

COMPOSITIONS AND METHODS FOR ACTIVATION OF INTEGRINS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/029,070, filed on May 22, 2020, U.S. Provisional Patent Application No. 63/009,020, filed on April 13, 2020, and U.S. Provisional Patent Application No. 62/935,732, filed on November 15, 2019, the disclosure of each of which is hereby incorporated by reference in its entirety.

DESCRIPTION OF THE TEXT FILE SUBMITTED ELECTRONICALLY

[0002] The Sequence Listing associated with this application is provided in text format in lieu of a paper copy, and is hereby incorporated by reference into the specification. The name of the text file containing the Sequence Listing is PLIA_001_05WO_SeqList_ST25.txt. The text file is ~150,414 bytes, was created on November 13, 2020, and is being submitted electronically via EFS-Web.

FIELD OF THE INVENTION

[0003] The invention relates generally to compositions and methods for activating integrin heterodimers that contain beta-1 integrin protein that specifically binds laminin protein. Such compositions and methods are useful for treating diseases related to muscle malfunction, including muscular dystrophies.

BACKGROUND OF THE INVENTION

[0004] Skeletal muscle cells are surrounded by a basement membrane bridging the muscle membrane (sarcolemma) to the interstitial extracellular matrix. The basement membrane plays key roles during development and in adults, supporting development, muscle integrity, synaptogenesis and muscle repair.

[0005] Mutations affecting functionality or synthesis of proteins involved in the extracellular matrix-basement membrane-skeletal muscle cells interactions are associated with muscular dystrophies. There are no current cures for any form of muscular dystrophy. Several types have been reported that can be categorized according to the function of the gene that is affected. These can be separated into several classes, with the most important one stemming from mutations in the plasma membrane cytoskeleton complex of the myofibers (the laminin/dystroglycan/sarcoglycan/dystrophin complex). This complex acts as a laminin receptor

anchoring the extracellular matrix to cytoskeletal proteins of the skeletal muscle cells.

[0006] The most common form of muscular dystrophy representing approximately half of the cases is that induced by mutations in the dystrophin gene (PNAS 1984; 81: 1189). The presence of a truncated, partially functional form of dystrophin leads to symptoms associated with Becker muscular dystrophy (an X-linked recessive disorder). A more severe form is observed in Duchenne muscular dystrophy (DMD) patients (representing half of all muscular dystrophy cases), who have a mutation that leads to absence of, or a non-functional form of, the dystrophin protein. The incidence of DMD is about 1 in 3500 newborn males. Mutations in dystrophin are also believed to exhaust the muscle stem cell (satellite cells) pool which is activated in response to muscle injury. Mutations in the sarcoglycan gene (sarcoglycanopathies) lead to malfunction of a protein complex facilitating the interaction between the extracellular matrix and muscle via laminin $\alpha 2$ (merosin)-dystroglycan-dystrophin. Such mutations also lead to autosomal recessive muscular dystrophy that closely mimics the Duchenne dystrophy (NEJM 1997;336: 618). Mutations in laminin $\alpha 2$ -chain (merosin), although rare, lead to the most severe form of myopathy as the muscle cells lose their extracellular matrix anchor (Nat Genetics 1995; 11: 216).

[0007] Another protein, the integrin $\alpha 7 \beta 1$, also bridges laminin and cytoskeletal protein and actively contributes to muscle biology as its deficiency is also associated with a form of muscular dystrophy (Nat Genetics 1998; 19:94; Nat Genetics 1997; 17: 318). Two other beta-1 containing heterodimers ($\alpha 3 \beta 1$, $\alpha 6 \beta 1$) bind to laminin, but there have been no reports of muscular dystrophy associated with mutations in these genes. $\alpha 7 \beta 1$ is the primary laminin receptor that is expressed in skeletal, cardiac and vascular smooth muscle cells, and its deficiency leads to delayed development and impaired mobility. The integrin $\alpha 7 \beta 1$ is believed to play a compensatory role in muscular dystrophies associated with mutations in dystrophin associated proteins. Indeed, its expression is upregulated in human and animal models of muscular dystrophies (J Cell Sci 1997; 110: 2873). Integrin $\alpha 7 \beta 1$ deficiency combined with dystrophin, utrophin or sarcoglycan deficiencies leads to even more severe forms of the disease (Hum Mol Gen 2006; 15: 989, J Cell Sci 2006; 119: 2185, J Cell Biol 2001; 152: 1207) and further causes myocardial dysfunction, fibrosis and calcification (Circ Res 2008; 102: 1109).

[0008] There remains a need for a pharmaceutical agent that can provide a therapeutic benefit to subjects with deficiency in or malfunctions of the laminin/dystroglycan/sarcoglycan/dystrophin complex.

SUMMARY OF THE INVENTION

[0009] The invention provides a pharmaceutical agent that is an agonist of at least one of $\alpha 7\beta 1$ integrin, $\alpha 6\beta 1$ integrin and $\alpha 3\beta 1$ integrin and that binds to the extracellular domain of at least one of $\alpha 7$ protein, $\alpha 6$ protein and $\alpha 3$ protein. In some embodiments, the pharmaceutical agent of claim 1, wherein the pharmaceutical agent binds at least one of: the laminin binding domain of at least one of $\alpha 7$ protein, $\alpha 6$ protein and $\alpha 3$ protein; the CALF-1 domain of at least one of $\alpha 7$ protein, $\alpha 6$ protein and $\alpha 3$ protein; and the CALF-2 domain of at least one of $\alpha 7$ protein, $\alpha 6$ protein and $\alpha 3$ protein. In some embodiments, a pharmaceutical agent is an agonist of $\alpha 7\beta 1$ integrin and binds specifically to the $\alpha 7$ protein. In some embodiments, a pharmaceutical agent does not increase the amount of $\alpha 7$ protein in a muscle cell of a subject when the pharmaceutical agent is administered to the subject.

[0010] In some embodiments, a pharmaceutical agent that is an agonist of at least one of $\alpha 7\beta 1$ integrin, $\alpha 6\beta 1$ integrin and $\alpha 3\beta 1$ integrin is an antibody. In some embodiments, an antibody is a monoclonal antibody. In certain embodiments, an antibody is a multispecific antibody (*e.g.*, a bispecific antibody). In some embodiments, an antibody of the invention is human, humanized or chimeric.

[0011] In some embodiments, the invention encompasses a pharmaceutical agent that activates at least one of $\alpha 7\beta 1$ integrin, $\alpha 6\beta 1$ integrin and $\alpha 3\beta 1$ integrin. In some embodiments, a pharmaceutical agent stabilizes the active conformation of at least one of $\alpha 7\beta 1$ integrin, $\alpha 6\beta 1$ integrin and $\alpha 3\beta 1$ integrin. In certain embodiments, a pharmaceutical agent does not bind specifically to the $\beta 1$ protein. In some embodiments, a pharmaceutical agent increases the adhesion of a myoblast to merosin. For example, the myoblast may be a healthy human myoblast or a healthy murine myoblast. Alternatively, the myoblast may be a human myoblast or a murine myoblast that is dystrophin deficient, comprises a mutation in dystrophin or comprises non-functioning dystrophin. In some embodiments, a pharmaceutical agent increases the adhesion of a myotube to merosin. For example, the myotube may be a healthy human myotube or a healthy murine myotube. Alternatively, the myotube may be a human myotube or a murine myotube that is dystrophin deficient, comprises a mutation in dystrophin or comprises non-functioning dystrophin.

[0012] The invention further provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin (*e.g.*, human $\alpha 7\beta 1$ integrin), or an antibody fragment thereof, wherein the antibody or the antibody fragment binds specifically to an epitope of $\alpha 7$ protein, wherein the epitope comprises, consists essentially of, or consists of: (i) the amino acid sequence of SEQ ID NO:

10 or **SEQ ID NO: 1**; (ii) 5-10, 10-15, 15-20, 20-25, 25-30, 30-35 or 35-40 amino acids of **SEQ ID NO: 10** or **SEQ ID NO: 1**; or (iii) 5-10, 10-15, 15-20, 20-25, 25-30, 30-35 or 35-40 amino acids of **SEQ ID NO: 24**.

[0013] The invention also provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment binds specifically to an epitope of $\alpha 7$ protein, wherein the epitope comprises SWWP (**SEQ ID NO: 25**). Further provided herein is a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment binds specifically to an epitope comprising the residues S977, W978, W979 and P980 of **SEQ ID NO: 24**. In some embodiments, the epitope comprises, consists essentially of, or consists of 5-10 or 10-15 amino acids of **SEQ ID NO: 24**. The invention further provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment binds specifically to an epitope comprising the residues R958, M976, S977, W978, W979 and P980 of **SEQ ID NO: 24**. In some embodiments, the epitope comprises, consists essentially of, or consists of 6-10 or 10-15 amino acids of **SEQ ID NO: 24**. In some embodiments, the epitope is continuous. In some embodiments, the epitope is discontinuous.

[0014] The invention further provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, that binds specifically to an epitope disclosed herein and comprises a heavy chain variable (VH) region comprising an HCDR1, an HCDR2 and an HCDR3, and a light chain variable (VL) region comprising an LCDR1, an LCDR2 and an LCDR3, (i) wherein the HCDR3 comprises **SEQ ID NO: 15**; and/or wherein the LCDR3 comprises **SEQ ID NO: 7**; (ii) wherein the HCDR3 comprises **SEQ ID NO: 66**; and/or wherein the LCDR3 comprises **SEQ ID NO: 7**; or (iii) wherein the HCDR3 comprises **SEQ ID NO: 68**; and/or wherein the LCDR3 comprises **SEQ ID NO: 7**.

[0015] In some embodiments, a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, binds specifically to an epitope disclosed herein and comprises a VH region comprising an HCDR1, an HCDR2 and an HCDR3, and a VL region comprising an LCDR1, an LCDR2 and an LCDR3, wherein the HCDR2 comprises **SEQ ID NO: 3**; and/or wherein the LCDR2 comprises **SEQ ID NO: 6**.

[0016] In some embodiments, a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, binds specifically to an epitope disclosed herein and comprises a VH region comprising an HCDR1, an HCDR2 and an HCDR3, and a VL region comprising an LCDR1, an LCDR2 and an LCDR3, (i) wherein the HCDR1 comprises **SEQ ID NO: 14**;

and/or wherein the LCDR1 comprises **SEQ ID NO: 5**; (ii) wherein the HCDR1 comprises **SEQ ID NO: 65**; and/or wherein the LCDR1 comprises **SEQ ID NO: 5**; (iii) wherein the HCDR1 comprises **SEQ ID NO: 14**; and/or wherein the LCDR1 comprises **SEQ ID NO: 69**; or (iv) wherein the HCDR1 comprises **SEQ ID NO: 14**; and/or wherein the LCDR1 comprises **SEQ ID NO: 71**.

[0017] The invention encompasses a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin (*e.g.*, human $\alpha 7\beta 1$ integrin), or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 2**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 4**, or a variant thereof having 5 or fewer conservative amino acid substitutions in HCDR1, HCDR2, and/or HCDR3; wherein the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 14**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 15**, or a variant thereof having 5 or fewer conservative amino acid substitutions in HCDR1, HCDR2, and/or HCDR3; wherein the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 65**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 66**, or a variant thereof having 5 or fewer conservative amino acid substitutions in HCDR1, HCDR2, and/or HCDR3; or wherein the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 14**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 68**, or a variant thereof having 5 or fewer conservative amino acid substitutions in HCDR1, HCDR2, and/or HCDR3.

[0018] The invention also encompasses a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a light chain variable (VL) region and a heavy chain variable (VH) region, wherein the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 5**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**, or a variant thereof having 5 or fewer conservative amino acid substitutions in LCDR1, LCDR2, and/or LCDR3; wherein the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 69**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**, or a variant thereof having 5 or fewer conservative amino acid substitutions in LCDR1, LCDR2, and/or LCDR3; or wherein the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 71**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**, or a variant thereof having 5 or fewer conservative amino acid substitutions in LCDR1, LCDR2, and/or LCDR3.

[0019] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the

antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein: (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 2**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 4**, or a variant thereof having 5 or fewer conservative amino acid substitutions in HCDR1, HCDR2, and/or HCDR3; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 5**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**, or a variant thereof having 5 or fewer conservative amino acid substitutions in LCDR1, LCDR2, and/or LCDR3; (ii) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 14**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 15**, or a variant thereof having 5 or fewer conservative amino acid substitutions in HCDR1, HCDR2, and/or HCDR3; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 5**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**, or a variant thereof having 5 or fewer conservative amino acid substitutions in LCDR1, LCDR2, and/or LCDR3; (iii) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 65**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 66**, or a variant thereof having 5 or fewer conservative amino acid substitutions in HCDR1, HCDR2, and/or HCDR3; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 5**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**, or a variant thereof having 5 or fewer conservative amino acid substitutions in LCDR1, LCDR2, and/or LCDR3; (iv) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 14**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 68**, or a variant thereof having 5 or fewer conservative amino acid substitutions in HCDR1, HCDR2, and/or HCDR3; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 69**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**, or a variant thereof having 5 or fewer conservative amino acid substitutions in LCDR1, LCDR2, and/or LCDR3; or (v) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 14**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 68**, or a variant thereof having 5 or fewer conservative amino acid substitutions in HCDR1, HCDR2, and/or HCDR3; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 71**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**, or a variant thereof having 5 or fewer conservative amino acid substitutions in LCDR1, LCDR2, and/or LCDR3.

[0020] The invention also encompasses an antibody or an antibody fragment thereof, wherein the VH region amino acid sequence comprises (i) **SEQ ID NO: 8**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 8**; (ii) **SEQ ID NO: 16**, or an amino acid sequence that is at least 95%, 96%, 97%, 98%

or 99% identical to the amino acid sequence of **SEQ ID NO: 16**; or (iii) **SEQ ID NO: 67**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 67**.

[0021] The invention encompasses an antibody or an antibody fragment thereof, wherein the VL region amino acid sequence comprises (i) **SEQ ID NO: 9**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 9**; (ii) **SEQ ID NO: 17**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 17**; (iii) **SEQ ID NO: 70**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 70**; or (iv) **SEQ ID NO: 72**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 72**.

[0022] The invention also encompasses an antibody or an antibody fragment thereof, wherein (i) the VH region amino acid sequence comprises **SEQ ID NO: 8**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 8**; and the VL region amino acid sequence comprises **SEQ ID NO: 9**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 9**; (ii) the VH region amino acid sequence comprises **SEQ ID NO: 16**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 16**; and the VL region amino acid sequence comprises **SEQ ID NO: 17**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 17**; (iii) the VH region amino acid sequence comprises **SEQ ID NO: 67**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 67**; and the VL region amino acid sequence comprises **SEQ ID NO: 17**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 17**; (iv) the VH region amino acid sequence comprises **SEQ ID NO: 16**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 16**; and the VL region amino acid sequence comprises **SEQ ID NO: 70**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 70**; or (v) the VH region amino acid sequence comprises **SEQ ID NO: 16**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 16**; and the VL region amino acid sequence comprises **SEQ ID NO: 72**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 72**.

[0023] In some embodiments, provided herein is a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody comprises a heavy chain and a light chain, (i) wherein the heavy chain amino acid sequence comprises **SEQ ID NO: 18**, and the light chain amino acid sequence comprises **SEQ ID NO: 19**; (ii) wherein the heavy chain amino acid sequence comprises **SEQ ID NO: 45**, and the light chain amino acid sequence comprises **SEQ ID NO: 53**; (iii) wherein the heavy chain amino acid sequence comprises **SEQ ID NO: 18**, and the light chain amino acid sequence comprises **SEQ ID NO: 62**; or (iv) wherein the heavy chain amino acid sequence comprises **SEQ ID NO: 18**, and the light chain amino acid sequence comprises **SEQ ID NO: 63**.

[0024] In some embodiments, an antibody or antibody fragment of the invention binds specifically to $\alpha 7$ protein. In some cases, the antibody or the antibody fragment binds specifically to an epitope of $\alpha 7$ protein comprising, consisting essentially of, or consisting of the (i) amino acid sequence of **SEQ ID NO: 10**; (ii) 5-10, 10-15, 15-20, 20-25, 25-30, 30-35 or 35-40 amino acids of **SEQ ID NO: 10**; or (iii) 5-10, 10-15, 15-20, 20-25, 25-30, 30-35 or 35-40 amino acids of **SEQ ID NO: 24**.

[0025] In some embodiments, an antibody fragment of the invention may be an Fab, an $F(ab')_2$, an Fab' , an scFv, a single domain antibody, a diabody or a single chain camelid antibody

[0026] The invention encompasses an isolated nucleic acid molecule encoding an antibody or an antibody fragment disclosed herein. The invention also provides an expression vector comprising the nucleic acid molecule disclosed herein. In some embodiments of expression vectors, the nucleic acid molecule is operatively linked to regulatory sequences suitable for expression of the nucleic acid segment in a host cell. Additionally, the invention provides a recombinant host cell comprising an expression vector disclosed herein. The invention encompasses a method for producing an antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, the method comprising: culturing a recombinant host cell comprising an expression vector disclosed herein under conditions whereby the nucleic acid molecule is expressed, thereby producing the antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof.

[0027] In some embodiments, the invention provides a pharmaceutical composition comprising a pharmaceutical agent, an antibody that is an agonist of at least one of $\alpha 7\beta 1$ integrin, $\alpha 6\beta 1$ integrin and $\alpha 3\beta 1$ integrin, or an antibody fragment thereof, and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, a

pharmaceutical composition of the invention further comprises an additional pharmaceutical agent that is an agonist of at least one of $\alpha 7\beta 1$ integrin, $\alpha 6\beta 1$ integrin and $\alpha 3\beta 1$ integrin.

[0028] The invention encompasses a method of treating a disorder or a disease in a subject comprising administering to the subject a therapeutically effective amount of a pharmaceutical agent, an antibody that is an agonist of at least one of $\alpha 7\beta 1$ integrin, $\alpha 6\beta 1$ integrin and $\alpha 3\beta 1$ integrin, or an antibody fragment thereof, thereby treating the disorder or the disease in the subject. The disorder or the disease can be characterized by one or more of: a malfunction of $\alpha 7\beta 1$ integrin in the subject; a dystrophin deficiency in the subject; a mutation in dystrophin in the subject; non-functioning dystrophin in the subject; or a muscle dysfunction other than $\alpha 7\beta 1$ malfunction, or dystrophin deficiency, mutation, or non-function.

[0029] In some embodiments, the muscle dysfunction is caused by or associated with one or more of: cancer, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disease, HIV infection/AIDS, anorexia nervosa, bulimia, malnutrition, exposure, nausea, type I diabetes, type II diabetes, metabolic syndrome, cachexia, anemia, heart failure, high blood pressure, rhabdomyolysis, sepsis, sarcopenia, physical inactivity, damage due to excess physical activity, hypothermia, hyperthermia, injury, denervation, amyotrophic lateral sclerosis, multiple sclerosis, spinal muscular atrophy, alcohol-associated myopathy, burn-associated myopathy, stroke, steroid therapy or the withdrawal of steroid therapy, dermatomyositis, Guillain-Barré syndrome, neuropathy, osteoarthritis, infection, polio, polymyositis, inflammation, rheumatoid arthritis, hypocholesterolemia, electrical injury, heat stroke, prolonged immobilization, lack of blood flow to a limb, or contact with venom. The methods of treatment of the invention may further comprise a step of identifying a subject having a muscle dysfunction.

[0030] In some embodiments, the disease is a muscle wasting disease. In some embodiments, a muscle wasting disease is a muscular dystrophy. In certain cases, the muscular dystrophy is Duchenne muscular dystrophy (DMD), Becker muscular dystrophy, merosin-deficient congenital muscular dystrophy type 1A or limb-girdle muscular dystrophy. The methods of treatment of the invention may further comprise a step of identifying a subject having a muscle wasting disease. In some embodiments, the administration of a therapeutically effective amount of a pharmaceutical agent, an antibody that is an agonist of at least one of $\alpha 7\beta 1$ integrin, $\alpha 6\beta 1$ integrin and $\alpha 3\beta 1$ integrin, or an antibody fragment thereof, reverses, stabilizes or slows muscle wasting or muscle dysfunction in the subject. In certain cases, the administration improves muscle function in the subject. In some embodiments, the

administration does not worsen muscle function in the subject. The methods of treatment of the invention may further comprise measuring muscle function in the subject after the administration step, wherein the rate of worsening of muscle function is reduced.

[0031] In some embodiments, administering to the subject the therapeutically effective amount of the pharmaceutical agent is effective to upregulate the activity and/or amount of $\alpha 7\beta 1$ integrin in the subject effective to treat the malfunction of $\alpha 7\beta 1$ integrin in the subject.

[0032] In some embodiments, administering to the subject the therapeutically effective amount of the pharmaceutical agent is effective to upregulate activity and/or amount of $\alpha 7\beta 1$ integrin in the subject, the upregulated activity and/or amount of $\alpha 7\beta 1$ integrin in the subject being effective to at least in part mitigate the effect of at least one of: the dystrophin deficiency in the subject; the mutation in dystrophin in the subject; or the non-functioning dystrophin in the subject.

[0033] In some embodiments, administering to the subject the therapeutically effective amount of the pharmaceutical agent is effective to mitigate muscle injury in the subject.

[0034] In some embodiments, administering to the subject the therapeutically effective amount of the pharmaceutical agent is effective to mitigate eccentric muscle injury in the subject.

[0035] In some embodiments, administering to the subject the therapeutically effective amount of the pharmaceutical agent is effective to improve diaphragm muscle function in the subject.

[0036] In some embodiments, a method of the invention further comprises administering to the subject one or more other therapies, the one or more other therapies directed to muscular dystrophy or muscle wasting. In some embodiments, the one or more other therapies comprises one or more of: an anticonvulsant; an immunosuppressant; an antibiotic; quinine; therapy for management of congestive heart failure; a gene replacement therapy; an exon skipping therapy; a nonsense suppression therapy; therapy using an engineered nuclease; cell therapy using muscle precursor cells or stem cells; upregulation of utrophin; an anti-inflammatory therapy; an antifibrotic therapy; a steroid therapy; a myostatin blocker; insulin growth factor; a phosphodiesterase-5 inhibitor; an ACE inhibitor; induction of angiogenesis through delivery of vascular endothelial growth factor (VEGF); downregulation of VEGF decoy-receptor type 1 (VEGFR-1 or Flt-1); physical therapy; occupational therapy; surgery; orthotic intervention; speech therapy; respiratory therapy; a pacemaker; and a respiratory assistance device.

[0037] The invention encompasses a method of activating $\alpha 7\beta 1$ integrin in a muscle cell of a subject, the method comprising: administering to the subject a therapeutically effective amount of a pharmaceutical agent, an antibody that is an agonist of at least one of $\alpha 7\beta 1$ integrin, $\alpha 6\beta 1$ integrin and $\alpha 3\beta 1$ integrin, or an antibody fragment thereof, thereby activating $\alpha 7\beta 1$ integrin in a muscle cell of the subject. The invention also provides a method of enhancing binding of $\alpha 7\beta 1$ integrin to its ligand in a muscle cell of a subject, the method comprising: administering to the subject a therapeutically effective amount of a pharmaceutical agent, an antibody that is an agonist of at least one of $\alpha 7\beta 1$ integrin, $\alpha 6\beta 1$ integrin and $\alpha 3\beta 1$ integrin, or an antibody fragment thereof, thereby enhancing binding of $\alpha 7\beta 1$ integrin to its ligand in a muscle cell of the subject.

