

Claims:

1. A compound comprising at least two components, a first component being the nLG3 domain from the C-terminus of human or mouse agrin, and at least one second component, selected from proteins or an antagonistic antibody that inhibit ActR2B-
 5 induced signaling activity in the presence of myostatin, the components being linked by means of linking entities.

2. A compound according to claim 1, selected from the group consisting of combinations of components, as follows:

10 A-L-B
 B-L-A
 A-L-C-L-B
 B-L-C-L-A
 C-L-B-L-A
 15 C-L-A-L-B
 B-L-A-L-C
 A-L-B-L-C
 A-L-D
 D-L-A
 20 A-L-E
 E-L-A

in which

A represents an agrin nLG3 domain-containing protein,
 25 B represents an extracellular domain of the ActRIB, ActRIC, ActRIIA, ActR2B receptor protein and follistatin
 C represents a "stabilizer" domain,

D represents ActR2B-mediated signal-inhibiting mAb against the ActRIB, ActRIC, ActRIIA, and ActR2B receptor protein,

E represents ActR2B-mediated signal-inhibiting mAb against a member of the TGF-beta super family

5 L represents a linking entity.

3. A compound according to claim 2, in which the combinations is chosen from B-L-C-L-A, D-L-A and E-L-A.

10 4. A compound according to claim 2, in which A is selected from (h)nLG3 and proteins that are at least 75%, 80%, 85%, 90% and 95% identical thereto.

5. A compound according to claim 4, in which A is at least 75%, 80%, 85%, 90%, 95% and completely identical with SEQ ID NO:10.

15 6. A compound according to claim 2, in which B is selected from the extracellular domain from ActRIB, ActRIC, ActRIIA, ActR2B and follistatin, and proteins that are at least 75%, 80%, 85%, 90% and 95% identical thereto.

20 7. A compound according to claim 6, in which B is selected from human ActR2B receptor as defined in SEQ ID NO: 12 (AAC64515.1, GI:3769443) and follistatin as defined in SEQ ID NO: 25.

25 8. A compound according to claim 2, in which C is an "Fc" domain selected from an IGG1, IGG2, IGG3 and IGG4 and "Fc" domains that are at least 75%, 80%, 85%, 90% and 95% identical thereto.

9. A compound according to claim 2, in which C is an "Fc" domain as defined in SEQ ID NO: 14 and proteins that are at least 75%, 80%, 85%, 90% and 95% identical thereto.

30 10. A compound according to claim 2, in which D is selected from signalling blocking mAbs against ActRIB, ActRIC, ActRIIA, ActR2B, or mAbs that are at least 75%, 80%, 85%, 90% and 95% identical thereto.

11. A compound according to claim 6, in which D is a mAb as defined by ActRmAb(LC),
(SEQ ID NO: 44) and ActRmAb(HC) (SEQ ID NO: 45) and mAbs that are at least 75%,
80%, 85%, 90% and 95% identical thereto.
12. A compound according to claim 2, in which E is selected from signalling blocking mAbs
against the TGF-beta super family, such as Activin B, Activin AB, Inhibin A, Inhibin B,
GDF3, GDF1 1 , Nodal, BMP2, BMP4, BMP7, BMP9, and BMP10 and that are at least
75%, 80%, 85%, 90% and 95% identical thereto.
13. A compound according to claim 2, in which the linking entity is selected the roughly
15 amino acid unstructured region at the C-terminal end of the extracellular domain
of ActR2B (the "tail"), and an artificial sequence of between 5 and 15, 20, 30, 50 or
more amino acids that are relatively free of secondary structure.
14. A compound according to claim 6, in which E is a mAb as defined MyomAb(LC) SEQ ID
NO: 32 and MyomAb(HC) SEQ ID NO: 31. and mAbs that are at least 75%, 80%, 85%,
90% and 95% identical thereto.
15. A compound according to claim 1, selected from the group consisting of ActR-Fc-nLG3
as defined in SEQ ID NO: 22, (h)ActR-Fc-(h)nLG3 as defined in SEQ ID NO: 23. Fol-Fc-
nLG3 as defined in SEQ ID NO: 27, ActRmAb(HC) linked to (h)nLG3 (ActRmAb(HC)-
(h)nLG3) as defined in SEQ ID NO: 30, MyomAb(HC linked to (h)nLG3) and
(MyomAb(HC)-(h)nLG3) as defined in SEQ ID NO: 33.
16. A compound according to claim 1 for use in therapy~~method of improving muscle
performance, comprising the administration of an effective amount of a compound
according to claim 1.~~
17. A pharmaceutical composition comprising at least one compound according to claim
1, formulated together with a pharmaceutically-acceptable carrier.
18. Use of aA- compound according to claim 1 in the manufacture of a medicament for the
~~method of treatment~~ of a pathological condition leading to the loss of muscle function,
wherein an effective amount of the medicament is to be administered~~comprising the~~

