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(54) Title: COMPOSITIONS COMPRISING SORTILIN-1

Compare	Identities	Positives	Gaps	Comment
hSORT1 vs mSORT1	787/864 (87%)	787/864 (91%)	40/864 (4%)	Highly conserved in VPS10P.
hSORT1 vs hSORCS1	147/595 (25%)	278/595 (46%)	55/595 (9%)	Not highly conserved in VPS10P.

Figure 1

(57) Abstract: The invention provides composition comprising a fragment, derivative or variant of sortilin, or a sortilin mimetic, for use in medicine, wherein the sortilin mimetic is not SorCS1, SorCS2, SorCSS or SorLA. The composition preferably for use in treating or preventing diabetes mellitus, insulin resistance, obesity, metabolic disorders, polycystic ovary syndrome, non-alcoholic fatty liver disease, retinopathy, neuropathy, nephropathy, Alzheimer's disease and/or cardiovascular disease in a subject in need thereof. Also provided are isolated polypeptides, nucleic acids encoding the polypeptides, vectors, host cells and expression systems containing the nucleic acids and methods for making the polypeptides.



COMPOSITIONS COMPRISING SORTILIN-1

Field of invention

The present invention relates to pharmaceutical compositions for use in the treatment of diseases including obesity, insulin resistance and diabetes mellitus.

Background

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have a negative impact on health. With 61.4 % of adults in England, for example, being overweight or obese, obesity represents a major public health issue. Obesity is known to increase the risk of a range of health problems, including insulin resistance and the subsequent development of type 2 diabetes mellitus. Insulin resistance occurs when an individual's cells fail to respond normally to the hormone insulin. To overcome this, the pancreas (the organ responsible for producing insulin) compensates by producing more insulin to meet the metabolic demand. Ultimately, the levels of insulin produced are no longer adequate and therefore cellular glucose uptake is impaired, leading to hyperglycaemia and the likely development of diabetes mellitus.

The above diseases are not only an economic burden in their own right but can lead to multiple secondary disease states, further exacerbating the problem. Additionally, current pharmaceutical interventions fail to display adequate efficacy in a large proportion of patients, highlighting the need for novel treatment strategies.

The vacuolar protein sorting 10p domain (Vps10pD) receptor family is a group of five type I membrane homologs, known to include Sort1 (sortilin), SorL1, SorCS1, SorCS2 and SorCS3. This domain family was characterised following the identification of the yeast-sorting protein, Vps10p, which transports enzymes from the *trans*-Golgi network to the vacuole. These proteins are characterised by a domain within their N terminus that represents a site for ligand binding. Functions known to be attributed to this family of receptors include protein trafficking, lipid metabolism and both intracellular and intercellular signalling in a range of cell types.

In addition to the Vps10pD, SorCS1, SorCS2, SorCS3 all contain a leucine-rich segment between the Vps10pD and the transmembrane domain. SorLA is further characterised by the presence of fibronectin-type III repeats, low-density lipoprotein receptor class A and B repeats and an EGF precursor-type repeat. The peptide sequence homology between SorCS1, SorCS2, SorCS3 and SorLA is high, which is in contrast to a very low homology of these receptors with sortilin (for example the homology between human sortilin and human SorCS1 in the Vps10 domain is 25 %).

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WO 2010/142296 claims a SorCS1-like agent for treating insulin resistance and/or a disease associated with insulin resistance in an individual, wherein said agent is capable of binding to and sensitising the insulin receptor at a SorCS1 binding site. Additionally, WO 2013/156031 claims the use of SorCS1 and SorCS1-like agents in a method of reducing appetite, suppressing hunger, increasing metabolism and treating obesity.

15

Different splice variants of SorCS1 display distinct patterns of tissue distribution and have been found to be present in tissues involved in glucose metabolism processes, such as adipose tissue, skeletal muscle and β -cells of the pancreas. SorCS1 knock-out mice show a reduced response to insulin when compared to wild-type control mice. Additionally, in a mouse model of diabetes mellitus, the over-expression of soluble SorCS1 reduced plasma levels of both glucose and insulin.

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Sortilin is known to be enriched in the nervous system, where it can regulate neuronal development, functionality and integrity, via the binding of neurotrophic factors, for example. It is also known that it plays an important role in controlling metabolic activities. Examples of the latter include the regulation of cholesterol metabolism and regulation of the trafficking of GLUT-4 containing vesicles (Kjolby et al. Curr Atherosclerosis Reports 17(4):496, 2015).

30

Previous work has suggested a role for sortilin in the cellular signalling pathways associated with diseases such as diabetes and obesity. Sortilin levels have been

shown to be modulated by the level of inflammation associated with these diseases. The pro-inflammatory cytokine, TNF α , reduces both mRNA levels and protein levels of sortilin in cultured mouse and human adipocytes, as well as *in vivo* when injected into mice (Kaddai et al. Diabetologia 52: 932-40, 2009). Sortilin
5 can also influence cytokine secretion: targeting sortilin in immune cells has been proposed to attenuate inflammation (Mortenson et al. J Clin Invest 124(12):5317-22, 2014). Additionally, US 2016/0331746 describes various scaffolds of small molecules capable of binding to the active site of sortilin. Sortilin is involved in the regulation of glucose uptake (Shi & Kandrór. Developmental Cell 9:99-108, 2005)
10 and the development of lipid disorder diseases (Gao et al. DNA and Cell Biology 36(12):1050-61, 2017).

Further, plasma sortilin levels have been reported to be a potential biomarker for identifying patients with either coronary heart disease or diabetes mellitus (Oh et
15 al. Cardiovascular Diabetology 16:92, 2017). Patients that showed increased sortilin levels within their plasma, and therefore identifiable as suffering from the above conditions, also displayed enhanced glucose levels suggesting sortilin as a therapeutic target for treating these conditions.

20 The listing or discussion of an apparently prior-published document in this specification should not necessarily be taken as an acknowledgment that the document is part of the state of the art or is common general knowledge.

Summary of Invention

25 The present invention is based on the surprising discovery by the inventors that fragments of sortilin, when administered to diabetic mice, are able to significantly lower blood glucose levels by increasing insulin sensitivity following glucose challenge. This is particularly surprising given the very low homology of sortilin to SorCS1 and related proteins, and the suggestion in the art that downregulation of
30 sortilin may be desirable for treating conditions relating to insulin resistance.

Accordingly, the present invention provides a composition comprising a fragment, derivative or variant of sortilin, or a sortilin mimetic, for use in medicine, wherein the sortilin mimetic is not SorCS1, SorCS2, SorCS3 or SorLA. In particular, the

composition may be for use in treating or preventing diabetes mellitus, insulin resistance, obesity, metabolic disorders, polycystic ovary syndrome, non-alcoholic fatty liver disease, retinopathy, neuropathy, nephropathy, Alzheimer's disease and/or cardiovascular disease in a subject in need thereof.

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The invention further provides an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22 or SEQ ID NO: 23, or an amino acid sequence having greater than 70 % homology to said amino acid sequence, or a fragment thereof.

Further provided are nucleic acids that encode the polypeptides of the invention and pharmaceutical compositions comprising the isolated polypeptides or nucleic acids of the invention and medical uses thereof.

The present invention also provides a method of manufacturing polypeptides or fragments thereof according to the invention comprising the step of expressing the nucleic acid of the invention in a host cell or other suitable expression system as indicated herein.

The invention will now be described in more detail with reference to the following figures and examples.

25

Figures

Figure 1: Alignment of hSORT1 and mSort1, hSORT1 and hSORCS1.

Figure 2: Sortilin and insulin receptor binding. Surface plasmon resonance of sortilin (50-500 nM) binding to immobilized (A) human insulin receptor (0.0609 pmol/mm²), and (B) murine insulin receptor (0.0607 pmol/mm²). Sortilin and insulin (C) is able to bind to the insulin receptor at the same time. (D) Co-immunoprecipitation with the insulin receptor and sortilin using DSP crosslinker. Immunoprecipitation of the insulin receptor resulted in co-precipitation of sortilin, and vice versa.

Figure 3. Effects of exogenous hSortilin given to *Lepr^{-/-}* (db/db) mice at t=-12 hrs and t=-1 hrs (100 µg/mouse x2). Mice were challenged with an IP dose of glucose (1 mg/g BW) at t=0 min. (A) Plasma glucose levels in the intraperitoneal glucose tolerance test (IPGTT), (B) individual plasma glucose levels in IPGTT, (C) area under the curve (AUC) without baseline, (D) total AUC in IPGTT, and (E) body weight prior to conducting the experiment. Statistics: Student's t-test, and 2-way-ANOVA in panel A. Values are Mean ± SEM.

Figure 4. Effects of treatment with sortilin +/- heparin in diabetic db/db mice on IPGTT response. (A) Initial bodyweight (g) (P=n.s), (B) basal glucose levels (mM) prior to IPGTT, (C) average IPGTT curves, and individual (D) curves. AUC (total) was lower in treated animals (E). Basal insulin levels (P=0.05 (soluble sortilin)) (F), and insulin IPGTT response curves (G-H), and insulin AUC (I). Insulin sensitivity index was calculated, HOMA1-IR (J), QUICKI Index (K), and plasma glucose vs insulin (L).

Detailed Description

The following description is presented to enable any person skilled in the art to make and use the invention. Various modifications to the disclosed embodiments will be readily apparent to those skilled in the art.

In a first aspect the present invention provides a composition comprising a fragment, derivative or variant of sortilin, or a sortilin mimetic, for use in medicine, wherein the sortilin mimetic is not SorCS1, SorCS2, SorCS3 or SorLA.

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Sortilin is a member of the Vps10p domain (Vps10pD) receptor family and has an amino acid sequence according to SEQ ID NO: 12 or SEQ ID NO: 13. Full length sortilin comprises a signal peptide, a propeptide, the Vps10p domain, a 10CC domain (10CCa + 10CCb), a transmembrane domain and a large cytoplasmic tail.

30 The luminal domain of sortilin has 6 potential *N*-linked glycosylation sites, whilst the cytoplasmic tail enables for the recruitment of various adapter proteins. Sortilin binds a vast number of ligands and membrane receptors and as a result engages in functions known to be important in cellular signalling and sorting.

The composition of the invention may include, in addition to the active pharmaceutical ingredient(s) (sortilin fragment, derivative, variant or mimetic), pharmaceutically acceptable carriers or excipients as would be understood by a person of skill in the art.