[0038] The invention provides a use of the pharmaceutical agent of a pharmaceutical agent, an antibody that is an agonist of at least one of $\alpha 7\beta 1$ integrin, $\alpha 6\beta 1$ integrin and $\alpha 3\beta 1$ integrin, or an antibody fragment thereof, in the manufacture of a medicament for treating a disorder or a disease characterized by a malfunction of $\alpha 7\beta 1$ integrin in a subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0039] **FIG. 1** is a graph showing that integrin $\beta 1$ protein activation by a $\beta 1$ agonist antibody (TS2/16) promotes human myoblast adhesion to merosin (laminin). “DMD” refers to myoblasts that are dystrophin deficient, possessing a mutation in dystrophin or non-functioning dystrophin.

[0040] **FIG. 2** is a graph showing that integrin $\beta 1$ protein activation by a $\beta 1$ agonist antibody (TS2/16) promotes human myotube adhesion to merosin (laminin). “DMD” refers to myoblasts that are dystrophin deficient, possessing a mutation in dystrophin or non-functioning dystrophin.

[0041] **FIG. 3** is a series of graphs showing that myoblast cells express multiple laminin integrins ($\alpha 3\beta 1$; $\alpha 6\beta 1$; $\alpha 7\beta 1$ and $\alpha 6\beta 4$) as measured by FACS analysis.

[0042] **FIG. 4** is a series of graphs showing that myotube cells express multiple laminin integrins ($\alpha 3\beta 1$; $\alpha 6\beta 1$; $\alpha 7\beta 1$ and $\alpha 6\beta 4$) as measured by FACS analysis.

[0043] **FIG. 5** is a graph showing that integrin $\alpha 7\beta 1$ heterodimer activation by a $\beta 1$ agonist antibody (TS2/16) promotes human myotube adhesion to merosin (laminin). “Anti $\alpha 3+\alpha 6$ ” refers to the combination of inhibitory antibodies against $\alpha 3\beta 1$ and $\alpha 6\beta 1$. “Anti $\alpha 3+\alpha 6+\alpha 7$ ” refers to the combination of inhibitory antibodies against $\alpha 3\beta 1$, $\alpha 6\beta 1$ and $\alpha 7\beta 1$. “DMD”

refers to myotubes that are dystrophin deficient, possessing a mutation in dystrophin or non-functioning dystrophin.

[0044] **FIG. 6** shows photomicrographs depicting myotube formation of C2C12 cells five days after differentiation.

[0045] **FIG. 7** is a graph showing relative expression of dystrophin as measured by QPCR (quantitative PCR) in C2C12 murine cells treated with either control siRNA or dystrophin-targeting siRNA.

[0046] **FIG. 8A** is a graph showing that integrin $\beta 1$ protein activation by a $\beta 1$ agonist antibody (TS2/16) promotes murine myotube adhesion to laminin in C2C12 murine myotube cells treated with either control siRNA or dystrophin-targeting siRNA.

[0047] **FIG. 8B** is a graph showing that the adhesion to laminin is mainly contributed by $\alpha 7\beta 1$ integrin upon stimulation by TS2/16. “Anti $\alpha 3+\alpha 6$ ” refers to the combination of inhibitory antibodies against $\alpha 3\beta 1$ and $\alpha 6\beta 1$. “Anti $\alpha 3+\alpha 6+\alpha 7$ ” refers to the combination of inhibitory antibodies against $\alpha 3\beta 1$, $\alpha 6\beta 1$ and $\alpha 7\beta 1$. “DMD(KD)” refers to myotubes cells treated with dystrophin-targeting siRNA. Mn^{2+} was used as a pan-integrin activator to reach the maximum level of cell adhesion to merosin achievable.

[0048] **FIG. 9** is a schematic of the process by which monoclonal antibodies binding to integrin $\alpha 7\beta 1$ protein were generated and characterized.

[0049] **FIG. 10A** is a graph showing the results of a solid phase binding assay of the activity of two activating antibodies (M10, M25) and one blocking antibody (M20) to $\alpha 7\beta 1$ integrin.

[0050] **FIG. 10B** is a graph showing the results of a cell adhesion assay of the activity of two activating antibodies (M10, M25) and one blocking antibody (M20) to $\alpha 7\beta 1$ integrin.

[0051] **FIG. 10C** is a series of graphs showing the results of direct ELISAs analyzing the binding of M10 and M25 antibodies and a $\beta 1$ agonist antibody (TS2/16) to $\beta 1$ -containing integrins.

[0052] **FIG. 11A** is a series of graphs showing that antibodies M36 and M38 bind to cell surfaces expressing $\alpha 7\beta 1$ integrins. K562/Mock (transfected with control empty vector), K562 $\alpha 7X2$ (transfected with plasmid encoding integrin $\alpha 7X2$ cDNA) and C2C12 cells were tested for binding of M36, M38 and $\alpha 7$ (3C12). 3C12 is a positive control antibody for integrin $\alpha 7$.

[0053] **FIG. 11B** is a series of graphs showing that antibodies M36 and M38 selectively bind to human and murine $\alpha 7\beta 1$ integrins (Hu_ $\alpha 7\beta 1$ and Mu_ $\alpha 7\beta 1$), as opposed to human $\alpha 6\beta 1$ (Hu_ $\alpha 6\beta 1$) or $\alpha 5\beta 1$ (Hu_ $\alpha 5\beta 1$) integrins.

[0054] **FIG. 12A** is a diagram of the integrin $\alpha 7$ protein structure and its domains. This figure also depicts the variable region sequences X1 (**SEQ ID NO: 1**) and X2 (**SEQ ID NO: 10**) found in the extracellular domain of integrin $\alpha 7$ protein.

[0055] **FIG. 12B** is a series of graphs showing that antibodies M36 and M38 preferentially bind to cell surfaces expressing the X2 form of $\alpha 7\beta 1$ integrin. K562 cell lines stably transfected with human integrin $\alpha 7X1$ or $\alpha 7X2$ cDNA are named as K562/Hu_ $\alpha 7X1$ or K562/Hu_ $\alpha 7X2$.

[0056] **FIG. 13A** is a graph showing that antibodies M36 and M38 enhance integrin $\alpha 7\beta 1$ (K562/ $\alpha 7X2$) cell adhesion to human laminin 211 (LN211). TS2/16 is a $\beta 1$ agonist antibody. M35 is a control antibody having no effect on adhesion to laminin.

[0057] **FIG. 13B** is a graph showing that antibodies M36 and M38 enhance the adhesion of mouse myotubes in which dystrophin has been knocked down (KD) to laminin.

[0058] **FIG. 14** is a graph showing that antibodies M36 and M38 convert integrin $\alpha 7\beta 1$ to an active conformation. Monoclonal antibody 9EG7 detects $\beta 1$ integrin activation. Different cations were used to adjust integrin conformations before the antibody treatment (less active (Mg^{2+} 1mM) and active (Mn^{2+} 0.125mM)).

[0059] **FIG. 15** is a series of graphs showing that the VL3VHK20TFT monoclonal antibody binds to cells co-transfected with integrin subunit alpha 7 (ITGA7) and integrin beta-1 (ITGB1). 3C12, 6A11, A1-1a M20, and A1-1a M24 are positive control antibodies for binding to ITGA7. These antibodies are described in Table 4. The optimal screening concentration for each monoclonal antibody is outlined by a box.

[0060] **FIG. 16** is a graph showing that the VL3VHK20TFT Fab binds to cells co-transfected with integrin subunit alpha 7 (ITGA7) and integrin beta-1 (ITGB1). The optimal screening concentration for the Fab is outlined by a box.

[0061] **FIG. 17** is a graph showing binding of the VL3VHK20TFT Fab to a library of cells co-transfected with an alanine scanning library of ITGA7 mutants.

[0062] **FIG. 18** is a crystal structure model showing the critical residues for binding of the VL3VHK20TFT Fab to integrin subunit alpha 7. Critical residues are shown as red spheres. Secondary residues are shown as blue spheres.

[0063] **FIG. 19** is a graph showing results from **Example 4** at various concentrations for VL3VHK20 TFT; 0.25 $\mu g/mL$ Human Integrin $\alpha 7\beta 1$; 1:1 binding.

[0064] **FIG. 20** is a graph showing results from **Example 4** at various concentrations for VLVH; 0.25 $\mu g/mL$ Human Integrin $\alpha 7\beta 1$; 1:1 binding.

[0065] **FIG. 21A** is a graph showing results from **Example 4** at various concentrations for VL3VHK20 TFT; 0.25 $\mu\text{g/mL}$ Mouse Integrin $\alpha 7\beta 1$; 1:1 binding.

[0066] **FIG. 21B** is a graph showing results from **Example 4** at various concentrations for VLVH; 0.25 $\mu\text{g/mL}$ Mouse Integrin $\alpha 7\beta 1$; 1:1 binding.

[0067] **FIG. 22A** is a graph showing results from **Example 4** of VL3VHK20TFT binding to cell surfaces expressing integrin $\alpha 7\beta 1$.

[0068] **FIG. 22B** is a graph showing results from **Example 4** of VL3VHK20TFT enhanced human $\alpha 7\beta 1$ -expressing cell adhesion to laminin.

[0069] **FIG. 22C** is a graph showing results from **Example 4** of VL3VHK20TFT enhanced murine $\alpha 7\beta 1$ -expressing cell adhesion to laminin.

[0070] **FIG. 23** is a graph showing results from **Example 5** for antibody concentration in $\mu\text{g/mL}$ vs cell index (integrin $\alpha 7\beta 1$ mediated cell adhesion) for both murine antibody (VLVH) and humanized antibody (VL3VHK20TFT) enhanced myoblast cell adhesion on laminin.

[0071] **FIG. 24** is a graph showing results from **Example 6** for contraction vs force (normalized to initial contraction) for the DBA2/IgG control, the mdx/IgG control, the mdx/Agonist antibody at 3 mg/kg, and the mdx/agonist antibody at 15 mg/kg.

[0072] **FIG. 25** is a graph showing results from **Example 7** for stimulation frequency in Hz vs force (normalized to muscle width, mN/mm) for the DBA2/IgG control, the mdx/IgG control, the mdx/Agonist antibody at 3 mg/kg, and the mdx/agonist antibody at 15 mg/kg.

[0073] **FIG. 26** is a bar graph showing the amount of serum creatine kinase, a biomarker for muscle damage, in the DBA2/IgG control, the mdx/IgG control, and treatment with the M36 agonist antibody.

[0074] **FIG. 27** is a bar graph showing the amount of skeletal troponin, a biomarker for muscular damage, in the DBA2/IgG control, the mdx/IgG control, and treatment with the M36 agonist antibody.

[0075] **FIG. 28** is a bar graph showing the amount of O-hydroxyproline, a measure of collagen formation/fibrosis in the gastrocnemius muscle in the DBA2/IgG control, the mdx/IgG control, and treatment with the M36 agonist antibody.

[0076] **FIG. 29** shows various sequence variants generated by site-mutagenesis on amino acids located in heavy chain CDR1 and CDR2, or light chain CDR1, of antibody VL3VHK20TFT. YGISF: **SEQ ID NO: 26**. GYTFTSYYMH: **SEQ ID NO: 27**. QGTSY: **SEQ ID NO: 28**. SGTSY: **SEQ ID NO: 29**. RASQSISSYLN: **SEQ ID NO: 30**.

[0077] **FIG. 30** is a bar graph showing binding to cell surface integrin $\alpha 7\beta 1$ by antibody sequence variants. The binding was measured by flow cytometry and normalized to an IgG4 isotype control.

[0078] **FIG. 31** is an illustration depicting the extracellular region of $\alpha 7\beta 1$ integrin and various domains therein. The α chain of such integrins, e.g., $\alpha 3$, $\alpha 6$ and $\alpha 7$ (shown), include four extracellular domains: a seven-bladed β -*propeller*, a thigh, and two *calf* domains (CALF-1 and CALF-2). The thigh and calf domains have similar, immunoglobulin-like, β -sandwich folds.

DETAILED DESCRIPTION OF THE INVENTION

[0079] The invention provides pharmaceutical agents that activate integrin heterodimers containing the beta-1 ($\beta 1$) protein that specifically bind laminin protein. An agonist of an integrin heterodimer containing the $\beta 1$ protein may provide therapeutic benefits to a subject with muscular dystrophy associated with a malfunction of one of the proteins of the laminin/dystroglycan/sarcoglycan/dystrophin complex or the laminin- $\alpha 2$ (merosin) protein.

[0080] Integrin heterodimers are composed of non-covalently associated α and β protein subunits and act as transmembrane adhesion receptors (Hynes, (2002) Cell 110:673–687). In some embodiments, a pharmaceutical agent described herein is an agonist of at least one of $\alpha 7\beta 1$ integrin, $\alpha 6\beta 1$ integrin and $\alpha 3\beta 1$ integrin. In certain cases, a pharmaceutical agent is an agonist of $\alpha 7\beta 1$ integrin, $\alpha 6\beta 1$ integrin and $\alpha 3\beta 1$ integrin. In other embodiments, a pharmaceutical agent is an agonist of $\alpha 7\beta 1$ integrin and $\alpha 6\beta 1$ integrin. In other embodiments, a pharmaceutical agent is an agonist of $\alpha 6\beta 1$ integrin and $\alpha 3\beta 1$ integrin. In yet other embodiments, a pharmaceutical agent is an agonist of $\alpha 7\beta 1$ integrin and $\alpha 3\beta 1$ integrin. In one embodiment, a pharmaceutical agent is an agonist of $\alpha 7\beta 1$ integrin. In another embodiment, a pharmaceutical agent is an agonist of $\alpha 6\beta 1$ integrin. In yet another embodiment, a pharmaceutical agent is an agonist of $\alpha 3\beta 1$ integrin. In some examples, the integrin proteins are human integrin proteins. In some embodiments, a pharmaceutical agent does not bind specifically to the $\beta 1$ protein.

[0081] The invention provides a pharmaceutical agent that is an agonist of at least one of $\alpha 7\beta 1$ integrin, $\alpha 6\beta 1$ integrin and $\alpha 3\beta 1$ integrin and that binds to the extracellular domain of at least one of $\alpha 7$ protein, $\alpha 6$ protein and $\alpha 3$ protein. In some embodiments, a pharmaceutical agent binds at least one of: the laminin binding domain of at least one of $\alpha 7$ protein, $\alpha 6$ protein and $\alpha 3$ protein; the CALF-1 domain of at least one of $\alpha 7$ protein, $\alpha 6$ protein and $\alpha 3$ protein; and the CALF-2 domain of at least one of $\alpha 7$ protein, $\alpha 6$ protein and $\alpha 3$ protein. An

illustration depicting the extracellular region of $\alpha 7\beta 1$ integrin and various domains therein, including the CALF domains, is provided in **FIG. 31**.

[0082] In certain cases, a pharmaceutical agent binds to the laminin binding domains of one or more of $\alpha 7$ protein (**SEQ ID NO: 11**), $\alpha 6$ protein (**SEQ ID NO: 12**) and $\alpha 3$ protein (**SEQ ID NO: 13**). In some embodiments, a pharmaceutical agent binds to the laminin binding domains of $\alpha 7$ protein (**SEQ ID NO: 11**), $\alpha 6$ protein (**SEQ ID NO: 12**) and $\alpha 3$ protein (**SEQ ID NO: 13**).

[0083] In some embodiments, a pharmaceutical agent binds to the CALF-1 domain of at least one of $\alpha 7$ protein, $\alpha 6$ protein and $\alpha 3$ protein. An exemplary sequence of a human CALF-1 domain is provided in **Table 1B**. In some embodiments, a pharmaceutical agent binds to a CALF-1 domain comprising **SEQ ID NO: 73**.

[0084] In some embodiments, a pharmaceutical agent binds to the CALF-2 domain of at least one of $\alpha 7$ protein, $\alpha 6$ protein and $\alpha 3$ protein. An exemplary sequence of a human CALF-2 domain is provided in **Table 1C**. In some embodiments, a pharmaceutical agent binds to a CALF-2 domain comprising **SEQ ID NO: 74**.

[0085] The invention relates to a pharmaceutical agent that is an agonist of $\alpha 7\beta 1$ integrin and that binds specifically to the $\alpha 7$ protein. In one embodiment, the invention provides a pharmaceutical agent that is an agonist of $\alpha 7\beta 1$ integrin and that binds specifically to the $\alpha 7$ protein with the negative proviso that the pharmaceutical agent does not increase the amount of $\alpha 7$ protein in a muscle cell of a subject when the pharmaceutical agent is administered to the subject.

[0086] In some embodiments, the invention provides a pharmaceutical agent that confers an activated state on an $\alpha 7\beta 1$ integrin heterodimer.

[0087] In some embodiments, a pharmaceutical agent described herein is an antibody.

ANTIBODIES

[0088] In some embodiments, the invention provides a pharmaceutical agent that is an antibody. In one embodiment, an antibody binds specifically to the $\alpha 7$ protein. In another embodiment, an antibody binds specifically to the $\alpha 6$ protein. In a further embodiment, an antibody binds specifically to the $\alpha 3$ protein.

[0089] As used herein, the term “antibody” refers to immunoglobulin (Ig) molecules and immunologically active portions or fragments of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site that specifically binds (immunoreacts with) an antigen (e.g., $\alpha 7$ protein, $\alpha 6$ protein or $\alpha 3$ protein). By “specifically binds” or “immunoreacts with” is

meant that the antibody reacts with one or more antigenic determinants of the desired antigen and does not react with other polypeptides. In certain embodiments, an antibody is said to specifically bind an antigen when it preferentially recognizes its target antigen in a complex mixture of proteins and/or macromolecules. The term "antibody" broadly refers to an immunoglobulin (Ig) molecule, generally comprising four polypeptide chains, two heavy (H) chains and two light (L) chains, or any functional fragment, mutant, variant, or derivative thereof, that retains the essential target binding features of an Ig molecule. Such mutant, variant, or derivative antibody formats are known in the art.

[0090] In a full-length antibody, each heavy chain comprises a heavy chain variable region (abbreviated herein as HCVR or VH region) and a heavy chain constant region. The heavy chain constant region comprises three domains, CH1, CH2 and CH3. Each light chain comprises a light chain variable region (abbreviated herein as LCVR or VL region) and a light chain constant region. The light chain constant region comprises one domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FRs). Each VH region and VL region is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. Immunoglobulin molecules can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY) and class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass. IgG, IgD, and IgE antibodies generally contain two identical heavy chains and two identical light chains and two antigen combining domains, each composed of a heavy chain variable region (VH) and a light chain variable region (VL). Generally IgA antibodies are composed of two monomers, each monomer composed of two heavy chains and two light chains (as for IgG, IgD, and IgE antibodies); in this way the IgA molecule has four antigen binding domains, each again composed of a VH and a VL. Certain IgA antibodies are monomeric in that they are composed of two heavy chains and two light chains. Secreted IgM antibodies are generally composed of five monomers, each monomer composed of two heavy chains and two light chains (as for IgG and IgE antibodies); in this way the IgM molecule has ten antigen binding domains, each again composed of a VH and a VL. A cell surface form of IgM also exists and this has two heavy chain/two light chain structure similar to IgG, IgD, and IgE antibodies.

[0091] The term "antigen binding fragment" or "antigen binding portion" of an antibody (or simply "antibody fragment" or "antibody portion"), as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen (e.g., $\alpha 7$

protein). It has been shown that the antigen binding function of an antibody can be performed by fragments of a full-length antibody. Antibody and antibody fragment embodiments may also be bispecific, trispecific, dual specific, or multi-specific formats; specifically binding to two or more different antigens. Examples of binding fragments encompassed within the term "antigen binding fragment" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a F(ab')₂ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) an Fd fragment consisting of the VH and CH1 domains; (iv) an Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a dAb fragment (Ward et al., (1989) Nature 341:544-546, Winter et al., PCT publication WO 90/05144 A1, each herein incorporated by reference in its entirety), which comprises a single variable domain; and (vi) an isolated complementarity determining region (CDR). The invention also encompasses an Fab' fragment. Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv); see e.g., Bird et al. (1988) Science 242:423-426; and Huston et al. (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883). Such single chain antibodies are also intended to be encompassed within the term "antigen binding fragment" of an antibody. In certain embodiments of the invention, scFv molecules may be incorporated into a fusion protein. In some embodiments, the invention includes a single chain camelid antibody. Other forms of single chain antibodies, such as diabodies are also included. Diabodies are bivalent, bispecific antibodies in which VH and VL domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites (see e.g., Holliger, P., et al. (1993) Proc. Natl. Acad. Sci. USA 90:6444-6448; Poljak, R. J., et al. (1994) Structure 2:1121-1123). Such antibody binding fragments are known in the art (Kontermann and Dubel eds., Antibody Engineering (2001) Springer-Verlag, New York, 790 pp.). In some aspects, the invention includes a single domain antibody. In general, the term "antibody" when used herein encompasses an "antibody fragment". An antibody fragment generally retains the antigen-binding properties of a full length antibody.

[0092] In certain embodiments, the invention provides antibodies and antibody fragments that are agonists of $\alpha 7 \beta 1$ integrin and that comprise one or more amino acid sequences shown in Table 2 or Table 3.

[0093] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 2**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 4**, or a variant thereof having 5 or fewer conservative amino acid substitutions in HCDR1, HCDR2, and/or HCDR3; wherein the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 14**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 15**, or a variant thereof having 5 or fewer conservative amino acid substitutions in HCDR1, HCDR2, and/or HCDR3; wherein the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 65**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 66**, or a variant thereof having 5 or fewer conservative amino acid substitutions in HCDR1, HCDR2, and/or HCDR3; or wherein the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 14**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 68**, or a variant thereof having 5 or fewer conservative amino acid substitutions in HCDR1, HCDR2, and/or HCDR3.

[0094] The invention also encompasses a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a light chain variable (VL) region and a heavy chain variable (VH) region, wherein the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 5**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**, or a variant thereof having 5 or fewer conservative amino acid substitutions in LCDR1, LCDR2, and/or LCDR3; wherein the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 69**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**, or a variant thereof having 5 or fewer conservative amino acid substitutions in LCDR1, LCDR2, and/or LCDR3; or wherein the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 71**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**, or a variant thereof having 5 or fewer conservative amino acid substitutions in LCDR1, LCDR2, and/or LCDR3.

[0095] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 2**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 4**, or a variant thereof having 5 or fewer conservative amino acid substitutions in HCDR1, HCDR2, and/or HCDR3; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 5**, LCDR2 of

SEQ ID NO: 6 and **LCDR3** of **SEQ ID NO: 7**, or a variant thereof having 5 or fewer conservative amino acid substitutions in **LCDR1**, **LCDR2**, and/or **LCDR3**; (ii) the **VH** region amino acid sequence comprises **HCDR1** of **SEQ ID NO: 14**, **HCDR2** of **SEQ ID NO: 3** and **HCDR3** of **SEQ ID NO: 15**, or a variant thereof having 5 or fewer conservative amino acid substitutions in **HCDR1**, **HCDR2**, and/or **HCDR3**; and the **VL** region amino acid sequence comprises **LCDR1** of **SEQ ID NO: 5**, **LCDR2** of **SEQ ID NO: 6** and **LCDR3** of **SEQ ID NO: 7**, or a variant thereof having 5 or fewer conservative amino acid substitutions in **LCDR1**, **LCDR2**, and/or **LCDR3**; (iii) the **VH** region amino acid sequence comprises **HCDR1** of **SEQ ID NO: 65**, **HCDR2** of **SEQ ID NO: 3** and **HCDR3** of **SEQ ID NO: 66**, or a variant thereof having 5 or fewer conservative amino acid substitutions in **HCDR1**, **HCDR2**, and/or **HCDR3**; and the **VL** region amino acid sequence comprises **LCDR1** of **SEQ ID NO: 5**, **LCDR2** of **SEQ ID NO: 6** and **LCDR3** of **SEQ ID NO: 7**, or a variant thereof having 5 or fewer conservative amino acid substitutions in **LCDR1**, **LCDR2**, and/or **LCDR3**; (iv) the **VH** region amino acid sequence comprises **HCDR1** of **SEQ ID NO: 14**, **HCDR2** of **SEQ ID NO: 3** and **HCDR3** of **SEQ ID NO: 68**, or a variant thereof having 5 or fewer conservative amino acid substitutions in **HCDR1**, **HCDR2**, and/or **HCDR3**; and the **VL** region amino acid sequence comprises **LCDR1** of **SEQ ID NO: 69**, **LCDR2** of **SEQ ID NO: 6** and **LCDR3** of **SEQ ID NO: 7**, or a variant thereof having 5 or fewer conservative amino acid substitutions in **LCDR1**, **LCDR2**, and/or **LCDR3**; or (v) the **VH** region amino acid sequence comprises **HCDR1** of **SEQ ID NO: 14**, **HCDR2** of **SEQ ID NO: 3** and **HCDR3** of **SEQ ID NO: 68**, or a variant thereof having 5 or fewer conservative amino acid substitutions in **HCDR1**, **HCDR2**, and/or **HCDR3**; and the **VL** region amino acid sequence comprises **LCDR1** of **SEQ ID NO: 71**, **LCDR2** of **SEQ ID NO: 6** and **LCDR3** of **SEQ ID NO: 7**, or a variant thereof having 5 or fewer conservative amino acid substitutions in **LCDR1**, **LCDR2**, and/or **LCDR3**.

