of active ingredients, it is often desirable to slow the absorption of active ingredients from subcutaneous or intramuscular injections. This may be accomplished by the use of liquid suspensions of crystalline or amorphous material with poor water solubility. The rate of absorption of active ingredients depends upon the rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

Rectal and vaginal administration

[00564] In some embodiments, compounds and/or compositions of the present disclosure may be administered rectally and/or vaginally. Compositions for rectal or vaginal administration are typically suppositories which can be prepared by mixing compositions

with suitable non-irritating excipients such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active ingredient.

Oral administration

[00565] In some embodiments, compounds and/or compositions of the present disclosure may be administered orally. Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, an active ingredient is mixed with at least one inert, pharmaceutically acceptable excipient such as sodium citrate or dicalcium phosphate and/or fillers or extenders (*e.g.* starches, lactose, sucrose, glucose, mannitol, and silicic acid), binders (*e.g.* carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia), humectants (*e.g.* glycerol), disintegrating agents (*e.g.* agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate), solution retarding agents (*e.g.* paraffin), absorption accelerators (*e.g.* quaternary ammonium compounds), wetting agents (*e.g.* cetyl alcohol and glycerol monostearate), absorbents (*e.g.* kaolin and bentonite clay), and lubricants (*e.g.* talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate), and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may comprise buffering agents.

Topical or transdermal administration

[00566] As described herein, compounds and/or compositions of the present disclosure may be formulated for administration topically. The skin may be an ideal target site for delivery as it is readily accessible. Three routes are commonly considered to deliver compounds and/or compositions of the present disclosure to the skin: (i) topical application (*e.g.* for local/regional treatment and/or cosmetic applications); (ii) intradermal injection (*e.g.* for local/regional treatment and/or cosmetic applications); and (iii) systemic delivery (*e.g.* for treatment of dermatologic diseases that affect both cutaneous and extracutaneous regions). Compounds and/or compositions of the present disclosure can be delivered to the skin by several different approaches known in the art.

[00567] In some embodiments, the disclosure provides for a variety of dressings (e.g., wound dressings) or bandages (e.g., adhesive bandages) for conveniently and/or effectively carrying out methods of the present disclosure. Typically dressing or bandages may comprise

sufficient amounts of compounds and/or compositions of the present disclosure described herein to allow users to perform multiple treatments.

[00568] Dosage forms for topical and/or transdermal administration may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants and/or patches. Generally, active ingredients are admixed under sterile conditions with pharmaceutically acceptable excipients and/or any needed preservatives and/or buffers. Additionally, the present disclosure contemplates the use of transdermal patches, which often have the added advantage of providing controlled delivery of compounds and/or compositions of the present disclosure to the body. Such dosage forms may be prepared, for example, by dissolving and/or dispensing compounds and/or compositions in the proper medium. Alternatively or additionally, rates may be controlled by either providing rate controlling membranes and/or by dispersing compounds and/or compositions in a polymer matrix and/or gel.

[00569] Formulations suitable for topical administration include, but are not limited to, liquid and/or semi liquid preparations such as liniments, lotions, oil in water and/or water in oil emulsions such as creams, ointments and/or pastes, and/or solutions and/or suspensions.

[00570] Topically-administrable formulations may, for example, comprise from about 1% to about 10% (w/w) active ingredient, although the concentration of active ingredient may be as high as the solubility limit of the active ingredient in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

Depot administration

[00571] As described herein, in some embodiments, compounds and/or compositions of the present disclosure are formulated in depots for extended release. Generally, specific organs or tissues ("target tissues") are targeted for administration.

[00572] In some aspects of the disclosure, compounds and/or compositions of the present disclosure are spatially retained within or proximal to target tissues. Provided are method of providing compounds and/or compositions to target tissues of mammalian subjects by contacting target tissues (which comprise one or more target cells) with compounds and/or compositions under conditions such that they are substantially retained in target tissues, meaning that at least 10, 20, 30, 40, 50, 60, 70, 80, 85, 90, 95, 96, 97, 98, 99, 99.9, 99.99 or greater than 99.99% of the composition is retained in the target tissues. Advantageously, retention is determined by measuring the amount of compounds and/or compositions that enter one or more target cells. For example, at least 1%, 5%, 10%, 20%, 30%, 40%, 50%,

60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.9%, 99.99% or greater than 99.99% of compounds and/or compositions administered to subjects are present intracellularly at a period of time following administration. For example, intramuscular injection to mammalian subjects may be performed using aqueous compositions comprising compounds and/or compositions of the present disclosure and one or more transfection reagent, and retention is determined by measuring the amount of compounds and/or compositions present in muscle cells.

[00573] Certain aspects of the disclosure are directed to methods of providing compounds and/or compositions of the present disclosure to a target tissues of mammalian subjects, by contacting target tissues (comprising one or more target cells) with compounds and/or compositions under conditions such that they are substantially retained in such target tissues. Compounds and/or compositions comprise enough active ingredient such that the effect of interest is produced in at least one target cell. In some embodiments, compounds and/or compositions generally comprise one or more cell penetration agents, although "naked" formulations (such as without cell penetration agents or other agents) are also contemplated, with or without pharmaceutically acceptable carriers.

[00574] In some embodiments, the amount of a growth factor present in cells in a tissue is desirably increased. Preferably, this increase in growth factor is spatially restricted to cells within the target tissue. Thus, provided are methods of increasing the amount of growth factor of interest in tissues of mammalian subjects. In some embodiments, formulations are provided comprising compounds and/or compositions characterized in that the unit quantity provided has been determined to produce a desired level of growth factor of interest in a substantial percentage of cells contained within predetermined volumes of target tissue.

[00575] In some embodiments, formulations comprise a plurality of different compounds and/or compositions, where one or more than one targets biomolecules of interest. Optionally, formulations may also comprise cell penetration agents to assist in the intracellular delivery of compounds and/or compositions. In such embodiments, determinations are made of compound and/or composition dose required to target biomolecules of interest in substantial percentages of cells contained within predetermined volumes of the target tissue (generally, without targeting biomolecules of interest in adjacent or distal tissues). Determined doses are then introduced directly into subject tissues. In some embodiments, the disclosure provides for compounds and/or compositions to be delivered in more than one administration or by split dose administration.

Pulmonary administration

[00576] In some embodiments, compounds and/or compositions of the present disclosure may be prepared, packaged, and/or sold in formulations suitable for pulmonary administration. In some embodiments, such administration is via the buccal cavity. In some embodiments, formulations may comprise dry particles comprising active ingredients. In such embodiments, dry particles may have a diameter in the range from about 0.5 nm to about 7 nm or from about 1 nm to about 6 nm. In some embodiments, formulations may be in the form of dry powders for administration using devices comprising dry powder reservoirs to which streams of propellant may be directed to disperse such powder. In some embodiments, self propelling solvent/powder dispensing containers may be used. In such embodiments, active ingredients may be dissolved and/or suspended in low-boiling propellant in sealed containers. Such powders may comprise particles wherein at least 98% of the particles by weight have diameters greater than 0.5 nm and at least 95% of the particles by number have diameters less than 7 nm. Alternatively, at least 95% of the particles by weight have a diameter greater than 1 nm and at least 90% of the particles by number have a diameter less than 6 nm. Dry powder compositions may include a solid fine powder diluent such as sugar and are conveniently provided in a unit dose form.

[00577] Low boiling propellants generally include liquid propellants having a boiling point of below 65 °F at atmospheric pressure. Generally propellants may constitute 50% to 99.9% (w/w) of the composition, and active ingredient may constitute 0.1% to 20% (w/w) of the composition. Propellants may further comprise additional ingredients such as liquid non-ionic and/or solid anionic surfactant and/or solid diluent (which may have particle sizes of the same order as particles comprising active ingredients).

[00578] Pharmaceutical compositions formulated for pulmonary delivery may provide active ingredients in the form of droplets of solution and/or suspension. Such formulations may be prepared, packaged, and/or sold as aqueous and/or dilute alcoholic solutions and/or suspensions, optionally sterile, comprising active ingredients, and may conveniently be administered using any nebulization and/or atomization device. Such formulations may further comprise one or more additional ingredients including, but not limited to, a flavoring agent such as saccharin sodium, a volatile oil, a buffering agent, a surface active agent, and/or a preservative such as methylhydroxybenzoate. Droplets provided by this route of administration may have an average diameter in the range from about 0.1 nm to about 200 nm.

Intranasal, nasal and buccal administration

[00579] In some embodiments, compounds and/or compositions of the present disclosure may be administered nasaly and/or intranasaly. In some embodiments, formulations described herein as being useful for pulmonary delivery may also be useful for intranasal delivery. In some embodiments, formulations for intranasal administration comprise a coarse powder comprising the active ingredient and having an average particle from about 0.2 μm to 500 μm. Such formulations are administered in the manner in which snuff is taken, *i.e.* by rapid inhalation through the nasal passage from a container of the powder held close to the nose.

[00580] Formulations suitable for nasal administration may, for example, comprise from about as little as 0.1% (w/w) and as much as 100% (w/w) of active ingredient, and may comprise one or more of the additional ingredients described herein. A pharmaceutical composition may be prepared, packaged, and/or sold in a formulation suitable for buccal administration. Such formulations may, for example, be in the form of tablets and/or lozenges made using conventional methods, and may, for example, 0.1% to 20% (w/w) active ingredient, the balance comprising an orally dissolvable and/or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations suitable for buccal administration may comprise powders and/or an aerosolized and/or atomized solutions and/or suspensions comprising active ingredients. Such powdered, aerosolized, and/or aerosolized formulations, when dispersed, may comprise average particle and/or droplet sizes in the range of from about 0.1 nm to about 200 nm, and may further comprise one or more of any additional ingredients described herein.

Ophthalmic or otic administration

[00581] In some embodiments, compounds and/or compositions of the present disclosure may be prepared, packaged, and/or sold in formulations suitable for ophthalmic and/or otic administration. Such formulations may, for example, be in the form of eye and/or ear drops including, for example, a 0.1/1.0% (w/w) solution and/or suspension of the active ingredient in aqueous and/or oily liquid excipients. Such drops may further comprise buffering agents, salts, and/or one or more other of any additional ingredients described herein. Other ophthalmically-administrable formulations which are useful include those which comprise active ingredients in microcrystalline form and/or in liposomal preparations. Subretinal inserts may also be used as forms of administration.

Payload administration: detectable agents and therapeutic agents

[00582] In some embodiments, compounds and/or compositions of the present disclosure may be used in a number of different scenarios in which delivery of a substance (the "payload") to a biological target is desired, for example delivery of detectable substances for detection of the target, or delivery of therapeutic and/or diagnostic agents. Detection methods may include, but are not limited to, both *in vitro* and *in vivo* imaging methods, *e.g.*, immunohistochemistry, bioluminescence imaging (BLI), Magnetic Resonance Imaging (MRI), positron emission tomography (PET), electron microscopy, X-ray computed tomography, Raman imaging, optical coherence tomography, absorption imaging, thermal imaging, fluorescence reflectance imaging, fluorescence microscopy, fluorescence molecular tomographic imaging, nuclear magnetic resonance imaging, X-ray imaging, ultrasound imaging, photoacoustic imaging, lab assays, or in any situation where tagging/staining/imaging is required.

[00583] In some embodiments, compounds and/or compositions may be designed to include both linkers and payloads in any useful orientation. For example, linkers having two ends may be used to attach one end to the payload and the other end to compounds and/or compositions. Compounds and/or compositions of the present disclosure may include more than one payload. In some embodiments, compounds and/or compositions may comprise one or more cleavable linker. In some embodiments, payloads may be attached to compounds and/or compositions via a linker and may be fluorescently labeled for *in vivo* tracking, *e.g.* intracellularly.

[00584] In some embodiments, compounds and/or compositions of the present disclosure may be used in reversible drug delivery into cells.

[00585] Compounds and/or compositions of the present disclosure may be used in intracellular targeting of payloads, *e.g.*, detectable or therapeutic agents, to specific organelles. In addition, compounds and/or compositions of the present disclosure may be used to deliver therapeutic agents to cells or tissues, *e.g.*, in living animals. For example, the compounds and/or compositions described herein may be used to deliver chemotherapeutic agents to kill cancer cells. Compounds and/or compositions may be attached to therapeutic agents through one or more linkers may facilitate membrane permeation allowing therapeutic agents to travel into cells to reach intracellular targets.

[00586] In some embodiments, payloads may be a therapeutic agent such as a cytotoxins, radioactive ions, chemotherapeutics, or other therapeutic agents. Cytotoxins and/or cytotoxic agents may include any agents that may be detrimental to cells. Examples include, but are not limited to, taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin,

etoposide, teniposide, vincristine, vinblastine, colchicine, doxorubicin, daunorubicin, dihydroxyanthracinedione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, puromycin, maytansinoids, *e.g.*, maytansinol (see U.S. Pat. No. 5,208,020 incorporated herein in its entirety), rachelmycin (CC-1065, see U.S. Pat. Nos. 5,475,092, 5,585,499, and 5,846,545, the contents of each of which are incorporated herein by reference in their entirety), and analogs or homologs thereof. Radioactive ions include, but are not limited to iodine (*e.g.*, ^{125}iodine or ^{131}iodine), ^{89}strontium, phosphorous, palladium, cesium, iridium, phosphate, cobalt, ^{90}yttrium, ^{153}samarium, and praseodymium. Other therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thiotepa chlorambucil, rachelmycin (CC-1065), melphalan, carmustine (BSNU), lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine, vinblastine, taxol and maytansinoids).

[00587] In some embodiments, payloads may be detectable agents, such as various organic small molecules, inorganic compounds, nanoparticles, enzymes or enzyme substrates, fluorescent materials, luminescent materials (e.g., luminol), bioluminescent materials (e.g., luciferase, luciferin, and aequorin), chemiluminescent materials, radioactive materials (e.g., ^{18}F, ^{67}Ga, ^{81m}Kr, ^{82}Rb, ^{111}In, ^{123}I, ^{133}Xe, ^{201}Tl, ^{125}I, ^{35}S, ^{14}C, ^{3}H, or ^{99m}Tc (e.g., as pertechnetate (technetate(VII), TcO_4^-)), and contrast agents (e.g., gold (*e.g.*, gold nanoparticles), gadolinium (e.g., chelated Gd), iron oxides (e.g., superparamagnetic iron oxide (SPIO), monocrystalline iron oxide nanoparticles (MIONs), and ultrasmall superparamagnetic iron oxide (USPIO)), manganese chelates (e.g., Mn-DPDP), barium sulfate, iodinated contrast media (iohexol), microbubbles, or perfluorocarbons). Such optically-detectable labels include for example, without limitation, 4-acetamido-4'-isothiocyanatostilbene-2,2′disulfonic acid; acridine and derivatives (e.g., acridine and acridine isothiocyanate); 5-(2′-aminoethyl)aminonaphthalene-1-sulfonic acid (EDANS); 4-amino-N-[3-vinylsulfonyl)phenyl]naphthalimide-3,5 disulfonate; N-(4-anilino-l-naphthyl)maleimide; anthranilamide; BODIPY; Brilliant Yellow; coumarin and derivatives (e.g., coumarin, 7-amino-4-methylcoumarin (AMC, Coumarin 120), and 7-amino-4-trifluoromethylcoumarin (Coumarin 151)); cyanine dyes; cyanosine; 4',6-diaminidino-2-phenylindole (DAPI); 5′ 5"-

dibromopyrogallol-sulfonaphthalein (Bromopyrogallol Red); 7-diethylamino-3-(4'-isothiocyanatophenyl)-4-methylcoumarin; diethylenetriamine pentaacetate; 4,4'-diisothiocyanatodihydro-stilbene-2,2′-disulfonic acid; 4,4'-diisothiocyanatostilbene-2,2′-disulfonic acid; 5-[dimethylamino]-naphthalene-1-sulfonyl chloride (DNS, dansylchloride); 4-dimethylaminophenylazophenyl-4'-isothiocyanate (DABITC); eosin and derivatives (e.g., eosin and eosin isothiocyanate); erythrosin and derivatives (e.g., erythrosin B and erythrosin isothiocyanate); ethidium; fluorescein and derivatives (e.g., 5-carboxyfluorescein (FAM), 5-(4,6-dichlorotriazin-2-yl)aminofluorescein (DTAF), 2′,7'-dimethoxy-4'5′-dichloro-6-carboxyfluorescein, fluorescein, fluorescein isothiocyanate, X-rhodamine-5-(and-6)-isothiocyanate (QFITC or XRITC), and fluorescamine); 2-[2-[3-[[1,3-dihydro-1,1-dimethyl-3-(3-sulfopropyl)-2H-benz[e]indol-2-ylidene]ethylidene]-2-[4-(ethoxycarbonyl)-1-piperazinyl]-1-cyclopenten-1-yl]ethenyl]-1,1-dimethyl-3-(3-sulforpropyl)-1H-benz[e]indolium hydroxide, inner salt, compound with n,n-diethylethanamine(1:1) (IR144); 5-chloro-2-[2-[3-[(5-chloro-3-ethyl-2(3H)-benzothiazol- ylidene)ethylidene]-2-(diphenylamino)-1-cyclopenten-1-yl]ethenyl]-3-ethyl benzothiazolium perchlorate (IR140); Malachite Green isothiocyanate; 4-methylumbelliferone orthocresolphthalein; nitrotyrosine; pararosaniline; Phenol Red; B-phycoerythrin; o-phthaldialdehyde; pyrene and derivatives(e.g., pyrene, pyrene butyrate, and succinimidyl 1-pyrene); butyrate quantum dots; Reactive Red 4 (CIBACRON^{TM} Brilliant Red 3B-A); rhodamine and derivatives (e.g., 6-carboxy-X-rhodamine (ROX), 6-carboxyrhodamine (R6G), lissamine rhodamine B sulfonyl chloride rhodarnine (Rhod), rhodamine B, rhodamine 123, rhodamine X isothiocyanate, sulforhodamine B, sulforhodamine 101, sulfonyl chloride derivative of sulforhodamine 101 (Texas Red), N,N,N',N'tetramethyl-6-carboxyrhodamine (TAMRA) tetramethyl rhodamine, and tetramethyl rhodamine isothiocyanate (TRITC)); riboflavin; rosolic acid; terbium chelate derivatives; Cyanine-3 (Cy3); Cyanine-5 (Cy5); cyanine-5.5 (Cy5.5), Cyanine-7 (Cy7); IRD 700; IRD 800; Alexa 647; La Jolta Blue; phthalo cyanine; and naphthalo cyanine.

[00588] In some embodiments, the detectable agent may be a non-detectable precursor that becomes detectable upon activation (e.g., fluorogenic tetrazine-fluorophore constructs (e.g., tetrazine-BODIPY FL, tetrazine-Oregon Green 488, or tetrazine-BODIPY TMR-X) or enzyme activatable fluorogenic agents (e.g., PROSENSE® (VisEn Medical))). In vitro assays in which the enzyme labeled compositions can be used include, but are not limited to, enzyme linked immunosorbent assays (ELISAs), immunoprecipitation assays, immunofluorescence, enzyme immunoassays (EIA), radioimmunoassays (RIA), and Western blot analysis.

Combinations

[00589] In some embodiments, compounds and/or compositions of the present disclosure may be used in combination with one or more other therapeutic, prophylactic, diagnostic, or imaging agents. By "in combination with," it is not intended to imply that the agents must be administered at the same time and/or formulated for delivery together, although these methods of delivery are within the scope of the present disclosure. Compounds and/or compositions of the present disclosure may be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. In some embodiments, the present disclosure encompasses the delivery of pharmaceutical, prophylactic, diagnostic, or imaging compositions in combination with agents that may improve their bioavailability, reduce and/or modify their metabolism, inhibit their excretion, and/or modify their distribution within the body.

[00590] In some cases, compounds and/or compositions of the present disclosure may be combined with one or more therapeutic agents known in the art. Such agents may include BYM338 (Novartis, Basel, Switzerland), wherein administration may comprise any of the methods disclosed in clinical trial number NCT01925209 entitled *Efficacy and Safety of Bimagrumab/BYM338 at 52 Weeks on Physical Function, Muscle Strength, Mobility in sIBM Patients* (*RESILIENT*). Other agents that may be used in combination with compounds and/or compositions of the present disclosure may include any of those disclosed in US Pub. No. 2013/0122007, US Pat. No. 8,415,459 or International Pub. No. WO 2011/151432, the contents of each of which are herein incorporated by reference in their entirety.

Dosing and Dosage Forms

[00591] The present disclosure encompasses delivery of compounds and/or compositions of the present disclosure for any of therapeutic, pharmaceutical, diagnostic or imaging by any appropriate route taking into consideration likely advances in the sciences of drug delivery. Delivery may be naked or formulated.

Naked Delivery

[00592] Compounds and/or compositions of the present disclosure may be delivered to cells, tissues, organs and/or organisms in naked form. As used herein in, the term "naked" refers to compounds and/or compositions delivered free from agents or modifications which promote transfection or permeability. The naked compounds and/or compositions may be

delivered to the cells, tissues, organs and/or organisms using routes of administration known in the art and described herein. In some embodiments, naked delivery may include formulation in a simple buffer such as saline or PBS.

Formulated Delivery

[00593] In some embodiments, compounds and/or compositions of the present disclosure may be formulated, using methods described herein. Formulations may comprise compounds and/or compositions which may be modified and/or unmodified. Formulations may further include, but are not limited to, cell penetration agents, pharmaceutically acceptable carriers, delivery agents, bioerodible or biocompatible polymers, solvents, and/or sustained-release delivery depots. Formulations of the present disclosure may be delivered to cells using routes of administration known in the art and described herein.

[00594] Compositions may also be formulated for direct delivery to organs or tissues in any of several ways in the art including, but not limited to, direct soaking or bathing, via a catheter, by gels, powder, ointments, creams, gels, lotions, and/or drops, by using substrates such as fabric or biodegradable materials coated or impregnated with compositions, and the like.

Dosing

[00595] The present disclosure provides methods comprising administering one or more compounds and/or compositions to subjects in need thereof. Compounds and/or compositions of the present disclosure, or prophylactic compositions thereof, may be administered to subjects using any amount and any route of administration effective for preventing, treating, diagnosing, or imaging diseases, disorders and/or conditions. The exact amount required will vary from subject to subject, depending on species, age and/or general subject condition, severity of disease, particular composition, mode of administration, mode of activity, and the like. Compositions in accordance with the disclosure are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of compositions of the present disclosure will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective, prophylactically effective, or appropriate imaging dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the

time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

[00596] In certain embodiments, compositions in accordance with the present disclosure may be administered at dosage levels sufficient to deliver from about 0.0001 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, from about 0.1 mg/kg to about 40 mg/kg, from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, or from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic, diagnostic, prophylactic, or imaging effect. The desired dosage may be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage may be delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

[00597] According to the present disclosure, compounds and/or compositions of the present disclosure may be administered in split-dose regimens. As used herein, a "split dose" is the division of single unit dose or total daily dose into two or more doses, e.g., two or more administrations of the single unit dose. As used herein, a "single unit dose" is a dose of any therapeutic administered in one dose/at one time/single route/single point of contact, i.e., single administration event. As used herein, a "total daily dose" is an amount given or prescribed in a 24 hour period. In some embodiments, compounds and/or compositions of the present disclosure may be administered as a single unit dose. In some embodiments, compounds and/or compositions of the present disclosure may be administered to subjects in split doses. In some embodiments, compounds and/or compositions of the present disclosure may be formulated in buffer only or in formulations described herein. Pharmaceutical compositions described herein may be formulated into dosage forms described herein, such as a topical, intranasal, intratracheal, or injectable (e.g., intravenous, intraocular, intravitreal, intramuscular, intracardiac, intraperitoneal, subcutaneous). General considerations in the formulation and/or manufacture of pharmaceutical agents may be found, for example, in Remington: The Science and Practice of Pharmacy 21st ed., Lippincott Williams & Wilkins, 2005 (incorporated herein by reference).

Coatings or Shells

[00598] Solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. Solid compositions of a similar type may be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose and/or milk sugar as well as high molecular weight polyethylene glycols and the like.

Assays

[00599] In some embodiments, recombinant proteins (including, but not limited to chimeric proteins) disclosed herein and/or antibodies directed to such proteins may be developed using assays described herein. In some embodiments, recombinant proteins (including, but not limited to chimeric proteins) disclosed herein and/or antibodies directed to such proteins may be used in assays to develop other recombinant proteins and/or antibodies of the present disclosure.

Binding assays

[00600] In some embodiments, the present disclosure provides binding assays. As used herein, the term "binding assay" refers to an assay used to assess the ability of two or more factors to associate. Such assays may assess the ability of a desired antigen to bind a desired antibody and then use one or more detection methods to detect binding. Binding assays of the disclosure may include, but are not limited to surface Plasmon resonance-based assays, ELISAs and fluorescence flow cytometry-based assays. Binding assays of the disclosure may comprise the use of one or more recombinant proteins described herein, including, but not limited to any TGF-β family member proteins, any chimeric proteins, any cofactors and any modules, combinations or fragments thereof.

Cell-based assays

[00601] In some embodiments, the present disclosure provides cell-based assays. As used herein, the term "cell-based assay" refers to an assay comprising at least one aspect that involves the use of a living cell or cell culture. In some embodiments, these may be useful for assessing the modulation of growth factor release from GPCs, referred to herein as "growth factor release assays". In some embodiments, cell-based assays may be useful for assessing

the modulation of growth factor activity, referred to herein as "growth factor activity assays". Cell-based assays of the present disclosure may comprise expression cells and/or responsive cells. Expression cells, as referred to herein, are cells that express one or more factors being analyzed in a particular assay. Such expression may be natural or may be the result of transfection and/or transduction of a foreign gene. In some embodiments, expression of one or more factors by expression cells may be enhanced or suppressed by the addition of one or more exogenous factors. In some embodiments, expression cells may comprise cell lines (e.g. HEK293 cells, HepG2 cells, CHO cells, TMLC cells, 293T/17 cells, Hs68 cells, CCD1112sk cells, HFF-1 cells, Keloid fibroblasts or Sw-480 cells). In some embodiments, cell lines comprising expression cells may express one or more recombinant proteins of the present disclosure (e.g. naturally and/or through transfection, stable transfection, and/or transduction).

[00602] In some embodiments, growth factor release/activity assays may comprise expression cells that express GPCs. In such embodiments, additional factors may be co-expressed in and/or combined with expression cells to determine their effect on growth factor release from such GPCs. In some embodiments, integrins (including, but not limited to $\alpha_v\beta_6$ integrin, $\alpha_v\beta_8$ integrin and/or $\alpha_9\beta_1$ integrin) are co-expressed and/or otherwise introduced to GPC-expressing expression cells. In some embodiments, such additional integrin expression may facilitate growth factor release. In some embodiments, extracellular proteins (e.g. LTBPs, fibrillins and/or GASPs) and/or variants thereof are coexpressed and/or otherwise introduced into expression cells.

[00603] In some embodiments, one or more genes may be knocked out, knocked down and/or otherwise modulated in expression cells depending on the focus of a particular assay. In some embodiments, one or more gene products may be modulated at the RNA and/or protein level. In some embodiments, gene products may be reduced through the introduction of siRNA molecules to expression cells. In some embodiments, gene products from extracellular protein (e.g. LTBPs, fibrillins and/or GASPs) genes may be reduced and/or eliminated from expression cells of the present disclosure.

[00604] Cell-based assays of the present disclosure, including, but not limited to growth factor release/activity assays, may comprise responsive cells. As used herein, the term "responsive cell" refers to a cell that undergoes a response to one or more factors introduced into an assay. In some embodiments, such responses may include a change in gene expression, wherein such cells modulate transcription of one or more genes upon contact with

one or more factors introduced. In some embodiments, responsive cells may undergo a change in phenotype, behavior and/or viability.

[00605] In some embodiments, responsive cells comprise one or more reporter genes. As used herein, the term "reporter gene" refers to a synthetic gene typically comprising a promoter and a protein coding region encoding one or more detectable gene products. Reporter genes are typically designed in a way such that their expression may be modulated in response to one or more factors being analyzed by a particular assay. This may be carried out by manipulating the promoter of reporter genes. As used herein, the term promoter refers to part of a gene that initiates transcription of that gene. Promoters typically comprise nucleotides at the 3' end of the antisense strand of a given gene and are not transcribed during gene expression. Promoters typically function through interaction with one or more transcription factors as well as RNA polymerase enzymes to initiate transcription of the protein encoding portion of the gene. Segments of the promoter that physically interact with one or more transcription factors and/or polymerase enzymes are referred to herein as response elements. In some embodiments, reporter genes are designed to comprise promoters and/or response elements known to be responsive to one or more factors (including, but not limited to growth factors) being analyzed in a given assay. Changes in responsive cell gene expression may be measured according to any methods available in the art to yield gene expression data. Such gene expression data may be obtained in the form of luciferase activity data [often measured in terms of relative light units (RLUs)].

[00606] In some cases, responsive cells undergo a change in viability in response to one or more factors introduced in an assay. Such responsive cells may be used in proliferation assays as described herein. Changes in responsive cell viability may be detected by cell counting and/or other methods known to those skilled the art to yield responsive cell viability data.

[00607] Protein encoding regions of reporter genes typically encode one or more detectable proteins. Detectable proteins refer to any proteins capable of detection through one or more methods known in the art. Such detection methods may include, but are not limited to Western blotting, ELISA, assaying for enzymatic activity of detectable proteins (e.g. catalase activity, β-galactosidase activity and/or luciferase activity), immunocytochemical detection, surface plasmon resonance detection and/or detection of fluorescent detectable proteins. When a reporter gene is used in an assay, the expression of detectable proteins correlates with the ability of factors being assayed to activate the promoter present in the reporter gene. In embodiments comprising growth factor release/activity assays, reporter gene promoters

typically respond to growth factor signaling. In such embodiments, the level of detectable protein produced correlates with level of growth factor signaling, indicating release and/or activity of a given growth factor.

[00608] In some embodiments, reporter genes encode luciferase enzymes. Chemical reactions between luciferase enzymes and substrate molecules are light-emitting reactions. Due to such light-emitting reactions, luciferase enzyme levels can be quantified through the addition of substrate molecules and subsequent photodetection of the emitted light. In some embodiments, reporter genes of the present disclosure encode firefly luciferase, the sequence of which was cloned from *Photinus pyralis*. In some embodiments, responsive cells of the present disclosure comprise reporter genes that express luciferase with promoters that are responsive to growth factors. In such embodiments, luciferase activity may correlate with growth factor activity levels allowing for growth factor activity and/or release from GPCs to be determined.

[00609] In some embodiments, reporter genes are inserted into bacterial plasmids to enable replication and/or facilitate introduction into cells. In some embodiments, such plasmids are designed to comprise sequences encoding detectable gene products and may be manipulated to insert promoter sequences that may be responsive to one or more factors of interest. These plasmids are referred to herein as reporter plasmids. In some embodiments of the present disclosure, promoters that may be responsive to one or more factors of interest may be inserted into reporter plasmids, upstream of sequences encoding detectable gene products to form functional reporter genes within such reporter plasmids. Reporter plasmids that comprise at least one functional reporter gene are referred to herein as reporter constructs. In some embodiments, reporter constructs of the present disclosure may comprise pGL2 reporter plasmids (Promega BioSciences, LLC, Madison, WI), pGL3 reporter plasmids (Promega BioSciences, LLC, Madison, WI), pGL4 reporter plasmids (Promega BioSciences, LLC, Madison, WI) or variants thereof. Such reporter constructs express firefly luciferase in response to promoter activation.

[00610] In some embodiments, reporter constructs may be introduced directly into expression cells or may be introduced into one or more responsive cells. Responsive cells of the present disclosure comprising one or more reporter genes are referred to herein as reporter cells. In some embodiments, reporter cells may be transiently transfected with reporter constructs or may comprise stable expression of such constructs (e.g. reporter constructs are successfully replicated along with genomic DNA during each round of cell division). Cell lines that stably comprise reporter constructs are referred to herein as reporter cell lines. In

some embodiments, reporter cells are mammalian. In some embodiments, reporter cells may comprise mouse cells, rabbit cells, rat cells, monkey cells, hamster cells and human cells. In some embodiments, cell lines useful for transient and/or stable expression of reporter genes may include, but are not limited to HEK293 cells, HepG2 cells, HeLa cells, Sw-480 cells, TMLC cells [as disclosed by Abe et al (Abe, M. et al., An assay for transforming growth factor-β using cells transfected with a plasminogen activator inhibitor-1 promoter-luciferase construct. Analytical Biochemistry. 1994. 216:276-84)], 293T/17 cells, Hs68 cells, CCD1112sk cells, HFF-1 cells, Keloid fibroblasts, A204 cells, L17 RIB cells [as disclosed by Cash et al (Cash, J.N et al., The structure of myostatin:follistatin 288: insights into receptor utilization and heparin binding. The EMBO Journal. 2009. 28:2662-76)], C_2C_{12} cells, HepG2 cells and EL4 T lymphoma cells.

[00611] In embodiments where one or more reporter cells and/or reporter cell lines are utilized, such cells may be cultured with expression cells as part of a co-culture system. In some embodiments reporter cells/reporter cell lines may be cultured separately from expression cells. In such embodiments, lysates and/or media from expression cells may be combined with reporter cell/reporter cell line cultures to assess expressed factors (including, but not limited to growth factors).

[00612] In some embodiments, cell-based assays of the present disclosure may only comprise expression cells and not responsive cells. In such embodiments, expressed proteins, including but not limited to GPCs and/or growth factors, may be detected by one or more methods that are not cell based. Such methods may include, but are not limited to Western Blotting, enzyme-linked immunosorbent assay (ELISA), immunocytochemistry, surface plasmon resonance and other methods known in the art for protein detection. In some embodiments, GDF release in expression cell cultures and/or culture medium may be detected by ELISA. In some embodiments, the GDF-8/myostatin quantikine ELISA kit (R&D Systems, Minneapolis, MN) may be used. Examples of anti-GDF-8/myostatin antibodies that may be used for detection include AF1539, MAB788 and AF788 (R&D Systems, Minneapolis, MN).

[00613] In some embodiments, reporter genes of the present disclosure comprise growth factor-responsive promoters. As used herein, the term "growth factor-responsive promoter" refers to a gene promoter that facilitates transcription of a downstream gene in response to growth factor cell signaling induced by one or more growth factors. In some embodiments, growth factor-responsive promoters are responsive to TGF-β family member growth factor signaling. In some embodiments, growth factor-responsive promoters of the present

disclosure comprise one or more sequences listed in Table 18 or fragments or variants thereof. These include two versions of the plasminogen activator inhibitor type 1 (PAI-1) promoter [V1 as disclosed by Abe et al (Abe, M. et al., An assay for transforming growth factor-β using cells transfected with a plasminogen activator inhibitor-1 promoter-luciferase construct. Analytical Biochemistry. 1994. 216:276-84) and V2 as disclosed in WO 2011/034935, the contents of which are hereby incorporated by reference in their entirety,] a collagen, type 1, alpha 1 promoter, a collagen, type 1, alpha 2 promoter, a FoxP3 promoter, a CAGA12 promoter [responsive to Smad-dependent signaling as reported by Thies et al (Thies, R.S. et al., GDF-8 propeptide binds to GDF-8 and antagonizes biological activity by inhibiting GDF-8 receptor binding. Growth Factors. 2001. 18:251-9) and an adenovirus major late promoter.

Table 18. Growth factor-responsive promoters

Promoter	Sequence	SEQ ID NO
PAI-1 (V1)	AGCTTACCATGGTAACCCCTGGTCCCGTTCAGCCACCACCACCC CACCCAGCACACCTCCAACCTCAGCCAGACAAGGTTGTTGACA CAAGAGAGCCCTCAGGGGCACAGAGAGAGTCTGGACACGTGG GGAGTCAGCCGTGTATCATCGGAGGCGGCCGGGCACATGGCAG GGATGAGGGAAAGACCAAGAGTCCTCTGTTGGGCCCAAGTCCT AGACAGACAAAACCTAGACAATCACGTGGCTGGCTGCATGCCT GTGGCTGTTGGGCTGGGCAGGAGGAGGGAGGGGCGCTCTTTCC TGGAGGTGGTCCAGAGCACCGGGTGGACAGCCCTGGGGGAAA ACTTCCACGTTTTGATGGAGGTTATCTTTGATAACTCCACAGTG ACCTGGTTCGCCAAAGGAAAAGCAGGCAACGTGAGCTGTTTTT TTTTTCTCCAAGCTGAACACTAGGGGTCCTAGGCTTTTTGGGTC ACCCGGCATGGCAGACAGTCAACCTGGCAGGACATCCGGGAG AGACAGACACAGGCAGAGGGCAGAAAGGTCAAGGGAGGTTCT CAGGCCAAGGCTATTGGGGTTTGCTCAATTGTTCCTGAATGCTC TTACACACGTACACACACAGAGCAGCACACACACACACACACA CATGCCTCAGCAAGTCCCAGAGAGGGAGGTGTCGAGGGGGAC CCGCTGGCTGTTCAGACGGACTCCCAGAGCCAGTGAGTGGGTG GGGCTGGAACATGAGTTCATCTATTTCCTGCCCACATCTGGTAT AAAAGGAGGCAGTGGCCCACAGAGGAGCACAGCTGTGTTTGG CTGCAGGGCCAAGAGCGCTGTCAAGAAGACCCACACGCCCCCC TCCAGCAGCTG	1628
PAI-1 (V2)	TTGGTCTCCTGTTTCCTTACCAAGCTTTTACCATGGTAACCCCTG GTCCCGTTCAGCCACCACCACCCCACCCAGCACACCTCCAACCT CAGCCAGACAAGGTTGTTGACACAAGAGAGCCCTCAGGGGCAC AGAGAGAGTCTGGACACGTGGGGAGTCAGCCGTGTATCATCGG AGGCGGCCGGGCACATGGCAGGGATGAGGGAAAGACCAAGAG TCCTCTGTTGGGCCCAAGTCCTAGACAGACAAAACCTAGACAA TCACGTGGCTGGCTGCATGCCCTGTGGCTGTTGGGCTGGGCCCA GGAGGAGGGAGGGGCGCTCTTTCCTGGAGGTGGTCCAGAGCAC CGGGTGGACAGCCCTGGGGGAAAACTTCCACGTTTTGATGGAG GTTATCTTTGATAACTCCACAGTGACCTGGTTCGCCAAAGGAA	1629

	AAGCAGGCAACGTGAGCTGTTTTTTTTTTCTCCAAGCTGAACAC TAGGGGTCCTAGGCTTTTTGGGTCACCCGGCATGGCAGACAGT CAACCTGGCAGGACATCCGGGAGAGACAGACACAGGCAGAGG GCAGAAAGGTCAAGGGAGGTTCTCAGGCCAAGGCTATTGGGGT TTGCTCAATTGTTCCTGAATGCTCTTACACACGTACACACACAG AGCAGCACACACACACACACACACATGCCTCAGCAAGTCCCAG AGAGGGAGGTGTCGAGGGGGACCCGCTGGCTGTTCAGACGGA CTCCCAGAGCCAGTGAGTGGGTGGGGCTGGAACATGAGTTCAT CTATTTCCTGCCCACATCTGGTATAAAAGGAGGCAGTGGCCCA CAGAGGAGCACAGCTGTGTTTGGCTGCAGGGCCAAGAGCGCTG TCAAGAAGACCCACACGCCCCCCTCCAGCAGCTGAATTCCTGC AGCTCAGCAGCCGCCGCCAGAGCAGGACGAACCGCCAATCGC AAGGCACCTCTGAGAACTTCAGGTA	
Col1A1	CCATGGCAAACAAAACTCTTCTCTAAGTCACCAATGATCACAG GCCTCCCACTAAAAATACTTCCCAACTCTGGGGTGGAAGAGTT TGGGGGATGAATTTTTAGGGGATTGCAAGCCCCAATCCCCACC TCTGTGTCCCTAGAATCCCCCACCCCTACCTTGGCTGCTCCATC ACCCAACCACCAAAGCTTTCTTCTGCAGAGGCCACCTAGTCAT GTTTCTCACCCTGCACCTCAGCCTCCCCACTCCATCTCTCAATC ATGCCTAGGGTTTGGAGGAAGGCATTTGATTCTGTTCTGGAGCA CAGCAGAAGAATTGACATCCTCAAAATTAAAACTCCCTTGCCT GCACCCCTCCCTCAGATATCTGATTCTTAATGTCTAGAAAGGAA TCTGTAAATTGTTCCCCAAATATTCCTAAGCTCCATCCCCTAGC CACACCAGAAGACACCCCCAAACAGGCACATCTTTTTAATTCC CAGCTTCCTCTGTTTTGGAGAGGTCCTCAGCATGCCTCTTTATG CCCCTCCCTTAGCTCTTGCCAGGATATCAGAGGGTGACTGGGG CACAGCCAGGAGGACCCCCTCCCCAACACCCCCAACCCTTCCA CCTTTGGAAGTCTCCCCACCCAGCTCCCCAGTTCCCCAGTTCCA CTTCTTCTAGATTGGAGGTCCCAGGAAGAGAGCAGAGGGGCAC CCCTACCCACTGGTTAGCCCACGCCATTCTGAGGACCCAGCTGC ACCCCTACCACAGCACCTCTGGCCCAGGCTGGGCTGGGGGGCT GGGGAGGCAGAGCTGCGAAGAGGGGAGATGTGGGGTGGACTC CCTTCCCTCCTCCTCCCCCTCTCCATTCCAACTCCCAAATTGGG GGCCGGGCCAGGCAGCTCTGATTGGCTGGGGCACGGGCGGCCG GCTCCCCCTCTCCGAGGGGCAGGGTTCCTCCCTGCTCTCCATCA GGACAGTATAAAAGGGGCCCGGGCCAGTCGTCGGAGCAGACG GGAGTTTCTCCTCGGGGTCGGAGCAGGAGGCACGCGGAGTGTG AGGCCACGCATGAGCGGACGCTAACCCCCTCCCCAGCCACAAA GAGTCTACATG	1630
Col1A2	TAGAGTTCGCAAAGCCTATCCTCCCTGTAGCCGGGTGCCAAGC AGCCTCGAGCCTGCTCCCCAGCCCACCTGCCAACAAAAGGCGC CCTCCGACTGCAACCCAGCCCTCCACAGACAGGACCCGCCCTT TCCCGAAGTCATAAGACAAAGAGAGTGCATCACTGCTGAAACA GTGGGCGCACACGAGCCCCAAAGCTAGAGAAAAGCTGGACGG GGCTGGGGGCGGGGTGCAGGGGTGGAGGGGCGGGGAGGCGGG CTCCGGCTGCGCCACGCTATCGAGTCTTCCCTCCCTCCTTCTCT GCCCCCTCCGCTCCCGCTGGAGCCCTCCACCCTACAAGTGGCCT ACAGGGCACAGGTGAGGCGGGACTGGACAGCTCCTGCTTTGAT CGCCGGAGATCTGCAAATTCTGCCCATGTCGGGGCTGCAGAGC ACTCCGACGTGTCCCATAGTGTTTCCAAACTTGGAAAGGGCGG GGGAGGGCGGGAGGATGCGGAGGGCGGAGGTATGCAGACAAC GAGTCAGAGTTTCCCCTTGAAAGCCTCAAAAGTGTCCACGTCCT CAAAAAGAATGGAACCAATTTAAGAAGCCAGCCCCGTGGCCAC GTCCCTTCCCCCATTCGCTCCCTCCTCTGCGCCCCCGCAGGCTC CTCCCAGCTGTGGCTGCCCGGGCCCCCAGCCCCAGCCCTCCCAT	1631

	TGGTGGAGGCCCTTTTGGAGGCACCCTAGGGCCAGGGAAACTT TTGCCGTATAAATAGGGCAGATCCGGGCTTTATTATTTTAGCAC CACGGCAGCAGGAGGTTTCGGCTAAGTTGGAGGTACTGGCCAC GACTGCATGCCCGCGCCCGCCAGGTGATACCTCCGCCGGTGAC CCAGGGGCTCTGCGACACAAGGAGTCTGCATGTCTAAGTGCTA GACATGCTCAGCTTTGTGGATACGCGGACTTTGTTGCTGCTTGC AGTAA	
FoxP3	AGTAAAAGACCCCAAAGGCTGAGGGCCTCAGAAGCATCAGGC CATGATGTTCCTGAAACAAGAGGGTCAGGGTCCCAATGGGCCT CTGGGGTTCATCGTGAGGATGGATGCATTAATATTGGGGACCT GCTAGGGACCTTCCCAGTGGGACAGTGGCTGGGTCAGGGCACT CAAGCCCTAAAACGTGATGAGGCGAGACTTTTCTCTCTTTCCTC ATTCAGTAACTGTCAGTAGATTCTGGGAGCCAGGGATTCTCCG ACTCTTCAAGTCCATGAATTTTAGGGGATGACAGTGGGCTCTCC GCTTTCTCCTCCATGAAGTAACTTACATGCCCCTCACCCTCTGT GGGAGGGGTGTTGCAGGGGGTGCAGAACTCCCCTCGCCGGGTA GTTCAAGCAATGGGGACCATATCAATTCCATCTATAGGGAAAC TGAGGCCTGGAGTAGGGCGAGGCCTCTGGGAACCCAGCCCTAT TCTGTCTCTTTCCCTGGCATTTCCCATCCACACATAGAGCTTCA GATTCTCTTTCTTTCCCCAGAGACCCTCAAATATCCTCTCACTC ACAGAATGGTGTCTCTGCCTGCCTCGGGTTGGCCCTGTGATTTA TTTTAGTTCTTTTCCCTTGTTTTTTTTTTTTCAAACTCTATACACT TTTGTTTTAAAAACTGTGGTTTCTCATGAGCCCTATTATCTCATT GATACCTCTCACCTCTGTGGTGAGGGGAAGAAATCATATTTTCA GATGACTCGTAAAGGGCAAAGAAAAAAACCCAAAATTTCAAA ATTTCCGTTTAAGTCTCATAATCAAGAAAAGGAGAAACACAGA GAGAGAGAAAAAAAAAACTATGAGAACCCCCCCCCACCCCGT GATTATCAGCGCACACACTCATCGAAAAAAATTTGGATTATTA GAAGAGAGAGGTCTGCGGCTTCCACACCGTACAGCGTGGTTTT TCTTCTCGGTATAAAAGCAAAGTTGTTTTTGATACGTGACAGTT TCCCACAAGCCAGGCTGATCCTTTTCTGTCAGTCCACTTCACCA	1632
CAGA12	AGCCAGACAAGCCAGACAAGCCAGACAAGCCAGACAAGCCAG ACAAGCCAGACAAGCCAGACAAGCCAGACAAGCCAGACAAGC CAGACAAGCCAGACAAGCCAGACA	1633
Adenovirus major late promoter	GGGCTATAAAAGGGGGTGGGGGCGCGTTCGTCCTCACTCTCTT CCG	1634

[00614] In some embodiments, mink lung epithelial/PAI reporter cell lines may be used. Mink lung epithelial cells do not produce TGF-β, but do express high levels of TGF-β receptors (Munger et al). Mink lung epithelial/PAI reporter cell lines comprise reporter constructs comprising promoter elements from the TGF-β-responsive genes PAI and/or COL1A that modulate the expression of the protein coding portion of the luciferase gene. In some embodiments, other reporter constructs may be used with mink lung epithelial cells. In some embodiments, SMAD3-responsive reporter constructs may be used.

[00615] CAGA promoter-based reporter assays may be used to test antibodies that modulate SMAD-dependent gene expression as reported by Thies et al (Thies, R.S. et al.,

Growth Factors. 2001. 18:251-9, the contents of which are herein incorporated by reference in their entirety). In some cases, CAGA reporter assays may be used to assess GDF-8 and/or GDF-11 growth factor activity in the presence and absence of an activating or inhibiting antibody. According to such methods, GDF-8 growth factor (or proGDF-8 subjected to furin and/or mTLL2 processing) may be cultured with reporter cells comprising the CAGA promoter linked to a reporter gene (e.g. luciferase) in the presence or absence of the antibody being tested.

Proliferation/differentiation assays

[00616] In some embodiments, cell-based assays of the present disclosure may comprise proliferation assays. As used herein, the term "proliferation assay" refers to an assay that determines the effect on one or more agents on cell proliferation.

[00617] In some embodiments, cell differentiation assays may be used to assess growth factor activity modulation by activating and/or inhibiting antibodies. Cell differentiation assays may include skeletal muscle differentiation assays. Such assays may be used to test GDF-8 activating and/or inhibiting antibodies. In some cases, skeletal muscle differentiation assays assess myoblast differentiation by looking at changes in the expression level of proteins that change during stages of differentiation. Such proteins may include, but are not limited to myogenin, myosin heavy chain and creatine kinase. GDF-8 inhibits myoblast differentiation, therefore GDF-8-inhibiting antibodies may be tested by examining their effect on GDF-8-dependent inhibition of myoblast differentiation.

Animal Models

[00618] In some embodiments, compounds and/or compositions of the present disclosure may be tested in animal models including mammalian models of muscles growth and development. These models may include but are not limited to mouse models of grip strength. Such models may include testing by determining the force (in grams) generated when a mouse is pulled from a force measuring lever. Additional models may include but are not limited to other strength and endurance tests such as the Morris water maze test for endurance and the wire hang test for motor deficits. Other mouse models may include, but are not limited to assays which determine changes in whole muscle weight and size.

[00619] In another embodiment, compounds and/or compositions of the present disclosure may be tested in non-mouse animal models including models of muscle growth and development where changes in muscle are observed. Such changes may include, but are not

limited to changes in muscle weight and size, muscle fiber length and diameter, number of fibers per muscle bundle, number of synaptic contacts per muscle fiber, and fiber strength.

[00620] In some embodiments, tissues from animals treated with compounds and/or compositions of the present disclosure may be analyzed by immunohistochemical analysis. Such analysis may include immunostaining of muscles, muscle fibers and muscle connections to show changes in response to treatment. Complete blood counts may be carried out pre and post study to enable monitoring of compounds and/or compositions of the present disclosure.

Kits and Devices

[00621] Any of the compounds and/or compositions of the present disclosure may be comprised in a kit. In a non-limiting example, reagents for generating compounds and/or compositions, including antigen molecules are included in one or more kit. In some embodiments, kits may further include reagents and/or instructions for creating and/or synthesizing compounds and/or compositions of the present disclosure. In some embodiments, kits may also include one or more buffers. In some embodiments, kits of the disclosure may include components for making protein or nucleic acid arrays or libraries and thus, may include, for example, solid supports.

