Summary of the invention

SorCS1 is one of five members of the mammalian Vps10p-domain (Vps10p-D) receptor family, which also comprises Sortilin, SorLA, SorCS2, and SorCS3. SorCS1 is unique among the Vps10p-D receptors as it exists in several distinct splice variants.

The present inventors have found that administration of SorCS1, and in particular the extracellular domain of a SorCS1 polypeptide (soluble SorCS1 or sSorCS1) to a subject results in a significant weight reduction in the treated subjects.

It is thus an object of the present disclosure ~~invention~~ to provide methods and agents capable of reducing appetite, and/or suppressing hunger, and/or increasing the suppression of hunger, and/or increasing the reduction of prospective consumption and/or increasing the reduction of appetite, and/or increasing satiety, and/or treating obesity, and/or promoting weight loss, and/or increasing metabolism, and/or transforming white fat into brown fat. The latter results in increased thermogenesis of the subject receiving SorCS1 therapy. Thus the disclosure ~~invention~~ also concerns a method of increasing thermogenesis in a subject.

Consequently in a main example ~~aspect~~ the present disclosure ~~invention~~ relates to an agent selected from the group consisting of:

a) an isolated polypeptide comprising:

i) the amino acid sequence of SEQ ID NOs: 15; or

ii) a biologically active sequence variant of the amino acid sequence of i) wherein the variant has at least 60% sequence identity to said SEQ ID NO: 15,

iii) a biologically active fragment of at least 15 contiguous amino acids of any one of i) through ii), said fragment having at least 60% sequence identity to SEQ ID NO: 15 in a range of overlap of at least 15 amino acids,

b) a nucleic acid sequence encoding a polypeptide as defined in a);

c) a vector comprising the nucleic acid molecule as defined in b),

d) an isolated host cell transformed or transduced with the nucleic acid of b) or the vector of c),

for use in a method for reducing appetite, and/or for promoting weight loss, and/or treating obesity, and/or increasing metabolism, and/or increasing thermogenesis, and/or converting white fat into brown fat.

The agent of the disclosure ~~invention~~ may be formulated in a manner suitable for delivery to a subject. Thus in one example ~~aspect~~ the invention concerns a pharmaceutical composition comprising the agent defined herein above. In one example ~~aspect~~ the disclosure ~~invention~~ concerns a kit comprising said pharmaceutical composition, and instructions for use such as instructions for administration to a subject.

In the first aspect, the present invention provides the use of an agent selected from the group consisting of:

a) an isolated soluble polypeptide comprising:

i) the amino acid sequence of SEQ ID NOs: 15; or

ii) a biologically active sequence variant of the amino acid sequence of i) wherein the variant has at least 90% sequence identity to said SEQ ID NO: 15,

iii) a biologically active fragment of at least 15 contiguous amino acids of any one of i) through ii), said fragment having at least 90% sequence identity to SEQ ID NO: 15 in a range of overlap of at least 15 amino acids,

b) a nucleic acid sequence encoding a polypeptide as defined in a);

c) a vector comprising the nucleic acid molecule as defined in b),

d) an isolated host cell transformed or transduced with the nucleic acid of b) or the vector of c),

for manufacturing of a medicament for treating obesity, wherein the agent is to be administered to a subject that does not suffer from insulin resistance or diabetes mellitus type 2.

In a second aspect, the present invention provides the use of an agent selected from the group consisting of:

a) an isolated soluble polypeptide comprising:

i) the amino acid sequence of SEQ ID NOs: 15; or

ii) a biologically active sequence variant of the amino acid sequence of i) wherein the variant has at least 90% sequence identity to said SEQ ID NO: 15,

iii)a biologically active fragment of at least 15 contiguous amino acids of any one of i) through ii), said fragment having at least 90% sequence identity to SEQ ID NO: 15 in a range of overlap of at least 15 amino acids,

b) a nucleic acid sequence encoding a polypeptide as defined in a);

c) a vector comprising the nucleic acid molecule as defined in b),

d) an isolated host cell transformed or transduced with the nucleic acid of b) or the vector of c),

for reducing appetite, and/or for promoting weight loss, and/or increasing metabolism, and/or increasing thermogenesis, and/or converting white fat into brown fat.

In a third aspect, the present invention provides the use of an agent selected from the group consisting of:

a) an isolated soluble polypeptide comprising:

i) the amino acid sequence of SEQ ID NOs: 15; or

ii) a biologically active sequence variant of the amino acid sequence of i) wherein the variant has at least 90% sequence identity to said SEQ ID NO: 15,

iii)a biologically active fragment of at least 15 contiguous amino acids of any one of i) through ii), said fragment having at least 90% sequence identity to SEQ ID NO: 15 in a range of overlap of at least 15 amino acids,

b) a nucleic acid sequence encoding a polypeptide as defined in a);

c) a vector comprising the nucleic acid molecule as defined in b),

d) an isolated host cell transformed or transduced with the nucleic acid of b) or the vector of c),

for reduction of appetite, and/or for promoting weight loss, and/or increasing metabolism, and/or increasing thermogenesis, and/or converting white fat into brown fat.

In a fourth aspect, the present invention provides the use of an agent selected from the group consisting of:

a) an isolated soluble polypeptide comprising:

i) the amino acid sequence of SEQ ID NOs: 15; or

ii) a biologically active sequence variant of the amino acid sequence of i) wherein the variant has at least 90% sequence identity to said SEQ ID NO: 15,

iii) a biologically active fragment of at least 15 contiguous amino acids of any one of i) through ii), said fragment having at least 90% sequence identity to SEQ ID NO: 15 in a range of overlap of at least 15 amino acids,

b) a nucleic acid sequence encoding a polypeptide as defined in a);

c) a vector comprising the nucleic acid molecule as defined in b),

d) an isolated host cell transformed or transduced with the nucleic acid of b) or the vector of c),

for increasing metabolism in an individual in need thereof.