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The present compositions may comprise sortilin fragments, derivatives or variants. By 'fragment' we intend any sequence of amino acids which partially constitute the full length amino acid sequence of sortilin. Therefore this includes any continuous length of amino acids with 100 % identity to a sortilin amino acid sequence. By 'derivative' we intend any sequence of natural or non-natural amino acids derived from reasonable modification of either the full length amino acid sequence of sortilin or the aforementioned sortilin fragments. Thus, the derivative may contain modified amino acids, D-amino acids, or amino acid mimics, which may be optimised for improved pharmacological properties, as would be understood by a person of skill in the art. By 'variant' we intend any form of sortilin or amino acid with high homology to sortilin and functional equivalent, which includes splice variants and homologues from organisms other than humans, for example, simian, murine or porcine homologues.

20 The present composition may comprise sortilin mimetics. The term 'sortilin mimetic' is intended to refer to any substance which exerts the same function as sortilin, sortilin fragments, derivatives or variants thereof. For example, such compounds may exhibit the same receptor binding capabilities as sortilin, even though they may not share structural homology to sortilin. However, "sortilin mimetic" does not include SorCS1, SorCS2, SorCS3 or SorLA. It is envisaged that these substances may include antibodies, nanobodies and aptamers which are able to interact with the sortilin binding epitope(s) within the insulin receptor. Methods for detecting such an interaction may involve techniques such as phage display, an *in vitro* screening technique designed for identifying ligands for proteins. The antibody used in the present invention may be, for example, a monoclonal antibody, a humanised antibody, a chimeric antibody, a recombinant antibody or a bispecific antibody. By 'bispecific antibody' we intend an antibody that can simultaneously bind to two different antigens. The latter may be a suitable method to bridge the insulin receptor with endogenous sortilin. Fragments of said

antibodies may also be used, specifically, antigen-binding fragments or single chain variable fragments. Preferred fragments will retain some or all the ability of an antibody to selectively bind to its target. By 'nanobodies' we intend the resulting protein based on single-domain antibody fragments that contain the unique structural and functional properties of naturally-occurring heavy chain only antibodies. By 'aptamer' we intend an oligonucleotide or peptide molecule capable of binding to a specific target molecule. Aptamers can bind to their target with high selectivity and specificity. Target recognition and binding may involve shape-dependent interactions as well as hydrophobic interactions, base-stacking and intercalation. Common targets for these molecules may include proteins, peptides, carbohydrates and small molecules. The methods by which the above antibodies, antibody fragments and aptamers are produced will be well known to the person skilled in the art.

It is envisaged that the present invention may useful for treating a range of diseases. The invention may be for use as a therapeutic and/or a prophylactic treatment. Specifically, the present invention is intended for use in diseases associated with insulin resistance. These diseases may be as a direct result of elevated blood glucose levels or as a secondary cause. Examples of such diseases include, but are not limited to, diabetes mellitus, obesity, metabolic disorders, polycystic ovary syndrome, non-alcoholic fatty liver disease, retinopathy, neuropathy, nephropathy, Alzheimer's disease, cardiovascular disease, stroke, coeliac disease, thyroid disease, mastopathy, muscular conditions, cirrhosis, hyperglycemia, hyperinsulinemia, arteriosclerosis, hypercholesterolemia, hypertriglyceridemia, dyslipidemia, hypercoagulability, hypertension, microalbuminuria and any combinations thereof.

In one embodiment of the composition for use according to the invention, the sortilin fragment, derivative or variant comprises the VPS10p, 10CCa, or 10CCb domain. Also included are sortilin fragments, derivatives or variants that include any combination of the above domains, for example, VPS10p + 10CCa + 10CCb domain, VPS10p + 10CCa domain, VPS10p + 10CCb domain or 10CCa + 10CCb domain. The composition for use may comprise a dimer of any of the aforementioned polypeptides. By 'dimer' we intend a macromolecular complex

formed by two single protein monomers, which may be expressed as a fusion protein.

The amino acid sequence of the Vps10p, 10CCa and 10CCb domain is provided herein as SEQ ID NO: 1, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 14 and SEQ ID NO: 18.

The amino acid sequence of the Vps10p + 10CCa + 10CCb domains, Vps10p + 10CCa domains, Vps10p + 10CCb domains and the 10CCa + 10CCb domains are provided herein as SEQ ID NO: 4, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 7, SEQ ID NO: 17, SEQ ID NO: 15, SEQ ID NO: 16 and SEQ ID NO: 19.

The above amino acid sequences may or may not include protein tags. The presence of said tags may result in superior expression and/or an easier purification process. One such example could be the use of a HIS-tag, located either at the C-terminal (SEQ ID NO: 26) or at the N-terminal (SEQ ID NO: 27) with an additional TEV cleavage site. C-terminal HIS tagged sortilin is designed to have the wild type N-terminal after furin cleavage (allowing for protein activation). N-terminal HIS tagged sortilin is designed to have an N-terminal HIS tag after furin-mediated cleavage of the propeptide in the Golgi. The HIS tag can be cleaved off using a TEV protease, the latter of which recognises a strict 7 amino acid sequence of ENLYFQ(G/S) (SEQ ID NOs: 24 and 25, respectively).

The amino acid sequence of the C-terminal HIS tagged sortilin is herein provided as SEQ ID NO: 8 and SEQ ID NO: 20, and the amino acid sequence of the N-terminal HIS tagged sortilin is herein provided as SEQ ID NO: 10 and SEQ ID NO: 22.

It is intended that the above amino acid sequences may comprise an additional moiety and/or undergo a modification process. The skilled person would recognise that these modifications may result in improvements across a number of parameters, for example, enhanced stability, enhanced efficacy, improved half-life and/or reduced toxicity levels. Suitable additional moieties may include linker molecules, such as glutamic acid. These linker molecules may be of varying

lengths, for example 2-31 amino acids in length. Lipophilic groups may also be attached. Examples of such lipophilic groups include fatty acids, isoprenoids, sterols, phospholipids and glycosylphosphatidyl inositol anchors. Possible modifications may include PEGylation, glycosylation or acetylation. PEGylation
5 may involve the covalent or non-covalent addition of single, or multiple, polyethylene glycol polymer chains to the amino acid sequence. Glycosylation may involve the addition of a carbohydrate which is covalently attached to the amino acid sequence and acetylation refers to the process of introducing an acetyl group into said sequence. Further modifications may include methods to reduce
10 binding of said sequence to proteoglycans or sulphur containing polysaccharides and oligosaccharides. Such modifications may utilise sulfatases to result in desulphation of said molecules.

The present invention provides any sortilin fragment or polypeptide with at least
15 70 % homology to the aforementioned amino acid sequences. For example, the sortilin fragment or polypeptide of the invention may have at least 70 %, at least 75 %, at least 80 %, at least 85 %, at least 90 %, at least 91 %, at least 92 %, at least 93 %, at least 94 %, at least 95 %, at least 96 %, at least 97 %, at least 98 % or at least 99 % homology to the isolated polypeptides of any of SEQ ID NOs:
20 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 14, 15, 16, 17, 18, 19, 20, 21, 22 and/or 23. Further, also included are polypeptides with one or more conservative substitutions. By 'conservative substitution' we intend an amino acid replacement that changes one or more amino acids whilst resulting in a substance with similar biochemical properties. These biochemical properties may include charge, hydrophobicity and
25 size, as would be understood by a person of skill in the art.

In an embodiment, the fragment, derivative or variant of sortilin, or sortilin mimetic may bind to an insulin receptor. It is preferred that the fragment, derivative or variant of sortilin, or sortilin mimetic binds to a human insulin receptor.
30 Alternatively, or additionally, the fragment, derivative or variant of sortilin, or sortilin mimetic may bind to an insulin receptor from any mammal, for example, a mouse, guinea pig, rat, rabbit, dog, cat, horse, cow, sheep or pig insulin receptor.

It is intended that the sortilin fragments, derivatives, variants or sortilin mimetics of the present invention interact with the insulin receptor, resulting in improved blood glucose level control. The present inventors have demonstrated that sortilin binds to the human/mouse insulin receptor in a dose-dependent manner with high affinity, displaying a K_d value of approximately 40 nM. The latter allows for the desired therapeutic effect (a reduction in blood glucose levels) of the sortilin fragments, derivative, variants or sortilin mimetics to occur at low concentrations, thus minimising the chances of associated adverse effects. The inventors also show that the presence of insulin does not affect the binding between sortilin and the insulin receptor, instead forming a trimeric receptor complex, thus allowing for continued insulin-driven cell signalling. Consequently, the use of subcutaneously administered human soluble sortilin is shown to significantly improve glucose handling after a glucose challenge in a diabetic mouse strain. This effect can be observed within less than 12 hours of treatment, displaying the impressive fast-acting properties of the compositions and polypeptides of the present invention.

In a second aspect, the invention provides an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22 or SEQ ID NO: 23, or an amino acid sequence having greater than 70 % homology to said amino acid sequence, or a fragment thereof.

In a further aspect, the invention provides a nucleic acid encoding any of the polypeptides as defined herein.

The invention also provides a nucleic acid that hybridises to a nucleic acid of the invention under low and/or high stringency conditions. Accordingly, the nucleic acid may be complementary to the nucleic acid encoding a polypeptide of the invention. By "high stringency conditions" we include high temperature and low salt content in hybridisation buffers. By "low stringency conditions" we include lower temperatures and high salt content in hybridisation buffers. The present invention may involve the use of siRNAs (commonly referred to as small interfering

or silencing RNA) or Morpholino oligomers, directed against the nucleotide sequences or regulatory portions thereof *in vivo*. By 'siRNA' we intend a class of double-stranded RNA molecules, commonly 20-25 base pairs in length. siRNAs operate within the RNA interference pathway and therefore interfere with gene expression. Most commonly, siRNAs prevent translation for the degradation of mRNA. By 'Morpholino oligomers' we intend an oligomer molecule wherein the structure has DNA bases attached to a backbone of methylenemorpholine rings, linked through phosphorodiamidate groups. These molecules commonly act via blocking the access of other molecules to specific sequences of the RNA molecule. The use of these molecules would be particularly relevant in the instance where the translation of the protein was inhibited, thus triggering a feedback loop wherein the transcript levels were in fact enhanced, leading to increased protein levels of sortilin fragments, derivatives or variants. Alternatively, these genetic tools could be targeted to transcripts known to be associated with protein regulation, in particular degradation, thus leading to an upregulation of sortilin protein.