[00622] In some embodiments, kit components may be packaged either in aqueous media or in lyophilized form. The container means of the kits will generally include at least one vial, test tube, flask, bottle, syringe or other container means, into which a component may be placed, and preferably, suitably aliquotted. Where there are more than one kit component, (labeling reagent and label may be packaged together), kits may also generally contain second, third or other additional containers into which additional components may be separately placed. In some embodiments, kits may also comprise second container means for containing sterile, pharmaceutically acceptable buffers and/or other diluents. In some embodiments, various combinations of components may be comprised in one or more vial. Kits of the present disclosure may also typically include means for containing compounds and/or compositions of the present disclosure, e.g., proteins, nucleic acids, and any other reagent containers in close confinement for commercial sale. Such containers may include injection or blow-molded plastic containers into which desired vials are retained.

[00623] In some embodiments, kit components are provided in one and/or more liquid solutions. In some embodiments, liquid solutions are aqueous solutions, with sterile aqueous solutions being particularly preferred. In some embodiments, kit components may be provided as dried powder(s). When reagents and/or components are provided as dry powders,

such powders may be reconstituted by the addition of suitable volumes of solvent. In some embodiments, it is envisioned that solvents may also be provided in another container means. In some embodiments, labeling dyes are provided as dried powders. In some embodiments, it is contemplated that 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120, 120, 130, 140, 150, 160, 170, 180, 190, 200, 300, 400, 500, 600, 700, 800, 900, 1000 micrograms or at least or at most those amounts of dried dye are provided in kits of the disclosure. In such embodiments, dye may then be resuspended in any suitable solvent, such as DMSO.

[00624] In some embodiments, kits may include instructions for employing kit components as well the use of any other reagent not included in the kit. Instructions may include variations that may be implemented.

[00625] In some embodiments, compounds and/or compositions of the present disclosure may be combined with, coated onto or embedded in a device. Devices may include, but are not limited to, dental implants, stents, bone replacements, artificial joints, valves, pacemakers and/or other implantable therapeutic device.

Definitions

[00626] At various places in the present specification, substituents of compounds of the present disclosure are disclosed in groups or in ranges. It is specifically intended that the present disclosure include each and every individual subcombination of the members of such groups and ranges. The following is a non-limiting list of term definitions.

[00627] *Activity:* As used herein, the term "activity" refers to the condition in which things are happening or being done. Compositions of the disclosure may have activity and this activity may involve one or more biological events. In some embodiments, such biological event may involve growth factors and/or growth factor signaling. In some embodiments, biological events may include cell signaling events associated with growth factor and receptor interactions. In some embodiments, biological events may include cell signaling events associated with TGF-β or TGF-β-related protein interactions with one or more corresponding receptors.

[00628] *Administered in combination:* As used herein, the term "administered in combination" or "combined administration" refers to simultaneous exposure of one or more subjects to two or more agents administered at the same time or within an interval such that the subject is at some point in time simultaneously exposed to both and/or such that there may be an overlap in the effect of each agent on the patient. In some embodiments, at least one dose of one or more agents is administered within about 24 hours, 12 hours, 6 hours, 3

hours, 1 hour, 30 minutes, 15 minutes, 10 minutes, 5 minutes, or 1 minute of at least one dose of one or more other agents. In some embodiments, administration occurs in overlapping dosage regimens. As used herein, the term "dosage regimen" refers to a plurality of doses spaced apart in time. Such doses may occur at regular intervals or may include one or more hiatus in administration. In some embodiments, the administration of individual doses of one or more compounds and/or compositions of the present disclosure, as described herein, are spaced sufficiently closely together such that a combinatorial (*e.g.*, a synergistic) effect is achieved.

[00629] *Animal:* As used herein, the term "animal" refers to any member of the animal kingdom. In some embodiments, "animal" refers to humans at any stage of development. In some embodiments, "animal" refers to non-human animals at any stage of development. In certain embodiments, the non-human animal is a mammal (*e.g.*, a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate, or a pig). In some embodiments, animals include, but are not limited to, mammals, birds, reptiles, amphibians, fish, and worms. In some embodiments, the animal is a transgenic animal, genetically-engineered animal, or a clone.

[00630] *Antigens of interest* or *desired antigens*: As used herein, the terms "antigens of interest" or "desired antigens" refers to those proteins and/or other biomolecules provided herein that are immunospecifically bound or interact with antibodies of the present disclosure and/or fragments, mutants, variants, and/or alterations thereof described herein. In some embodiments, antigens of interest may comprise TGF-β-related proteins, growth factors, prodomains, GPCs, protein modules or regions of overlap between them.

[00631] *Approximately:* As used herein, the term "approximately" or "about," as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In certain embodiments, the term "approximately" or "about" refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

[00632] *Associated with:* As used herein, the terms "associated with," "conjugated," "linked," "attached," and "tethered," when used with respect to two or more moieties, mean that the moieties are physically associated or connected with one another, either directly or via one or more additional moieties that serve as linking agents, to form a structure that is sufficiently stable so that the moieties remain physically associated under the conditions in

which the structure is used, *e.g.*, physiological conditions. An "association" need not be strictly through direct covalent chemical bonding. It may also suggest ionic or hydrogen bonding or a hybridization based connectivity sufficiently stable such that the "associated" entities remain physically associated.

[00633] *Biomolecule:* As used herein, the term "biomolecule" is any natural molecule which is amino acid-based, nucleic acid-based, carbohydrate-based or lipid-based, and the like.

[00634] *Biologically active*: As used herein, the phrase "biologically active" refers to a characteristic of any substance that has activity in a biological system and/or organism. For instance, a substance that, when administered to an organism, has a biological effect on that organism, is considered to be biologically active. In particular embodiments, a compounds and/or compositions of the present disclosure may be considered biologically active if even a portion of is biologically active or mimics an activity considered to biologically relevant.

[00635] *Biological system*: As used herein, the term "biological system" refers to a group of organs, tissues, cells, intracellular components, proteins, nucleic acids, molecules (including, but not limited to biomolecules) that function together to perform a certain biological task within cellular membranes, cellular compartments, cells, tissues, organs, organ systems, multicellular organisms, or any biological entity. Biological systems may be in vitro or in vivo. In some embodiments, biological systems are cell signaling pathways comprising intracellular and/or extracellular cell signaling biomolecules. In some embodiments, biological systems comprise growth factor signaling events within the extracellular matrix, cellular matrix and/or cellular niches.

[00636] *Candidate antibody*: As used herein, the term "candidate antibody" refers to an antibody from a pool of one or more antibody from which one or more desired antibodies may be selected.

[00637] *Cellular matrix*: As used herein, the term "cellular matrix" refers to the biochemical and structural environment associated with the outer portion of the cell membrane. Such cell membranes may also include platelet membranes. Components of the cellular matrix may include, but are not limited to proteoglycans, carbohydrate molecules, integral membrane proteins, glycolipids and the like. In some cases, cellular matrix components may include growth factors and/or modulators of growth factor activity. Some cellular matrix proteins include integrins, GARP and LRRC33.

[00638] *Compound:* As used herein, the term "compound," refers to a distinct chemical entity The term may be used herein to refer to peptides, proteins, protein complexes or

antibodies of the disclosure. In some embodiments, a particular compound may exist in one or more isomeric or isotopic forms (including, but not limited to stereoisomers, geometric isomers and isotopes). In some embodiments, a compound is provided or utilized in only a single such form. In some embodiments, a compound is provided or utilized as a mixture of two or more such forms (including, but not limited to a racemic mixture of stereoisomers). Those of skill in the art appreciate that some compounds exist in different such forms, show different properties and/or activities (including, but not limited to biological activities). In such cases it is within the ordinary skill of those in the art to select or avoid particular forms of the compound for use in accordance with the present disclosure. For example, compounds that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis.

[00639] *Conserved*: As used herein, the term "conserved" refers to nucleotides or amino acid residues of polynucleotide or polypeptide sequences, respectively, that are those that occur unaltered in the same position of two or more sequences being compared. Nucleotides or amino acids that are relatively conserved are those that are conserved among more related sequences than nucleotides or amino acids appearing elsewhere in the sequences.

[00640] In some embodiments, two or more sequences are said to be "completely conserved" if they are 100% identical to one another. In some embodiments, two or more sequences are said to be "highly conserved" if they are at least 70% identical, at least 80% identical, at least 90% identical, or at least 95% identical to one another. In some embodiments, two or more sequences are said to be "highly conserved" if they are about 70% identical, about 80% identical, about 90% identical, about 95%, about 98%, or about 99% identical to one another. In some embodiments, two or more sequences are said to be "conserved" if they are at least 30% identical, at least 40% identical, at least 50% identical, at least 60% identical, at least 70% identical, at least 80% identical, at least 90% identical, or at least 95% identical to one another. In some embodiments, two or more sequences are said to be "conserved" if they are about 30% identical, about 40% identical, about 50% identical, about 60% identical, about 70% identical, about 80% identical, about 90% identical, about 95% identical, about 98% identical, or about 99% identical to one another. Conservation of sequence may apply to the entire length of an oligonucleotide or polypeptide or may apply to a portion, region or feature thereof.

[00641] In one embodiment, conserved sequences are not contiguous. Those skilled in the art are able to appreciate how to achieve alignment when gaps in contiguous alignment are present between sequences, and to align corresponding residues not withstanding insertions or deletions present.

[00642] *Delivery:* As used herein, "delivery" refers to the act or manner of delivering a compound, substance, entity, moiety, cargo or payload.

[00643] *Delivery Agent*: As used herein, "delivery agent" refers to any agent which facilitates, at least in part, the *in vivo* delivery of one or more substances (including, but not limited to a compounds and/or compositions of the present disclosure) to a cell, subject or other biological system cells.

[00644] *Desired antibody:* As used herein, the term "desired antibody" refers to an antibody that is sought after, in some cases from a pool of candidate antibodies.

[00645] *Destabilized:* As used herein, the term "destable," "destabilize," or "destabilizing region" means a region or molecule that is less stable than a starting, reference, wild-type or native form of the same region or molecule.

[00646] *Detectable label:* As used herein, "detectable label" refers to one or more markers, signals, or moieties which are attached, incorporated or associated with another entity, which markers, signals or moieties are readily detected by methods known in the art including radiography, fluorescence, chemiluminescence, enzymatic activity, absorbance, immunological detection and the like. Detectable labels may include radioisotopes, fluorophores, chromophores, enzymes, dyes, metal ions, ligands, biotin, avidin, streptavidin and haptens, quantum dots, polyhistidine tags, myc tags, flag tags, human influenza hemagglutinin (HA) tags and the like. Detectable labels may be located at any position in the entity with which they are attached, incorporated or associated. For example, when attached, incorporated in or associated with a peptide or protein, they may be within the amino acids, the peptides, or proteins, or located at the N- or C- termini.

[00647] *Distal:* As used herein, the term "distal" means situated away from the center or away from a point or region of interest.

[00648] *Engineered:* As used herein, embodiments of the disclosure are "engineered" when they are designed to have a feature or property, whether structural or chemical, that varies from a starting point, wild type or native molecule. Thus, engineered agents or entities are those whose design and/or production include an act of the hand of man.

[00649] *Epitope:* As used herein, an "epitope" refers to a surface or region on a molecule that is capable of interacting with components of the immune system, including, but not

limited to antibodies. In some embodiments, when referring to a protein or protein module, an epitope may comprise a linear stretch of amino acids or a three dimensional structure formed by folded amino acid chains.

[00650] *Expression*: As used herein, "expression" of a nucleic acid sequence refers to one or more of the following events: (1) production of an RNA template from a DNA sequence (*e.g.*, by transcription); (2) processing of an RNA transcript (*e.g.*, by splicing, editing, 5′ cap formation, and/or 3′ end processing); (3) translation of an RNA into a polypeptide or protein; (4) folding of a polypeptide or protein; and (5) post-translational modification of a polypeptide or protein.

[00651] *Extracellular matrix*: As used herein, the term, "extracellular matrix," or "ECM" refers to the area surrounding cells and/or the area between cells that typically comprises structural proteins as well as cell signaling molecules. Components of the extracellular matrix may include, but are not limited to proteins, nucleic acids, membranes, lipids and sugars that may be directly or indirectly associated with structural components of the extracellular environments. Structural components of the extracellular matrix may include, but are not limited to proteins, polysaccharides (e.g. hyaluronic acid), glycosaminoglycans and proteoglycans (e.g. heparin sulfate, chondroitin sulfate and keratin sulfate). Such structural components may include, but are not limited to fibrous components (e.g. collagens and elastins), fibrillins, fibronectin, laminins, agrin, perlecan, decorin and the like. Other proteins that may be components of the extracellular matrix include GASPs and LTBPs. Extracellular matrix components may also include growth factors and/or modulators of growth factor activity.

[00652] *Feature:* As used herein, a "feature" refers to a characteristic, a property, or a distinctive element.

[00653] *Formulation*: As used herein, a "formulation" includes at least a compound and/or composition of the present disclosure and a delivery agent.

[00654] *Fragment:* A "fragment," as used herein, refers to a portion. For example, fragments of proteins may comprise polypeptides obtained by digesting full-length protein isolated from cultured cells. In some embodiments, a fragment of a protein includes at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 150, 200, 250 or more amino acids. In some embodiments, fragments of an antibody include portions of an antibody subjected to enzymatic digestion or synthesized as such.

[00655] *Functional*: As used herein, a "functional" biological molecule is a biological entity with a structure and in a form in which it exhibits a property and/or activity by which it is characterized.

[00656] *Homology*: As used herein, the term "homology" refers to the overall relatedness between polymeric molecules, *e.g.* between nucleic acid molecules (*e.g.* DNA molecules and/or RNA molecules) and/or between polypeptide molecules. In some embodiments, polymeric molecules are considered to be "homologous" to one another if their sequences are at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical or similar. The term "homologous" necessarily refers to a comparison between at least two sequences (polynucleotide or polypeptide sequences). In accordance with the disclosure, two polynucleotide sequences are considered to be homologous if the polypeptides they encode are at least about 50%, 60%, 70%, 80%, 90%, 95%, or even 99% for at least one stretch of at least about 20 amino acids. In some embodiments, homologous polynucleotide sequences are characterized by the ability to encode a stretch of at least 4–5 uniquely specified amino acids. For polynucleotide sequences less than 60 nucleotides in length, homology is typically determined by the ability to encode a stretch of at least 4–5 uniquely specified amino acids. In accordance with the disclosure, two protein sequences are considered to be homologous if the proteins are at least about 50%, 60%, 70%, 80%, or 90% identical for at least one stretch of at least about 20 amino acids. In many embodiments, homologous protein may show a large overall degree of homology and a high degree of homology over at least one short stretch of at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50 or more amino acids. In many embodiments, homologous proteins share one or more characteristic sequence elements. As used herein, the term "characteristic sequence element" refers to a motif present in related proteins. In some embodiments, the presence of such motifs correlates with a particular activity (such as biological activity).

[00657] *Identity*: As used herein, the term "identity" refers to the overall relatedness between polymeric molecules, *e.g.*, between oligonucleotide molecules (*e.g.* DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Calculation of the percent identity of two polynucleotide sequences, for example, may be performed by aligning the two sequences for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second nucleic acid sequences for optimal alignment and non-identical sequences can be disregarded for comparison purposes). In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, at least 40%, at least 50%, at least

60%, at least 70%, at least 80%, at least 90%, at least 95%, or 100% of the length of the reference sequence. The nucleotides at corresponding nucleotide positions are then compared. When a position in the first sequence is occupied by the same nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which needs to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. For example, the percent identity between two nucleotide sequences can be determined using methods such as those described in Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; Computer Analysis of Sequence Data, Part I, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; each of which is incorporated herein by reference. For example, the percent identity between two nucleotide sequences can be determined, for example using the algorithm of Meyers and Miller (CABIOS, 1989, 4:11-17), which has been incorporated into the ALIGN program (version 2.0) using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. The percent identity between two nucleotide sequences can, alternatively, be determined using the GAP program in the GCG software package using an NWSgapdna.CMP matrix. Methods commonly employed to determine percent identity between sequences include, but are not limited to those disclosed in Carillo, H., and Lipman, D., SIAM J Applied Math., 48:1073 (1988); incorporated herein by reference. Techniques for determining identity are codified in publicly available computer programs. Exemplary computer software to determine homology between two sequences include, but are not limited to, GCG program package, Devereux, J., *et al.*, *Nucleic Acids Research*, 12(1), 387 (1984)), BLASTP, BLASTN, and FASTA Altschul, S. F. *et al.*, *J. Molec. Biol.*, 215, 403 (1990)).

[00658] *Inhibit expression of a gene:* As used herein, the phrase "inhibit expression of a gene" means to cause a reduction in the amount of an expression product of the gene. The expression product may be RNA transcribed from the gene (*e.g.* mRNA) or a polypeptide translated from mRNA transcribed from the gene. Typically a reduction in the level of

mRNA results in a reduction in the level of a polypeptide translated therefrom. The level of expression may be determined using standard techniques for measuring mRNA or protein.

[00659] *In vitro*: As used herein, the term "*in vitro*" refers to events that occur in an artificial environment, *e.g.*, in a test tube or reaction vessel, in cell culture, in a Petri dish, *etc.*, rather than within an organism (*e.g.*, animal, plant, or microbe).

[00660] *In vivo*: As used herein, the term "*in vivo*" refers to events that occur within an organism (*e.g.*, subject, animal, plant, or microbe or cell, niche, body fluid, tissue, organ or organ system thereof).

[00661] *Isolated*: As used herein, the term "isolated" is synonymous with "separated", but carries with it the inference separation was carried out by the hand of man. In one embodiment, an isolated substance or entity is one that has been separated from at least some of the components with which it was previously associated (whether in nature or in an experimental setting). Isolated substances may have varying levels of purity in reference to the substances from which they have been associated. Isolated substances and/or entities may be separated from at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or more of the other components with which they were initially associated. In some embodiments, isolated agents are more than about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% pure. As used herein, a substance is "pure" if it is substantially free of other components.

[00662] *Substantially isolated*: By "substantially isolated" is meant that the compound is substantially separated from the environment in which it was formed or detected. Partial separation can include, for example, a composition enriched in the compound of the present disclosure. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compound of the present disclosure, or salt thereof. Methods for isolating compounds and their salts are routine in the art. In some embodiments, isolation of a substance or entity includes disruption of chemical associations and/or bonds. In some embodiments, isolation includes only the separation from components with which the isolated substance or entity was previously combined and does not include such disruption.

[00663] *Linker:* As used herein, a linker refers to a moiety that connects two or more domains, moieties or entities. In one embodiment, a linker may comprise 10 or more atoms. In a further embodiment, a linker may comprise a group of atoms, e.g., 10-1,000 atoms, and

can be comprised of the atoms or groups such as, but not limited to, carbon, amino, alkylamino, oxygen, sulfur, sulfoxide, sulfonyl, carbonyl, and imine. In some embodiments, a linker may comprise one or more nucleic acids comprising one or more nucleotides. In some embodiments, the linker may comprise an amino acid, peptide, polypeptide or protein. In some embodiments, a moiety bound by a linker may include, but is not limited to an atom, a chemical group, a nucleoside, a nucleotide, a nucleobase, a sugar, a nucleic acid, an amino acid, a peptide, a polypeptide, a protein, a protein complex, a payload (e.g., a therapeutic agent). or a marker (including, but not limited to a chemical, fluorescent, radioactive or bioluminescent marker). The linker can be used for any useful purpose, such as to form multimers or conjugates, as well as to administer a payload, as described herein. Examples of chemical groups that can be incorporated into the linker include, but are not limited to, alkyl, alkenyl, alkynyl, amido, amino, ether, thioether, ester, alkylene, heteroalkylene, aryl, or heterocyclyl, each of which can be optionally substituted, as described herein. Examples of linkers include, but are not limited to, unsaturated alkanes, polyethylene glycols (e.g., ethylene or propylene glycol monomeric units, e.g., diethylene glycol, dipropylene glycol, triethylene glycol, tripropylene glycol, tetraethylene glycol, or tetraethylene glycol), and dextran polymers, Other examples include, but are not limited to, cleavable moieties within the linker, such as, for example, a disulfide bond (-S-S-) or an azo bond (-N=N-), which can be cleaved using a reducing agent or photolysis. Non-limiting examples of a selectively cleavable bonds include an amido bond which may be cleaved for example by the use of tris(2-carboxyethyl)phosphine (TCEP), or other reducing agents, and/or photolysis, as well as an ester bond which may be cleaved for example by acidic or basic hydrolysis.

[00664] *Modified:* As used herein, the term "modified" refers to a changed state or structure of a molecule or entity as compared with a parent or reference molecule or entity. Molecules may be modified in many ways including chemically, structurally, and functionally. In some embodiments, compounds and/or compositions of the present disclosure are modified by the introduction of non-natural amino acids.

[00665] *Mutation*: As used herein, the term "mutation" refers to a change and/or alteration. In some embodiments, mutations may be changes and/or alterations to proteins (including peptides and polypeptides) and/or nucleic acids (including polynucleic acids). In some embodiments, mutations comprise changes and/or alterations to a protein and/or nucleic acid sequence. Such changes and/or alterations may comprise the addition, substitution and or deletion of one or more amino acids (in the case of proteins and/or peptides) and/or nucleotides (in the case of nucleic acids and or polynucleic acids). In embodiments wherein

mutations comprise the addition and/or substitution of amino acids and/or nucleotides, such additions and/or substitutions may comprise 1 or more amino acid and/or nucleotide residues and may include modified amino acids and/or nucleotides.

[00666] *Naturally occurring:* As used herein, "naturally occurring" means existing in nature without artificial aid, or involvement of the hand of man.

[00667] *Niche*: As used herein, the term "niche" refers to a place, zone and/or habbitat. In some embodiments, niches comprise cellular niches. As used herein, the term "cell niche" refers to a unique set of physiologic conditions in a cellular system within a tissue, organ or organ system within or derived from a mammalian organism. A cell niche may occur *in vivo, in vitro, ex vivo,* or *in situ*. Given the complex nature and the dynamic processes involved in growth factor signaling, a cell niche may be characterized functionally, spatially or temporally or may be used to refer to any environment that encompasses one or more cells. As such, in some embodiments a cell niche includes the environment of any cell adjacent to another cell that provides support, such as for example a nurse cell. In some embodiments, niches may include those described in International Patent Application No. WO2014074532, the contents of which are herein incorporated by reference in their entirety.

[00668] *Non-human vertebrate:* As used herein, a "non-human vertebrate" includes all vertebrates except *Homo sapiens*, including wild and domesticated species. Examples of non-human vertebrates include, but are not limited to, mammals, such as alpaca, banteng, bison, camel, cat, cattle, deer, dog, donkey, gayal, goat, guinea pig, horse, llama, mule, pig, rabbit, reindeer, sheep water buffalo, and yak.

[00669] *Off-target:* As used herein, "off target" refers to any unintended effect on any one or more target, gene and/or cellular transcript.

[00670] *Operably linked:* As used herein, the phrase "operably linked" refers to a functional connection between two or more molecules, constructs, transcripts, entities, moieties or the like.

[00671] *Paratope:* As used herein, a "paratope" refers to the antigen-binding site of an antibody.

[00672] *Passive adsorption*: As used herein, "passive adsorption" refers to a method of immobilizing solid-phase reactants on one or more surfaces (e.g. membranes, dishes, culture dishes, assay plates, etc.). Immobilization typically occurs due to affinity between such reactants and surface components.

[00673] *Patient:* As used herein, "patient" refers to a subject who may seek or be in need of treatment, requires treatment, is receiving treatment, will receive treatment, or a subject who is under care by a trained (e.g., licensed) professional for a particular disease or condition.

[00674] *Peptide:* As used herein, the term "peptide" refers to a chain of amino acids that is less than or equal to about 50 amino acids long, e.g., about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acids long.

[00675] *Pharmaceutically acceptable*: The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00676] *Pharmaceutically acceptable excipients:* As used herein, the term "pharmaceutically acceptable excipient," as used herein, refers to any ingredient other than active agents (e.g., as described herein) present in pharmaceutical compositions and having the properties of being substantially nontoxic and non-inflammatory in subjects. In some embodiments, pharmaceutically acceptable excipients are vehicles capable of suspending and/or dissolving active agents. Excipients may include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspending or dispersing agents, sweeteners, and waters of hydration. Exemplary excipients include, but are not limited to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

[00677] *Pharmaceutically acceptable salts*: Pharmaceutically acceptable salts of the compounds described herein are forms of the disclosed compounds wherein the acid or base moiety is in its salt form (e.g., as generated by reacting a free base group with a suitable organic acid). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic

residues such as carboxylic acids; and the like. Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. Pharmaceutically acceptable salts include the conventional non-toxic salts, for example, from non-toxic inorganic or organic acids. In some embodiments a pharmaceutically acceptable salt is prepared from a parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418, *Pharmaceutical Salts: Properties, Selection, and Use*, P.H. Stahl and C.G. Wermuth (eds.), Wiley-VCH, 2008, and Berge et al., *Journal of Pharmaceutical Science*, 66, 1-19 (1977), each of which is incorporated herein by reference in its entirety. *Pharmaceutically acceptable solvate*: The term "pharmaceutically acceptable solvate," as used herein, refers to a crystalline form of a compound wherein molecules of a suitable solvent are incorporated in the crystal lattice. For example, solvates may be prepared by crystallization, recrystallization, or precipitation from a solution that includes organic solvents, water, or a mixture thereof. Examples of suitable solvents are ethanol, water (for example, mono-, di-, and tri-hydrates), *N*-methylpyrrolidinone (NMP), dimethyl sulfoxide (DMSO), *N*,*N*'-dimethylformamide (DMF), *N*,*N*'-dimethylacetamide (DMAC), 1,3-dimethyl-2-imidazolidinone (DMEU), 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (DMPU), acetonitrile (ACN), propylene glycol, ethyl acetate, benzyl alcohol, 2-pyrrolidone, benzyl benzoate, and the like. When water is the solvent, the solvate is

referred to as a "hydrate." In some embodiments, the solvent incorporated into a solvate is of a type or at a level that is physiologically tolerable to an organism to which the solvate is administered (e.g., in a unit dosage form of a pharmaceutical composition).

[00678] *Pharmacokinetic:* As used herein, "pharmacokinetic" refers to any one or more properties of a molecule or compound as it relates to the determination of the fate of substances administered to living organisms. Pharmacokinetics are divided into several areas including the extent and rate of absorption, distribution, metabolism and excretion. This is commonly referred to as ADME where: (A) Absorption is the process of a substance entering the blood circulation; (D) Distribution is the dispersion or dissemination of substances throughout the fluids and tissues of the body; (M) Metabolism (or Biotransformation) is the irreversible transformation of parent compounds into daughter metabolites; and (E) Excretion (or Elimination) refers to the elimination of the substances from the body. In rare cases, some drugs irreversibly accumulate in body tissue.

[00679] *Physicochemical:* As used herein, "physicochemical" means of or relating to a physical and/or chemical property.

[00680] *Preventing*: As used herein, the term "preventing" refers to partially or completely delaying onset of an infection, disease, disorder and/or condition; partially or completely delaying onset of one or more symptoms, features, or clinical manifestations of a particular infection, disease, disorder, and/or condition; partially or completely delaying onset of one or more symptoms, features, or manifestations of a particular infection, disease, disorder, and/or condition; partially or completely delaying progression from an infection, a particular disease, disorder and/or condition; and/or decreasing the risk of developing pathology associated with the infection, the disease, disorder, and/or condition.

[00681] *Prodrug*: The present disclosure also includes prodrugs of the compounds described herein. As used herein, "prodrugs" refer to any substance, molecule or entity which is in a form predicate for that substance, molecule or entity to act as a therapeutic upon chemical or physical alteration. Prodrugs may be covalently bonded or sequestered in some way until converted into the active drug moiety prior to, upon or after administration to a mammalian subject. Prodrugs can be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds wherein hydroxyl, amino, sulfhydryl, or carboxyl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, sulfhydryl, or carboxyl group respectively. Preparation and use of prodrugs is discussed in T. Higuchi and V. Stella, "Pro-

drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are hereby incorporated by reference in their entirety.

[00682] *Proliferate:* As used herein, the term "proliferate" means to grow, expand, replicate or increase or cause to grow, expand, replicate or increase. "Proliferative" means having the ability to proliferate. "Anti-proliferative" means having properties counter to or in opposition to proliferative properties.

[00683] *Protein of interest:* As used herein, the terms "proteins of interest" or "desired proteins" include those provided herein and fragments, mutants, variants, and alterations thereof.

[00684] *Proximal:* As used herein, the term "proximal" means situated nearer to the center or to a point or region of interest.

[00685] *Purified:* As used herein, the term "purify" means to make substantially pure or clear from unwanted components, material defilement, admixture or imperfection. "Purified" refers to the state of being pure. "Purification" refers to the process of making pure.

[00686] *Region:* As used herein, the term "region" refers to a zone or general area. In some embodiments, when referring to a protein or protein module, a region may comprise a linear sequence of amino acids along the protein or protein module or may comprise a three dimensional area, an epitope and/or a cluster of eptiopes. In some embodiments, regions comprise terminal regions. As used herein, the term "terminal region" refers to regions located at the ends or termini of a given agent. When referring to proteins, terminal regions may comprise N- and/or C-termini. N-termini refer to the end of a protein comprising an amino acid with a free amino group. C-termini refer to the end of a protein comprising an amino acid with a free carboxyl group. N- and/or C-terminal regions may there for comprise the N- and/or C-termini as well as surrounding amino acids. In some embodiments, N- and/or C-terminal regions comprise from about 3 amino acid to about 30 amino acids, from about 5 amino acids to about 40 amino acids, from about 10 amino acids to about 50 amino acids, from about 20 amino acids to about 100 amino acids and/or at least 100 amino acids. In some embodiments, N-terminal regions may comprise any length of amino acids that includes the N-terminus, but does not include the C-terminus. In some embodiments, C-terminal regions may comprise any length of amino acids, that include the C-terminus, but do not comprise the N-terminus.

[00687] *Region of antibody recognition*: As used herein, the term "region of antibody recognition" refers to one or more regions on one or more antigens or between two or more antigens that are specifically recognized and bound by corresponding antibodies. In some embodiments, regions of antibody recognition may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or at least 10 amino acid residues. In some embodiments, regions of antibody recognition comprise a junction between two proteins or between two domains of the same protein that are in close proximity to one another.

[00688] *Sample:* As used herein, the term "sample" refers to an aliquot or portion taken from a source and/or provided for analysis or processing. In some embodiments, a sample is from a biological source such as a tissue, cell or component part (e.g. a body fluid, including but not limited to blood, mucus, lymphatic fluid, synovial fluid, cerebrospinal fluid, saliva, amniotic fluid, amniotic cord blood, urine, vaginal fluid and semen). In some embodiments, a sample may be or comprise a homogenate, lysate or extract prepared from a whole organism or a subset of its tissues, cells or component parts, or a fraction or portion thereof, including but not limited to, for example, plasma, serum, spinal fluid, lymph fluid, the external sections of the skin, respiratory, intestinal, and genitourinary tracts, tears, saliva, milk, blood cells, tumors, organs. In some embodiments, a sample is or comprises a medium, such as a nutrient broth or gel, which may contain cellular components, such as proteins or nucleic acid molecule. In some embodiments, a "primary" sample is an aliquot of the source. In some embodiments, a primary sample is subjected to one or more processing (e.g., separation, purification, etc.) steps to prepare a sample for analysis or other use.

[00689] *Signal Sequences:* As used herein, the phrase "signal sequences" refers to a sequence which can direct the transport or localization of a protein.

[00690] *Single unit dose*: As used herein, a "single unit dose" is a dose of any therapeutic administered in one dose/at one time/single route/single point of contact, i.e., single administration event. In some embodiments, a single unit dose is provided as a discrete dosage form (e.g., a tablet, capsule, patch, loaded syringe, vial, etc.).

[00691] *Similarity*: As used herein, the term "similarity" refers to the overall relatedness between polymeric molecules, *e.g.* between polynucleotide molecules (*e.g.* DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Calculation of percent similarity of polymeric molecules to one another can be performed in the same manner as a calculation of percent identity, except that calculation of percent similarity takes into account conservative substitutions as is understood in the art.

[00692] *Split dose*: As used herein, a "split dose" is the division of single unit dose or total daily dose into two or more doses.

[00693] *Stable:* As used herein "stable" refers to a compound or entity that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and preferably capable of formulation into an efficacious therapeutic agent.

[00694] *Stabilized:* As used herein, the term "stabilize", "stabilized," "stabilized region" means to make or become stable. In some embodiments, stability is measured relative to an absolute value. In some embodiments, stability is measured relative to a reference compound or entity.

[00695] *Subject:* As used herein, the term "subject" or "patient" refers to any organism to which a composition in accordance with the disclosure may be administered, *e.g.*, for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Typical subjects include animals (*e.g.*, mammals such as mice, rats, rabbits, non-human primates, and humans) and/or plants.

[00696] *Substantially*: As used herein, the term "substantially" refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. One of ordinary skill in the biological arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term "substantially" is therefore used herein to capture the potential lack of completeness inherent in many biological and chemical phenomena.

[00697] *Substantially equal*: As used herein as it relates to time differences between doses, the term means plus/minus 2%.

[00698] *Substantially simultaneously*: As used herein and as it relates to plurality of doses, the term typically means within about 2 seconds.

[00699] *Suffering from*: An individual who is "suffering from" a disease, disorder, and/or condition has been diagnosed with or displays one or more symptoms of a disease, disorder, and/or condition.

[00700] *Susceptible to*: An individual who is "susceptible to" a disease, disorder, and/or condition has not been diagnosed with and/or may not exhibit symptoms of the disease, disorder, and/or condition but harbors a propensity to develop a disease or its symptoms. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition (for example, cancer) may be characterized by one or more of the following: (1) a genetic mutation associated with development of the disease, disorder, and/or condition; (2) a genetic

polymorphism associated with development of the disease, disorder, and/or condition; (3) increased and/or decreased expression and/or activity of a protein and/or nucleic acid associated with the disease, disorder, and/or condition; (4) habits and/or lifestyles associated with development of the disease, disorder, and/or condition; (5) a family history of the disease, disorder, and/or condition; and (6) exposure to and/or infection with a microbe associated with development of the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will develop the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will not develop the disease, disorder, and/or condition.

[00701] *Synthetic*: The term "synthetic" means produced, prepared, and/or manufactured by the hand of man. Synthesis of polynucleotides or polypeptides or other molecules of the present disclosure may be chemical or enzymatic.

[00702] *Targeted Cells:* As used herein, "targeted cells" refers to any one or more cells of interest. The cells may be found *in vitro*, *in vivo*, *in situ* or in the tissue or organ of an organism. The organism may be an animal, preferably a mammal, more preferably a human and most preferably a patient.

[00703] *Target site*: The term "target site" as used herein, refers to a region or area targeted by a given compound, composition or method of the disclosure. Target sites may include, but are not limited to cells, tissues, organs, organ systems, niches and the like.

[00704] *Therapeutic Agent:* The term "therapeutic agent" refers to any agent that, when administered to a subject, has a therapeutic, diagnostic, and/or prophylactic effect and/or elicits a desired biological and/or pharmacological effect.

[00705] *Therapeutically effective amount:* As used herein, the term "therapeutically effective amount" means an amount of an agent to be delivered (*e.g.*, nucleic acid, drug, therapeutic agent, diagnostic agent, prophylactic agent, *etc.*) that is sufficient, when administered to a subject suffering from or susceptible to an infection, disease, disorder, and/or condition, to treat, improve symptoms of, diagnose, prevent, and/or delay the onset of the infection, disease, disorder, and/or condition. In some embodiments, a therapeutically effective amount is provided in a single dose. In some embodiments, a therapeutically effective amount is administered in a dosage regimen comprising a plurality of doses. Those skilled in the art will appreciate that in some embodiments, a unit dosage form may be considered to comprise a therapeutically effective amount of a particular agent or entity if it comprises an amount that is effective when administered as part of such a dosage regimen.

[00706] *Therapeutically effective outcome*: As used herein, the term "therapeutically effective outcome" means an outcome that is sufficient in a subject suffering from or susceptible to an infection, disease, disorder, and/or condition, to treat, improve symptoms of, diagnose, prevent, and/or delay the onset of the infection, disease, disorder, and/or condition.

[00707] *Total daily dose:* As used herein, a "total daily dose" is an amount given or prescribed in a 24 hr period. It may be administered as a single unit dose.

[00708] *Transcription factor:* As used herein, the term "transcription factor" refers to a DNA-binding protein that regulates transcription of DNA into RNA, for example, by activation or repression of transcription. Some transcription factors effect regulation of transcription alone, while others act in concert with other proteins. Some transcription factor can both activate and repress transcription under certain conditions. In general, transcription factors bind a specific target sequence or sequences highly similar to a specific consensus sequence in a regulatory region of a target gene. Transcription factors may regulate transcription of a target gene alone or in a complex with other molecules.

[00709] *Treating*: As used herein, the term "treating" refers to partially or completely alleviating, ameliorating, improving, relieving, delaying onset of, inhibiting progression of, reducing severity of, and/or reducing incidence of one or more symptoms or features of a particular infection, disease, disorder, and/or condition. For example, "treating" cancer may refer to inhibiting survival, growth, and/or spread of a tumor. Treatment may be administered to a subject who does not exhibit signs of a disease, disorder, and/or condition and/or to a subject who exhibits only early signs of a disease, disorder, and/or condition for the purpose of decreasing the risk of developing pathology associated with the disease, disorder, and/or condition.

[00710] *Unmodified*: As used herein, "unmodified" refers to any substance, compound or molecule prior to being changed in any way. Unmodified may, but does not always, refer to the wild type or native form of a biomolecule or entity. Molecules or entities may undergo a series of modifications whereby each modified product may serve as the "unmodified" starting molecule or entity for a subsequent modification.

EQUIVALENTS AND SCOPE

[00711] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments in accordance with the disclosure described herein. The scope of the present disclosure is not intended to be limited to the above Description, but rather is as set forth in the appended claims.

[00712] In the claims, articles such as "a," "an," and "the" may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The disclosure includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The disclosure includes embodiments in which more than one, or the entire group members are present in, employed in, or otherwise relevant to a given product or process.

[00713] It is also noted that the term "comprising" is intended to be open and permits but does not require the inclusion of additional elements or steps. When the term "comprising" is used herein, the term "consisting of" is thus also encompassed and disclosed.

[00714] Where ranges are given, endpoints are included. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or subrange within the stated ranges in different embodiments of the disclosure, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[00715] In addition, it is to be understood that any particular embodiment of the present disclosure that falls within the prior art may be explicitly excluded from any one or more of the claims. Since such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the compositions of the disclosure (*e.g.*, any nucleic acid or protein encoded thereby; any method of production; any method of use; *etc.*) can be excluded from any one or more claims, for any reason, whether or not related to the existence of prior art.

[00716] All cited sources, for example, references, publications, databases, database entries, and art cited herein, are incorporated into this application by reference, even if not expressly stated in the citation. In case of conflicting statements of a cited source and the instant application, the statement in the instant application shall control.

[00717] Section and table headings are not intended to be limiting.

EXAMPLES

Example 1. Protein expression method

[00718] Cells (293-6E cells) transiently expressing tagged proteins are cultured in serum-free medium (FreeStyle F17 medium, Life Technologies, Carlsbad, CA) supplemented with 4

mM glutamine, 0.1% Kolliphor P 188 and 25 μg/ml G418. Once their viability drops below 50%, tissue culture supernatant is collected and cleared by centrifugation for 10 minutes at 450 x gravity at 4°C. Supernatant is then filtered by passing it through a 0.22 μm pore filter. Filtered supernatant is combined with Tris, NaCl and NiCl2 for a final concentration of 50 mM Tris pH 8.0, 350 mM NaCl and 0.5 mM NiCl2. 1 ml of the adjusted solution is collected for later analysis by SDS-poly acrylamide gel electrophoresis (PAGE) or Western blot. The remaining portion of the adjusted solution is combined with washed Ni-NTA resin (Qiagen, Valencia, CA) at a ratio dependent upon the expression level of the protein, which has been previously determined during small scale trials of the protein. This combined solution is then stirred at 4°C overnight using a suspended magnetic stir bar (to prevent grinding of Ni-NTA resin). Ni-NTA resin is collected the next morning using an Econo-glass column (BioRad, Waltham, MA) with a porous bottom membrane. Repeated direct application of the combined solution to the top of the column loads the Ni NTA resin in a uniform fashion onto the column, alternatively a siphoning system is used to continuously load large volumes of combined solution.

[00719] Next, the column is washed with 10 column volumes (CV) of wash buffer (20 mM Tris, pH 8.0, 500 mM NaCl and 20 mM imidazole). An aliquot of the last wash is collected for analysis. The column is then eluted with elution buffer (20 mM Tris, pH 8.0, 500 mM NaCl and 300 mM imidazole) in increments of 1 CV after incubating on the Ni-NTA resin for 5 minutes at 4C, until no protein remains on the Ni NTA resin.

[00720] The absorbance at 280 nm is measured in each of the eluted fractions collected and compared to the absorbance at 280 nm of blank elution buffer. Earlier fractions typically have negative absorption due to the imidazole gradient; however, fractions containing higher amounts of protein have positive values. Collected fractions are then run on SDS-PAGE for analysis and relevant fractions are pooled and concentrated for further purification.

[00721] The protein is further purified by size exclusion chromatography (SEC) using a variety of columns including but not limited to (S200, SRT10, S200 Prep Grade, Superose 6) equilibrated in a variety of buffers including but not limited to PBS, or 20 mM Hepes pH 7.5, 500 mM NaCl. Peak fractions are pooled and concentrated to a concentration of 1-2 mg/mL and aliquots are flash-frozen and stored at -80C.

[00722] Parental FLP-INTM T-REXTM 293 cells (Life Technologies, Carlsbad, CA) are cultured in DMEM media according to the manufacturer's instructions under Zeocin and Blasticidin selection (100ug/ml Zeocin and 15 ug/ml Blasticidin) to maintain their naïve state. To introduce a protein expression construct of interest into the parental cell line,

selection is removed 24 hours in advance and the media switched to Opti-MEM after plating the cells in 6-well plates. Cells are transfected with Lipofectamine 2000 from Life Technologies (Carlsbad, CA), using a ratio of 9:1 pOG44 plasmid (Flp recombinase plasmid) to pcDNA5/TO (Life Technologies, Carlsbad, CA) plasmid with the expression construct of interest in the multiple cloning site. After 24 hours, cells are switched back to DMEM and 24 hours subsequently cells are expanded to 10cm plates. When the cells have adhered, selection with Hygromycin and Blasticidin is applied at 100 ug/ml and 15 ug/ml. Upon integration at the Flp site in the genome, Zeocin resistance is lost and Hygromycin resistance is gained in addition to the protein expression construct of interest.

[00723] To induce protein expression, stable Flp-In Trex 293 cells are grown to 90% confluence in DMEM. Cells are then washed with PBS and switched to F17 media supplemented with 4 mM GlutaMax (Life Technologies, Carlsbad, CA) in the dish. To induce protein expression, 1 ug/ml tetracycline is added. One day later, Trytone N1 is added to 0.5% weight/volume to provide nutrients for protein expression. Culture continues for up to five days before the supernatant is collected. For certain expression constructs, fresh F17 with 1 ug/ml tetracycline is added to the cells and culture continued for another five days. Tryptone N1 is again added one day after refreshing the cells with new media. Collected supernatant is processed and purified as in paragraph described above.

[00724] To increase yield per liter, ease of culture, and volume of culture, stable adherent Flp-IN T-Rex 293 cell lines for certain constructs are adapted to suspension shaking culture in two steps, first to serum free growth and then shaking growth. Cells are slowly transitioned from DMEM complete media recommended by Life Technologies (Carlsbad, CA) to F17 supplemented with 4 mM GlutaMax, and then shaking culture as 0.2% Kolliphor P188 is added to the F17 supplemented with 4mM GlutaMax. Selection is not maintained during the transition, instead it is reapplied after adaptation to F17 and then again after adaption to shaking culture. To adapt to F17, a stepwise dilution of DMEM with F17 is pursued in increments of 25%. At the last step, a small amount of FBS is added to the F17 – approximately 0.2% final concentration - before the final split which is into 100% F17. Cells are split at high ratios of 1:3 or lower, decreasing the time out of selection. As these cells grow robustly, the entire adaption can be completed in about 10 days. After the adaptation is complete, selection is reapplied for at least two passages at 20ug/ml Hygromycin and 2 ug/ml Blasticidin.

[00725] Following adaptation to F17 in adherent culture and the reapplication of selection, the adherent cells can then be adapted to suspension culture. Two 15 cm diameter dishes are

grown to confluency and trypsinized, counted and then seeded in fresh F17 supplemented with 0.2% Kolliphor P 188 and 4 mM GlutaMax at greater than 0.75 x 106/ml. Cell viability decreases initially, but then increases as does cell number. When the cell doubling time approaches 30 hours, Blasticidin and Hygromycin is in some cases reapplied at 2 ug/ml and 20 ug/ml respectively, but only in the fresh media added to split cells in order to gradually re-introduce the selection.

[00726] Some of the proteins produced comprise additional amino acids encoding one or more detectable labels for purification [e.g. polyhistidine tag, flag tag (DYKDDDDK; SEQ ID NO: 67), etc.] Some proteins are N-terminally labeled, C-terminally labeled and/or biotinylated.

[00727] Some of the proteins produced comprise additional amino acids encoding one or more 3C protease cleavage site (LEVLFQGP; SEQ ID NO: 68) Such sites allow for cleavage between residues Q and G of the 3C protease cleavage site upon treatment with 3C protease, including with rhinovirus 3C protease. In some cases, cleavage sites are introduced to allow for removal of detectable labels from recombinant proteins.

Example 2. Generation of antibodies

Antibodies produced by standard monoclonal antibody generation

[00728] Antibodies are generated in knockout mice, lacking the gene that encodes for desired target antigens. Such mice are not tolerized to target antigens and therefore generate antibodies against such antigens that may cross react with human and mouse forms of the antigen. For the production of monoclonal antibodies, host mice are immunized with recombinant proteins to elicit lymphocytes that specifically bind to these proteins. Lymphocytes are collected and fused with immortalized cell lines. The resulting hybridoma cells are cultured in a suitable culture medium with selection agents to support the growth of only fused cells.

[00729] Desired hybridoma cell lines are then identified through binding specificity analysis of the secreted antibodies for the target peptide and clones of these cells are subcloned through limiting dilution procedures and grown by standard methods. Antibodies produced by these cells are isolated and purified from the culture medium by standard immunoglobulin purification procedures

Antibodies produced recombinantly

[00730] Recombinant antibodies are produced using the hybridoma cells produced above. Heavy and light chain variable region cDNA sequences of the antibodies are determined using standard biochemical techniques. Total RNA are extracted from antibody-producing hybridoma cells and converted to cDNA by reverse transcriptase (RT) polymerase chain reaction (PCR). PCR amplification is carried out on the resulting cDNA using primers specific for amplification of the heavy and light chain sequences. PCR products are then subcloned into plasmids for sequence analysis. Once sequenced, antibody coding sequences are placed into expression vectors. For humanization, coding sequences for human heavy and light chain constant domains are used to substitute for homologous murine sequences. The resulting constructs are transfected into mammalian cells capable of large scale translation.

Antibodies produced by using antibody fragment display library screening techniques

[00731] Antibodies of the present disclosure may be produced using high throughput methods of discovery. Synthetic antibodies are designed by screening target antigens using a phage display library. The phage display libraries are composed of millions to billions of phage particles, each expressing a unique single chain variable fragment (scFv) on their viral coat. In scFv libraries, the cDNA encoding each fragment contains a similar sequence with the exception of unique sequences encoding the variable loops of the complementarity determining regions (CDRs). V_H domains are expressed as fusion proteins, linked to the N-terminus of the viral pIII coat protein. V_L domains are expressed separately and assemble with the V_H domain in the periplasm prior to incorporation of the complex into the viral coat. Target antigens are incubated, in vitro, with members of phage display libraries and bound phage particles are precipitated. The cDNA encoding the scFvs of the bound Fab subunits is sequenced from the bound phage. The cDNA sequence is directly incorporated into antibody sequences for recombinant antibody production, or mutated and utilized for further optimization through in vitro affinity maturation.

Antibodies produced using affinity maturation techniques

[00732] scFvs capable of binding target antigens are identified using the libraries described above and high affinity mutants are derived from these through the process of affinity maturation. Affinity maturation technology is used to identify sequences encoding CDRs that have the highest affinity for the target antigen. Using this technology, the CDR sequences isolated using the phage display library selection process described above are mutated randomly as a whole or at specific residues to create millions to billions of variants. These

variants are expressed in scFv fusion proteins in a phage display library and screened for their ability to bind the target antigen. Several rounds of selection, mutation and expression are carried out to identify antibody fragment sequences with the highest affinity for the target antigen. These sequences can be directly incorporated into antibody sequences for recombinant antibody production.

Example 3. Identification and characterization of antibodies directed to recombinant proteins

[00733] Recombinant proteins are synthesized according to the method of Example 1 or obtained from commercial sources. Recombinant proteins expressed include those listed in Table 19.

Table 19. Recombinant proteins

Protein	SEQ ID NO
proGDF-8	5
GDF-8 prodomain	38
GDF-8 prodomain D76A	70
proGDF-8 AXXA	71
proGDF-8 D76A	72
proGDF-8 AXXA D76A	73
proGDF-11	4
proGDF-11 D98A	74
proGDF-11 D2G	75
proGDF-11 AxxA	76
proGDF-11 AxxA D98A	77
GDF-11 prodomain D98A	78
GDF-11 prodomain	39

[00734] Both human and non-human (including, but not limited to mouse) isoforms of the recombinant proteins listed in Table 19 are expressed.

[00735] Antibodies are generated according to the methods described in Example 2, which bind to recombinant proteins expressed and are subjected to screening to identify antibodies with desired binding properties. ELISA assays are used initially to identify antibody candidates that demonstrate affinity for desired antigens, while showing reduced or no affinity for undesired antigens.