In a fifth aspect, the present invention provides the use of an agent selected from the group consisting of:

a) an isolated soluble polypeptide comprising:

i) the amino acid sequence of SEQ ID NOs: 15; or

ii) a biologically active sequence variant of the amino acid sequence of i) wherein the variant has at least 90% sequence identity to said SEQ ID NO: 15,

iii) a biologically active fragment of at least 15 contiguous amino acids of any one of i) through ii), said fragment having at least 90% sequence identity to SEQ ID NO: 15 in a range of overlap of at least 15 amino acids,

b) a nucleic acid sequence encoding a polypeptide as defined in a);

c) a vector comprising the nucleic acid molecule as defined in b),

d) an isolated host cell transformed or transduced with the nucleic acid of b) or the vector of c),

for increasing thermogenesis in a mammal.

In a sixth aspect, the present invention provides an *in vitro* method for converting white fat into brown fat, the method comprising contacting a cell with an effective amount of an agent selected from the group consisting of:

a) an isolated soluble polypeptide comprising:

i) the amino acid sequence of SEQ ID NOs: 15; or

ii) a biologically active sequence variant of the amino acid sequence of i) wherein the variant has at least 90% sequence identity to said SEQ ID NO: 15,

iii)a biologically active fragment of at least 15 contiguous amino acids of any one of i) through ii), said fragment having at least 90% sequence identity to SEQ ID NO: 15 in a range of overlap of at least 15 amino acids,

b) a nucleic acid sequence encoding a polypeptide as defined in a);

c) a vector comprising the nucleic acid molecule as defined in b),

d) an isolated host cell transformed or transduced with the nucleic acid of b) or the vector of c).

In a seventh aspect, the present invention provides a cosmetic method for reducing appetite, and/or for promoting weight loss, and/or for increasing metabolism, and/or for increasing thermogenesis, and/or for converting white fat into brown fat, the method comprising administering to an individual in need thereof a therapeutically effective amount of an agent selected from the group consisting of:

a) an isolated soluble polypeptide comprising:

i) the amino acid sequence of SEQ ID NOs: 15; or

ii) a biologically active sequence variant of the amino acid sequence of i) wherein the variant has at least 90% sequence identity to said SEQ ID NO: 15,

iii)a biologically active fragment of at least 15 contiguous amino acids of any one of i) through ii), said fragment having at least 90% sequence identity to SEQ ID NO: 15 in a range of overlap of at least 15 amino acids,

b) a nucleic acid sequence encoding a polypeptide as defined in a);

c) a vector comprising the nucleic acid molecule as defined in b),

d) an isolated host cell transformed or transduced with the nucleic acid of b) or the vector of c).

Detailed description of the invention

Definitions

Unless specifically indicated otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which this invention belongs. For purposes of the present invention, the following terms are defined.

Acylation: The term “acylation” or "acylation group" as used herein means an R-(C=O)-group, wherein R is selected from straight-chain or branched, saturated or unsaturated carbon chains, optionally comprising one or more O, N, S, or P, such as a straight-chain or branched alkane carboxylic acid. Various examples of suitable acylation groups are described in WO2006/037810, WO00/34331, WO2006/097537, WO2011/080103. In particular examples of suitable acylation groups have the structure $CH3(CH2)_nCO$-, wherein n is 4 to 40, e.g. 8 to 22, such as an acylation group selected from the group comprising:

Claims

1. An agent selected from the group consisting of:
    a) an isolated polypeptide comprising:
        i) the amino acid sequence of SEQ ID NOs: 15; or
        ii) a biologically active sequence variant of the amino acid sequence of i) wherein the variant has at least 60% sequence identity to said SEQ ID NO: 15,
        iii) a biologically active fragment of at least 15 contiguous amino acids of any one of i) through ii), said fragment having at least 60% sequence identity to SEQ ID NO: 15 in a range of overlap of at least 15 amino acids,
    b) a nucleic acid sequence encoding a polypeptide as defined in a);
    c) a vector comprising the nucleic acid molecule as defined in b),
    d) an isolated host cell transformed or transduced with the nucleic acid of b) or the vector of c),

    for use in a method for reducing appetite, and/or for treating obesity, and/or for promoting weight loss, and/or increasing metabolism, and/or increasing thermogenesis, and/or converting white fat into brown fat.

2. The agent according to claim 1 wherein the agent is a polypeptide, wherein the polypeptide is a biologically active sequence variant comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 15, 5, 1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 55, 56, 57, 58, 59, 60, 61, 62, 63 and 64.

3. The agent according to claim 1 wherein the agent is a polypeptide, wherein the polypeptide is a biologically active sequence variant having an amino acid sequence selected from the group consisting of SEQ ID NOs: 15, 5, 1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 55, 56, 57, 58, 59, 60, 61, 62, 63 and 64.

4. The agent according to claim 1, wherein the polypeptide is a naturally occurring allelic variant of a sequence selected from the group consisting of SEQ ID NOs: 15, 5, 1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 55, 56, 57, 58, 59, 60, 61, 62, 63 and 64.

5. The agent according to claim 1, wherein the polypeptide comprises an amino acid sequence of a soluble SorCS1 selected from the group consisting of: SEQ ID NOs: 15, 5, 63, 62, 21, 27, 33, 37, 39, 43, 47, 51.

6. The agent according to any one of the preceding claims, wherein the polypeptide is a variant polypeptide described therein, wherein any amino acid specified in the selected sequence is altered to provide a conservative substitution, with the proviso that no more than 200 amino acids are so altered.

