CLAIMS

1. An antibody or antigen-binding fragment thereof that specifically binds to human pro/latent myostatin with a KD of less than 1 nM as measured by a surface plasmon resonance (SPR)-based technique (e.g., BIACORE®),

wherein the antibody or antigen-binding fragment cross-blocks with Ab2 and binds the amino acid sequence(s) FVQILRLIKPMKDGTRYTGIRSLK (SEQ ID NO: 57) and/or KALDEN (SEQ ID NO: 118),

wherein the antibody or antigen-binding fragment is capable of inhibiting mTLL-2-induced myostatin activation with an IC50 of less than 1 nM as measured by functional ELISA as described in Example 1, and wherein the antibody or antigen-binding fragment is not Ab2.

2. An antibody or antigen-binding fragment thereof that competes for binding to a prodomain of human pro/latent myostatin with Ab2 or binds to a region of the prodomain of human pro/latent myostatin at an epitope that comprises one or more amino acid residues of the sequence FVQILRLIKPMKDGTRYTGIRSLK (SEQ ID NO: 57) (amino acid positions 147-170 of human proMyostatin, as numbered according to SEQ ID NO: 52) and/or one or more amino acid residues of the sequence KALDEN (SEQ ID NO: 118) (amino acid positions 205-210 of human proMyostatin, as numbered according to SEQ ID NO: 52), wherein the antibody or antigen-binding fragment is not Ab2;

wherein the antibody or antigen-binding fragment dissociates from bound antigen in a pH-dependent manner as measured by a BLI-based in vitro binding assay (e.g., Octet®); and/or

wherein the antibody or antigen-binding fragment is capable of inhibiting myostatin activation with an IC50 of less than 1 nM as measured by functional ELISA, comprising detection of the presence of mature myostatin in an immunoassay in which mTLL-2-induced activation of myostatin is measured in the presence or absence of the antibody or antigen-binding fragment.

3. The antibody or antigen-binding fragment thereof of claim 2, wherein the antibody or antigen-binding fragment dissociates from bound antigen at a higher rate in an acidic condition than in a neutral condition.

4. The antibody or antigen-binding fragment thereof of claim 1 or claim 2, wherein:

i) the L-CDR1 of the antibody or antigen-binding fragment shares no more than 20% sequence identity with the L-CDR1 of Ab2; ii) the L-CDR2 of the antibody or antigen-binding fragment shares no more than 30% sequence identity with the L-CDR2 of Ab2; and/or, iii) the L-CDR3 of the antibody or antigen-binding fragment shares no more than 10% of sequence identity with the L-CDR3 of Ab2; or

the heavy chain and light chain variable domains of the antibody or antigen-binding fragment share a cumulative sequence identity of less than 70% with the heavy chain variable region and light chain variable region sequences of Ab2.

5. The antibody or antigen binding fragment thereof of claim 1 or claim 2, wherein the antibody or antigen binding fragment comprises six complementarity determining regions (CDRs), an H-CDR1, an H-CDR2, an H-CDR3, an L-CDR1, an L-CDR2, and an L-CDR3, wherein:

H-CDR1 comprises the sequence GFTFSSYG (SEQ ID NO: 3);

H-CDR2 comprises the sequence FTGSGGX_1 (SEQ ID NO: 291) wherein X_1 is selected from T and A;

H-CDR3 comprises the sequence ARDLLIRFLEWSHYYGMDV (SEQ ID NO: 257);

L-CDR1 comprises the sequence QSLLHSSGHNF (SEQ ID NO: 258);

L-CDR2 comprises the sequence EVSNRVS (SEQ ID NO: 289); and

L-CDR3 comprises the sequence X_1QQTQYPX_2T (SEQ ID NO: 292), wherein X_1 is M or Q and X_2 is selected from P and G, wherein the CDR sequences are numbered according to the IMGT numbering system.

6. The antibody or antigen binding fragment thereof of claim 5, comprising:

(a) a heavy chain variable domain sequence that is at least 90% identical to any one of SEQ ID NOs: 402, 409, or 420, and/or a light chain variable domain sequence that is at least 90% identical to any one of SEQ ID NOs: 412, 419, 421, or 422; or

(b) a pair of variable domain sequences comprising SEQ ID NOs: 402 and 412, SEQ ID NOs: 409 and 419, SEQ ID NOs: 420 and 421, or SEQ ID NOs: 420 and 422.