Example 4. Myostatin proliferation assay

[00736] C_2C_{12} murine myoblasts (ATCC, Manassas, VA) are cultured in Dulbecco's modified essential medium (DMEM; Life Technologies, Carlsbad, CA) with 10% fetal bovine serum (FBS; Life Technologies, Carlsbad, CA) prior to carrying out the assay. The percentage of FBS is varied and/or replaced with bovine serum albumin (BSA) at varying concentrations. Cell proliferation assays are conducted in uncoated 96-well plates. C_2C_{12} cultures are seeded at 1000 cells per well. After allowing the cells to attach for 16 hours, myostatin test media is added. Recombinant human myostatin (R&D Systems, Minneapolis, MN) is used for standard curve generation. For experimental systems, the supernatant from 293E cells overexpressing myostatin is added, following treatment with experimental antibodies. All samples are run in replicates of 8. Plates are incubated for 72 hours in an atmosphere of 37°C and 5% CO_2. Proliferation is assessed using a CellTiter-Glo® Luminescent Cell Viability Assay (Promega BioSciences, LLC, Madison, WI) whereby cell lysis generates a luminescent signal proportional to the amount of ATP present, which is directly proportional to the number of cells present in culture (Thomas, M. et al., Myostatin, a negative regulator of muscle growth, functions by inhibiting myoblast proliferation. 2000. 275(51):40235-43).

Example 5. Protein expression and purification by Ni-NTA

[00737] Cells (293-6E cells or FLP-IN™ T-REX™ 293 cells) expressing His-tagged proteins are cultured in serum-free medium (FreeStyle F17 medium, Life Technologies, Carlsbad, CA) supplemented with 4 mM glutamine, 0.1% Pluronic F68 and 25 µg/ml G418. Once their viability drops below 50%, tissue culture supernatant is collected and cleared by centrifugation for 10 minutes at 200 x gravity at 4°C. Supernatant is then filtered by passing it through a 0.22 or 0.45 µm pore filter. Filtered supernatant is combined with Tris, NaCl and $NiCl_2$ for a final concentration of 50 mM Tris pH 8.0, 500 mM NaCl and 0.5 mM $NiCl_2$. 1 ml of the adjusted solution is collected for later analysis by SDS-poly acrylamide gel electrophoresis (PAGE) or Western blot, while another portion of the adjusted solution is combined with washed Ni-NTA resin (Life Technologies, Carlsbad, CA) at a concentration of 5-10 ml of Ni-NTA resin per 300 ml of the adjusted solution. This combined solution is then stirred at 4°C using a suspended magnetic stir bar (to prevent grinding of Ni-NTA agarose). Ni-NTA resin is next collected by centrifugation at 200 x gravity at 4°C for 10 minutes.

[00738] Next, the column is washed with 15 column volumes (CV) of wash buffer (20 mM Tris, pH 8.0, 500 mM NaCl and 20 mM imidazole). An aliquot of the last wash is collected

for analysis. The column is then eluted with 3 CV of elution buffer (20 mM Tris, pH 8.0, 500 mM NaCl and 300 mM imidazole) and 1/3 column volume fractions are collected for analysis.

[00739] The absorbance at 280 nm is measured in each of the eluted fractions collected and compared to the absorbance at 280 nm of blank elution buffer. Earlier fractions typically have negative absorption due to the imidazole gradient; however, fractions containing higher amounts of protein have positive values. Collected fractions are then run on SDS-PAGE for analysis and relevant fractions are pooled for further purification.

[00740] The protein is further purified by size exclusion chromatography (SEC) using an S200 column equilibrated either in PBS, or 20 mM Hepes pH 7.5, 500 mM NaCl. Peak fractions are pooled and concentrated to a concentration of 1-2 mg/mL and aliquots are flash-frozen and stored at -80C.

Example 6. Design of GDF-8/GDF-11/activin chimeras

[00741] The structure-based alignment, conducted between GDF-8 (myostatin), GDF-11, Inhibin A and a GDF-8 dimer (FIG. 10), was used to construct three-dimensional models of potential chimeric proteins comprising combinations of modules from GDF-8 and GDF-11 using the Schrodinger Bioluminate software. A chimeric model of GDF-8 comprising an arm region of GDF-11 (SEQ ID NO: 187) revealed a region of potential steric clash involving GDF-11 residue F95. According to the model, F95 from the GDF-11 arm causes destabilization of the α2 helix of the chimeric GPC. Therefore, GDF8/GDF11/Activin chimeras were designed so that the ARM region of the chimera contains the 2 helix.

[00742] Chimeric proteins designed include those listed in Table 20. The first of these is comprised of residues 1-64 of GDF-8 followed by residues 87-274 of GDF-11 and residues 244-352 of GDF-8. The second is comprised of residues 1-64 of GDF-8 follwed by residues 87-274 of GDF-11. These chimeric proteins were further combined with N-terminal secretion signal peptides, flag tags, histidine tags and 3C protease cleavage site.

Table 20. Chimeric proteins

Protein	Amino Acid Sequence	SEQ ID NO
GDF-8/11 chimeric protein 1	MDMRVPAQLLGLLLLWFSGVLGDYKDDDDKHHHHHHLEVLFQ GPVDLNENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKIQILSKL RLETAPNISKDVIRQLLPKAPPLQQILDLHDFQGDALQPEDFLEED EYHATTETVISMAQETDPAVQTDGSPLCCHFHFSPKVMFTKVLKA QLWVYLRPVPRPATVYLQILRLKPLTGEGTAGGGGGGRRHIRIRS	1635

	LKIELHSRSGHWQSIDFKQVLHSWFRQPQSNWGIEINAFDPSGTDL AVTSLGPGAEGLHPFMELRVLENTKRSRRDFGLDCDEHSTESRCC RYPLTVDFEAFGWDWIIAPKRYKANYCSGECEFVFLQKYPHTHL VHQANPRGSAGPCCTPTKMSPINMLYFNGKEQIIYGKIPAMVVDR CGCS	
GDF-8/11 chimeric protein 2	MDMRVPAQLLGLLLLWFSGVLGDYKDDDDKHHHHHHLEVLFQ GPNENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKIQILSKLRLE TAPNISKDVIRQLLPKAPPLQQILDLHDFQGDALQPEDFLEEDEYH ATTETVISMAQETDPAVQTDGSPLCCHFHFSPKVMFTKVLKAQL WVYLRPVPRPATVYLQILRLKPLTGEGTAGGGGGGRRHIRIRSLKI ELHSRSGHWQSIDFKQVLHSWFRQPQSNWGIEINAFDPSGTDLAV TSLGPGAEGLHPFMELRVLENTKRSRR	1636

Example 7. Analysis of recombinantly expressed GDF-8

[00743] Histidine-tagged proGDF-8 was expressed according to the methods of Example 1. Purified proteins were analyzed by SDS-PAGE under either reducing or non-reducing conditions (to maintain protein dimers). FIG. 11 depicts the results indicating successful expression of these proteins and protein complexes.

Example 8. Fc Fusion constructs

[00744] GDF-8 and GDF-11 fusion constructs were designed to improve expression antigens needed for antibody production, selection and/or testing (see Table 21). These constructs were developed to comprise the GDF-11 or GDF-8 prodomain amino acid sequence joined C-terminally to an Fc domain. The constructs were further designed to comprise an N-terminal secretion signal and a C-terminal histidine tag.

Table 21. Fc fusion proteins

Protein	Amino Acid Sequence	SEQ ID NO
GDF-8 prodomain Fc-fusion protein	MDMRVPAQLLGLLLLWFSGVLGNENSEQKENVEKEGLCNACTW RQNTKSSRIEAIKIQILSKLRLETAPNISKDVIRQLLPKAPPLRELID QYDVQRDDSSDGSLEDDDYHATTETIITMPTESDFLMQVDGKPKC CFFKFSSKIQYNKVVKAQLWIYLRPVETPTTVFVQILRLIKPMKDG TRYTGIRSLKLDMNPGTGIWQSIDVKTVLQNWLKQPESNLGIEIK ALDENGHDLAVTFPGPGEDGLNPFLEVKVTDTPKRSDKTHTCPPC PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKHHH HHH	1637
GDF-8 prodomain D76A	MDMRVPAQLLGLLLLWFSGVLGNENSEQKENVEKEGLCNACTW RQNTKSSRIEAIKIQILSKLRLETAPNISKDVIRQLLPKAPPLRELID QYDVQRADSSDGSLEDDDYHATTETIITMPTESDFLMQVDGKPKC CFFKFSSKIQYNKVVKAQLWIYLRPVETPTTVFVQILRLIKPMKDG	1638

Fc fusion Protein	TRYTGIRSLKLDMNPGTGIWQSIDVKTVLQNWLKQPESNLGIEIK ALDENGHDLAVTFPGPGEDGLNPFLEVKVTDTPKRSDKTHTCPPC PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKHHH HHH	
GDF-11 prodomain D98A Fc-fusion protein	MDMRVPAQLLGLLLLWFSGVLGAEGPAAAAAAAAAAAAAGVG GEASSAPAPSVAPEPDGCPVCVWRQHSRELRLESIKSQILSKLRLK EAPNISREVVKQLLPKAPPLQQILDLHDFQGDALQPEDFLEEDEYH ATTETVISMAQETDPAVQTDGSPLCCHFHFSPKVMFTKVLKAQL WVYLRPVPRPATVYLQILRLKPLTGEGTAGGGGGGRRHIRIRSLKI ELHSRSGHWQSIDFKQVLHSWFRQPQSNWGIEINAFDPSGTDLAV TSLGPGAEGLHPFMELRVLENTKRSDKTHTCPPCPAPELLGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGKHHHHHH	1639
GDF-11 prodomain Fc-fusion protein	MDMRVPAQLLGLLLLWFSGVLGAEGPAAAAAAAAAAAAAGVG GERSSRPAPSVAPEPDGCPVCVWRQHSRELRLESIKSQILSKLRLK EAPNISREVVKQLLPKAPPLQQILDLHDFQGDALQPEDFLEEDEYH ATTETVISMAQETDPAVQTDGSPLCCHFHFSPKVMFTKVLKAQL WVYLRPVPRPATVYLQILRLKPLTGEGTAGGGGGGRRHIRIRSLKI ELHSRSGHWQSIDFKQVLHSWFRQPQSNWGIEINAFDPSGTDLAV TSLGPGAEGLHPFMELRVLENTKRSDKTHTCPPCPAPELLGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGKHHHHHH	1640

Example 9. GASP constructs

[00745] GASP constructs were designed using fragments from published sequences. Constructs were designed with various combinations of signal sequences, 3C protease cleavage sites, histidine tags and biotinylation sequences. The designed constructs include those listed in the Table below.

Table 22. GASP constructs

Protein	Sequence	SEQ ID NO
GASP1 construct with residue 303-576 of NP_783165.1	MDMRVPAQLLGLLLLWFSGVLGSVVRGHQAAAT SESSPNGTAFPAAECLKPPDSEDCGEEQTRWHFD AQANNCLTFTFGHCHRNLNHFETYEACMLACMS GPLAACSLPALQGPCKAYAPRWAYNSQTGQCQS FVYGGCEGNGNNFESREACEESCPFPRGNQRCRA CKPRQKLVTSFCRSDFVILGRVSELTEEPDSGRAL	1641

	VTVDEVLKDEKMGLKFLGQEPLEVTLLHVDWAC PCPNVTVSEMPLIIMGEVDGGMAMLRPDSFVGAS SARRVRKLREVMHKKTCDVLKEFLGLHLEVLFQ GPHHHHHHHGLNDIFEAQKIEWHE	
GASP1 construct with residue 35-576 of NP_783165.1	MDMRVPAQLLGLLLLWFSGVLGLPPIRYSHAGIC PNDMNPNLWVDAQSTCRRECETDQECETYEKCC PNVCGTKSCVAARYMDVKGKKGPVGMPKEATC DHFMCLQQGSECDIWDGQPVCKCKDRCEKEPSFT CASDGLTYYNRCYMDAEACSKGITLAVVTCRYH FTWPNTSPPPPETTMHPTTASPETPELDMAAPALL NNPVHQSVTMGETVSFLCDVVGRPRPEITWEKQL EDRENVVMRPNHVRGNVVVTNIAQLVIYNAQLQ DAGIYTCTARNVAGVLRADFPLSVVRGHQAAATS ESSPNGTAFPAAECLKPPDSEDCGEEQTRWHFDA QANNCLTFTFGHCHRNLNHFETYEACMLACMSG PLAACSLPALQGPCKAYAPRWAYNSQTGQCQSF VYGGCEGNGNNFESREACEESCPFPRGNQRCRAC KPRQKLVTSFCRSDFVILGRVSELTEEPDSGRALV TVDEVLKDEKMGLKFLGQEPLEVTLLHVDWACP CPNVTVSEMPLIIMGEVDGGMAMLRPDSFVGASS ARRVRKLREVMHKKTCDVLKEFLGLHLEVLFQG PHHHHHHGLNDIFEAQKIEWHE	1642
GASP1 construct with residue 384-576 of NP_783165.1	MDMRVPAQLLGLLLLWFSGVLGGLNDIFEAQKIE WHEHHHHHHLEVLFQGPAACSLPALQGPCKAYA PRWAYNSQTGQCQSFVYGGCEGNGNNFESREAC EESCPFPRGNQRCRACKPRQKLVTSFCRSDFVILG RVSELTEEPDSGRALVTVDEVLKDEKMGLKFLGQ EPLEVTLLHVDWACPCPNVTVSEMPLIIMGEVDG GMAMLRPDSFVGASSARRVRKLREVMHKKTCDV LKEFLGLH	1643
GASP1 construct with residue 438-576 of NP_783165.1	MDMRVPAQLLGLLLLWFSGVLGFPRGNQRCRAC KPRQKLVTSFCRSDFVILGRVSELTEEPDSGRALV TVDEVLKDEKMGLKFLGQEPLEVTLLHVDWACP CPNVTVSEMPLIIMGEVDGGMAMLRPDSFVGASS ARRVRKLREVMHKKTCDVLKEFLGLHLEVLFQG PHHHHHHGLNDIFEAQKIEWHE	1644
GASP construct with residue 279-548 of NP_444514.1	MDMRVPAQLLGLLLLWFSGVLGSVVQREPARDA APSIPAPAECLPDVQACTGPTSPHLVLWHYDPQR GGCMTFPARGCDGAARGFETYEACQQACARGPG DACVLPAVQGPCRGWEPRWAYSPLLQQCHPFVY GGCEGNGNNFHSRESCEDACPVPRTPPCRACRLR SKLALSLCRSDFAIVGRLTEVLEEPEAAGGIARVA LEDVLKDDKMGLKFLGTKYLEVTLSGMDWACPC PNMTAGDGPLVIMGEVRDGVAVLDAGSYVRAAS EKRVKKILELLEKQACELLNRFQDLEVLFQGPHH HHHHGLNDIFEAQKIEWHE	1645
GASP construct with residue 20-548 of NP_444514.1	MDMRVPAQLLGLLLLWFSGVLGAGLLPGLGSHP GVCPNQLSPNLWVDAQSTCERECSRDQDCAAAE KCCINVCGLHSCVAARFPGSPAAPTTAASCEGFVC PQQGSDCDIWDGQPVCRCRDRCEKEPSFTCASDG LTYYNRCYMDAEACLRGLHLHIVPCKHVLSWPPS SPGPPETTARPTPGAAPVPPALYSSPSPQAVQVGG TASLHCDVSGRPPPAVTWEKQSHQRENLIMRPDQ MYGNVVVTSIGQLVLYNARPEDAGLYTCTARNA	1646

	AGLLRADFPLSVVQREPARDAAPSIPAPAECLPDV QACTGPTSPHLVLWHYDPQRGGCMTFPARGCDG AARGFETYEACQQACARGPGDACVLPAVQGPCR GWEPRWAYSPLLQQCHPFVYGGCEGNGNNFHSR ESCEDACPVPRTPPCRACRLRSKLALSLCRSDFAI VGRLTEVLEEPEAAGGIARVALEDVLKDDKMGL KFLGTKYLEVTLSGMDWACPCPNMTAGDGPLVI MGEVRDGVAVLDAGSYVRAASEKRVKKILELLE KQACELLNRFQDLEVLFQGPHHHHHHHGLNDIFEA QKIEWHE	
GASP construct with residue 357-548 of NP_444514.1	MDMRVPAQLLGLLLLWFSGVLGGLNDIFEAQKIE WHEHHHHHHLEVLFQGPDACVLPAVQGPCRGW EPRWAYSPLLQQCHPFVYGGCEGNGNNFHSRESC EDACPVPRTPPCRACRLRSKLALSLCRSDFAIVGR LTEVLEEPEAAGGIARVALEDVLKDDKMGLKFLG TKYLEVTLSGMDWACPCPNMTAGDGPLVIMGEV RDGVAVLDAGSYVRAASEKRVKKILELLEKQACE LLNRFQD	1647
GASP construct with residue 411-548 of NP_444514.1	MDMRVPAQLLGLLLLWFSGVLGVPRTPPCRACR LRSKLALSLCRSDFAIVGRLTEVLEEPEAAGGIAR VALEDVLKDDKMGLKFLGTKYLEVTLSGMDWA CPCPNMTAGDGPLVIMGEVRDGVAVLDAGSYVR AASEKRVKKILELLEKQACELLNRFQDLEVLFQGP HHHHHHGLNDIFEAQKIEWHE	1648

Example 10. Perlecan construct

[00746] Perlecan constructs were designed using fragments from published sequences. Constructs were designed with various combinations of signal sequences, 3C protease cleavage sites, histidine tags and biotinylation sequences. The designed constructs include those listed in Table 23.

Table 23. Perlecan construct

Protein	Sequence	SEQ ID NO
Perlecan construct with residues 3653-4392 of NP_001278789.1	MDMRVPAQLLGLLLLWFSGVLGAFAHLQVPERVVPYFTQTPYS FLPLPTIKDAYRKFEIKITFRPDSADGMLLYNGQKRVPGSPTNLA NRQPDFISFGLVGGRPEFRFDAGSGMATIRHPTPLALGHFHTVTL LRSLTQGSLIVGDLAPVNGTSQGKFQGLDLNEELYLGGYPDYGA IPKAGLSSGFIGCVRELRIQGEEIVFHDLNLTAHGISHCPTCRDRP CQNGGQCHDSESSSYVCVCPAGFTGSRCEHSQALHCHPEACGP DATCVNRPDGRGYTCRCHLGRSGLRCEEGVTVTTPSLSGAGSYL ALPALTNTHHELRLDVEFKPLAPDGVLLFSGGKSGPVEDFVSLA MVGGHLEFRYELGSGLAVLRSAEPLALGRWHRVSAERLNKDGS LRVNGGRPVLRSSPGKSQGLNLHTLLYLGGVEPSVPLSPATNMS AHFRGCVGEVSVNGKRLDLTYSFLGSQGIGQCYDSSPCERQPCQ HGATCMPAGEYEFQCLCRDGFKGDLCEHEENPCQLREPCLHGG TCQGTRCLCLPGFSGPRCQQGSGHGIAESDWHLEGSGGNDAPG QYGAYFHDDGFLAFPGHVFSRSLPEVPETIELEVRTSTASGLLLW QGVEVGEAGQGKDFISLGLQDGHLVFRYQLGSGEARLVSEDPIN	1649

	DGEWHRVTALREGRRGSIQVDGEELVSGRSPGPNVAVNAKGSV YIGGAPDVATLTGGRFSSGITGCVKNLVLHSARPGAPPPQPLDLQ HRAQAGANTRPCPSLEVLFQGPHHHHHHHGLNDIFEAQKIEWHE	

Example 11. ELISA analysis

[00747] Enzyme-linked immunosorbent assay (ELISA) analysis is carried out to assess antibody binding. 96-well ELISA assay plates are coated with neutravidin, a deglycosylated version of streptavidin with a more neutral pI. Target proteins are expressed with or without histidine (His) tags and subjected to biotinylation. Biotinylated target proteins are incubated with neutravidin-coated ELISA assay plates for two hours at room temperature and unbound proteins are removed by washing three times with wash buffer (either 25 mM Tris, 150 mM NaCl, 0.05% TWEEN®-20, or 20 mM Hepes pH 7.5, 500 mM NaCl, 0.05% TWEEN®-20). Primary antibodies being tested are added to each well and allowed to incubate at room temperature for 1 hour or more. Unbound antibody is then removed by washing three times with wash buffer. Secondary antibodies capable of binding to primary antibodies being tested and conjugated with detectable labels are then incubated in each well for 30 minutes at room temperature. Unbound secondary antibodies are removed by washing three times with wash buffer. Finally, bound secondary antibodies are detected by enzymatic reaction, fluorescence detection and/or luminescence detection, depending on the detectable label present on secondary antibodies being detected.

Example 12. Identification of antibodies that modulate GDF-8 activity

[00748] Antibody development campaigns were carried out to generate antibodies capable of modulating GDF-8 activity. For selection of antibody variable domain binding partners, a phage library, constructed according to the methods described by McCafferty et al (McCafferty, et al., 1990. Nature. 348:552-4), was used to enrich for phage using antigens including primary antigens listed in Table 24.

Table 24. Recombinant antigens

Program #	Primary antigen (for panning & primary screen)	Screening antigens
1	proGDF-8 (SEQ ID NO: 5, 10% furin cleaved)	proGDF-8, proGDF-11, and murine proTGF- 1 C4S (His control)
2	Latent proGDF-8 (SEQ ID NO: 5, 90% furin cleaved)	Latent proGDF-8, proGDF-8, proGDF-11, and murine proTGF- 1 C4S (His control)

[00749] The goal of programs 1 and 2 was to develop antibodies capable of modulating proGDF-8 processing and/or GDF-8 growth factor release from proGDF-8 and/or the latent proGDF-8 complex. When synthesized, proGDF-8 requires cleavage by furin to cleave the GDF-8 prodomain from the growth factor and to allow formation of the latent GPC. In order for release of growth factor from this latent complex to occur, a second cleavage is required by a member of the BMP-1/Tolloid-like proteinase (B/TP) family, which includes mTLL2. In order to maximize opportunities for the generation of inhibiting antibodies, proGDF-8 antigens with reduced (program 1) or enhanced (program 2) furin processing were used as antigens for phage enrichment.

[00750] Both solid as well as solution-phase enrichment procedures were carried out. Solid-phase enrichment comprised the use of biotinylated antigen coated onto neutravidin plates or direct absorption of non-biotinylated antigen onto plastic plates. Solution-phase enrichment utilized biotinylated antigens bound to streptavidin beads. Non-specific antibodies were removed by extensive washing and specific phage antibodies retained by immobilized antigens were recovered by elution. Eluted phage were used to infect E. coli cultures, together with helper phage, to generate an amplified output library for the next round of panning (wherein one round of panning includes incubation, washing, elution and amplification. The success of selection at each round was monitored by comparing output size with a background panning without antigen coating. A subset of clones were sequenced at each round of panning and diversity was evaluated by analysis of CDR-H3 sequences. Multiple rounds of panning were carried out and aliquots of phage from each selection round were preserved for future use. Thousands of scFvs selected during panning were subjected to ELISA screening to assess antigen binding to identify lead candidates for antibody production. Initial screening according to program 1 led to the isolation of 214 clones of which 103 were selected based on an ELISA signal threshold and antigen binding specificity . Clones isolated according to program 1 included SEQ ID NOs: 230-381. Initial screening according to program 2 also resulted in a large number of clones, a portion of which were selected based on an ELISA signal threshold and antigen binding specificity analysis. These clones included SEQ ID NOs: 382-436.

Example 13. Identification of antibodies that activate the release of GDF-11 growth factor from the latent GPC

[00751] Production of a diverse panel of antibodies is carried out to identify antibodies that bind the prodomain of GDF-11 and activate the release of mature growth factor. Antibody

generation is carried out according to the methods of Example 12 wherein recombinant GDF-11 prodomain is used for solid-phase enrichment and biotinylated GDF-11 prodomain is used for solution-phase enrichment. Antigen preparations are tested for aggregation levels to ensure that >95% are monomeric species. In ELISA analysis of enriched clones, binding to six antigens is assessed (GDF-11 prodomain, proGDF-11, GDF-11 growth factor, GDF-8 prodomain, murine GDF-11 prodomain and proTGF-β1 C4S). Clones selected based on ELISA analysis are sequenced and antibodies are developed according to the methods of Example 12.

[00752] A second program utilizes constructs with portions of GDF-11. These constructs, listed in Table 25, are alternated during subsequent rounds of enrichment to obtain phage particles that bind to the GDF-11 portions of the proteins.

Table 25. Recombinant antigens

Protein	Amino acid sequence	SEQ ID NO
GDF-8/11 chimera (GDF-8 1-64, GDF-11 87-274)	MDMRVPAQLLGLLLLWFSGVLGDYKDDDDKHHHHHHL EVLFQGPNENSEQKENVEKEGLCNACTWRQNTKSSRIEA IKIQILSKLRLETAPNISKDVIRQLLPKAPPLQQILDLHDFQ GDALQPEDFLEEDEYHATTETVISMAQETDPAVQTDGSP LCCHFHFSPKVMFTKVLKAQLWVYLRPVPRPATVYLQIL RLKPLTGEGTAGGGGGGRRHIRIRSLKIELHSRSGHWQSI DFKQVLHSWFRQPQSNWGIEINAFDPSGTDLAVTSLGPG AEGLHPFMELRVLENTKRSRR	1650
GDF-11/8 chimera (GDF-11 1-86, GDF-8 65-243)	AEGPAAAAAAAAAAAAAGVGGERSSRPAPSVAPEPDGC PVCVWRQHSRELRLESIKSQILSKLRLKEAPNISREVVKQ LLPKAPPLRELIDQYDVQRDDSSDGSLEDDDYHATTETIIT MPTESDFLMQVDGKPKCCFFKFSSKIQYNKVVKAQLWIY LRPVETPTTVFVQILRLIKPMKDGTRYTGIRSLKLDMNPG TGIWQSIDVKTVLQNWLKQPESNLGIEIKALDENGHDLA VTFPGPGEDGLNPFLEVKVTDTPKRSRR	1651
GDF-11/Inh Beta A chimera (GDF-11 1-86, Inh Beta A 65-290)	AEGPAAAAAAAAAAAAAGVGGERSSRPAPSVAPEPDGC PVCVWRQHSRELRLESIKSQILSKLRLKEAPNISREVVKQ LLPKAPPLNAIRKLHVGKVGENGYVEIEDDIGRRAEMNE LMEQTSEIITFAESGTARKTLHFEISKEGSDLSVVERAEVW LFLKVPKANRTRTKVTIRLFQQQKHPQGSLDTGEEAEEV GLKGERSELLLSEKVVDARKSTWHVFPVSSSIQRLLDQG KSSLDVRIACEQCQESGASLVLLGKKKKKEEEGEGKKKG GGEGGAGADEEKEQSHRPFLMLQARQSEDHPHRRRRR	1652
Inhibin Beta A/GDF-11 chimera (Inh Beta A 1-64, GDF-11 87-274)	SPTPGSEGHSAAPDCPSCALAALPKDVPNSQPEMVEAVK KHILNMLHLKKRPDVTQPVPKAALLQQILDLHDFQGDAL QPEDFLEEDEYHATTETVISMAQETDPAVQTDGSPLCCHF HFSPKVMFTKVLKAQLWVYLRPVPRPATVYLQILRLKPL TGEGTAGGGGGGRRHIRIRSLKIELHSRSGHWQSIDFKQV LHSWFRQPQSNWGIEINAFDPSGTDLAVTSLGPGAEGLHP FMELRVLENTKRSRR	201

Example 14. Identification of antibodies that modulate the release of GDF-11 growth factor from the latent GPC

[00753] Production of a diverse panel of antibodies is carried out to identify antibodies that bind proGDF-11 and modulate the release of mature growth factor. Antibody generation is carried out according to the methods of Example 12. Biotinylated proGDF-11 is used for both solid-phase enrichment and for solution-phase enrichment. Antigen preparations are tested for aggregation levels to ensure that >95% are monomeric species. Clones selected based on ELISA analysis are sequenced and antibodies are developed according to the methods of Example 12.

Example 15. Epitope binning

[00754] Selected clones are subjected to epitope binning by epitope-relatedness using surface plasmon resonance technology (or equivalent approach). Dissociation constants (k_{off}) for each are determined and clones are selected for further characterization.

Example 16. Conversion to IgG format

[00755] Final candidates are expressed in IgG format. Variable domain cDNA is amplified and cloned into mammalian expression vectors. Resulting colonies are screened to ensure proper insertion. Plasmids are prepared by midi-scale DNA preparation for transfection of HEK293 cells at a 50-100 ml scale. Transfected cells are cultured and expressed IgGs are purified from the culture supernatant by affinity chromatography. For some IgG antibodies produced, k_{off} values are determined by surface plasmon resonance. Cell-based functional assays are used to characterize purified bivalent antibodies.

Example 17. 293T CAGA-luciferase assay for GDF-8 activity

[00756] CAGA-luciferase assays are carried out to test antibodies that modulate GDF-8 and/or GDF-11 activity. 100 µl of 0.01% poly-L-lysine solution is added to each well of a 96-well plate. Plates are incubated for 10 min at room temperature before washed with water. 293T cells comprising transient or stable expression of pGL4 (Promega, Madison, WI) under the control of a control promoter or promoter comprising smad1/2 responsive CAGA sequences are then used to seed poly-L-lysine-coated wells (4×10^4 cell/well in complete growth medium). The next day, cells are washed with 150 µl/well of cell culture medium with 0.1% bovine serum albumin (BSA) before treatment with furin and/or mTLL2 processed proGDF-8 with or without test antibody. Cells are incubated at 37° for 6 hours before

detection of luciferase expression using BRIGHT-GLO™ reagent (Promega, Madison, WI) according to manufacturer's instructions.

Example 18. Tolloid-dependent cleavage of GDF-8 and GDF-11

[00757] Samples of proGDF-8, latent GDF-8, latent GDF-11, or proGDF-11 were incubated with pro-protein convertase (either Furin/PACE3 or PCSK5), Tolloid proteinase (either BMP-1 or mTLL2), a combination of both proteases or no proteases. The samples were incubated at 37C for 16hrs. Treated samples were analyzed by adding them to 293T or HepG2 cells carrying a CAGA luciferase response plasmid and incubated for six hours. GDF-8 or GDF-11 activity was assessed by measuring CAGA-dependent luciferase activity in the cell lysates. As shown in FIG. 12, GDF-11 activity resulting from treatment with combined protease lysate (Tolloid proteinase and proprotein convertase) was nearly equal to treatment with recombinant GDF-11 (R&D Systems, Minneapolis, MN). The results of further assays are presented in FIG. 14 demonstrating growth factor release from proGDF-11 after treatment with various proteases in both cell lines. Surprisingly, treatment with mTLL-2 and Furin resulted in the highest level of activity in comparison to other protease treatment conditions.

Example 19. Skeletal muscle differentiation assay

[00758] GDF-8 inhibits skeletal muscle differentiation characterized by myogenin, myosin heavy chain and creatine kinase expression. Modulation of GDF-8 activity by candidate antibodies is tested using a skeletal muscle differentiation assay. 387550 Lonza cells (Lonza, Basel, Switzerland) are plated in 24-well plates at 4 x 10^4 cells/well. The next day, cell media is replaced with differentiation media [dulbecco's modified eagle medium (DMEM)/F12 with 2% horse serum.] Varying concentrations of GDF-8 are also included in differentiation media in the presence or absence of test antibodies. Cells are then allowed to differentiate for 2 days or 5 days.

[00759] After the 2 day period, differentiation status of each well is analyzed through analysis of myogenin expression levels. Cells from each treatment group are pooled and subjected to treatment using the Transcription Factor Buffer Set from BD Pharmingen (BD Biosciences, Franklin Lakes, New Jersey), product number 562574 according to manufacturers instructions. After fixation and permeabilization, 5 µl of phycoerythrin (PE)-myogenin or 1.25 µl of PE-control are added to the cells and incubated at 4°C for 50 mins. Cells are then washed and resuspended in FACS buffer before analysis of cellular fluorescence by flow cytometry.

[00760] To assess the effect of candidate antibodies on differentiation over longer periods, expression levels of myosin heavy chain and/or expression levels of creatine kinase are assessed at day 5.

Example 20. GDF-11 processing by protease treatment

[00761] Partially proconvertase-cleaved proGDF-11 was run on an SDS PAGE gel under non-reducing and reducing conditions (see FIG. 13). Under non-reducing conditions, the protein bands consisted of the proGDF-11 dimer (~100 kD), proGDF-11 monomer (~60 kD), GDF-11 prodomain (~38 kD) and GDF-11 growth factor dimer (~20 kD). Under reducing conditions, the growth factor dimer was reduced to the monomer (~12 kD).

Example 21. GDF-11 antibody discovery

[00762] A large panel of diverse scFvs that bind specifically to human GDF-11 prodomain (or chimeric versions, e.g. those from Table 25) are precipitated using phage display technology. Accordingly, a naïve phage library (approximately 1 x 10^{11} scFv) constructed in a similar manner as described by McCafferty et al (McCafferty, et al., 1990. Nature. 348:552-4) is panned with specific GDF-11 antigens for three to five rounds of selection. Both solid and solution phase panning methods using biotinylated antigen are employed. Up to five thousand individual clones are selected and tested by ELISA for positive binding to GDF-11 prodomain antigens and up to five hundred scFv binders are sequenced. Specificity of binding to GDF11 but not to GDF8 or TGF-β is determined. Fifty candidates with good diversity of distinct VH and VL regions that bind specifically to the GDF-11 prodomain are selected for further development. These candidates are converted to full IgGs, expressed and purified from mammalian cell conditioned media. Additional ELISA-based screening to confirm species cross-reactivity, epitope binning [e.g. with Octet® system (ForteBio, Menlo Park, CA) using standard methods] and cell-based assay analysis are carried out. Candidates that functionally block or activate the release of GDF-11 in cell-based assays are further tested in appropriate preclinical models.

Example 22. Structural analysis

[00763] The proteins of Table 4, 5, 9, 10, 20, 21, 24 and 25 are subjected to structural analysis by X-ray crystallography, cryo- or negative stain single particle electron microscopy, NMR spectroscopy or hydrogen/deuterium exchange mass spectrometry methods. Among these are uncleaved proGDF-8, prodomain convertase-cleaved proGDF-8 (latent GDF-8) and Tolloid-cleaved (activated) GDF-8. Tertiary and quaternary structures are determined and the

structural insights gained are used in the development of GDF-8 inhibitory and activating antibodies.

[00764] Further structural analysis is carried out to identify specific epitopes recognized by antibodies of the disclosure. Antibody-antigen complexes are produced and analyzed by X-ray crystallography. Structural insights gained are used in the development of additional GDF-8 inhibitory and activating antibodies.

Example 23. Conversion to IgG format

[00765] Clones selected according to Programs 1 and 2 were expressed in IgG format. Variable domain cDNA was amplified and cloned into mammalian expression vectors. Resulting colonies were screened to ensure proper insertion. Plasmids were prepared by midi-scale DNA preparation for transfection of HEK293 cells at a 50-100 ml scale. Transfected cells were cultured and expressed IgGs were purified from the culture supernatant by affinity chromatography.

Example 24. Testing of Program 1 and 2 antibodies

[00766] Program 1 and 2 IgGs were tested for binding specificity. ELISA analysis was carried out to assess antibody binding to antigens used in panning (proGDF-8 and latent proGDF-8). Binding to proGDF-11 was also assessed as well as binding to ICAM control antigen. 96-well ELISA assay plates were prepared as described in Example 11 and primary antibodies being tested were added to each well and allowed to incubate at room temperature for 1 hour or more. Unbound antibody was removed by washing three times with wash buffer. Labeled secondary antibodies were then incubated in each well for 30 minutes at room temperature. Unbound secondary antibodies were removed by washing three times with wash buffer. Finally, relative light units (RLUs) were measured for each condition. Antibodies were screened for affinity by selecting those which yielded readings greater than 3 standard deviations above control readings. These are indicated with a "+" for each antigen in the following Table.

Table 26. Antibody binding

Antibody	proGDF-8	latent proGDF-8
BP15a-1	+	-
BP1a-1	+	-
BP1b-1	+	-
BP2a-1	+	-
BP16b-4	+	+

BP16b-3	+	+
BP16b-1	+	+
BP16b-2	+	+
BP18b-1	+	+
BP18b-2	+	+
BP18b-4	+	+
BP18b-5	+	+
BP18b-6	+	+
BP18b-7	+	+
BP20b-1	+	+
BP16a-1	+	+
BP18a-1	+	+
BP18a-2	+	+
BP19b-2	+	+
BP17b-1	+	+
BP19a-3	+	+
BP18b-3	+	+
BP19a-1	+	+
BP19a-2	+	+
BP19b-1	+	+
BP19b-3	+	+
BP22b-1	+	+
BP3a-2	+	+
BP3a-3	+	+
BP12b-1	+	+
BP5a-2	+	+
BP5a-1	+	+
BP5a-4	+	+
BP5a-5	+	+
BP5b-6	+	+
BP8b-1	+	+
BP5b-1	+	+
BP5b-2	+	+
BP5b-3	+	+
BP5b-5	+	+
BP5b-8	+	+
BP11a-1	+	+
BP4a-1	+	+
BP5a-3	+	+
BP3a-1	+	+
BP6a-21	+	+
BP6b-4	+	+
BP10b-1	+	+
BP5b-9	+	+

BP5b-4	+	+
BP7b-1	+	+
BP6b-9	+	+
BP9b-1	+	+
BP21b-1	+	+
BP6a-11	+	+
BP6a-26	+	+
BP5b-7	+	+
BP6a-1	+	+
BP6a-7	+	+
BP6a-2	+	+
BP6a-3	+	+
BP6a-4	+	+
BP6a-8	+	+
BP6a-5	+	+
BP6a-9	+	+
BP6a-10	+	+
BP6a-6	+	+
BP6a-12	+	+
BP6a-13	+	+
BP6a-14	+	+
BP6a-15	+	+
BP6a-16	+	+
BP6a-17	+	+
BP6a-18	+	+
BP6a-19	+	+
BP6a-20	+	+
BP6a-22	+	+
BP6a-23	+	+
BP6a-24	+	+
BP6a-25	+	+
BP6a-27	+	+
BP6b-3	+	+
BP6b-5	+	+
BP6b-6	+	+
BP6b-1	+	+
BP6b-7	+	+
BP6b-8	+	+
BP6b-11	+	+
BP6b-12	+	+
BP6b-10	+	+
BP6b-2	+	+
BP13a-1	+	+
BP14a-1	+	+

[00767] All antibodies tested significantly bound both proGDF-8 and latent proGDF-8 with the exception of BP2a-1, BP1a-1, BP1b-1 and BP15a-1 (which only significantly bound to proGDF-8).

[00768] To assess antibody binding to conformation-dependent epitopes, proGDF-8 and latent proGDF-8 were separated by gel electrophoresis under reducing or non-reducing conditions and subjected to Western blot analysis using IgG antibodies BP6a-7, BP5a-1, BP6a-5 and BP2a-1. Interestingly, BP6a-7, BP5a-1 and BP2a-1 were only able to bind to proteins run under non-reducing conditions, suggesting a conformation-dependent epitope. BP6a-5 was able to bind to both reduced and non-reduced forms of proGDF-8.

Example 25. In vivo testing of anti-GDF-8 antibodies

[00769] Five (5) groups of ten (10) female mice (n=10) with severe combined immune deficiency (SCID) were treated with myostatin antibodies and assessed for changes in muscle size and function. One week following an acclimation period, animals were divided into 5 groups (see Table 27). Blood was collected once via retro-orbital bleed for assessment of complete blood counts (CBC) and grip strength was measured. For this assessment animals were held against a bar which was connected to a force recorder until they grabbed the bar. Once the animal grabbed the bar they were moved away from the device until they dropped the bar. The force required to pull the animal from the bar was recorded in grams force (gf). Animals were treated by intraperitoneal (IP) injection once a week with a PBS vehicle control or one of the myostatin IgG antibodies BP6a-7 (comprising the VH of SEQ ID NO: 462 and the VL of SEQ ID NO: 1037), BP6a-5 (comprising the VH of SEQ ID NO: 472 and the VL of SEQ ID NO: 1047), BP5a-1 (comprising the VH of SEQ ID NO: 448 and the VL of SEQ ID NO: 1023) or BP2a-1 (comprising the VH of SEQ ID NO: 502 and the VL of SEQ ID NO: 1077) all at 25 mg/kg/week.

Table 27. Treatment of each group

Group	Treatment
1	Vehicle
2	BP6a-7
3	BP6a-5
4	BP2a-1
5	BP5a-1

[00770] Body weight and behavioral observations were recorded daily and animals were monitored for toxicity of treatments. Changes in overall body weight were recorded to indicate changes in overall muscle in response to antibody treatment. Six weeks following the

initial injection, grip assessments were redone, the animals were sacrificed by CO_2 overdose and blood collected via cardiac puncture for a terminal CBC. The remaining blood was prepared for plasma using K2EDTA as an anti-coagulant. Tissues were isolated, weighed and collected in formalin, OCT or simply snap frozen. Terminal tissue weights were determined for the gastrocnemius, pectoralis, soleus, tricep, tibialis anterior, diaphragm, plantaris, quadriceps (Rectus femoris), heart, kidney, spleen, liver and inguinal white adipose tissue. Muscle immunohistochemistry was performed on the gastrocnemius.

[00771] The daily animal weight changes were recorded as an average percentage of weight change per group and compared across all treatments (see Table 28, SD is "standard deviation").

Table 28. Average daily % weight changes

Day of Treatment	Group 1	Group 1 (SD)	Group 2	Group 2 (SD)	Group 3	Group 3 (SD)	Group 4	Group 4 (SD)	Group 5	Group 5 (SD)
0	0	0	0	0	0	0	0	0	0	0
1	-1.58	1.00	-2.03	0.50	-0.71	0.52	-1.33	0.31	-3.32	0.68
2	.025	1.03	0.21	0.56	0.12	0.56	--0.34	0.55	-1.04	0.59
3	0.07	1.37	0.87	0.50	1.06	0.47	0.55	0.66	-0.62	0.55
4	-0.39	1.45	1.05	0.65	1.48	0.69	-0.37	0.58	-0.35	0.63
5	0.47	1.29	1.06	0.70	4.08	0.95	0.82	0.54	-0.86	0.51
6	2.10	1.10	2.16	0.78	4.54	1.22	1.19	0.65	0.69	0.58
7	1.72	1.16	1.75	0.74	4.36	1.13	0.63	0.65	0.05	0.75
8	1.94	1.51	2.39	0.79	5.44	0.92	2.76	0.59	3.36	0.79
9	5.17	1.27	5.95	1.07	8.27	1.07	4.79	0.70	4.99	0.82
10	5.45	1.88	5.50	0.98	7.66	1.13	4.02	1.09	2.88	0.74
11	4.08	1.63	4.25	1.00	7.22	1.01	3.02	0.98	3.06	0.72
12	1.52	1.44	2.61	1.24	5.48	1.10	2.55	0.86	3.19	0.86
13	3.40	1.29	3.66	1.39	7.38	1.21	4.14	0.90	4.40	0.77
14	4.01	1.54	4.63	1.36	7.31	1.25	4.81	0.89	5.11	0.79
15	4.51	1.64	5.72	1.01	9.68	1.04	7.25	1.06	4.55	0.68
16	3.76	1.55	6.95	1.09	8.85	1.29	5.86	1.06	4.71	0.60
17	3.63	1.54	5.67	1.09	8.92	10.9	5.50	0.89	4.29	0.62
18	4.02	1.64	6.17	0.96	9.04	1.24	6.23	0.93	3.10	0.69
19	6.10	1.56	7.71	0.94	10.53	1.43	7.89	0.92	5.66	0.91
20	5.06	1.59	7.21	0.97	11.74	1.41	7.55	0.91	5.06	0.57
21	4.68	1.97	5.71	0.90	10.75	1.20	7.01	1.04	4.42	0.84
22	5.01	1.84	7.29	1.09	11.64	1.22	7.75	1.07	4.87	0.83
23	5.99	1.80	7.10	1.42	11.72	1.30	8.64	1.43	4.80	0.80
24	5.18	1.75	6.05	1.72	11.50	1.25	7.18	1.50	5.03	0.84
25	4.25	1.69	7.22	1.42	11.95	1.39	6.68	1.21	5.12	0.86
26	4.19	1.67	7.73	1.15	11.81	1.21	8.62	1.34	4.97	0.89
27	4.66	1.91	7.18	1.30	12.12	0.95	7.57	1.25	5.62	1.15
28	4.40	2.16	7.46	1.20	11.54	1.20	6.52	1.53	3.56	0.99
29	5.26	1.75	7.79	1.12	13.36	1.22	8.52	1.65	4.79	1.12

30	5.09	1.83	8.50	1.26	12.64	1.32	7.82	1.51	4.60	1.42
31	4.79	1.94	8.64	1.10	12.00	1.36	7.41	1.53	4.75	1.13
32	5.15	1.89	8.90	0.94	12.98	1.23	8.54	1.49	4.63	1.20
33	3.94	2.04	10.14	1.21	14.12	1.28	9.39	1.56	7.04	1.27
34	4.97	2.10	9.11	1.10	13.37	1.22	9.21	1.62	6.46	1.20
35	5.00	2.34	10.41	1.04	13.86	1.28	9.84	1.77	6.53	1.03
36	5.78	1.93	10.80	1.24	14.85	1.32	10.05	1.73	5.98	1.08
37	6.56	2.02	10.85	1.29	15.01	1.36	10.25	1.64	6.40	1.10
38	7.02	2.08	11.92	1.45	14.60	1.15	11.19	1.55	7.02	1.33
39	7.29	2.10	11.82	1.45	15.45	1.35	9.70	1.70	7.10	1.58
40	6.58	2.07	11.97	1.35	16.43	1.42	11.89	1.37	7.44	1.24
41	6.26	2.03	12.36	1.15	15.97	1.27	11.99	1.49	7.96	1.41
42	7.74	1.96	12.42	1.09	14.58	1.28	10.33	1.53	7.44	1.43

[00772] Antibody treatment in Group 3, gave a surprisingly large increase in overall body weight. This increase was over 10% from vehicle control treated Group 1.

[00773] To determine if the increase in muscle size led to positive changes in muscle function, a grip strength test was done both pre and post antibody treatments. Grip strength was measured in grams force (gf). Each animal underwent five trials and the average of the three best grip strength scores was determined (see the following Table, SD is "standard deviation").

Table 29. Grip strength assay results (gf)

Day	Group 1	Group 1 (SD)	Group 2	Group 2 (SD)	Group 3	Group 3 (SD)	Group 4	Group 4 (SD)	Group 5	Group 5 (SD)
0	139.43	15.18	135.67	12.27	141.67	15.08	131.90	9.52	134.50	5.47
42	128.37	6.46	134.57	10.98	145.07	7.32	133.20	8.50	133.97	11.49

[00774] Group 1 mice had a nearly 8% decrease in grip strength over the course of the study while Groups 2 and 5 decreased slightly and Group 4 increased slightly. Group 3 mice had the largest increase in grip strength with an increase of 2.4%.

[00775] Terminal tissue weights are presented in the following Table. Standard error values are presented in parenthesis.

Table 30. Average terminal tissue weights (g)

Tissue	Group 1	Group 2	Group 3	Group 4	Group 5
Gastrocnemius	0.106 (0.007)	0.122 (0.005)	0.135 (0.005)	0.106 (0.006)	0.118 (0.007)

Pectoralis	0.052 (0.005)	0.058 (0.008)	0.064 (0.007)	0.067 (0.005)	0.058 (0.004)
Soleus	0.014 (0.002)	0.008 (0.001)	0.011 (0.002)	0.016 (0.003)	0.017 (0.003)
Tricep	0.078 (0.008)	0.078 (0.005)	0.085 (0.004)	0.063 (0.006)	0.062 (0.006)
Tibialis Anterior	0.042 (0.005)	0.036 (0.003)	0.048 (0.005)	0.042 (0.003)	0.042 (0.004)
Diaphragm	0.056 (0.004)	0.076 (0.006)	0.084 (0.007)	0.076 (0.005)	0.072 (0.010)
Plantaris	0.152 (0.005)	0.156 (0.005)	0.170 (0.009)	0.167 (0.009)	0.170 (0.006)
Quadriceps	0.136 (0.009)	0.159 (0.014)	0.162 (0.012)	0.130 (0.005)	0.130 (0.009)
Heart	0.116 (0.005)	0.118 (0.006)	0.129 (0.005)	0.116 (0.006)	0.118 (0.004)
Kidney	0.257 (0.013)	0.234 (0.011)	0.224 (0.021)	0.233 (0.019)	0.234 (0.020)
Spleen	0.036 (0.002)	0.034 (0.002)	0.032 (0.002)	0.031 (0.003)	0.043 (0.005)
Liver	0.883 (0.021)	0.833 (0.018)	0.848 (0.025)	0.885 (0.018)	0.864 (0.019)
Inguinal White Adipose Tissue	0.084 (0.016)	0.067 (0.009)	0.097 (0.012)	0.067 (0.011)	0.099 (0.016)

[00776] Group 3 animals had the highest muscle tissue weights in 6 out of the 9 muscle tissues tested with muscle tissue weights larger than controls in 8 out of the 9 muscle tissues tested.

Example 26. Antibody activity across species

[00777] CAGA-luciferase assays were carried out to test modulation of human or mouse GDF-8 or GDF-11 activity by IgG antibodies BP6a-7 (comprising the VH of SEQ ID NO: 462 and the VL of SEQ ID NO: 1037), BP6a-5 (comprising the VH of SEQ ID NO: 472 and the VL of SEQ ID NO: 1047), BP5a-1 (comprising the VH of SEQ ID NO: 448 and the VL of SEQ ID NO: 1023) and BP2a-1 (comprising the VH of SEQ ID NO: 502 and the VL of SEQ ID NO: 1077). 100 µl of 0.01% poly-L-lysine solution was added to each well of a 96-well plate. Plates were incubated for 10 min at room temperature before washing with water. The plates were dried overnight. The next day, cells expressing pGL4 (Promega, Madison, WI) under the control of a promoter comprising smad1/2 responsive CAGA sequences were

then used to seed poly-L-lysine-coated wells (4 x 104 cell/well in complete growth medium) and the proteolytic reaction was set up. Human proGDF-8, murine proGDF-8 or human proGDF-11 with or without test antibody were incubated at 37°C for 30 min. Then the proteins with or without test antibody were treated with activating enzymes furin and mTLL2 (or without mTLL2, as a negative control) at 37°C for ~16 hours. The next day, cells were washed with 150 µl/well of cell culture medium with 0.1% bovine serum albumin (BSA). 100x of the proteolytic reaction was added to the cellsand incubated at 37°C for 6 hours before detection of luciferase expression using BRIGHT-GLOTM reagent (Promega, Madison, WI) according to manufacturer's instructions. Results were used to calculate the % inhibition for each condition (see the following Table, % inhibition = 100 x ((Reading with test antibody – reading without mTLL2)/(reading without antibody - reading without mTLL2)), standard deviation values are shown in parenthesis).