In a further aspect, the present invention provides an expression vector comprising a nucleic acid according to the invention. The expression vector may be used to manufacture the polypeptides of the invention *in vitro* (for subsequent formulation and delivery) or indeed to be delivered direct to the patient to be treated where the expression of the polypeptides of the invention will occur in the patient themselves. Thus, the expression vector may be used in gene therapy to treat a condition identified herein.

The vector may be any suitable vector for *ex vivo* or *in vivo* expression. For example, the vector may be a vector suitable for use in human gene therapy. The vector may alternatively be any vector suitable for use for expression in bacteria, mammalian cell lines, plants, yeasts, protozoa or cell free expression systems. Suitable examples of vectors according to the invention are viruses or plasmids. Examples of appropriate viruses include, but are not limited to, retroviruses, adenoviruses, adeno-associated viruses and the herpes simplex virus. Non-viral vector systems may also be used, for example, lipid DNA complexes. The promoter used to achieve activation of said nucleotide sequence may be selected

from the group comprising: lentivirus, adeno-associated virus (AAV), cytomegalovirus (CMV), Rous sarcoma virus (RSV), elongation factor 1 alpha (EF1 α), Tet-regulatable promoter, platelet-derived growth factor beta (PDGF β), murine leukemia virus long terminal repeat (Mo-MLV-L TR), phosphoglycerate kinase (PGK), Mx1 and calmodulin-dependent protein kinase II (CaMK II). Ideally, the promoter will be tissue-specific to restrict unwanted transgene expression and to facilitate persistent transgene expression, preferentially in liver, adipose tissue or muscle. Liver specific promoters may include albumin (Palb), α 1-antitrypsin (Pa1AT), hemopexin (Phpx), apolipoprotein A2 (APOA2), serpin peptidase inhibitor (SERPINA1), cytochrome p450 (CYP3A4), microRNA 122 (MIR122). Adipose tissue specific promoters may include adiponectin (AdipoQ) and muscle specific promoters may include muscle creatine kinase (MCK), myosin heavy chain 6 (Myh6), myosin light chain 2 (MYL2) and (tropomyosin 3) TPM3.

In a further aspect, the present invention provides a host cell or cell free expression system comprising an expression vector according to the invention. This may be for purposes of producing said polypeptide or for the purpose of advanced cell therapy techniques. The latter may involve isolation and manipulation of a patient's own cells to produce a desired alteration, before re-delivery to the patient. The host cell may be mammalian, bacterial, yeast, plant or insect derived. 'Mammalian' is taken to include cells from human, feline, porcine, simian, canine, murine and rat origin and may include the use of muscle cells, hepatocytes, adipocytes and cells of the pancreas, such as α , β and δ cells. Conveniently Chinese hamster ovary (CHO) or Human embryonic kidney (HEK) cells may be utilised but any other suitable host cell may be used as would be understood by a person of skill in the art. Yeast systems which may be used include *Pichia pastoris*, *Kluyveromyces lactis* and *Saccharomyces cerevisiae*. Bacterial systems which would be appropriate for this purpose may include *Escherichia coli*, *Corynebacterium*, and *Pseudomonas fluorescens*. A cell free expression system may also be utilised wherein protein production is performed *in vitro*, using purified RNA polymerase, ribosomes, tRNA and ribonucleotides.

In a further aspect, the present invention provides a pharmaceutical composition comprising the isolated polypeptide or derivative or mimic, nucleic acid,

expression vector or host cell of the preceding aspects and embodiments in combination with a pharmaceutically acceptable carrier or excipient. The excipients and carriers may enhance stability of the pharmaceutically active component, improve the biopharmaceutical profile and patient acceptability as well as simplify the manufacturing process, as would be understood by a person of skill in the art. Examples of suitable carriers or excipients include; sterile water, olive oil, ethyl oleate, glycols carbohydrates, especially monosaccharides such as fructose, glucose and galactose; non-reducing disaccharides such as sucrose, lactose and trehalose; non-reducing oligosaccharides such as raffinose and melezitose; non reducing starch derived polysaccharides products such as maltodextrins, dextrans and cyclodextrins; and non-reducing alditols such as mannitol and xylitol. Further suitable excipients include cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). Mixtures of two or more of any of the above excipients are also envisaged. Specifically, it is envisaged that simple saline solutions may be used for this purpose. Formulations that the present invention may take include lyophilised formulations and depot formulations, whereby the depot injection is given subcutaneously, intradermal or intramuscularly. Specific encapsulation techniques may be used as a drug delivery device, for example, PLGA (polylactic-co-glycolic acid) microspheres.

The present invention also provides the pharmaceutical composition according to the preceding aspect for use in medicine. In particular, the pharmaceutical composition for use herein may be for use in treating, or in the prevention of, diabetes mellitus, insulin resistance, obesity, metabolic disorders, polycystic ovary syndrome, non-alcoholic fatty liver disease, retinopathy, neuropathy, nephropathy, Alzheimer's disease and/or cardiovascular disease in a subject in need thereof.

30

Pharmaceutical compositions may be in the form of liquids, solutions, suspensions, emulsions, elixirs, syrups, tablets, lozenges, granules, powders, capsules, cachets, pills, ampoules, suppositories, pessaries, ointments, gels,

pastes, creams, sprays, mists, foams, lotions, pills, boluses, electuaries, or aerosols.

The pharmaceutical compositions may be prepared as suitable according to the intended route of administration. Possible routes of administration of said pharmaceutical composition include oral, sublingual, rectal, topical, parenteral and intravenous injection administration. Preferably, the chosen route of administration would be a subcutaneous injection, also known as SC, SQ, sub-cu, sub-Q or subcut. The site of injection may be the upper arm, the abdomen, the thigh, the upper back or the upper buttock.

The dose of the present invention is envisaged to be in the range of 0.01 to 1 mg/kg. The dose may be a daily dose of 0.05 mg/kg but ideally is administered once a week. The dosing regime may involve a single dose or multiple doses. It is understood that the exact dose and dosing regime will be dependent on the disease in question.

The present invention also provides for the use of a composition comprising a fragment, derivative or variant of sortilin, or a sortilin mimetic as defined herein, in the manufacture of a medicament for treating or preventing diabetes mellitus, insulin resistance, obesity, metabolic disorders, polycystic ovary syndrome, non-alcoholic fatty liver disease, retinopathy, neuropathy, nephropathy, Alzheimer's disease and/or cardiovascular disease in a subject in need thereof, wherein the sortilin mimetic is not SorCS1, SorCS2, SorCS3 or SorLA.

The invention further provides a method of treating or preventing a condition selected from diabetes mellitus, insulin resistance, obesity, metabolic disorders, polycystic ovary syndrome, non-alcoholic fatty liver disease, retinopathy, neuropathy, nephropathy, Alzheimer's disease and/or cardiovascular disease in a subject in need thereof, the method comprising administering a composition comprising a fragment, derivative or variant of sortilin, or a sortilin mimetic as defined herein to the subject.

The present invention also includes a method of manufacturing polypeptides or fragments thereof according to the invention comprising the step of expressing the nucleic acid of the invention in a host cell or other suitable expression system as indicated herein.

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In order that the invention may be more clearly understood, embodiments thereof will now be described by way of example.

Examples

10 Example 1:

The percentage level of identity between hSORT1 and hSORCS1 were investigated by aligning the protein sequences. Alignment software used by the inventors can be accessed via Uniprot.org.

15 The data shows that between the human and murine forms of SORT1, there is a high level of homology (87 %). However, when comparing the homology within the Vps10p domain between hSORT1 and hSORCS1, it was found to be substantially lower (25 %) (Figure 1).

20 Example 2:

Sortilin and insulin receptor binding was investigated using surface plasmon resonance analysis.

Soluble sortilin in concentrations ranging from 50-500 nM was assayed for binding
25 to immobilized human insulin receptor (0.0609 pmol/mm²) and murine insulin receptor (0.0607 pmol/mm²) (Figure 2A and B). Sortilin showed dose-dependent binding to both the human and murine insulin receptor, with a K_d of approximately 40 nM. Insulin did not affect the binding between sortilin and the insulin receptor (Figure 2C), indicating the formation of a trimeric receptor complex. Co-
30 immunoprecipitation confirmed a physical interaction between sortilin and the human receptor with DSP crosslinker.

The data shows that sortilin and the insulin receptor are able to physically interact in a cell free system (Biacore). The interaction between sortilin and the insulin receptor does not impact on the binding of insulin to the insulin receptor.

5 **Example 3:**

RAP-purified soluble sortilin was tested in diabetic animal models (Db/Db) to investigate effects on plasma glucose levels, in steady state (basal fasting plasma glucose) and in dynamic state (IPGTT).

- 10 18 mice were ordered, aged 5 weeks at the point of delivery. The animals were allowed to acclimatise for 3 weeks prior to performing the experimental work. The animals were test fasted for 4 hrs and blood sampled 5 days before the experiment took place. The animals were randomised to either treatment or sham groups based on weight and plasma glucose levels. Following randomisation, the 18
- 15 db/db mice, now aged 8 weeks, were injected IP with 100 µg RAP-purified soluble sortilin (n=8) or saline (n=10) at 22:00 and at 08:00 the following morning. All animals were fasted from 22:00. The animals were subjected to an IPGTT at 09:00, with the dose of 1 mg/g BW in 200 mg/ml glucose (40 g = 200 µL) (Figure 3). The IPGTT curve showed a significant lower basal plasma glucose, and lower
- 20 IPGTT AUC, both with and without correction for baseline plasma glucose (t=0 min).

Example 4:

- 25 The RAP-purified construct has a C-terminal HIS-tag which may engage with the heparin-sulfate proteoglycans to inhibit its activity. Therefore, this interaction and the effects on plasma glucose levels were investigated.