[0096] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (**VH**) region and a light chain variable (**VL**) region, wherein (i) the **VH** region amino acid sequence comprises a **HCDR1** sequence comprising **SEQ ID NO: 14** with an amino acid substitution at its eight amino acid residue, **HCDR2** of **SEQ ID NO: 3** and **HCDR3** of **SEQ ID NO: 4**, **SEQ ID NO: 66** or **SEQ ID NO: 68**; and the **VL** region amino acid sequence comprises **LCDR1** of **SEQ ID NO: 5**, **SEQ ID NO: 69** or **SEQ ID NO: 71**, **LCDR2** of **SEQ ID NO: 6** and **LCDR3** of **SEQ ID NO: 7**.

[0097] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the VH region amino acid sequence comprises (i) **SEQ ID NO: 8**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 8**; (ii) **SEQ ID NO: 16**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 16**; or (iii) **SEQ ID NO: 67**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 67**.

[0098] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 2**, **SEQ ID NO: 14** or **SEQ ID NO: 65**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 4**, **SEQ ID NO: 15**, **SEQ ID NO: 66** or **SEQ ID NO: 68**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 5**, **SEQ ID NO: 69** or **SEQ ID NO: 71**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[0099] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 2**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 15**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 5**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00100] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 2**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 15**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 69**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00101] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable

(VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 2**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 15**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 71**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00102] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 2**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 66**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 5**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00103] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 2**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 66**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 69**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00104] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 2**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 66**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 71**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00105] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 2**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 68**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 5**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00106] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the

antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 2**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 68**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 69**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00107] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 2**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 68**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 71**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00108] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 14**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 15**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 5**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00109] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 14**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 15**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 69**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00110] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 14**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 15**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 71**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00111] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 14**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 66**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 5**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00112] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 14**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 66**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 69**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00113] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 14**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 66**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 71**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00114] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 14**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 68**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 5**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00115] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 14**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 68**; and the VL region

amino acid sequence comprises LCDR1 of **SEQ ID NO: 69**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00116] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 14**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 68**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 71**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00117] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 65**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 15**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 5**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00118] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 65**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 15**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 69**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00119] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 65**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 15**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 71**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00120] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID**

NO: 65, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 66**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 5**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00121] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 65**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 66**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 69**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00122] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 65**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 66**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 71**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00123] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 65**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 68**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 5**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00124] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 65**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 68**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 69**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00125] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable

(VL) region, wherein (i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 65**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 68**; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 71**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**.

[00126] In some embodiments, the invention encompasses a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a light chain variable (VL) region and a heavy chain variable (VH) region, wherein the VL region amino acid sequence comprises (i) **SEQ ID NO: 9**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 9**; (ii) **SEQ ID NO: 17**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 17**; (iii) **SEQ ID NO: 70**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 70**; or (iv) **SEQ ID NO: 72**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 72**.

[00127] The invention further provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein (i) the VH region amino acid sequence comprises **SEQ ID NO: 8**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 8**; and the VL region amino acid sequence comprises **SEQ ID NO: 9**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 9**; (ii) the VH region amino acid sequence comprises **SEQ ID NO: 16**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 16**; and the VL region amino acid sequence comprises **SEQ ID NO: 17**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 17**; (iii) the VH region amino acid sequence comprises **SEQ ID NO: 67**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 67**; and the VL region amino acid sequence comprises **SEQ ID NO: 17**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 17**; (iv) the VH region amino acid sequence comprises **SEQ ID NO: 16**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 16**; and the VL region amino acid sequence comprises **SEQ ID NO: 70**, or an amino acid

sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 70**; or (v) the VH region amino acid sequence comprises **SEQ ID NO: 16**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 16**; and the VL region amino acid sequence comprises **SEQ ID NO: 72**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 72**.

[00128] In some embodiments, provided herein is a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody comprises a heavy chain and a light chain, (i) wherein the heavy chain amino acid sequence comprises **SEQ ID NO: 18**, and the light chain amino acid sequence comprises **SEQ ID NO: 19**; (ii) wherein the heavy chain amino acid sequence comprises **SEQ ID NO: 45**, and the light chain amino acid sequence comprises **SEQ ID NO: 53**; (iii) wherein the heavy chain amino acid sequence comprises **SEQ ID NO: 18**, and the light chain amino acid sequence comprises **SEQ ID NO: 62**; (iv) wherein the heavy chain amino acid sequence comprises **SEQ ID NO: 18**, and the light chain amino acid sequence comprises **SEQ ID NO: 63**.

[00129] In some embodiments, provided herein is a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody is hIgG4-1, hIgG4-2, hIgG4-3, hIgG4-4, hIgG4-5, hIgG4-6, hIgG4-7, hIgG4-8, hIgG4-9, hIgG4-10, hIgG4-11, hIgG4-12, hIgG4-13, hIgG4-14, hIgG4-15, hIgG4-16, hIgG4-17, hIgG4-18, hIgG4-19, hIgG4-20, hIgG4-21, hIgG4-22, hIgG4-23, hIgG4-24, hIgG4-25, hIgG4-26, hIgG4-27, hIgG4-28, hIgG4-29, hIgG4-30, hIgG4-31, hIgG4-32, hIgG4-33, hIgG4-34, hIgG4-35, hIgG4-36, hIgG4-37, hIgG4-38, hIgG4-39, hIgG4-40, hIgG4-41, hIgG4-42, hIgG4-43, hIgG4-44, hIgG4-45, hIgG4-46, hIgG4-47, hIgG4-48, or hIgG4-49. The combinations of heavy chain and light chain sequences forming these antibodies are provided in **Table 10**.

[00130] In some embodiments, an anti- $\alpha 7$ antibody or an $\alpha 7$ -binding antibody fragment comprises a polypeptide having one or more amino acid substitutions, deletions or insertions as compared to a polypeptide having an amino acid sequence of one or more of **SEQ ID NOs: 2-9, 14-19 and 31-72**. For example, an anti- $\alpha 7$ antibody or an $\alpha 7$ -binding antibody fragment may have 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more amino acid substitutions, deletions or insertions. Substitutions, deletions or insertions may be introduced by standard techniques, such as site-directed mutagenesis or PCR-mediated mutagenesis of a nucleic acid molecule encoding a polypeptide of an anti- $\alpha 7$ antibody or an $\alpha 7$ -binding antibody fragment.

[00131] In some embodiments, conservative amino acid substitutions are made at one or more positions in the amino acid sequences of antibodies or antibody fragments disclosed

herein. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. In certain embodiments, conservative amino acid substitutions are made only in the FR sequences and not in the CDR sequences of an antibody or antibody fragment. Families of amino acid residues having similar side chains have been defined in the art, including basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan; histidine). Thus, an amino acid residue in a polypeptide of an anti- $\alpha 7$ antibody or an $\alpha 7$ -binding antibody fragment may be replaced with another amino acid residue from the same side chain family. In some embodiments, a string of amino acids can be replaced with a structurally similar string that differs in order and/or composition of side chain family members. In some embodiments, a substitution may replace the original amino acid residue with a relatively more hydrophobic amino acid residue. In some embodiments, a substitution may replace the original amino acid residue with a relatively less hydrophobic amino acid residue. Those skilled in the art will be able to evaluate whether an anti- $\alpha 7$ antibody or an $\alpha 7$ -binding antibody fragment comprising a polypeptide having one or more amino acid substitutions, deletions or insertions as compared to a polypeptide having an amino acid sequence of one or more of **SEQ ID NOs: 2-9, 14-19 and 31-72** binds $\alpha 7$ protein by utilizing art-recognized methods including, but not limited to, ELISAs, Western blots, phage display, etc.

[00132] Calculations of sequence homology or identity (the terms are used interchangeably herein) between sequences may be performed as follows.

[00133] To determine the percent identity of two amino acid sequences, or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-homologous sequences can be disregarded for comparison purposes). In a preferred embodiment, the length of a reference sequence aligned for comparison purposes is at least 30%, preferably at least 40%, more preferably at least 50%, even more preferably at least 60%, and even more preferably at least 70%, 75%, 80%, 82%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% of the length of the reference sequence. The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a

position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position (as used herein amino acid or nucleic acid "identity" is equivalent to amino acid or nucleic acid "homology"). 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 need to be introduced for optimal alignment of the two sequences.

[00134] The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In one embodiment, the percent identity between two amino acid sequences is determined using the Needleman et al. ((1970) J. Mol. Biol. 48:444-453) algorithm which has been incorporated into the GAP program in the GCG software package (available at www.gcg.com), using either a BLOSUM 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet another embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package (available at www.gcg.com), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. One set of parameters (and the one that can be used if the practitioner is uncertain about what parameters should be applied to determine if a molecule is within a sequence identity or homology limitation of the invention) is a BLOSUM 62 scoring matrix with a gap penalty of 12, a gap extend penalty of 4, and a frameshift gap penalty of 5.

[00135] The percent identity between two amino acid or nucleotide sequences can be determined using the algorithm of Meyers et al. ((1989) CABIOS 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.

[00136] In some embodiments, an antibody is a monoclonal antibody. In some embodiments, an antibody is a polyclonal antibody. The term "monoclonal antibody" refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope of an antigen. A monoclonal antibody composition thus typically displays a single binding affinity for a particular protein with which it immunoreacts.

[00137] In some embodiments, an antibody of the invention is humanized, chimeric or human.

[00138] In some embodiments, an antibody of the invention is a humanized antibody and an integrin agonist. "Humanized antibody" as the term is used herein refers to an antibody that has been engineered to comprise one or more human framework regions in the variable region together with non-human (e.g., mouse, rat, or hamster) complementarity-determining regions (CDRs) of the heavy and/or light chain. In certain embodiments, a humanized antibody comprises sequences that are entirely human except for the CDR regions. Humanized antibodies are typically less immunogenic to humans, relative to non-humanized antibodies, and thus offer therapeutic benefits in certain situations. Those skilled in the art will be aware of humanized antibodies, and will also be aware of suitable techniques for their generation. See for example, Hwang, W. Y. K., et al., *Methods* 36:35, 2005; Queen et al., *Proc. Natl. Acad. Sci. USA*, 86:10029-10033, 1989; Jones et al., *Nature*, 321:522-25, 1986; Riechmann et al., *Nature*, 332:323-27, 1988; Verhoeyen et al., *Science*, 239:1534-36, 1988; Orlandi et al., *Proc. Natl. Acad. Sci. USA*, 86:3833-37, 1989; U.S. Pat. Nos. 5,225,539; 5,530,101; 5,585,089; 5,693,761; 5,693,762; 6,180,370; and Selick et al., WO 90/07861, each of which is incorporated herein by reference in its entirety. In some embodiments, an antibody or antigen-binding fragment of the invention may comprise a VH region amino acid sequence that comprises HCDR1 of **SEQ ID NO: 2**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 4**; and a VL region amino acid sequence that comprises LCDR1 of **SEQ ID NO: 5**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**; and one or more human framework region sequences. In some embodiments, an antibody or antigen-binding fragment of the invention may comprise a VH region amino acid sequence that comprises HCDR1 of **SEQ ID NO: 14**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 15**; and a VL region amino acid sequence that comprises LCDR1 of **SEQ ID NO: 5**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**; and one or more human framework region sequences. In some embodiments, an antibody or antigen-binding fragment of the invention may comprise a VH region amino acid sequence that comprises HCDR1 of **SEQ ID NO: 65**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 66**; and a VL region amino acid sequence that comprises LCDR1 of **SEQ ID NO: 5**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**; and one or more human framework region sequences. In some embodiments, an antibody or antigen-binding fragment of the invention may comprise a VH region amino acid sequence that comprises HCDR1 of **SEQ ID NO: 14**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 68**; and a VL region amino acid sequence that comprises LCDR1 of **SEQ ID NO: 69**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**; and one or more human framework region sequences. In some embodiments, an antibody or

antigen-binding fragment of the invention may comprise a VH region amino acid sequence that comprises HCDR1 of **SEQ ID NO: 14**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 68**; and a VL region amino acid sequence that comprises LCDR1 of **SEQ ID NO: 71**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**; and one or more human framework region sequences.

[00139] In some embodiments, an antibody of the invention is a chimeric antibody and an integrin agonist. “Chimeric antibody” as the term is used herein refers to an antibody that has been engineered to comprise at least one human constant region. For example, one or all the variable regions of the light chain(s) and/or one or all the variable regions of the heavy chain(s) of a mouse antibody (e.g., a mouse monoclonal antibody) may each be joined to a human constant region, such as, without limitation an IgG1 human constant region. Chimeric antibodies are typically less immunogenic to humans, relative to non-chimeric antibodies, and thus offer therapeutic benefits in certain situations. Those skilled in the art will be aware of chimeric antibodies, and will also be aware of suitable techniques for their generation. See, for example, Cabilly et al., U.S. Pat. No. 4,816,567; Shoemaker et al., U.S. Pat. No. 4,978,775; Beavers et al., U.S. Pat. No. 4,975,369; and Boss et al., U.S. Pat. No. 4,816,397, each of which is incorporated herein by reference in its entirety. In some embodiments, an antibody or antigen-binding fragment of the invention may comprise a VH region comprising **SEQ ID NO: 8**; a VL region comprising **SEQ ID NO: 9**, and a human constant region. In some embodiments, an antibody or antigen-binding fragment of the invention may comprise a VH region comprising **SEQ ID NO: 16**; a VL region comprising **SEQ ID NO: 17**, and a human constant region. In some embodiments, an antibody or antigen-binding fragment of the invention may comprise a VH region comprising **SEQ ID NO: 67**; a VL region comprising **SEQ ID NO: 17**, and a human constant region. In some embodiments, an antibody or antigen-binding fragment of the invention may comprise a VH region comprising **SEQ ID NO: 16**; a VL region comprising **SEQ ID NO: 70**, and a human constant region. In some embodiments, an antibody or antigen-binding fragment of the invention may comprise a VH region comprising **SEQ ID NO: 16**; a VL region comprising **SEQ ID NO: 72**, and a human constant region.

[00140] In some embodiments, a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, may comprise an immunoglobulin constant region. In some embodiments, the immunoglobulin constant region is IgG1, IgG2, IgG3, IgG4, IgA1 or IgA2. In some embodiments, the immunoglobulin constant region is IgG1, IgG2, IgG3, IgG1null, IgG4(S228P), IgA1 or IgA2. The antibody molecule or antigen-binding portion thereof may

comprise an immunologically inert constant region. In some embodiments, a monoclonal antibody or an antibody fragment thereof may comprise an immunoglobulin constant region comprising a wild-type human IgG1 constant region, a human IgG1 constant region comprising the amino acid substitutions L234A, L235A and G237A or a human IgG1 constant region comprising the amino acid substitutions L234A, L235A, G237A and P331S. In some embodiments, a monoclonal antibody or an antibody fragment thereof may comprise an immunoglobulin constant region comprising a wild-type human IgG2 constant region or a wild-type human IgG4 constant region. In some embodiments, a monoclonal antibody or an antibody fragment thereof may comprise an immunoglobulin constant region comprising an amino acid sequence of an Fc region of human IgG4, human IgG4(S228P), human IgG2, human IgG1, human IgG1-3M or human IgG1-4M. For example, the human IgG4(S228P) Fc region comprises the following substitution compared to the wild-type human IgG4 Fc region: S228P. For example, the human IgG1-3M Fc region comprises the following substitutions compared to the wild-type human IgG1 Fc region: L234A, L235A and G237A, while the human IgG1-4M Fc region comprises the following substitutions compared to the wild-type human IgG1 Fc region: L234A, L235A, G237A and P331S. In some embodiments, a position of an amino acid residue in a constant region of an immunoglobulin molecule is numbered according to EU nomenclature (Ward *et al.*, 1995 *Therap. Immunol.* 2:77-94).

[00141] In some embodiments, a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, may comprise an immunoglobulin light chain constant region that is a kappa light chain constant region or a lambda light chain constant region.

[00142] In some embodiments, the invention provides a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment binds specifically to an epitope of $\alpha 7$ protein. In some embodiments, an epitope of $\alpha 7$ protein bound by an antibody or antibody fragment is continuous. In some embodiments, an epitope of $\alpha 7$ protein bound by an antibody or antibody fragment is discontinuous.

[00143] In some embodiments, a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, binds specifically to the extracellular domain of $\alpha 7$ protein. $\alpha 7$ protein may have two different extracellular sequences (designated "X1" and "X2") due to post-transcriptional modifications. The region that is variable between the X1 and X2 sequences is located between the III and IV homology repeat domains of $\alpha 7$ protein, near the putative ligand binding site. In certain embodiments, a monoclonal antibody or an antibody fragment thereof that is an agonist of $\alpha 7\beta 1$ integrin binds specifically to a region of $\alpha 7$

protein between the III and IV homology repeat domains near the putative ligand binding site. The X1 sequence consists of, consists essentially of, or comprises TARVELCAQGSADLAHLDDGPYEAGGEKEQDPRLIPVPANSYFG (**SEQ ID NO: 1**). The X2 sequence consists of, consists essentially of, or comprises LLFVTNIDSSDPDQLVYKTLDPADRLPGPAGDLALNSYLG (**SEQ ID NO: 10**). The X2 sequence is preferentially expressed in adult skeletal cells. In some embodiments, a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, binds specifically to an epitope of $\alpha 7$ protein that comprises, consists essentially of, or consists of **SEQ ID NO: 10**. In some embodiments, a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, binds specifically to an epitope of $\alpha 7$ protein that comprises, consists essentially of, or consists of 5-10, 10-15, 15-20, 20-25, 25-30, 30-35 or 35-40 amino acids of **SEQ ID NO: 10**. In some embodiments, a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, binds specifically to an epitope of $\alpha 7$ protein that comprises, consists essentially of, or consists of **SEQ ID NO: 1**. In some embodiments, a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, binds specifically to an epitope of $\alpha 7$ protein that comprises, consists essentially of, or consists of 5-10, 10-15, 15-20, 20-25, 25-30, 30-35, 35-40 or 40-44 amino acids of **SEQ ID NO: 1**.

[00144] In some embodiments, a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, binds specifically to an epitope of $\alpha 7$ protein that comprises, consists essentially of, or consists of 5-10, 10-15, 15-20, 20-25, 25-30, 30-35 or 35-40 amino acids of **SEQ ID NO: 24**.

[00145] In some embodiments, an antibody binds to a CALF-2 domain of $\alpha 7$ protein (*e.g.*, human $\alpha 7$ protein).

[00146] In some embodiments, a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, binds specifically to an epitope of $\alpha 7$ protein, wherein the epitope comprises SWWP (**SEQ ID NO: 25**). In some embodiments, a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, binds specifically to an epitope of $\alpha 7$ protein, wherein the epitope comprises SWWP (**SEQ ID NO: 25**), and wherein the epitope comprises, consists essentially of, or consists of 5-10 or 10-15 amino acids of **SEQ ID NO: 24**. In some embodiments, a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, binds specifically to an epitope comprising the residues S977, W978, W979 and P980 of **SEQ ID NO: 24**. In some embodiments, a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof,

binds specifically to an epitope comprising the residues S977, W978, W979 and P980 of **SEQ ID NO: 24**, wherein the epitope comprises, consists essentially of, or consists of 5-10 or 10-15 amino acids of **SEQ ID NO: 24**. In some embodiments, a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, binds specifically to an epitope comprising the residues R958, M976, S977, W978, W979 and P980 of **SEQ ID NO: 24**. In some embodiments, a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, binds specifically to an epitope comprising the residues R958, M976, S977, W978, W979 and P980 of **SEQ ID NO: 24**, wherein the epitope comprises, consists essentially of, or consists of 6-10 or 10-15 amino acids of **SEQ ID NO: 24**.

[00147] In some embodiments, a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, binds specifically to an epitope disclosed herein and comprises a heavy chain variable (VH) region comprising an HCDR1, an HCDR2 and an HCDR3, and a light chain variable (VL) region comprising an LCDR1, an LCDR2 and an LCDR3, (i) wherein the HCDR3 comprises **SEQ ID NO: 15**; and/or wherein the LCDR3 comprises **SEQ ID NO: 7**; (ii) wherein the HCDR3 comprises **SEQ ID NO: 66**; and/or wherein the LCDR3 comprises **SEQ ID NO: 7**; or (iii) wherein the HCDR3 comprises **SEQ ID NO: 68**; and/or wherein the LCDR3 comprises **SEQ ID NO: 7**. In some embodiments, a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, binds specifically to an epitope disclosed herein and comprises a VH region comprising an HCDR1, an HCDR2 and an HCDR3, and a VL region comprising an LCDR1, an LCDR2 and an LCDR3, wherein the HCDR2 comprises **SEQ ID NO: 3**; and/or wherein the LCDR2 comprises **SEQ ID NO: 6**. In some embodiments, a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, binds specifically to an epitope disclosed herein and comprises a VH region comprising an HCDR1, an HCDR2 and an HCDR3, and a VL region comprising an LCDR1, an LCDR2 and an LCDR3, (i) wherein the HCDR1 comprises **SEQ ID NO: 14**; and/or wherein the LCDR1 comprises **SEQ ID NO: 5**; (ii) wherein the HCDR1 comprises **SEQ ID NO: 65**; and/or wherein the LCDR1 comprises **SEQ ID NO: 5**; (iii) wherein the HCDR1 comprises **SEQ ID NO: 14**; and/or wherein the LCDR1 comprises **SEQ ID NO: 69**; or (iv) wherein the HCDR1 comprises **SEQ ID NO: 14**; and/or wherein the LCDR1 comprises **SEQ ID NO: 71**. In some embodiments, a monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, binds specifically to an epitope disclosed herein and comprises a VH region comprising an HCDR1, an HCDR2 and an HCDR3, and a VL region comprising an LCDR1, an LCDR2 and an LCDR3, wherein the CDRs comprise one or more of the following amino acid sequences:

HCDR1: SEQ ID NO: 14 or SEQ ID NO: 65, HCDR2: SEQ ID NO: 3, HCDR3: SEQ ID NO: 15, SEQ ID NO: 66 or SEQ ID NO: 68, LCDR1: SEQ ID NO: 5, SEQ ID NO: 69 or SEQ ID NO: 71, LCDR2: SEQ ID NO: 6, and LCDR3: SEQ ID NO: 7.

[00148] In some embodiments, an antibody or antibody fragment specifically binds to the laminin binding domain (or an epitope within the laminin binding domain) of $\alpha 7$ protein, $\alpha 6$ protein and/or $\alpha 3$ protein. In some cases, a monoclonal antibody or an antibody fragment thereof that is an agonist of $\alpha 7\beta 1$ integrin binds specifically to an epitope of $\alpha 7$ protein that comprises, consists essentially of, or consists of 5-10, 10-15, 15-20, 20-25, 25-30, 30-35 or 35-40 amino acids of the laminin binding domain of $\alpha 7$ protein, $\alpha 6$ protein and/or $\alpha 3$ protein.