7. The agent according to any one of the preceding claims, wherein the polypeptide is a variant polypeptide described therein, wherein any amino acid specified in the selected sequence is altered to provide a conservative substitution, with the proviso that no more than 100 amino acids are so altered.

8. The agent according to any one of the preceding claims, wherein the polypeptide is a variant polypeptide described therein, wherein any amino acid specified in the selected sequence is altered to provide a conservative substitution, with the proviso that no more than 50 amino acids are so altered.

9. The agent according to any one of the preceding claims, wherein the polypeptide is a variant polypeptide described therein, wherein any amino acid specified in the selected sequence is altered to provide a conservative substitution, with the proviso that no more than 25 amino acids are so altered.

10. The agent according to any one of the preceding claims, wherein said polypeptide has at least 65%, more preferably at least 70%, more preferably at least 75%, preferably at least 80%, more preferably at least 85%, more preferably at least 90%, more preferably at least 91%, more preferably at least 92%, more preferably at least 93%, more preferably at least 94%, more preferably at least 95%, more preferably at least 96%, more preferably at least 97%, more preferably at least 98%, more preferably at least 99% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 15, 5, 1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 55, 56, 57, 58, 59, 60, 61, 62, 63 and 64.

11. The agent according to any one of the preceding claims, wherein said agent is a polypeptide, wherein the polypeptide is selected from the group consisting of SEQ ID NOs: 1, 2, 3, 4, 6, 7, 8, 9, 11, 12, 13, 14, 61 and 62.

12. The agent according to any one of the preceding claims, wherein the polypeptide is selected from the group consisting of SEQ ID NOs: 16, 17, 18, 19, 20, 22, 26, 28, 29, 30, 31 and 32.

13. The agent according to any one of the preceding claims, wherein the agent is a polypeptide selected from the group consisting of SEQ ID NOs: 61, 62, 63 and 64.

14. The agent according to any one of the preceding claims, wherein the agent is a polypeptide selected from the group consisting of SEQ ID NOs: 55, 56, 57, 58, 59 and 60.

15. The agent according to any one of the preceding claims, wherein the agent is a polypeptide selected from the group consisting of SEQ ID NOs: 62 and 64.

16. The agent according to claim 1, wherein the agent is a biologically active fragment, wherein the fragment comprises less than 500 contiguous amino acid residues, such as less than 450 contiguous amino acid residues, for example less than 400 contiguous amino acid residues, such as less than 350 contiguous amino acid residues, for example less than 300 contiguous amino acid residues,

for example less than 250 contiguous amino acid residues, such as less than 240 contiguous amino acid residues, for example less than 225 contiguous amino acid residues, such as less than 200 contiguous amino acid residues, for example less than 180 contiguous amino acid residues, such as less than 160 contiguous amino acid residues, for example less than 150 contiguous amino acid residues, such as less than 140 contiguous amino acid residues, for example less than 130 contiguous amino acid residues, such as less than 120 contiguous amino acid residues, for example less than 110 contiguous amino acid residues, such as less than 100 contiguous amino acid residues, for example less than 90 contiguous amino acid residues, such as less than 85 contiguous amino acid residues, for example less than 80 contiguous amino acid residues, such as less than 75 contiguous amino acid residues, for example less than 70 contiguous amino acid residues, such as less than 65 contiguous amino acid residues, for example less than 60 contiguous amino acid residues, such as less than 55 contiguous amino acid residues, for example less than 50 contiguous amino acid residues, such as less than 45 contiguous amino acid residues, for example less than 40 contiguous amino acid residues, such as 35 contiguous amino acid residues, for example 30 contiguous amino acid residues, such as 25 contiguous amino acid residues, such as 20 contiguous amino acid residues, for example 15 contiguous amino acid residues of an any one of the amino acid sequences selected from the group consisting of SEQ ID NOs: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63 and 64.

17. The agent according to claim 1, wherein the agent is a biologically active fragment, wherein the fragment comprises at least 15 contiguous amino acid residues, such as more than 20 contiguous amino acid residues, for example more than 25 contiguous amino acid residues, for example more than 50 contiguous amino acid residues, such as more than 75 contiguous amino acid residues, for example more than 100 contiguous amino acid residues, such as more than 125 contiguous amino acid residues, for example more than 150 contiguous amino acid residues, such as more than 175 contiguous amino acid residues, for example more than 200 contiguous amino acid residues, such as more than 225 contiguous amino acid residues, for example more than 250

contiguous amino acid residues, such as more than 275 contiguous amino acid residues, for example more than 300 contiguous amino acid residues, such as more than 325 contiguous amino acid residues, for example more than 350 contiguous amino acid residues, such as more than 375 contiguous amino acid residues, for example more than 400 contiguous amino acid residues, such as more than 425 contiguous amino acid residues, for example more than 450 contiguous amino acid residues, such as more than 475 contiguous contiguous amino acid residues, for example more than 500 contiguous amino acid residues, such as more than 525 contiguous amino acid residues, for example more than 550 contiguous amino acid residues, such as more than 575 contiguous amino acid residues, for example more than 600 contiguous amino acid residues, such as more than 625 contiguous amino acid residues, for example more than 650 contiguous amino acid residues, such as more than 675 contiguous amino acid residues, such as more than 700 contiguous amino acid residues of any one of the amino acid sequences selected from the group consisting of SEQ ID NOs: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63 and 64.

18. The agent according to any one of the preceding claims wherein the polypeptide is glycosylated.

19. The agent according to claim 18, wherein the polypeptide is N-glycosylated in one or more asparagin amino acid residues corresponding to amino acid positions positions 184, 352, 433, 765, 776, 816, 847, 908 and 929 of SEQ ID NO: 1.