- 20 mice were ordered, aged 5 weeks at delivery. The animals were allowed to acclimatise for 2 weeks prior to performing the experimental work. The animals
- 30 were test fasted for 4 hrs and sampled 5 days before the experiment took place. The animals were then randomised to either treatment or sham groups based on weight (approximately 30 g) and plasma glucose levels. The 20 db/db mice, now aged 7 weeks, were injected IP with 100 µg RAP-purified soluble sortilin and heparin (200 U/kg) (n=7) or without heparin (n=6), or saline (n=7) at 22:00 and at

08:00 the following morning. All animals were fasted from 22:00. The animals were subjected to an IPGTT at 09:00, with a dose of 1 mg/g BW in 200 mg/ml glucose (40 g = 200 ul) (Figure 4). The IPGTT curve showed a trend towards a lower basal plasma glucose, and lower IPGTT AUC, both total and baseline
5 corrected. There was an effect of RAP-purified sortilin and no effect of added heparin. Insulin response after glucose challenge was improved when animals were treated with soluble sortilin (+/- heparin).

HOMA1-IR (resistance index) is calculated as $(FPI \times FPG)/405 = \text{HOMA1-IR}$,
10 where FPI is fasting plasma insulin levels (mU/L), FPG is fasting plasma glucose (mg/dL) (Mather K. Am J Physiol Endocrinol Metab 296: E398–E399, 2009). QUICKI (sensitivity) Index is calculated as $1/(\log(FPI \text{ mU/L}) + \log(FPG \text{ mg/dL}))$ (Katz et al. JCEM 2000). Both QUICKI and HOMA1-IR indicates lower insulin resistance.

15

The data shows that RAP-purified soluble sortilin is active regardless of the presence of heparin during the glucose tolerance test.

Sequences referenced throughout the specification and forming part of the description.

SEQ ID NO: 1 (VPS10p Domain- isoform 1)

```

5   1  RGGRWRRSAP GEDEECGRVR DFVAKLANNT HQHVFDDLRLG SVSLSWVGDS
    51  TGVILVLTTF HVPLVIMTFG QSKLYRSEDY GKNFKDITDL INNTFIRTEF
    101 GMAIGPENSG KVVLTAEVSG GSRGGRIFRS SDFAKNFVQT DLPFHPLTQM
    151 MYSPQNSDYL LALSTENGLW VSKNFGGKWE EHKAVCLAK WGSNTIFFT
    201 TYANGSCKAD LGALELWRTS DLGKSFKTIG VKIYSFGLGG RFLFASVMAD
10  251 KDTTRRIHVS TDQGDWWSMA QLPSVGQEQF YSILAANDDM VFMHVDEPGD
    301 TGFGTIFTSD DRGIVYSKSL DRHLYTTTGG ETDFTNVTSL RGVYITSVLS
    351 EDNSIQTMIT FDQGGRWTHL RKPENSECDA TAKNKNECSL HIHASYSISQ
    401 KLNVPMAPLS EPNAVGVIA HGSVGDAISV MVPDVYISDD GGYSWTKMLE
    451 GPHYTYILDS GGIIVAIHS SRPINVIKFS TDEGQCWQTY TFTRDPIYFT
15  501 GLASEPGARS MNISIWGFTE SFLTSQWWSY TIDFKDILER

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SEQ ID NO: 2 (VPS10p Domain + 10CCa Domain- isoform 1)

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    1  RGGRWRRSAP GEDEECGRVR DFVAKLANNT HQHVFDDLRLG SVSLSWVGDS
20  51  TGVILVLTTF HVPLVIMTFG QSKLYRSEDY GKNFKDITDL INNTFIRTEF
    101 GMAIGPENSG KVVLTAEVSG GSRGGRIFRS SDFAKNFVQT DLPFHPLTQM
    151 MYSPQNSDYL LALSTENGLW VSKNFGGKWE EHKAVCLAK WGSNTIFFT
    201 TYANGSCKAD LGALELWRTS DLGKSFKTIG VKIYSFGLGG RFLFASVMAD
    251 KDTTRRIHVS TDQGDWWSMA QLPSVGQEQF YSILAANDDM VFMHVDEPGD
25  301 TGFGTIFTSD DRGIVYSKSL DRHLYTTTGG ETDFTNVTSL RGVYITSVLS
    351 EDNSIQTMIT FDQGGRWTHL RKPENSECDA TAKNKNECSL HIHASYSISQ
    401 KLNVPMAPLS EPNAVGVIA HGSVGDAISV MVPDVYISDD GGYSWTKMLE
    451 GPHYTYILDS GGIIVAIHS SRPINVIKFS TDEGQCWQTY TFTRDPIYFT
    501 GLASEPGARS MNISIWGFTE SFLTSQWWSY TIDFKDILER NCEEKDYTIW
30  551 LAHSTDPEY EDGCILGYKE QFLRLRKSSM CQNGRDYVVT KQPSICL

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SEQ ID NO: 3 (VPS10p Domain + 10CCb Domain- isoform 1)

```

    1  RGGRWRRSAP GEDEECGRVR DFVAKLANNT HQHVFDDLRLG SVSLSWVGDS
35  51  TGVILVLTTF HVPLVIMTFG QSKLYRSEDY GKNFKDITDL INNTFIRTEF
    101 GMAIGPENSG KVVLTAEVSG GSRGGRIFRS SDFAKNFVQT DLPFHPLTQM
    151 MYSPQNSDYL LALSTENGLW VSKNFGGKWE EHKAVCLAK WGSNTIFFT
    201 TYANGSCKAD LGALELWRTS DLGKSFKTIG VKIYSFGLGG RFLFASVMAD
    251 KDTTRRIHVS TDQGDWWSMA QLPSVGQEQF YSILAANDDM VFMHVDEPGD
40  301 TGFGTIFTSD DRGIVYSKSL DRHLYTTTGG ETDFTNVTSL RGVYITSVLS
    351 EDNSIQTMIT FDQGGRWTHL RKPENSECDA TAKNKNECSL HIHASYSISQ
    401 KLNVPMAPLS EPNAVGVIA HGSVGDAISV MVPDVYISDD GGYSWTKMLE
    451 GPHYTYILDS GGIIVAIHS SRPINVIKFS TDEGQCWQTY TFTRDPIYFT
    501 GLASEPGARS MNISIWGFTE SFLTSQWWSY TIDFKDILER CSLEDFLCDF
45  551 GYYRPENDSK CVEQPELKGH DLEFCLYGRE EHLTTNGYRK IPGDKCQGGV
    601 NPVREVKDLK KKCTSNFLSP EKQ

```

SEQ ID NO: 4 (VPS10p Domain + 10CCa Domain + 10CCb Domain- isoform 1)

```

50  1  RGGRWRRSAP GEDEECGRVR DFVAKLANNT HQHVFDDLRLG SVSLSWVGDS
    51  TGVILVLTTF HVPLVIMTFG QSKLYRSEDY GKNFKDITDL INNTFIRTEF
    101 GMAIGPENSG KVVLTAEVSG GSRGGRIFRS SDFAKNFVQT DLPFHPLTQM
    151 MYSPQNSDYL LALSTENGLW VSKNFGGKWE EHKAVCLAK WGSNTIFFT
    201 TYANGSCKAD LGALELWRTS DLGKSFKTIG VKIYSFGLGG RFLFASVMAD
55  251 KDTTRRIHVS TDQGDWWSMA QLPSVGQEQF YSILAANDDM VFMHVDEPGD

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301 TGFGTIFTSD DRGIVYSKSL DRHLYTTTGG ETDFTNVTSL RGVYITSVLS
 351 EDNSIQTMIT FDQGGRWTHL RKPENSECDA TAKNKNECSL HIHASYSISQ
 401 KLNVPMAPLS EPNAVGVIA HGSVGDAISV MVPDVYISDD GGYSWTKMLE
 451 GPHYTYILDS GGIIVAIHS SRPINVIKFS TDEGQCWQTY TFTRDPIYFT
 5 501 GLASEPGARS MNISIWGFTE SFLTSQWWSY TIDFKDILER NCEEKDYTIW
 551 LAHSTDPEDY EDGCILGYKE QFLRLRKSSM CQNGRDYVVT KQPSICLCSL
 601 EDFLCDFGY YRPENDSKCVE QPELKGHDLE FCLYGREEHL TTNGYRKIPG
 651 DKCQGGVNPV REVKDLKKKC TSNFLSPEKQ

10 SEQ ID NO: 5 (10CCa Domain- isoform 1)

1 NCEEKDYTIW LAHSTDPEDY EDGCILGYKE QFLRLRKSSM CQNGRDYVVT
 51 KQPSICL

15 SEQ ID NO: 6 (10CCb Domain- isoform 1)

1 CSLEDFLCDF GYYRPENDSK CVEQPELKGH DLEFCLYGRE EHLTTNGYRK
 51 IPGDKCQGGV NPVREVKDLK KKCTSNFLSP EKQ

20 SEQ ID NO: 7 (10CCa + 10CCb Domain- isoform 1)

1 NCEEKDYTIW LAHSTDPEDY EDGCILGYKE QFLRLRKSSM CQNGRDYVVT
 51 KQPSICLCSL EDFLCDFGY YRPENDSKCVE QPELKGHDLE FCLYGREEHL
 101 TTNGYRKIPG DKCQGGVNPV REVKDLKKKC TSNFLSPEKQ

25

SEQ ID NO: 8 (IST218 after furin site plus HIS tag- isoform 1)

1 SAPGEDEECG RVRDFVAKLA NNTHQHVFDL LRGSVSLSWV GDSTGVILVL
 51 TTFHVPLVIM TFGQSKLYRS EDYGNFKDI TDLINNTFIR TFGMAIGPE
 30 101 NSGKVVLTAE VSGGSRGGRI FRSSDFAKNF VQTDLPFHPL TQMMYSPQNS
 151 DYLLALSTEN GLWWSKNFGG KWEEIHKAVC LAKWGSNTI FFTTYANGSC
 201 KADLGALELW RTSDLGKSFK TIGVKIYSFG LGGRFLFASV MADKDTTRRI
 251 HVSTDQGDW SMAQLPSVGQ EQFYSLAAN DDMVFMHVDE PGDTGFGTIF
 301 TSDDRIGIVYS KSLDRHLYTT TGGETDFTNV TSLRGVYITS VLSEDNSIQT
 35 351 MITFDQGGRW THLRKPENSE CDATAKNKNE CSLHIHASYS ISQKLNVPMA
 401 PLSEPNVAVI VIAHGSVGDA ISVMVPDVYI SDDGGYSWTK MLEGPHYTYI
 451 LDSGGIIVAI EHSSRPINVI KFSTDEGQCW QTYTFTRDPI YFTGLASEPG
 501 ARSMNISIWG FTESFLTSQW VSYTIDFKDI LERNCEEKDY TIWLAHSTDP
 551 EDYEDGCILG YKEQFLRLRK SSMCQNGRDY VTKQPSICL CSLEDFLCDF
 40 601 GYYRPENDSK CVEQPELKGH DLEFCLYGRE EHLTTNGYRK IPGDKCQGGV
 651 NPVREVKDLK KKCTSNFLSP EKQNSKNSH HHHHH