[00149] As used herein, the term "epitope" includes any protein determinant capable of specific binding to an immunoglobulin or an immunoglobulin fragment. Epitopic determinants usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics. The term "epitope" also refers to a unit of structure conventionally bound by an immunoglobulin heavy chain variable (VH) region and a light chain variable (VL) region pair. An epitope may define the minimum binding site for an antibody, and thus represent the target of specificity of an antibody.

[00150] As used herein, the terms "immunological binding," and "immunological binding properties" refer to the non-covalent interactions of the type which occur between an immunoglobulin molecule (e.g., antibody) and an antigen for which the immunoglobulin is specific. The strength, or affinity of immunological binding interactions can be expressed in terms of the dissociation constant (K_d) of the interaction, wherein a smaller K_d represents a greater affinity. Immunological binding properties of selected polypeptides can be quantified using methods well known in the art. One such method entails measuring the rates of antigen-binding site/antigen complex formation and dissociation, wherein those rates depend on the concentrations of the complex partners, the affinity of the interaction, and geometric parameters that equally influence the rate in both directions. Thus, both the "on rate constant" (K_{on}) and the "off rate constant" (K_{off}) can be determined by calculation of the concentrations and the actual rates of association and dissociation. (See Nature 361:186-87 (1993)). The ratio of K_{off}/K_{on} enables the cancellation of all parameters not related to affinity, and is equal to the dissociation constant K_d . (See, generally, Davies et al. (1990) *Annual Rev Biochem* 59:439-473). An antibody of the present invention is said to specifically bind to a PD-L1 epitope when the equilibrium binding constant (K_d) is $\leq 10 \mu M$, preferably $\leq 10 nM$, more

preferably ≤ 10 nM, and most preferably ≤ 100 pM to about 1 pM, as measured by assays such as radioligand binding assays or similar assays known to those skilled in the art.

[00151] In certain aspects, an antibody of the invention is monovalent or bivalent and comprises a single or double chain. Functionally, the binding affinity of an antibody may be within the range of 10^{-5} M to 10^{-12} M. For example, the binding affinity of an antibody is from 10^{-6} M to 10^{-12} M, from 10^{-7} M to 10^{-12} M, from 10^{-8} M to 10^{-12} M, from 10^{-9} M to 10^{-12} M, from 10^{-5} M to 10^{-11} M, from 10^{-6} M to 10^{-11} M, from 10^{-7} M to 10^{-11} M, from 10^{-8} M to 10^{-11} M, from 10^{-9} M to 10^{-11} M, from 10^{-10} M to 10^{-11} M, from 10^{-5} M to 10^{-10} M, from 10^{-6} M to 10^{-10} M, from 10^{-7} M to 10^{-10} M, from 10^{-8} M to 10^{-10} M, from 10^{-9} M to 10^{-10} M, from 10^{-5} M to 10^{-9} M, from 10^{-6} M to 10^{-9} M, from 10^{-7} M to 10^{-9} M, from 10^{-8} M to 10^{-9} M, from 10^{-5} M to 10^{-8} M, from 10^{-6} M to 10^{-8} M, from 10^{-7} M to 10^{-8} M, from 10^{-5} M to 10^{-7} M, from 10^{-6} M to 10^{-7} M or from 10^{-5} M to 10^{-6} M.

EFFECTS OF PHARMACEUTICAL AGENTS

[00152] The invention encompasses pharmaceutical agents (e.g., antibodies) that activate at least one of $\alpha 7\beta 1$ integrin, $\alpha 6\beta 1$ integrin and $\alpha 3\beta 1$ integrin. In some embodiments, a pharmaceutical agent stimulates the binding of the integrin complex to the laminins. In some embodiments, a pharmaceutical agent stabilizes the active conformation of at least one of $\alpha 7\beta 1$ integrin, $\alpha 6\beta 1$ integrin and $\alpha 3\beta 1$ integrin.

[00153] In certain aspects, a pharmaceutical agent increases the adhesion of a myoblast to laminin- $\alpha 2$ (merosin). In some cases, a myoblast is a healthy human myoblast or a healthy murine myoblast. In other cases, a myoblast is a human myoblast or a murine myoblast that is dystrophin deficient, comprises a mutation in dystrophin or comprises non-functioning dystrophin.

[00154] In some embodiments, a pharmaceutical agent increases the adhesion of a myotube to laminin- $\alpha 2$ (merosin). In some cases, a myotube is a healthy human myotube or a healthy murine myotube. In other cases, a myotube is a human myotube or a murine myotube that is dystrophin deficient, comprises a mutation in dystrophin or comprises non-functioning dystrophin.

[00155] In some aspects, activation of an integrin heterodimer by a pharmaceutical agent may have one or more of the following effects: i) enhancement of the strength of the bonds existing between muscular cells, myoblast/myotubes and their extracellular environment; ii) enhancement of the synthesis of extracellular matrix by the muscular cells; iii) enhancement

of survival of muscular cells; and iv) enhancement of the recruitment and migration of satellite cells that provide the regenerative capacity of skeletal muscle.

NUCLEIC ACID MOLECULES, VECTORS, HOST CELLS AND METHODS OF PRODUCING PHARMACEUTICAL AGENTS

[00156] One aspect of the invention encompasses a nucleic acid molecule (e.g., an isolated nucleic acid molecule) encoding an antibody or an antibody fragment described herein (or a VH region, a VL region, or both a VH region and a VL region of an antibody or antibody fragment). In some embodiments, an isolated nucleic acid molecule encodes a VH region amino acid sequence comprising **SEQ ID NO: 8**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 8**. In some embodiments, an isolated nucleic acid molecule encodes a VH region amino acid sequence comprising **SEQ ID NO: 16**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 16**. In some embodiments, an isolated nucleic acid molecule encodes a VH region amino acid sequence comprising **SEQ ID NO: 67**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 67**. In some embodiments, an isolated nucleic acid molecule encodes a VL region amino acid sequence comprising **SEQ ID NO: 9**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 9**. In some embodiments, an isolated nucleic acid molecule encodes a VL region amino acid sequence comprising **SEQ ID NO: 17**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 17**. In some embodiments, an isolated nucleic acid molecule encodes a VL region amino acid sequence comprising **SEQ ID NO: 70**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 70**. In some embodiments, an isolated nucleic acid molecule encodes a VL region amino acid sequence comprising **SEQ ID NO: 72**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 72**.

[00157] In some embodiments, an isolated nucleic acid molecule encodes (i) a VH region amino acid sequence comprising **SEQ ID NO: 8**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 8**; and (ii) a VL region amino acid sequence comprising **SEQ ID NO: 9**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 9**. In some embodiments, an isolated nucleic acid molecule encodes (i) a VH region

amino acid sequence comprising **SEQ ID NO: 16**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 16**; and (ii) a VL region amino acid sequence comprising **SEQ ID NO: 17**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 17**. In some embodiments, an isolated nucleic acid molecule encodes (i) a VH region amino acid sequence comprising **SEQ ID NO: 67**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 67**; and (ii) a VL region amino acid sequence comprising **SEQ ID NO: 17**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 17**. In some embodiments, an isolated nucleic acid molecule encodes (i) a VH region amino acid sequence comprising **SEQ ID NO: 16**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 16**; and (ii) a VL region amino acid sequence comprising **SEQ ID NO: 70**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 70**. In some embodiments, an isolated nucleic acid molecule encodes (i) a VH region amino acid sequence comprising **SEQ ID NO: 16**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 16**; and (ii) a VL region amino acid sequence comprising **SEQ ID NO: 72**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 72**.

[00158] Further provided herein is a nucleic acid molecule (e.g., an isolated nucleic acid molecule) encoding (i) a heavy chain, (ii) a light chain, or (iii) both a heavy chain and a light chain of an antibody or an antibody fragment disclosed herein. In some embodiments, an isolated nucleic acid molecule encodes a heavy chain amino acid sequence comprising **SEQ ID NO: 18**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 18**. In some embodiments, an isolated nucleic acid molecule encoding a heavy chain comprises **SEQ ID NO: 20** or a nucleotide sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the nucleotide sequence of **SEQ ID NO: 20**. In some embodiments, an isolated nucleic acid molecule encodes a heavy chain amino acid sequence comprising **SEQ ID NO: 45**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 45**. In some embodiments, an isolated nucleic acid molecule encodes a light chain amino acid sequence comprising **SEQ ID NO: 19**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 19**. In some

embodiments, an isolated nucleic acid molecule encoding a light chain comprises **SEQ ID NO: 21** or a nucleotide sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the nucleotide sequence of **SEQ ID NO: 21**. In some embodiments, an isolated nucleic acid molecule encodes a light chain amino acid sequence comprising **SEQ ID NO: 53**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 53**. In some embodiments, an isolated nucleic acid molecule encodes a light chain amino acid sequence comprising **SEQ ID NO: 62**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 62**. In some embodiments, an isolated nucleic acid molecule encodes a light chain amino acid sequence comprising **SEQ ID NO: 63**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 63**.

[00159] In some embodiments, an isolated nucleic acid molecule encodes (i) a heavy chain amino acid sequence comprising **SEQ ID NO: 18**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 18**; and (ii) a light chain amino acid sequence comprising **SEQ ID NO: 19**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 19**. In some embodiments, an isolated nucleic acid molecule comprises (i) **SEQ ID NO: 20** or a nucleotide sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the nucleotide sequence of **SEQ ID NO: 20**; and (ii) **SEQ ID NO: 21** or a nucleotide sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the nucleotide sequence of **SEQ ID NO: 21**. In some embodiments, an isolated nucleic acid molecule encodes (i) a heavy chain amino acid sequence comprising **SEQ ID NO: 45**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 45**; and (ii) a light chain amino acid sequence comprising **SEQ ID NO: 53**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 53**. In some embodiments, an isolated nucleic acid molecule encodes (i) a heavy chain amino acid sequence comprising **SEQ ID NO: 18**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 18**; and (ii) a light chain amino acid sequence comprising **SEQ ID NO: 62**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 62**. In some embodiments, an isolated nucleic acid molecule encodes (i) a heavy chain amino acid sequence comprising **SEQ ID NO: 18**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 18**; and (ii) a light chain amino acid sequence comprising **SEQ ID**

NO: 63, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 63**.

[00160] The invention also encompasses an expression vector comprising a nucleic acid molecule described herein. In certain vectors, a nucleic acid molecule is operatively linked to one or more regulatory sequences suitable for expression of the nucleic acid segment in a host cell. In some cases, an expression vector comprises sequences that mediate replication and comprises one or more selectable markers.

[00161] The invention further provides a recombinant host cell comprising an expression vector disclosed herein. An expression vector can be transfected into a host cell by standard techniques. Non-limiting examples include electroporation, calcium-phosphate precipitation, DEAE-dextran transfection and the like.

[00162] In some aspects, the invention contemplates a method for producing an antibody or an antibody fragment that is an agonist of $\alpha 7\beta 1$ integrin, the method comprising: culturing a recombinant host cell comprising an expression vector described herein under conditions whereby the nucleic acid segment is expressed, thereby producing the antibody or the antibody fragment that is an agonist of $\alpha 7\beta 1$ integrin. Anti- $\alpha 7$ antibodies and $\alpha 7$ -binding fragments thereof can be produced by any of a variety of methods known to those skilled in the art. In certain embodiments, anti- $\alpha 7$ antibodies and $\alpha 7$ -binding antibody fragments can be produced recombinantly. For example, nucleic acid sequences encoding one or more of **SEQ ID NOs: 2-9, 14-19 and 31-72**, or portions thereof, may be introduced into a bacterial cell (e.g., *E. coli*, *B. subtilis*) or a eukaryotic cell (e.g., a yeast such as *S. cerevisiae*, or a mammalian cell such as a CHO cell line, various Cos cell lines, a HeLa cell, various myeloma cell lines, or a transformed B-cell or hybridoma), or into an *in vitro* translation system, and the translated polypeptide may be isolated. In some embodiments, antibody light chain proteins and heavy chain proteins are produced in a cell with a leader sequence (also referred to as a signal sequence) that is removed upon production of a mature anti- $\alpha 7$ antibody or $\alpha 7$ -binding fragment thereof. In some embodiments, the leader sequence is MDPKGSLSWRILLFLSLAFELSYG (**SEQ ID NO: 22**) or METDTLLLWVLLLWVPGSTG (**SEQ ID NO: 23**).

[00163] Those skilled in the art will be able to determine whether an antibody or fragment comprising a given polypeptide sequence binds to $\alpha 7$ protein without undue experimentation using standard methodologies such as, without limitation, Western blots, ELISA assays, and the like.

USES OF PHARMACEUTICAL AGENTS

[00164] The invention encompasses methods and uses of the pharmaceutical agents described herein for providing a therapeutic benefit to a subject with a disorder or a disease. In some aspects, a method comprises administering to a subject in need a therapeutically effective amount of a pharmaceutical agent (e.g., an antibody or an antibody fragment) described herein (e.g., an agonist of at least one of $\alpha 7\beta 1$ integrin, $\alpha 6\beta 1$ integrin and $\alpha 3\beta 1$), thereby treating the disorder or the disease in the subject. The disorder or the disease can be characterized by a malfunction of $\alpha 7\beta 1$ integrin in the subject. For example, the subject may have a mutation in $\alpha 7\beta 1$ integrin. The subject may not have sufficient $\alpha 7\beta 1$ integrin. The disorder or the disease can be characterized by a dystrophin deficiency in the subject. The disorder or the disease can be characterized by a mutation in dystrophin in the subject. The disorder or the disease can be characterized by non-functioning dystrophin in the subject. The disorder or the disease can be characterized by a muscle dysfunction other than $\alpha 7\beta 1$ malfunction, or dystrophin deficiency, mutation, or non-function in the subject.

[00165] In some embodiments, the muscle dysfunction in a subject is caused by or associated with one or more of: cancer, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disease, HIV infection/AIDS, anorexia nervosa, bulimia, malnutrition, exposure, nausea, type I diabetes, type II diabetes, metabolic syndrome, cachexia, anemia, heart failure, high blood pressure, rhabdomyolysis, sepsis, sarcopenia, physical inactivity, damage due to excess physical activity, hypothermia, hyperthermia, injury, denervation, amyotrophic lateral sclerosis, multiple sclerosis, spinal muscular atrophy, alcohol-associated myopathy, burn-associated myopathy, stroke, steroid therapy or the withdrawal of steroid therapy, dermatomyositis, Guillain-Barré syndrome, neuropathy, osteoarthritis, infection, polio, polymyositis, inflammation, rheumatoid arthritis, hypocholesterolemia, electrical injury, heat stroke, prolonged immobilization, lack of blood flow to a limb, or contact with venom. In some embodiments, a method of the invention further comprises identifying a subject having or at risk of having a muscle dysfunction.

[00166] In some embodiments, a disease that can be treated by the methods and compositions of the invention is a muscle wasting disease. In some cases, a muscle wasting disease is a dystroglycan deficiency, a sarcoglycan deficiency or a merosin deficiency. In one example, a muscle wasting disease can be a muscular dystrophy. Non-limiting examples of muscular dystrophy include Duchenne muscular dystrophy (DMD), Becker muscular dystrophy, merosin-deficient congenital muscular dystrophy type 1A and limb-girdle muscular

dystrophy. In some embodiments, a method of the invention further comprises identifying a subject having or at risk of having a muscle wasting disease.

[00167] In some embodiments, the efficacy of a composition of the invention on treating a muscle wasting disease may be analyzed by using an animal model. Non-limiting examples of animal models of DMD include the mouse model Mdx/C57BL/10 (affected protein: dystrophin), the mouse model Mdx/D2 (affected protein: dystrophin), the mouse model mdx-utrn^{-/-} (affected proteins: dystrophin and utrophin), and the rat model Mdx knockout rat (affected protein: dystrophin). A non-limiting example of an animal model of limb girdle muscular dystrophy is the Sgca-null mouse (affected protein: alpha-sarcoglycan). A non-limiting example of an animal model of merosin-deficient congenital muscular dystrophy type 1A (MDC1A) is the LAMA2^{dyw/dyw} mouse (affected protein: laminin alpha2).

[00168] In some embodiments, administering a pharmaceutical agent described herein to a subject in need thereof reverses, stabilizes or slows muscle wasting or muscle dysfunction in the subject. In other embodiments, administering a pharmaceutical agent described herein to a subject in need thereof does not worsen muscle function in the subject. A method of the invention may further comprise measuring muscle function in the subject after the administration step, wherein the rate of worsening of muscle function is reduced.

[00169] In some embodiments, administering to the subject the therapeutically effective amount of the pharmaceutical agent can be effective to upregulate the activity and/or amount of $\alpha 7\beta 1$ integrin in the subject effective to treat the malfunction of $\alpha 7\beta 1$ integrin in the subject.

[00170] In some embodiments, administering to the subject the therapeutically effective amount of the pharmaceutical agent can be effective to upregulate activity and/or amount of $\alpha 7\beta 1$ integrin in the subject. The upregulated activity and/or amount of $\alpha 7\beta 1$ integrin in the subject can be effective to at least in part mitigate the effect of the dystrophin deficiency in the subject. The upregulated activity and/or amount of $\alpha 7\beta 1$ integrin in the subject can be effective to at least in part mitigate the effect of the mutation in dystrophin in the subject. The upregulated activity and/or amount of $\alpha 7\beta 1$ integrin in the subject can be effective to at least in part mitigate the effect of the non-functioning dystrophin in the subject.

[00171] In some embodiments, administering to the subject the therapeutically effective amount of the pharmaceutical agent can be effective to mitigate muscle injury in the subject. For example, administering to the subject the therapeutically effective amount of the pharmaceutical agent can be effective to mitigate eccentric muscle injury in the subject.

Administering to the subject the therapeutically effective amount of the pharmaceutical agent can be effective to improve diaphragm muscle function in the subject.

[00172] In several embodiments, the method can include administering to the subject one or more other therapies. The one or more other therapies can be directed to muscular dystrophy or muscle wasting, for example, any conventional or experimental therapy for muscular dystrophy. The one or more other therapies can include medication, surgery with or without transplantation, a physical intervention such as physical therapy, or a medical device. For example, the one or more other therapies can include an anticonvulsant. The one or more other therapies can include an immunosuppressant. The one or more other therapies can include an antibiotic. The one or more other therapies can include quinine. The one or more other therapies can include therapy for management of congestive heart failure. The one or more other therapies can include a gene replacement therapy. The one or more other therapies can include an exon skipping therapy. The one or more other therapies can include a nonsense suppression therapy. The one or more other therapies can include therapy using an engineered nuclease. The one or more other therapies can include cell therapy using muscle precursor cells or stem cells. The one or more other therapies can include upregulation of utrophin. The one or more other therapies can include an anti-inflammatory. The one or more other therapies can include an antifibrotic. The one or more other therapies can include a steroid therapy. In some embodiments, a steroid therapy comprises a corticosteroid or an anabolic steroid. The one or more other therapies can include a myostatin blocker. The one or more other therapies can include insulin growth factor. The one or more other therapies can include a phosphodiesterase-5 inhibitor; an ACE inhibitor. The one or more other therapies can include induction of angiogenesis through delivery of vascular endothelial growth factor (VEGF). The one or more other therapies can include downregulation of VEGF decoy-receptor type 1 (VEGFR-1 or Flt-1). The one or more other therapies can include physical therapy; occupational therapy. The one or more other therapies can include surgery. The one or more other therapies can include orthotic intervention. The one or more other therapies can include speech therapy. The one or more other therapies can include respiratory therapy. The one or more other therapies can include a pacemaker. The one or more other therapies can include a respiratory assistance device.

[00173] In various embodiments, the method can further include administering to the subject one or more other therapies. The one or more other therapies can be directed to mitigating muscular dystrophy. The one or more other therapies can be directed to mitigating muscle wasting.

[00174] In some embodiments, the one or more other therapies can include one or more of, e.g.: an anticonvulsant; an immunosuppressant, e.g. prednisone and deflazacort; an antibiotic; and quinine.

[00175] In several embodiments, the one or more other therapies may include therapy for management of congestive heart failure, e.g., dilated cardiomyopathy, e.g., using anti-congestive medications and/or cardiac transplantation. Examples of therapies which may be used for congestive heart failure include, e.g.: angiotensin-converting enzyme (ACE) inhibitors (ACE-I); angiotensin receptor blockers (ARBs); beta-adrenergic blocking agents (beta blockers); hydralazine; nitrates such as isosorbide dinitrate; an aldosterone antagonist; digoxin; diuretics, e.g., loop diuretics, thiazide-like diuretics, and potassium-sparing diuretics; an anticoagulant; a vasopressin receptor antagonist, e.g., conivaptan; sacubitril/valsartan; ivabradine; iron supplementation; fluid restriction; and sodium restriction.

[00176] In various embodiments, the one or more other therapies can include one or more genetic therapies, e.g., gene replacement therapy. For example, one genetic therapy involves dystrophin gene replacement using virus vectors. For example, adeno-associated viruses including microdystrophins have been injected into a canine model of DMD, resulting in substantial benefit to muscle histopathology. Clinical trials are underway to replace defective genes in DMD human subjects with DMD using recombinant adeno-associated viruses. Examples include, e.g., rAAV2.5-CMV-Mini-dystrophy, rAAVrh74.MCK-Mini-dystrophy, and rAAV1.CMV.huFollistatin344.

[00177] In some embodiments, the one or more genetic therapies can include, e.g., exon skipping, in which synthetic antisense oligonucleotide sequences are used to update dystrophin gene mutations. Specific exons are skipped during pre-messenger RNA (pre-mRNA) splicing of the dystrophin gene, which restores the reading frame and partial production of an internally truncated protein. Exon skipping therapies can include agents for skipping, e.g.: exon 53, such as SRP4053 (Serapta), PRO053 (Prosensa), and NS-065/NCNP-01; exon 51, such as PRO051, eteplirsen (AVI-4658), and drisapersen (GSK2402968); exon 45, such as DS-5141, PRO045, and SRP4045; and exon 44, such as PRO044. For example, PRO051, a 2'-O-methyl-phosphorothioate oligoribonucleotide which skips exon 51 in dystrophin pre-mRNA has been injected into human DMD subjects, resulting in 17%–35% restoration of dystrophin. Further, for example, eteplirsen (AVI-4658) is a phosphoramidate morpholino oligomer which also skips exon 51 in dystrophin pre-mRNA.

[00178] In several embodiments, the one or more genetic therapies can include, e.g., nonsense suppression therapy. About 10%–15% of DMD cases are due to point mutations forming a premature stop codon. Such premature stop codons usually cause loss of the functional protein. Recognition of such premature stop codons can be mitigated by nonsense mutation suppression agents effective to restore translation and production of a modified dystrophin protein. Nonsense mutation suppression agents can include, e.g., aminoglycosides such as gentamicin, Ataluren (Translarna), and arbekacin sulfate (NPC-14).

[00179] In various embodiments, the one or more genetic therapies can include, e.g., using engineered nucleases such as CRISPR-Cas9. For example, mdx mice treated with RNA-guided clustered regularly interspaced short palindromic repeats-Cas9 endonucleases delivered by adeno-associated virus, mitigated dystrophic changes in skeletal muscle fibers, cardiomyocytes, and muscle satellite cells.

[00180] In some embodiments, the one or more other therapies can include one or more cell therapies, e.g., using muscle precursor cells or stem cells, e.g., myoblast transfer, intra-arterial transplantation of human leukocyte antigen-matched sibling donor mesoangioblasts, induced pluripotent stem cells, umbilical cord based allogenic mesenchymal stem cells, and bone marrow autologous and mononuclear stem cells.