administration of an effective amount of the compound according to claim 1, the pathological condition being one or more of:

- 5
 - muscle atrophy as a result of treatment with a glucocorticoid ~~such as cortisol, dexamethasone, betamethasone, prednisone, methylprednisolone, or prednisolone;~~
 - muscle atrophy as a result of denervation due to nerve trauma or a result of degenerative, metabolic, or inflammatory neuropathy ~~(e.g., Guillian-Barre syndrome, peripheral neuropathy, or exposure to environmental toxins or drugs);~~
- 10
 - muscle atrophy as a result of myopathy ~~, such as myotonia; a congenital myopathy;~~ including nemaline myopathy, multi/minicore myopathy and myotubular ~~(centronuclear) myopathy; mitochondrial myopathy; familial periodic paralysis; inflammatory myopathy; metabolic myopathy, such as caused by a glycogen or lipid storage disease; dermatomyositis; polymyositis; inclusion body myositis; myositis ossificans; rhabdomyolysis and myoglobinurias;~~
- 15
 - myopathy caused by a muscular dystrophy syndrome ~~, such as Duchenne, Becker, myotonic, fascioscapulohumeral, Emery-Dreifuss, oculopharyngeal, scapulohumeral, limb girdle, Fukuyama, a congenital muscular dystrophy, or hereditary distal myopathy~~
- 20
 - musculoskeletal diseases ~~such as osteoporosis, bone fracture, short stature, or dwarfism;~~
 - adult motor neuron disease, infantile spinal muscular atrophy, amyotrophic lateral sclerosis, juvenile spinal muscular atrophy, autoimmune motor neuropathy with multifocal conductor block, paralysis due to stroke or spinal cord injury, skeletal immobilization due to trauma, prolonged bed rest, voluntary inactivity, involuntary
- 25
 - inactivity, metabolic stress or nutritional insufficiency ~~, cancer, AIDS, fasting, a thyroid gland disorder, diabetes, benign congenital hypotonia, central core disease, burn injury, chronic obstructive pulmonary disease, liver diseases (examples such as fibrosis, cirrhosis), sepsis, renal failure, congestive heart failure, ageing, space travel or time spent in a zero gravity environment;~~
- 30
 - age-related conditions ~~, such as sarcopenia, skin atrophy, muscle wasting, brain~~

- atrophy, atherosclerosis, arteriosclerosis, pulmonary emphysema, osteoporosis, osteoarthritis, immunologic incompetence, high blood pressure, dementia, Huntington's disease, Alzheimer's disease, cataracts, age-related macular degeneration, prostate cancer, stroke, diminished life expectancy, frailty, memory loss, wrinkles, impaired kidney function, and age-related hearing loss; metabolic disorders, including Type II Diabetes, Metabolic Syndrome, hyperglycemia, and obesity. Of course, patients may simultaneously suffer from one or more of these conditions, for example, sarcopenia and pulmonary emphysema, or sarcopenia and impaired kidney function.
- 10 -pathological disorders such as acute and/or chronic renal disease or failure, liver fibrosis or cirrhosis, cancer such as breast cancer, Parkinson's Disease; conditions associated with neuronal death, such as ALS, brain atrophy, or dementia and anemia. In addition, there are losses suffered as a consequence of age, trauma or inactivity.
- 15 - cachexia, particularly cachexia associated with a rheumatoid arthritis and cachexia associated with cancer.