20. The agent according to any one of the preceding claims, wherein the polypeptide comprises one of more of the following sequences:

SEQ ID NO: 1 aa 103-124
SEQ ID NO: 1 aa 125-143
SEQ ID NO: 1 aa 144-162
SEQ ID NO: 1 aa 197-218

SEQ ID NO: 1 aa 391-409
SEQ ID NO: 1 aa 661-684
SEQ ID NO: 1 aa 763-783
SEQ ID NO: 1 aa 859-876.

21. The polypeptide of claim 1, wherein the signal peptide has been replaced by a heterologous signal peptide.

22. The agent according to any one of the preceding claims, wherein the polypeptide is capable of forming at least one intramolecular cystin bridge.

23. The agent according any one of the preceding claims, comprising a dimer of said polypeptide linked through at least one intermolecular cystin bridge.

24. The agent according to any one of the preceding claims, wherein said polypeptide further comprises an affinity tag, such as a polyhis tag, a GST tag, a HA tag, a Flag tag, a C-myc tag, a HSV tag, a V5 tag, a maltose binding protein tag, a cellulose binding domain tag.

25. The agent according to claim 1, wherein the vector further comprises a promoter operably linked to the nucleic acid sequence.

26. The agent according to claim 25, wherein the promoter is selected from the group consisting of: CMV, human UbiC, RSV, Tet-regulatable promoter, Mo-MLV-LTR, Mx1, EF-1alpha, PDGF beta and CaMK II.

27. The agent according to claim 1, wherein the vector is selected from the group consisting of vectors derived from the Retroviridae family including lentivirus, HIV, SIV, FIV, EAIV, CIV.

28. The agent according to claim 1, wherein the vector is selected from the group consisting of adeno associated virus, adenovirus, alphavirus, baculovirus, HSV, coronavirus, Bovine papilloma virus, Mo-MLV.

29. The agent according to claim 1, wherein the vector is adeno associated virus (AAV).

30. The agent according to claim 1, wherein the host cell is selected from the group consisting of Saccharomyces cerevisiae, E. coli, Aspergillus and insect cells such as Sf9 insect cells.

31. The agent according to claim 1, wherein the host cell is selected from the group consisting of mammalian cells selected from the group consisting of human, feline, porcine, simian, canine, murine and rat cells.

32. The agent according to claim 31 wherein said mammalian cell is selected from the group consisting of muscle cells, hepatocytes, adipocytes and cells of the pancreas such as α cells, β cells and δ cells.

33. The agent according to claim 1, wherein said host cell is selected from the group consisting of CHO, CHO-K1, HEI193T, HEK293, COS, HiB5, RN33b and BHK cells.

34. The agent of claim 1, wherein said subject does not suffer from insulin resistance and/or diabetes mellitus type 2.

35. The agent according to any one of the preceding claims, wherein the agent is chemically modified in order to increase its half-life when administered to a patient, in particular its plasma half-life.

36. The agent according to any one of the preceding claims, wherein the agent is chemically modified in order to increase its half-life when administered to a patient, in particular its plasma half-life.

37. The agent according to any one of the preceding claims, wherein said agent further comprises a moiety conjugated to said agent, thus generating a moiety-conjugated agent

38. The agent according to claim 37, wherein the moiety-conjugated agent has a plasma and/or serum half-life being longer than the plasma and/or serum half-life of the non-moiety conjugated agent.

39. The agent according to claim 37, wherein the moiety facilitates transport across the blood brain barrier.

40. The agent according to claim 37, wherein the moiety is an antibody from a camelid species such as a recombinant or native single-chain antibody from dromedaries, camels, llamas, alpacas, vicuñas, or guanacos.

41. The agent according to any one of claims 37 to 40, wherein the moiety conjugated to the agent is one or more type of moieties selected from the group consisting of albumin, fatty acids, polyethylene glycol (PEG), acylation groups, antibodies and antibody fragments.

42. The agent according to any one of claims 37 to 41, wherein the agent and the moiety are conjugated to each-other by a linker.

43. The agent according to any one of claims 37 to 41, wherein the more than one moiety is conjugated to the agent.

44. The agent according to any one of claims 42 and 43, wherein the linker is a peptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 65, 66, 67, 68 and 69.

45. A pharmaceutical composition comprising the agent of any one of the preceding claims.

46. The pharmaceutical composition according to claim 45 further comprising a pharmaceutically acceptable carrier.

47. The pharmaceutical composition according to any one of claims 45 and 46 wherein the pH of the composition is between pH 4 and pH 10.

48. The pharmaceutical composition according to any one of claims 45 to 47 wherein the composition is formulated for parenteral administration.

49. The pharmaceutical composition according to any one of claims 45 to 47 wherein the composition is formulated for oral administration.

50. The pharmaceutical composition according to claim 48 wherein the parenteral administration is by injection.

51. The pharmaceutical composition according to any one of claims 48 and 49, wherein the administration is intravenous, intramuscular, intraspinal, intraperitoneal, subcutaneous, a bolus or a continuous administration.

52. The pharmaceutical composition according to any one of claims 45 to 51, wherein the administration occurs at intervals of 30 minutes to 24 hours, such as at intervals of 1 to 6 hours, such as three times a day.

53. The pharmaceutical composition according to any one of claims 45 to 52, wherein the duration of the treatment is from 6 to 72 hours.

54. The pharmaceutical composition according to any one of claims 45 to 52, wherein the duration of the treatment is from 24 hours to 7 days.