[00181] In several embodiments, the one or more other therapies can include membrane stabilization and upregulation of cytoskeletal proteins. For example, upregulation of utrophin, alpha-7-beta-1 integrin, 110 biglycan, and sarcospan stabilized the sarcolemma in mdx mice. For example, the compounds SMT C1100 and SMT022357 were shown to target the utrophin-A promoter and increase the production of utrophin and reduce dystrophic changes in skeletal and cardiac muscle.

[00182] In various embodiments, the one or more other therapies can include one or more anti-inflammatory therapies. Anti-inflammatory drugs can include, e.g., VBP15; givinostat (HDAC inhibitor); NEMO-binding domain peptide; CAT-1004 (Edasalonexent, NF- κ B inhibitor); flavocoxid; TAS-205 (PDGD2 synthase inhibitor); idebenone; pentoxifylline; coenzyme Q10; N-acetylcysteine; green tea extract; melatonin; pentoxifylline; and oxatomide. For example, NF- κ B inhibition using the NEMO-binding domain peptide resulted in improved pathology and muscle function in mouse models of muscular dystrophy.

[00183] In some embodiments, the one or more other therapies can include one or more antifibrotic therapies, e.g., TGF- β blockers such as losartan, an angiotensin II-type 1 receptor blocker that reduces the expression of TGF- β ; lisinopril; HT-100 (halofuginone); FG-3019 (monoclonal antibody to CTGF); and targeted microRNAs.

[00184] In several embodiments, the one or more other therapies can include muscle regeneration therapies. For example, suitable agents can include: myostatin blockers such as ACE-031, MYO-029, follistatin, PF-06252616; and BMS-986089; or insulin growth factor, alone or further combined with mesenchymal stromal cells.

[00185] In various embodiments, the one or more other therapies can include treatment of muscle ischemia, e.g., by inhibition of phosphodiesterase-5 using tadalafil, sildenafil, and vardenafil; ACE inhibitors; induction of angiogenesis through delivery of vascular endothelial growth factor (VEGF); and downregulation of the VEGF decoy-receptor type 1 (VEGFR-1 or Flt-1).

[00186] In some embodiments, the one or more other therapies can include one or more physical interventions, e.g.: physical therapy, occupational therapy, surgery, orthotic intervention (e.g., ankle-foot orthosis), speech therapy, and respiratory therapy.

[00187] In several embodiments, the one or more other therapies can include one or more medical devices, e.g.: a pacemaker; or a respiratory assistance device such as a ventilator or a continuous positive airway pressure device.

[00188] The invention further provides a method of activating $\alpha 7\beta 1$ integrin in a muscle cell of a subject, the method comprising: administering to the subject a therapeutically effective amount of a pharmaceutical agent (e.g., an antibody or an antibody fragment) described herein, thereby activating $\alpha 7\beta 1$ integrin in a muscle cell of the subject.

[00189] The invention also provides a method of enhancing binding of $\alpha 7\beta 1$ integrin to its ligand in a muscle cell of a subject, the method comprising: administering to the subject a therapeutically effective amount of a pharmaceutical agent (e.g., an antibody or an antibody fragment) described herein, thereby enhancing binding of $\alpha 7\beta 1$ integrin to its ligand in a muscle cell of the subject.

[00190] As used herein, the term “patient in need” or “subject in need” refers to a patient or subject at risk of, or suffering from, a disease, disorder or condition that is amenable to treatment or amelioration with an agonist of an integrin heterodimer comprising a $\beta 1$ protein or a composition comprising such an agonist provided herein. A patient or subject in need may, for instance, be a patient or subject diagnosed with a disease associated with the malfunction of $\alpha 7\beta 1$ integrin, such as a muscle wasting disease. A subject may have a mutation or a malfunction in one of the proteins in the laminin/dystroglycan/sarcoglycan/dystrophin complex. In other embodiments, a subject may have a mutation or malfunction in laminin- $\alpha 2$ (merosin). “Subject” and “patient” are used interchangeably herein.

[00191] In certain embodiments, a subject may be a human, a non-human primate, a pig, a horse, a cow, a dog, a cat, a mouse or a rat.

[00192] As used herein, the term "effective amount" or "therapeutically effective amount" refers to the amount of a pharmaceutical agent, e.g., an antibody, which is sufficient to reduce or ameliorate the severity and/or duration of a disorder, e.g., muscular dystrophy, or one or more symptoms thereof, prevent the advancement of a disorder, cause regression of a disorder, prevent the recurrence, development, onset or progression of one or more symptoms associated with a disorder, detect a disorder, or enhance or improve the prophylactic or therapeutic effect(s) of another therapy (e.g., prophylactic or therapeutic agent). The effective amount of an antibody may, for example, enhance muscle regeneration, maintenance or repair, and/or relieve to some extent one or more of the symptoms associated with the muscle wasting disease.

[00193] In certain aspects, a subject in need thereof may be treated with a pharmaceutical agent described herein and an additional pharmaceutical agent that has a different mechanism of action (e.g., gene correction, increasing muscle regeneration or decreasing inflammation and fibrosis) that is used to treat muscle wasting disease.

[00194] The invention further contemplates a use of a pharmaceutical agent (e.g., an antibody or an antibody fragment) described herein in the manufacture of a medicament for treating a disorder or a disease characterized by a malfunction of $\alpha 7\beta 1$ integrin in a subject. The invention also includes a use of a pharmaceutical agent (e.g., an antibody or an antibody fragment) described herein for treating a disorder or a disease characterized by a malfunction of $\alpha 7\beta 1$ integrin in a subject.

PHARMACEUTICAL COMPOSITIONS

[00195] The pharmaceutical agents of the invention (also referred to herein as "active compounds"), and derivatives, fragments, analogs and homologs thereof, can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise an antibody and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, a pharmaceutical composition comprises a pharmaceutical agent that is an agonist of $\alpha 7\beta 1$ integrin. In other embodiments, a pharmaceutical composition comprises at least two, at least three or at least four different pharmaceutical agents that are agonists of at least one of $\alpha 7\beta 1$ integrin, $\alpha 6\beta 1$ integrin and $\alpha 3\beta 1$ integrin. As used herein, the term "pharmaceutically acceptable" refers to molecular entities and compositions that do not generally produce allergic or other serious adverse reactions when administered using routes

well known in the art. Molecular entities and compositions approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans are considered to be "pharmaceutically acceptable." As used herein, the term "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Suitable carriers are described in the most recent edition of Remington's Pharmaceutical Sciences, a standard reference text in the field, which is incorporated herein by reference. Some examples of such carriers or diluents include, but are not limited to, water, saline, Ringer's solutions, dextrose solution, and 5% human serum albumin. Liposomes and non-aqueous vehicles such as fixed oils may also be used. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[00196] A pharmaceutical composition of the invention may be formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (i.e., topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfate; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[00197] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL® (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under

the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[00198] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[00199] Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primojel[®], or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[00200] For administration by inhalation, the compounds may be delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

[00201] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[00202] The pharmaceutical agents can also be prepared in the form of suppositories (e.g., with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

[00203] In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[00204] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

[00205] The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[00206] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited herein, including but not limited to patents, patent applications, articles, books, and treatises, are hereby expressly incorporated by reference in their entirety for any purpose. In the event that one or more of the incorporated documents or portions of documents define a term that contradicts that term's definition in the application, the definition that appears in this application controls. However, mention of any reference, article, publication, patent, patent publication, and patent application cited herein is not, and should not be taken as an acknowledgment, or any form of suggestion, that they constitute valid prior art or form part of the common general knowledge in any country in the world.

[00207] In the present description, any concentration range, percentage range, ratio range, or integer range is to be understood to include the value of any integer within the recited range and, when appropriate, fractions thereof (such as one tenth and one hundredth of an integer), unless otherwise indicated. It should be understood that the terms "a" and "an" as used herein refer to "one or more" of the enumerated components unless otherwise indicated. The use of the alternative (e.g., "or") should be understood to mean either one, both, or any combination thereof of the alternatives. As used herein, the terms "include" and "comprise" are used synonymously.

[00208] The invention will be further described in the following examples, which do not limit the scope of the invention described in the claims.

Table 1A. Exemplary integrin alpha protein laminin binding head domain sequences

Integrin alpha7 head domain amino acid sequence

FNLDVMGALRKEGEPGSLFGFSVALHRQLQPRPQSWLLVGAPQALALPGQQANRTG
GLFACPLSLEETDCYRVDIDQGADMQKESKENQWLGVSVRSQGPQGGKIVTCAHRYE
ARQRVDQILETRDMIGRCFVLSQDLAIRDELDDGGGEWKFCGRPQGHEQFGFCQGGT
AAAFSPDSHYLLFGAPGTYNWKG TARVELCAQGSADLAHLDDGPYEAGGEKEQDP
RLIPVPANSYFGFSIDSGKGLVRAEELS FVAGAPRANHKGAVVILRKDSASRLVPEVM
LSGERLTSGFGYSLAVADLNSDGWPD LIVGAPYFFERQEELGGAVYVYLNQGGHWA
GISPLRLCGSPDSMFGISLAVLGDLNQDGFDPDIAGAPFDGDGKVFYHGGSSLGVVAK
PSQVLEGEAVGIKSFGYSLSGSLDMDGNQYPDLLVGS LADTAVLFRARPIL (SEQ ID
NO: 11)

Integrin alpha6 head domain amino acid sequence

FNLDTRDNVIRKYGDPSLFGFSLAMHWQLQPEDKRLLL VGAPRAEALPLQRANR
TGGLYSCDITARGPCTRIEFDNDADPTSESKEDQWMGVTVQSQGPQGGKVVTCAHRY
EKRQHVNTKQESRDIFGRCYVLSQNLRIEDDMDGGDWSFCDGRLRGHEKFGSCQQG
VAATFTKDFHYIVFGAPGTYNWKGIVRVEQKNNTFFDMNIFEDGPYEVGGETEHD
SLVPVPANSYLGFSLDSGKGIVSKDEITFVSGAPRANHSGAVVLLKRDMKSAHLLPE

HIFDGEGLASSFGYDVAVVDLNKDGWQDIVIGAPQYFDRDGEVGGAVYVYMNQQG
 RWNNVKPIRLNGTKDSMFGITVKNIGDINQDGYPDIAVGAPYDDLKGVFIYHGSANG
 INTKPTQVLKGISPYFGYSIAGNMDLDRNSYPDVAVGSLSDSVTIFRSRPVI (SEQ ID
 NO: 12)

Integrin alpha3 head domain amino acid sequence

FNLDTFLVVKKEAGNPGSLFGYSVALHRQTERQQRYLLLAGAPRELAVPDGYTNRT
 GAVYLCPLTAHKDDCERMNITVKNDPGHHIIEDMWLGVTVASQGPAGRVLVCAHR
 YTQVLWSGSEDQRRMVGKCYVRGNDLELDSSDDWQTYHNEMCNSNTDYLETGMC
 QLGTSGGFTQNTVYFAGPAGYNWKGNSYMIQRKEWDLSEYSYKDPEDQGNLYIGY
 TMQVGSFILHPKNITIVTGAPRHRHMGAVFLLSQEAGGDLRRRQVLEGSQVGAYFGS
 AIALADLNNDGWQDLLVGAPYYFERKEEVGGAIYVFMNQAGTSFPAHPSLLLHGPS
 GSAFGLSVASIGDINQDGFQDIAVGAPFEGLGKVYIYHSSSKGLLRQPQQVIHGEKLG
 LPGLATFGYSLSGQMDVDENFYPDLLVGSLSDHIVLLRARPI (SEQ ID NO: 13)

Table 1B. Exemplary integrin alpha protein CALF-1 domain sequence

DNVCKPKLEVSVDSDQKKIYIGDDNPLTLIVKAQNQGEGAYEAEIIVSIPLQADFIGV
 VRNNEALARLSCAFKTENQTRQVVCDLGNPMKAGTQLLAGLRFSVHQQSEMDTSV
 KFDLQIQSSNLFDKVSPVVS HKVDLA (SEQ ID NO: 73)

Table 1C. Exemplary integrin alpha protein CALF-2 domain sequence

VLA AVEIRGVSSPDHVFLPIPNWEHKENPETEEDVGPVVQHIYELRNNGPSSFSKAML
 HLQWPYKYNNNTLLYILHYDIDGPMNCTSDMEINPLRIKISSLQTTEKNDTVAGQGE
 RDHLITKRDLALSEGDIHTLGCGVAQCLKIVCQVGRDLRGKSAILYVKSLLWTETFM
 NKENQNHSYSLKSSASFNVIEFPYKNLPIEDITNSTLVTNTVTWGIQ (SEQ ID NO: 74)

EXAMPLES

Example 1: β 1 protein agonist provides compensatory effects in cells with a dystrophin deficiency

[00209] Myoblasts and myotubes from healthy and dystrophin deficient human patients were treated with the β 1 agonist antibody TS2/16 (J. Immunol, 1984, 132:3011). Cell adhesion assays were used to evaluate the cell attachment to laminin through integrins. Microplates were coated overnight with 10 μ g/ml merosin at 4°C, and blocked with 2% BSA/PBS for 30min before the assay. Myoblast or myotube cells were detached and washed in PBS. After that, the cells were resuspended in IMEM at 1.0×10^6 cells/ml, and fifty microliters of cell suspension and fifty microliters of antibody solution were added into the plate. The plates were incubated for one hour at 37°C in humidified 5% carbon dioxide. Non-adherent cells were removed by centrifugation top side down at 58g for 5min. The attached cells were fixed and stained with 0.5% crystal violet (in 20% methanol and 1% formaldehyde) and the wells washed with PBS. Crystal violet was dissolved in 2% Triton-X in PBS. The relative number

of cells in each well was evaluated by the absorbance at 595 nm in a microplate reader (Tecan).

[00210] Treatment with TS2/16 promoted human myoblast adhesion to merosin (laminin) in both healthy control and dystrophin deficient myoblasts (**FIG. 1**) and myotubes (**FIG. 2**). $\alpha 7\beta 1$ integrin is up-regulated upon differentiation into myotubes. Myotube adhesion to merosin can be enhanced by $\beta 1$ activation. Human myoblast cells express multiple laminin integrins on the cell surface as determined by FACS (**FIGs. 3 and 4**). The enhanced cell adhesion mediated by $\beta 1$ activation was mainly contributed by integrin $\alpha 7\beta 1$ (**FIG. 5**) as it was not inhibited by functional blocking $\alpha 3$ and $\alpha 6$ antibodies, but blocked by a blocking $\alpha 7$ antibody.

[00211] The $\beta 1$ agonist antibody TS2/16 also enhanced myotube adhesion to laminin in an $\alpha 7\beta 1$ -dependent manner in healthy murine myoblasts in which dystrophin expression was knocked down with siRNA. C2C12 cells (Nature, 1977, 270:725) are murine myoblasts expressing multiple laminin integrins. C2C12 cells express three laminin receptors ($\alpha 3$, $\alpha 6$ and $\alpha 7\beta 1$) on their surface (J Cell Sci, 1996, 109: 3139). $\alpha 7A$ is upregulated during skeletal muscle differentiation. $\alpha 7$ expression levels in C2C12 cells increase during muscle differentiation (Xiao et al. (2003) J. Biol. Chem., 278:49780-49788). C2C12 cells were differentiated to myotubes (**FIG. 6**). Dystrophin expression in the myotubes was knocked down using siRNA (**FIG. 7**; Ghahramani Seno et al. (2008) Human Molecular Genetics, 17:2622-2632). TS2/16 enhanced murine myotube cell adhesion to laminin in murine myotubes treated with control siRNA and with dystrophin siRNA (**FIG. 8A**). The TS2/16-enhanced murine myotube cell adhesion to laminin was mainly contributed by integrin $\alpha 7\beta 1$ (**FIG. 8B**).

Example 2: Generation of $\alpha 7\beta 1$ agonist antibodies

[00212] Monoclonal antibodies were generated by immunizing mice with human integrin $\alpha 7\beta 1$ protein ectodomain. A general schematic of the process is shown in **FIG. 9**. Hybridomas were produced by standard techniques. From a total of 9,000 clones, 110 clones were selected as integrin $\alpha 7\beta 1$ binders. Multiple antagonist (blocking) and four agonist (activating) antibodies were identified in functional biochemistry and cellular assays. These antibodies were characterized as either activating or blocking in a solid phase binding assay and a cell adhesion assay. The activating antibodies are referred to as M10, M25, M36 and M38. **FIG. 10A** shows an example of results from a solid phase binding assay, and **FIG. 10B**

shows an example of results from a cell adhesion assay performed with two activating antibodies (M10, M25) and one blocking antibody (M20). The activating antibodies were further characterized (for example, by ELISA or flow cytometry) to determine whether the activation takes place through the $\alpha 7$ protein or the $\beta 1$ protein. M10 and M25 were found to bind the $\beta 1$ protein as the two antibodies stimulated binding not only to $\alpha 7\beta 1$ but also to $\alpha 6\beta 1$ integrin and to $\alpha v\beta 1$ integrin (**FIG. 10C**).

[00213] Antibodies M36 and M38 were found to bind to cell surfaces expressing $\alpha 7\beta 1$ (both human (K562/ $\alpha 7X2$) and murine (C2C12) integrins). See **FIG. 11A**. Binding of M36 and M38 to human and murine $\alpha 7\beta 1$ integrin was dose-dependent and not mediated through the $\beta 1$ subunit of the heterodimer, as M36 and M38 did not bind to $\alpha 6\beta 1$ or $\alpha 5\beta 1$ integrin (**FIG. 11B**).

[00214] Integrin $\alpha 7$ protein can have two different extracellular sequences (designated “X1” and “X2”) due to post-transcriptional modification. The variable region sequence (X1 or X2) is located between the III and IV homology repeat domains near the putative ligand-binding site (**FIG. 12A**). There are 40 amino acids in the X2 variable region sequence. Antibodies M36 and M38 preferentially bind to cell surfaces expressing the $\alpha 7\beta 1$ X2 form (**FIG. 12B**), which is preferentially expressed in adult skeletal cells. Due to the specificity of the binding on the $\alpha 7X2$ isoform, but not the $\alpha 7X1$ isoform, it is concluded that M36 and M38 are specifically binding the $\alpha 7X2$ subunit of the $\alpha 7\beta 1$ heterodimer integrin (**FIG. 12B**).

[00215] Antibodies M36 and M38 were found to enhance integrin $\alpha 7\beta 1$ -mediated adhesion of K562/ $\alpha 7x2\beta 1$ cells to laminin (LN211). Antibodies M36 and M38 enhanced integrin $\alpha 7\beta 1$ cell adhesion to human laminin 211 (EC50s: 1.09nM and 1.27nM). See **FIG. 13A**. Control antibody M35 had no effect. Antibodies M36 and M38 enhanced mouse myotube, in which dystrophin has been knockdown, adhesion to laminin. See **FIG. 13B**. This effect could be reversed by $\alpha 7$ blocking antibody.

[00216] Antibodies M36 and M38 were found to activate integrin $\alpha 7\beta 1$ through a conformational change. Monoclonal antibody 9EG7 selectively binds to activated $\beta 1$ integrins (Bazzoni et al., J Biol Chem. 1995; 270(43):25570-7). Mn^{2+} mediates $\beta 1$ integrin activation and this can be detected by 9EG7 (white bar, **FIG. 14**). As shown in **FIG. 14**, antibodies M36 and M38 enhance the binding of 9EG7 (dark and light grey bars) over the $\alpha 7$ control (con functional) antibody (white bar), which indicates change of integrin $\alpha 7\beta 1$ into a more activated conformation.

[00217] The M36 and M38 antibody heavy and light chain variable regions were sequenced and were found to be identical. These sequences are provided in **Table 2**.

Table 2. Amino acid sequences of antibody M36 and antibody M38

HCDR1	GYNFTKYW	SEQ ID NO: 2
HCDR2	IYPGSSTS	SEQ ID NO: 3
HCDR3	VRGDD	SEQ ID NO: 4
LCDR1	ESVDNYGISF	SEQ ID NO: 5
LCDR2	AAS	SEQ ID NO: 6
LCDR3	HQSKEVPYT	SEQ ID NO: 7
VH	QVQLQQPGAELVKPGASVKLSCKASGYNFTKYWINWVKQ RPGQGLEWIGIIYPGSSTSNYNEKFKTKATLTVEISSTTAYM QLSSLTSDDSAVYYCVRGDDWGQGTTLTVSS	SEQ ID NO: 8
VL	DIVLTQSPASLAVSLGQRATISCRASESVDNYGISFMNWFQQ KPGQPPKLLIYAASDLGSGVPARFTGSGSGTDFSLNIHPMEE DDSAMYFCHQSKEVPYTFGGGKLEIK	SEQ ID NO: 9

Example 3: Generation and Characterization of Humanized $\alpha 7\beta 1$ agonist antibodies

[00218] The sequence of the M36/M38 antibody was subsequently humanized. The antibody sequence was analyzed for three dimensional structure and was built by homology modeling. Key positions supporting the CDR loop structure and VH-VL interface were identified. Multiple humanized variants were designed for both heavy and light chains. The humanness of humanized variants were assessed by the T20 humanness score described in Gao et al., (2013) *BMC Biotechnology*, 13:55. The humanized antibodies as well as a chimeric version (rodent variable regions, human constant regions) were expressed at the 10 mL scale in CHO cells (TunaCHO™ Process) and purified. Binding affinity of each antibody produced was tested by flow cytometry and ELISA.

[00219] A humanized antibody referred to as “VL3VHK20TFT” was isolated. The amino acid and nucleotide sequences of various regions of VL3VHK20TFT are provided in **Table 3**. VL3VHK20TFT belongs to the IgG4 isotype and S228P subclass. The light chain isotype of VL3VHK20TFT is human kappa.