Table 31. % Inhibition of growth factor activity

Antibody	Human proGDF-8	Murine proGDF-8	Human proGDF-11
BP6a-7	100.6 (1.3)	89.5 (1.0)	27.2 (15.9)
BP6a-5	89.0 (0.9)	91.1 (0.3)	26.0 (2.7)
BP5a-1	68.7 (7.2)	39.7 (2.6)	7.9 (6.0)
BP2a-1	89.7 (1.1)	92.0 (0.6)	31.1 (4.0)

[00778] [00641] All antibodies demonstrated the ability to inhibit human and murine GDF-8 activity. Inhibitory activity was not significant for human GDF-11.

Example 27. Antibody inhibitory activity

[00779] Antibodies were assessed for inhibition of GDF-8 activity using CAGA promoter assays in 293T cells or with HepG2 cells. 100 µl of 0.01% poly-L-lysine solution was added to each well of a 96-well plate. Plates were incubated for 10 min at room temperature before washing with water. The plates were dried overnight. The next day, cells expressing pGL4 (Promega, Madison, WI) under the control of a promoter comprising smad1/2 responsive CAGA sequences were then used to seed poly-L-lysine-coated wells (4 x 104 cell/well in complete growth medium) and the proteolytic reaction was set up. Human proGDF-8 or latent proGDF-8 with or without test antibody were incubated at 37°C for 30 min. Then the proteins with or without test antibody were treated with activating enzymes furin and mTLL2 (or without mTLL2, as a negative control) at 37°C for ~16 hours. The next day, cells were washed with 150 µl/well of cell culture medium with 0.1% bovine serum albumin (BSA). 100x of the proteolytic reaction was added to the cellsand incubated at 37°C for 6 hours before detection of luciferase expression using BRIGHT-GLOTM reagent (Promega,

Madison, WI) according to manufacturer's instructions. Results were used to calculate the % inhibition for each condition (% inhibition = 100 x ((Reading with test antibody – reading without mTLL2)/(reading without antibody/reading without mTLL2)). IgG antibodies BP6b-6 (comprising the VH of SEQ ID NO: 581 and the VL of SEQ ID NO: 1153), BP19b-1 (comprising the VH of SEQ ID NO: 442 and the VL of SEQ ID NO: 1017), BP6b-3 (comprising the VH of SEQ ID NO: 464 and the VL of SEQ ID NO: 1039), BP18b-4 (comprising the VH of SEQ ID NO: 593 and the VL of SEQ ID NO: 1166), BP7b-1 (comprising the VH of SEQ ID NO: 598 and the VL of SEQ ID NO: 1171), BP6b-7 (comprising the VH of SEQ ID NO: 626 and the VL of SEQ ID NO: 1199) and BP10b-1 (comprising the VH of SEQ ID NO: 645 and the VL of SEQ ID NO: 1218) demonstrated inhibitory activity (see the following Table).

Table 32. % inhibition of growh factor activity

Antibody	293T cells		HepG2 cells	
	proGDF-8	latent proGDF-8	proGDF-8	latent proGDF-8
BP6b-6	44	51	53	56
BP19b-1	-1	53	3	51
BP6b-3	42	N/A	51	N/A
BP18b-4	89	92	85	97
BP7b-1	82	67	89	92
BP6b-7	74	51	78	69
BP10b-1	51	N/A	59	N/A

[00780] Antibody BP18b-4 had the highest percent inhibition in both cell types and with both proGDF-8 and latent proGDF-8. Interestingly, antibody BP19b-1 only inhibited latent proGDF-8.

Example 28. "Primed" complexes

[00781] A "primed" complex is predicted to exist for both GDF-8 GPCs and GDF-11 GPCs. Primed complexes are GPCs that adopt active conformations after cleavage at both the furin cleavage site and the BMP-1/Tolloid cleavage site. A schematic demonstrating formation of primed complexes is presented in FIG. 15. Activity may be the result of a conformational shift that relieves steric interference by the alpha 1 helical region. GDF-8 GPCs and GDF-11 GPCs are expressed and subjected to enzymatic cleavage to cleave both furin and BMP-1/Tolloid cleavage sites. Resulting primed complexes are tested for activity by CAGA assay and compared to free GDF-8 growth factors or GDF-11 growth factors; GDF-8 prodomain complexes or GDF-11 prodomain complexes (e.g., proGDF-8 or proGDF-

11, prior to furin or BMP-1/Tolloid cleavage); and latent GDF-8 complexes or latent GDF-11 complexes. GDF-8 primed complexes demonstrate signaling activity that is nearly equivalent with that of free GDF-8 growth factor. GDF-11 primed complexes demonstrate signaling activity that is nearly equivalent with that of GDF-11 growth factor.

Example 29. Antibodies with selected binding profiles

[00782] Antibodies designed to bind human proMyostatin were tested for binding to human proMyostatin (SEQ ID NO: 5); murine proMyostatin (SEQ ID NO: 88); human latent Myostatin (SEQ ID NO: 5); human GDF-8 prodomain (SEQ ID NO: 38); human GDF-11 ARM8 prodomain (SEQ ID NO: 181); human proGDF11ARM8 (SEQ ID NO: 179); human mature GDF-8 (SEQ ID NO: 42); human proGDF11 (SEQ ID NO: 4); murine latent myostatin (SEQ ID NO: 88); and human latent proGDF11 ARM8 (SEQ ID NO: 179). Binding of the various antibody clones, shown in Table 33, to the antigens was performed using an ELISA as described below. Table 33 shows the selected binding profiles for the various antibody clones. Initially, clones BP10b-1 and BP12b-1 were selected as binders to human proMyostatin. However, subsequent binding tests showed these antibodies bound human latent Myostatin and not human pro Myostatin.

Table 33. Selected Myostatin binding profiles

Antibody clone	pro Myo (h)	Pro Myo (m)	Lat Myo (h)	GDF8 Prod (h)	GDF11 ARM8 prod (h)	proGDF11 ARM8 (h)	mat GDF8 (h)	pro GDF11 (h)	lat Myo (m)	lat proGDF11 ARM8 (h)
BP1a-1	+	+	-	-	-	-	-			
BP1b-1	+	+	-	-	-	-	-	-	-	-
BP2a-1	+	+	-	-	-	+	-			
BP3a-1	+	+	+	-	-	-	-			
BP3a-2	+	+	+	-	-	-	-			
BP3a-3	+	+	+	-	-	-	-			
BP4a-1	+	+	+	+	-	-	-			
BP5a-1	+	+	+	-	-	+	-			
BP5b-1	+	+	+	-	-	+	-	-	+	+
BP5a-2	+	+	+	-	-	+	-			
BP5a-3	+	+	+	-	-	+	-			
BP5a-4	+	+	+	-	-	+	-			
BP5a-5	+	+	+	-	-	+	-			
BP5b-2	+	+	+	-	-	+	-	-	+	+
BP5b-3	+	+	+	-	-	+	-	-	+	+
BP5b-4	+	+	+	-	-	+	-	-	+	+

BP5b-5	+	+	+	-	-	+	-	-	+	+
BP5b-6	+	+	+	-	-	+	-	-	+	+
BP5b-7	+	+	+	-	-	+	-	-	+	+
BP5b-8	+	+	+	-	-	+	-	-	+	+
BP5b-9	+	+	+	-	-	+	-	-	+	+
BP6a-1	+	+	+	+	+	+	-			
BP6a-2	+	+	+	+	+	+	-			
BP6a-3	+	+	+	+	+	+	-			
BP6a-4	+	+	+	+	+	+	-			
BP6a-5	+	+	+	+	+	+	-			
BP6a-6	+	+	+	+	+	+	-			
BP6b-1	+	+	+	+	+	+	-	-	+	+
BP6b-2	+	+	+	+	+	+	-	-	+	+
BP6a-7	+	+	+	+	+	+	-			
BP6a-8	+	+	+	+	+	+	-			
BP6a-9	+	+	+	+	+	+	-			
BP6a-10	+	+	+	+	+	+	-			
BP6a-11	+	+	+	+	+	+	-			
BP6a-12	+	+	+	+	+	+	-			
BP6a-13	+	+	+	+	+	+	-			
BP6a-14	+	+	+	+	+	+	-			
BP6a-15	+	+	+	+	+	+	-			
BP6a-16	+	+	+	+	+	+	-			
BP6a-17	+	+	+	+	+	+	-			
BP6a-18	+	+	+	+	+	+	-			
BP6a-19	+	+	+	+	+	+	-			
BP6a-20	+	+	+	+	+	+	-			
BP6a-21	+	+	+	+	+	+	-			
BP6a-22	+	+	+	+	+	+	-			
BP6a-23	+	+	+	+	+	+	-			
BP6a-24	+	+	+	+	+	+	-			
BP6a-25	+	+	+	+	+	+	-			
BP6a-26	+	+	+	+	+	+	-			
BP6a-27	+	+	+	+	+	+	-			
BP6b-3	+	+	+	+	+	+	-	-	+	+
BP6b-4	+	+	+	+	+	+	-	-	+	+
BP6b-5	+	+	+	+	+	+	-	-	+	+
BP6b-6	+	+	+	+	+	+	-	-	+	+
BP6b-7	+	+	+	+	+	+	-	-	+	+
BP6b-8	+	+	+	+	+	+	-	-	+	+
BP6b-9	+	+	+	+	+	+	-	-	+	+
BP6b-10	+	+	+	+	+	+	-	-	+	+
BP6b-11	+	+	+	+	+	+	-	-	+	+
BP6b-12	+	+	+	+	+	+	-	-	+	+

BP7b-1	+	+	+	+/-	+/-	+	-	-	+	+
BP8b-1	+	+	+	-	-	+/-	-	-	+	+
BP9b-1	+	+	+	+/-	-	+/-	-	-	+	+
BP10b-1	-	-	+	-	-	-	-	-	+	+
BP11a-1	+	+	+	-	-	+	+			
BP12b-1	-	-	+	-	-	-	+	-	+	-
BP13a-1	+	+/-	+	-	-	+	-			
BP14a-1	+	+/-	+	+/-	-	+	-			
BP15a-1	+	-	-	+	-	-	-			
BP16b-1	+	-	+	-	-	-	-	-	-	-
BP16b-2	+	-	+	-	-	-	-	-	-	-
BP16b-3	+	-	+	-	-	-	-	-	-	-
BP16b-4	+	-	+	-	-	-	-	-	-	-
BP16a-1	+	-	+	-	-	-	-			
BP17b-1	+	-	+	-	-	-	-	-	-	+/-
BP18b-1	+	-	+	-	-	+	-	-	-	+
BP18b-2	+	-	+	-	-	+	-	-	-	+
BP18b-3	+	-	+	-	-	+	-	-	-	+
BP18b-4	+	-	+	-	-	+	-	-	-	+
BP18b-5	+	-	+	-	-	+	-	-	-	+
BP18b-6	+	-	+	-	-	+	-	-	-	+
BP18b-7	+	-	+	-	-	+	-	-	-	+
BP18a-1	+	-	+	-	-	+	-			
BP18a-2	+	-	+	-	-	+	-			
BP19b-1	+	-	+	+	+	+	-	-	-	+
BP19b-2	+	-	+	+	+	+	-	-	-	+
BP19b-3	+	-	+	+	+	+	-	-	-	+
BP19a-1	+	-	+	+	+	+	-			
BP19a-2	+	-	+	+	+	+	-			
BP19a-3	+	-	+	+	+	+	-			
BP20b-1	+	-	+	-	-	+/-	-	-	-	+/-
BP21b-1	+	+	+	-	-	+	-	+	+	+
BP22b-1	+	+	+	-	-	-	-	+	+	+

Table 33 shows the binding profile of antibody clones to the following antigens: proMyo(h) = human proMyostatin (SEQ ID NO: 5); ProMyo(m) = murine proMyostatin (SEQ ID NO: 88);

LatMyo(h) = human latent Myostatin (SEQ ID NO: 5); GDF8Prod(h) = human GDF-8 prodomain (SEQ ID NO: 38); GDF11ARM8prod(h) = human GDF-11 ARM8 prodomain (SEQ ID NO: 181); proGDF11ARM8(h) = human proGDF11ARM8 (SEQ ID NO: 179); matGDF8(h) = human mature GDF-8 (SEQ ID NO: 42); proGDF11(h) = human proGDF11 (SEQ ID NO: 4); latMyo(m) = murine latent myostatin (SEQ ID NO: 88); latproGDF11ARM8(h) = human latent proGDF11 ARM8 (SEQ ID NO: 179). As described

elsewhere herein, binding of an antibody clone to an antigen is indicated by a "+". A "-" indicates that the antibody does not bind the antigen. A "+/-" indicates that the antibody is at or near a threshold of binding the antigen as determined by the assay parameters. The code "BP[Number][Letter]" refers to particular binding profiles indicated in the table.

ELISA Screening Protocol

[00783] The purpose of this protocol is to allow for a method to screen Myostatin Program antibodies for potential binding to biotinylated antigens. This protocol makes use of the NeutrAvidin Coating of 96-Well Plates SOP for NeutrAvidin coated and BSA blocked plates. The plates should be designed in such a way that each sample and control is performed in triplicate and each plate contains an anti-his coating control. The coating control measures the degree to which each biotinylated antigen is captured by the plate and allows for ease of data analysis. Multiple plates may be required per experiment.

[00784] The materials used include: solid, white Solid white 96-well plates from the NeutrAvidin Coating of 96-Well Plates SOP, Biotinylated antigen, Maine Biotechnology Services Anti-His antibody MAB230P, Jackson ImmunoResearch Laboratories Peroxidase Affinipure Goat α-human FCγ Fragment-Specific (Catalogue number 109-035-008), Jackson ImmunoResearch Laboratories Affinipure Goat α-mouse FCγ Fragment Specific (Catalogue number 115-035-008), and SuperSignal ELISA Femto Substrate (Pierce Biotech catalog number 37075).

[00785] The following equipment was used: multi-channel pipette, P200 tips, tabletop ultracentrifuge, 1.5 mL centrifuge tubes, 0.5 mL centrifuge tubes, P1000, P1000 tips, P200, P10, P10 tips, 15 mL Falcon tubes, 50 mL Falcon tubes, Biotek ELx 405 Select CW plate washer, multidrop, and Biotek Synergy H1 plate reader.

[00786] Wash Buffer: TBS (Tris-Buffered Saline; 50 mM Tris-Cl, 150 mM NaCl, pH 7.6) with 0.05% Tween-20. For manual (hand) wash add 0.1% BSA as BSA is sticky and should not be used with the automated plate washer system.

[00787] Sample Buffer: TBS (Tris-Buffered Saline; 50 mM Tris-Cl, 150 mM NaCl, pH 7.6) with 0.05% Tween-20 and 0.1% BSA.

[00788] ELISA 3X protocol: Wash protocol on the Biotek ELx 405 Select CW plate washer. Washes with 200μL of wash buffer. Repeats the wash two additional times. Specifications: 3 cycles. No shaking. Dispenses 200 μL per well. Dispense flow rate setting 7 (range 1 – 10). Dispense height 15.24 mm. Horizontal x dispense position 0 mm. Horizontal

y dispense position 0 mm. Aspirate height 3.048 mm. horizontal x aspirate position 1.372 mm. horizontal aspirate y position 0.452 mm. Aspiration rate 3.4 mm/second. Aspiration delay 0 milliseconds. Crosswire aspiration on final wash. Crosswire height 3.048 mm. Crosswire horizontal x position: -1.829 mm. Crosswire horizontal y position: -0.457 mm.

[00789] Remove a pre-coated and pre-blocked 96-well plate from 4°C. If a 96-well plate is not already prepared, prepare one with the NeutrAvidin Coating of 96-Well Plates protocol (see below). Remove the 1xPBS pH 1%BSA with 0.1% Tween-20 from the plate and forcefully hit the plate on a Styrofoam pad lined with paper towels. Dilute the biotinylated antigen in sample buffer. Optimal capture concentration should first be determined by titration for each individual protein. For human and murine promyostatin this concentration is 2 μg/mL. Add 100 μl per well. Wash plates using the plate washer with wash buffer using the ELISA 3X protocol. Dilute the antibody in sample buffer. Screening of antibodies is performed at 1 μg/mL. Prepare α-His coating control antibody (Maine Biotechnology Services catalogue number: MAB230P) at 1 μg/mL in sample buffer. Place 100 μL of diluted antibody on designated wells. Incubate at room temperature for 1 hour. Wash plates using the plate washer with wash buffer using the ELISA 3X protocol. Dilute human secondary antibody (Jackson ImmunoResearch Laboratories Peroxidase Affinipure Goat α-human FCγ Fragment Specific. Catalogue number 109-035-008)
1:25,000 in sample buffer. For α-his wells, dilute mouse secondary antibody (Jackson ImmunoResearch Laboratories Affinipure Goat α-mouse FCγ Fragment Specific. Catalogue number 115-035-008) 1:50,000 in sample buffer. Place 100 μL of diluted antibody on designated wells. Incubate at room temperature for 1 hour. Wash plates using the plate washer with wash buffer using the ELISA 3X protocol. Prepare SuperSignal ELISA Femto Substrate (Pierce Biotech catalog number 37075) working solution by mixing 1 part luminol/enhancer solution with 1 part stable peroxide substrate. It is important to use separate pipettes in order to prevent cross-contamination and damaging of the substrate solution. Ten mL will be needed for one plate. Working solution is stable for up to 4 hour at room temperature. Place 100 μL SuperSignal ELISA Femto Substrate working solution per well. Wait one minute and read on the plate reader using the lum fiber method or by measuring with a luminometer at 425nm.

[00790] Assay output values are in relative light units (RLU) and data analysis can be performed in Microsoft Excel. All experiment samples should be performed in triplicate. Triplicate values should be averaged together. Error bars should be expressed as the standard error using the following equation: x = stdev / sqrt (n) where n is 3. Hits are determined by

calculating the standard deviation across all samples and then setting a threshold of 3x that standard deviation. All samples above the 3x standard deviation threshold are hits.

NeutrAvidin Coating of 96-Well Plates

[00791] The purpose of this protocol is to coat 96-well high binding plates with neutravidin for ELISA assays.

[00792] Materials used include the following: Costar 96-well assay plate (high binding). (manufacturer product numbers: 3922 (solid white), 3925 (solid black), 3361 (clear)), UltraPure Distilled Water (Invitrogen). Manufacturer product number 10977-015, 1x Carbonate Buffer pH 9.4 made from BupH Carbonate – Bicarbonate Buffer Packs (Thermo Scientific, manufacturer product number 28382), NeutrAvidin Biotin-Binding Protein (salt-free), 10 mg (Pierce, manufacturer product number: 31000).

[00793] Equipment used includes the following: multi-channel pipette, P200 tips, tabletop ultracentrifuge, 1.5 mL centrifuge tubes, 0.5 mL centrifuge tubes, milligram range balance, P1000, P1000 tips, P200, P10, P10 tips, 15 mL Falcon tubes, nanodrop, and Ultrafree-MC-GV 0.22 μm filter device (Millipore, manufacturer product number UFC30GVNB).

[00794] Wash buffer includes TBS (Tris-Buffered Saline; 50 mM Tris-Cl, 150 mM NaCl, pH 7.6) with 0.05% Tween-20. For manual (hand) wash add 0.1% BSA as BSA is sticky and should not be used with the automated plate washer system.

[00795] Measure an appropriate amount of lyophilized NeutrAvidin (> 1 mg) and dilute into an appropriate amount of ultrapure water (1000 μL > x > 100 μL). Do not exceed 10 mg/mL. Resuspend and dissolve carefully. Filter dissolved NeutrAvidin with a 0.22 μm centrifuge filter device at 12,000 x g for 4 minutes and determine protein concentration via Nanodrop. The A280 of NeutrAvidin is 1.66 at 1 mg/mL. Dilute NeutrAvidin to 1 mg/mL in 1x carbonate buffer pH 9.4 to make a 1 mg/mL stock solution. Do not exceed 1 mg/mL as NeutrAvidin is not directly soluble in buffer. Aliquot 1 mg/mL NeutrAvidin solution into 20 μL aliquots. Snap freeze in liquid nitrogen and store at -80°C. Thaw appropriate numbers of NeutrAvidin aliquots by hand. Spin the 1 mg/mL NeutrAvidin stock solution at 16,100 x g for 10 minutes. For one plate, remove 5 μL from the top of the 1 mg/mL NeutrAvidin stock solution and dilute it into 10 mL of 1x carbonate buffer pH 9.4. Mix by inverting the falcon tube. Using a multi-channel pipette, place 100 μL in each well of the Corning high binding 96-well assay plate. Incubate the 96-well plate overnight at 4°C. Wash the 96-well plate with 200 μL of wash buffer per well. Repeat this step two additional times. The plate should be

washed for a total of three times. Block the plate with 200 μL per well of 1% BSA in PBS pH 7.4. Incubate the plate for 1 hour at 37°C or overnight at 4°C.

[00796] Antibodies were scored as specific binders "+" if their binding signal was 5 standard deviations above background. Antibodies were scored as not specific binders "-" if their binding signal was below 5 standard deviations above background. Antibodies scored with a "+/-" indicates that the antibody is at or near the threshold of binding the antigen as determined by the assay parameters.

Example 30. Binding primed Myostatin complexes and determining inhibitory activity

[00797] Antibody clones BP5a-1, BP6a-7, BP6a-5, BP6b-7, BP11a-1, BP12b-1, BP16a-1 were tested *in vitro* using a CAGA promoter-based reporter assay as described herein. The CAGA promoter-based reporter assays may be used to test antibodies that modulate SMAD-dependent gene expression as reported by Thies et al (Thies, R.S. et al., Growth Factors. 2001. 18:251-9, the contents of which are herein incorporated by reference in their entirety). Here, a CAGA reporter assays was used to assess primed Myostatin growth factor activity in the presence of an various antibody clones. Antibody clone BP6a-5 was tested for binding to human primed Myostatin using an ELISA assay.

Table 34. Binding and inhibiting primed Myostatin complexes

Antibody Clone	Bind Human Primed Myostatin	Inhibit Human Primed Myostatin Signaling
BP5a-1		no
BP6a-7		no
BP6a-5	Yes (BP6a-5 GL)	no (BP6a-5 WT and BP6a-5 GL)
BP6b-7		no
BP11a-1		no
BP12b-1		no
BP16a-1		no

Table 34 shows the ability of various antibody clones to inhibit human primed Myostatin signaling and the ability of various antibody clones to bind human primed Myostatin.

Example 31. Binding affinity to proMyostatin and latent Myostatin

[00798] The binding affinity of various antibody clones to human proMyostatin or human latent Myostatin was determined using two independent menthods. In one method, the dissociation constant (Kd) was determined using the Octet® (ForteBio, Menlo Park, CA) instrument. In another method, the EC50 was determined using an ELISA (Table 35).

Table 35. Binding affinity to proMyostatin and latent Myostatin

	Kd by Octet			ELISA EC50 (nM)		
Antibody Clone	**proMyostatin (human)**	**latent Myostatin (human)**	**mature Myostatin (human)**	**proMyostatin (human)**	**proMyostatin (human)**	**latent Myostatin (human)**
BP1b-1					202.5	0
BP1a-1	8.023E-09	not detect.		23.96		
BP2a-1	5.42E-10	not detect.		4.75		
BP3a-2	2.662E-09	1.282E-08		6.7		
BP3a-3	6.643E-11	9.507E-11		14.58		
BP3a-1	5.248E-10	2.771E-10		5.786		
BP4a-1				1773		
BP5b-3					81.39	
BP5a-1				36.4		
BP5b-4					254.9	
BP5b-6					1403	
BP5b-5					834	
BP5a-4	1.15E-08	1.12E-08	not detect.	1611		
BP5b-1					19.15	
BP5a-3				605		
BP5b-2					35.06	
BP5a-2	1.06E-09	8.308E-10		2.835		
BP5b-7					978742	3942000
BP5a-5				3440		
BP5b-8						55.64
BP5b-9						83.47
BP6b-4					34.32	0
BP6a-8				2.2		
BP6a-23				372		
BP6a-11				15.4		
BP6a-14				19.5		
BP6a-27				not detect.		
BP6a-13				19.17		
BP6a-19				130.9		
BP6a-6				12.62		
BP6a-20				193.1		

BP6a-24				631		
BP6a-22				342.4		
BP6a-4				1.417		
BP6a-7				1.13		
BP6a-16				20.36		
BP6b-3					0.3268	103.3
BP6a-2				1.3		
BP6a-3				1.4		
BP6b-1					4.18	
BP6a-5	1.296E-08			2.392		
BP6a-10				9.4		
BP6a-1				0.2993		
BP6a-26				987.5		
BP6b-5					35.94	
BP6a-12				18.77		
BP6a-9				5.279		
BP6a-18				78.9		
BP6a-25				916.5		
BP6b-6					37.95	
BP6a-15				19.7		
BP6b-2						8.07
BP6b-11						
BP6b-10						60.85
BP6a-21				242.9		
BP6b-9						55.48
BP6b-7						0.29
BP6b-8						3.88
BP6b-12						
BP6a-17				20.37		
BP7b-1						38.43
BP8b-1					170.2	
BP9b-1						not detect.
BP10b-1	5.174E-09	4.676E-09			19631	722.4
BP11a-1	1.71E-09	4.48E-09	7.56E-09	15.9		
BP12b-1	not detect.	1.83E-09				15.41
BP13a-1				315.7		
BP14a-1				8.625		
BP15a-1				not detect.		
BP16b-1						5.66
BP16b-2						not detect.
BP16b-3						48.17
BP16b-4						4.24

BP16a-1				2.8		
BP17b-1						22.31
BP18b-1					19.38	222916
BP18a-1				22.25		
BP18a-2				29.26		
BP18b-2					6091	21844
BP18b-3					10559	19279
BP18b-4						0.075
BP18b-5						0.24
BP18b-6						0.61
BP18b-7						
BP19b-1					0.18	
BP19b-2					2.87	2074
BP19a-1				0.24		
BP19a-2				75.38		
BP19b-3						160
BP19a-3				15.2		
BP20b-1						not detect.
BP21b-1					1.57	1.717
BP22b-1						28.10

Table 35 shows the binding affinity of various antibody clones to human proMyostatin or human latent Myostatin using two independent methods, a Kd measurement using Octet® (ForteBio, Menlo Park, CA) and an EC50 using an ELISA.

Example 32. Inhibition of proMyostatin and latent Myostatin *in vitro*

[00799] The ability of antibody clones to inhibit proMyostatin or latent Myostatin was tested *in vitro* using a CAGA promoter-based reporter assay as described herein. The CAGA promoter-based reporter assays may be used to test antibodies that modulate SMAD-dependent gene expression as reported by Thies et al (Thies, R.S. et al., Growth Factors. 2001. 18:251-9, the contents of which are herein incorporated by reference in their entirety). Here, a CAGA reporter assays was used to assess proMyostatin and latent Myostatin growth factor activity in the presence of an various antibody clones. According to such methods, proMyostatin, or latent Myostatin were cultured with reporter cells (either 293T or HepG2 reporter cells) comprising the CAGA promoter linked to a reporter gene (e.g. luciferase) in the presence of the antibody shown in Tables 36 and 37.

Table 36. Inhibition of proMyostatin *in vitro*

Antibody Clone	293T %Inhibition Exp 1	HepG2 %Inhibition Exp 1	293T %Inhibition Exp 2	HepG2 %Inhibition Exp 2	HepG2 %Inhibition Murine GDF8
BP6a-8	52	35	38	42	39
BP13a-1	55	7	44	44	19
BP6a-23	-5	8			
BP5a-1	55	13	47	39	36
BP6a-11	12	-17			
BP18a-1	7	24	14	9	11
BP11a-1	63	26	1	3	43
BP6a-14	61	22	10	12	55
BP6a-27	28	21	-11	7	8
BP6a-13	22	14			
BP4a-1	-14	31	10	6	36
BP6a-19	28	5			
BP1a-1	45	22	8	20	37
BP6a-6	46	9			
BP6a-20	7	-10			
BP3a-2	46	-2			
BP6a-24	-6	-19			
BP6a-22	-6	-19			
BP6a-4	11	5			
BP19a-1	83	93	89	90	25
BP6a-7	42	61	69	66	59
BP6a-16	61	26	17	18	12
BP18a-2	6	33	31	21	13
BP19a-2	55	9			
BP6a-2	-16	-13	23	10	14
BP6a-3	15	1			
BP6a-5	70	48	68	58	42
BP6a-10	24	7			
BP6a-1	6	-15			
BP15a-1	-12	1			
BP6a-26	55	21	2	20	74
BP3a-3	-30	-9			
BP6a-12	26	4			
BP5a-4	3	3			
BP5a-3	12	17			
BP14a-1	3	7			
BP3a-1	-34	3			
BP6a-9	-44	-22			
BP6a-18	49	6	27	20	21

BP6a-25	-33	18			
BP5a-2	54	-9	62	51	98
BP6a-15	50	28	20	6	4
BP2a-1	35	47	55	43	23
BP6a-21	21	6			
BP5a-5	46	16			
BP16a-1	50	48	42	38	26
BP6a-17	0	18			
BP19a-3	19	6			

Table 36 shows the % inhibition of human proMyostatin and murine proMyostatin activity in the presence of various antibody clones using two independent reporter cells (293T and HepG2). Note: Experiment 1 = July-2014, Experiment 2 = Aug-2014

Table 37. Inhibition of proMyostatin and latent Myostatin *in vitro*

Antibody Clone	293T proMyostatin (human)	293T latent Myostatin (human)	HepG2 proMyostatin (human)	HepG2 latent Myostatin (human)
BP18b-1	9	2	11	9
BP19b-1	-1	53	3	51
BP6b-4	20	-1	8	6
BP5b-3	29	19	32	23
BP1b-1	19	58	0	25
BP5b-4	-34	-14	-33	-20
BP5b-6	-3	2	-14	-3
BP19b-2	14	1	25	8
BP5b-5	6	-7	-3	3
BP6b-3	42	1	51	-4
BP18b-2	8	6	12	6
BP21b-1	35	13	36	15
BP6b-1	6	-15	-21	-13
BP6b-5	8	0	-16	-9
BP5b-1	6	3	-16	4
BP18b-3	30	4	21	8
BP8b-1	23	-12	-5	-2
BP5b-2	17	-25	-1	-11
BP6b-6	44	51	53	56

BP6b-2	28	-2	15	0
BP6b-11	21	35	10	1
BP18b-4	89	92	85	97
BP6b-10	7	26	-1	46
BP16b-1	-6	11	-13	20
BP16b-2	-6	24	-11	11
BP18b-5	18	13	32	31
BP7b-1	82	67	89	92
BP5b-7	25	21	23	4
BP18b-6	1	0	13	16
BP20b-1	10	-1	-2	8
BP19b-3	5	-10	20	11
BP18b-7	32	31	15	24
BP17b-1	3	-8	23	10
BP16b-3	2	2	17	19
BP5b-8	11	-3	5	0
BP16b-4	4	-15	23	-2
BP9b-1	-10	-16	10	0
BP12b-1	-4	-36	6	-43
BP10b-1	51	23	59	17
BP6b-9	4	-7	15	-2
BP6b-7	74	51	78	69
BP6b-8	18	-3	27	-6
BP5b-9	-8	-2	6	-26
BP22b-1	11	1	13	2
BP6b-12	5	9	11	33

Table 37 shows the % inhibition of human proMyostatin and human latent Myostatin activity in the presence of various antibody clones using two independent reporter cells (293T and HepG2).

Example 33. pH sensitive dissociation from proMyostatin

[00800] The pH sensitivity of antibody clones, including clones BP1a-1, BP2a-1, BP3a-2, BP5a-1, BP5b-4, BP5b-1, BP5b-2, BP5a-2, BP6a-11, BP6a-6, BP6a-4, BP6a-7, BP6a-2, BP6a-3, BP6a-5, BP6a-1, BP6b-9, BP11a-1, BP14a-1, BP16b-4, BP18b-2, BP18b-7 and

BP22b-1 was determined usig Bio-Layer Interferometry (BLI). Data relating to the pH sensitivity of antibody clones provided herein is shown in FIGs. 16-25 and Table 38.

[00801] Bio-Layer Interferometry (BLI) is a label-free technology for measuring biomolecular interactions. It is an optical analytical technique that analyzes the interference pattern of white light reflected from two surfaces: a layer of immobilized protein on the biosensor tip, and an internal reference layer. Any change in the number of molecules bound to the biosensor tip causes a shift in the interference pattern that can be measured in real-time.

[00802] The binding between a ligand immobilized on the biosensor tip surface and an analyte in solution produces an increase in optical thickness at the biosensor tip, which results in a wavelength shift, $\Delta\lambda$, which is a direct measure of the change in thickness of the biological layer. Interactions are measured in real time, providing the ability to monitor binding specificity, rates of association and dissociation, or concentration, with precision and accuracy.

[00803] Only molecules binding to or dissociating from the biosensor can shift the interference pattern and generate a response profile on the Octet® System. Unbound molecules, changes in the refractive index of the surrounding medium, or changes in flow rate do not affect the interference pattern. This is a unique characteristic of BLI and extends its capability to perform in crude samples used in applications for protein:protein binding, quantitation, affinity, and kinetics.

Table 38. pH sensitive dissociation from proMyostatin

Antibody Clone	pH sensitive dissociation	k_d pH 5/ k_d pH 7.4
BP1a-1	no	1.5
BP2a-1	yes	1.8
BP3a-2	yes	2.2
BP5a-1	no	0.5
BP5b-4	yes	18.6
BP5b-1	yes	5.9
BP5b-2	no	0
BP5a-2	no	1.7
BP6a-11	no	0.6
BP6a-6	yes	32.9
BP6a-4	no	1.2
BP6a-7	no	0.0004
BP6a-2	no	1.8

BP6a-3	no	1.4
BP6a-5	yes	18.5
BP6a-1	no	0.001
BP6b-9	no	0.57
BP11a-1	yes	13.2
BP14a-1	yes	2.1
BP16b-4	yes	6.2
BP18b-2	yes	7.2
BP18b-7	no	2.3
BP22b-1	yes	14

Table 38 shows the ratio of the Kd at pH 5 to the Kd at pH7, indicating the antibodies that are sensitive to pH.

[00804] While several embodiments of the present disclosure have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for performing the functions and/or obtaining the results and/or one or more of the advantages described herein, and each of such variations and/or modifications is deemed to be within the scope of the present disclosure. More generally, those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be exemplary and that the actual parameters, dimensions, materials, and/or configurations will depend upon the specific application or applications for which the teachings of the present disclosure is/are used. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the disclosure described herein. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto, the disclosure may be practiced otherwise than as specifically described and claimed. The present disclosure is directed to each individual feature, system, article, material, and/or method described herein. In addition, any combination of two or more such features, systems, articles, materials, and/or methods, if such features, systems, articles, materials, and/or methods are not mutually inconsistent, is included within the scope of the present disclosure.

[00805] The indefinite articles “a” and “an,” as used herein in the specification and in the claims, unless clearly indicated to the contrary, should be understood to mean “at least one.”

[00806] The phrase “and/or,” as used herein in the specification and in the claims, should be understood to mean “either or both” of the elements so conjoined, i.e., elements that are

conjunctively present in some cases and disjunctively present in other cases. Other elements may optionally be present other than the elements specifically identified by the "and/or" clause, whether related or unrelated to those elements specifically identified unless clearly indicated to the contrary. Thus, as a non-limiting example, a reference to "A and/or B," when used in conjunction with open-ended language such as "comprising" can refer, in one embodiment, to A without B (optionally including elements other than B); in another embodiment, to B without A (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

[00807] As used herein in the specification and in the claims, "or" should be understood to have the same meaning as "and/or" as defined above. For example, when separating items in a list, "or" or "and/or" shall be interpreted as being inclusive, i.e., the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items. Only terms clearly indicated to the contrary, such as "only one of" or "exactly one of," or, when used in the claims, "consisting of," will refer to the inclusion of exactly one element of a number or list of elements. In general, the term "or" as used herein shall only be interpreted as indicating exclusive alternatives (i.e. "one or the other but not both") when preceded by terms of exclusivity, such as "either," "one of," "only one of," or "exactly one of." "Consisting essentially of," when used in the claims, shall have its ordinary meaning as used in the field of patent law.

[00808] As used herein in the specification and in the claims, the phrase "at least one," in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements. This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase "at least one" refers, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, "at least one of A and B" (or, equivalently, "at least one of A or B," or, equivalently "at least one of A and/or B") can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet another embodiment, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

[00809] In the claims, as well as in the specification above, all transitional phrases such as "comprising," "including," "carrying," "having," "containing," "involving," "holding," and the like are to be understood to be open-ended, i.e., to mean including but not limited to. Only the transitional phrases "consisting of" and "consisting essentially of" shall be closed or semi-closed transitional phrases, respectively, as set forth in the United States Patent Office Manual of Patent Examining Procedures, Section 2111.03.

[00810] Use of ordinal terms such as "first," "second," "third," etc., in the claims to modify a claim element does not by itself connote any priority, precedence, or order of one claim element over another or the temporal order in which acts of a method are performed, but are used merely as labels to distinguish one claim element having a certain name from another element having a same name (but for use of the ordinal term) to distinguish the claim elements.

CLAIMS

What is claimed is:

1. An antibody that specifically binds human proMyostatin, human latent Myostatin, human GDF-8 prodomain, human GDF-11 ARM8 prodomain, and human proGDF11 ARM8, but does not specifically bind human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

2. An antibody that specifically binds human proMyostatin, murine proMyostatin, human latent Myostatin, human GDF-8 prodomain, human GDF-11 ARM8 prodomain, and human proGDF11 ARM8, but does not specifically bind human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

3. The antibody of claim 1 or 2, wherein the human proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 5.

4. The antibody of claim 2 or 3, wherein the murine proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 88.

5. The antibody of any one of claims 1 to 4, wherein the human latent Myostatin has an amino acid sequence as set forth in SEQ ID NO: 5.

6. The antibody of any one of claims 1 to 5, wherein the human GDF-8 prodomain has an amino acid sequence as set forth in SEQ ID NO: 38.

7. The antibody of any one of claims 1 to 6, wherein the human GDF-11 ARM8 prodomain has an amino acid sequence as set forth in SEQ ID NO: 181.

8. The antibody of any one of claims 1 to 7, wherein the human proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179.

9. The antibody of any one of claims 1 to 8, wherein the antibody specifically binds human latent proGDF11 ARM8, but does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4.

10. The antibody of any one of claims 2 to 8, wherein the antibody specifically binds murine latent myostatin and human latent proGDF11 ARM8, but does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4.

11. The antibody of claim 10, wherein the murine latent myostatin has an amino acid sequence as set forth in SEQ ID NO: 88.

12. The antibody of any one of claims 9 to 11, wherein the human latent proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179.

13. The antibody of any one of claims 1 to 12, wherein the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 752, 780, 815, 772, 784, 770, 774, 756, 796, 785, 761, 788, 767, 765, 799, 749, 802, 809, 750, 803, 800, 806, 759, 805, 797, 787, or 766, 782, 967, 776, 755, 876, 891, 963, 996, 993, 970, 968 or 1008.

14. The antibody of any one of claims 1 to 13, wherein the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1367, 1394, 1660, 1387, 1397, 1385, 1388, 1371, 1409, 1398, 1376, 1401, 1382, 1380, 1656, 1364, 1413, 1418, 1365, 1658, 1657, 1415, 1374, 1659, 1410, 1400, 1381, 1395, 1582, 1390, 1370, 1670, 1485, 1578, 1611, 1608, 1585, 1583, or 1623.

15. The antibody of any one of claims 1 to 14, wherein the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP6a-1, BP6a-2, BP6a-3, BP6a-4, BP6a-5, BP6a-6, BP6a-7, BP6a-8, BP6a-9, BP6a-10, BP6a-11, BP6a-12, BP6a-13, BP6a-14, BP6a-15, BP6a-16, BP6a-17, BP6a-18, BP6a-19, BP6a-20, BP6a-21, BP6a-22, BP6a-23, BP6a-24, BP6a-25, BP6a-26, BP6a-27, BP6b-1, BP6b-2, BP6b-3, BP6b-4, BP6b-5, BP6b-6, BP6b-7, BP6b-8, BP6b-9, BP6b-10, BP6b-11 or BP6b-12 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP6a-1, BP6a-2, BP6a-3, BP6a-4, BP6a-5, BP6a-6, BP6a-7, BP6a-8, BP6a-9, BP6a-10, BP6a-11, BP6a-12, BP6a-13, BP6a-14, BP6a-15, BP6a-16, BP6a-17, BP6a-18, BP6a-19, BP6a-20, BP6a-21, BP6a-22, BP6a-23, BP6a-24, BP6a-25, BP6a-26, BP6a-27, BP6b-1, BP6b-2, BP6b-3, BP6b-4, BP6b-5, BP6b-6, BP6b-7, BP6b-8, BP6b-9, BP6b-10, BP6b-11 or BP6b-12 as set forth in Table 16.

16. The antibody of any one of claims 1 to 15, wherein the antibody comprises a variable heavy chain amino acid sequence of clone BP6a-1, BP6a-2, BP6a-3, BP6a-4, BP6a-5, BP6a-6, BP6a-7, BP6a-8, BP6a-9, BP6a-10, BP6a-11, BP6a-12, BP6a-13, BP6a-14, BP6a-15, BP6a-16, BP6a-17, BP6a-18, BP6a-19, BP6a-20, BP6a-21, BP6a-22, BP6a-23, BP6a-24, BP6a-25, BP6a-26, BP6a-27, BP6b-1, BP6b-2, BP6b-3, BP6b-4, BP6b-5, BP6b-6, BP6b-7, BP6b-8, BP6b-9, BP6b-10, BP6b-11 or BP6b-12 as set forth in Table 14.

17. The antibody of any one of claims 1 to 16, wherein the antibody comprises the variable light chain amino acid sequence of clone BP6a-1, BP6a-2, BP6a-3, BP6a-4, BP6a-5, BP6a-6, BP6a-7, BP6a-8, BP6a-9, BP6a-10, BP6a-11, BP6a-12, BP6a-13, BP6a-14, BP6a-15, BP6a-16, BP6a-17, BP6a-18, BP6a-19, BP6a-20, BP6a-21, BP6a-22, BP6a-23, BP6a-24, BP6a-25, BP6a-26, BP6a-27, BP6b-1, BP6b-2, BP6b-3, BP6b-4, BP6b-5, BP6b-6, BP6b-7, BP6b-8, BP6b-9, BP6b-10, BP6b-11 or BP6b-12 as set forth in Table 16.

18. An antibody that specifically binds human proMyostatin, and human proGDF11 ARM8 but does not specifically bind human latent Myostatin having an amino acid sequence as set forth in SEQ ID NO: 5, human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

19. An antibody that specifically binds human proMyostatin, murine proMyostatin and human proGDF11 ARM8 but does not specifically bind human latent Myostatin having an amino acid sequence as set forth in SEQ ID NO: 5, human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

20. The antibody of claim 18 or 19, wherein the human proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 5.

21. The antibody of claim 19 or 20, wherein the murine proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 88.

22. The antibody of any one of claims 18 to 21, wherein the human proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179.

23. The antibody of any one of claims 18 to 22, wherein the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 813.

24. The antibody of any one of claims 18 to 23, wherein the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1422.

25. The antibody of any one of claims 18 to 24, wherein the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP2a-1 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP2a-1 as set forth in Table 16.

26. The antibody of any one of claims 18 to 25, wherein the antibody comprises a variable heavy chain amino acid sequence of clone BP2a-1 as set forth in Table 14.

27. The antibody of any one of claims 18 to 26, wherein the antibody comprises the variable light chain amino acid sequence of clone BP2a-1 as set forth in Table 16.

28. An antibody that specifically binds human proMyostatin, and human latent Myostatin, but does not specifically bind human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179, or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

29. An antibody that specifically binds human proMyostatin, murine proMyostatin, and human latent Myostatin, but does not specifically bind human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8

having an amino acid sequence as set forth in SEQ ID NO: 179, or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

30. The antibody of claim 28 or 29, wherein the human proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 5.

31. The antibody of claim 29 or 30, wherein the murine proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 88.

32. The antibody of any one of claims 28 to 31, wherein the human latent Myostatin has an amino acid sequence as set forth in SEQ ID NO: 5.

33. The antibody of any one of claims 28 to 32, wherein the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 794, 804, or 751.

34. The antibody of any one of claims 28 to 33, wherein the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1407, 1414, or 1366.

35. The antibody of any one of claims 28 to 34, wherein the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP3a-1, BP3a-2 or BP3a-3 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP3a-1, BP3a-2 or BP3a-3 as set forth in Table 16.

36. The antibody of any one of claims 28 to 35, wherein the antibody comprises a variable heavy chain amino acid sequence of clone BP3a-1, BP3a-2 or BP3a-3 as set forth in Table 14.

37. The antibody of any one of claims 28 to 36, wherein the antibody comprises the variable light chain amino acid sequence of clone BP3a-1, BP3a-2 or BP3a-3 as set forth in Table 16.

38. An antibody that specifically binds human proMyostatin, human latent Myostatin and human GDF8 prodomain but does not specifically bind human GDF-11 ARM8 prodomain

having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179 or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

39. An antibody that specifically binds human proMyostatin, murine proMyostatin, human latent Myostatin and human GDF8 prodomain but does not specifically bind human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179 or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

40. The antibody of claim 38 or 39, wherein the human proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 5.

41. The antibody of claim 39 or 40, wherein the murine proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 88.

42. The antibody of any one of claims 38 to 41, wherein the human latent Myostatin has an amino acid sequence as set forth in SEQ ID NO: 5.

43. The antibody of any one of claims 38 to 42, wherein the human GDF-8 prodomain has an amino acid sequence as set forth in SEQ ID NO: 38.

44. The antibody of any one of claims 38 to 43, wherein the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 768.

45. The antibody of any one of claims 38 to 44, wherein the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1383.

46. The antibody of any one of claims 38 to 45, wherein the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP4a-1 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP4a-1 as set forth in Table 16.

47. The antibody of any one of claims 38 to 46, wherein the antibody comprises a variable heavy chain amino acid sequence of clone BP4a-1 as set forth in Table 14.

48. The antibody of any one of claims 38 to 47, wherein the antibody comprises the variable light chain amino acid sequence of clone BP4a-1 as set forth in Table 16.

49. An antibody that specifically binds human proMyostatin, human latent Myostatin, and human proGDF11 ARM8, but does not specifically bind human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

50. An antibody that specifically binds human proMyostatin, murine proMyostatin, human latent Myostatin, and human proGDF11 ARM8, but does not specifically bind human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

51. The antibody of claim 49 or 50, wherein the human proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 5.

52. The antibody of claim 50 or 51, wherein the murine proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 88.

53. The antibody of any one of claims 49 to 52, wherein the human latent Myostatin has an amino acid sequence as set forth in SEQ ID NO: 5.

54. The antibody of any one of claims 49 to 53, wherein the human proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179.

55. The antibody of any one of claims 50 to 54, wherein the antibody specifically binds human latent proGDF11 ARM8, but does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4.

56. The antibody of any one of claims 50 to 54, wherein the antibody specifically binds murine latent myostatin and human latent proGDF11 ARM8, but does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4.

57. The antibody of claim 56, wherein the murine latent myostatin has an amino acid sequence as set forth in SEQ ID NO: 88.

58. The antibody of any one of claims 55 to 57, wherein the human latent proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179.

59. The antibody of any one of claims 49 to 58, wherein the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 760, 798, 792, 789, 801, 790, 812, 758, 762, 775, 834, 974, 985, or 1002.

60. The antibody of any one of claims 59 to 59, wherein the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1375, 1411, 1405, 1402, 1412, 1403, 1421, 1373, 1377, 1389, 1661, 1589, 1600, or 1617.

61. The antibody of any one of claims 49 to 60, wherein the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP5a-1, BP5a-2, BP5a-3, BP5a-4 or BP5a-5, BP5b-1, BP5b-2, BP5b-3, BP5b-4, BP5b-5, BP5b-6, BP5b-7, BP5b-8 or BP5b-9 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP5a-1, BP5a-2, BP5a-3, BP5a-4 or BP5a-5, BP5b-1, BP5b-2, BP5b-3, BP5b-4, BP5b-5, BP5b-6, BP5b-7, BP5b-8 or BP5b-9 as set forth in Table 16.

62. The antibody of any one of claims 49 to 61, wherein the antibody comprises a variable heavy chain amino acid sequence of clone BP5a-1, BP5a-2, BP5a-3, BP5a-4 or BP5a-5, BP5b-1, BP5b-2, BP5b-3, BP5b-4, BP5b-5, BP5b-6, BP5b-7, BP5b-8 or BP5b-9 as set forth in Table 14.

63. The antibody of any one of claims 49 to 62, wherein the antibody comprises the variable light chain amino acid sequence of clone BP5a-1, BP5a-2, BP5a-3, BP5a-4 or BP5a-

5, BP5b-1, BP5b-2, BP5b-3, BP5b-4, BP5b-5, BP5b-6, BP5b-7, BP5b-8 or BP5b-9 as set forth in Table 16.

64. An antibody that specifically binds human proMyostatin but does not specifically bind human latent Myostatin having an amino acid sequence as set forth in SEQ ID NO: 5, human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179,or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

65. An antibody that specifically binds human proMyostatin and murine proMyostatin but does not specifically bind human latent Myostatin having an amino acid sequence as set forth in SEQ ID NO: 5, human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179,or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

66. The antibody of claim 64 or 65, wherein the human proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 5.

67. The antibody of claim 65 or 66, wherein the murine proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 88).

68. The antibody of any one of claims 64 to 67, wherein the antibody does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4, or human latent proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179.

69. The antibody of any one of claims 65 to 67, wherein the antibody does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4, murine latent myostatin having an amino acid sequence as set forth in SEQ ID NO: 88

or human latent proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179.