SEQ ID NO: 9 (IST218 after furin site minus HIS tag- isoform 1)

45 1 SAPGEDEECG RVRDFVAKLA NNTHQHVFDL LRGSVSLSWV GDSTGVILVL
 51 TTFHVPLVIM TFGQSKLYRS EDYGNFKDI TDLINNTFIR TFGMAIGPE
 101 NSGKVVLTAE VSGGSRGGRI FRSSDFAKNF VQTDLPFHPL TQMMYSPQNS
 151 DYLLALSTEN GLWWSKNFGG KWEEIHKAVC LAKWGSNTI FFTTYANGSC
 201 KADLGALELW RTSDLGKSFK TIGVKIYSFG LGGRFLFASV MADKDTTRRI
 50 251 HVSTDQGDW SMAQLPSVGQ EQFYSLAAN DDMVFMHVDE PGDTGFGTIF
 301 TSDDRIGIVYS KSLDRHLYTT TGGETDFTNV TSLRGVYITS VLSEDNSIQT
 351 MITFDQGGRW THLRKPENSE CDATAKNKNE CSLHIHASYS ISQKLNVPMA
 401 PLSEPNVAVI VIAHGSVGDA ISVMVPDVYI SDDGGYSWTK MLEGPHYTYI
 451 LDSGGIIVAI EHSSRPINVI KFSTDEGQCW QTYTFTRDPI YFTGLASEPG
 55 501 ARSMNISIWG FTESFLTSQW VSYTIDFKDI LERNCEEKDY TIWLAHSTDP
 551 EDYEDGCILG YKEQFLRLRK SSMCQNGRDY VTKQPSICL CSLEDFLCDF
 601 GYYRPENDSK CVEQPELKGH DLEFCLYGRE EHLTTNGYRK IPGDKCQGGV

651 NPVREVKDLK KKCTSNFLSP EKQNSKSNS

SEQ ID NO: 10 (SKT1 after furin site plus HIS tag + TEV site- isoform 1)

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5   1   SAPGHHHHHH HENLYFQSED EECGRVRDFV AKLANNTHQH VFDDLGRGSVS
    51  LSWVGDSTGV ILVLTTFHVP LVIMTFGQSK LYRSEDYGKN FKDITDLINN
    101 TFIREFGMA IGPENSGKV LTAEVSGGSR GGRIFRSSDF AKNFVQTDLP
    151 FHPLTQMMYS PQNSDYLLAL STENGLWWSK NFGGKWEEIH KAVCLAKWGS
    201 DNTIFFTTYA NGSCKADLGA LELWRTSDLG KSFKTIGVKI YSFGLGGRFL
10  251 FASVMADKDT TRRIHVSTDQ GDTWSMAQLP SVGQEQFYSI LAANDDMVFM
    301 HVDEPGDTGF GTIFTSDDRQ IVYSKSLDRH LYTTTGGETD FTNVTSLRGV
    351 YITSVLSEDN SIQTMITFDQ GGRWTHLRKP ENSECDATAK NKNECSLHIH
    401 ASYSISQKLN VPMAPLSEPN AVGIVIAHGS VGDAISVMVP DVYISDDGGY
    451 SWTKMLEGPH YYTILDSSGI IVAIEHSSRP INVIKFSTDE GQCWQTYTFT
15  501 RDPYFTGLA SEPGARSMNI SIWGFTEFL TSQWWSYTID FKDILERNCE
    551 EKDYTIWLAH STDPEDYEDG CILGYKEQFL RLRKSSMCQN GRDYVVTQKP
    601 SICLCSLEDF LCDFGYYRPE NDSKCVEQPE LKGHDLEFCL YGREEHLTTN
    651 GYRKIPGDKC QGGVNPVREV KDLKKKCTSN

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20 SEQ ID NO: 11 (SKT1 after furin site minus HIS tag + TEV site- isoform 1)

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    1   EDEECGRVRD FVAKLANNTH QHVDDLGRS VLSWVG DST GVILVLTTFH
    51  VPLVIMTFGQ SKLYRSEDYG KNFKDITDLI NNTFIREFG MAIGPENSGK
    101 VVLTAEVSGG SRGGRIFRSS DFAKNFVQTD LPFHPLTQMM YSPQNSDYLL
25  151 ALSTENGLWV SKNFGGKWEE IHKAVCLAKW GSDNTIFFTT YANGSCKADL
    201 GALELWRTSD LGKSFKTIGV KIYSFGLGGR FLFASVMADK DTTTRRIHVST
    251 DQGDWTSMAQ LPSVGQEQFY SILAANDDMV FMHVDEPGDT GFGTIFTSDD
    301 RGIVYSKSLD RHLYTTTGGE TDFTNVTSLR GVIYITSVLSE DNSIQTMITF
    351 DQGGRWTHLR KPENSECDAT AKNKNECSLH IHASYSISQK LNVPMAPLSE
30  401 PNAVGIVIAH GSVGDAISVM VPDVYISDDG GYSWTKMLEG PHYTYTILDSG
    451 GIIVAEHSS RPINVIKFST DEGQCWQTYT FTRDPIYFTG LASEPGARSM
    501 NISIWGFTE FLTSQWWSYT IDFKDILERN CEEKDYTIWL AHSTDPEDYE
    551 DGCILGYKEQ FLRLRKSSMC QNGRDYVVTQ QPSICLCSLE DFLCDFGYYR
    601 PENDSKCVEQ PELKGHDLEF CLYGREEHLT TNGYRKIPGDKC QGGVNPVR
35  651 EVKDLKKKCT SN

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SEQ ID NO: 12 (full length sortilin- isoform 1)

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    1   MERPWGAADG LSRWPHGLGL LLLLQLLPPS TLSQDRLDAP PPPAAPLPRW
40  51  SGPIGVSWGL RAAAAGGAFP RGGRWRRSAP GEDEECGRVR DVAKLANNT
    101 HQHVFDLGRG SVLSWVGDS TGVILVLTTF HVPLVIMTFG QSKLYRSEDY
    151 GKNFKDITDL INNTFIREFG MAIGPENSG KVVLTAEVSG GSRGGRIFRS
    201 SFAKNFVQTD LPPFHPLTQM MYSPQNSDY LALSTENGLW VSKNFGGKWE
    251 EIHKAVCLAK WGSNTIFFTT TYANGSCKAD LGALELWRTS DLGKSFKTIG
45  301 VKIYSFGLGG RFLFASVMAD KDTTRRIHVS TDQGDWTSMA QLPSVGQEQF
    351 YSILAANDDM VFMHVDEPGD TGFGTIFTS DRGIVYSKSL DRHLYTTTG
    401 ETDFTNVTSL RGVIYITSVLS EDNSIQTMIT FDQGGRWTHL RKPENSECDA
    451 TAKNKNECSL HIHASYSISQ KLVNPMAPLS EPNAVGIVIA HGSVGDAISV
    501 MVPDVYISDD GGYSWTKMLE GPHYTYTILDS GGIIVAEHS SRPINVIKFS
    551 TDEGQCWQTY TTRDPIYFT GLASEPGARS MNISIWGFTE SFLTSQWWSY
    601 TIDFKDILER NEEKDYTIW LAHSTDPEDY EDGCILGYKE QFLRLRKSSM
    651 CQNGRDYVVT KQPSICLCSL EDFLCDFGYY RPENDSKCVE QPELKGHDLE
    701 FCLYGREEHL TTNGYRKIPG DKCQGGVNPV REVKDLKKKC TSNFLSPEKQ
    751 NSKSNSVPII LAIVGLMLVT VVAGVLIVKK YVCGGRFLVH RYSVLQQHAE
55  801 ANGVGDVDAL DTASHTNKSG YHDDSDDELL E

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SEQ ID NO: 13 (full length sortilin- isoform 2)

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1  MERPWGAADG LSRWPHGLGL LLLLQLLPPS TLSQDRLDAP PPPAAPLPRW
5  51  SGPIGVSWGL RAAAAGGAFP RGGRWRRSAP GEDEECGRVR DFVAKLANNT
101 HQHVFDLLRG SVLSWVGDS TGVILVLTTF HVPLVIMTFG QSKLYRSEDY
151 GKNFKDITDL INNTFIRTEF GMAIGPENSG KVVLTAEVSG GSRGGRIFRS
201 SDFAKNFVQT DLPFHPLTQM MYSPQNSDYL LALSTENGLW VSKNFGGKWE
251 EHKAVCLAK WGSNTIFFT TYANGSCTDL GALELWRTSD LGKSFKTIGV
10  301 KIYSFGLGGR FLFASVMADK DTTTRRIHVST DQGDWWSMAQ LPSVGQEQFY
351 SILAANDDMV FMHVDEPGDT GFGTIFTSDD RGIVYSKSLD RHLYTTTGGE
401 TDFTNVTSLR GVIYITVLSE DNSIQTMITF DQGGRWTHLR KPENSECDAT
451 AKNKNECSLH IHASYSISQK LNVPMAPLSE PNAVGIVIAH GSVGDAISVM
501 VPDVYISDDG GYSWTKMLEG PHYITILDSG GIIVAIHSS RPINVIKFS
15  551 DEGQCWQTYT FTRDPIYFTG LASEPGARSM NISIWGFTES FLTSQWWSYT
601 IDFKDILERN CEEKDYTIWL AHSTDPEDYE DGCILGYKEQ FLRLRKSSVC
651 QNGRDYVVK QPSICLCSLE DFLCDFGYR PENDSKCSEQ PELKGHDLEF
701 CLYGREEHLT TNGYRKIPGD KCQGGVNPVR EVKDLKKKCT SNFLSPEKQN
751 SKNSVPIIL AIVGLMLVT VAGVLIVKKY VCGGRFLVHR YSVLQQHAEA
20  801 NGVDGVDALD TASHTNKGSGY HDDSDEDLLE