Table 3. Amino acid and nucleotide sequences of antibody VL3VHK20TFT

HCDR1	GYTFTKYW	SEQ ID NO: 14
HCDR2	IYPGSSTS	SEQ ID NO: 3

HCDR3	VKNDN	SEQ ID NO: 15
LCDR1	ESVDNYGISF	SEQ ID NO: 5
LCDR2	AAS	SEQ ID NO: 6
LCDR3	HQSKEVPYT	SEQ ID NO: 7
VH (CDR sequences are underlined)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTKYWINWVRQ APGQGLEWMGIIYPGSSTSNYNEKFKTRVTMTVDTSTSTAY MELSSLRSED ~~TAVYYC~~ <u>VKNDN</u> WGQGT ~~LVTVSS~~	SEQ ID NO: 16
VL (CDR sequences are underlined)	DIQMTQSPSSLSASVGDRVTITCRASESVDNYGISFMNWFQ QKPGKAPKLLIY <u>AAS</u> DLGSGVPSRFSGSGSGTDFTLTISSLQP EDFATYYCH <u>QSK</u> EV ~~PYTF~~ GQG ~~TKLEIK~~	SEQ ID NO: 17
Heavy Chain amino acid sequence (the S228P mutation is in bold font)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTKYWINWVRQ APGQGLEWMGIIYPGSSTSNYNEKFKTRVTMTVDTSTSTAY MELSSLRSED ~~TAVYYC~~ <u>VKNDN</u> WGQGT ~~LVTVSS~~ ASTKGPSV FPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNV ~~DH~~ KPSNT KVDKRVESKYGPPCP ~~CP~~ APEFLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTYRVVSVLT ~~VL~~ HQDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSR WQEGNVFSCSVMEALHNHYTQKSLSLSLG	SEQ ID NO: 18
Light Chain amino acid sequence	DIQMTQSPSSLSASVGDRVTITCRASESVDNYGISFMNWFQ QKPGKAPKLLIY AASDLGSGVPSRFSGSGSGTDFTLTISSLQP EDFATYYCHQSK ~~EV~~ PYTFGQGT ~~TKLEIK~~ RTVAAPSVFIFPPSD EQLKSGTASV ~~V~~ CLLN ~~F~~ YPREAKVQWKVDNALQSGNSQES VTEQDSKDS ~~T~~ YSL ~~S~~ TL ~~T~~ LSKADYEKHKVYACEVTHQGLSS PVT ~~K~~ SFNRGEC	SEQ ID NO: 19
Heavy Chain nucleotide Sequence	ATGGACCCCAAGGGCAGCCTGAGCTGGAGAATCCTGCT GTTCTGAGCCTGGCCTTCGAGCTGAGCTACGGCCAGGT GCAGCTGGTGCAGAGCGGTGCGGAAGTGAAGAAGCCC GGTGCCAGCGTGAAGGTGAGCTGCAAGGCCAGCGGCTA CACCTTCACCAAGTACTGGATCAACTGGGTGAGGCAGG CACCCGGCCAAGGCCTGGAGTGGATGGGCATCATCTAC CCCGGCAGCAGCACCAGCAATTACAACGAGAAGTTCAA GACCCGAGTAACCATGACCGTGGACACCTCCACCAGCA CCGCCTACATGGAGCTGAGCAGCCTGAGGAGCGAGGAC ACCGCAGTGTACTACTGCGTGAAGAACGACAACTGGGG CCAGGGCACCCCTGGTGACCGTCAGCTCTGCTAGCACCA AGGGCCCCAGCGTGTTTCTCTCGCTCCCTGCAGCCGGA	SEQ ID NO: 20

	GCACATCCGAGAGCACCGCTGCTCTGGGCTGTCTCGTG AAGGACTACTTCCCTGAACCCGTCACCGTCAGCTGGAA TAGCGGCGCCCTGACATCCGGCGTCCACACATTCCCCGC TGTCCTGCAGAGCAGCGGCCTGTACAGCCTGAGCTCCG TGGTCACCGTGCCTAGCAGCAGCCTGGGAACAAAGACC TACACCTGCAACGTGGACCATAAGCCCTCCAACACCAA GGTGGACAAGCGGGTGGAAATCCAAGTATGGACCCCCCT GTCTCCTTGCCCTGCTCCTGAATTTCTCGGAGGCCCT CCGTCTTCCTGTTTCCCCCAAGCCCAAGGACACCCTGA TGATCTCCCGGACACCCGAAGTCACCTGCGTCGTGGTG GATGTCAGCCAGGAAGATCCCGAGGTGCAGTTCAACTG GTACGTGGACGGAGTGGAGGTGCATAACGCCAAAACCA AGCCCAGGGAAGAGCAGTTCAACAGCACCTATCGGGTC GTGTCCGTGCTCACCGTCCTGCATCAGGATTGGCTCAAC GGCAAGGAGTACAAGTGCAAGGTGTCCAACAAGGGCCT GCCCTCCTCCATCGAGAAGACCATCTCCAAGGCTAAGG GCCAACCTCGGGAGCCCCAAGTGTATACCCTCCCTCCCA GCCAGGAGGAGATGACCAAGAATCAAGTGAGCCTGACC TGCTCGTGAAGGGATTTTACCCCTCCGACATCGCTGTG GAATGGGAAAGCAATGGCCAACCTGAGAACAACCTACA AGACCACACCCCCCGTGCTGGACTCCGATGGCTCCTTCT TCCTGTACAGCAGGCTGACCGTGGACAAATCCCGGTGG CAAGAGGGAAACGTGTTACAGCTGCTCCGTGATGCACGA GGCTCTCCACAACCACTACACCCAGAAGAGCCTCTCCCT GAGCCTCGGCTAG	
Light Chain nucleotide sequence	ATGGAGACCGACACCCTGCTGCTCTGGGTGCTGCTGCTCT GGGTGCCCCGGCTCCACCGGAGACATCCAGATGACCCAGA GCCCCAGCAGCCTGTCCGCTAGCGTAGGCGACAGGGTCA CCATCACCTGTAGGGCCAGTGAGAGCGTGGACAACCTACG GCATCAGCTTTATGAACTGGTTCCAGCAGAAGCCCCGGCA AGGCCCCCAAGCTGCTGATTTACGCCGCCAGCGACCTGG GCAGCGGCGTGCCAGTAGGTTACGCGGCTCCGGTAGCG GCACCGACTTCACCCTGACTATCAGCTCTCTGCAGCCCGA GGACTTCGCCACCTACTACTGCCACCAGAGCAAGGAGGT CCCCATACCTTCGGCCAAGGCACCAAGTTGGAGATCAA GCGGACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCTCCC AGCGACGAGCAGCTGAAGTCTGGCACCGCCAGCGTGGTG TGCTTGCTGAACAACCTTCTACCCCCGCGAGGCCAAGGTG CAGTGGAAGGTGGACAACGCCCTGCAGAGCGGCAACAG CCAGGAGAGCGTGACCGAGCAGGACTCCAAGGACAGCA CCTACAGCCTGAGCAGCACCTGACCCTGAGCAAGGCCG ACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCC ACCAGGGACTGTCTAGCCCCGTGACCAAGAGCTTCAACC GGGCGGAGTGCTAA	SEQ ID NO: 21

*Note that the following sequences are identical: SEQ ID NO: 15, SEQ ID NO: 66, SEQ ID NO: 68.

[00220] Conditions for binding and screening of monoclonal antibodies and Fabs using high-throughput flow cytometry were optimized using wild-type target protein cloned into a

proprietary vector and expressed in HEK-293T cells. The target protein is human integrin alpha-7 (ITGA7; UniProt ID Q13683; **SEQ ID NO: 24**). The binding of the VL3VHK20TFT monoclonal antibody and the VL3VHK20TFT Fab to HEK-293T cells co-transfected (1:1) with integrin beta-1 precursor (ITGB1) and integrin subunit alpha 7 (ITGA7) or with vector alone (negative control) was evaluated by high-throughput flow cytometry. The antibodies 3C12, 6A11, A1-1a M20, and A1-1a M24 were used as positive controls for ITGA7 binding. These antibodies and the parameters for high-throughput flow cytometry are provided in **Table 4**.

Table 4. Experimental parameters optimized for high-throughput flow cytometry

Experimental Parameter	Test MAb	Control MAb	Control MAb	Control MAb	Control MAb
Cell Type	HEK-293T	HEK-293T	HEK-293T	HEK-293T	HEK-293T
Fixative	None	None	None	None	None
Blocking Buffer	10% Goat Serum	10% Goat Serum	10% Goat Serum	10% Goat Serum	10% Goat Serum
Primary Antibody					
Name	VL3VHK20TFT MAb	3C12 MAb (MBL)	6A11 MAb (MBL)	A1-1a M20 MAb	A1-1a M24 MAb
Target	ITGA7	ITGA7	ITGA7	ITGA7	ITGA7
Optimal Conc.	0.5 µg/ml	0.5 µg/ml	2.0 µg/ml	0.13 µg/ml	0.5 µg/ml
Incubation (25°C)	60 min	60 min	60 min	60 min	60 min
Secondary Antibody					
Target	Human IgG	Mouse IgG	Mouse IgG	Mouse IgG	Mouse IgG
Optimal Conc.	1:400 (3.75 µg/ml)	1:400 (3.75 µg/ml)	1:400 (3.75 µg/ml)	1:400 (3.75 µg/ml)	1:400 (3.75 µg/ml)
Incubation (25°C)	30 min	30 min	30 min	30 min	30 min
Manufacturer	Jackson ImmunoResearch	Jackson ImmunoResearch	Jackson ImmunoResearch	Jackson ImmunoResearch	Jackson ImmunoResearch
Cat #	109-545-003	115-545-003	115-545-003	115-545-003	115-545-003
Antibody ID	AlexaFluor® 488 AffiniPure Goat Anti-Human IgG (H+L)	AlexaFluor® 488 AffiniPure Goat Anti-Mouse IgG (H+L)	AlexaFluor® 488 AffiniPure Goat Anti-Mouse IgG (H+L)	AlexaFluor® 488 AffiniPure Goat Anti-Mouse IgG (H+L)	AlexaFluor® 488 AffiniPure Goat Anti-Mouse IgG (H+L)
Wash Buffer	PBS (Ca ²⁺ , Mg ²⁺ free)	PBS (Ca ²⁺ , Mg ²⁺ free)	PBS (Ca ²⁺ , Mg ²⁺ free)	PBS (Ca ²⁺ , Mg ²⁺ free)	PBS (Ca ²⁺ , Mg ²⁺ free)
Signal:Background	18:1	16:1	16:1	17:1	16:1

[00221] The parameters used for high-throughput flow cytometry with VL3VHK20TFT Fab are provided in **Table 5**.

Table 5. Experimental parameters optimized for high-throughput flow cytometry.

Experimental Parameter	Test Fab
Cell Type	HEK-293T
Fixative	None
Blocking Buffer	10% Goat Serum

Primary Antibody	
Name	VL3VHK20TFT Fab
Target	ITGA7
Optimal Conc.	2.0 µg/ml
Incubation (25°C)	60 min
Secondary Antibody	
Target	Human F(ab') ₂
Optimal Conc.	1:200 (7.50 µg/ml)
Incubation (25°C)	30 min
Manufacturer	Jackson ImmunoResearch
Cat #	109-546-006
Antibody ID	AlexaFluor® 488 AffiniPure Goat Anti- Human IgG F(ab') ₂ Fragment
Wash Buffer	PBS (Ca ²⁺ , Mg ²⁺ free)
Signal:Background	12:1

[00222] As FIG. 15 and FIG. 16 show, VL3VHK20TFT mAb (FIG. 15) and VL3VHK20TFT Fab (FIG. 16) bind selectively to cells containing the target protein ITGA7 and do not bind to cells that do not contain the target (vector). Each point in FIG. 15 and FIG. 16 represents the mean of four replicates. The optimal screening concentration for each antibody or Fab (outlined in a box) was determined based on the raw signal values and signal-to-background calculations.

[00223] In order to map the epitope of VL3VHK20TFT, an alanine-scan library of the target protein (ITGA7; SEQ ID NO: 24) was constructed. Shotgun mutagenesis epitope mapping was performed using the general procedure described in Davidson and Doranz, 2014, *Immunology* 143, 13-20. Briefly, a mutation library of the target protein was created by high-throughput, site-directed mutagenesis. Each residue was individually mutated to alanine, with alanine codons mutated to serine. The mutant library was arrayed in 384-well microplates and transiently transfected into HEK-293T cells. Following transfection, cells were incubated with the indicated antibodies (VL3VHK20TFT Fab or 6A11 monoclonal antibody (mAb)) at concentrations pre-determined using an independent immunofluorescence titration curve on wild type protein. The antibodies were detected using an Alexa Fluor 488-conjugated secondary antibody, and mean cellular fluorescence was determined using Intellicyt® iQue flow cytometry platform. Mutated residues were identified as being critical to the

VL3VHK20TFT Fab epitope if they did not support the reactivity of the VL3VHK20TFT Fab but did support the reactivity of the reference 6A11 mAb. This counterscreen strategy facilitates the exclusion of mutants that are locally misfolded or that have an expression defect.

[00224] Library screens of very-high-affinity MABs sometimes fail to yield critical residues for antibody binding. Conversion of a high-affinity MAB to a Fab usually weakens binding sufficiently to allow identification of critical residues for binding. For cases where Fab screens under standard conditions are still insufficient to identify critical residues for binding, high stringency conditions are implemented. These conditions include combinations of increased pH, increased salinity, increased temperature, and/or increased wash time. Antibodies that required high stringency conditions are denoted “HS”.

[00225] The binding of VL3VHK20TFT Fab and 6A11 mAb to each mutant clone in an alanine scanning library of ITGA7 mutants was determined, in duplicate, by high-throughput flow cytometry. For each point, background fluorescence was subtracted from the raw data, which were then normalized to antibody (Ab) reactivity with wild-type (WT) target protein. For each mutant clone, the mean binding value was plotted as a function of expression (represented by control reactivity). To identify preliminary primary critical clones (red circles), a threshold (dashed lines) of >70% WT binding to control Ab and <20% WT binding to test Abs was applied. Secondary clones (blue circles) are highlighted for clones that did not meet the set thresholds but whose decreased binding activity and proximity to critical residues suggested that the mutated residue may be part of the antibody epitope. **FIG. 17** shows a graph containing primary critical clones and secondary clones.

[00226] The critical residues for antibody binding are listed in **Table 6**. Mean binding reactivities (and ranges) are listed for all identified critical residues. Critical residues for Ab binding (S977, W978, W979, P980) were residues whose mutations were negative for binding to test Abs, but positive for binding to control antibody. Additional secondary residues (R958, M976) were identified that did not meet the threshold guidelines, but whose decreased binding activity and proximity to critical residues suggested that they may be part of the antibody epitope.

[00227] Critical residues (red spheres) were visualized on a crystal structure model of the target protein, based on an integrin alpha(x)beta(2) structure (PDB ID# 3K71 in Xie et al., 2010, *Embo. J.* 29, 666-679) as shown in **FIG. 18**. Secondary residues (blue spheres) that may contribute to binding are also shown. One residue (R958) is not available on the model. Critical residues whose mutation gave the lowest reactivities with VL3VHK20TFT Fab are

underlined in **Table 6**. Validated critical residues represent amino acids whose side chains make the highest energetic contributions to the antibody-epitope interaction (Bogan and Thorn, 1998, *J. Mol. Biol.* 280, 1-9; Lo Conte et al., 1999, *J. Mol. Biol.* 285, 2177-2198.); therefore, the highlighted residues (S977, W978, W979, P980) are likely the major energetic contributors to binding.

Table 6. Critical Residues for Antibody Binding

Binding Reactivity (% WT)		
Mutation	VL3VHK20TFT Fab HS	6A11 MAb
R958A	27.8 (0)	114.3 (66)
M976A	29.5 (7)	149.4 (45)
<u>S977A</u>	8.0 (1)	97.6 (44)
<u>W978A</u>	-0.3 (0)	96.4 (32)
<u>W979A</u>	-0.7 (2)	87.9 (17)
<u>P980A</u>	1.1 (0)	111.8 (67)

Table 7. Human integrin alpha-7 (ITGA7; UniProt ID Q13683) amino acid sequence

MAGARSRDPWGASGICYLFGSLIVELLFSRAVAFNLDVMGALRKEGEPGSLFGFSVALHR
 QLQPRPQSWLLVGAPQALALPGQQANRTGGLFACPLSLEETDCYRVDIDQGADMQKESKE
 NQWLGVSVRSQGPGGKIVTCAHRYEARQRVDQILETRDMIGRCFVLSQDLAIRDELGGGE
 WKFCGRPQGHEQFGFCQQGTAAAFSPDSHYLLFGAPGTYNWKG TARVELCAQGSADLAH
 LDDGPYEAGGEKEQDPRLIPVPANSYFGLLFVTNIDSSDPDQLVYKTLDPADRLPGPAGD
 LALNSYLGFSIDSGKGLVRAEELS FVAGAPRANHKGAVVILRKDSASRLVPEVMLSGERL
 TSGFGYSLAVADLNSDGWPD LIVGAPYFFERQEELGGAVYVYLNQGGHWAGISPLRLCGS
 PDSMFGISLAVLGD LNQDGFDPDI AVGAPFDGDGKVFIYHGSSLGVVAKPSQVLEGEAVGI
 KSGYSLSGSLDMDGNQYPDLLVGS LADTAVLFRARPILHVSHEVSIAPRSIDLEQPNCA
 GGHSVCVDLRVCFYSYIAVPSSYSPTVALDYVLDADTDRLRGQVPRVTFLSRNLEEPKHQ
 ASGTVWLKHQHDRVCGDAMFQLQENVKDKLRAIVVTLSYSLQTPRLRRQAPGQGLPPVAP
 ILNAHQ PSTQRAEIHFLKQGCGEDKICQSNLQLVRARFCTRVSDTEFQPLPMDVDGTTAL
 FALSGQP VIGLELMVTNLPSDPAQPQADGDDAHEAQLLVMLPDSLHYSGVRALDPAEKPL
 CLSNENASHVECELG NPMKRGAQVTFYLILSTSGIS IETTELEV ELLLATISEQELHPVS
 ARARVFIELPLSIAGMAIPQQLFFSGVVRGERAMQSERDVGSKVKYEVT VSNQGQSLRTL

GSAFLNIMWPHEIANGKWLlyPMQVELEGGQGPQKGLCSRPNIHLHDVDSRDRRRREL
 EPPEQQEPGERQEPMSWWPVSSAEKKKNITLDCARGTANCVVFSCPLYSFDRRAVLHVW
 GRLWNSTFLEEYSVAVKSLEVIVRANITVKSSIKNLMLRDASTVIPVMVYLDPMVVAEGV
 PWWVILLAVLAGLLVLALLVLLLWKMGGFFKRAKHPEATVPQYHAVKIPREDRQQFKEEKT
 GTILRNNWGS PRREGPDAPILAADGHPELGPDPGPGTA (SEQ ID NO: 24)

Example 4: Evaluation of mouse and humanized antibodies to $\alpha\beta 1$ integrin

[00228] Antibody binding to human and mouse integrin $\alpha\beta 1$ was evaluated. The mouse $\alpha\beta 1$ antibody VLVH (Chimera with human IgG4 Fc, also referred to as hIgG4-23 in **Table 10**) and humanized $\alpha\beta 1$ antibody VL3VHK20TFT were both found to cross react with human and mouse integrin $\alpha\beta 1$. A comparison of the affinity measurement listed in **Table 8** shows that humanized antibody VL3VHK20TFT had a lower KD for binding to both human and mouse integrin $\alpha\beta 1$. The humanized antibody had about 3.33-fold lower KD for binding to human $\alpha\beta 1$ and about 11.1-fold lower KD for binding to mouse $\alpha\beta 1$ integrin. These data show an overall substantial affinity improvement for the humanized antibody VL3VHK20TFT over the chimera antibody with mouse hybridoma Fab region. **FIG. 19** is a graph showing results at various concentrations for VL3VHK20TFT; 0.25 $\mu\text{g/mL}$ Human Integrin $\alpha\beta 1$; 1:1 binding. **FIG. 20** is a graph showing results at various concentrations for VLVH; 0.25 $\mu\text{g/mL}$ Human Integrin $\alpha\beta 1$; 1:1 binding. **FIG. 21A** is a graph showing results at various concentrations for VL3VHK20 TFT; 0.25 $\mu\text{g/mL}$ Mouse Integrin $\alpha\beta 1$; 1:1 binding. **FIG. 21B** is a graph showing results at various concentrations for VLVH; 0.25 $\mu\text{g/mL}$ Mouse Integrin $\alpha\beta 1$; 1:1 binding.

[00229] Antibody binding to cell surface integrin $\alpha\beta 1$ was evaluated by flow cytometry. K562 cells expressing human integrin $\alpha\beta 1$ were used for VL3VHK20TFT antibody binding. **FIG. 22A** is a graph showing the antibody cell surface binding at various concentrations. Antibody VL3VHK20TFT was found to enhance both human $\alpha\beta 1$ (**FIG. 22B**) and murine $\alpha\beta 1$ (**FIG. 22C**) mediated adhesion to laminin.

Table 8: Evaluation of mouse and humanized antibodies to $\alpha\beta 1$ integrin

Kinetics model	Capture 1 Solution	Analyte 1 Solution	Kinetics Chi ² (RU ²)	ka (1/Ms)	kd (1/s)	KD (M)
1:1 binding	0.25 $\mu\text{g/mL}$ Human Integrin $\alpha\beta 1$	VL3VHK20TFT	1.11E-01	2.58E+05	1.53E-04	5.93E-10

1:1 binding	0.25 µg/mL Human Integrin $\alpha 7\beta 1$	VLVH	7.36E-03	3.33E+05	6.52E-04	1.96E-09
1:1 binding	0.25 µg/mL Mouse Integrin $\alpha 7\beta 1$	VL3VHK20TFT	6.85E-03	2.39E+05	4.69E-04	1.96E-09
1:1 binding	0.25 µg/mL Mouse Integrin $\alpha 7\beta 1$	VLVH	6.70E-03	9.76E+04	2.13E-03	2.18E-08

Example 5: $\alpha 7\beta 1$ Agonist Antibody Enhanced DMD Myoblast Cell Adhesion to Laminin

[00230] Method: Real-time monitoring of cellular reattachment from suspension was measured using an electrical impedance assay with an xCELLigence RTCA SP real-time cell-sensing device. DMD myoblast cells were seeded into E-plates coated with laminin 211. Cells were treated with antibodies respectively. The attachment rate was expressed as the cell index, with values expressed as the cell index $\pm$ SD of triplicate wells.

[00231] Results: **FIG. 23** is a graph showing antibody concentration in µg/mL vs cell index (integrin $\alpha 7\beta 1$ mediated cell adhesion) for both murine antibody (VLVH) and humanized antibody (VL3VHK20TFT) enhanced myoblast cell adhesion on laminin. The humanized antibody was about 5-fold more potent than the murine antibody.

Example 6: $\alpha 7\beta 1$ Agonist Antibody Protects Gastrocnemius Muscle From Injury

[00232] Method: Four murine test groups were established: a DBA2/IgG control, a mdx/IgG control, a mdx/Agonist antibody at 3 mg/kg, and a mdx/agonist antibody at 15 mg/kg. Muscle performance was measured *in vivo* with a 305C muscle lever system. The knee was isolated using a pin pressed against the tibial head and the foot firmly fixed to a footplate on the motor shaft. For the plantar flexor muscle group, contractions were elicited by percutaneous electrical stimulation of the sciatic nerve. A series of 20 tetanic stimulations (80Hz, 0.2ms pulse, 500ms duration) were delivered at 0.1Hz frequency. The foot was rotated against the direction of contraction by 10° over 250 ms, resulting in an eccentric contraction.

[00233] Results: **FIG. 24** is a graph showing contraction vs force (normalized to initial contraction) for the DBA2/IgG control, the mdx/IgG control, the mdx/Agonist antibody at 3 mg/kg, and the mdx/agonist antibody at 15 mg/kg. Force for mdx mice dropped much more than the healthy control mice (DBA2). Integrin $\alpha 7\beta 1$ agonist antibody treatment protected from eccentric injury with both doses (3 mg/kg and 15 mg/kg).

Example 7: $\alpha 7\beta 1$ Agonist Antibody Agonist Antibody Improved Diaphragm Function

[00234] Method: Using the four murine groups from Example 6, muscle performance was measured *in vitro* with a 305C muscle lever system (Aurora Scientific Inc., Aurora, CAN) adapted with a horizontal perfusion bath. The entire diaphragm was placed in the horizontal bath of the 305C muscle lever system and perfused with physiological buffer oxygenated with 95% O₂/5% CO₂ and kept at 37°C. A series of 1Hz and 100 Hz field stimulations (0.2 ms pulse, 100 ms duration) at 0.01 Hz frequency were delivered via platinum electrodes flanking the muscle to ensure that the sutures were tight and that the maximal developed force was stable.

[00235] Results: **FIG. 25** is a graph showing stimulation frequency in Hz vs force (normalized to muscle width, mN/mm) for the DBA2/IgG control, the mdx/IgG control, the mdx/Agonist antibody at 3 mg/kg, and the mdx/agonist antibody at 15 mg/kg. The mdx mice force dropped much more than the healthy control mice (DBAS). Treatment with the integrin $\alpha 7\beta 1$ agonist antibody protected from eccentric injury with both doses (3 mg/kg and 15 mg/kg).

Example 8: $\alpha 7\beta 1$ Agonist Antibody Treatment Improves Biomarkers

[00236] Method: Various biomarkers associated with muscular dystrophic damage were measured in mice and found to be improved with treatment.

[00237] **FIG. 26** is a bar graph showing the amount of serum creatine kinase, a biomarker for muscle damage, in the DBA2/IgG control, the mdx/IgG control, and treatment with the M36 agonist antibody. Treatment with the M36 agonist antibody substantially reduced serum creatine kinase as compared to the mdx/IgG control.

[00238] **FIG. 27** is a bar graph showing the amount of skeletal troponin, a biomarker for muscular damage, in the DBA2/IgG control, the mdx/IgG control, and treatment with the M36 agonist antibody. Treatment with the M36 agonist antibody substantially reduced skeletal troponin as compared to the mdx/IgG control.