55. The pharmaceutical composition according to any one of claims 45 to 52, wherein the duration of the treatment is from 4 days to 150 days.

56. The pharmaceutical composition according to any one of claims 45 to 52, wherein the duration of the treatment is lifelong.

57. The pharmaceutical composition according to any one of claims 35 to 43, wherein the dosage of the active ingredient is between 10 µg to 500 mg per kg body mass, such as from 50 µg to 250 mg per kg body mass.

58. A kit comprising the pharmaceutical composition according to any one of claims 45 to 57, and instructions for use.

59. Use of an agent selected from the group consisting of:

a) an isolated polypeptide comprising:

i) the amino acid sequence of SEQ ID NOs: 15; or

ii) a biologically active sequence variant of the amino acid sequence of i) wherein the variant has at least 60% sequence identity to said SEQ ID NO: 15,

iii) a biologically active fragment of at least 15 contiguous amino acids of any one of i) through ii), said fragment having at least 60% sequence identity to SEQ ID NO: 15 in a range of overlap of at least 15 amino acids,

b) a nucleic acid sequence encoding a polypeptide as defined in a);

c) a vector comprising the nucleic acid molecule as defined in b),

d) an isolated host cell transformed or transduced with the nucleic acid of b) or the vector of c),

for the preparation of a medicament for reduction of appetite, and/or for promoting weight loss, and/or treating obesity, and/or increasing metabolism, and/or increasing thermogenesis, and/or converting white fat into brown fat.

60. Use of an agent selected from the group consisting of:

a) an isolated polypeptide comprising:

i) the amino acid sequence of SEQ ID NOs: 15; or

ii) a biologically active sequence variant of the amino acid sequence of i) wherein the variant has at least 60% sequence identity to said SEQ ID NO: 15,

iii) a biologically active fragment of at least 15 contiguous amino acids of any one of i) through ii), said fragment having at least 60% sequence identity to SEQ ID NO: 15 in a range of overlap of at least 15 amino acids,

b) a nucleic acid sequence encoding a polypeptide as defined in a);

c) a vector comprising the nucleic acid molecule as defined in b),

d) an isolated host cell transformed or transduced with the nucleic acid of b) or the vector of c),

in the manufacture of a medicament for treating obesity in an individual in need thereof.

~~61. Use of an agent selected from the group consisting of:~~

a) an isolated polypeptide comprising:

i) the amino acid sequence of SEQ ID NOs: 15; or

ii) a biologically active sequence variant of the amino acid sequence of i) wherein the variant has at least 60% sequence identity to said SEQ ID NO: 15,

iii) a biologically active fragment of at least 15 contiguous amino acids of any one of i) through ii), said fragment having at least 60% sequence identity to SEQ ID NO: 15 in a range of overlap of at least 15 amino acids,

b) a nucleic acid sequence encoding a polypeptide as defined in a);

c) a vector comprising the nucleic acid molecule as defined in b),

d) an isolated host cell transformed or transduced with the nucleic acid of b) or the vector of c),

in the manufacture of a medicament for increasing metabolism in an individual in need thereof.

62. Use of an agent selected from the group consisting of:

a) an isolated polypeptide comprising:

i) the amino acid sequence of SEQ ID NOs: 15; or

ii) a biologically active sequence variant of the amino acid sequence of i) wherein the variant has at least 60% sequence identity to said SEQ ID NO: 15,

iii) a biologically active fragment of at least 15 contiguous amino acids of any one of i) through ii), said fragment having at least 60% sequence identity to SEQ ID NO: 15 in a range of overlap of at least 15 amino acids,

b) a nucleic acid sequence encoding a polypeptide as defined in a);

c) a vector comprising the nucleic acid molecule as defined in b),

d) an isolated host cell transformed or transduced with the nucleic acid of b) or the vector of c),

in the manufacture of a medicament for increasing thermogenesis in a mammal.

~~63. An in vitro method for converting white fat into brown fat, the method comprising contacting~~ a cell with an effective amount of an agent selected from the group consisting of:

a) an isolated polypeptide comprising:

i) the amino acid sequence of SEQ ID NOs: 15; or

ii) a biologically active sequence variant of the amino acid sequence of i) wherein the variant has at least 60% sequence identity to said SEQ ID NO: 15,

iii) a biologically active fragment of at least 15 contiguous amino acids of any one of i) through ii), said fragment having at least 60% sequence identity to SEQ ID NO: 15 in a range of overlap of at least 15 amino acids,

b) a nucleic acid sequence encoding a polypeptide as defined in a);

c) a vector comprising the nucleic acid molecule as defined in b),

d) an isolated host cell transformed or transduced with the nucleic acid of b) or the vector of c).

Claims

1. Use of an agent selected from the group consisting of:
    a) an isolated soluble polypeptide comprising:

        i) the amino acid sequence of SEQ ID NOs: 15; or

        ii) a biologically active sequence variant of the amino acid sequence of i) wherein the variant has at least 90% sequence identity to said SEQ ID NO: 15,

        iii) a biologically active fragment of at least 15 contiguous amino acids of any one of i) through ii), said fragment having at least 90% sequence identity to SEQ ID NO: 15 in a range of overlap of at least 15 amino acids,

    b) a nucleic acid sequence encoding a polypeptide as defined in a);

    c) a vector comprising the nucleic acid molecule as defined in b),

    d) an isolated host cell transformed or transduced with the nucleic acid of b) or the vector of c),

    for manufacturing of a medicament for treating obesity, wherein the agent is to be administered to a subject that does not suffer from insulin resistance or diabetes mellitus type 2.