70. The antibody of any one of claims 64 to 69, wherein the antibody comprises a CDR-H3 amino acid sequence as set forth in SEQ ID NO: 769 or 827.

71. The antibody of any one of claims 64 to 70, wherein the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1384 or 1435.

72. The antibody of any one of claims 64 to 71, wherein the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP1a-1 or BP1b-1 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP1a-1 or BP1b-1 as set forth in Table 16.

73. The antibody of any one of claims 64 to 72, wherein the antibody comprises a variable heavy chain amino acid sequence of clone BP1a-1 or BP1b-1 as set forth in Table 14.

74. The antibody of any one of claims 64 to 73, wherein the antibody comprises the variable light chain amino acid sequence of clone BP1a-1 or BP1b-1 as set forth in Table 16.

75. An antibody that specifically binds human latent Myostatin but does not specifically bind human proMyostatin having an amino acid sequence as set forth in SEQ ID NO: 5, human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179, human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42 or human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4).

76. An antibody that specifically binds human latent Myostatin but does not specifically bind murine proMyostatin having an amino acid sequence as set forth in SEQ ID NO: 88, human proMyostatin having an amino acid sequence as set forth in SEQ ID NO: 5, human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human

GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179, human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42 or human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4).

77. The antibody of claim 75 or 76, wherein the human latent Myostatin has an amino acid sequence as set forth in SEQ ID NO: 5.

78. The antibody of any one of claims 75 to 77, wherein the antibody specifically binds human latent proGDF11 ARM8.

79. The antibody of claim 76 or 77, wherein the antibody specifically binds murine latent myostatin and human latent proGDF11 ARM8.

80. The antibody of claim 79, wherein the murine latent myostatin has an amino acid sequence as set forth in SEQ ID NO: 88.

81. The antibody of any one of claims 78 to 80, wherein the human latent proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179.

82. The antibody of any one of claims 75 to 81, wherein the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 990.

83. The antibody of any one of claims 75 to 82, wherein the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1605.

84. The antibody of any one of claims 75 to 83, wherein the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP10b-1 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP10b-1 as set forth in Table 16.

85. The antibody of any one of claims 75 to 84, wherein the antibody comprises a variable heavy chain amino acid sequence of clone BP10b-1 as set forth in Table 14.

86. The antibody of any one of claims 75 to 85, wherein the antibody comprises the variable light chain amino acid sequence of clone BP10b-1as set forth in Table 16.

87. An antibody that specifically binds human proMyostatin, human latent Myostatin, human proGDF11 ARM8 and human mature GDF-8 but does not specifically bind human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38 or human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181.

88. An antibody that specifically binds human proMyostatin, murine proMyostatin, human latent Myostatin, human proGDF11 ARM8 and human mature GDF-8 but does not specifically bind human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38 or human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181.

89. The antibody of claim 87 or 88, wherein the human proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 5.

90. The antibody of claim 88 or 89, wherein the murine proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 88.

91. The antibody of any one of claims 87 to 90, wherein the human latent Myostatin has an amino acid sequence as set forth in SEQ ID NO: 5.

92. The antibody of any one of claims 87 to 91, wherein the human proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179.

93. The antibody of any one of claims 87 to 92, wherein the human mature GDF-8 has an amino acid sequence as set forth in SEQ ID NO: 42.

94. The antibody of any one of claims 87 to 93, wherein the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 764.

95. The antibody of any one of claims 87 to 94, wherein the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1379.

96. The antibody of any one of claims 87 to 95, wherein the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP11a-1 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP11a-1 as set forth in Table 16.

97. The antibody of any one of claims 87 to 96, wherein the antibody comprises a variable heavy chain amino acid sequence of clone BP11a-1 as set forth in Table 14.

98. The antibody of any one of claims 87 to 97, wherein the antibody comprises the variable light chain amino acid sequence of clone BP11a-1 as set forth in Table 16.

99. An antibody that specifically binds human latent Myostatin and human mature GDF-8 but does not specifically bind human proMyostatin having an amino acid sequence as set forth in SEQ ID NO: 5, human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181 or human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179.

100. An antibody that specifically binds human latent Myostatin and human mature GDF-8 but does not specifically bind murine proMyostatin having an amino acid sequence as set forth in SEQ ID NO: 88, human proMyostatin having an amino acid sequence as set forth in SEQ ID NO: 5, human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181 or human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179.

101. The antibody of claim 99 or 100, wherein the human latent Myostatin has an amino acid sequence as set forth in SEQ ID NO: 5.

102. The antibody of any one of claims 99 to 101, wherein the human mature GDF-8 has an amino acid sequence as set forth in SEQ ID NO: 42.

103. The antibody of any one of claims 100 to 102, wherein the antibody does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4 or human latent proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179.

104. The antibody of any one of claims 100 to 102, wherein the antibody specifically binds murine latent myostatin but does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4 or human latent proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179.

105. The antibody of claim 104, wherein the murine latent myostatin has an amino acid sequence as set forth in SEQ ID NO: 88.

106. The antibody of any one of claims 99 to 105, wherein the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 989.

107. The antibody of any one of claims 99 to 106, wherein the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1604.

108. The antibody of any one of claims 99 to 107, wherein the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP12b-1 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP12b-1as set forth in Table 16.

109. The antibody of any one of claims 99 to 108, wherein the antibody comprises a variable heavy chain amino acid sequence of clone BP12b-1 as set forth in Table 14.

110. The antibody of any one of claims 99 to 109, wherein the antibody comprises the variable light chain amino acid sequence of clone BP12b-1 as set forth in Table 16.

111. An antibody that specifically binds human proMyostatin and human GDF-8 prodomain, but does not specifically bind human latent Myostatin having an amino acid sequence as set forth in SEQ ID NO: 5, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179 or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

112. An antibody that specifically binds human proMyostatin and human GDF-8 prodomain, but does not specifically bind murine proMyostatin having an amino acid sequence as set forth in SEQ ID NO: 88, human latent Myostatin having an amino acid sequence as set forth in SEQ ID NO: 5, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179 or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

113. The antibody of claim 111 or 112, wherein the human proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 5.

114. The antibody of any one of claims 111 to 113, wherein the human GDF-8 prodomain has an amino acid sequence as set forth in SEQ ID NO: 38.

115. The antibody of any one of claims 111 to 114, wherein the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 786.

116. The antibody of any one of claims 111 to 115, wherein the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1399.

117. The antibody of any one of claims 111 to 116, wherein the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP15a-1 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP15a-1 as set forth in Table 16.

118. The antibody of any one of claims 111 to 117, wherein the antibody comprises a variable heavy chain amino acid sequence of clone BP15a-1 as set forth in Table 14.

119. The antibody of any one of claims 111 to 118, wherein the antibody comprises the variable light chain amino acid sequence of clone BP15a-1 as set forth in Table 16.

120. An antibody that specifically binds human proMyostatin and human latent Myostatin but does not specifically bind human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179 or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

121. An antibody that specifically binds human proMyostatin and human latent Myostatin but does not specifically bind murine proMyostatin having an amino acid sequence as set forth in SEQ ID NO: 88, human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179 or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

122. The antibody of claim 120 or 121, wherein the human proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 5.

123 The antibody of any one of claims 121 to 122, wherein the human latent Myostatin has an amino acid sequence as set forth in SEQ ID NO: 5.

124. The antibody of any one of claims 121 to 123, wherein the antibody does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4 or human latent proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179.

125. The antibody of any one of claims 121 to 123, wherein the antibody does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID

NO: 4, murine latent myostatin having an amino acid sequence as set forth in SEQ ID NO: 88 or human latent proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179.

126. The antibody of any one of claims 120 to 125, wherein the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 810, 855, 971, 983, or 986.

127. The antibody of any one of claims 120 to 126, wherein the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1419, 1662, 1586, 1598, or 1601 .

128. The antibody of any one of claims 120 to 127, wherein the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP16a-1, BP16b-1, BP16b-2, BP16b-3 or BP16b-4 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP16a-1, BP16b-1, BP16b-2, BP16b-3 or BP16b-4 as set forth in Table 16.

129. The antibody of any one of claims 120 to 128, wherein the antibody comprises a variable heavy chain amino acid sequence of clone BP16a-1, BP16b-1, BP16b-2, BP16b-3 or BP16b-4 as set forth in Table 14.

130. The antibody of any one of claims 120 to 129, wherein the antibody comprises the variable light chain amino acid sequence of clone BP16a-1, BP16b-1, BP16b-2, BP16b-3 or BP16b-4 as set forth in Table 16.

131. An antibody that specifically binds human proMyostatin and human latent Myostatin but does not specifically bind human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179, human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42 or human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4.

132. An antibody that specifically binds human proMyostatin and human latent Myostatin but does not specifically bind murine proMyostatin having an amino acid sequence as set forth in SEQ ID NO: 88, human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179, human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42, human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4 or murine latent myostatin having an amino acid sequence as set forth in SEQ ID NO: 88.

133. The antibody of claim 131 or 132, wherein the human proMyostatin has amino acid sequence as set forth in SEQ ID NO: 5.

134. The antibody of any one of claims 131 to 133, wherein the human latent Myostatin has an amino acid sequence as set forth in SEQ ID NO: 5.

135. The antibody of any one of claims 131 to 134, wherein the antibody specifically binds human latent proGDF11 ARM8.

136. The antibody of claim 135, wherein the human latent proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179.

137. The antibody of any one of claims 131 to 134, wherein the antibody does not specifically bind human latent proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179.

138. The antibody of any one of claims 131 to 137, wherein the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 982.

139. The antibody of any one of claims 131 to 138, wherein the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1597.

140. The antibody of any one of claims 131 to 139, wherein the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid

sequence of clone BP17b-1 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP17b-1 as set forth in Table 16.

141. The antibody of any one of claims 131 to 140, wherein the antibody comprises a variable heavy chain amino acid sequence of clone BP17b-1 as set forth in Table 14.

142. The antibody of any one of claims 131 to 141, wherein the antibody comprises the variable light chain amino acid sequence of clone BP17b-1 as set forth in Table 16.

143. An antibody that specifically binds human proMyostatin, human latent Myostatin and human proGDF11 ARM8 but does not specifically bind human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181 or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

144. An antibody that specifically binds human proMyostatin, human latent Myostatin and human proGDF11 ARM8 but does not specifically bind murine proMyostatin having an amino acid sequence as set forth in SEQ ID NO: 88, human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181 or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

145. The antibody of claim 143 or 144, wherein the human proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 5.

146. The antibody of any one of claims 143 to 145, wherein the human latent Myostatin has an amino acid sequence as set forth in SEQ ID NO: 5.

147. The antibody of any one of claims 143 to 146, wherein the human proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179.

148. The antibody of any one of claims 143 to 147, wherein the antibody specifically binds human latent proGDF11 ARM8 but does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4.

149. The antibody of any one of claims 144 to 147, wherein the antibody specifically binds human latent proGDF11 ARM8 but does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4 or murine latent myostatin having an amino acid sequence as set forth in SEQ ID NO: 88.

150. The antibody of claim 148 or 149, wherein the human latent proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179.

151. The antibody of any one of claims 143 to 150, wherein the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 763, 814, 753, 777, 795, 969, 972, 976, or 981.

152. The antibody of any one of claims 143 to 151, wherein the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1378, 1423, 1368, 1391, 1408, 1584, 1587, 1591, or 1596.

153. The antibody of any one of claims 143 to 152, wherein the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP18a-1 or BP18a-2, BP18b-1, BP18b-2, BP18b-3, BP18b-4, BP18b-5, BP18b-6 or BP18b-7 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP18a-1 or BP18a-2, BP18b-1, BP18b-2, BP18b-3, BP18b-4, BP18b-5, BP18b-6 or BP18b-7as set forth in Table 16.

154. The antibody of any one of claims 143 to 153, wherein the antibody comprises a variable heavy chain amino acid sequence of clone BP18a-1 or BP18a-2, BP18b-1, BP18b-2, BP18b-3, BP18b-4, BP18b-5, BP18b-6 or BP18b-7 as set forth in Table 14.

155. The antibody of any one of claims 143 to 154, wherein the antibody comprises the variable light chain amino acid sequence of clone BP18a-1 or BP18a-2, BP18b-1, BP18b-2, BP18b-3, BP18b-4, BP18b-5, BP18b-6 or BP18b-7 as set forth in Table 16.

156. An antibody that specifically binds human proMyostatin, human latent Myostatin, human GDF-8 prodomain, human GDF-11 ARM8 prodomain and human proGDF11 ARM8 but does not specifically bind human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

157. An antibody that specifically binds human proMyostatin, human latent Myostatin, human GDF-8 prodomain, human GDF-11 ARM8 prodomain and human proGDF11 ARM8 but does not specifically bind murine proMyostatin having an amino acid sequence as set forth in SEQ ID NO: 88 or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

158. The antibody of claim 156 or 157, wherein the human proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 5.

159. The antibody of any one of claims 156 to 158, wherein the human latent Myostatin has an amino acid sequence as set forth in SEQ ID NO: 5.

160. The antibody of any one of claims 156 to 159, wherein the human GDF-8 prodomain has an amino acid sequence as set forth in SEQ ID NO: 38.

161. The antibody of any one of claims 156 to 160, wherein the human GDF-11 ARM8 prodomain has an amino acid sequence as set forth in SEQ ID NO: 181.

162. The antibody of any one of claims 156 to 161, wherein the human proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179.

163. The antibody of any one of claims 156 to 162, wherein the antibody specifically binds human latent proGDF11 ARM8 but does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4.

164. The antibody of any one of claims 157 to 162, wherein the antibody specifically binds human latent proGDF11 ARM8 but does not specifically bind human proGDF11 having an amino acid sequence as set forth in SEQ ID NO: 4 or murine latent myostatin having an amino acid sequence as set forth in SEQ ID NO: 88.

165. The antibody of claim 163 or 164 wherein the human latent proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179.

166. The antibody of any one of claims 156 to 165, wherein the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 773, 807, 811, 754, 771, or 978.

167. The antibody of any one of claims 156 to 166, wherein the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1655, 1416, 1420, 1369, 1386, or 1593.

168. The antibody of any one of claims 156 to 167, wherein the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP19a-1, BP19a-2 or BP19a-3, BP19b-1, BP19b-2 or BP19b-3 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP19a-1, BP19a-2 or BP19a-3, BP19b-1, BP19b-2 or BP19b-3 as set forth in Table 16.

169. The antibody of any one of claims 156 to 168, wherein the antibody comprises a variable heavy chain amino acid sequence of clone BP19a-1, BP19a-2 or BP19a-3, BP19b-1, BP19b-2 or BP19b-3 as set forth in Table 14.

170. The antibody of any one of claims 156 to 169, wherein the antibody comprises the variable light chain amino acid sequence of clone BP19a-1, BP19a-2 or BP19a-3, BP19b-1, BP19b-2 or BP19b-3 as set forth in Table 16.

171. An antibody that specifically binds human proMyostatin, human latent Myostatin, human proGDF11 ARM8, human proGDF11 or human latent proGDF11 ARM8 but does not specifically bind human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set

forth in SEQ ID NO: 181 or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

172. An antibody that specifically binds human proMyostatin, murine proMyostatin, human latent Myostatin, human proGDF11 ARM8, human proGDF11, murine latent myostatin or human latent proGDF11 ARM8 but does not specifically bind human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181 or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

173. The antibody of claim 171 or 172, wherein the human proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 5.

174. The antibody of claim 172 or 173, wherein the murine proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 88.

175. The antibody of any one of claims 171 to 174, wherein the human latent Myostatin has an amino acid sequence as set forth in SEQ ID NO: 5.

176. The antibody of any one of claims 171 to 175, wherein the human proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179.

177. The antibody of any one of claims 171 to 176, wherein the human proGDF11 has an amino acid sequence as set forth in SEQ ID NO: 4.

178. The antibody of any one of claims 172 to 177, wherein the murine latent myostatin has an amino acid sequence as set forth in SEQ ID NO: 88.

179. The antibody of any one of claims 171 to 178, wherein the human latent proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179.

180. The antibody of any one of claims 171 to 179, wherein the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 779.

181. The antibody of any one of claims 171 to 180, wherein the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1393.

182. The antibody of any one of claims 171 to 181, wherein the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP21b-1 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP21b-1 as set forth in Table 16.

183. The antibody of any one of claims 171 to 182, wherein the antibody comprises a variable heavy chain amino acid sequence of clone BP21b-1 as set forth in Table 14.

184. The antibody of any one of claims 171 to 183, wherein the antibody comprises the variable light chain amino acid sequence of clone BP21b-1 as set forth in Table 16.

185. An antibody that specifically binds human proMyostatin, human latent Myostatin, human proGDF11, and human latent proGDF11 ARM8 but does not specifically bind human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179 or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

186. An antibody that specifically binds human proMyostatin, murine proMyostatin, human latent Myostatin, human proGDF11, murine latent myostatin and human latent proGDF11 ARM8 but does not specifically bind human GDF-8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 38, human GDF-11 ARM8 prodomain having an amino acid sequence as set forth in SEQ ID NO: 181, human proGDF11 ARM8 having an amino acid sequence as set forth in SEQ ID NO: 179 or human mature GDF-8 having an amino acid sequence as set forth in SEQ ID NO: 42.

187. The antibody of claim 185 or 186, wherein the human proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 5.

188. The antibody of claim 186 or 187, wherein the murine proMyostatin has an amino acid sequence as set forth in SEQ ID NO: 88.

189. The antibody of any one of claims 185 to 188, wherein the human latent Myostatin has an amino acid sequence as set forth in SEQ ID NO: 5.

190. The antibody of any one of claims 185 to 189, wherein the human proGDF11 has an amino acid sequence as set forth in SEQ ID NO: 4.

191. The antibody of any one of claims 186 to 190, wherein the murine latent myostatin has an amino acid sequence as set forth in SEQ ID NO: 88.

192. The antibody of any one of claims 185 to 191, wherein the human latent proGDF11 ARM8 has an amino acid sequence as set forth in SEQ ID NO: 179.

193. The antibody of any one of claims 185 to 192, wherein the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 1006.

194. The antibody of any one of claims 185 to 193, wherein the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1621.

195. The antibody of any one of claims 185 to 194, wherein the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP22b-1 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP22b-1as set forth in Table 16.

196. The antibody of any one of claims 185 to 195, wherein the antibody comprises a variable heavy chain amino acid sequence of clone BP22b-1 as set forth in Table 14.

197. The antibody of any one of claims 185 to 196, wherein the antibody comprises the variable light chain amino acid sequence of clone BP22b-1 as set forth in Table 16.

198. An antibody that specifically binds proMyostatin and/or latent Myostatin, wherein the antibody has an affinity to the proMyostatin and/or latent Myostatin that is pH sensitive.

199. An antibody that specifically binds proMyostatin and/or latent Myostatin with a greater affinity at a pH in a range from 6.5 to 7.5 than it does at a pH in a range from 4.6 to 6.0.

200. The antibody of claim 198 or 199, wherein the antibody has a Kd of binding to pro/latent-Myostatin in a range from10^{-3} M to 10^{-8} M under binding conditions having a pH in a range from 4.6 to 6.0.

201. The antibody of any one of claims 198 to 200, wherein the antibody has a Kd of binding to pro/latent-Myostatin in a range from10^{-6} M to 10^{-11} M, when the pH is in a range from 6.5 to 7.5.

202. The antibody of any one of claims 198 to 201, wherein the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 813, 804, 790, 762, 784, 770, 764, 986, 777, or 1006.

203. The antibody of any one of claims 198 to 202, wherein the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1422, 1414, 1403, 1377, 1397, 1385, 1379, 1601, 1391, or 1621.

204. The antibody of any one of claims 198 to 203, wherein the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP2a-1, BP3a-2, BP5b-1, BP5b-4, BP6a-5, BP6a-6, BP11a-1, BP16b-4, BP18b-2 or BP22b-1 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP2a-1, BP3a-2, BP5b-1, BP5b-4, BP6a-5, BP6a-6, BP11a-1, BP16b-4, BP18b-2 or BP22b-1 as set forth in Table 16.

205. The antibody of any one of claims 198 to 204, wherein the antibody comprises a variable heavy chain amino acid sequence of clone BP2a-1, BP3a-2, BP5b-1, BP5b-4, BP6a-5, BP6a-6, BP11a-1, BP16b-4, BP18b-2 or BP22b-1as set forth in Table 14.

206. The antibody of any one of claims 198 to 205, wherein the antibody comprises the variable light chain amino acid sequence of clone BP2a-1, BP3a-2, BP5b-1, BP5b-4, BP6a-5, BP6a-6, BP11a-1, BP16b-4, BP18b-2 or BP22b-1as set forth in Table 16.

207. An isolated antibody or antigen binding fragment thereof having at least one variable domain with an amino acid sequence having at least 95% sequence identity to one or more of those listed in Table 14 or 16.

208. The isolated antibody or antigen binding fragment thereof of claim 207 wherein said at least one variable domain comprises a variable domain pair, said variable domain pair comprising a heavy chain variable domain (VH) and a light chain variable domain (VL), wherein said variable domain pair comprises at least 95% sequence identity to a variable domain pair present in an scFv selected from any of those listed in Table 13.

209. An isolated antibody or antigen binding fragment thereof comprising at least one variable domain, said at least one variable domain comprising at least one complementarity determining region (CDR) sequence comprising at least 70% sequence identity to one or more of those listed in Table 15 or 17.

210. The isolated antibody or antigen binding fragment thereof of claim 209, wherein said at least one CDR sequence comprises at least 70% sequence identity to a heavy chain variable domain CDR (CDR-H) selected from any of those listed in Table 15.

211. The isolated antibody or antigen binding fragment thereof of claim 209, comprising at least one variable domain pair, said variable domain pair comprising a VH and a VL.

212. The isolated antibody or antigen binding fragment thereof of claim 211, wherein said VH comprises at least one CDR-H sequence with at least 70% sequence identity to a sequence selected from any of those listed in Table 15.

213. The isolated antibody or antigen binding fragment thereof of claim 211, wherein said VL comprises at least one CDR-L sequence with at least 70% sequence identity to a CDR-L sequence selected from any of those listed in Table 17.

214. An isolated antibody or antigen binding fragment thereof that comprises:
   i. a VH sequence with at least 95% sequence identity to a sequence listed in Table 14, and
   ii. a VL sequence with at least 95% sequence identity to a sequence listed in Table 16.

215. An isolated antibody or antigen binding fragment thereof that comprises:
   i. a CDR-H1 sequence with at least 70% sequence identity to a sequence listed in Table 15,
   ii. a CDR-H2 sequence with at least 70% sequence identity to a sequence listed in Table 15,
   iii. a CDR-H3 sequence with at least 70% sequence identity to a sequence listed in Table 15,
   iv. a CDR-L1 sequence with at least 70% sequence identity to a sequence listed in Table 17,
   v. a CDR-L2 sequence with at least 70% sequence identity to a sequence listed in Table 17, and
   vi. a CDR-L3 sequence with at least 70% sequence identity to a sequence listed in Table 17.

216. The isolated antibody or antigen binding fragment thereof of any of claims 207-215, comprising an antibody, wherein said antibody is a monoclonal antibody.

217. The isolated antibody or antigen binding fragment thereof of any of claims 207-216, comprising an antibody, wherein said antibody comprises an IgG isotype.

218. The antibody of claim 217, wherein said antibody comprises an IgG1 isotype.

219. The isolated antibody or antigen binding fragment thereof of any of claim 207-218, wherein said antibody binds to one or more recombinant antigens listed in Table 24 and/or one or more polypeptides comprising an amino acid sequence with at least 95% sequence identity to any of those listed in Tables 1, 2, 4, 5, 9, 10, 19, 20 or 25.

220. The isolated antibody or antigen binding fragment thereof of claim 219, wherein said polypeptide comprises pro-growth differentiation factor (GDF)-8 (proGDF-8) (SEQ ID NO: 5).

221. The isolated antibody or antigen binding fragment thereof of any of claims 207-218, wherein said antibody binds to a latent GDF-8 growth factor prodomain complex (GPC).

222. A method of modulating growth factor activity in a biological system comprising contacting said biological system with the antibody or antigen binding fragment thereof of any of claims 1-206 or 207-221.

223. The method of claim 222, wherein said growth factor activity comprises GDF-8 activity.

224. The method of claim 222 or 223, wherein said antibody is a stabilizing antibody and wherein contacting said biological system with said stabilizing antibody results in inhibition of release of at least 5% of total GDF-8 mature growth factor in said biological system.

225. The method of claim 224, wherein said stabilizing antibody comprises at least one variable domain comprising a VH and VL pair selected from the group consisting of the VH of SEQ ID NO: 462 and the VL of SEQ ID NO: 1037, the VH of SEQ ID NO: 472 and the VL of SEQ ID NO: 1047, the VH of SEQ ID NO: 448 and the VL of SEQ ID NO: 1023, the VH of SEQ ID NO: 502 and the VL of SEQ ID NO: 1077, the VH of SEQ ID NO: 581 and the VL of SEQ ID NO: 1153, the VH of SEQ ID NO: 442 and the VL of SEQ ID NO: 1017, the VH of SEQ ID NO: 464 and the VL of SEQ ID NO: 1039, the VH of SEQ ID NO: 593 and the VL of SEQ ID NO: 1166, the VH of SEQ ID NO: 598 and the VL of SEQ ID NO: 1171, the VH of SEQ ID NO: 626 and the VL of SEQ ID NO: 1199 and the VH of SEQ ID NO: 645 and the VL of SEQ ID NO: 1218.

226. The method of claim 223, wherein said antibody is a releasing antibody and wherein contacting said biological system with said releasing antibody results in release of at least 5% of total GDF-8 mature growth factor in said biological system.

227. A method of treating a TGF- -related indication in a subject comprising contacting said subject with the antibody or antigen binding fragment thereof of any of claims 1-206 or 207-221.

228. The method of claim 227, wherein said TGF- -related indication comprises a muscle disorder and/or injury.

229. The method of claim 228, wherein said muscle disorder and/or injury comprises a muscle disorder selected from the group consisting of cachexia, inclusion body myositis (IBM) and sarcopenia.

230. The method of claim 227, wherein said TGF- -related indication comprises chronic obstructive pulmonary disease (COPD).

231. A recombinant antigen comprising a growth differentiation factor (GDF) prodomain fused to an Fc-fusion protein.

232. The recombinant antigen of claim 231, wherein said GDF is selected from the group consisting of GDF-8 and GDF-11.

233. The recombinant antigen of claim 231, wherein said Fc-fusion protein comprises the sequence
DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
K (SEQ ID NO: 222).

234. The recombinant antigen of claim 231, comprising a sequence selected from any of those presented in Table 12.

235. A recombinant antigen comprising a chimeric protein selected from any of those in Tables 20 and 21.

236. An isolated antibody or antigen binding fragment thereof that binds to a recombinant antigen of any of claims 231-235.

237. The isolated antibody or antigen binding fragment thereof of claim 236, wherein said recombinant antigen comprises latent GDF-11 growth factor prodomain complex (GPC).

238. A method of modulating growth factor activity in a biological system comprising contacting said biological system with the antibody or antigen binding fragment thereof of any of claims 1-206, 236 or 237.

239. The method of claim 238, wherein said growth factor activity comprises GDF-11 activity.

240. The method of claim 238 or 239, wherein said isolated antibody or antigen binding fragment thereof is a stabilizing antibody and wherein contacting said biological system with said stabilizing antibody results in inhibition of release of at least 5% of total GDF-11 mature growth factor in said biological system.

241. The method of claim 238, wherein said antibody is a releasing antibody and wherein contacting said biological system with said releasing antibody results in release of at least 5% of total GDF-11 mature growth factor in said biological system.

242. A method of treating a TGF- -related indication in a subject comprising contacting said subject with the antibody or antigen binding fragment thereof of any one of claims 1-206, 236 or 237.

243. The method of claim 242, wherein said TGF- -related indication comprises a cardiovascular indication selected from the group consisting of cardiac hypertrophy, cardiac atrophy, atherosclerosis and restenosis.

244. The method of claim 242, wherein said TGF-β-related indication comprises a GDF-11-related indication.

245. The method of claim 244, wherein said GDF-11-related indication comprises anemia and/or β-thalassemia.

246. A method of enhancing skeletal muscle rejuvenation, cerebral circulation, neurogenesis and/or erythropoiesis comprising administering to a subject the antibody or antigen binding fragment thereof of any one of claims 1-206, 236 or 237.

247. The antibody or antigen binding fragment thereof of any one of claims 1-206, 236 or 237, wherein said antibody is a monoclonal antibody.

248. The antibody or antigen binding fragment thereof of either of claims 236 or 237, wherein said antibody comprises an IgG isotype.

249. The antibody of claim 247 or 248, wherein said antibody comprises an IgG1 isotype.

250. The isolated antibody or antigen binding fragment thereof of any of claims 207-215, 236 or 237 comprising a bispecific antibody.

251. An assay comprising the use of one or more of the recombinant antigens of any of claims 231-235 and/or any of the antibody or antigen binding fragment thereof of any of claims 1-206, 207-221, 236, 237 or 246-249.

252. A method of developing an antibody comprising the use of the assay of claim 240.

253. A composition comprising the antibody or antigen binding fragment thereof of any of claims 1-206, 207-221, 236, 237 or 247-249 and an excipient.

254. A nucleic acid encoding the antibody or antigen binding fragment thereof of any of claims 1-206, 207-221, 236, 237 or 247-249.

255. A nucleic acid encoding the recombinant antigen of any of claims 231-235.

256. A vector comprising the nucleic acid of claims 254 or 255.

257. A cell comprising the nucleic acid of claims 254 or 255.

258. A kit comprising the composition of claim 256 and instructions for use thereof.

259. A method of developing an antibody comprising:

i. selecting a protein from the group consisting of any of those listed in Tables 4, 5, 9, 10, 20, 21, 24 and 25,
ii. subjecting said protein to structural analysis,
iii. identifying at least one epitope, and
iv. developing at least one antibody against said at least one epitope.

260. The method of claim 259, wherein said protein is subjected to prodomain convertase cleavage prior to structural analysis.

261. The method of claim 260, wherein the prodomain convertase cleaved protein is further subjected to cleavage with an enzyme selected from the group consisting of BMP-1, mammalian tolloid protein (mTLD), mammalian tolloid-like 1 (mTLL1) and mammalian tolloid-like 2 (mTLL2).

262. The method of any of claims 259-261, wherein said protein comprises proGDF-8 (SEQ ID NO: 5) or proGDF-11 (SEQ ID NO: 4).

263. A method of increasing muscle mass in a subject comprising contacting said subject with the antibody or antigen binding fragment thereof of any of claims 1-206 or 207-221.

264. The method of claim any one of claims 259-263, wherein said isolated antibody or antigen binding fragment thereof comprises at least one variable domain comprising a VH and VL pair selected from the group consisting of the VH of SEQ ID NO: 462 and the VL of SEQ ID NO: 1037, the VH of SEQ ID NO: 472 and the VL of SEQ ID NO: 1047, the VH of SEQ ID NO: 448 and the VL of SEQ ID NO: 1023, the VH of SEQ ID NO: 502 and the VL of SEQ ID NO: 1077, the VH of SEQ ID NO: 581 and the VL of SEQ ID NO: 1153, the VH of SEQ ID NO: 442 and the VL of SEQ ID NO: 1017, the VH of SEQ ID NO: 464 and the VL of SEQ ID NO: 1039, the VH of SEQ ID NO: 593 and the VL of SEQ ID NO: 1166, the VH of SEQ ID NO: 598 and the VL of SEQ ID NO: 1171, the VH of SEQ ID NO: 626 and

the VL of SEQ ID NO: 1199 and the VH of SEQ ID NO: 645 and the VL of SEQ ID NO: 1218.

265. An inhibitor of at least one BMP-1/Tolloid-like proteinase (B/TP), wherein said inhibitor comprises a polypeptide.

266. The inhibitor of claim 265, wherein said inhibitor prevents cleavage of a latent GPC.

267. The inhibitor of claim 266, wherein said latent GPC is selected from the group consisting of latent GDF-8 and latent GDF-11.

268. The inhibitor of claim 267, wherein said inhibitor prevents cleavage of a BMP/Tolloid cleavage site on said latent GPC.

269. The inhibitor of claim 268, wherein said B/TP is selected from the group consisting of BMP-1, mammalian tolloid protein (mTLD), mammalian tolloid-like 1 (mTLL1), and mammalian tolloid-like 2 (mTLL2).

270. The inhibitor of any one of claims 265-269, comprising an inhibiting antibody.

271. The inhibiting antibody of claim 270, comprising an anti-primed complex antibody.

272. An antibody that binds at or within 10 amino acid residues of a proprotein convertase cleavage site of proMyostatin or latent Myostatin.

273 The antibody of claim 272, wherein the proprotein convertase cleavage site comprises the amino acid sequence (SEQ ID NO: 1667 or 1668).

274. An antibody that binds at or within 10 amino acid residues of a proprotein convertase docking site of proMyostatin or latent Myostatin.

275. The antibody of claim 274, wherein the proprotein convertase docking site comprises the amino acid sequence (SEQ ID NO: 1667 or 1668).

276. An antibody that binds at or within 10 amino acid residues of a tolloid protease cleavage site of proMyostatin or latent Myostatin.

277 The antibody of claim 272, wherein the tolloid protease cleavage site comprises the amino acid sequence (SEQ ID NO: 1665 or 1666).

278. An antibody that binds at or within 10 amino acid residues of a tolloid protease docking site of proMyostatin or latent Myostatin.

279. The antibody of claim 274, wherein the tolloid protease docking site comprises the amino acid sequence (SEQ ID NO: 1665 or 1666).

280. The antibody of any one of claims 272-279, wherein the antibody is the antibody of any one of claims 1-206, 207-221, 236, 237, or 247-249.

281. The antibody of any one of claims 272-280, wherein binding of the antibody to the proMyostatin or the latent Myostatin inhibits proteolytic cleavage of the proMyostatin or the latent Myostatin by a proprotein convertase or a tolloid protease.

282. An antibody that competes for binding to an epitope with any one of the antibodies of claims 1-206, 207-221, 236, 237, or 247-249.

283. An antibody that binds to the same epitope as any one of the antibodies of claims 1-206, 207-221, 236, 237, or 247-249.

284. An antibody that competes for binding to an epitope of human proMyostatin or an epitope of human latent Myostatin with the antibody of any one of claims 1-206, 207-221, 236, 237, or 247-249.

285. The antibody of claim S3, wherein the antibody specifically binds to an epitope of human proMyostatin or human latent Myostatin at the same epitope as the antibody of any one of claims 1-206, 207-221, 236, 237, or 247-249.

286. The antibody of claims 282 or 283, wherein the antibody competes for binding to the epitope with an equilibrium dissociation constant (Kd) between the antibody and the epitope of less than 10^{-6} M.

287. The antibody of claim 286, wherein the Kd is in a range of 10^{-11} M to 10^{-6} M.

288. A composition comprising the antibody of any one of claims 1-206, 207-221, 236, 237, 247-249, or 282-287 and a carrier.

289. The composition of claim 288, wherein the composition is a pharmaceutical composition comprising (i) a therapeutically effective amount of the antibody of any one of claims 1-206, 207-221, 236, 237, 247-249, or 282-287, and (ii) a pharmaceutically acceptable carrier.

290. The composition of claim 288 or 289 for use in preventing muscle wasting or increasing muscle mass, comprising a therapeutically effective amount of the antibody of any one of claims 1-206, 207-221, 236, 238, 247-249, or 282-287.

291. The composition of any one of claims 288 to 290, wherein the carrier is a pharmaceutically acceptable carrier.

292. The composition of any one of claims 288 to 290, wherein the antibody and carrier are in a lyophilized form.

293. The composition of any one of claims 288 to 290, wherein the antibody and carrier are in solution.

294. The composition of any one of claims 288 to 290, wherein the antibody and carrier are frozen.

294. The composition of claim 294, wherein the antibody and carrier are frozen at a temperature less than or equal to -65°C.

296. The antibody of any one of claims 1-206, 207-221, 236, 237, 247-249, or 282-287, wherein the antibody is a sweeping antibody.

297. The antibody of any one of claims 1-206, 207-221, 236, 237, 247-249, or 282-285, wherein the antibody is a recycling antibody.

298. The antibody of claim 296 or 297, wherein the antibody comprises an Fc portion.

299. The antibody of any one of claims 296 to 298, wherein the antibody binds the neonatal Fc receptor FcRn.

300. The antibody of claim 298, wherein the Fc portion binds the neonatal Fc receptor FcRn.

301. The antibody of claim 299 or 300, wherein the antibody binds FcRn at a pH greater than 6.0.

302. The antibody of claim 301, wherein the antibody binds FcRn at a pH in a range from 7.0 to 7.5.

303. The antibody of claim 302, wherein the a Kd of binding of the antibody to the FcRN is in a range from10^{-3} M to 10^{-8} M.

304. The antibody of claim 302, wherein the a Kd of binding of the antibody to the FcRN is in a range from10^{-4} M to 10^{-8} M.

305. The antibody of claim 302, wherein the a Kd of binding of the antibody to the FcRN is in a range from10^{-5} M to 10^{-8} M.

306. The antibody of claim 302, wherein the a Kd of binding of the antibody to the FcRN is in a range from10^{-6} M to 10^{-8} M.

307. The antibody of any one of claims 296 to 306, wherein the antibody comprises a CDR-H3 amino acid sequence set forth in SEQ ID NO: 813, 804, 790, 762, 784, 770, 764, 986, 777, or 1006.

308. The antibody of any one of claims 296 to 307, wherein the antibody comprises a CDR-L3 amino acid sequence set forth in any one of SEQ ID NO: 1422, 1414, 1403, 1377, 1397, 1385, 1379, 1601, 1391, or 1621.

309. The antibody of any one of claims 296 to 308, wherein the antibody comprises a CDR-H1, a CDR-H2, and/or a CDR-H3 from the variable heavy chain (VH) amino acid sequence of clone BP2a-1, BP3a-2, BP5b-1, BP5b-4, BP6a-5, BP6a-6, BP11a-1, BP16b-4, BP18b-2 or BP22b-1 as set forth in Table 14, and/or a CDR-L1, a CDR-L2, and/or a CDR-L3 from the variable light chain (VL) amino acid sequence of clone BP2a-1, BP3a-2, BP5b-1, BP5b-4, BP6a-5, BP6a-6, BP11a-1, BP16b-4, BP18b-2 or BP22b-1 as set forth in Table 16.

310. The antibody of any one of claims 296 to 309, wherein the antibody comprises a variable heavy chain amino acid sequence of clone BP2a-1, BP3a-2, BP5b-1, BP5b-4, BP6a-5, BP6a-6, BP11a-1, BP16b-4, BP18b-2 or BP22b-1as set forth in Table 14.

311. The antibody of any one of claims 296 to 310, wherein the antibody comprises the variable light chain amino acid sequence of clone BP2a-1, BP3a-2, BP5b-1, BP5b-4, BP6a-5, BP6a-6, BP11a-1, BP16b-4, BP18b-2 or BP22b-1 as set forth in Table 16.

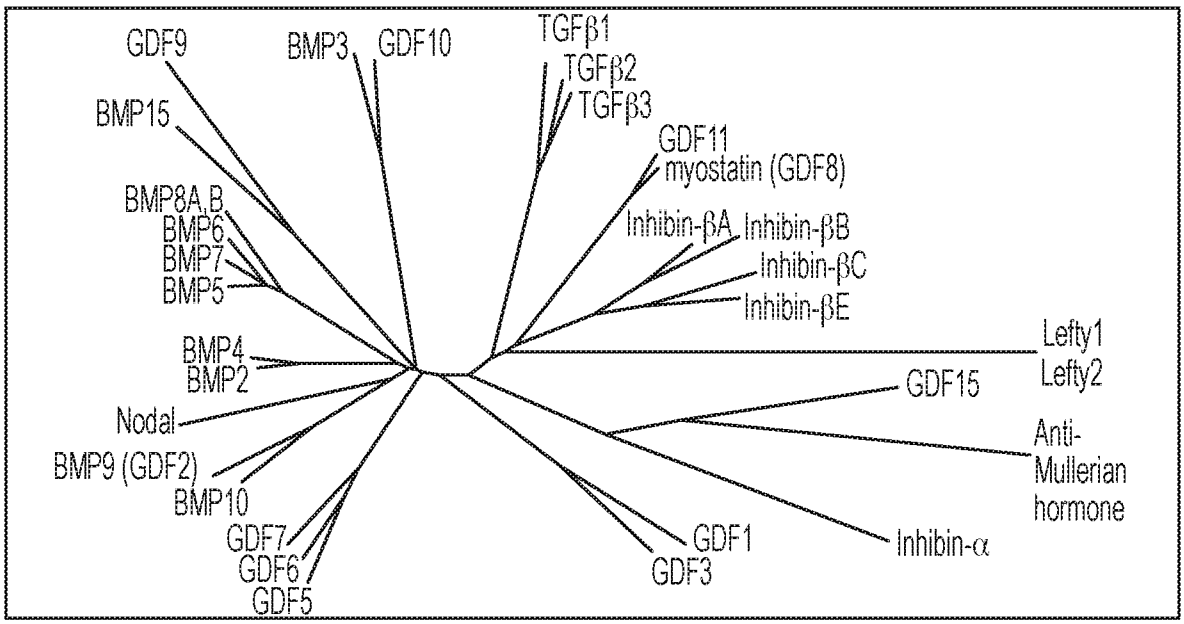

GDF9
BMP3
GDF10
TGFβ1
TGFβ2
TGFβ3
BMP15
GDF11
myostatin (GDF8)
BMP8A,B
BMP6
BMP7
BMP5
Inhibin-βA
Inhibin-βB
Inhibin-βC
Inhibin-βE
Lefty1
Lefty2
BMP4
BMP2
GDF15
Nodal
Anti-
Mullerian
hormone
BMP9 (GDF2)
BMP10
GDF7
GDF6
GDF5
GDF1
GDF3
Inhibin-α

FIG. 1

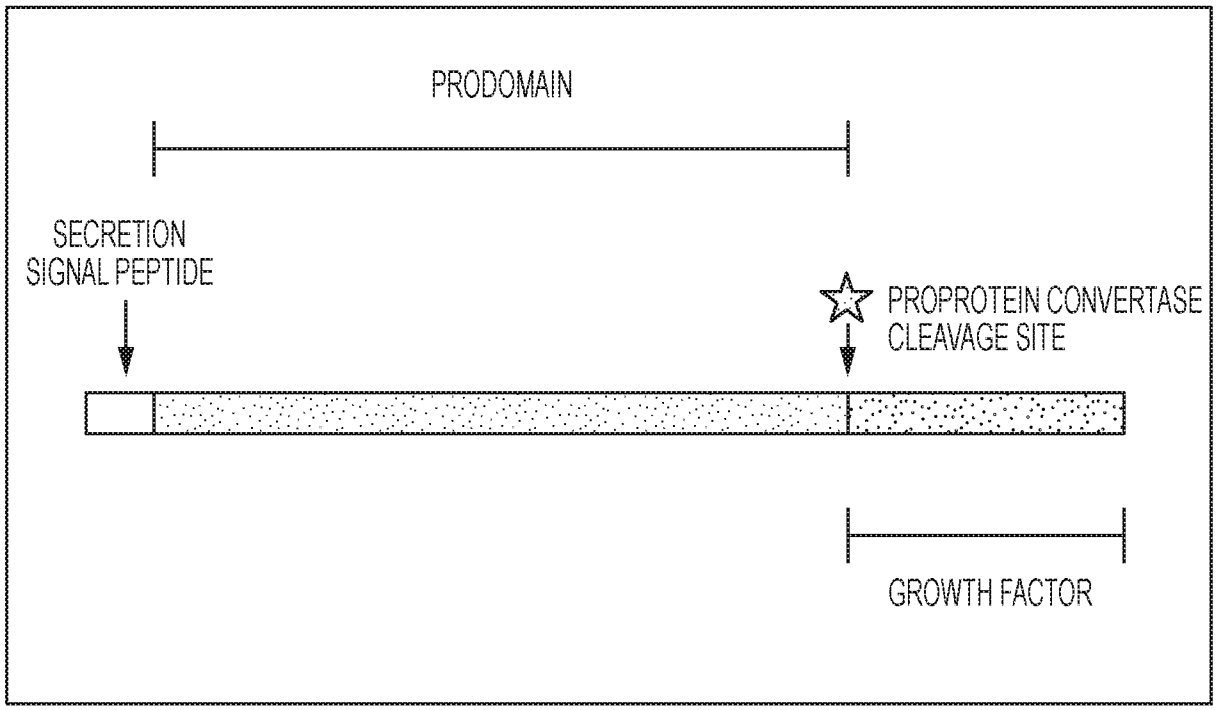

PRODOMAIN
SECRETION
SIGNAL PEPTIDE
PROPROTEIN CONVERTASE
CLEAVAGE SITE
GROWTH FACTOR

FIG. 2

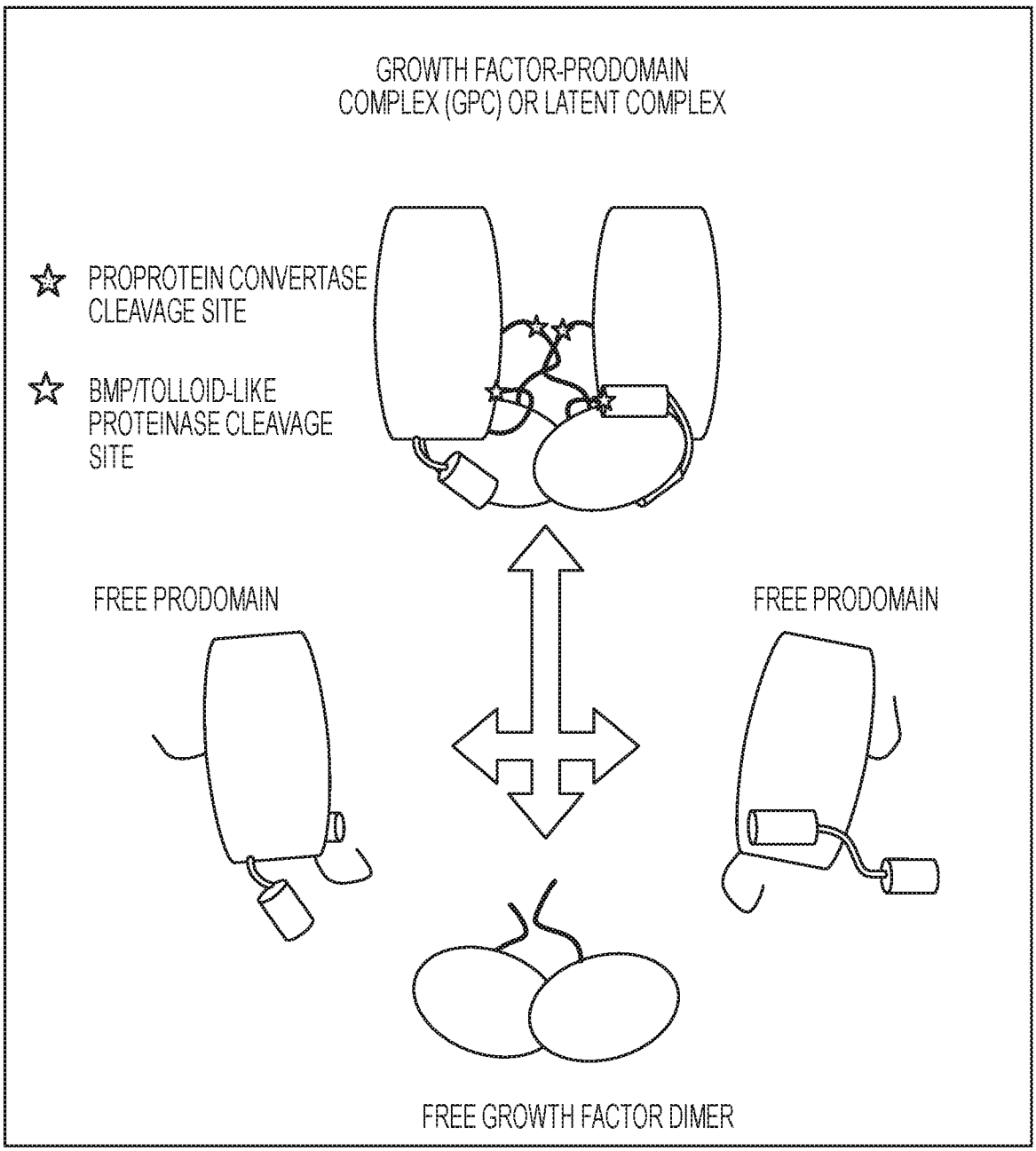

GROWTH FACTOR-PRODOMAIN
COMPLEX (GPC) OR LATENT COMPLEX
PROPROTEIN CONVERTASE
CLEAVAGE SITE
BMP/TOLLOID-LIKE
PROTEINASE CLEAVAGE
SITE
FREE PRODOMAIN
FREE PRODOMAIN
FREE GROWTH FACTOR DIMER