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SEQ ID NO: 14 (VPS10p Domain- isoform 2)

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1  RGGRWRRSAP GEDEECGRVR DFVAKLANNT HQHVFDLLRG SVLSWVGDS
51  TGVILVLTTF HVPLVIMTFG QSKLYRSEDY GKNFKDITDL INNTFIRTEF
25  101 GMAIGPENSG KVVLTAEVSG GSRGGRIFRS SDFAKNFVQT DLPFHPLTQM
151 MYSPQNSDYL LALSTENGLW VSKNFGGKWE EHKAVCLAK WGSNTIFFT
201 TYANGSCTDL GALELWRTSD LGKSFKTIGV KIYSFGLGGR FLFASVMADK
251 DTTTRRIHVST DQGDWWSMAQ LPSVGQEQFY SILAANDDMV FMHVDEPGDT
300 GFGTIFTSDD RGIVYSKSLD RHLYTTTGGE TDFTNVTSLR GVIYITVLSE
30  351 DNSIQTMITF DQGGRWTHLR KPENSECDAT AKNKNECSLH IHASYSISQK
400 LNVPMAPLSE PNAVGIVIAH GSVGDAISVM VPDVYISDDG GYSWTKMLEG
401 PHYITILDSG GIIVAIHSS RPINVIKFS DEGQCWQTYT FTRDPIYFTG
451 LASEPGARSM NISIWGFTES FLTSQWWSYT IDFKDILER

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35 SEQ ID NO: 15 (VPS10p Domain + 10CCa Domain- isoform 2)

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1  RGGRWRRSAP GEDEECGRVR DFVAKLANNT HQHVFDLLRG SVLSWVGDS
51  TGVILVLTTF HVPLVIMTFG QSKLYRSEDY GKNFKDITDL INNTFIRTEF
101 GMAIGPENSG KVVLTAEVSG GSRGGRIFRS SDFAKNFVQT DLPFHPLTQM
40  151 MYSPQNSDYL LALSTENGLW VSKNFGGKWE EHKAVCLAK WGSNTIFFT
201 TYANGSCTDL GALELWRTSD LGKSFKTIGV KIYSFGLGGR FLFASVMADK
251 DTTTRRIHVST DQGDWWSMAQ LPSVGQEQFY SILAANDDMV FMHVDEPGDT
300 GFGTIFTSDD RGIVYSKSLD RHLYTTTGGE TDFTNVTSLR GVIYITVLSE
351 DNSIQTMITF DQGGRWTHLR KPENSECDAT AKNKNECSLH IHASYSISQK
45  400 LNVPMAPLSE PNAVGIVIAH GSVGDAISVM VPDVYISDDG GYSWTKMLEG
401 PHYITILDSG GIIVAIHSS RPINVIKFS DEGQCWQTYT FTRDPIYFTG
451 LASEPGARSM NISIWGFTES FLTSQWWSYT IDFKDILERN CEEKDYTIWL
501 AHSTDPEDYE DGCILGYKEQ FLRLRKSSVC QNGRDYVVK QPSICL

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50 SEQ ID NO: 16 (VPS10p Domain + 10CCb Domain- isoform 2)

```

1  RGGRWRRSAP GEDEECGRVR DFVAKLANNT HQHVFDLLRG SVLSWVGDS
51  TGVILVLTTF HVPLVIMTFG QSKLYRSEDY GKNFKDITDL INNTFIRTEF
101 GMAIGPENSG KVVLTAEVSG GSRGGRIFRS SDFAKNFVQT DLPFHPLTQM
55  151 MYSPQNSDYL LALSTENGLW VSKNFGGKWE EHKAVCLAK WGSNTIFFT
201 TYANGSCTDL GALELWRTSD LGKSFKTIGV KIYSFGLGGR FLFASVMADK

```

251 DTTTRRIHVST DQGDWTSMAQ LPSVGQEQFY SILAANDDMV FMHVDEPGDT
 300 GFGTIFTSDD RGIVYSKSLD RHLYTTTGGE TDFTNVTSLR GVIYTSVLSE
 351 DNSIQTMITF DQGGRWTHLR KPENSECDAT AKNKNECSLH IHASYSISQK
 400 LNVPMAPLSE PNAVGIVIAH GSVGDAISVM VPDVYISDDG GYSWTKMLEG
 5 401 PHYTTILDSG GIIVAIHSS RPINVIKFST DEGQCWQTYT FTRDPIYFTG
 451 LASEPGARSM NISIWGFTES FLTSQWWSYT IDFKDILERC SLEDFLCDFG
 501 YYRPENDSKC VEQPELKGHD LEFCLYGREE HLTNGYRKI PGDKCQGGVN
 551 PVREVKDLKK KCTSNFLSPE KQ

10 SEQ ID NO: 17 (VPS10p Domain + 10CCa Domain + 10CCb Domain- isoform 2)

1 RGGRWRRSAP GEDEECGRVR DFVAKLANNT HQHVFDLRLG SVLSWVGDS
 51 TGVILVLTTF HVPLVIMTFG QSKLYRSEDY GKNFKDITDL INNTFIRTEF
 15 101 GMAIGPENSG KVVLTAEVSG GSRGGRIFRS SDFAKNFVQT DLPFHPLTQM
 151 MYSPQNSDYL LALSTENGLW VSKNFGGKWE EHKAVCLAK WGSNTIFFT
 201 TYANGSCTDL GALELWRTSD LGKSFKTIGV KIYSFGLGGR FLFASVMADK
 251 DTTTRRIHVST DQGDWTSMAQ LPSVGQEQFY SILAANDDMV FMHVDEPGDT
 300 GFGTIFTSDD RGIVYSKSLD RHLYTTTGGE TDFTNVTSLR GVIYTSVLSE
 20 351 DNSIQTMITF DQGGRWTHLR KPENSECDAT AKNKNECSLH IHASYSISQK
 400 LNVPMAPLSE PNAVGIVIAH GSVGDAISVM VPDVYISDDG GYSWTKMLEG
 401 PHYTTILDSG GIIVAIHSS RPINVIKFST DEGQCWQTYT FTRDPIYFTG
 451 LASEPGARSM NISIWGFTES FLTSQWWSYT IDFKDILERN CEEKDYTIWL
 501 AHSTDPEDYE DGCILGYKEQ FLRLRKSSVC QNGRDYVVK QPSICLCSLE
 25 551 DFLCDFGYR PENDSKCVEQ PELKGHDLEF CLYGREEHLT TNGYRKIPGD
 601 KCQGGVNPVR EVKDLKKKCT SNFLSPEKQ

SEQ ID NO: 18 (10CCa Domain- isoform 2)

30 1 NEEKDYTIW LAHSTDPEDY EDGCILGYKE QFLRLRKSSV CQNGRDYVVT
 51 KQPSICL

SEQ ID NO: 19 (10CCa Domain + 10CCb Domain- isoform 2)

35 1 NEEKDYTIW LAHSTDPEDY EDGCILGYKE QFLRLRKSSV CQNGRDYVVT
 51 KQPSICLCSL EDFLCDFGYR PENDSKCVE QPELKGHDLE FCLYGREEHL
 101 TTNGYRKIPG DKCQGGVNPV REVKDLKKKC TSNFLSPEKQ

40 SEQ ID NO: 20 (IST218 after furin site plus HIS tag- isoform 2)

1 SAPGEDEECG RVRDFVAKLA NNTHQHVFDL LRGSVLSWV GDSTGVILVL
 51 TTFHVPLVIM TFGQSKLYRS EDYGKNFKDI TDLINNTFIR TFGMAIGPE
 101 NSGKVVLTAE VSGGSRGGRI FRSSDFAKNF VQTDLPFHPL TQMMYSPQNS
 45 151 DYLLALSTEN GLWWSKNFGG KWEEIHKAVC LAKWGSNTI FFTTYANGSC
 201 TDLGALELWR TSDLGKSFKT IGVKIYSFGL GGRFLFASVM ADKDTTRRIH
 251 VSTDQGDWTS MAQLPSVGQE QFYSILAAND DMVFMHVDEP GDTGFGTIFT
 301 SDDRGIYYSK SLDRHLYTTT GGETDFTNVT SLRGVYITSV LSEDNSIQTM
 351 ITFDQGGRWTHLRKPENSEC DATAKNKNEC SLHIHASYSI SQKLNVPMAP
 50 401 LSEPNVAVGIV IAHGSGVDI SVMVPDVYIS DDGGYSWTKM LEGPHYTTIL
 451 DSGGIIVAIH HSSRPINVIK FSTDEGQCWQ TYTFTRDPIY FTGLASEPGA
 501 RSMNISIWGF TESFLTSQWV SYTIDFKDIL ERNCEEKDYT IWLHSTDP
 551 DYEDGCILGY KEQFLRLRKS SVCQNGRDYV VTKQPSICLC SLEDFLCDFG
 601 YYRPENDSKC VEQPELKGHD LEFCLYGREE HLTNGYRKI PGDKCQGGVN
 55 651 PVREVKDLKK KCTSNFLSPE KQNSKNSHH HHHH

SEQ ID NO: 21 (IST218 after furin site minus HIS tag- isoform 2)

1 SAPGEDEECG RVRDFVAKLA NNTHQHVFD LRGSVLSWV GDSTGVILVL
 5 51 TTFHVPLVIM TFGQSKLYRS EDYGNFKDI TDLINNTFIR TFGMAIGPE
 101 NSGKVLTAE VSGGSRGGRI FRSSDFAKNF VQTDLPFHPL TQMMYSPQNS
 151 DYLLALSTEN GLWWSKNFGG KWEEIHKAVC LAKWGSNTI FFTTYANGSC
 201 TDLGALELWR TSDLGKSFKT IGVKIYSFGL GGRFLFASVM ADKDTTRRIH
 251 VSTDQGDWTS MAQLPSVGQE QFYSILAAND DMVFMHVDEP GDTGFGTIFT
 10 301 SDDRGIVYSK SLDRHLYTTT GGETDFTNVT SLRGVYITSV LSEDNSIQTM
 351 ITFDQGGRTW HLRKPENSEC DATAKNKNEC SLHIHASYSI SQKLNVPMP
 401 LSEPNAVGIIV IAHGSGVDI SVMVPDVYIS DDGGYSWTKM LEGPHYITIL
 451 DSGGIIVAIIE HSSRPINVIK FSTDEGQCWQ TYTFTTRDPIY FTGLASEPGA
 501 RSMNISIWGF TESFLTQWV SYTIDFKDIL ERNCEEKDYT IWLHSTDPE
 15 551 DYEDGCILGY KEQFLRLRS SVCQNGRDYV VTKQPSICLC SLEDFLCDFG
 601 YYRPENDSKC VEQPELKGHD LEFCLYGREE HLTNGYRKI PGDKCQGGVN
 651 PVREVKDLKK KCTSNFLSPE KQNSKSNS