2. Use of an agent selected from the group consisting of:
    a) an isolated soluble polypeptide comprising:

        i) the amino acid sequence of SEQ ID NOs: 15; or

        ii) a biologically active sequence variant of the amino acid sequence of i) wherein the variant has at least 90% sequence identity to said SEQ ID NO: 15,

iii) a biologically active fragment of at least 15 contiguous amino acids of any one of i) through ii), said fragment having at least 90% sequence identity to SEQ ID NO: 15 in a range of overlap of at least 15 amino acids,

b) a nucleic acid sequence encoding a polypeptide as defined in a);

c) a vector comprising the nucleic acid molecule as defined in b),

d) an isolated host cell transformed or transduced with the nucleic acid of b) or the vector of c),

for reducing appetite, and/or for promoting weight loss, and/or increasing metabolism, and/or increasing thermogenesis, and/or converting white fat into brown fat.

3. The use according to any one of the preceding claims, wherein the agent is a polypeptide, wherein the polypeptide is a biologically active sequence variant comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 15, 5, 1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 61, 62, 63 and 64.

4. The use according to any one of the preceding claims, wherein the agent is a polypeptide, wherein the polypeptide is a biologically active sequence variant having an amino acid sequence selected from the group consisting of SEQ ID NOs: 15, 5, 1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 61, 62, 63 and 64.

5. The use according to any one of the preceding claims, wherein the polypeptide is a naturally occurring allelic variant of a sequence selected from the group consisting of SEQ ID NOs: 15, 5, 1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 61, 62, 63 and 64.

6. The use according to any one of the preceding claims, wherein the polypeptide comprises an amino acid sequence of a soluble SorCS1 selected from the group consisting of: SEQ ID NOs: 15, 5, 63, 62, 21, 27, 33, 37, 39, 43, and 47.

7. The use according to any one of the preceding claims, wherein the polypeptide is a variant polypeptide described therein, wherein any amino acid specified in the selected sequence is altered to provide a conservative substitution, with the proviso that no more than 200 amino acids are so altered.

8. The use according to any one of the preceding claims, wherein the polypeptide is a variant polypeptide described therein, wherein any amino acid specified in the selected sequence is altered to provide a conservative substitution, with the proviso that no more than 100 amino acids are so altered.

9. The use according to any one of the preceding claims, wherein the polypeptide is a variant polypeptide described therein, wherein any amino acid specified in the selected sequence is altered to provide a conservative substitution, with the proviso that no more than 50 amino acids are so altered.

10. The use according to any one of the preceding claims, wherein the polypeptide is a variant polypeptide described therein, wherein any amino acid specified in the selected sequence is altered to provide a conservative substitution, with the proviso that no more than 25 amino acids are so altered.

11. The use according to any one of the preceding claims, wherein said polypeptide has at least 91%, more preferably at least 92%, more preferably at least 93%, more preferably at least 94%, more preferably at least 95%, more preferably at least 96%, more preferably at least 97%, more preferably at least 98%, more preferably at least 99% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 15, 5, 1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 61, 62, 63 and 64.

12. The use according to any one of the preceding claims, wherein said agent is a polypeptide, wherein the polypeptide is selected from the group consisting of SEQ ID NOs: 1, 2, 3, 4, 6, 7, 8, 9, 11, 12, 13, 14, 61 and 62.

13. The use according to any one of the preceding claims, wherein the polypeptide is selected from the group consisting of SEQ ID NOs: 16, 17, 18, 19, 20, 22, 26, 28, 29, 30, 31 and 32.

14. The use according to any one of the preceding claims, wherein the agent is a polypeptide selected from the group consisting of SEQ ID NOs: 61, 62, 63 and 64.

15. The use according to any one of the preceding claims, wherein the agent is a polypeptide selected from the group consisting of SEQ ID NOs: 62 and 64.

16. The use according to claim 1 or 2, wherein the agent is a biologically active fragment, wherein the fragment comprises less than 500 contiguous amino acid residues, such as less than 450 contiguous amino acid residues, for example less than 400 contiguous amino acid residues, such as less than 350 contiguous amino acid residues, for example less than 300 contiguous amino acid residues, for example less than 250 contiguous amino acid residues, such as less than 240 contiguous amino acid residues, for example less than 225 contiguous amino acid residues, such as less than 200 contiguous amino acid residues, for example less than 180 contiguous amino acid residues, such as less than 160 contiguous amino acid residues, for example less than 150 contiguous amino acid residues, such as less than 140 contiguous amino acid residues, for example less than 130 contiguous amino acid residues, such as less than 120 contiguous amino acid residues, for example less than 110 contiguous amino acid residues, such as less than 100 contiguous amino acid residues, for example less than 90 contiguous amino acid residues, such as less than 85 contiguous amino acid residues, for example less than 80 contiguous amino acid residues, such as less than 75 contiguous amino acid residues, for example less than 70 contiguous amino acid residues, such as less than 65 contiguous amino acid residues, for example less than 60 contiguous amino acid residues, such as less than 55 contiguous amino acid residues, for example less than 50 contiguous amino acid residues, such as less than 45 contiguous amino acid residues, for example less than 40 contiguous amino acid residues, such as 35 contiguous amino acid residues, for example 30 contiguous amino acid residues, such as 25 contiguous amino acid residues, such as 20 contiguous amino acid residues, for example 15 contiguous amino acid residues of an any one of the amino acid sequences selected from the group consisting of SEQ ID NOs: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 61, 62, 63 and 64.