FIG. 3

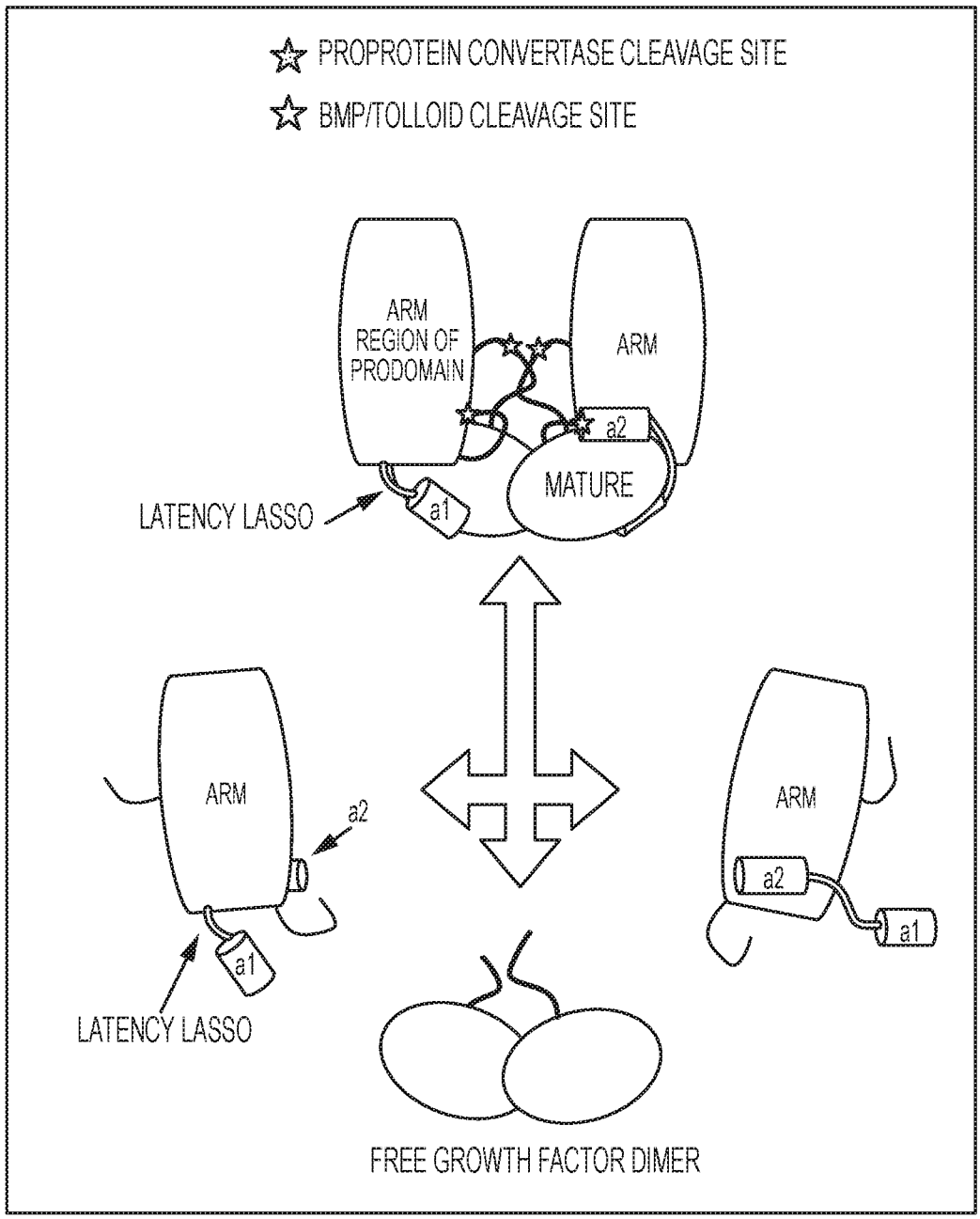

PROPROTEIN CONVERTASE CLEAVAGE SITE
BMP/TOLLOID CLEAVAGE SITE
ARM REGION OF PRODOMAIN
ARM
a2
MATURE
LATENCY LASSO
a1
ARM
a2
a1
LATENCY LASSO
ARM
a2
a1
FREE GROWTH FACTOR DIMER

FIG. 4

	TGFB1hu	TGFB1po	TGFB2	TGFB3	GDF11	GDF8	InhBetaA	InhAlphaA	BMP9	BMP2	BMP4	BMP7	BMP6	BMP8	LEFTY1
TGFB1hu	100	94	42	46	19	22	16	14	14	19	18	18	16	17	15
TGFB1po	94	100	42	46	20	22	15	14	14	19	19	18	15	17	15
TGFB2	42	42	100	55	18	20	13	12	13	21	19	18	15	16	15
TGFB3	46	46	55	100	19	21	14	13	14	19	18	20	17	19	14
GDF11	19	20	18	19	100	61	21	15	15	18	18	17	18	16	13
GDF8	22	22	20	21	61	100	24	14	16	20	18	18	17	19	12
InhBetaA	16	15	13	14	21	24	100	12	15	18	18	17	15	19	9
InhAlphaA	14	14	12	13	15	14	12	100	14	11	12	13	10	13	13
BMP9	14	14	13	14	15	16	15	14	100	24	25	21	20	21	11
BMP2	19	19	21	19	18	20	18	11	24	100	59	26	23	25	15
BMP4	18	19	19	18	18	18	18	12	25	59	100	25	24	26	14
BMP7	18	18	18	20	17	18	17	13	21	26	25	100	54	50	12
BMP6	16	15	15	17	18	17	15	10	20	23	24	54	100	42	11
BMP8	17	17	16	19	16	19	19	13	21	25	26	50	42	100	12
LEFTY1	15	15	15	14	13	12	9	13	11	15	14	12	11	12	100

FIG. 5A

	TGFB1hu	TGFB1po	TGFB2	TGFB3	GDF11	GDF8	InhBetaA	InhAlphaA	BMP9	BMP2	BMP4	BMP7	BMP6	BMP8	LEFTY1
TGFB1hu	100	100	83	86	48	47	44	34	36	43	44	44	46	41	32
TGFB1po	100	100	83	86	48	47	44	34	36	43	44	44	46	41	32
TGFB2	83	83	100	89	50	49	47	37	37	47	47	48	49	46	30
TGFB3	86	86	89	100	50	49	46	36	36	47	46	46	50	44	30
GDF11	48	48	50	50	100	94	52	37	45	47	44	50	50	45	29
GDF8	47	47	49	49	94	100	51	34	44	47	44	49	50	45	27
InhBetaA	44	44	47	46	52	51	100	40	47	53	52	55	56	52	27
InhAlphaA	34	34	37	36	37	34	40	100	40	41	39	42	42	39	26
BMP9	36	36	37	36	45	44	47	40	100	60	56	56	59	57	28
BMP2	43	43	47	47	47	47	53	41	60	100	88	69	71	68	30
BMP4	44	44	47	46	44	44	52	39	56	88	100	66	66	67	29
BMP7	44	44	48	46	50	49	55	42	56	69	66	100	90	78	29
BMP6	46	46	49	50	50	50	56	42	59	71	66	90	100	81	30
BMP8	41	41	46	44	45	45	52	39	57	68	67	78	81	100	31
LEFTY1	32	32	30	30	29	27	27	26	28	30	29	29	30	31	100

FIG. 5B

	TGFB1hu	TGFB1po	TGFB2	TGFB3	GDF11	GDF8	InhBetaA	InhAlphaA	BMP9	BMP2	BMP4	BMP7	BMP6	BMP8	LEFTY1
TGFB1hu	100	92	30	34	14	17	10	10	9	14	14	13	11	13	13
TGFB1po	92	100	31	35	15	17	10	11	10	14	14	13	10	13	13
TGFB2	30	31	100	46	13	16	7	8	8	17	14	13	10	11	14
TGFB3	34	35	46	100	13	16	9	9	9	15	14	15	11	14	11
GDF11	14	15	13	13	100	50	16	12	9	12	13	11	12	10	13
GDF8	17	17	16	16	50	100	19	11	10	13	13	11	10	13	11
InhBetaA	10	10	7	9	16	19	100	9	9	10	11	9	8	13	8
InhAlphaA	10	11	8	9	12	11	9	100	11	8	9	10	7	11	11
BMP9	9	10	8	9	9	10	9	11	100	16	17	13	12	13	10
BMP2	14	14	17	15	12	13	10	8	16	100	49	17	14	16	14
BMP4	14	14	14	14	13	13	11	9	17	49	100	17	16	17	13
BMP7	13	13	13	15	11	11	9	10	13	17	17	100	46	43	11
BMP6	11	10	10	11	12	10	8	7	12	14	16	46	100	34	8
BMP8	13	13	11	14	10	13	13	11	13	16	17	43	34	100	9
LEFTY1	13	13	14	11	13	11	8	11	10	14	13	11	8	9	100

FIG. 5C

```
                                                                  α1 HELIX
                  1         10        20        30        40        50
TGFB1hu     1     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~LSTCKTIDMEL  11
TGFB1cyno   1     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~LSTCKTIDMEL  11
TGFB1mu     1     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~LSTCKTIDMEL  11
TGFB1po     1     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~LSTCKTIDMEL  11
TGFB2       1     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~SLSTCSTLDMDQ  12
TGFB3       1     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~SLSLSTCTTLDFGH  14
GDF11       1     ~~~~~AEGPAAAAAAAAAAAAAGVGGERSSRPAPSVAPEPDG~CPVCVWRQH  46
GDF11mu     1     ~~~~~AEGP~~AAAAAAAAAAAGVGGERSSRPAPSAPPEPDG~CPVCVWRQH  44
GDF8        1     ~~~~~~~~~~~~~~~~~~~~~~~~~~NENSEQKENV~~EKEGLCNACTWRQN  24
GDF8cyno    1     ~~~~~~~~~~~~~~~~~~~~~~~~~~NENSEQKENV~~EKEGLCNACTWRQN  24
GDF8mu      1     ~~~~~~~~~~~~~~~~~~~~~~~~~~NEGSEREENV~~EKEGLCNACAWRQN  24
InhBetaA    1     ~~~~~~~~~~~~~~~~~~~~~SPTPGSEGHSAAPDC~~PSCALAALPKDVPN  29
InhAlphaA   1     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~CQGLEL  6
BMP9        1     ~~~~~~~~~~~~~~~~~~~KPLQSWGRGSAGGNAHS~~PLGVPGGGLPEHTF  31
BMP2        1     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~LVPELGR~~RKFAAASSGRPSSQ  21
BMP4        1     ~~~~~~~~~~~~~~~~~~~~GASHASLIPETGKKKV~~AEIQGHAGGRRSGQ  30
BMP7        1     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~DF~~SLDNEVHSSFIHRR  16
BMP6        1     CCGPPPLRPPLPAAAAAAAAGGQLLGDGGSPGRTEQP~~PPSPQSSSGFLYRR  50
BMP8        1     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~GG~~GPGLRPPPGCPQRR  16
LEFTY1            ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

                                           LATENCY LASSO
                        60        70        80        90        100
TGFB1hu     12    VKRKRIEAIRGQILSKLRLASPPSQGEV~~~~~~~~~~~~~~~~~~~~~PP~  41
TGFB1cyno   12    VKRKRIEAIRGQILSKLRLASPPSQGEV~~~~~~~~~~~~~~~~~~~~~PP~  41
TGFB1mu     12    VKRKRIEAIRGQILSKLRLASPPSQGEV~~~~~~~~~~~~~~~~~~~~~PP~  41
TGFB1po     12    VKRKRIEAIRGQILSKLRLASPPSQGDV~~~~~~~~~~~~~~~~~~~~~PP~  41
TGFB2       13    FMRKRIEAIRGQILSKLKLTSPPEDY~~~~~~~~~~~~~~~~~~~~~~~PE~  40
TGFB3       15    IKKKRVEAIRGQILSKLRLTSPPE~~~~~~~~~~~~~~~~~~~~~~~~~PT~  40
GDF11       47    SRELRLESIKSQILSKLRLKEAPNISREVVKQLL~~~~~~~~~~~~~~~PK~  82
GDF11mu     45    SRELRLESIKSQILSKLRLKEAPNISREVVKQLL~~~~~~~~~~~~~~~PK~  80
GDF8        25    TKSSRIEAIKIQILSKLRLETAPNISKDVIRQLL~~~~~~~~~~~~~~~PK~  60
GDF8cyno    25    TKSSRIEAIKIQILSKLRLETAPNISKDAIRQLL~~~~~~~~~~~~~~~PK~  60
GDF8mu      25    TRYSRIEAIKIQILSKLRLETAPNISKDAIRQLL~~~~~~~~~~~~~~~PR~  60
InhBetaA    30    SQPEMVEAVKKHILNMLHLKKRP~~~~DV~TQPV~~~~~~~~~~~~~~~PK~  60
InhAlphaA   7     ARELVLAKVRALFLDAL~~~GPPAVTREGGD~~~~~~~~~~~~~~~~~~PG~  36
BMP9        32    NLKMFLENVKVDFLRSLNLSGVPSQDKTRVEP~~~~~~~~~~~~~~~~~PQ~  65
BMP2        22    PSDEVLSEFELRLLSMFGLKQRPT~~~~~~~~~~~~~~~~~~~~~~~~~PS~  47
BMP4        31    ~SHELLRDFEATLLQMFGLRRRPQ~~~~~~~~~~~~~~~~~~~~~~~~~PS~  55
BMP7        17    LRSQERREMQREILSILGLPHRPR~~~~~~~~~~~~~~~~~~~~~~~~~PH~  42
BMP6        51    LKTQEKREMQKEILSVLGLPHRPRPLHGLQQPQPPALRQQEEQQQQQQLPRG 102
BMP8        17    LGARERRDVQREILAVLGLPGRPR~~~~~~~~~~~~~~~~~~~~~~~~~PRA  43
LEFTY1      1     ---LTGEQLLGSLLRQLQKEVPTLDRADMEELVI~~~~~~~~~~~~~~~PT~  34
```

FIG. 6A

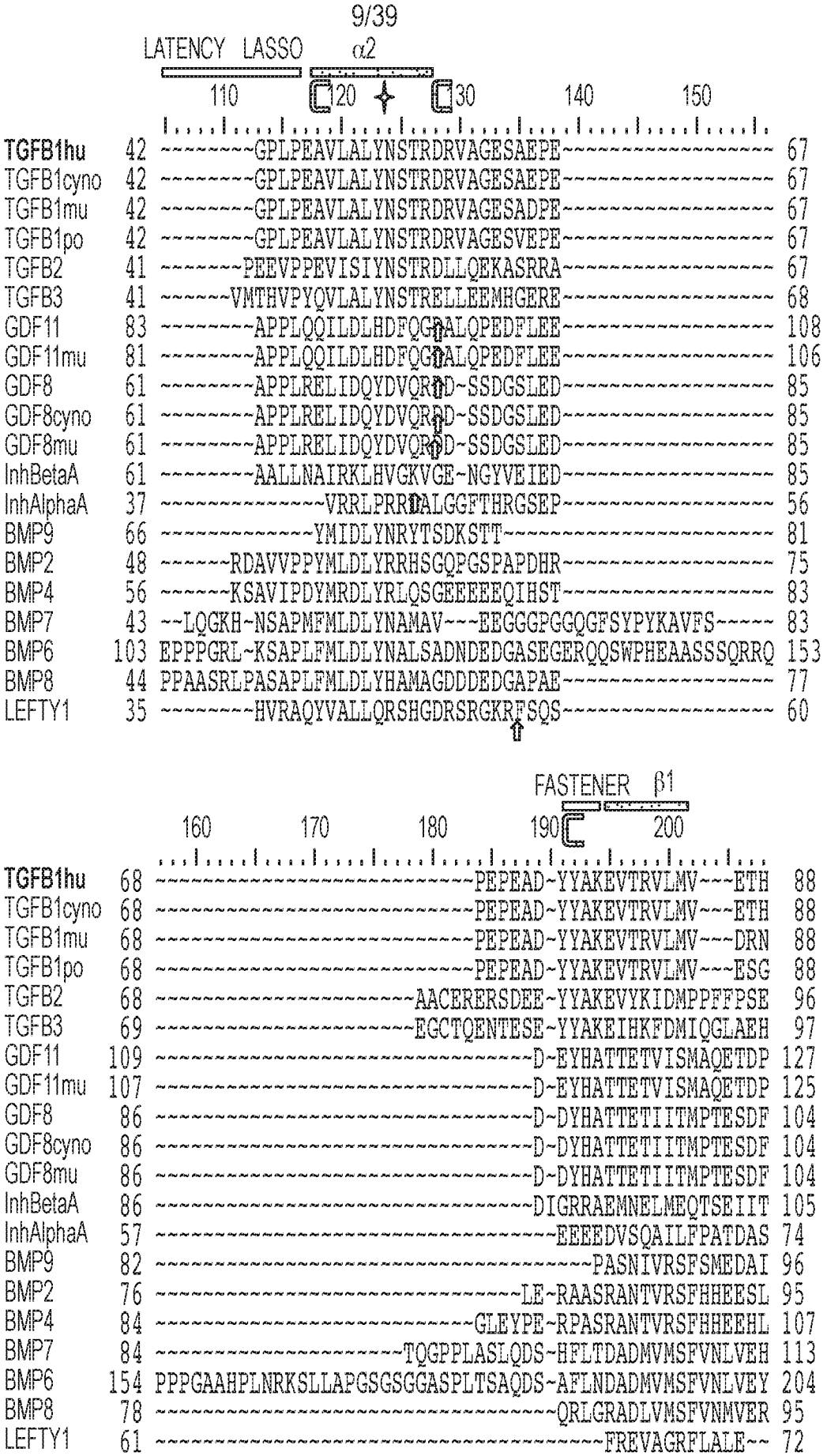

LATENCY LASSO
α2
110
120
130
140
150
TGFB1hu 42 ~~~~~~~~GPLPEAVLALYNSTRDRVAGESAEPE~~~~~~~~~~~~~~~~~~ 67
TGFB1cyno 42 ~~~~~~~~GPLPEAVLALYNSTRDRVAGESAEPE~~~~~~~~~~~~~~~~~~ 67
TGFB1mu 42 ~~~~~~~~GPLPEAVLALYNSTRDRVAGESADPE~~~~~~~~~~~~~~~~~~ 67
TGFB1po 42 ~~~~~~~~GPLPEAVLALYNSTRDRVAGESVEPE~~~~~~~~~~~~~~~~~~ 67
TGFB2 41 ~~~~~~~~PEEVPPEVISIYNSTRDLLQEKASRRA~~~~~~~~~~~~~~~~~~ 67
TGFB3 41 ~~~~~~VMTHVPYQVLALYNSTRELLEEMHGERE~~~~~~~~~~~~~~~~~~ 68
GDF11 83 ~~~~~~~~APPLQQILDLHDFQGDALQPEDFLEE~~~~~~~~~~~~~~~~~~ 108
GDF11mu 81 ~~~~~~~~APPLQQILDLHDFQGDALQPEDFLEE~~~~~~~~~~~~~~~~~~ 106
GDF8 61 ~~~~~~~~APPLRELIDQYDVQRDD~SSDGSLED~~~~~~~~~~~~~~~~~~ 85
GDF8cyno 61 ~~~~~~~~APPLRELIDQYDVQRDD~SSDGSLED~~~~~~~~~~~~~~~~~~ 85
GDF8mu 61 ~~~~~~~~APPLRELIDQYDVQRDD~SSDGSLED~~~~~~~~~~~~~~~~~~ 85
InhBetaA 61 ~~~~~~~~AALLNAIRKLHVGKVGE~NGYVEIED~~~~~~~~~~~~~~~~~~ 85
InhAlphaA 37 ~~~~~~~~~~~~~~~VRRLPRRDALGGFTHRGSEP~~~~~~~~~~~~~~~~~~ 56
BMP9 66 ~~~~~~~~~~~~~~YMIDLYNRYTSDKSTT~~~~~~~~~~~~~~~~~~~~~~~~ 81
BMP2 48 ~~~~~~RDAVVPPYMLDLYRRHSGQPGSPAPDHR~~~~~~~~~~~~~~~~~~ 75
BMP4 56 ~~~~~~KSAVIPDYMRDLYRLQSGEEEEEQIHST~~~~~~~~~~~~~~~~~~ 83
BMP7 43 ~~LQGKH~NSAPMFMLDLYNAMAV~~~EEGGGPGGQGFSYPYKAVFS~~~~~ 83
BMP6 103 EPPPGRL~KSAPLFMLDLYNALSADNDEDGASEGERQQSWPHEAASSSQRRQ 153
BMP8 44 PPAASRLPASAPLFMLDLYHAMAGDDDEDGAPAE~~~~~~~~~~~~~~~~~~ 77
LEFTY1 35 ~~~~~~~~HVRAQYVALLQRSHGDRSRGKRFSQS~~~~~~~~~~~~~~~~~~ 60
FASTENER β1
160
170
180
190
200
TGFB1hu 68 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~PEPEAD~YYAKEVTRVLMV~~~ETH 88
TGFB1cyno 68 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~PEPEAD~YYAKEVTRVLMV~~~ETH 88
TGFB1mu 68 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~PEPEAD~YYAKEVTRVLMV~~~DRN 88
TGFB1po 68 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~PEPEAD~YYAKEVTRVLMV~~~ESG 88
TGFB2 68 ~~~~~~~~~~~~~~~~~~~~~~~~AACERERSDEE~YYAKEVYKIDMPPFFPSE 96
TGFB3 69 ~~~~~~~~~~~~~~~~~~~~~~~~EGCTQENTESE~YYAKEIHKFDMIQGLAEH 97
GDF11 109 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~D~EYHATTETVISMAQETDP 127
GDF11mu 107 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~D~EYHATTETVISMAQETDP 125
GDF8 86 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~D~DYHATTETIITMPTESDF 104
GDF8cyno 86 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~D~DYHATTETIITMPTESDF 104
GDF8mu 86 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~D~DYHATTETIITMPTESDF 104
InhBetaA 86 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~DIGRRAEMNELMEQTSEIIT 105
InhAlphaA 57 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~EEEEDVSQAILFPATDAS 74
BMP9 82 ~~~~~~PASNIVRSFSMEDAI 96
BMP2 76 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~LE~RAASRANTVRSFHHEESL 95
BMP4 84 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~GLEYPE~RPASRANTVRSFHHEEHL 107
BMP7 84 ~~~~~~~~~~~~~~~~~~~~~~TQGPPLASLQDS~HFLTDADMVMSFVNLVEH 113
BMP6 154 PPPGAAHPLNRKSLLAPGSGSGGASPLTSAQDS~AFLNDADMVMSFVNLVEY 204
BMP8 78 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~QRLGRADLVMSFVNMVER 95
LEFTY1 61 ~~~~~~FREVAGRFLALE~~ 72

FIG. 6B

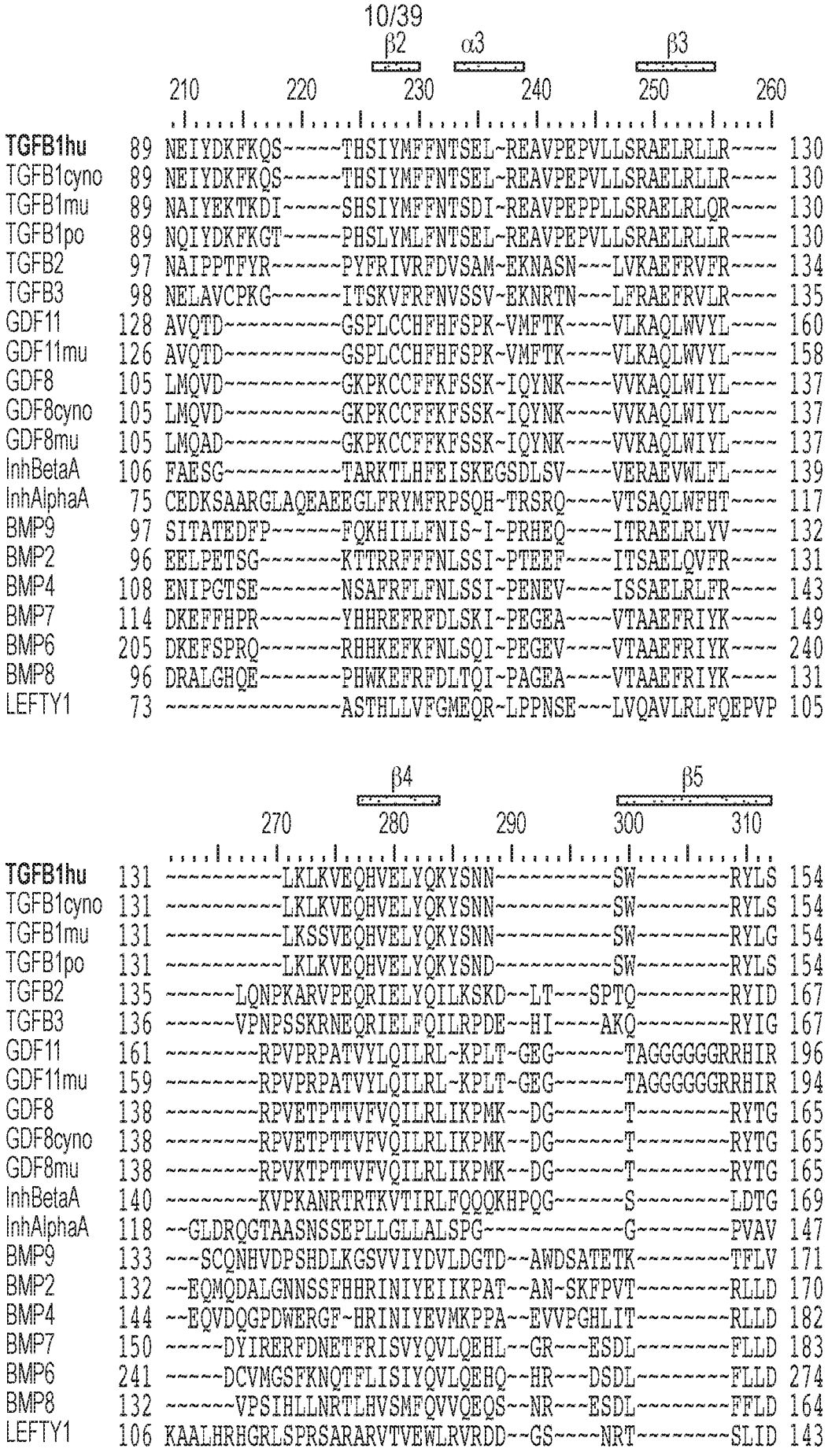


FIG. 6B
CONTINUED

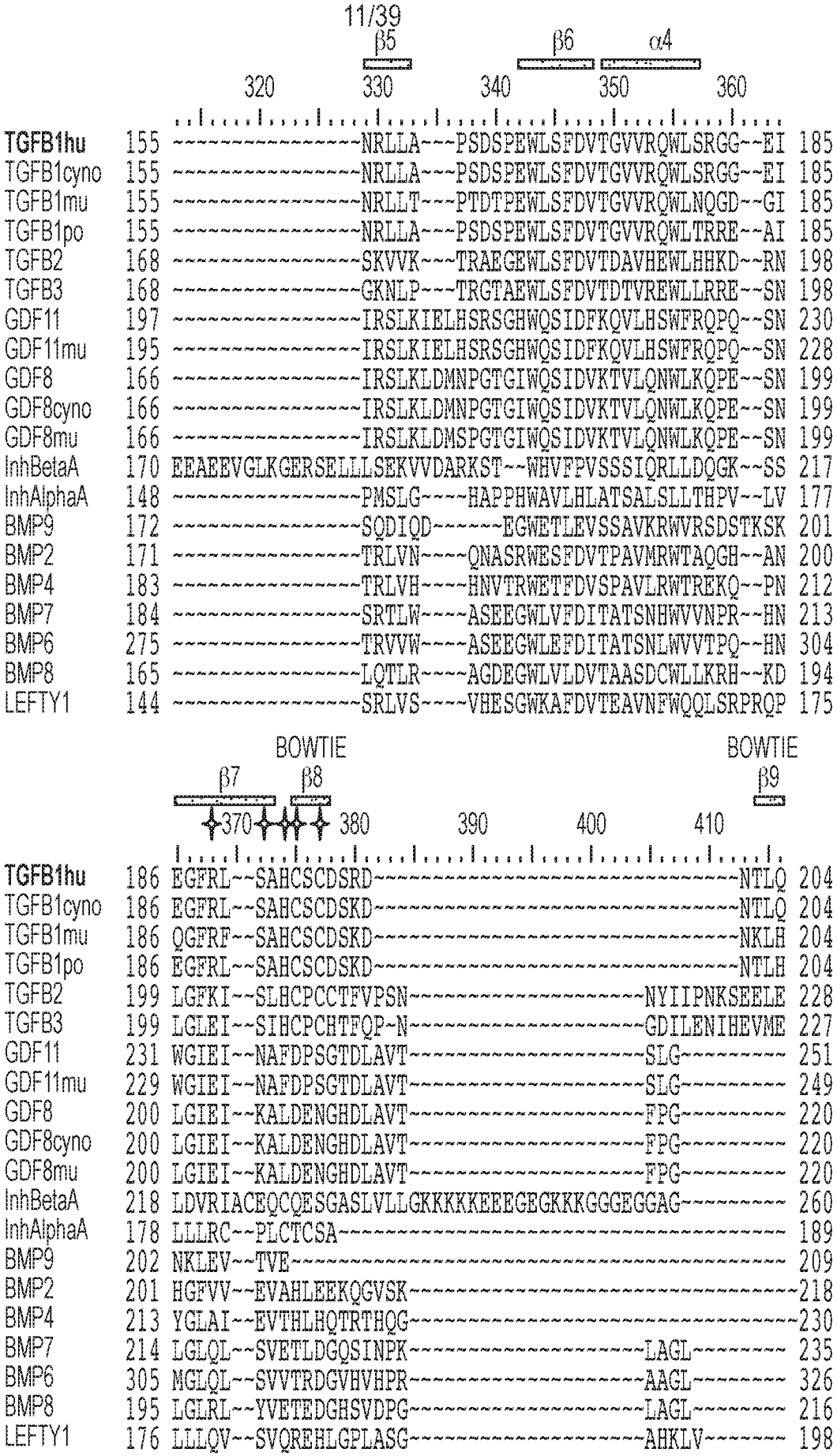


FIG. 6B
CONTINUED

```
            BOWTIE
            β9        TRIGGER LOOP                β10      α5
              420       430       440       450       460

TGFB1hu    205 VDINGFT~~~~~~~~~TGRRGDLATIHG~~~MNRPF~~LLLMATPLERAQH~ 241
TGFB1cyno  205 VDINGFT~~~~~~~~~TGRRGDLATIHG~~~MNRPF~~LLLMATPLERAQH~ 241
TGFB1mu    205 VEINGIS~~~~~~~~~PKRRGDLGTIHD~~~MNRPF~~LLLMATPLERAQH~ 241
TGFB1po    205 VEINGFN~~~~~~~~~SGRRGDLATIHG~~~MNRPF~~LLLMATPLERAQH~ 241
TGFB2      229 ARFAGIDGTSTYTSGDQKTIKSTRKKNS~~~GKTPH~~LLLMLLPSYRLESQ 275
TGFB3      228 IKFKGVDNED~~~DHGRGDLGRLKKQKD~~~HHNPH~~LILMMIPPHRLDNP 271
GDF11      252 ~~~~~~~~~~~~~~~~~~~~~~~~PGAE~~~GLHPF~~MELRVLE~~~~~~~ 267
GDF11mu    250 ~~~~~~~~~~~~~~~~~~~~~~~~PGAE~~~GLHPF~~MELRVLE~~~~~~~ 265
GDF8       221 ~~~~~~~~~~~~~~~~~~~~~~~~PGED~~~GLNPF~~LEVKVTD~~~~~~~ 236
GDF8cyno   221 ~~~~~~~~~~~~~~~~~~~~~~~~PGED~~~GLNPF~~LEVKVTD~~~~~~~ 236
GDF8mu     221 ~~~~~~~~~~~~~~~~~~~~~~~~PGED~~~GLNPF~~LEVKVTD~~~~~~~ 236
InhBetaA   261 ~~~~~~~~~~~~~~~~~~~~~~~~ADEEKEQSHRPFLMLQARQSE~~~~~~~ 281
InhAlphaA  190 ~~~~~~~~~~~~~~~~~~~~~~~~~~RP~~~EATPF~~LVAHTRTRPP~~~~ 206
BMP9       210 ~~~~~~~~~~~SHRKGCDTLDISVPPGS~~~RNLPF~~FVVFSNDH~~~~~~ 239
BMP2       219 ~~~~~~~~~~~RHVRISRSLHQDEHSWS~~~QIRPL~~LVTFGHDGKG~~~~ 250
BMP4       231 ~~~~~~~~~~~QHVRISRSLPQGSGNWA~~~QLRPL~~LVTFGHDGRG~~~~ 262
BMP7       236 ~~~~~~~~~~~~~~~~~~~~~IGRHGPQ~~~NKQPF~~MVAFFKATEVHFRS 261
BMP6       327 ~~~~~~~~~~~~~~~~~~~~~VGRDGPY~~~DKQPF~~MVAFFKVSEVHVRT 352
BMP8       217 ~~~~~~~~~~~~~~~~~~~~~LGQRAPR~~~SQQPF~~VVTFFRASPSPIRT 242
LEFTY1     199 ~~~~~~~~~~~~~~~~~~RFASQGAPAG~~~LGEPQ~~LELHTLDLGDYGAQ 227

                 470       480       490       500       510       520

TGFB1hu    242 ~~~LQSSRHRR~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~ 249
TGFB1cyno  242 ~~~LQSSRHRR~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~ 249
TGFB1mu    242 ~~~LHSSRHRR~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~ 249
TGFB1po    242 ~~~LHSSRHRR~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~ 249
TGFB2      276 ~~~QTNRRKKR~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~ 283
TGFB3      272 ~~GQGGQRKKR~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~ 280
GDF11      268 ~~~~NTKRSRR~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~ 274
GDF11mu    266 ~~~~NTKRSRR~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~ 272
GDF8       237 ~~~~TPKRSRR~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~ 243
GDF8cyno   237 ~~~~TPKRSRR~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~ 243
GDF8mu     237 ~~~~TPKRSRR~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~ 243
InhBetaA   282 ~~~~DHPHRRRRR~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~ 290
InhAlphaA  207 ~~~SGGERARR~~~~~~~~~~~~~~~~~~~~~~~~~~~~STPLMSWPWSPSA 227
BMP9       240 ~~~SSGTKETRLELREMISHEQESVLKKLSKDGSTEAGESSHEEDTDGHVAA 288
BMP2       251 ~~~HPL~~HKREKR~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~ 259
BMP4       263 ~~~HALTRRRRAKR~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~ 273
BMP7       262 IR~STGSKQRSQNRSK~~~~~~~~~~~~~~~~~~~~~~~~~~~TPKNQEALR 285
BMP6       353 TR~SASSRRRQQSRNR~~~~~~~~~~~~~~~~~~~~~~~~~~~STQSQDVAR 376
BMP8       243 PR~AVRPLRRRQP~KK~~~~~~~~~~~~~~~~~~~~~~~~~~~SNELPQANR 265
LEFTY1     228 GD~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~ 229
```

FIG. 6B
CONTINUED

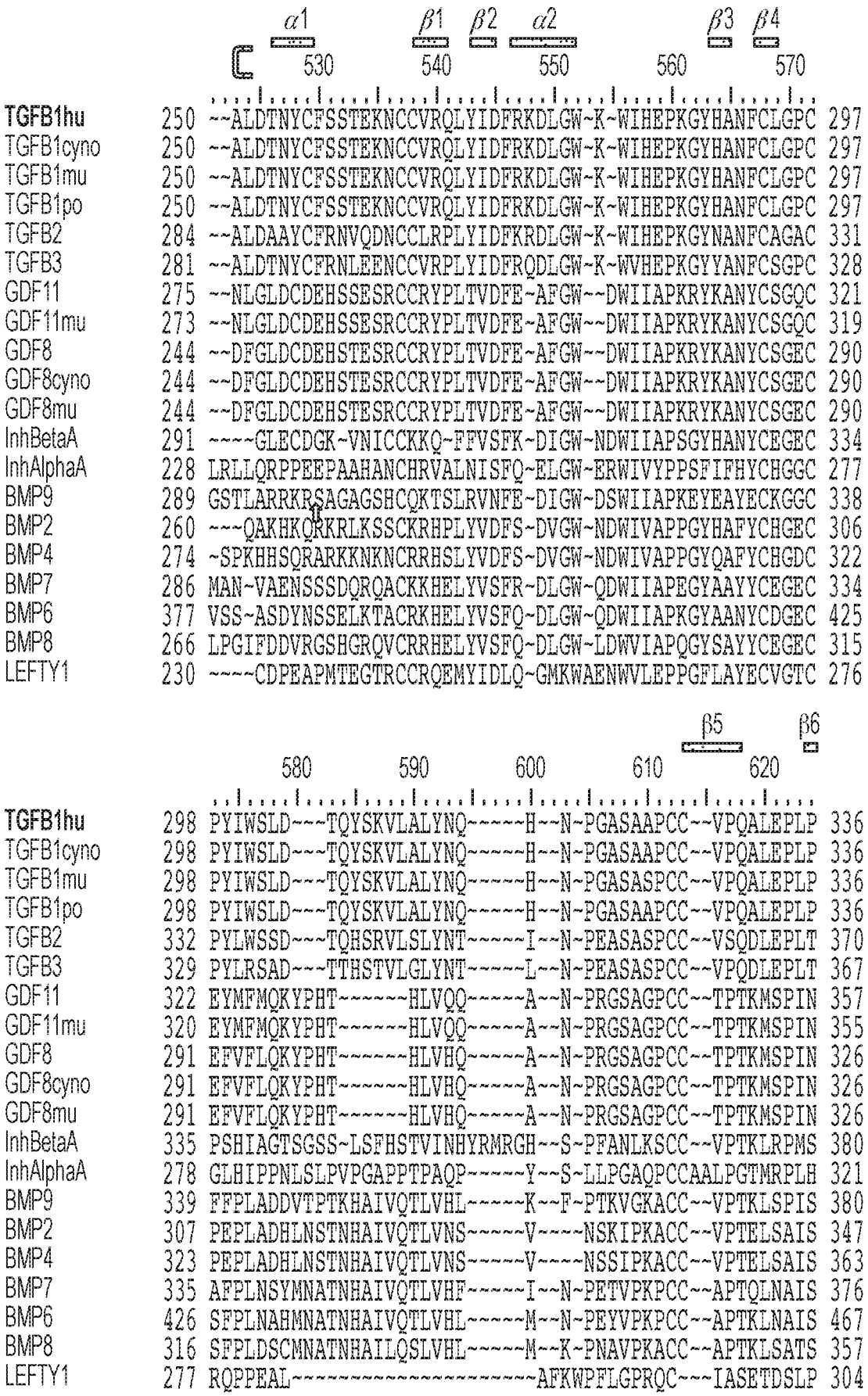


FIG. 6B
CONTINUED

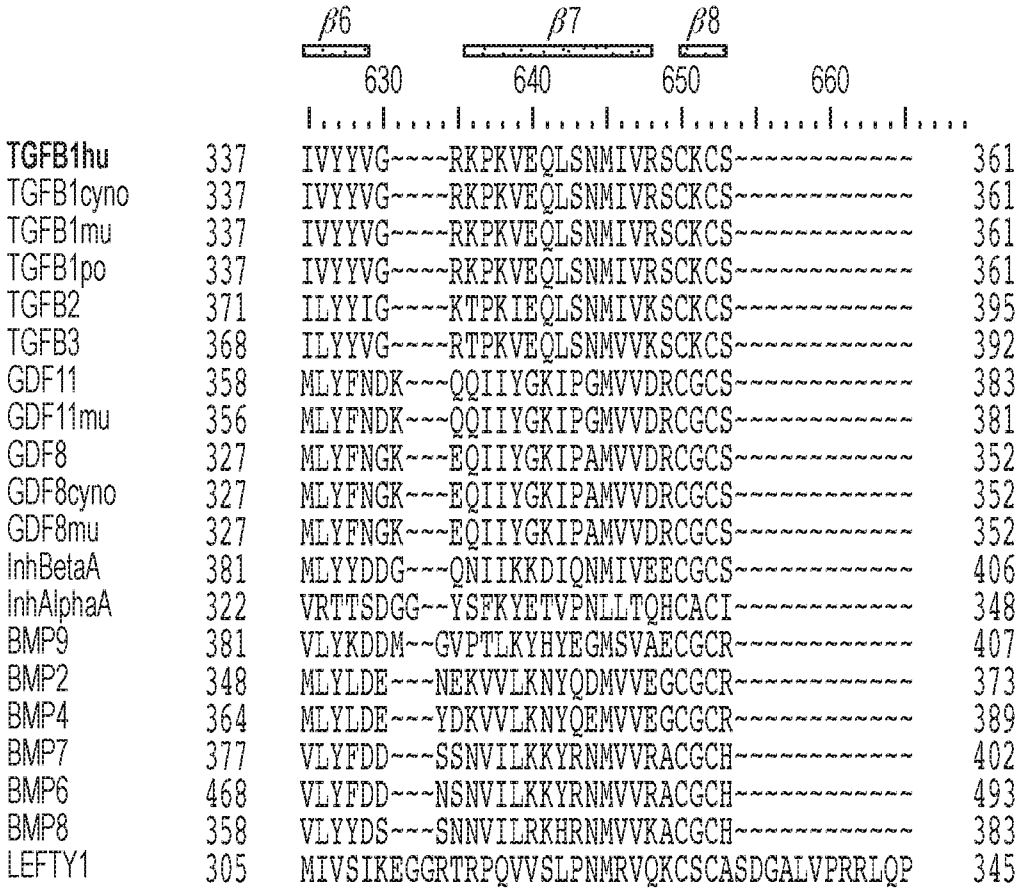

β6
β7
β8
630
640
650
660
TGFB1hu 337 IVYYVG----RKPKVEQLSNMIVRSCKCS---------- 361
TGFB1cyno 337 IVYYVG----RKPKVEQLSNMIVRSCKCS---------- 361
TGFB1mu 337 IVYYVG----RKPKVEQLSNMIVRSCKCS---------- 361
TGFB1po 337 IVYYVG----RKPKVEQLSNMIVRSCKCS---------- 361
TGFB2 371 ILYYIG----KTPKIEQLSNMIVKSCKCS---------- 395
TGFB3 368 ILYYVG----RTPKVEQLSNMVVKSCKCS---------- 392
GDF11 358 MLYFNDK---QQIIYGKIPGMVVDRCGCS---------- 383
GDF11mu 356 MLYFNDK---QQIIYGKIPGMVVDRCGCS---------- 381
GDF8 327 MLYFNGK---EQIIYGKIPAMVVDRCGCS---------- 352
GDF8cyno 327 MLYFNGK---EQIIYGKIPAMVVDRCGCS---------- 352
GDF8mu 327 MLYFNGK---EQIIYGKIPAMVVDRCGCS---------- 352
InhBetaA 381 MLYYDDG---QNIIKKDIQNMIVEECGCS---------- 406
InhAlphaA 322 VRTTSDGG--YSFKYETVPNLLTQHCACI---------- 348
BMP9 381 VLYKDDM--GVPTLKYHYEGMSVAECGCR---------- 407
BMP2 348 MLYLDE---NEKVVLKNYQDMVVEGCGCR---------- 373
BMP4 364 MLYLDE---YDKVVLKNYQEMVVEGCGCR---------- 389
BMP7 377 VLYFDD---SSNVILKKYRNMVVRACGCH---------- 402
BMP6 468 VLYFDD---NSNVILKKYRNMVVRACGCH---------- 493
BMP8 358 VLYYDS---SNNVILRKHRNMVVKACGCH---------- 383
LEFTY1 305 MIVSIKEGGRTRPQVVSLPNMRVQKCSCASDGALVPRRLQP 345

FIG. 6C

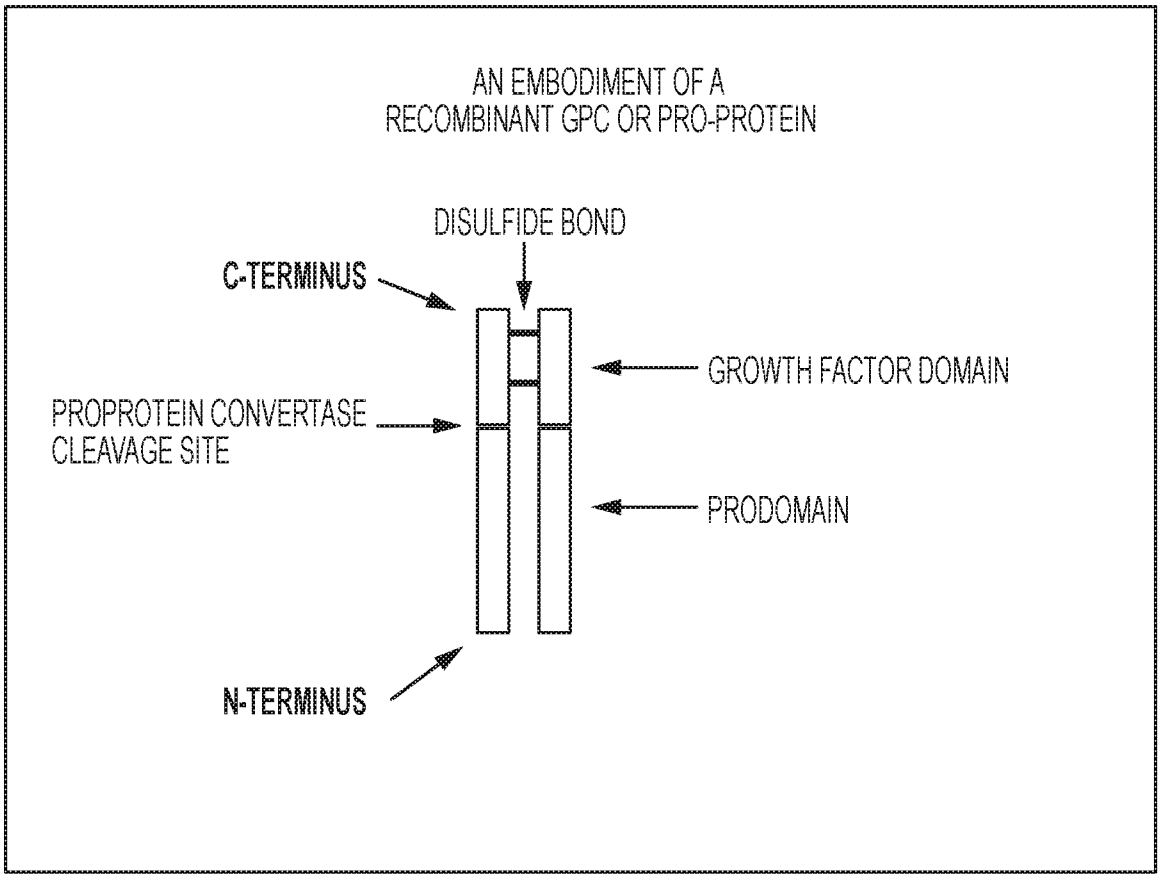

AN EMBODIMENT OF A
RECOMBINANT GPC OR PRO-PROTEIN
DISULFIDE BOND
C-TERMINUS
GROWTH FACTOR DOMAIN
PROPROTEIN CONVERTASE
CLEAVAGE SITE
PRODOMAIN
N-TERMINUS

FIG. 7

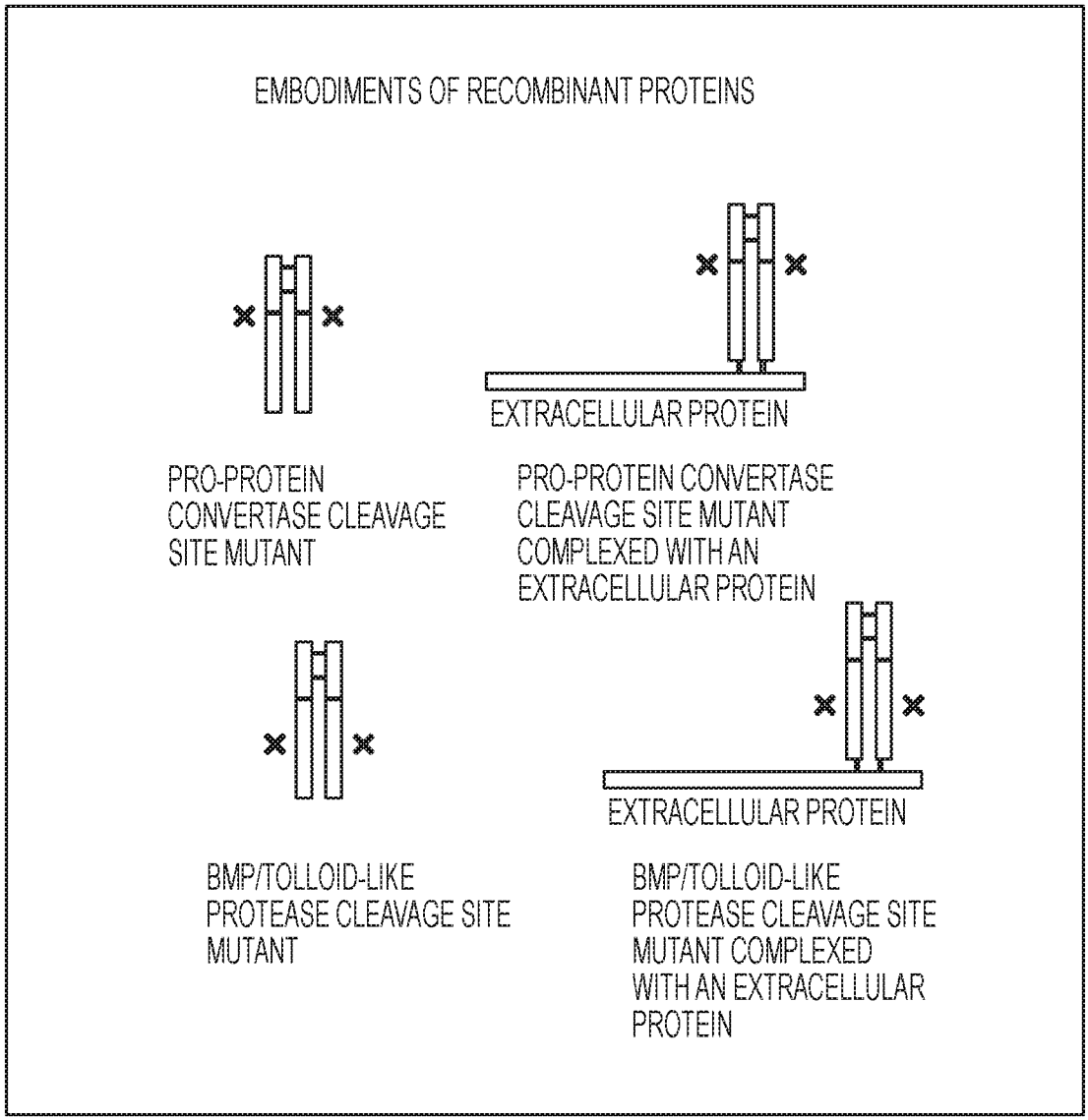

EMBODIMENTS OF RECOMBINANT PROTEINS
EXTRACELLULAR PROTEIN
PRO-PROTEIN CONVERTASE CLEAVAGE SITE MUTANT
PRO-PROTEIN CONVERTASE CLEAVAGE SITE MUTANT COMPLEXED WITH AN EXTRACELLULAR PROTEIN
EXTRACELLULAR PROTEIN
BMP/TOLLOID-LIKE PROTEASE CLEAVAGE SITE MUTANT
BMP/TOLLOID-LIKE PROTEASE CLEAVAGE SITE MUTANT COMPLEXED WITH AN EXTRACELLULAR PROTEIN