[00239] **FIG. 28** is a bar graph showing the amount of O-hydroxyproline, a measure of collagen formation/fibrosis in the gastrocnemius muscle in the DBA2/IgG control, the mdx/IgG control, and treatment with the M36 agonist antibody. Treatment with the M36 agonist antibody substantially reduced collagen formation/fibrosis as determined by O-hydroxyproline when compared to the mdx/IgG control.

Example 9: Improved Properties of Modified $\alpha\beta 1$ Agonist Antibodies

[00240] Amino acid substitutions, as shown in **FIG. 29**, were generated by site-directed mutagenesis of sequences of antibody VL3VHK20TFT (original sequences provided in **Table 3**) and were evaluated for an ability to reduce antibody polyspecificity. As shown further here, some of the variants that included hIgG-38 in the variable region of the heavy chain, and hIgG-44, 45 and 46 in the variable region of the light chain were found to retain integrin $\alpha\beta 1$ binding activity (**FIG. 30**). An ELISA-based approach which employs the membrane proteins presented on the surface of a baculovirus particle (BVP) was used as a reagent to capture antibodies with cross-interaction propensity. Hydrophobic interaction chromatography (HIC) was used as an analytical technique to probe antibody hydrophobicity. hIgG-38, 44 and 45 were shown to have more favorable biophysical properties, as shown in **Table 9**. Sequences of these antibodies are provided in **Table 11**, **Table 12** and **Table 13**.

Table 9: BVP and HIC scores for humanized antibody variants

	BVP	HIC
hIgG-36	12.5	16.29
hIgG-38	3.8	12.43
hIgG-44	6.4	8.19
hIgG-45	7.5	8.26
hIgG-46	18.1	12.01

Example 10: Additional $\alpha\beta 1$ Agonist Antibodies

[00241] **Table 10** shows a range of $\alpha\beta 1$ agonist IgG antibodies prepared from combinations of heavy chains and light chains whose amino acid sequences are provided after **Table 10**.

[00242] Heavy chain sequences VHK2, VHK4, VHK11, VHK12, VHK14, VHK20, VHK22, VHK33, VHK48, and VHK51 are humanized heavy chain sequences comprising variation in the HCDR3 sequence. Heavy chain sequences VHK20TFT-A to VHK20TFT-F comprise variation in the HCDR1 and HCDR2 sequences. Light chain sequences VL1 – VL10 are humanized kappa chain sequences. Light chain sequences VL11, VL12 and VL13 comprise variation in the LCDR1 sequence. The sequences named “VH” and “VL” are chimeric molecules comprising murine IgG M36 variable regions and human IgG4 constant regions.

Table 10: Exemplary $\alpha\beta 1$ IgG antibodies

Human IgG antibody name	Light chain sequence	Heavy chain sequence	Other name for antibody
hIgG4-1	VL1	VHK33	VL1VHK33

hIgG4-2	VL1	VHK20	VL1VHK20
hIgG4-3	VL1	VHK22	VL1 VHK22
hIgG4-4	VL1	VHK48	VL1 VHK48
hIgG4-5	VL1	VHK14	VL1 VHK14
hIgG4-6	VL1	VHK7	VL1 VHK7
hIgG4-7	VL1	VHK51	VL1 VHK51
hIgG4-8	VL1	VHK11	VL1 VHK11
hIgG4-9	VL1	VHK2	VL1 VHK2
hIgG4-10	VL1	VHK4	VL1 VHK4
hIgG4-11	VL2	VHK33	VL2 VHK33
hIgG4-12	VL2	VHK20	VL2 VHK20
hIgG4-13	VL2	VHK22	VL2 VHK22
hIgG4-14	VL2	VHK48	VL2 VHK48
hIgG4-15	VL2	VHK14	VL2 VHK14
hIgG4-16	VL2	VHK7	VL2 VHK7
hIgG4-17	VL2	VHK51	VL2 VHK51
hIgG4-18	VL2	VHK11	VL2 VHK11
hIgG4-19	VL2	VHK2	VL2 VHK2
hIgG4-20	VL2	VHK4	VL2 VHK4
hIgG4-21	VL1	VHK12	VL1 VHK12
hIgG4-22	VL2	VHK12	VL2 VHK12
hIgG4-23	VL	VH	VL VH
hIgG4-24	VL1	VH3	VL1 VH3
hIgG4-25	VL2	VH3	VL2 VH3
hIgG4-26	VL	VHK20	VL VHK20
hIgG4-27	VL	VH3	VL VH3
hIgG4-28	VL3	VHK20	VL3 VHK20
hIgG4-29	VL4	VHK20	VL4 VHK20
hIgG4-30	VL5	VHK20	VL5 VHK20
hIgG4-31	VL6	VHK20	VL6 VHK20
hIgG4-32	VL7	VHK20	VL7 VHK20
hIgG4-33	VL8	VHK20	VL8 VHK20
hIgG4-34	VL9	VHK20	VL9 VHK20
hIgG4-35	VL10	VHK20	VL10 VHK20
hIgG4-36	VL3	VHK20TFT	VL3 VHK20TFT
hIgG4-37	VL3	VHK20NTA	VL3 VHK20NTA
hIgG4-38	VL3	VHK20TFT-A	VL3 VHK20TFT-A
hIgG4-39	VL3	VHK20TFT-B	VL3 VHK20TFT-B
hIgG4-40	VL3	VHK20TFT-C	VL3 VHK20TFT-C
hIgG4-41	VL3	VHK20TFT-D	VL3 VHK20TFT-D
hIgG4-42	VL3	VHK20TFT-E	VL3 VHK20TFT-E
hIgG4-43	VL3	VHK20TFT-F	VL3 VHK20TFT-F
hIgG4-44	VL11	VHK20TFT	VL11 VHK20TFT
hIgG4-45	VL12	VHK20TFT	VL12 VHK20TFT

hIgG4-46	VL13	VHK20TFT	VL13 VHK20TFT
hIgG4-47	VL13	VHK20TFT-F	VL13 VHK20TFT-F
hIgG4-48	VL	VHK20TFT	VL VHK20TFT
hIgG4-49	VL3	VH	VL3 VH

Heavy chain sequences (underlined portions in each sequence are, in order, HCDR1, HCDR2 and HCDR3)

VHK33

QVQLVQSGAEVKKPGASVKVSCKASGYNFTKYWINWVRQAPGQGLEWMGIIYPGSSTSNY
NEKFKTRVTMTVDSTSTAYMELSSLRSEDTAVYYCYVRGDEWGQGLTVTVSSASTKGPSVF
PLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP
SSSLGTKTYTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRT
PEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNHYTQKS
LSLSLG (SEQ ID NO: 31)

VHK20

QVQLVQSGAEVKKPGASVKVSCKASGYNFTKYWINWVRQAPGQGLEWMGIIYPGSSTSNY
NEKFKTRVTMTVDSTSTAYMELSSLRSEDTAVYYCYKNDNWGQGLTVTVSSASTKGPSVF
PLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP
SSSLGTKTYTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRT
PEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNHYTQKS
LSLSLG (SEQ ID NO: 32)

VHK22

QVQLVQSGAEVKKPGASVKVSCKASGYNFTKYWINWVRQAPGQGLEWMGIIYPGSSTSNY
NEKFKTRVTMTVDSTSTAYMELSSLRSEDTAVYYCYKNDVWGQGLTVTVSSASTKGPSVF
PLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP
SSSLGTKTYTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRT
PEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNHYTQKS
LSLSLG (SEQ ID NO: 33)

VHK48

QVQLVQSGAEVKKPGASVKVSCKASGYNFTKYWINWVRQAPGQGLEWMGIIYPGSSTSNY
NEKFKTRVTMTVDSTSTAYMELSSLRSEDTAVYYCYVRRDNWGQGLTVTVSSASTKGPSVF
PLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP
SSSLGTKTYTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRT
PEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNHYTQKS
LSLSLG (SEQ ID NO: 34)

VHK14

QVQLVQSGAEVKKPGASVKVSCKASGYNFTKYWINWVRQAPGQGLEWMGIYPGSSTSNY
NEKFKTRVTMTVDSTSTAYMELSSLRSEDTAVYYCYKGDVWGQGLTVTVSSASTKGPSVF
PLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP
SSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRT
PEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKS
LSLSLG (SEQ ID NO: 35)

VHK7

QVQLVQSGAEVKKPGASVKVSCKASGYNFTKYWINWVRQAPGQGLEWMGIYPGSSTSNY
NEKFKTRVTMTVDSTSTAYMELSSLRSEDTAVYYCYKGDWVGQGLTVTVSSASTKGPSVF
PLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP
SSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRT
PEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKS
LSLSLG (SEQ ID NO: 36)

VHK51

QVQLVQSGAEVKKPGASVKVSCKASGYNFTKYWINWVRQAPGQGLEWMGIYPGSSTSNY
NEKFKTRVTMTVDSTSTAYMELSSLRSEDTAVYYCYRRDTWGQGLTVTVSSASTKGPSVF
LAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPS
SSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRT
PEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAV
WESNGQPENNYKTTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKS
LSLSLG (SEQ ID NO: 37)

VHK11

QVQLVQSGAEVKKPGASVKVSCKASGYNFTKYWINWVRQAPGQGLEWMGIYPGSSTSNY
NEKFKTRVTMTVDSTSTAYMELSSLRSEDTAVYYCYKGDQWGQGLTVTVSSASTKGPSVF
PLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP
SSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRT
PEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKS
LSLSLG (SEQ ID NO: 38)

VHK2

QVQLVQSGAEVKKPGASVKVSCKASGYNFTKYWINWVRQAPGQGLEWMGIYPGSSTSNY
NEKFKTRVTMTVDSTSTAYMELSSLRSEDTAVYYCYKGDWVGQGLTVTVSSASTKGPSVF
PLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP
SSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRT
PEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKS
LSLSLG (SEQ ID NO: 39)

VHK4

QVQLVQSGAEVKKPGASVKVSCKASGYNFTKYWINWVRQAPGQGLEWMGIIYPGSSTSNY
NEKFKTRVTMTVDTSTSTAYMELSSLRSEDTAVYYCYKGDEWGQGLTVTVSSASTKGPSVF
PLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP
SSSLGTKTYTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRT
PEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNHYTQKS
LSLSLG (SEQ ID NO: 40)

VHK12

QVQLVQSGAEVKKPGASVKVSCKASGYNFTKYWINWVRQAPGQGLEWMGIIYPGSSTSNY
NEKFKTRVTMTVDTSTSTAYMELSSLRSEDTAVYYCYKGDSWGQGLTVTVSSASTKGPSVF
PLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP
SSSLGTKTYTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRT
PEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNHYTQKS
LSLSLG (SEQ ID NO: 41)

VH

QVQLQPGAELVKPGASVKLSCKASGYNFTKYWINWVKRPGQGLEWIGIIYPGSSTSNYNE
KFKTKATLTVEISSTAYMQLSSLTSDDSAVYYCYRGDDWGQGLTVTVSSASTKGPSVFPLA
PCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSL
GTKTYTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEV
TCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEY
KCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNHYTQKSLSLS
LG (SEQ ID NO: 42)

VH3

QVQLVQSGAEVKKPGASVKVSCKASGYNFTKYWINWVRQAPGQGLEWMGIIYPGSSTSNY
NEKFKTRVTMTVDTSTSTAYMELSSLRSEDTAVYYCYRGDDWGQGLTVTVSSASTKGPSVF
PLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP
SSSLGTKTYTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRT
PEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNHYTQKS
LSLSLG (SEQ ID NO: 43)

VHK20NFA

QVQLVQSGAEVKKPGASVKVSCKASGYNFAKYWINWVRQAPGQGLEWMGIIYPGSSTSNY
NEKFKTRVTMTVDTSTSTAYMELSSLRSEDTAVYYCYKNDNWGQGLTVTVSSASTKGPSVF
PLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP
SSSLGTKTYTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRT
PEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNHYTQKS
LSLSLG (SEQ ID NO: 44)

VHK20TFT-A

QVQLVQSGAEVKKPGASVKVSCKASGYTFTKYHINWVRQAPGQGLEWMGIYPGSSTSNYN
EKFKTRVTMTVDTSTSTAYMELSSLRSED~~TAVYYCVKNDN~~WGQGLTVTVSSASTKGPSVFP
LAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS
SSLGTKTYTCNV~~DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRT~~
EVTCTVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTTPVLDS~~SDGSFFLYSRLTVDKSRWQEGNVFSCSV~~MHEALHNHYTQKSL
LSLSLG (SEQ ID NO: 45)

VHK20TFT-B

QVQLVQSGAEVKKPGASVKVSCKASGYTFTKYINWVRQAPGQGLEWMGIYPGSSTSNYN
EKFKTRVTMTVDTSTSTAYMELSSLRSED~~TAVYYCVKNDN~~WGQGLTVTVSSASTKGPSVFP
LAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS
SSLGTKTYTCNV~~DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRT~~
EVTCTVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTTPVLDS~~SDGSFFLYSRLTVDKSRWQEGNVFSCSV~~MHEALHNHYTQKSL
LSLSLG (SEQ ID NO: 46)

VHK20TFT-C

QVQLVQSGAEVKKPGASVKVSCKASGYTFTKYWINWVRQAPGQGLEWMGTIQPGSSTSNY
NEKFKTRVTMTVDTSTSTAYMELSSLRSED~~TAVYYCVKNDN~~WGQGLTVTVSSASTKGPSVFP
PLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS
SSSLGTKTYTCNV~~DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRT~~
PEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTTPVLDS~~SDGSFFLYSRLTVDKSRWQEGNVFSCSV~~MHEALHNHYTQKS
LSLSLG (SEQ ID NO: 47)

VHK20TFT-D

QVQLVQSGAEVKKPGASVKVSCKASGYTFTKYWINWVRQAPGQGLEWMGTIHPGSSTSNY
NEKFKTRVTMTVDTSTSTAYMELSSLRSED~~TAVYYCVKNDN~~WGQGLTVTVSSASTKGPSVFP
PLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS
SSSLGTKTYTCNV~~DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRT~~
PEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTTPVLDS~~SDGSFFLYSRLTVDKSRWQEGNVFSCSV~~MHEALHNHYTQKS
LSLSLG (SEQ ID NO: 48)

VHK20TFT-E

QVQLVQSGAEVKKPGASVKVSCKASGYTFTKYWINWVRQAPGQGLEWMGTINPGSSTSNY
NEKFKTRVTMTVDTSTSTAYMELSSLRSED~~TAVYYCVKNDN~~WGQGLTVTVSSASTKGPSVFP
PLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS
SSSLGTKTYTCNV~~DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRT~~
PEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTTPVLDS~~SDGSFFLYSRLTVDKSRWQEGNVFSCSV~~MHEALHNHYTQKS
LSLSLG (SEQ ID NO: 49)

VHK20TFT-F

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYMHWVRQAPGGLEWMGIYPGSSTSNY
NEKFKTRVTMTVDSTSTAYMELSSLRSEDTAVYYCVKNDNWGGTLTVTVSSASTKGPSVF
PLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTV
SSSLGTKTYTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRT
PEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTPPVLDSDGSFFLYSLRTVDDKSRWQEGNVFSCSVMEALHNHYTQKS
LSLSLG (SEQ ID NO: 50)

**Light chain sequences (underlined portions in each sequence are, in order, LCDR1,
LCDR2 and LCDR3)**

VL1

DIQMTQSPSSLSASVGDRVTITCRASESDNYGISFMNWFQKPGKAPKLLIYAASDLGSGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCHQSKEVPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQ
LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKAD
YEKHKVYACEVTHQGLSPVTKSFNRGEC (SEQ ID NO: 51)

VL2

DIQLTQSPSFLSASVGDRVTITCRASESDNYGISFMNWFQKPGKAPKLLIYAASDLGSGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCHQSKEVPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQ
LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKAD
YEKHKVYACEVTHQGLSPVTKSFNRGEC (SEQ ID NO: 52)

VL3

DIQMTQSPSSLSASVGDRVTITCRASESDNYGISFMNWFQKPGKAPKLLIYAASDLGSGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCHQSKEVPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQ
LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKAD
YEKHKVYACEVTHQGLSPVTKSFNRGEC (SEQ ID NO: 53)

VL4

DIQLTQSPSSLSVSVGDRATITCRASESDNYGISFMNWFQKPGKAPKLLIYAASDLGSGVP
SRFSGSGSGTDFTLTISSMQPEDFATYYCHQSKEVPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQ
LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKAD
YEKHKVYACEVTHQGLSPVTKSFNRGEC (SEQ ID NO: 54)

VL5

DIQLTQSPSSLSVSVGDRATITCRASESDNYGISFMNWFQKPGKAPKLLIYAASDLGSGVP
SRFSGSGSGTDFTLTISSMQPEDSATYYCHQSKEVPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQ
LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKAD
YEKHKVYACEVTHQGLSPVTKSFNRGEC (SEQ ID NO: 55)

VL

DIVLTQSPASLAIVSLGQRATISCRASESDNYGISFMNWFQKPGQPPKLLIYAASDLGSGVP
ARFTGSGSGTDFSLNIHPMEEDDSAMYFCHQSKEVPYTFGGGTKLEIKRTVAAPSVFIFPPSDE
QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKA
DYEKHKVYACEVTHQGLSPVTKSFNRGEC (SEQ ID NO: 56)

VL6

DIQLTQSPSSLSASVGDRVITITCRASESVDNYGISFMNWFQKPGKAPKLLIYAASDLGSGVP
SRFSGSGSGTDFTLTISLQPEDFATYFCHQSKEVPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQ
LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSTYLSSTLTLSKAD
YEKHKVYACEVTHQGLSPVTKSFNRGEC (SEQ ID NO: 57)

VL7

DIQLTQSPSSLSASVGDRVITITCRASESVDNYGISFMNWFQKPGKAPKLLIYAASDLGSGVP
SRFTGSGSGTDFTLTISLQPEDFATYFCHQSKEVPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQ
LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSTYLSSTLTLSKAD
YEKHKVYACEVTHQGLSPVTKSFNRGEC (SEQ ID NO: 58)

VL8

DIQLTQSPSSLSASVGDRATITCRASESVDNYGISFMNWFQKPGKAPKLLIYAASDLGSGVP
SRFTGSGSGTDFTLTISLQPEDFATYFCHQSKEVPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQ
LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSTYLSSTLTLSKAD
YEKHKVYACEVTHQGLSPVTKSFNRGEC (SEQ ID NO: 59)

VL9

DIQMTQSPSSLSASVGDRVITITCRASESVDNYGISFMNWFQKPGKAPKLLIYAASDLGSGVP
SRFSGSGSGTDFTLTISLQPEDFATYFCHQSKEVPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQ
LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSTYLSSTLTLSKAD
YEKHKVYACEVTHQGLSPVTKSFNRGEC (SEQ ID NO: 60)

VL10

DIQLTQSPSFLSASVGDRVITITCRASESVDNYGISFMNWFQKPGKAPKLLIYAASDLGSGVP
SRFSGSGSGTDFTLTISLQPEDFATYFCHQSKEVPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQ
LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSTYLSSTLTLSKAD
YEKHKVYACEVTHQGLSPVTKSFNRGEC (SEQ ID NO: 61)

VL11

DIQMTQSPSSLSASVGDRVITITCRASESVDNQGTSMNWFQKPGKAPKLLIYAASDLGSGV
PSRFSGSGSGTDFTLTISLQPEDFATYYCHQSKEVPYTFGQGTKLEIKRTVAAPSVFIFPPSDE
QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSTYLSSTLTLSKA
DYKHKVYACEVTHQGLSPVTKSFNRGEC (SEQ ID NO: 62)

VL12

DIQMTQSPSSLSASVGDRVITITCRASESVDNSGTSMNWFQKPGKAPKLLIYAASDLGSGV
PSRFSGSGSGTDFTLTISLQPEDFATYYCHQSKEVPYTFGQGTKLEIKRTVAAPSVFIFPPSDE
QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSTYLSSTLTLSKA
DYKHKVYACEVTHQGLSPVTKSFNRGEC (SEQ ID NO: 63)

VL13

DIQMTQSPSSLSASVGDRVITITCRASQSISSYLNFSMNWFQKPGKAPKLLIYAASDLGSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCHQSKEVPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQL
KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSTYLSSTLTLSKADY
EKHKVYACEVTHQGLSPVTKSFNRGEC (SEQ ID NO: 64)

Table 11. Amino acid sequences of antibody hIgG-38

HCDR1	GYTFTKYH	SEQ ID NO: 65
HCDR2	IYPGSSTS	SEQ ID NO: 3
HCDR3	VKNDN	SEQ ID NO: 66
LCDR1	ESVDNYGISF	SEQ ID NO: 5
LCDR2	AAS	SEQ ID NO: 6
LCDR3	HQSKEVPYT	SEQ ID NO: 7
VH (CDR sequences are underlined)	QVQLVQSGAEVKKPGASVKVSCASGYTFTKYHINWVRQAPGQ GLEWMGHI <u>IYPGSSTS</u> SNYNEKFKTRVTMTVDTSTSTAYMELSSLRS EDTAVYYC <u>VKNDN</u> WGQGLTVTVSS	SEQ ID NO: 67
VL (CDR sequences are underlined)	DIQMTQSPSSLSASVGDRTITCRASE <u>SVDNYGISF</u> MNWFQKPG KAPKLLIY <u>AAS</u> DLGSGVPSRFSGSGSGTDFTLTISLQPEDFATYY <u>CHQSKEVPYT</u> FGQGTKLEIK	SEQ ID NO: 17
Heavy Chain amino acid sequence (IgG4) (CDR sequences are underlined)	QVQLVQSGAEVKKPGASVKVSCASGYTFTKYHINWVRQAPGQ GLEWMGHI <u>IYPGSSTS</u> SNYNEKFKTRVTMTVDTSTSTAYMELSSLRS EDTAVYYC <u>VKNDN</u> WGQGLTVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGKTKYTCNVDHKPSNTKVDKRVESKYGPCCPPCPA PEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYS RLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLSLG	SEQ ID NO: 45
Light Chain amino acid sequence (CDR sequences are underlined)	DIQMTQSPSSLSASVGDRTITCRASE <u>SVDNYGISF</u> MNWFQKPG KAPKLLIY <u>AAS</u> DLGSGVPSRFSGSGSGTDFTLTISLQPEDFATYY <u>CHQSKEVPYT</u> FGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSS TLTSLKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 53

Table 12. Amino acid sequences of antibody hIgG-44

HCDR1	GYTFTKYW	SEQ ID NO: 14
HCDR2	IYPGSSTS	SEQ ID NO: 3
HCDR3	VKNDN	SEQ ID NO: 68

LCDR1	ESVDNQGTSY	SEQ ID NO: 69
LCDR2	AAS	SEQ ID NO: 6
LCDR3	HQSKEVPYT	SEQ ID NO: 7
VH (CDR sequences are underlined)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTKYWINWVRQAPGQ GLEWMGIIYPGSSTSNYNEKFKTRVTMTVDTSTSTAYMELSSLRS EDTAVYYC <u>VKNDN</u> WGQGTLLTVSS	SEQ ID NO: 16
VL (CDR sequences are underlined)	DIQMTQSPSSLSASVGDRVTITCRASE <u>SVDNQGTSY</u> MNWFQQKP GKAPKLLIY <u>AAS</u> DLGSGVPSRFSGSGSGTDFTLTISLQPEDFATY YCH <u>QSK</u> EVPTFTFGQGTKLEIK	SEQ ID NO: 70
Heavy Chain amino acid sequence (IgG4) (CDR sequences are underlined)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTKYWINWVRQAPGQ GLEWMGIIYPGSSTSNYNEKFKTRVTMTVDTSTSTAYMELSSLRS EDTAVYYC <u>VKNDN</u> WGQGTLLTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGKTKYTCNVDHKPSNTKVDKRVESKYGPCCPCPA PEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYS RLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLSLG	SEQ ID NO: 18
Light Chain amino acid sequence (CDR sequences are underlined)	DIQMTQSPSSLSASVGDRVTITCRASE <u>SVDNQGTSY</u> MNWFQQKP GKAPKLLIY <u>AAS</u> DLGSGVPSRFSGSGSGTDFTLTISLQPEDFATY YCH <u>QSK</u> EVPTFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 62

Table 13. Amino acid sequences of antibody hIgG-45

HCDR1	GYTFTKYW	SEQ ID NO: 14
HCDR2	IYPGSSTS	SEQ ID NO: 3
HCDR3	VKNDN	SEQ ID NO: 68
LCDR1	ESVDNSGTSY	SEQ ID NO: 71
LCDR2	AAS	SEQ ID NO: 6

LCDR3	HQSKEVPYT	SEQ ID NO: 7
VH (CDR sequences are underlined)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTKYWINWVRQAPGQ GLEWMGHI <u>Y</u> PGSSSTSNYNEKFKTRVTMTVDTSTSTAYMELSSLRS EDTAVYYC <u>VKND</u> NWGQGTLLTVSS	SEQ ID NO: 16
VL (CDR sequences are underlined)	DIQMTQSPSSLSASVGDRVTITCRASESVDNSGTSYMNWFQQKPG KAPKLLIY <u>AAS</u> DLGSGVPSRFSGSGSGTDFTLTISLQPEDFATYY <u>CHQSKEVPYT</u> FGQGTKLEIK	SEQ ID NO: 72
Heavy Chain amino acid sequence (IgG4) (CDR sequences are underlined)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTKYWINWVRQAPGQ GLEWMGHI <u>Y</u> PGSSSTSNYNEKFKTRVTMTVDTSTSTAYMELSSLRS EDTAVYYC <u>VKND</u> NWGQGTLLTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGKTYTCNVDPKPSNTKVDKRVESKYGPCCP <u>PC</u> PA PEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYS RLTVDKSRWQEGNVFSCSVMHREALHNHYTQKSLSLSLG	SEQ ID NO: 18
Light Chain amino acid sequence (CDR sequences are underlined)	DIQMTQSPSSLSASVGDRVTITCRASESVDNSGTSYMNWFQQKPG KAPKLLIY <u>AAS</u> DLGSGVPSRFSGSGSGTDFTLTISLQPEDFATYY <u>CHQSKEVPYT</u> FGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYSLSS TLTLKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 63

[00243] Each document cited herein, including publications, patents, patent applications and published patent applications, is entirely incorporated by reference herein.