17. The use according to claim 1 or 2, wherein the agent is a biologically active fragment, wherein the fragment comprises at least 15 contiguous amino acid residues, such as more than 20 contiguous amino acid residues, for example more than 25 contiguous amino acid residues, for example more than 50 contiguous amino acid residues, such as more than 75 contiguous amino acid residues, for example more than 100 contiguous amino acid residues, such as more than 125 contiguous amino acid residues, for example more than 150 contiguous amino acid residues, such as more than 175 contiguous amino acid residues, for example more than 200 contiguous amino acid residues, such as more than 225 contiguous amino acid residues, for example more than 250 contiguous amino acid residues, such as more than 275 contiguous amino acid residues, for example more than 300 contiguous amino acid residues, such as more than 325 contiguous amino acid residues, for example more than 350 contiguous amino acid residues, such as more than 375 contiguous amino acid residues, for example more than 400 contiguous amino acid residues, such as more than 425 contiguous amino acid residues, for example more than 450 contiguous amino acid residues, such as more than 475 contiguous contiguous amino acid residues, for example more than 500 contiguous amino acid residues, such as more than 525 contiguous amino acid residues, for example more than 550 contiguous amino acid residues, such as more than 575 contiguous amino acid residues, for example more than 600 contiguous amino acid residues, such as more than 625 contiguous amino acid residues, for example more than 650 contiguous amino acid residues, such as more than 675 contiguous amino acid residues, such as more than 700 contiguous amino acid residues of any one of the amino acid sequences selected from the group consisting of SEQ ID NOs: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 61, 62, 63 and 64.

18. The use according to any one of the preceding claims wherein the polypeptide is glycosylated.

19. The use according to claim 18, wherein the polypeptide is N-glycosylated in one or more asparagin amino acid residues corresponding to amino acid positions positions 184, 352, 433, 765, 776, 816, 847, 908 and 929 of SEQ ID NO: 1.

20. The use according to any one of the preceding claims, wherein the polypeptide comprises one of more of the following sequences:

SEQ ID NO: 1 aa 103-124
SEQ ID NO: 1 aa 125-143
SEQ ID NO: 1 aa 144-162
SEQ ID NO: 1 aa 197-218
SEQ ID NO: 1 aa 391-409
SEQ ID NO: 1 aa 661-684
SEQ ID NO: 1 aa 763-783
SEQ ID NO: 1 aa 859-876.

21. The use of claim 1 or 2, wherein a signal peptide of the polypeptide has been replaced by a heterologous signal peptide.

22. The use according to any one of the preceding claims, wherein the polypeptide is capable of forming at least one intramolecular cystin bridge.

23. The use according any one of the preceding claims, comprising a dimer of said polypeptide linked through at least one intermolecular cystin bridge.

24. The use according to any one of the preceding claims, wherein said polypeptide further comprises an affinity tag, such as a polyhis tag, a GST tag, a HA tag, a Flag tag, a C-myc tag, a HSV tag, a V5 tag, a maltose binding protein tag, a cellulose binding domain tag.

25. The use according to claim 1 or 2, wherein the vector further comprises a promoter operably linked to the nucleic acid sequence.

26. The use according to claim 25, wherein the promoter is selected from the group consisting of: CMV, human UbiC, RSV, Tet-regulatable promoter, Mo-MLV-LTR, Mx1, EF-1alpha, PDGF beta and CaMK II.

27. The use according to claim 1 or 2, wherein the vector is selected from the group consisting of vectors derived from the Retroviridae family including lentivirus, HIV, SIV, FIV, EAIV, CIV.

28. The use according to claim 1 or 2, wherein the vector is selected from the group consisting of adeno associated virus, adenovirus, alphavirus, baculovirus, HSV, coronavirus, Bovine papilloma virus, Mo-MLV.

29. The use according to claim 1 or 2, wherein the vector is adeno associated virus (AAV).

30. The use according to claim 1 or 2, wherein the host cell is selected from the group consisting of Saccharomyces cerevisiae, E. coli, Aspergillus and insect cells such as Sf9 insect cells.

31. The use according to claim 1 or 2, wherein the host cell is selected from the group consisting of mammalian cells selected from the group consisting of human, feline, porcine, simian, canine, murine and rat cells.

32. The use according to claim 31 wherein said mammalian cell is selected from the group consisting of muscle cells, hepatocytes, adipocytes and cells of the pancreas such as α cells, β cells and δ cells.

33. The use according to claim 1 or 2, wherein said host cell is selected from the group consisting of CHO, CHO-K1, HEI193T, HEK293, COS, HiB5, RN33b and BHK cells.

34. The use according to any one of the preceding claims, wherein the agent is chemically modified in order to increase its half-life when administered to a patient, in particular its plasma half-life.

35. The use according to any one of the preceding claims, wherein said agent further comprises a moiety conjugated to said agent, thus generating a moiety-conjugated agent

36. The use according to claim 35, wherein the moiety-conjugated agent has a plasma and/or serum half-life being longer than the plasma and/or serum half-life of the non-moiety conjugated agent.

37. The use according to claim 35, wherein the moiety facilitates transport across the blood brain barrier.

38. The use according to claim 35, wherein the moiety is an antibody from a camelid species such as a recombinant or native single-chain antibody from dromedaries, camels, llamas, alpacas, vicuñas, or guanacos.

39. The use according to any one of claims 35 to 38, wherein the moiety conjugated to the agent is one or more type of moieties selected from the group consisting of albumin, fatty acids, polyethylene glycol (PEG), acylation groups, antibodies and antibody fragments.

40. The use according to any one of claims 35 to 39, wherein the agent and the moiety are conjugated to each-other by a linker.

41. The use according to any one of claims 35 to 39, wherein the more than one moiety is conjugated to the agent via a linker.

42. The use according to any one of claims 40 and 41, wherein the linker is a peptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 65, 66, 67, 68 and 69.

43. The use according to claim 1 and any of the preceding claims 3 to 42, wherein said agent is comprised in a pharmaceutical composition.