FIG. 8

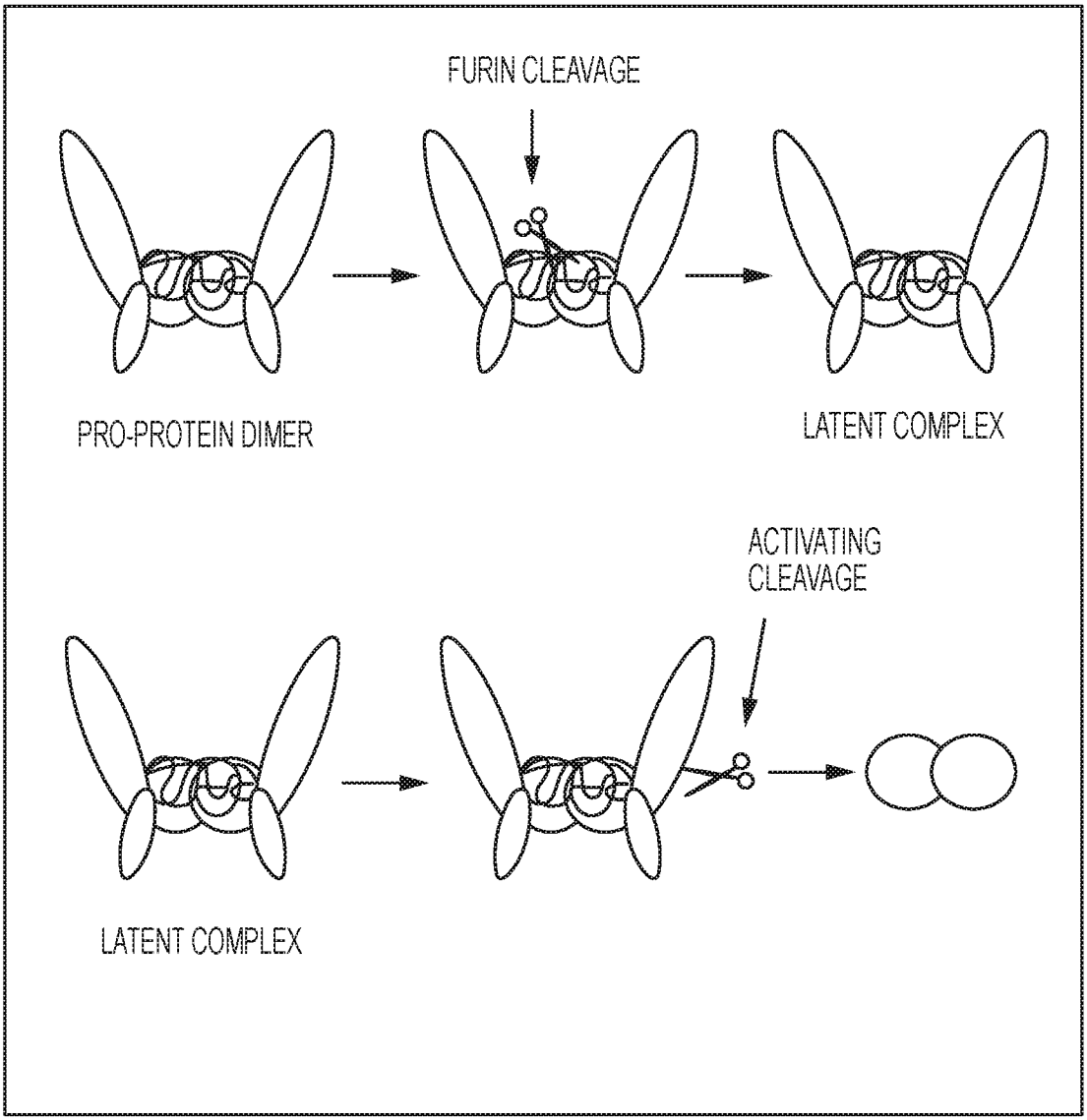

FURIN CLEAVAGE
PRO-PROTEIN DIMER
LATENT COMPLEX
ACTIVATING
CLEAVAGE
LATENT COMPLEX

FIG. 9

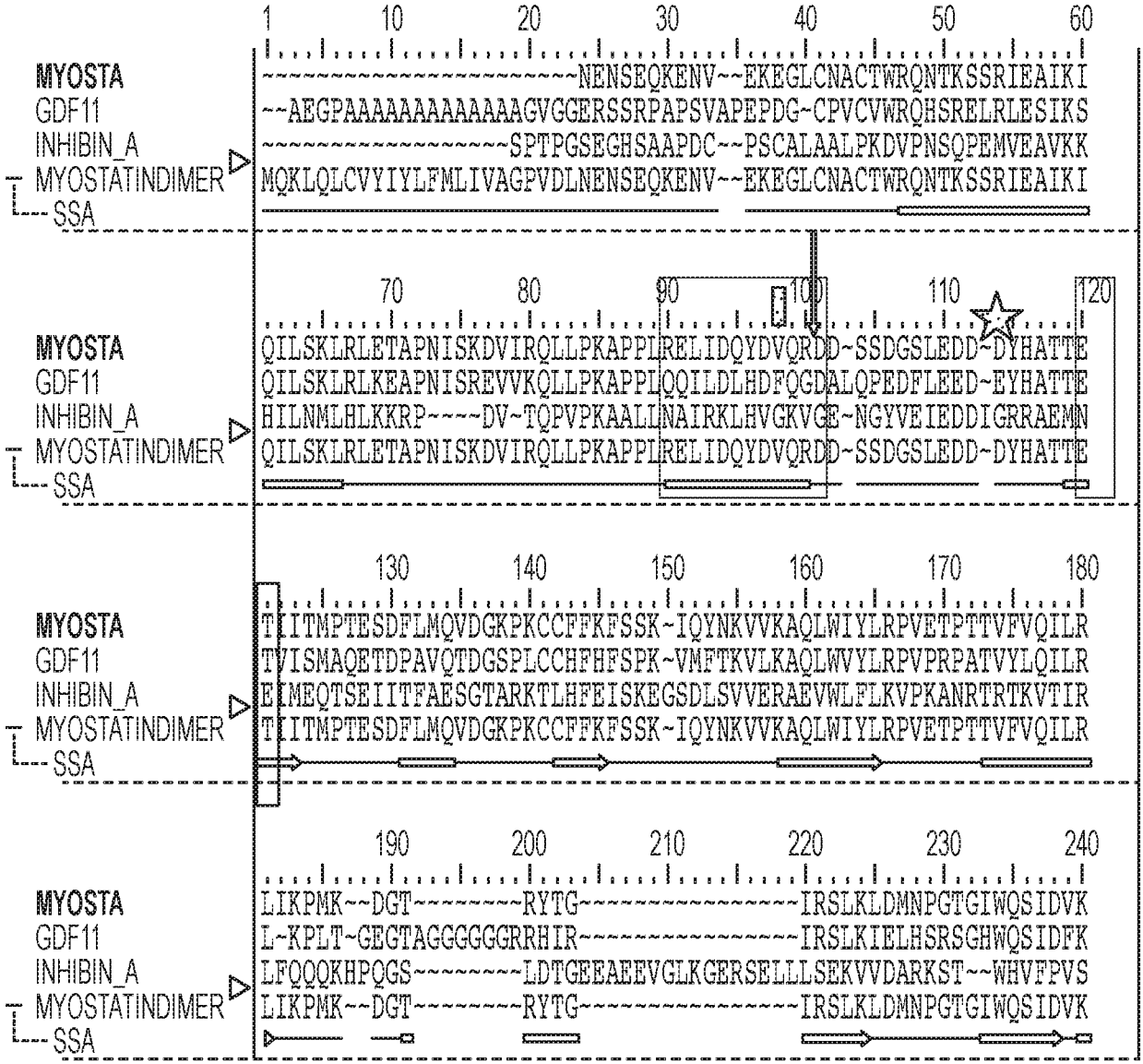

1 10 20 30 40 50 60
MYOSTA ~~~~~~~~~~~~~~~~~~~~~~~~NENSEQKENV~~EKEGLCNACTWRQNTKSSRIEAIKI
GDF11 ~~AEGPAAAAAAAAAAAAAGVGGERSSRPAPSVAPEPDG~CPVCVWRQHSRELRLESIKS
INHIBIN_A ~~~~~~~~~~~~~~~~~~~SPTPGSEGHSAAPDC~~PSCALAALPKDVPNSQPEMVEAVKK
MYOSTATINDIMER MQKLQLCVYIYLFMLIVAGPVDLNENSEQKENV~~EKEGLCNACTWRQNTKSSRIEAIKI
SSA
70 80 90 100 110 120
MYOSTA QILSKLRLETAPNISKDVIRQLLPKAPPLRELIDQYDVQRDD~SSDGSLEDD~DYHATTE
GDF11 QILSKLRLKEAPNISREVVKQLLPKAPPLQQILDLHDFQGDALQPEDFLEED~EYHATTE
INHIBIN_A HILNMLHLKKRP~~~~DV~TQPVPKAALLNAIRKLHVGKVGE~NGYVEIEDDIGRRAEMN
MYOSTATINDIMER QILSKLRLETAPNISKDVIRQLLPKAPPLRELIDQYDVQRDD~SSDGSLEDD~DYHATTE
SSA
130 140 150 160 170 180
MYOSTA TIITMPTESDFLMQVDGKPKCCFFKFSSK~IQYNKVVKAQLWIYLRPVETPTTVFVQILR
GDF11 TVISMAQETDPAVQTDGSPLCCHFHFSPK~VMFTKVLKAQLWVYLRPVPRPATVYLQILR
INHIBIN_A EIMEQTSEIITFAESGTARKTLHFEISKEGSDLSVVERAEVWLFLKVPKANRTRTKVTIR
MYOSTATINDIMER TIITMPTESDFLMQVDGKPKCCFFKFSSK~IQYNKVVKAQLWIYLRPVETPTTVFVQILR
SSA
190 200 210 220 230 240
MYOSTA LIKPMK~~DGT~~~~~~~~RYTG~~~~~~~~~~~~~~~~IRSLKLDMNPGTGIWQSIDVK
GDF11 L~KPLT~GEGTAGGGGGGRRHIR~~~~~~~~~~~~~~~~IRSLKIELHSRSGHWQSIDFK
INHIBIN_A LFQQQKHPQGS~~~~~~~~LDTGEEAEEVGLKGERSELLLSEKVVDARKST~~WHVFPVS
MYOSTATINDIMER LIKPMK~~DGT~~~~~~~~RYTG~~~~~~~~~~~~~~~~IRSLKLDMNPGTGIWQSIDVK
SSA

FIG. 10

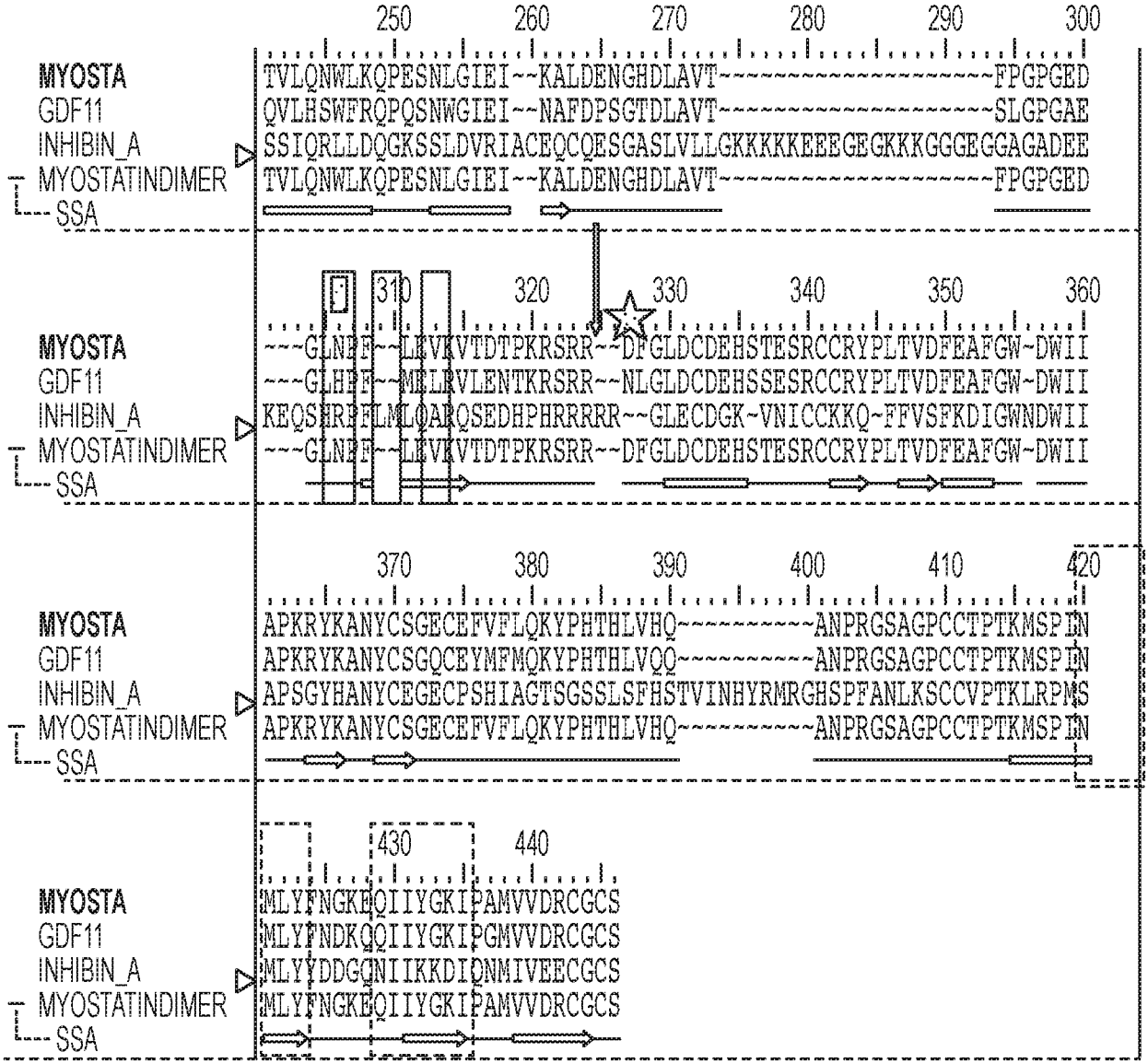


FIG. 10
CONTINUED

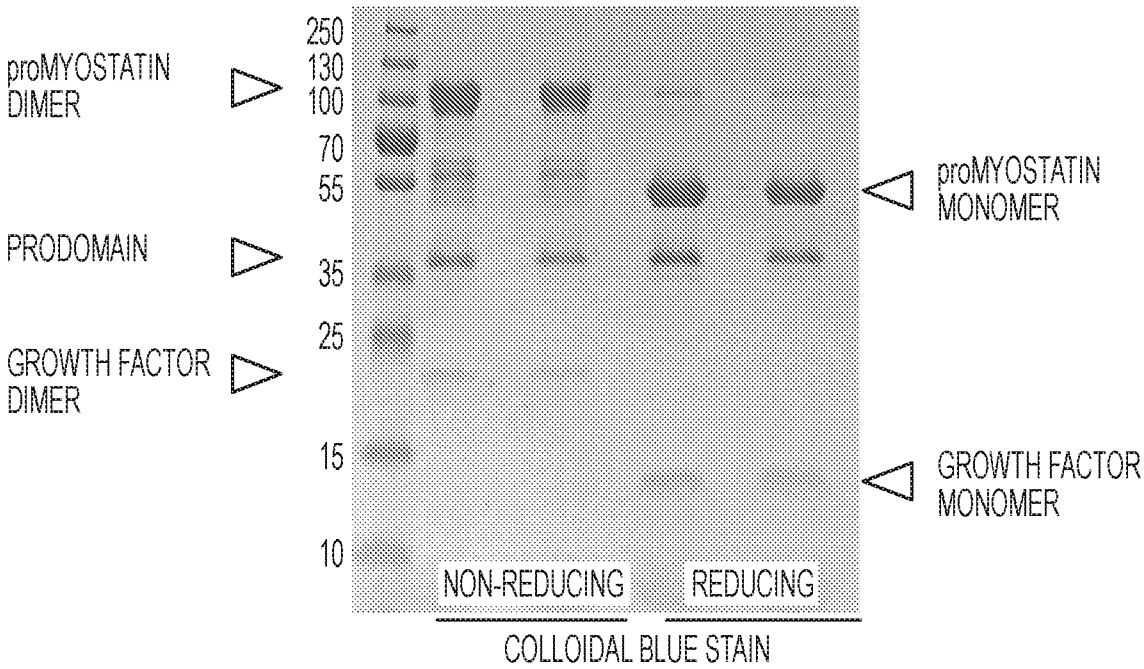

proMYOSTATIN DIMER
PRODOMAIN
GROWTH FACTOR DIMER
250
130
100
70
55
35
25
15
10
proMYOSTATIN MONOMER
GROWTH FACTOR MONOMER
NON-REDUCING
REDUCING
COLLOIDAL BLUE STAIN

FIG. 11

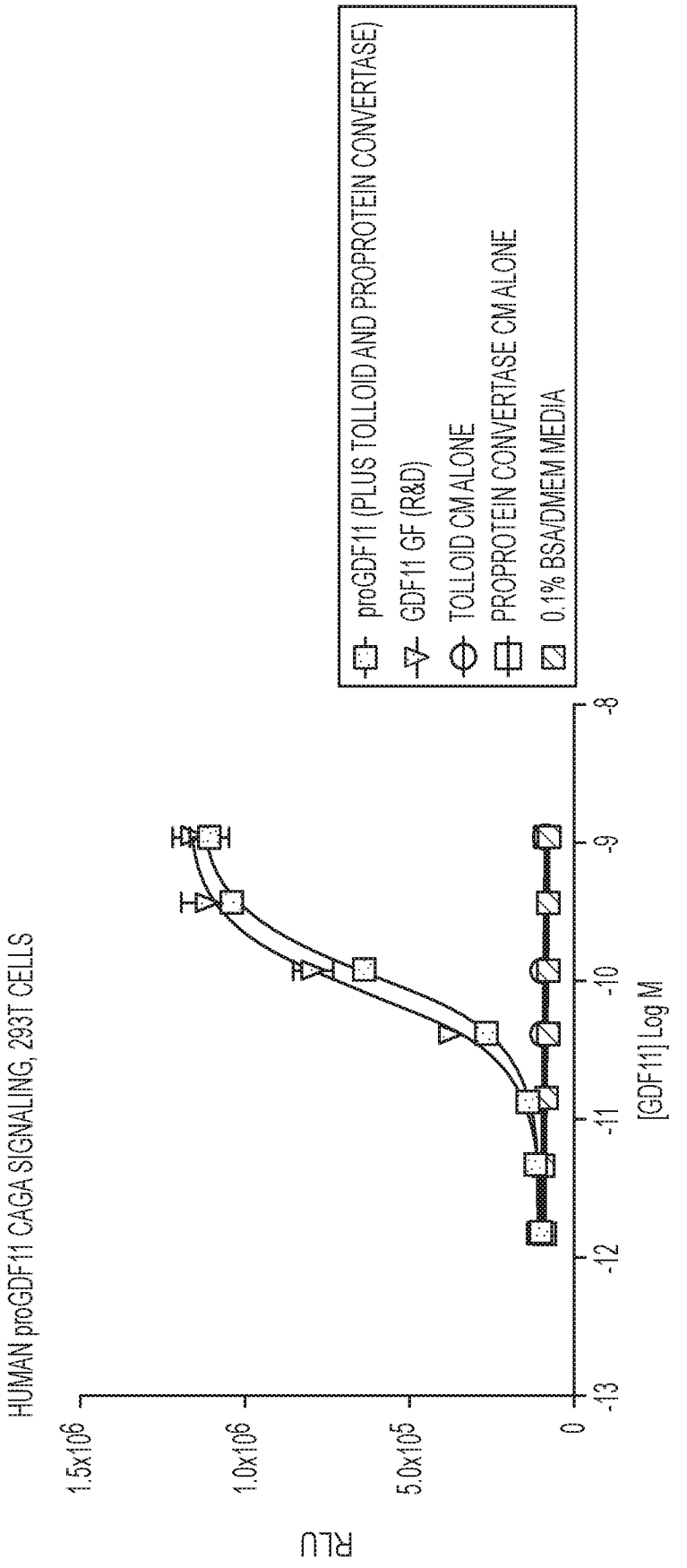

HUMAN proGDF11 CAGA SIGNALING, 293T CELLS
RLU
1.5x10^6
1.0x10^6
5.0x10^5
0
-13
-12
-11
-10
-9
-8
[GDF11] Log M
proGDF11 (PLUS TOLLOID AND PROPROTEIN CONVERTASE)
GDF11 GF (R&D)
TOLLOID CM ALONE
PROPROTEIN CONVERTASE CM ALONE
0.1% BSA/DMEM MEDIA

FIG. 12

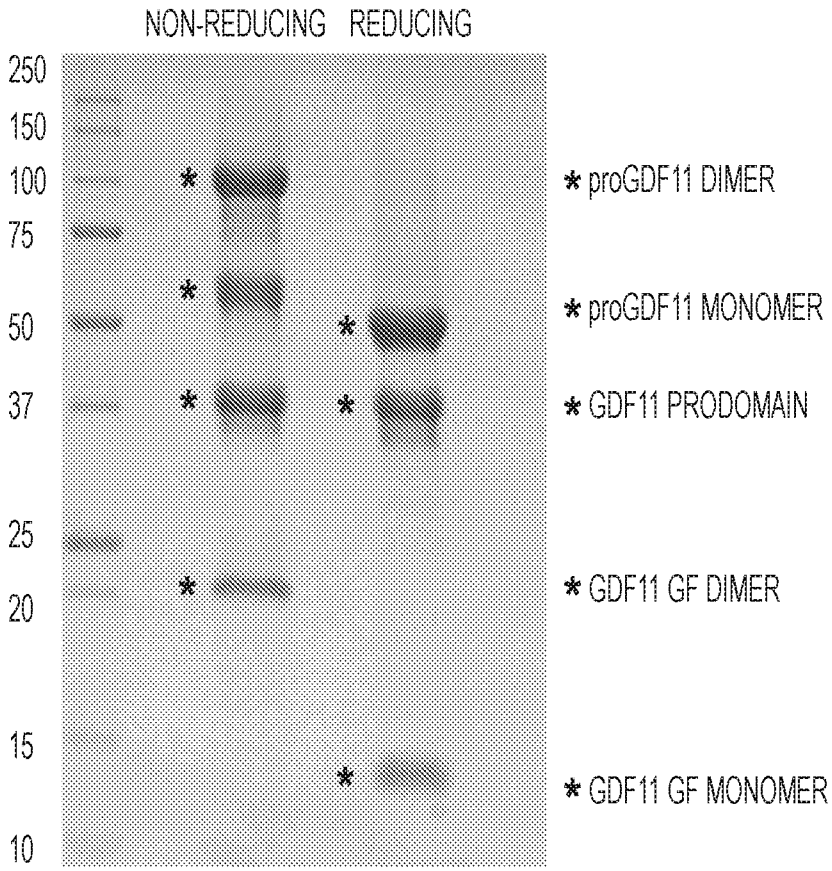

NON-REDUCING
REDUCING
250
150
100
75
50
37
25
20
15
10
* proGDF11 DIMER
* proGDF11 MONOMER
* GDF11 PRODOMAIN
* GDF11 GF DIMER
* GDF11 GF MONOMER

FIG. 13

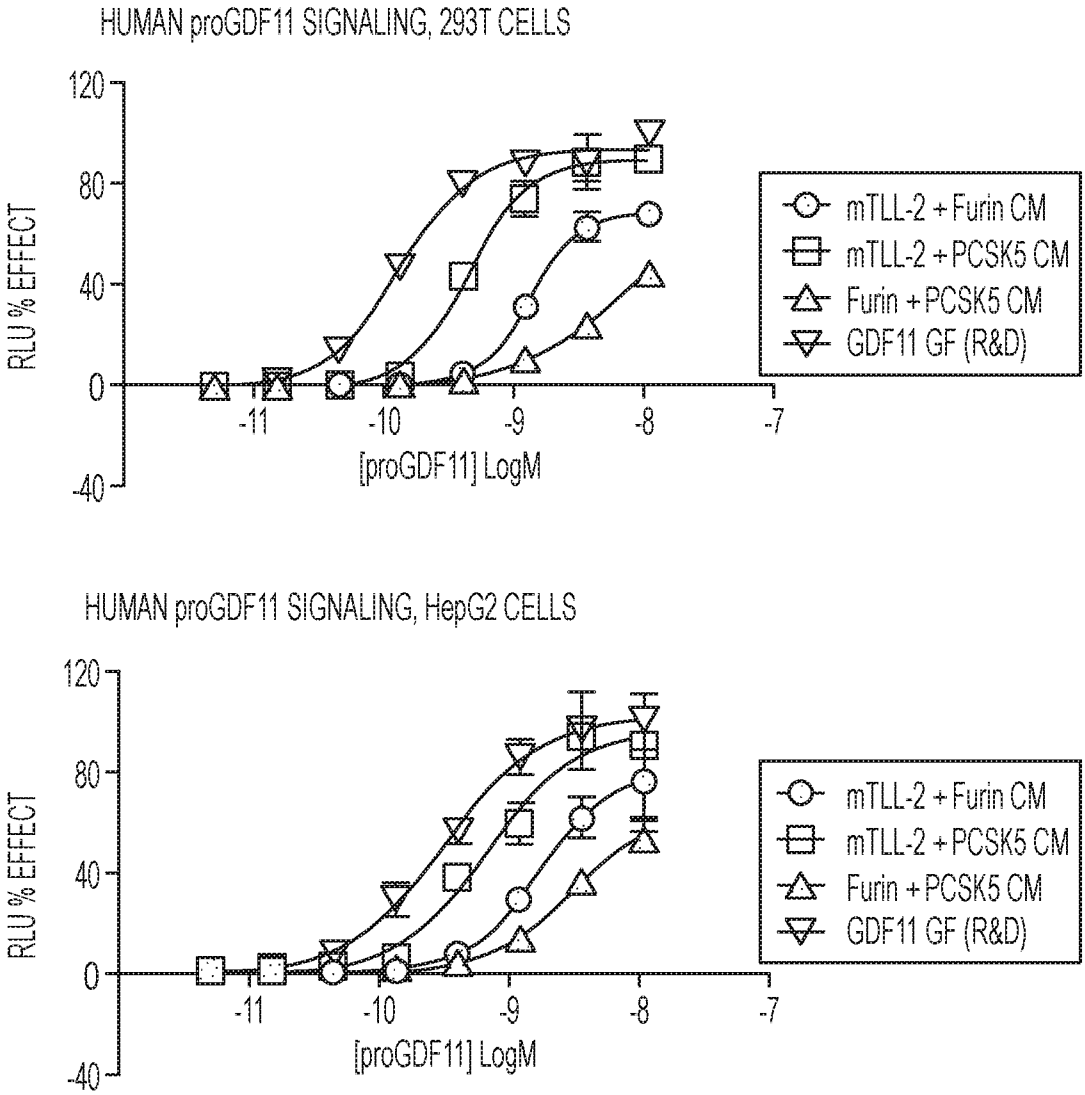

HUMAN proGDF11 SIGNALING, 293T CELLS
RLU % EFFECT
120
80
40
0
-40
-11
-10
-9
-8
-7
[proGDF11] LogM
mTLL-2 + Furin CM
mTLL-2 + PCSK5 CM
Furin + PCSK5 CM
GDF11 GF (R&D)
HUMAN proGDF11 SIGNALING, HepG2 CELLS
RLU % EFFECT
120
80
40
0
-40
-11
-10
-9
-8
-7
[proGDF11] LogM
mTLL-2 + Furin CM
mTLL-2 + PCSK5 CM
Furin + PCSK5 CM
GDF11 GF (R&D)

FIG. 14

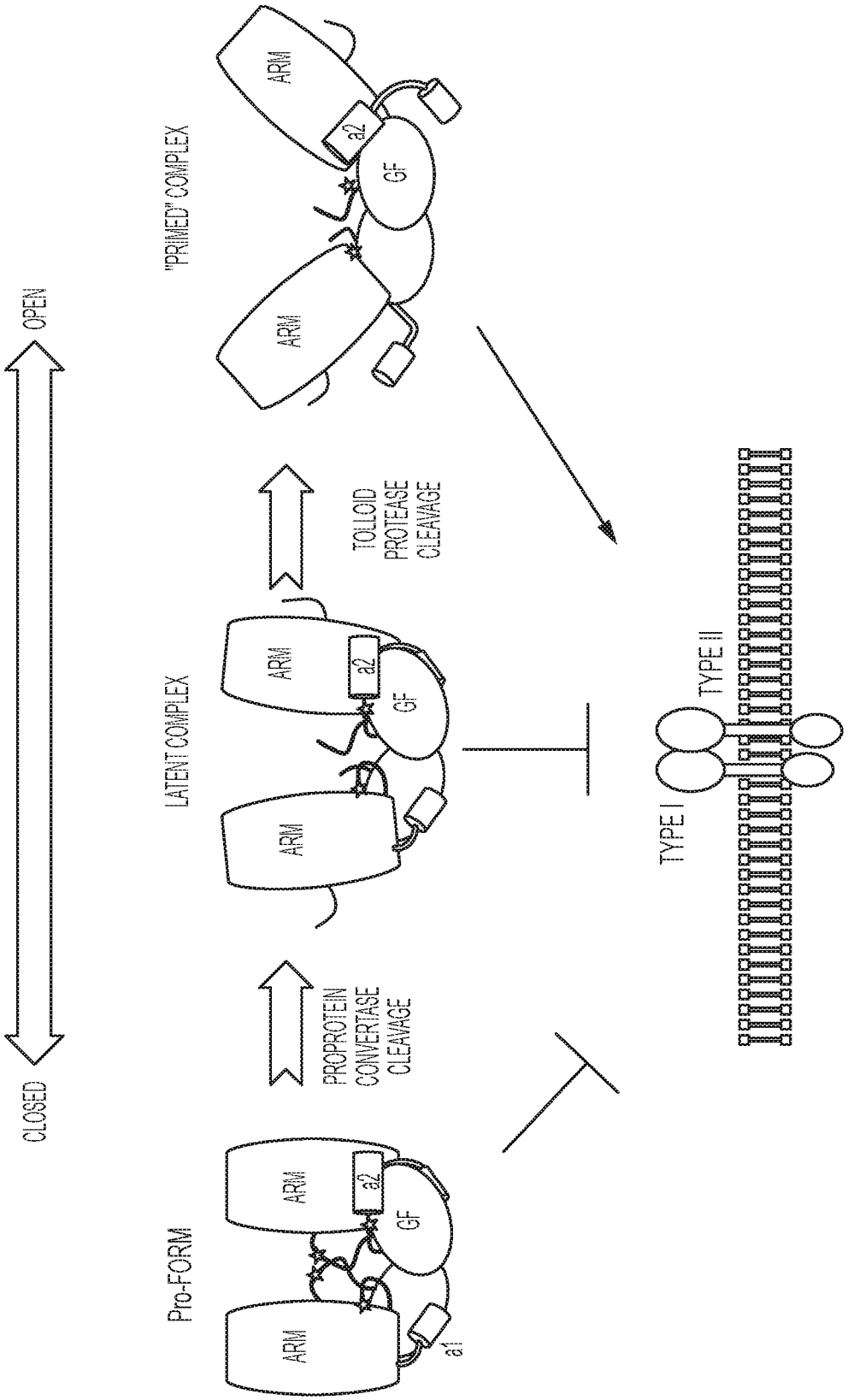

OPEN
CLOSED
Pro-FORM
ARM
a2
GF
a1
PROPROTEIN CONVERTASE CLEAVAGE
LATENT COMPLEX
TOLLOID PROTEASE CLEAVAGE
"PRIMED" COMPLEX
TYPE I
TYPE II

FIG. 15

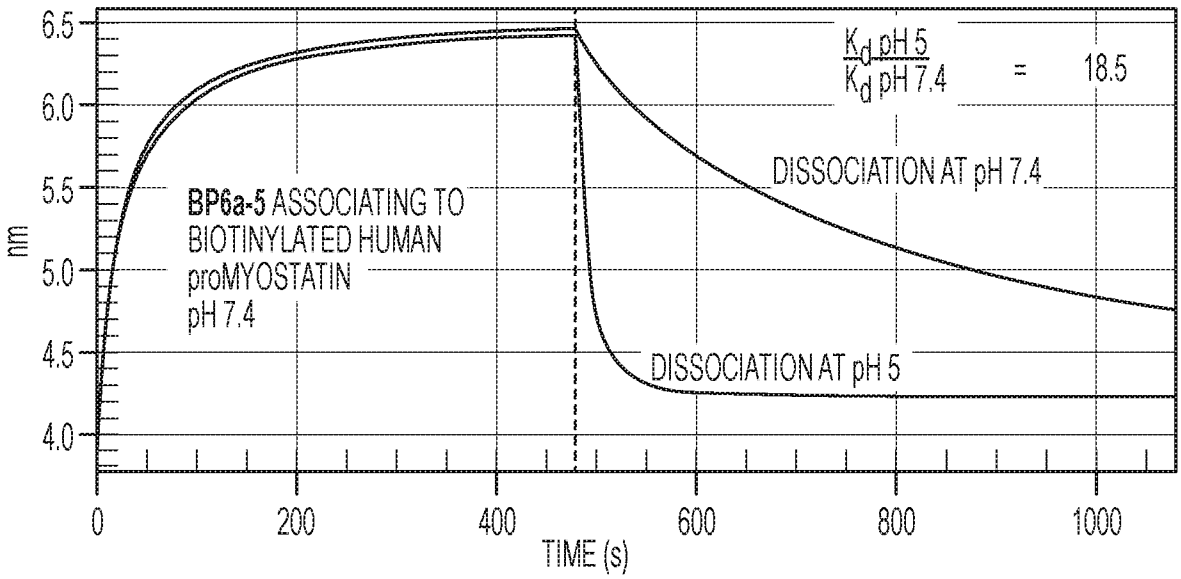

6.5
6.0
5.5
5.0
4.5
4.0
nm
0
200
400
600
800
1000
TIME (s)
BP6a-5 ASSOCIATING TO BIOTINYLATED HUMAN proMYOSTATIN pH 7.4
DISSOCIATION AT pH 7.4
DISSOCIATION AT pH 5
$\frac{K_d \text{ pH 5}}{K_d \text{ pH 7.4}}$ = 18.5

FIG. 16

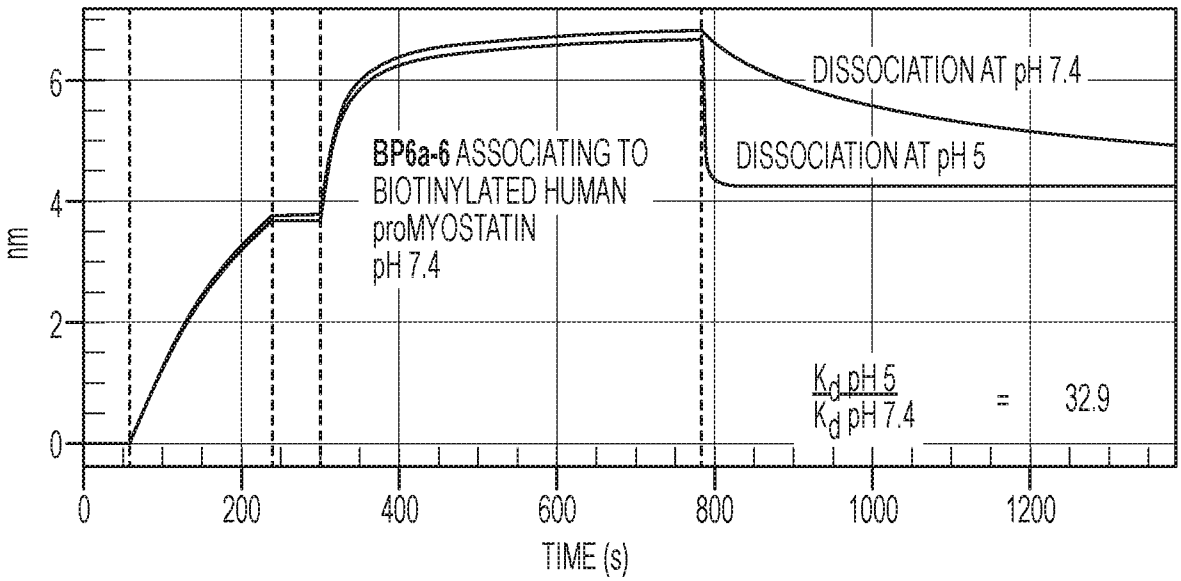

6
4
2
0
nm
0
200
400
600
800
1000
1200
TIME (s)
BP6a-6 ASSOCIATING TO BIOTINYLATED HUMAN proMYOSTATIN pH 7.4
DISSOCIATION AT pH 7.4
DISSOCIATION AT pH 5
$\frac{K_d \text{ pH 5}}{K_d \text{ pH 7.4}}$ = 32.9

FIG. 17

	K_d pH 5/K_d pH 7.4	BINDING PROFILE
BP5b-4	18.6	5
BP5b-1	5.9	5
BP6a-4	18.5	6
BP6a-6	32.9	6
BP11a-1	13.2	11
BP16b-4	6.2	16
BP18b-2	7.2	18
BP22b-1*	14	22

FIG. 18

CDRH3 SEQUENCES

BP5b-4	PAG**H**ICSGGSCQYYYYGMDV
BP11a-1	VDGLEYSSG**H**NFDY
BP6a-6	DR**H**LYRRGYSSVDGMDV
BP18b-2	**H**PIGSGYDY
BP6a-5	DLLVRFLEWS**H**YYGMDV
BP16b-4	EGYNA**H**YFDY
BP22b-1	GLGY**H**PLFDY
BP5b-1	EISDTAMGFDY

FIG. 19

	K_d pH 5/pH 7.4	BINDING PROFILE
BP5b-4	18.6	5
BP6a-5	18.5	6
BP6a-6	32.9	6
BP11a-1	13.2	11

FIG. 20

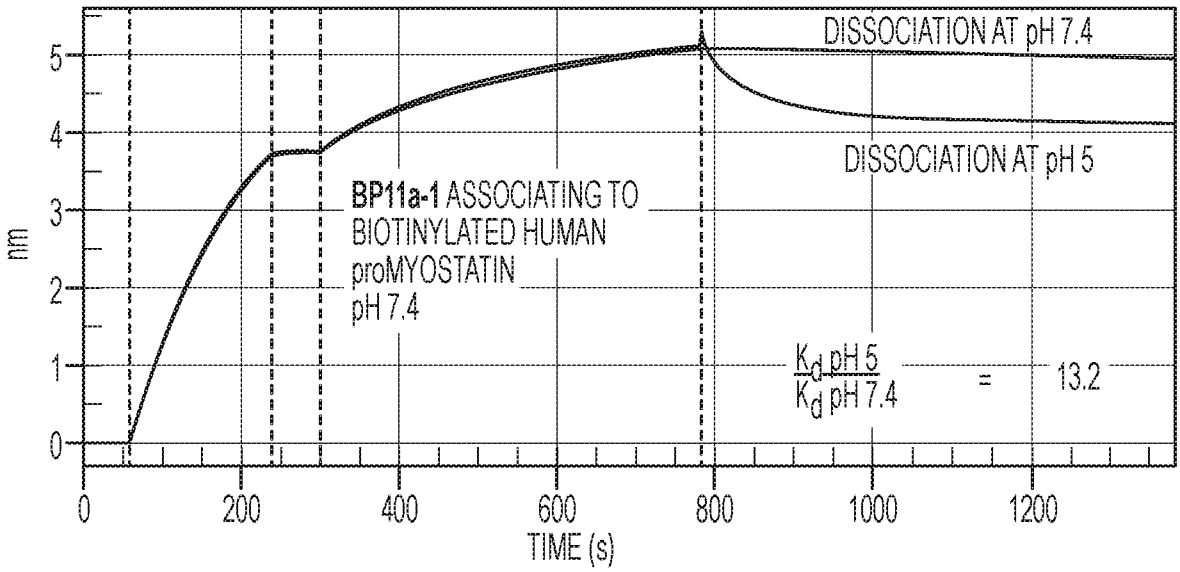

DISSOCIATION AT pH 7.4
DISSOCIATION AT pH 5
BP11a-1 ASSOCIATING TO BIOTINYLATED HUMAN proMYOSTATIN pH 7.4
$\frac{K_d \text{ pH 5}}{K_d \text{ pH 7.4}}$ = 13.2
nm
TIME (s)
0
1
2
3
4
5
0
200
400
600
800
1000
1200

FIG. 21

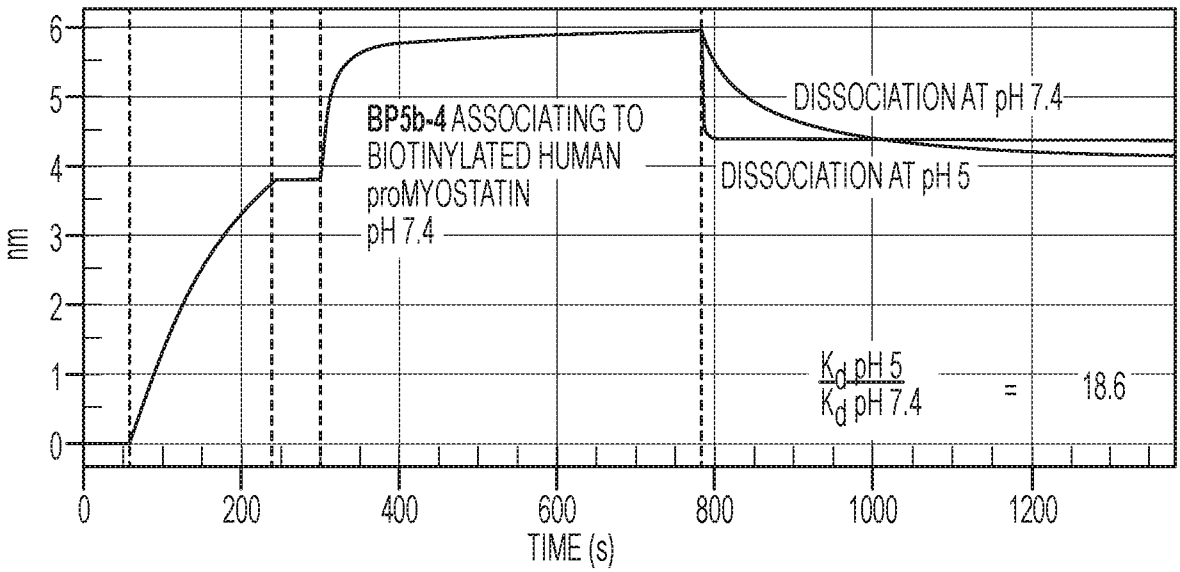

BP5b-4 ASSOCIATING TO BIOTINYLATED HUMAN proMYOSTATIN pH 7.4
DISSOCIATION AT pH 7.4
DISSOCIATION AT pH 5
$\frac{K_d \text{ pH 5}}{K_d \text{ pH 7.4}}$ = 18.6
nm
TIME (s)
0
1
2
3
4
5
6
0
200
400
600
800
1000
1200