7. The antibody or antigen binding fragment of claim 5 or claim 6, comprising:

(a) a heavy chain variable domain sequence selected from the amino acid sequences of SEQ ID NOs: 402 or 420; or

(b) a light chain variable domain sequence selected from the amino acid sequences of SEQ ID NOs: 412, 421, or 422.

8. The antibody or antigen binding fragment thereof of claim 5, comprising:

(a) a heavy chain sequence that is at least 70% identical to any one of SEQ ID NOs: 503, 507, or 509, and/or a light chain sequence that is at least 70% identical to any one of SEQ ID NOs: 504, 508, 510, or 511; or

(b) a pair of heavy chain and light chain sequences comprising SEQ ID NOs: 503 and 504; SEQ ID NOs: 507 and 508; SEQ ID NOs: 509 and 510; or SEQ ID NOs: 509 and 511.

9. An antibody or antigen-binding fragment thereof that specifically binds to pro/latent myostatin, wherein the antibody or antigen-binding fragment comprises six complementarity determining regions (CDRs), an H-CDR1, an H-CDR2, an H-CDR3, an L-CDR1, an L-CDR2, and an L-CDR3, wherein:

a) the H-CDR1 comprises the amino acid sequence of SEQ ID NO: 201, the H-CDR2 comprises the amino acid sequence of SEQ ID NO: 219, the H-CDR3 comprises the amino acid sequence of SEQ ID NO: 220, the L-CDR1 comprises the amino acid sequence of SEQ ID NO: 216, the L-CDR2 comprises the amino acid sequence of SEQ ID NO: 222, and the L-CDR3 comprises the amino acid sequence of SEQ ID NO: 223, wherein the CDR sequences are numbered according to the Kabat numbering system;

b) the H-CDR1 comprises the amino acid sequence of SEQ ID NO: 234, the H-CDR2 comprises the amino acid sequence of SEQ ID NO: 235, the H-CDR3 comprises the amino acid sequence of SEQ ID NO: 236, the L-CDR1 comprises the amino acid sequence of SEQ ID NO: 237, the L-CDR2 comprises the amino acid sequence EVS, and the L-CDR3 comprises the amino acid sequence of SEQ ID NO: 239, wherein the CDR sequences are numbered according to the Chothia numbering system; or

c) the H-CDR1 comprises the amino acid sequence of SEQ ID NO: 3, the H-CDR2 comprises the amino acid sequence of SEQ ID NO: 256, the H-CDR3 comprises the amino acid sequence of SEQ ID NO: 257, the L-CDR1 comprises the amino acid sequence of SEQ ID NO: 258, the L-CDR2 comprises the amino acid sequence EVS, and the L-CDR3 comprises the

amino acid sequence of SEQ ID NO: 260, wherein the CDR sequences are numbered according to the IMGT numbering system.

10. The antibody or antigen-binding fragment thereof of claim 9, comprising:

(a) a heavy chain variable domain that is at least 90% identical to the amino acid sequence of SEQ ID NO: 402, a light chain variable domain that is at least 90% identical to the amino acid sequence of SEQ ID NO: 412, or a combination thereof; or

(b) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 402 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 412.

11. The antibody or antigen-binding fragment thereof of claim 9 or claim 10, wherein the antibody is a human antibody of the IgG1 subtype or of the IgG4 subtype.

12. The antibody or antigen-binding fragment thereof of any one of claims 9-11, wherein the antibody comprises an S228P mutation.

13. The antibody or antigen-binding fragment thereof of any one of claims 9-12, comprising:

(a) a heavy chain that is at least 90% identical to the amino acid sequence of SEQ ID NO: 503, a light chain that is at least 90% identical to the amino acid sequence of SEQ ID NO: 504, or a combination thereof; or

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 503 and a light chain comprising the amino acid sequence of SEQ ID NO: 504.

14. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of any one of claims 1-13 and a pharmaceutically acceptable excipient.

15. The pharmaceutical composition of claim 14, wherein the composition is formulated for subcutaneous or intravenous administration.