44. The use according to claim 43, wherein said pharmaceutical composition further comprises a pharmaceutically acceptable carrier.

45. The use according to any one of claims 43 and 44 wherein the pH of the composition is between pH 4 and pH 10.

46. The use according to any one of claims 43 to 45 wherein the composition is formulated for parenteral administration.

47. The use according to any one of claims 43 to 45 wherein the composition is formulated for oral administration.

48. The use according to claim 46 wherein the parenteral administration is by injection.

49. The use according to any one of claims 46 and 48, wherein the administration is intravenous, intramuscular, intraspinal, intraperitoneal, subcutaneous, a bolus or a continuous administration.

50. The use according to any one of claims 43 to 49, wherein administration occurs at intervals of 30 minutes to 24 hours, such as at intervals of 1 to 6 hours, such as three times a day.

51. The use according to any one of claims 43 to 50, wherein the duration of the treatment is from 6 to 72 hours.

52. The use according to any one of claims 43 to 50, wherein the duration of the treatment is from 24 hours to 7 days.

53. The use according to any one of claims 43 to 50, wherein the duration of the treatment is from 4 days to 150 days.

54. The use according to any one of claims 43 to 50, wherein the duration of the treatment is lifelong.

55. The use according to any one of claims 43 to 54, wherein the dosage of the active ingredient is between 10 µg to 500 mg per kg body mass, such as from 50 µg to 250 mg per kg body mass.

56. Use of an agent selected from the group consisting of:
    a) an isolated soluble polypeptide comprising:

        i) the amino acid sequence of SEQ ID NOs: 15; or

ii) a biologically active sequence variant of the amino acid sequence of i) wherein the variant has at least 90% sequence identity to said SEQ ID NO: 15,

iii) a biologically active fragment of at least 15 contiguous amino acids of any one of i) through ii), said fragment having at least 90% sequence identity to SEQ ID NO: 15 in a range of overlap of at least 15 amino acids,

b) a nucleic acid sequence encoding a polypeptide as defined in a);

c) a vector comprising the nucleic acid molecule as defined in b),

d) an isolated host cell transformed or transduced with the nucleic acid of b) or the vector of c),

for reduction of appetite, and/or for promoting weight loss, and/or increasing metabolism, and/or increasing thermogenesis, and/or converting white fat into brown fat.

57. Use of an agent selected from the group consisting of:

a) an isolated soluble polypeptide comprising:

i) the amino acid sequence of SEQ ID NOs: 15; or

ii) a biologically active sequence variant of the amino acid sequence of i) wherein the variant has at least 90% sequence identity to said SEQ ID NO: 15,

iii) a biologically active fragment of at least 15 contiguous amino acids of any one of i) through ii), said fragment having at least 90% sequence identity to SEQ ID NO: 15 in a range of overlap of at least 15 amino acids,

b) a nucleic acid sequence encoding a polypeptide as defined in a);

c) a vector comprising the nucleic acid molecule as defined in b),

d) an isolated host cell transformed or transduced with the nucleic acid of b) or the vector of c),

for increasing metabolism in an individual in need thereof.

58. Use of an agent selected from the group consisting of:

a) an isolated soluble polypeptide comprising:

i) the amino acid sequence of SEQ ID NOs: 15; or

ii) a biologically active sequence variant of the amino acid sequence of i) wherein the variant has at least 90% sequence identity to said SEQ ID NO: 15,

iii) a biologically active fragment of at least 15 contiguous amino acids of any one of i) through ii), said fragment having at least 90% sequence identity to SEQ ID NO: 15 in a range of overlap of at least 15 amino acids,

b) a nucleic acid sequence encoding a polypeptide as defined in a);

c) a vector comprising the nucleic acid molecule as defined in b),

d) an isolated host cell transformed or transduced with the nucleic acid of b) or the vector of c),

for increasing thermogenesis in a mammal.

59. An *in vitro* method for converting white fat into brown fat, the method comprising contacting a cell with an effective amount of an agent selected from the group consisting of:

a) an isolated soluble polypeptide comprising:

i) the amino acid sequence of SEQ ID NOs: 15; or

ii) a biologically active sequence variant of the amino acid sequence of i) wherein the variant has at least 90% sequence identity to said SEQ ID NO: 15,

iii) a biologically active fragment of at least 15 contiguous amino acids of any one of i) through ii), said fragment having at least 90% sequence identity to SEQ ID NO: 15 in a range of overlap of at least 15 amino acids,

b) a nucleic acid sequence encoding a polypeptide as defined in a);

c) a vector comprising the nucleic acid molecule as defined in b),

d) an isolated host cell transformed or transduced with the nucleic acid of b) or the vector of c).

60. A cosmetic method for reducing appetite, and/or for promoting weight loss, and/or for increasing metabolism, and/or for increasing thermogenesis, and/or for converting white fat into brown fat, the method comprising administering to an individual in need thereof a therapeutically effective amount of an agent selected from the group consisting of:

a) an isolated soluble polypeptide comprising:

i) the amino acid sequence of SEQ ID NOs: 15; or

ii) a biologically active sequence variant of the amino acid sequence of i) wherein the variant has at least 90% sequence identity to said SEQ ID NO: 15,

iii) a biologically active fragment of at least 15 contiguous amino acids of any one of i) through ii), said fragment having at least 90% sequence identity to SEQ ID NO: 15 in a range of overlap of at least 15 amino acids,

b) a nucleic acid sequence encoding a polypeptide as defined in a);

c) a vector comprising the nucleic acid molecule as defined in b),

d) an isolated host cell transformed or transduced with the nucleic acid of b) or the vector of c).