FIG. 22

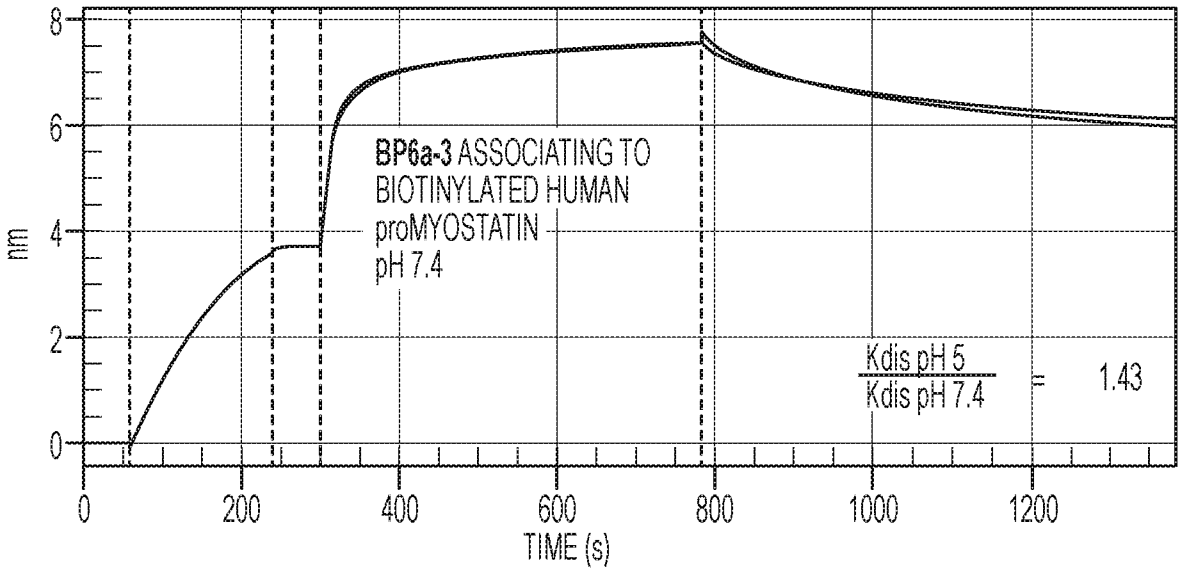


FIG. 23

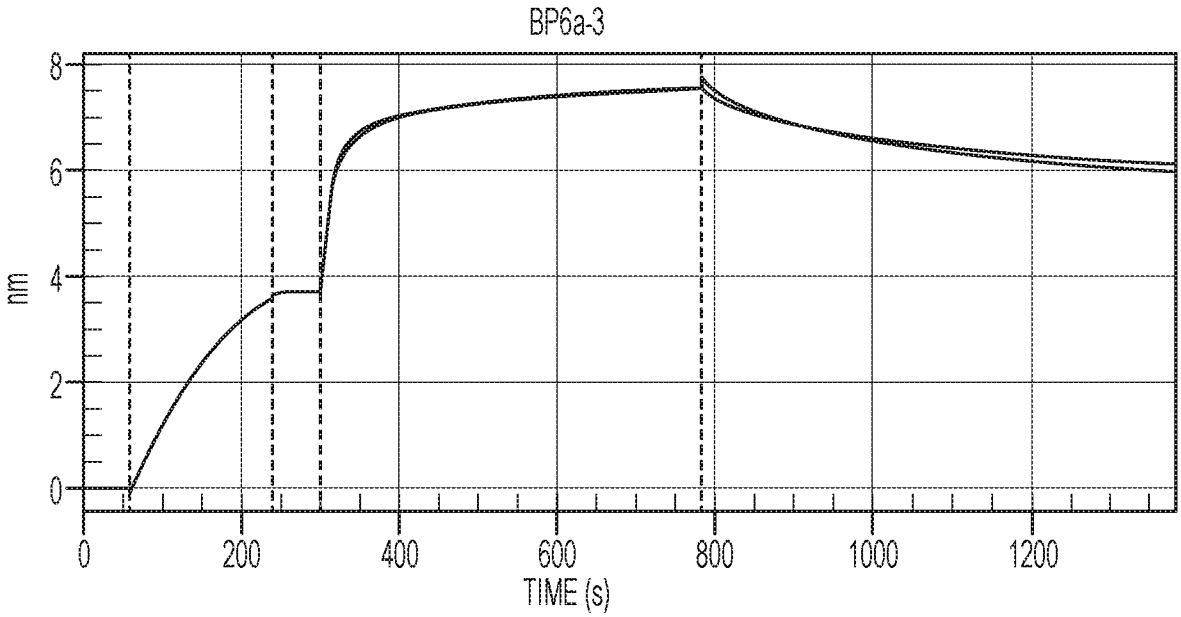


FIG. 24A

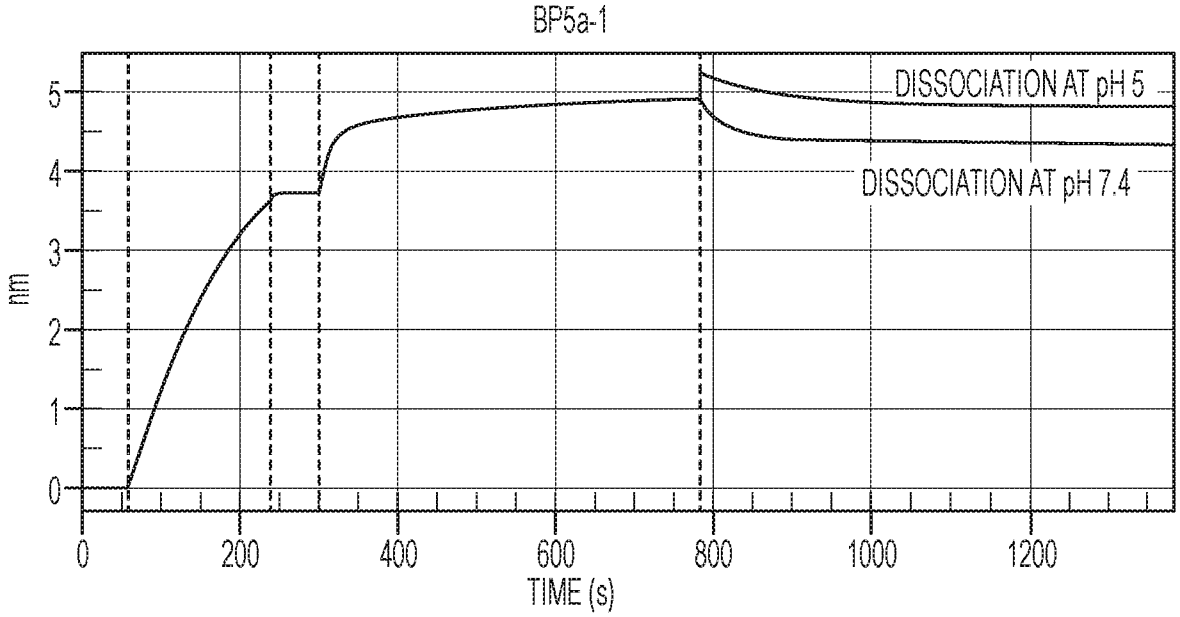


FIG. 24B

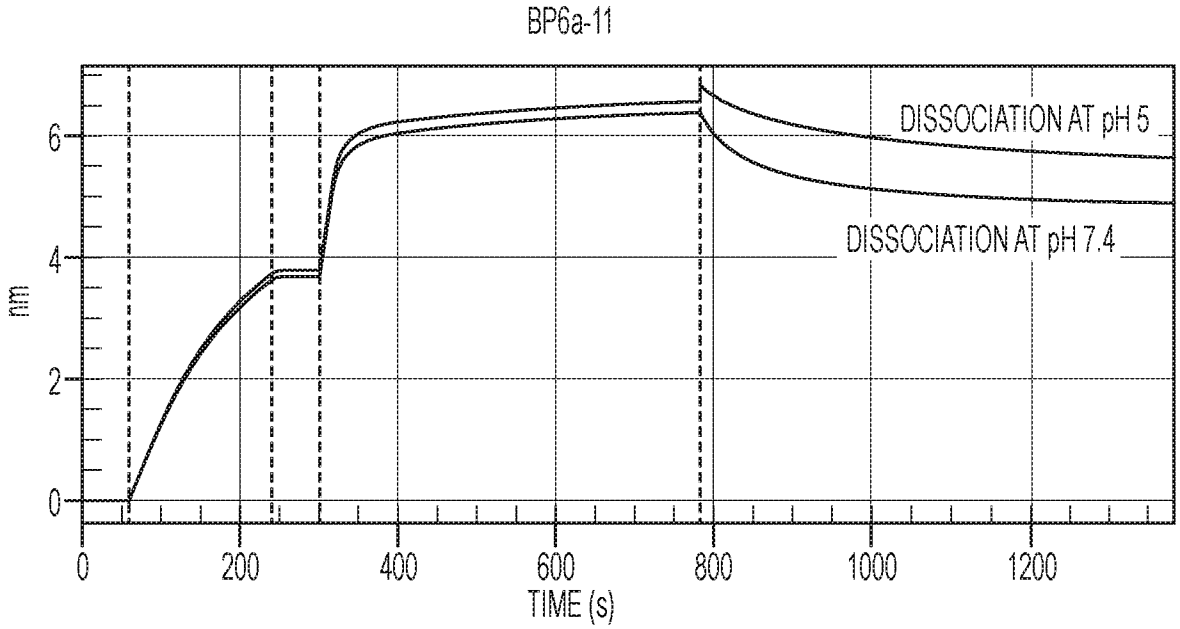


FIG. 24C

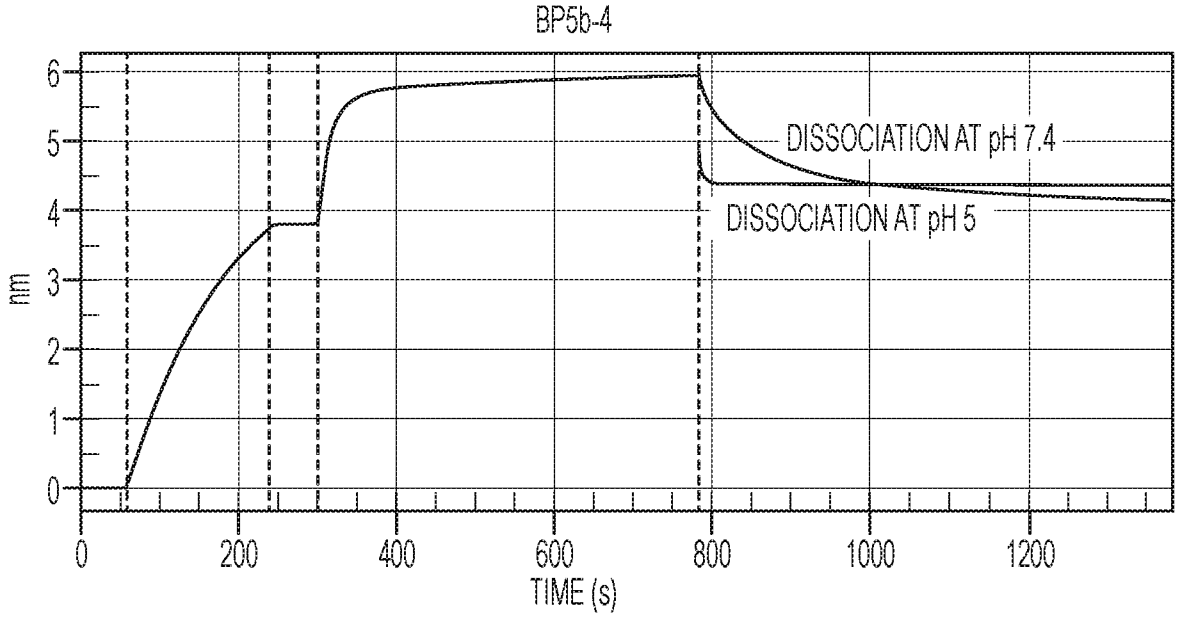


FIG. 24D

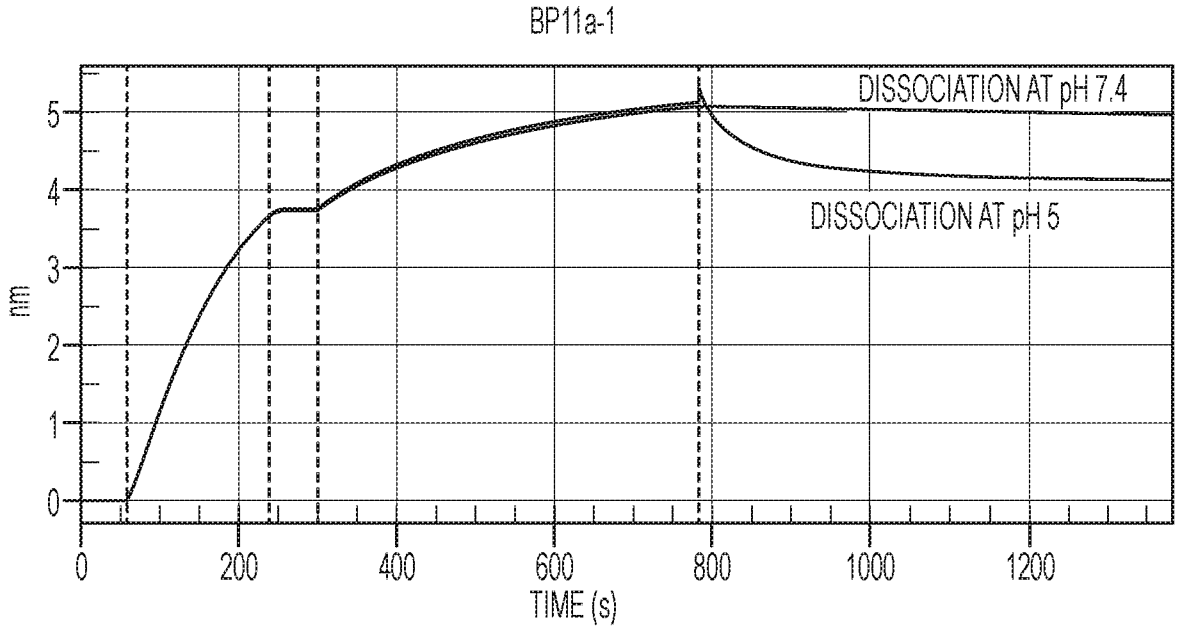


FIG. 24E

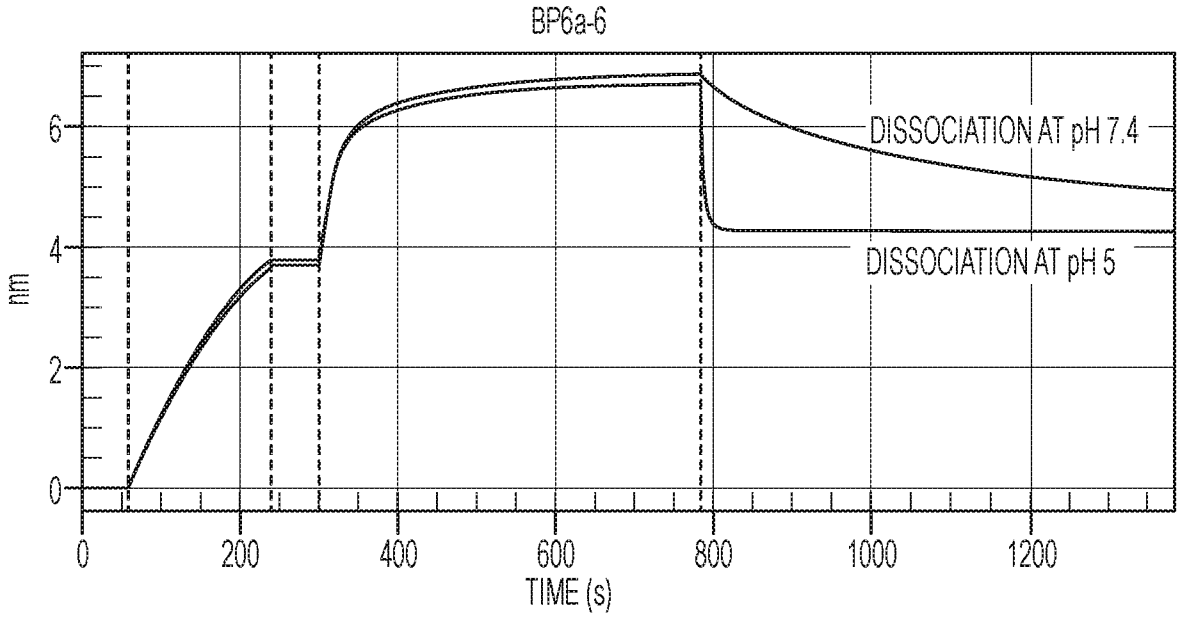


FIG. 24F

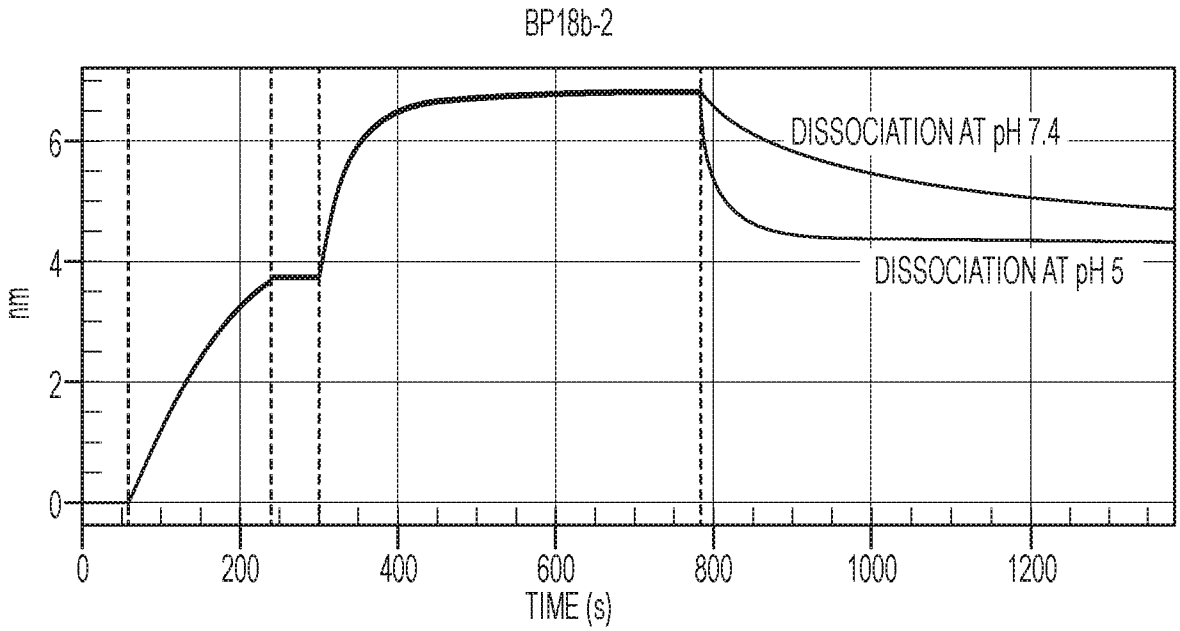


FIG. 24G

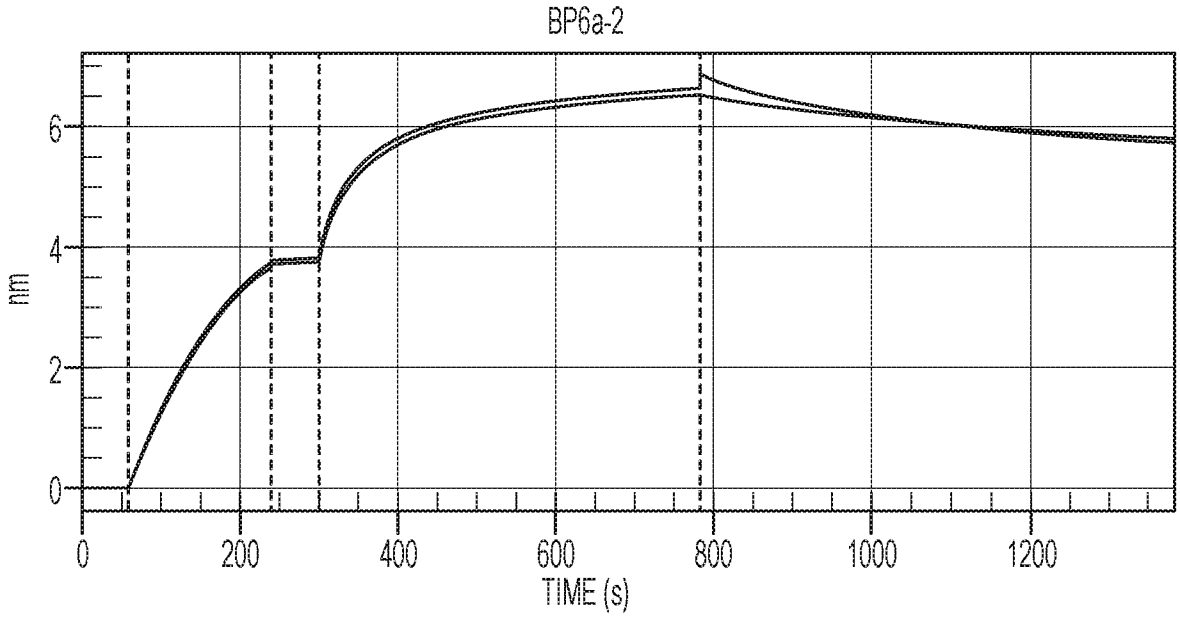


FIG. 24H

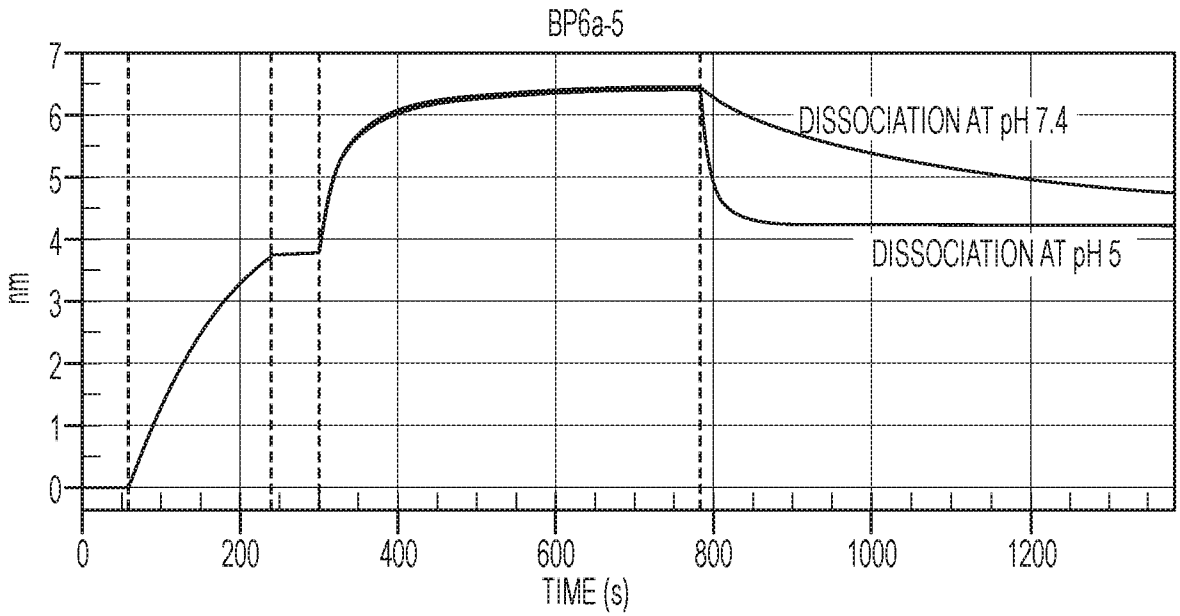


FIG. 24I

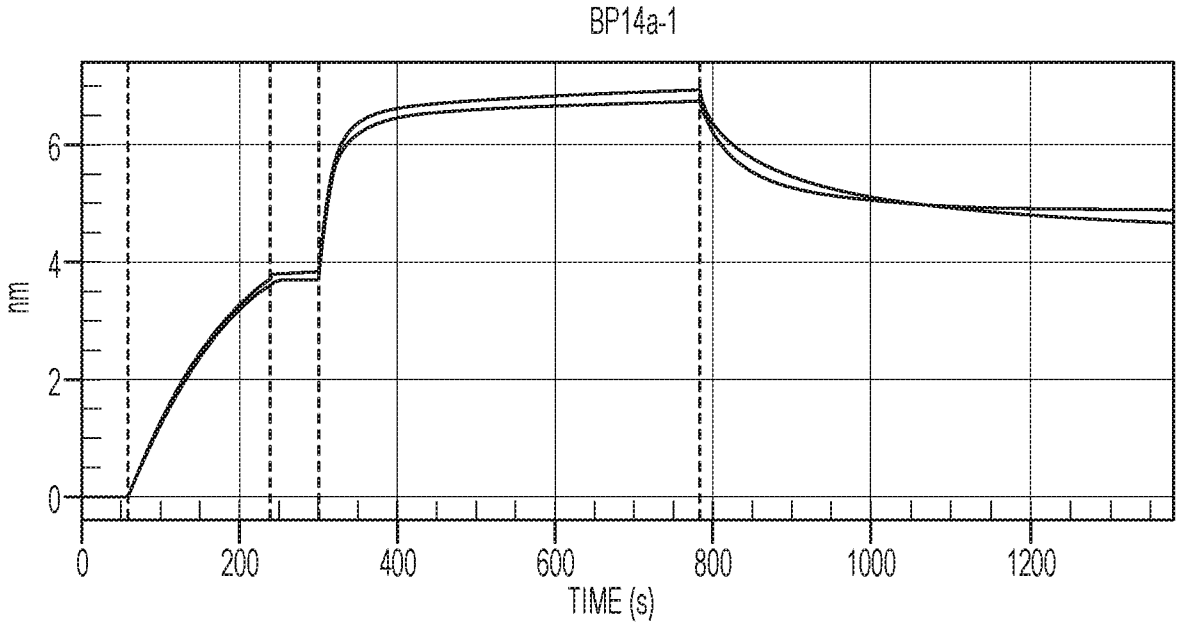


FIG. 24J

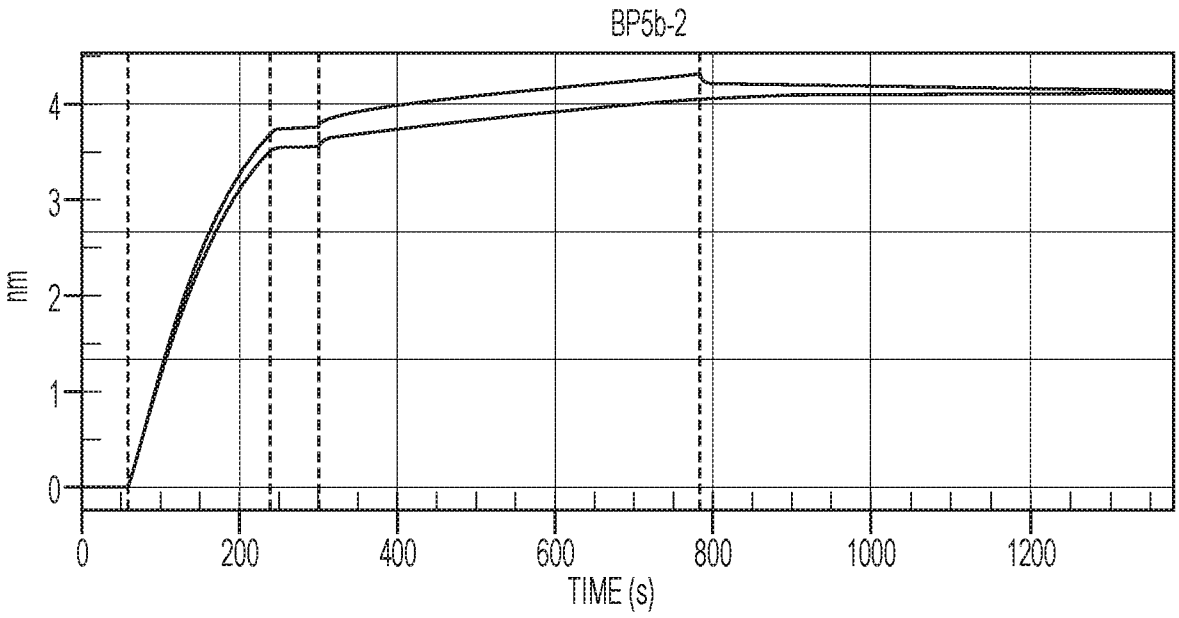


FIG. 24K

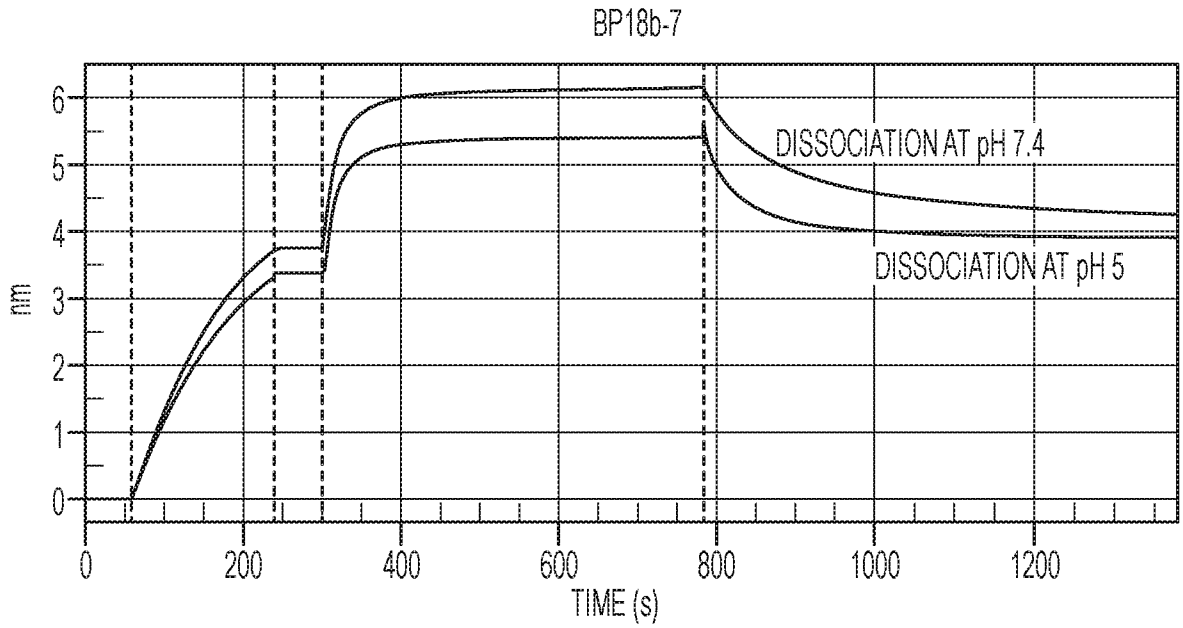


FIG. 24L

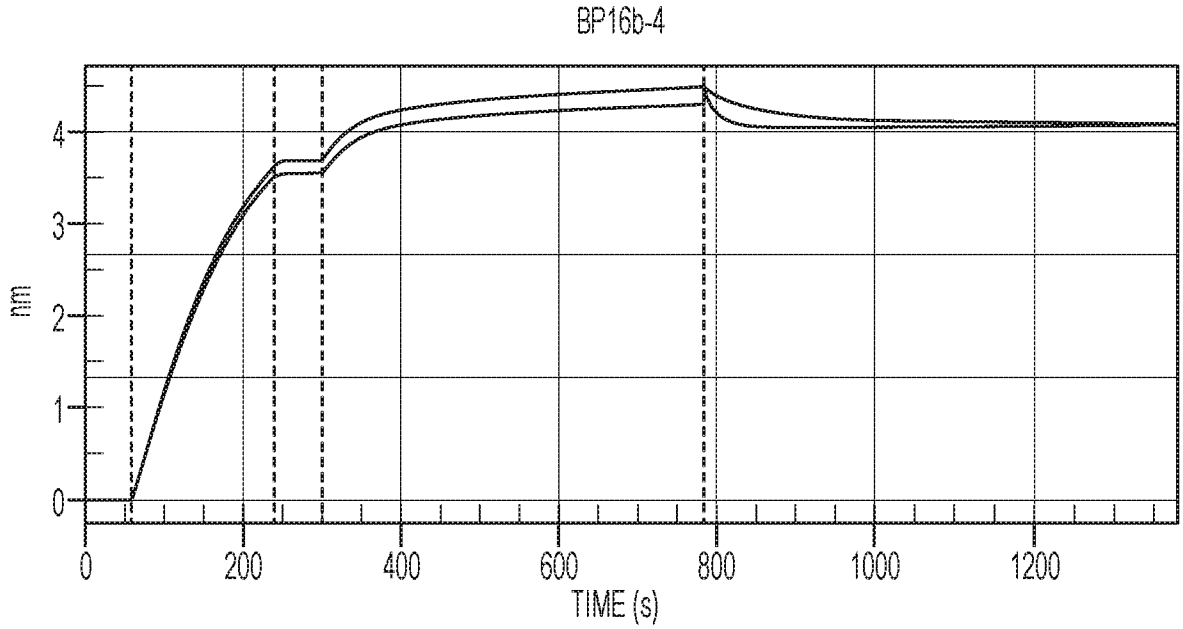


FIG. 25A

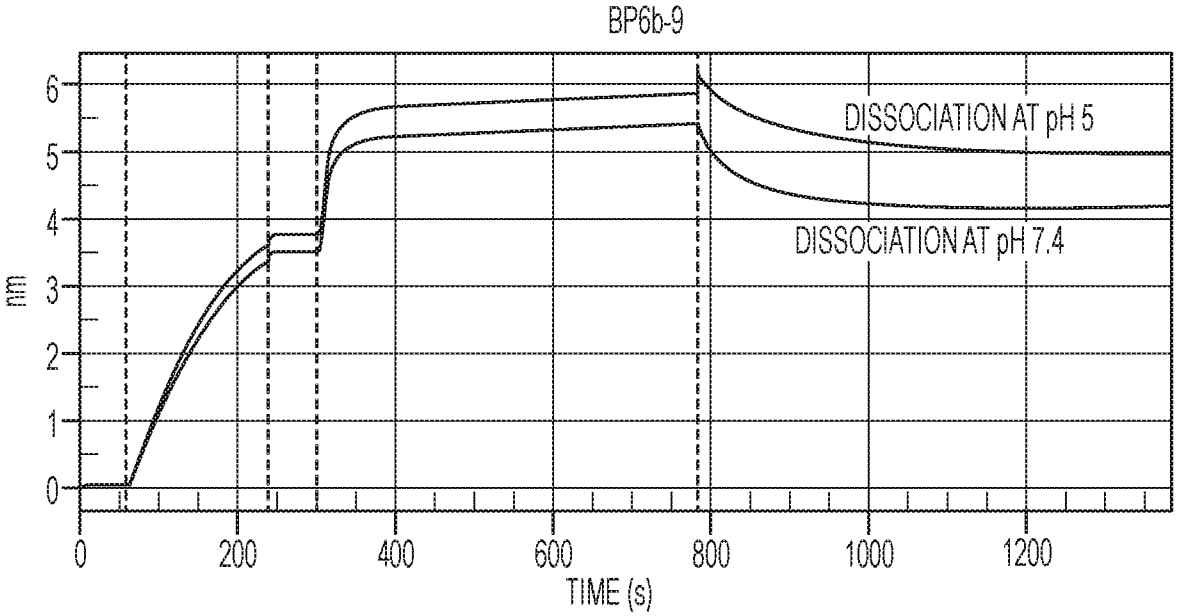


FIG. 25B

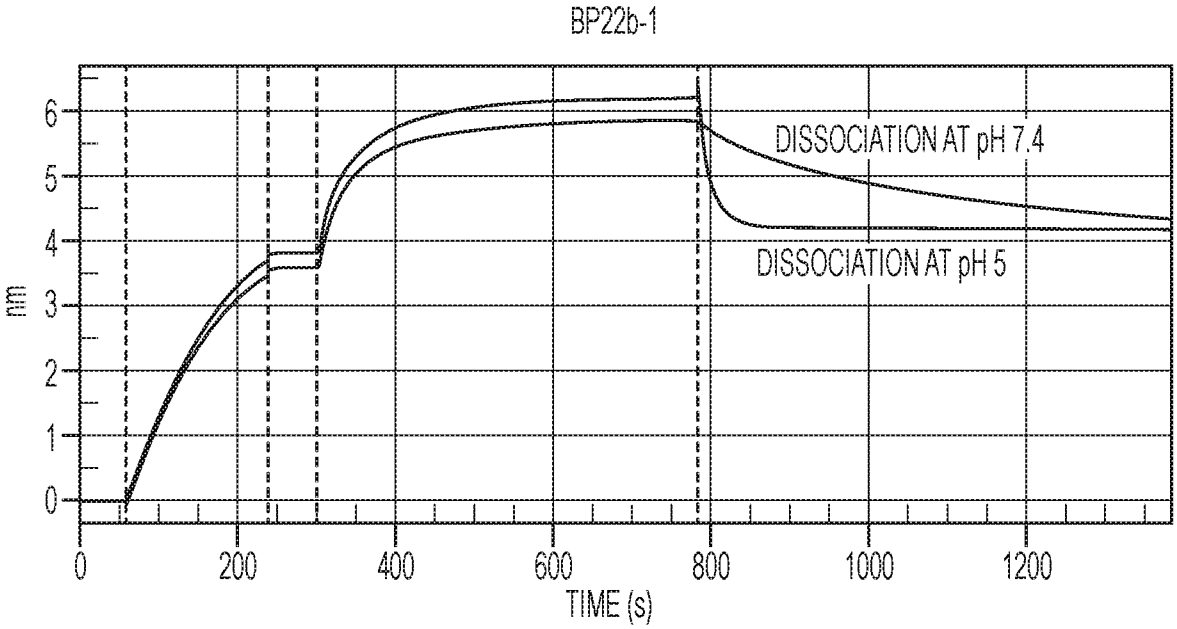


FIG. 25C

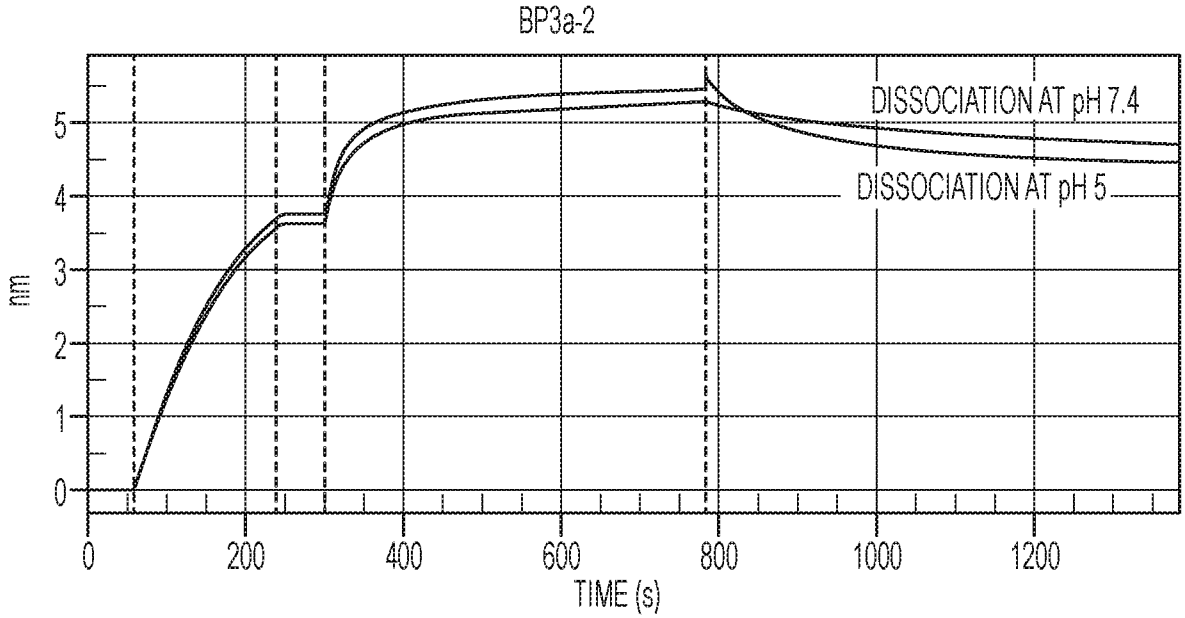


FIG. 25D

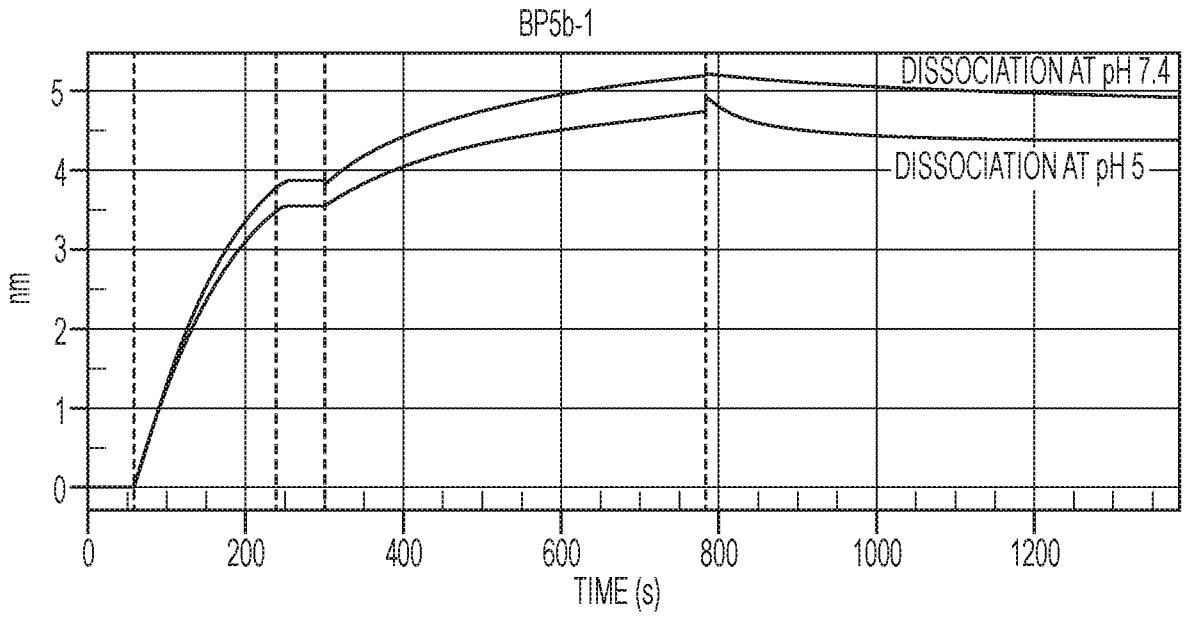


FIG. 25E

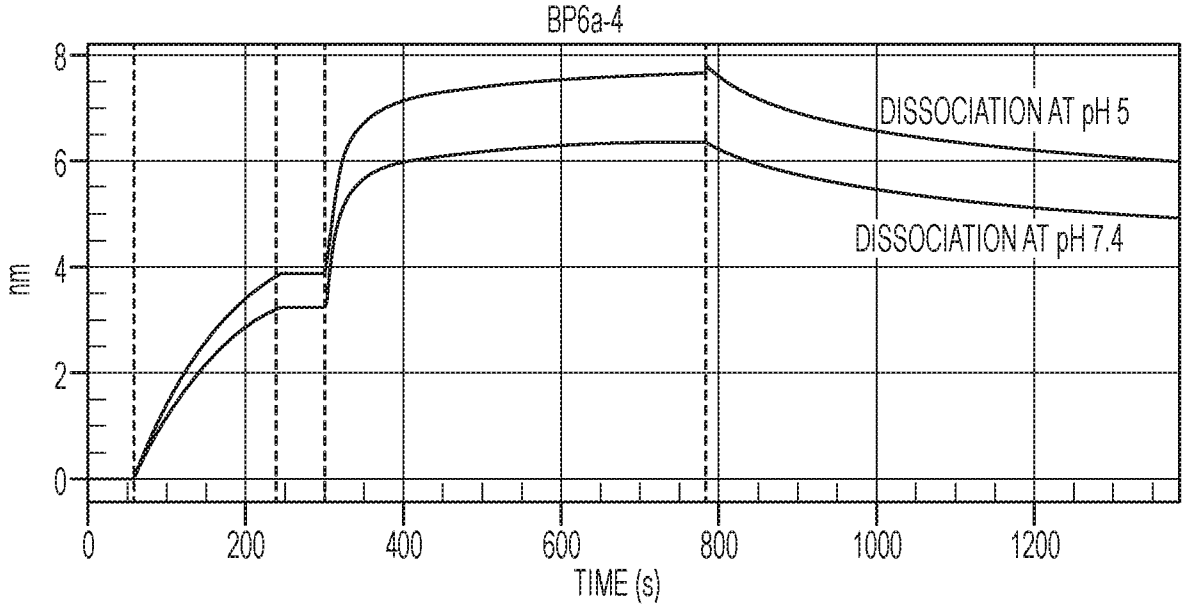


FIG. 25F

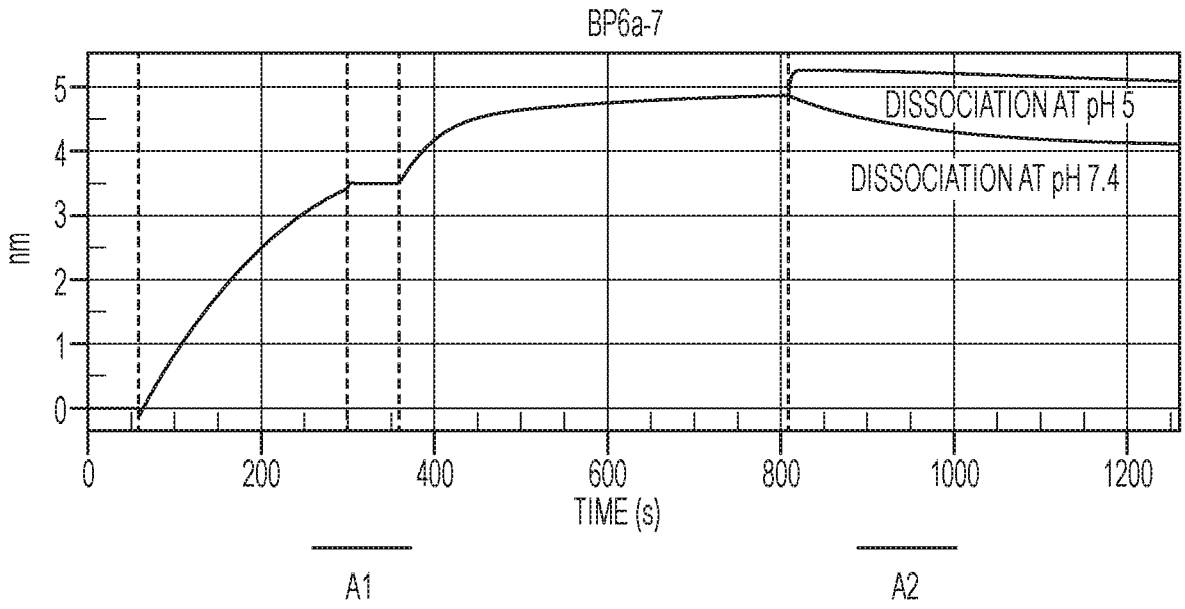


FIG. 25G

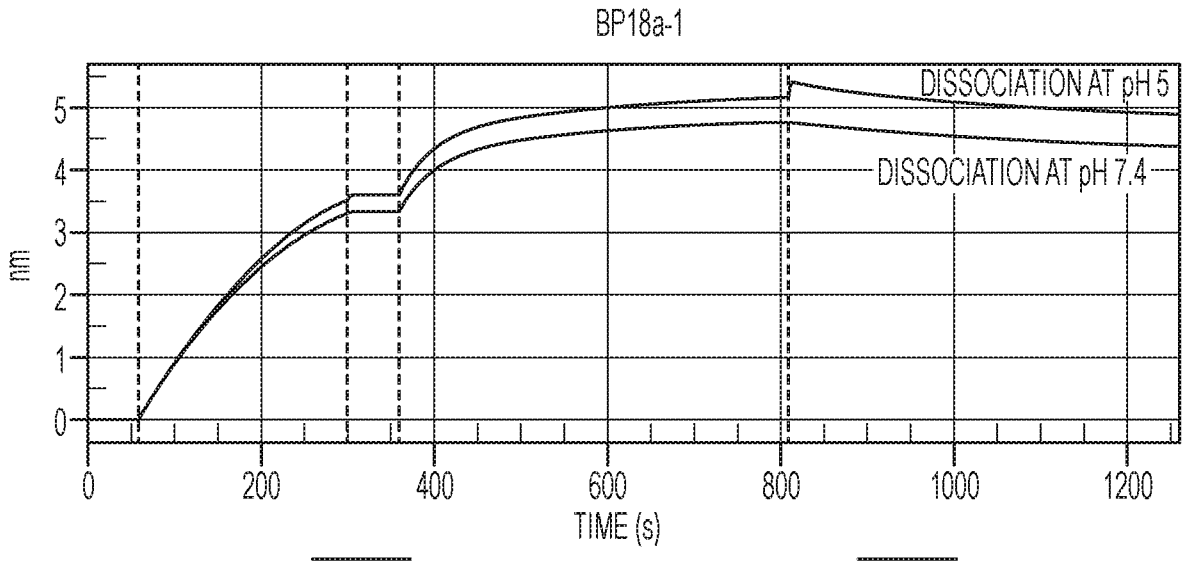


FIG. 25H

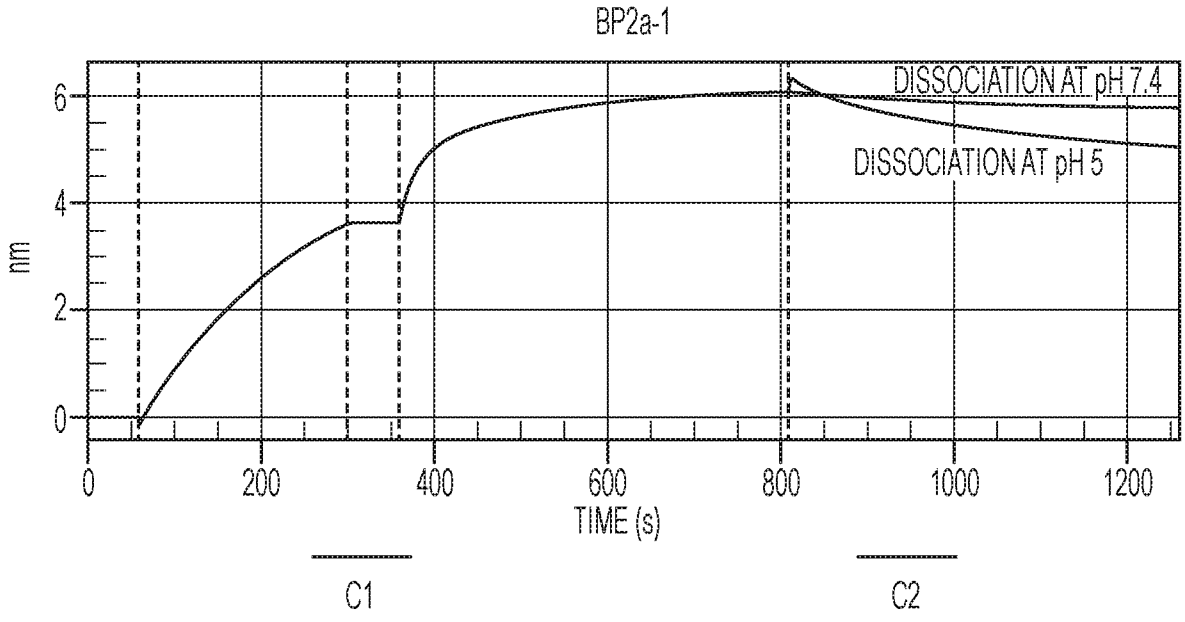


FIG. 25I

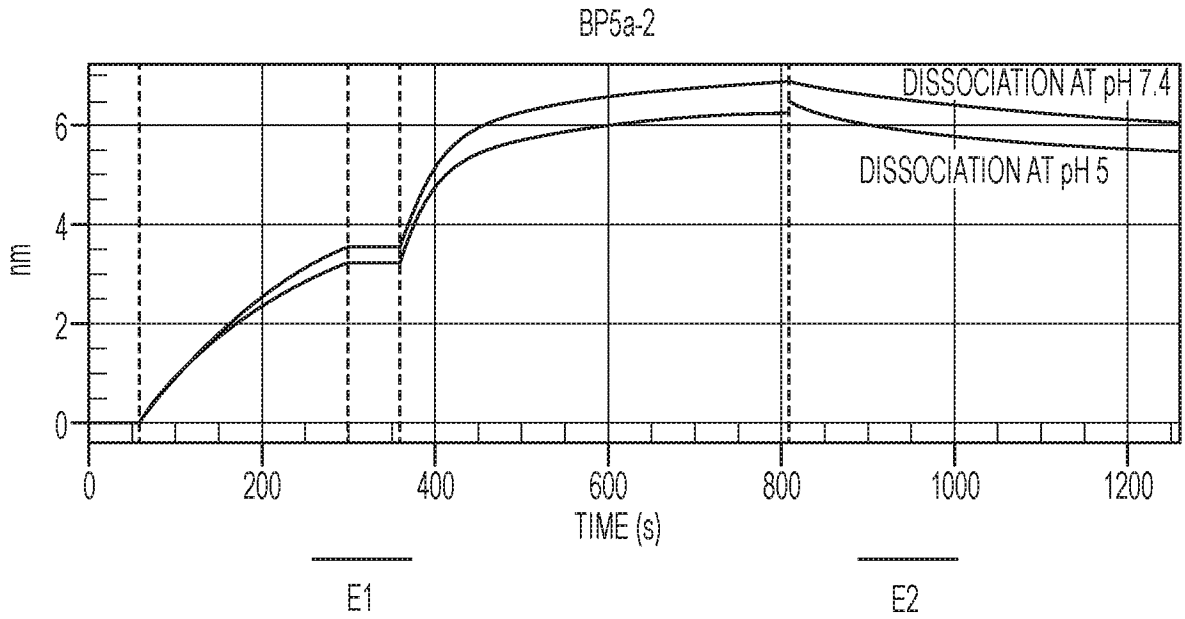


FIG. 25J

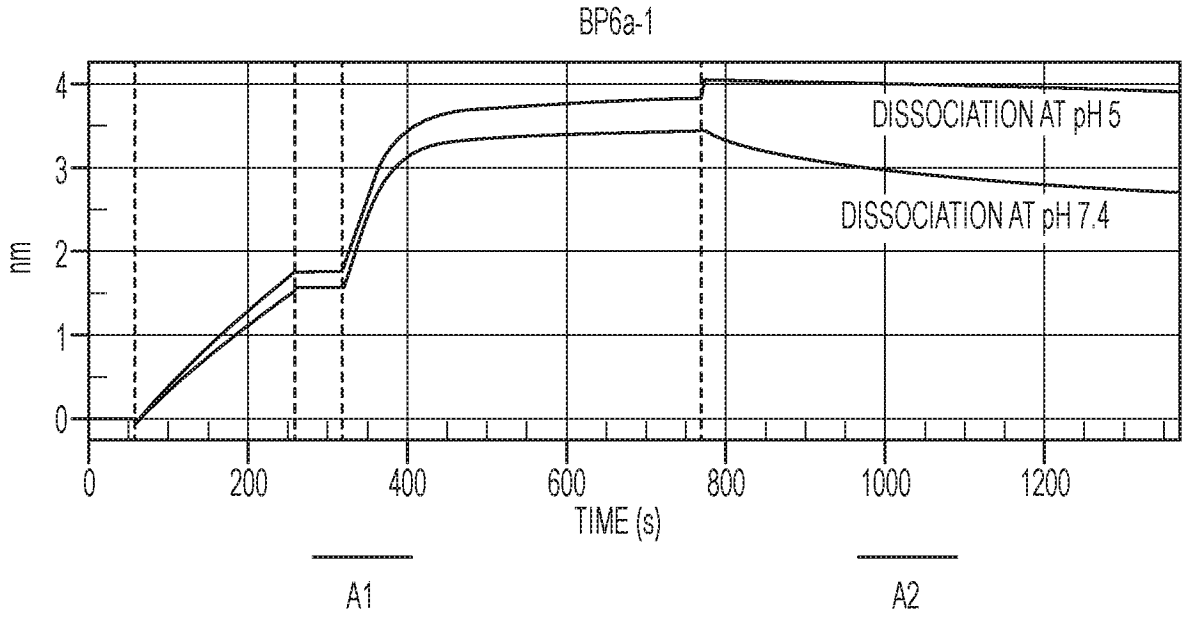


FIG. 25K