SEQ ID NO: 22 (SKT1 after furin site plus HIS tag + TEV site- isoform 2)

20 1 SAPGHHHHHH HENLYFQSED EECGRVRDFV AKLANNTHQH VFDDLGRSVS
 51 LSWVGDSTGV ILVLTTFHVP LVIMTFGQSK LYRSEDYGN FDKITDLINN
 101 TFI RTEFGMA IGPENSGKV LTAEVSGGSR GGRIFRSSD AKNFVQTDLP
 151 FHPLTQMMYS PQNSDYLLAL STENGLWWSK NFGGKWEEIH KAVCLAKWGS
 25 201 DNTIFFTTYA NGCTDLGAL ELWRTSDLGK SFTIGVKIY SFGLGGRFLF
 251 ASVMADKDTT RRIHVSTDQG DTWSMAQLPS VGQEQFYSIL AANDDMVFMH
 301 VDEPGDTGFG TIFTSDDRGI VYSKSLDRHL YTTTGGETDF TNVTSLRGVY
 351 ITSVLSEDNS IQTMITFDQG GRWTHLRKPE NSECDAKKN KNECSLHIHA
 401 SYSISQKLNVP MAPLSEPNA VGIVIAHGSV GDAISVMVPD VYISDDGGYS
 30 451 WTKMLEGPHY YTILDSGGII VAIHSSRPV NVIKFSTDEG QCWQTYTFT
 501 DPIYFTGLAS EPGARSMNIS IWGFTESFLT SQWWSYTIDF KDILERNCEE
 551 KDYTIWLAHS TDPEDYEDGC ILGYKEQFLR LKSSVCQNG RDYVVTQPS
 601 ICLCSLEDFL CDFGYYPEN DSKCQEPEL KGHDLFCLY GREEHLTTNG
 651 YRKIPGDKCQ GGVNPVREVK DLKKKCTSN

SEQ ID NO: 23 (SKT1 after furin site minus HIS tag + TEV site- isoform 2)

1 EDEECGRVRD FVAKLANNTH QHVFDLGRS VLSWVGDST GVILVLTTFH
 51 VPLVIMTFGQ SKLYRSEDYGN FDKITDLI NNTFIRTEFG MAIGPENSGK
 40 101 VVLTAEVSGG SRGGRIFRSS DFAKNFVQTD LPFHPLTQMM YSPQNSDYLL
 151 ALSTENGLWV SKNFGGKWEE IHKAVCLAKW GSDNTIFFTT YANGSCTDLG
 201 ALELWRTSDL GKSFTIGVK IYSFGLGGRF LFASVMADKD TTRRIHVSTD
 251 QGDTWSMAQL PSVGQEQFYS ILAANDDMVF MHVDEPGDTG FGIFTSDDR
 301 GIVYSKSLDR HLYTTTGGET DFTNVTSLRG VYITSVLSED NSIQTMITFD
 45 351 QGGRWTHLRK PENSECDATA KNKNECSLHI HASYSISQKL NVPMPAPLSEP
 401 NAVGIVIAHG SVGDAISVMV PDVYISDDGG YSWTKMLEGP HYYTILDSGG
 451 IIVAIHSSR PINVIKSTD EGQCWQTYTF TRDPIYFTGL ASEPARGSMN
 501 ISIWGFTESE LTSQWWSYTI DFKDILERNCEE KDYTIWLA HSTDPEYED
 551 GCILGYKEQF LRLRKSSVCQ NGRDYVVTQ PSICLCSLED FLCDFGYYP
 50 601 ENDSKCVQEP ELKGHDLEFC LYGREEHLTT NGYRKIPGDK CQGGVNPVRE
 651 VKDLKKKCTS N

SEQ ID NO: 24 (TEV cleavage site option 1)

5 1 ENLYFQG

SEQ ID NO: 25 (TEV cleavage site option 2)

10 1 ENLYFQS

SEQ ID NO: 26 (C terminal HIS tag)

15 1 HHHHHH

SEQ ID NO: 27 (N terminal HIS tag)

20 1 HHHHHHH

CLAIMS

1. A composition comprising a fragment, derivative or variant of sortilin, or a sortilin mimetic, for use in medicine, wherein the sortilin mimetic is not SorCS1, SorCS2, SorCS3 or SorLA.
5
2. The composition for use according to claim 1, wherein the composition is for use in treating or preventing diabetes mellitus, insulin resistance, obesity, metabolic disorders, polycystic ovary syndrome, non-alcoholic fatty liver disease, retinopathy, neuropathy, nephropathy, Alzheimer's
10 disease and/or cardiovascular disease in a subject in need thereof.
3. The composition for use according to claim 1 or 2, wherein said sortilin mimetic is an antibody, nanobody or aptamer.
- 15 4. The composition for use according to claim 1 or 2, wherein said fragment, derivative or variant comprises a VPS10p, 10CCa or 10CCb domain.
5. The composition for use according to claim 1, 2 or 4, wherein said fragment, derivative or variant of sortilin comprises the amino acid
20 sequence of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22 or SEQ ID NO: 23, or an amino acid
25 sequence having greater than 70 % homology to said amino acid sequence.
6. The composition for use according to any of claims 1 to 5, wherein said fragment, derivative or variant of sortilin, or sortilin mimetic, comprises an
30 additional moiety and/or a modification, optionally, wherein the additional moiety is a linker molecule and/or wherein the modification is PEGylation, glycosylation or acetylation.

7. The composition for use according to any of claims 1 to 6, wherein the fragment, derivative or variant of sortilin, or sortilin mimetic binds to an insulin receptor, preferably a human and/or murine insulin receptor.
- 5 8. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, 10 SEQ ID NO: 22 or SEQ ID NO: 23, or an amino acid sequence having greater than 70 % homology to said amino acid sequence, or a fragment thereof.
9. A nucleic acid encoding a polypeptide according to claim 8.
- 15 10. A nucleic acid that hybridises to a nucleic acid according to claim 9.
11. An expression vector comprising a nucleic acid according to claim 9 or 10.
- 20 12. A host cell or cell free expression system comprising an expression vector according to claim 11.
- 25 13. A pharmaceutical composition comprising an isolated polypeptide, nucleotide, vector or host cell according to any of claim 8, 9, 10, 11 or 12 and pharmaceutically acceptable carriers or excipients.
14. The pharmaceutical composition according to claim 13 for use in medicine.
- 30 15. The pharmaceutical composition for use according to claim 14, wherein the composition is for use in treating or preventing diabetes mellitus, insulin resistance, obesity, metabolic disorders polycystic ovary syndrome, non-alcoholic fatty liver disease, retinopathy, neuropathy, nephropathy, Alzheimer's disease and/or cardiovascular disease in a subject in need thereof.

Compare	Identities	Positives	Gaps	Comment
hSORT1 vs mSORT1	787/864 (87%)	787/864 (91%)	40/864 (4%)	Highly conserved in VPS10P.
hSORT1 vs hSORCS1	147/595 (25%)	278/595 (46%)	55/595 (9%)	Not highly conserved in VPS10P.