16. The antibody or antigen-binding fragment thereof of any one of claims 1-13, or the pharmaceutical composition of claim 14 or claim 15, for use in the treatment or prevention of one or more of the following conditions in a human subject: muscle disorders (e.g., muscle atrophies, myopathies), metabolic disorders (e.g., overweight/obesity, diabetes), bone disorders (e.g., bone loss, frequent fractures), cardiovascular diseases (e.g., heart failure), and chronic

inflammation and inflammatory diseases (e.g., chronic kidney disease (CKD), idiopathic pulmonary fibrosis (IPF), rheumatoid arthritis (RA)), and/or a liver disease (e.g., fatty liver disease, NAFLD, NASH);

wherein the treatment comprises administration of the antibody, antigen-binding fragment, or pharmaceutical composition to a human subject in an effective amount to treat or prevent the one or more of conditions.

17. The antibody or antigen-binding fragment thereof or pharmaceutical composition for use of claim 16, wherein the muscle disorder is a muscular dystrophy, wherein optionally the muscular dystrophy is selected from Duchenne Muscular Dystrophy (DMD), Becker Muscular Dystrophy (BMD), Facioscapulohumeral muscular dystrophy (FSHD), Emery-Dreifuss muscular dystrophy, oculopharyngeal muscular dystrophy, scapulohumeral muscular dystrophy, Fukuyama congenital muscular dystrophy, and Limb-girdle muscular dystrophy (LGMD).

18. The antibody or antigen-binding fragment thereof or pharmaceutical composition for use of claim 16, wherein the human subject has a muscular atrophy, wherein optionally the muscular atrophy is spinal muscular atrophy (SMA).

19. The antibody or antigen-binding fragment thereof or pharmaceutical composition for use of claim 16, wherein the human subject has a metabolic disorder, wherein optionally the metabolic disorder is obesity or overweight, type 2 diabetes mellitus, type 2 diabetes mellitus associated with obesity, or metabolic syndrome.

20. The antibody or antigen-binding fragment thereof or pharmaceutical composition for use of any one of claims 16-19, wherein the antibody or antigen-binding fragment is administered in conjunction with a second agent, wherein optionally the second agent is a GLP-1 pathway activator (e.g., a GLP-1R agonist or GLP-1 analog) and/or a biguanide (e.g., metformin).

21. The antibody or antigen-binding fragment thereof or pharmaceutical composition for use of any one of claims 16-20, wherein the one or more conditions comprises:

(a) a metabolic disorder associated with impaired neurological signaling, wherein, optionally, the metabolic disorder is associated with a muscle disorder, wherein optionally the muscle disorder is spinal cord injury, muscular dystrophy, or muscular atrophy;

(b) a cardiovascular disease, wherein optionally the cardiovascular disease comprises heart failure; or

(c) chronic inflammation or an inflammatory disease, wherein optionally the chronic inflammation or inflammatory disease comprises CKD, IPF, or RA.

22. The antibody or antigen-binding fragment thereof or pharmaceutical composition for use of claim 21, wherein the condition associated with impaired neurological signaling is a neuromuscular disorder.

23. The antibody or antigen-binding fragment thereof or pharmaceutical composition for use of any one of claims 16-22, wherein the pharmaceutical composition, antibody, or antigen-binding fragment is administered in conjunction with a GLP-1 pathway activator, wherein, optionally, the subject is on a diet and/or exercise regimen.

24. Use of the antibody or antigen-binding fragment thereof according to any one of claims 1-13 in the manufacture of a medicament for the treatment or prevention of one or more of the following conditions in a human subject: muscle disorders (e.g., muscle atrophies, myopathies), metabolic disorders (e.g., overweight/obesity, diabetes), bone disorders (e.g., bone loss, frequent fractures), cardiovascular diseases (e.g., heart failure), and chronic inflammation and inflammatory diseases (e.g., chronic kidney disease (CKD), idiopathic pulmonary fibrosis (IPF), or rheumatoid arthritis (RA)), and/or a liver disease (e.g., fatty liver disease, NAFLD, or NASH).

25. A myostatin-selective inhibitor for use in the improvement of bone strength and/or the prevention of bone loss in a subject, wherein the myostatin-selective inhibitor is administered in an amount effective to improve bone strength and/or prevent bone loss as compared to a subject who has not been administered the myostatin-selective inhibitor.