[00244] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is apparent to those skilled in the art that certain minor changes and modifications will be practiced. The description and examples should not be construed as limiting the scope of the invention.

NUMBERED EMBODIMENTS

[00245] Notwithstanding the appended claims, the disclosure sets forth the following numbered embodiments:

- [00246] 1. A pharmaceutical agent that is an agonist of at least one of $\alpha 7\beta 1$ integrin, $\alpha 6\beta 1$ integrin and $\alpha 3\beta 1$ integrin and that binds to the extracellular domain of at least one of $\alpha 7$ protein, $\alpha 6$ protein and $\alpha 3$ protein.
- [00247] 2. The pharmaceutical agent of embodiment 1, wherein the pharmaceutical agent binds at least one of:
- the laminin binding domain of at least one of $\alpha 7$ protein, $\alpha 6$ protein and $\alpha 3$ protein;
 - the CALF-1 domain of at least one of $\alpha 7$ protein, $\alpha 6$ protein and $\alpha 3$ protein; and
 - the CALF-2 domain of at least one of $\alpha 7$ protein, $\alpha 6$ protein and $\alpha 3$ protein.
- [00248] 3. The pharmaceutical agent of embodiment 1 that is an agonist of $\alpha 7\beta 1$ integrin and that binds specifically to the $\alpha 7$ protein.
- [00249] 4. The pharmaceutical agent of embodiment 1, with the negative proviso that the pharmaceutical agent does not increase the amount of $\alpha 7$ protein in a muscle cell of a subject when the pharmaceutical agent is administered to the subject.
- [00250] 5. The pharmaceutical agent of any one of embodiments 1-4, wherein the pharmaceutical agent is an antibody.
- [00251] 6. The pharmaceutical agent of embodiment 5, wherein the antibody is a monoclonal antibody.
- [00252] 7. The pharmaceutical agent of embodiment 5, wherein the antibody is a multispecific antibody.
- [00253] 8. The pharmaceutical agent of embodiment 7, wherein the multispecific antibody is a bispecific antibody.
- [00254] 9. The pharmaceutical agent of embodiment 5, wherein the antibody is human, humanized or chimeric.
- [00255] 10. The pharmaceutical agent of embodiment 1, wherein the pharmaceutical agent activates at least one of $\alpha 7\beta 1$ integrin, $\alpha 6\beta 1$ integrin and $\alpha 3\beta 1$ integrin.
- [00256] 11. The pharmaceutical agent of embodiment 1, wherein the pharmaceutical agent stabilizes the active conformation of at least one of $\alpha 7\beta 1$ integrin, $\alpha 6\beta 1$ integrin and $\alpha 3\beta 1$ integrin.
- [00257] 12. The pharmaceutical agent of embodiment 3, wherein the pharmaceutical agent does not bind specifically to the $\beta 1$ protein.
- [00258] 13. The pharmaceutical agent of any one of embodiments 1-12, wherein the pharmaceutical agent increases the adhesion of a myoblast to merosin.
- [00259] 14. The pharmaceutical agent of embodiment 13, wherein the myoblast is a healthy human myoblast or a healthy murine myoblast.

[00260] 15. The pharmaceutical agent of embodiment 13, wherein the myoblast is a human myoblast or a murine myoblast that is at least one of: dystrophin deficient, comprises a mutation in dystrophin or comprises non-functioning dystrophin.

[00261] 16. The pharmaceutical agent of any one of embodiments 1-12, wherein the pharmaceutical agent increases the adhesion of a myotube to merosin.

[00262] 17. The pharmaceutical agent of embodiment 16, wherein the myotube is a healthy human myotube or a healthy murine myotube.

[00263] 18. The pharmaceutical agent of embodiment 16, wherein the myotube is a human myotube or a murine myotube that is at least one of: dystrophin deficient, comprises a mutation in dystrophin or comprises non-functioning dystrophin.

[00264] 19. A monoclonal antibody that is an agonist of $\alpha 7 \beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment binds specifically to an epitope of $\alpha 7$ protein, wherein the epitope comprises, consists essentially of, or consists of:

(i) the amino acid sequence of **SEQ ID NO: 10** or **SEQ ID NO: 1**;

(ii) 5-10, 10-15, 15-20, 20-25, 25-30, 30-35 or 35-40 amino acids of **SEQ ID NO: 10** or **SEQ ID NO: 1**; or

(iii) 5-10, 10-15, 15-20, 20-25, 25-30, 30-35 or 35-40 amino acids of **SEQ ID NO: 24**.

[00265] 20. A monoclonal antibody that is an agonist of $\alpha 7 \beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment binds specifically to an epitope of $\alpha 7$ protein, wherein the epitope comprises SWWP (**SEQ ID NO: 25**).

[00266] 21. A monoclonal antibody that is an agonist of $\alpha 7 \beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment binds specifically to an epitope comprising the residues S977, W978, W979 and P980 of **SEQ ID NO: 24**.

[00267] 22. The antibody or the antibody fragment of embodiment 20 or 21, wherein the epitope comprises, consists essentially of, or consists of 5-10 or 10-15 amino acids of **SEQ ID NO: 24**.

[00268] 23. A monoclonal antibody that is an agonist of $\alpha 7 \beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment binds specifically to an epitope comprising the residues R958, M976, S977, W978, W979 and P980 of **SEQ ID NO: 24**.

[00269] 24. The antibody or the antibody fragment of embodiment 23, wherein the epitope comprises, consists essentially of, or consists of 6-10 or 10-15 amino acids of **SEQ ID NO: 24**.

[00270] 25. The antibody or the antibody fragment of any one of embodiments 20-24, wherein the epitope is continuous.

[00271] 26. The antibody or the antibody fragment of any one of embodiments 20-24, wherein the epitope is discontinuous.

[00272] 27. The antibody or the antibody fragment of any one of embodiments 20-26, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region comprising an HCDR1, an HCDR2 and an HCDR3, and a light chain variable (VL) region comprising an LCDR1, an LCDR2 and an LCDR3,

(i) wherein the HCDR3 comprises **SEQ ID NO: 15**; and/or wherein the LCDR3 comprises **SEQ ID NO: 7**;

(ii) wherein the HCDR3 comprises **SEQ ID NO: 66**; and/or wherein the LCDR3 comprises **SEQ ID NO: 7**; or

(iii) wherein the HCDR3 comprises **SEQ ID NO: 68**; and/or wherein the LCDR3 comprises **SEQ ID NO: 7**.

[00273] 28. The antibody or the antibody fragment of embodiment 27, wherein the HCDR2 comprises **SEQ ID NO: 3**; and/or wherein the LCDR2 comprises **SEQ ID NO: 6**.

[00274] 29. The antibody or the antibody fragment of embodiment 27 or 28,

(i) wherein the HCDR1 comprises **SEQ ID NO: 14**; and/or wherein the LCDR1 comprises **SEQ ID NO: 5**;

(ii) wherein the HCDR1 comprises **SEQ ID NO: 65**; and/or wherein the LCDR1 comprises **SEQ ID NO: 5**;

(iii) wherein the HCDR1 comprises **SEQ ID NO: 14**; and/or wherein the LCDR1 comprises **SEQ ID NO: 69**; or

(iv) wherein the HCDR1 comprises **SEQ ID NO: 14**; and/or wherein the LCDR1 comprises **SEQ ID NO: 71**.

[00275] 30. A monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region,

wherein the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 2**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 4**, or a variant thereof having 5 or fewer conservative amino acid substitutions in HCDR1, HCDR2, and/or HCDR3;

wherein the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 14**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 15**, or a variant thereof having 5 or fewer conservative amino acid substitutions in HCDR1, HCDR2, and/or HCDR3;

wherein the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 65**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 66**, or a variant thereof having 5 or fewer conservative amino acid substitutions in HCDR1, HCDR2, and/or HCDR3; or

wherein the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 14**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 68**, or a variant thereof having 5 or fewer conservative amino acid substitutions in HCDR1, HCDR2, and/or HCDR3.

[00276] 31. A monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a light chain variable (VL) region and a heavy chain variable (VH) region,

wherein the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 5**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**, or a variant thereof having 5 or fewer conservative amino acid substitutions in LCDR1, LCDR2, and/or LCDR3;

wherein the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 69**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**, or a variant thereof having 5 or fewer conservative amino acid substitutions in LCDR1, LCDR2, and/or LCDR3; or

wherein the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 71**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**, or a variant thereof having 5 or fewer conservative amino acid substitutions in LCDR1, LCDR2, and/or LCDR3.

[00277] 32. A monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody or the antibody fragment comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein:

(i) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 2**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 4**, or a variant thereof having 5 or fewer conservative amino acid substitutions in HCDR1, HCDR2, and/or HCDR3; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 5**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**, or a variant thereof having 5 or fewer conservative amino acid substitutions in LCDR1, LCDR2, and/or LCDR3;

(ii) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 14**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 15**, or a variant thereof having 5 or fewer conservative amino acid substitutions in HCDR1, HCDR2, and/or HCDR3; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 5**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**, or a variant thereof having 5 or fewer conservative amino acid substitutions in LCDR1, LCDR2, and/or LCDR3;

(iii) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 65**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 66**, or a variant thereof having 5 or fewer conservative amino acid substitutions in HCDR1, HCDR2, and/or HCDR3; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 5**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**, or a variant thereof having 5 or fewer conservative amino acid substitutions in LCDR1, LCDR2, and/or LCDR3;

(iv) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 14**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 68**, or a variant thereof having 5 or fewer conservative amino acid substitutions in HCDR1, HCDR2, and/or HCDR3; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 69**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**, or a variant thereof having 5 or fewer conservative amino acid substitutions in LCDR1, LCDR2, and/or LCDR3; or

(v) the VH region amino acid sequence comprises HCDR1 of **SEQ ID NO: 14**, HCDR2 of **SEQ ID NO: 3** and HCDR3 of **SEQ ID NO: 68**, or a variant thereof having 5 or fewer conservative amino acid substitutions in HCDR1, HCDR2, and/or HCDR3; and the VL region amino acid sequence comprises LCDR1 of **SEQ ID NO: 71**, LCDR2 of **SEQ ID NO: 6** and LCDR3 of **SEQ ID NO: 7**, or a variant thereof having 5 or fewer conservative amino acid substitutions in LCDR1, LCDR2, and/or LCDR3.

[00278] 33. The antibody or the antibody fragment of embodiment 30, wherein the VH region amino acid sequence comprises

- (i) **SEQ ID NO: 8**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 8**;
- (ii) **SEQ ID NO: 16**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 16**; or
- (iii) **SEQ ID NO: 67**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 67**.

[00279] 34. The antibody or the antibody fragment of embodiment 31, wherein the VL region amino acid sequence comprises

- (i) **SEQ ID NO: 9**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 9**;
- (ii) **SEQ ID NO: 17**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 17**;
- (iii) **SEQ ID NO: 70**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 70**; or

(iv) **SEQ ID NO: 72**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 72**.

[00280] 35. The antibody or the antibody fragment of embodiment 32, wherein

(i) the VH region amino acid sequence comprises **SEQ ID NO: 8**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 8**; and the VL region amino acid sequence comprises **SEQ ID NO: 9**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 9**;

(ii) the VH region amino acid sequence comprises **SEQ ID NO: 16**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 16**; and the VL region amino acid sequence comprises **SEQ ID NO: 17**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 17**;

(iii) the VH region amino acid sequence comprises **SEQ ID NO: 67**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 67**; and the VL region amino acid sequence comprises **SEQ ID NO: 17**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 17**;

(iv) the VH region amino acid sequence comprises **SEQ ID NO: 16**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 16**; and the VL region amino acid sequence comprises **SEQ ID NO: 70**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 70**; or

(v) the VH region amino acid sequence comprises **SEQ ID NO: 16**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 16**; and the VL region amino acid sequence comprises **SEQ ID NO: 72**, or an amino acid sequence that is at least 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of **SEQ ID NO: 72**.

[00281] 36. A monoclonal antibody that is an agonist of $\alpha 7\beta 1$ integrin, or an antibody fragment thereof, wherein the antibody comprises a heavy chain and a light chain,

(i) wherein the heavy chain amino acid sequence comprises **SEQ ID NO: 18**, and the light chain amino acid sequence comprises **SEQ ID NO: 19**;

(ii) wherein the heavy chain amino acid sequence comprises **SEQ ID NO: 45**, and the light chain amino acid sequence comprises **SEQ ID NO: 53**;

(iii) wherein the heavy chain amino acid sequence comprises **SEQ ID NO: 18**, and the light chain amino acid sequence comprises **SEQ ID NO: 62**; or

(iv) wherein the heavy chain amino acid sequence comprises **SEQ ID NO: 18**, and the light chain amino acid sequence comprises **SEQ ID NO: 63**.

[00282] 37. The antibody or the antibody fragment of any one of embodiments 30-36, wherein the antibody or the antibody fragment binds specifically to $\alpha 7$ protein.

[00283] 38. The antibody or the antibody fragment of any one of embodiments 30-37, wherein the antibody or the antibody fragment binds specifically to an epitope of $\alpha 7$ protein, the epitope of $\alpha 7$ protein comprising, consisting essentially of, or consisting of the amino acid sequence of

(i) **SEQ ID NO: 10**;

(ii) 5-10, 10-15, 15-20, 20-25, 25-30, 30-35 or 35-40 amino acids of **SEQ ID NO: 10**; or

(iii) 5-10, 10-15, 15-20, 20-25, 25-30, 30-35 or 35-40 amino acids of **SEQ ID NO: 24**.

[00284] 39. The pharmaceutical agent of any one of embodiments 1-18 or the antibody or the antibody fragment of any one of embodiments 19-38, wherein the $\alpha 7\beta 1$ integrin is human $\alpha 7\beta 1$ integrin.

[00285] 40. The antibody fragment of any one of embodiments 19-39, wherein the antibody fragment is an Fab, an $F(ab')_2$, an Fab' , an scFv, a single domain antibody, a diabody or a single chain camelid antibody.

[00286] 41. An isolated nucleic acid molecule encoding the antibody or the antibody fragment of any one of embodiments 30-40.

[00287] 42. An expression vector comprising the nucleic acid molecule of embodiment 41.

[00288] 43. The expression vector of embodiment 42, wherein the nucleic acid molecule is operatively linked to regulatory sequences suitable for expression of the nucleic acid segment in a host cell.

[00289] 44. A recombinant host cell comprising the expression vector of embodiment 42 or 43.

[00290] 45. A method for producing an antibody or an antibody fragment that is an agonist of $\alpha 7\beta 1$ integrin, the method comprising: culturing a recombinant host cell comprising the expression vector of embodiment 42 or 43 under conditions effective to express the nucleic acid molecule to produce the antibody or the antibody fragment that is an agonist of $\alpha 7\beta 1$ integrin.

[00291] 46. A pharmaceutical composition comprising: the pharmaceutical agent of any one of embodiments 1-18 or the antibody or the antibody fragment of any one of embodiments 19-40, and a pharmaceutically acceptable carrier, diluent or excipient.

[00292] 47. The pharmaceutical composition of embodiment 46, further comprising an additional pharmaceutical agent that is an agonist of at least one of: $\alpha 7\beta 1$ integrin, $\alpha 6\beta 1$ integrin and $\alpha 3\beta 1$ integrin.

[00293] 48. A method of treating a disorder or a disease in a subject, comprising administering to the subject a therapeutically effective amount of the pharmaceutical agent of any one of embodiments 1-19 or the antibody or the antibody fragment of any one of embodiments 19-40, thereby treating the disorder or the disease in the subject;

wherein the disorder or the disease is characterized by one or more of:

a malfunction of $\alpha 7\beta 1$ integrin in the subject;

a dystrophin deficiency in the subject;

a mutation in dystrophin in the subject;

non-functioning dystrophin in the subject; or

a muscle dysfunction other than $\alpha 7\beta 1$ malfunction, or dystrophin deficiency,

mutation, or non-function.

[00294] 49. The method of embodiment 48, wherein the muscle dysfunction is caused by or associated with one or more of: cancer, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disease, HIV infection/AIDS, anorexia nervosa, bulimia, malnutrition, exposure, nausea, type I diabetes, type II diabetes, metabolic syndrome, cachexia, anemia, heart failure, high blood pressure, rhabdomyolysis, sepsis, sarcopenia, physical inactivity, damage due to excess physical activity, hypothermia, hyperthermia, injury, denervation, amyotrophic lateral sclerosis, multiple sclerosis, spinal muscular atrophy, alcohol-associated myopathy, burn-associated myopathy, stroke, steroid therapy or the withdrawal of steroid therapy, dermatomyositis, Guillain-Barré syndrome, neuropathy, osteoarthritis, infection, polio, polymyositis, inflammation, rheumatoid arthritis, hypocholesterolemia, electrical injury, heat stroke, prolonged immobilization, lack of blood flow to a limb, or contact with venom.

[00295] 50. The method of embodiment 48, wherein the disease is a muscle wasting disease.

[00296] 51. The method of embodiment 50, wherein the muscle wasting disease is a muscular dystrophy.

[00297] 52. The method of embodiment 51, wherein the muscular dystrophy is Duchenne muscular dystrophy (DMD), Becker muscular dystrophy, merosin-deficient congenital muscular dystrophy type 1A or limb-girdle muscular dystrophy.

- [00298] 53. The method of embodiment 49, further comprising identifying a subject having a muscle dysfunction.
- [00299] 54. The method of embodiment 50, further comprising identifying a subject having a muscle wasting disease.
- [00300] 55. The method of any one of embodiments 49-54, wherein the administering reverses, stabilizes or slows muscle wasting or muscle dysfunction in the subject.
- [00301] 56. The method of any one of embodiments 49-54, wherein the administering improves muscle function in the subject.
- [00302] 57. The method of any one of embodiments 49-54, wherein the administering does not worsen muscle function in the subject.
- [00303] 58. The method of any one of embodiments 49-54, further comprising measuring muscle function in the subject after the administration step, wherein the rate of worsening of muscle function is reduced.
- [00304] 59. The method of any one of embodiments 50-52 and 54, wherein administering to the subject the therapeutically effective amount of the pharmaceutical agent is effective to upregulate the activity and/or amount of $\alpha 7\beta 1$ integrin in the subject effective to treat the malfunction of $\alpha 7\beta 1$ integrin in the subject.
- [00305] 60. The method of any one of embodiments 50-52 and 54, wherein administering to the subject the therapeutically effective amount of the pharmaceutical agent is effective to upregulate activity and/or amount of $\alpha 7\beta 1$ integrin in the subject, the upregulated activity and/or amount of $\alpha 7\beta 1$ integrin in the subject being effective to at least in part mitigate the effect of at least one of: the dystrophin deficiency in the subject; the mutation in dystrophin in the subject; or the non-functioning dystrophin in the subject.
- [00306] 61. The method of any one of embodiments 49-54, wherein administering to the subject the therapeutically effective amount of the pharmaceutical agent is effective to mitigate muscle injury in the subject.
- [00307] 62. The method of any one of embodiments 49-54, wherein administering to the subject the therapeutically effective amount of the pharmaceutical agent is effective to mitigate eccentric muscle injury in the subject.
- [00308] 63. The method of any one of embodiments 49-54, wherein administering to the subject the therapeutically effective amount of the pharmaceutical agent is effective to improve diaphragm muscle function in the subject.

[00309] 64. The method of any one of embodiments 49-54, further comprising administering to the subject one or more other therapies, the one or more other therapies directed to muscular dystrophy or muscle wasting.

[00310] 65. The method of any one of embodiments 49-54, wherein the one or more other therapies comprises one or more of: an anticonvulsant; an immunosuppressant; an antibiotic; quinine; therapy for management of congestive heart failure; a gene replacement therapy; an exon skipping therapy; a nonsense suppression therapy; therapy using an engineered nuclease; cell therapy using muscle precursor cells or stem cells; upregulation of utrophin; an anti-inflammatory therapy; an antifibrotic therapy; a steroid therapy; a myostatin blocker; insulin growth factor; a phosphodiesterase-5 inhibitor; an ACE inhibitor; induction of angiogenesis through delivery of vascular endothelial growth factor (VEGF); downregulation of VEGF decoy-receptor type 1 (VEGFR-1 or Flt-1); physical therapy; occupational therapy; surgery; orthotic intervention; speech therapy; respiratory therapy; a pacemaker; and a respiratory assistance device.

[00311] 66. A method of activating $\alpha 7\beta 1$ integrin in a muscle cell of a subject, the method comprising: administering to the subject a therapeutically effective amount of the pharmaceutical agent of any one of embodiments 1-18 or the antibody or the antibody fragment of any one of embodiments 19-40, thereby activating $\alpha 7\beta 1$ integrin in a muscle cell of the subject.

[00312] 67. A method of enhancing binding of $\alpha 7\beta 1$ integrin to its ligand in a muscle cell of a subject, the method comprising:

administering to the subject a therapeutically effective amount of the pharmaceutical agent of any one of embodiments 1-18 or the antibody or the antibody fragment of any one of embodiments 19-40, thereby enhancing binding of $\alpha 7\beta 1$ integrin to its ligand in a muscle cell of the subject.

[00313] 68. Use of the pharmaceutical agent of any one of embodiments 1-18 or the antibody or the antibody fragment of any one of embodiments 19-40 in the manufacture of a medicament for treating a disorder or a disease characterized by a malfunction of $\alpha 7\beta 1$ integrin in a subject.