Figure 1

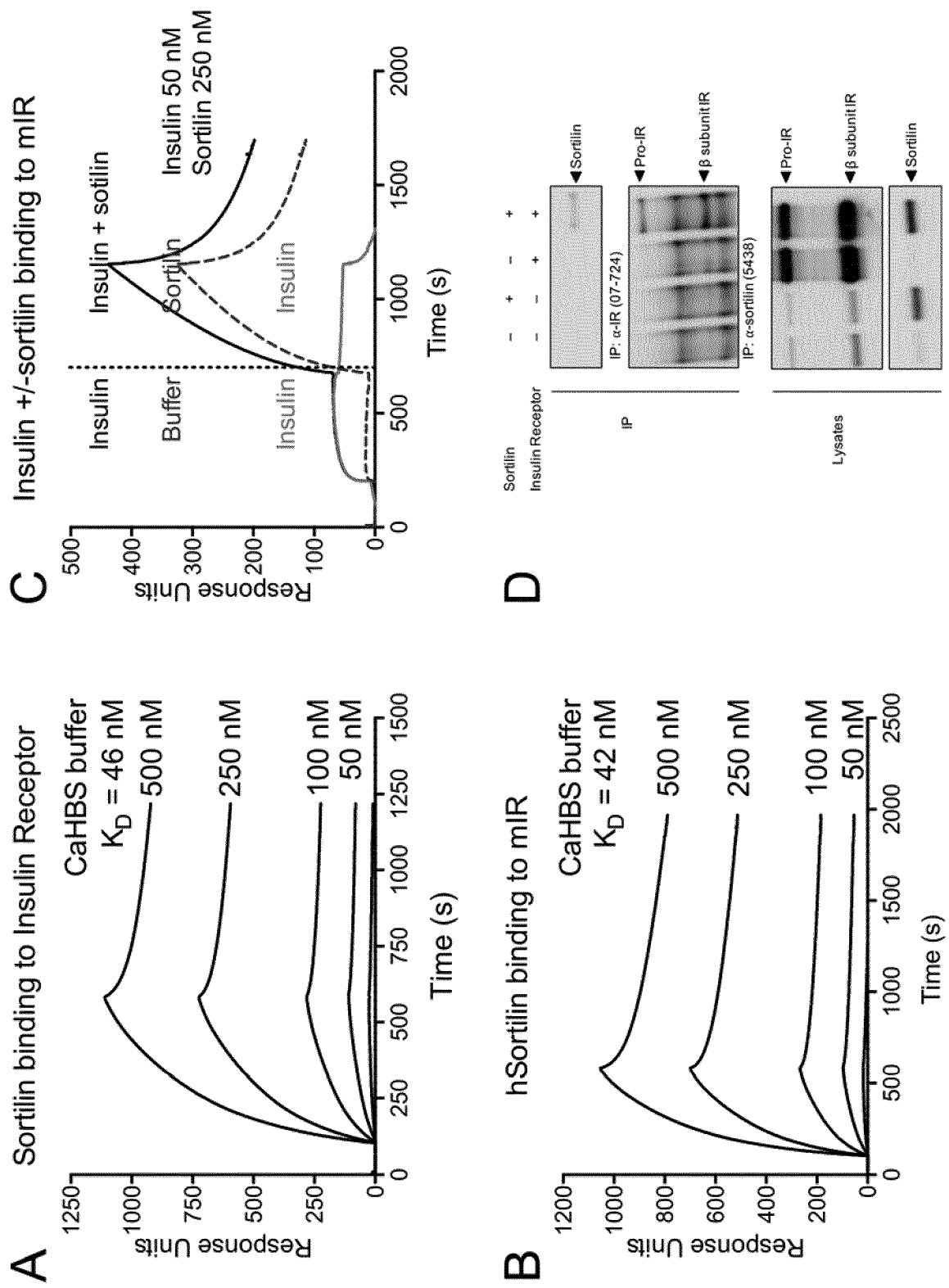


Figure 2

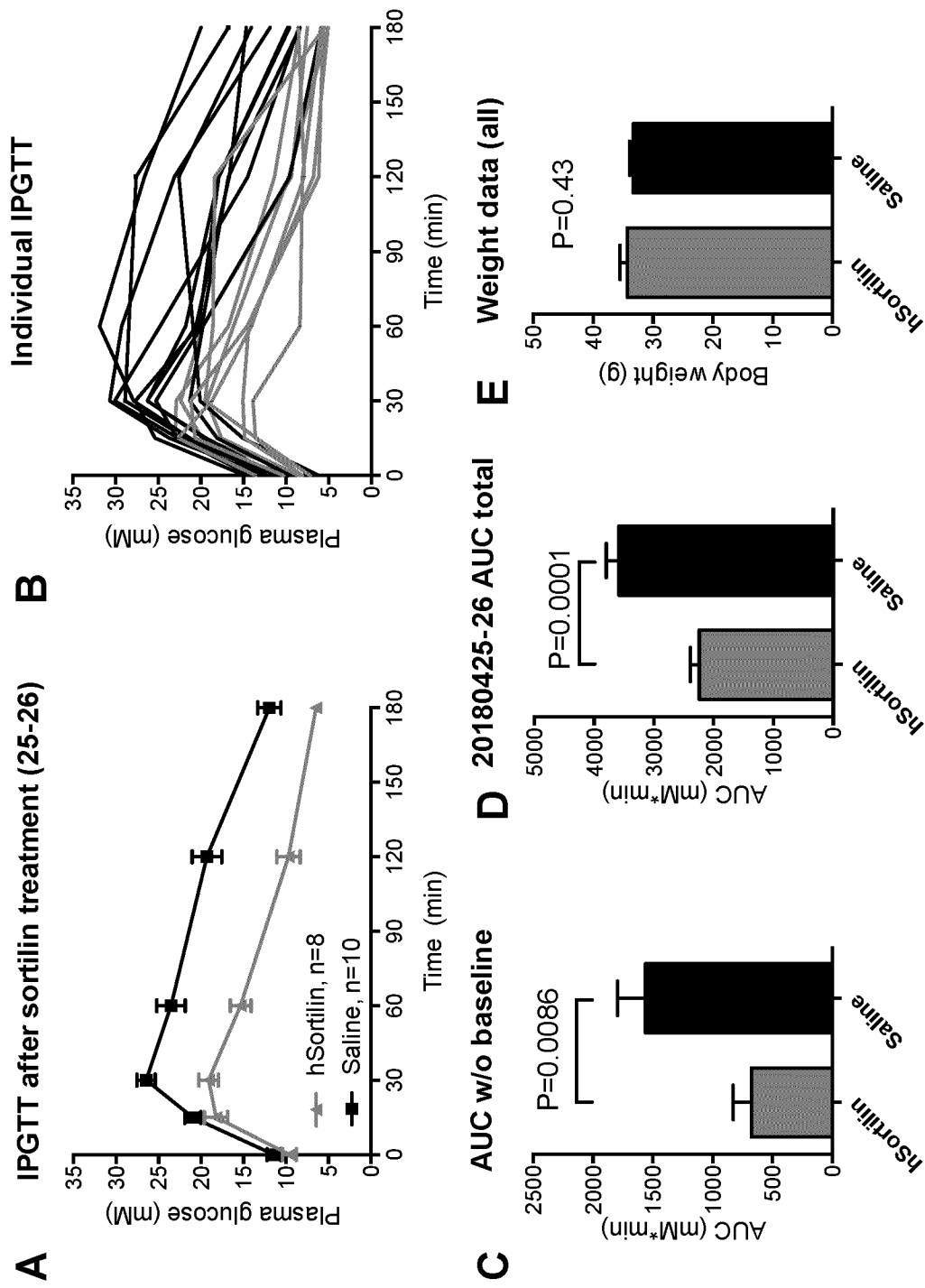


Figure 3

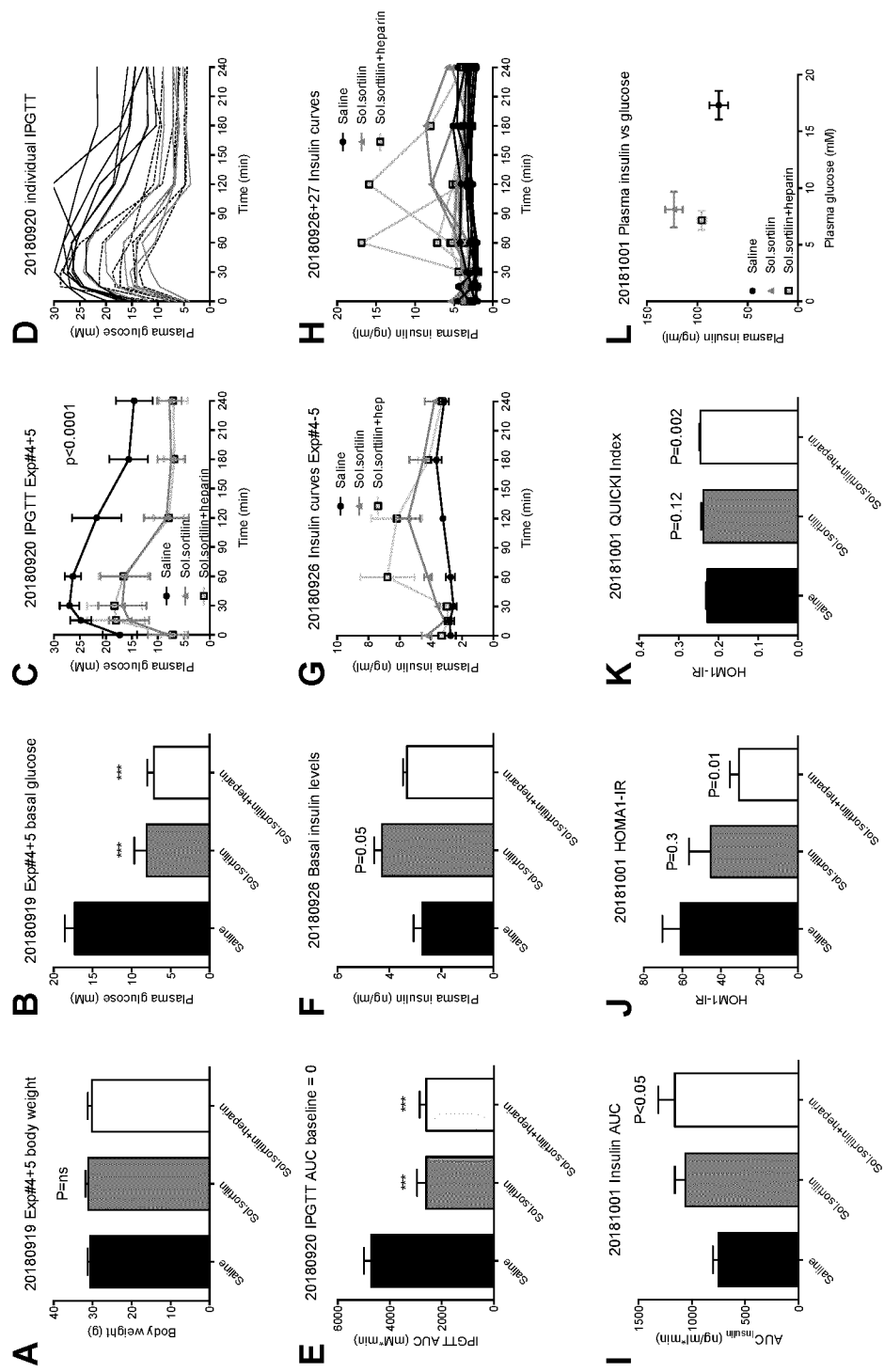


Figure 4
4/4

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/085100

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K38/17 C07K14/705 A61P3/10
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, Sequence Search, EMBASE, FSTA, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2017/014476 A1 (PEDERSEN KAREN-MARIE [DK] ET AL) 19 January 2017 (2017-01-19) par. 415-421, examples 31-33 -----	1-15
X	WO 2010/142296 A1 (UNIV AARHUS [DK]; PEDERSEN KAREN-MARIE [DK]; NYKJAER ANDERS [DK]) 16 December 2010 (2010-12-16) pages 4, 69, claims 33-39 -----	1-15
X	WO 2013/156031 A2 (UNIV AARHUS [DK]) 24 October 2013 (2013-10-24) examples 7-9 -----	1-15
A	WO 2012/174359 A1 (UNIV JOHNS HOPKINS [US]; POWELL JONATHAN DAVID [US]; XIAO BO [US]; WOR) 20 December 2012 (2012-12-20) the whole document ----- -/-	1-15



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

27 January 2020

Date of mailing of the international search report

05/02/2020

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/085100

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2006/042002 A2 (UNIV OREGON HEALTH & SCIENCE [US]; CLINTON GAIL M [US]; ROBERTS CHARLE) 20 April 2006 (2006-04-20) the whole document -----	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

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