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(73) Patenthaver: **Aarhus Universitet, Nordre Ringgade 1, 8000 Århus C, Danmark**

(72) Opfinder: **PEDERSEN, Karen-Marie, Vingevej 39D, Ã¿rum, 8830 Tjele, Danmark**
NYKJÃ¿R, Anders, Skolevangs Allé 1B, 8240 Risskov, Danmark

(74) Fuldmægtig i Danmark: **HØIBERG A/S, Adelgade 12, 1304 København K, Danmark**

(54) Benævnelse: **SorCS1-lignende middel til anvendelse til behandling af insulinresistens og sygdomme, som er forbundet dermed**

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DESCRIPTION

Field of invention

[0001] The present invention relates to the use of SorCS1-like agents, such as SorCS1 and fragments and variants thereof, for the preparation of a medicament for the treatment, reduction or delay of insulin resistance in patients. The invention furthermore relates to the use of SorCS1-like agents, such as SorCS1 and fragments and variants thereof for sensitizing insulin receptors. The invention also relates to the use of the SorCS1 knockout mouse as an animal model of insulin resistance.

Background of the invention

The insulin resistance syndrome.

[0002] The prevalence of metabolic disturbance, collectively known as metabolic syndrome or insulin resistance syndrome, has reached an epidemic proportion in industrialized countries. The insulin resistance syndrome refers to a constellation of findings, including glucose intolerance, obesity, an altered lipid profile (dyslipidemia) and hypertension, that promote the development of type 2 diabetes, cardiovascular disease, cancer, polycystic ovarian disease, and other disorders. In all of these disorders, a central component of the pathophysiology is insulin resistance. The underlying causes of this syndrome are overweight/obesity, physical inactivity and a series of currently not yet well-defined genetic polymorphisms (reviewed in 1+2). Lifestyle interventions and pharmacological treatment of the pathologies of the syndrome are only partially efficient and new therapeutic approaches are urgently needed.

Insulin and insulin resistance.

[0003] Insulin is a hormone produced by β-cells in the islets of Langerhans in the pancreas. Insulin release is stimulated as blood glucose levels rise and glucose is removed from the blood by insulin dependent stimulation of glucose transporters located in the cell membranes of target tissue, in particular in adipose tissue, skeletal muscle and liver. Insulin exerts its biological effects by binding to and activating the membrane-bound insulin receptor (IR), thereby initiating a cascade of intracellular signaling events, which regulates multiple biological processes such as glucose and lipid metabolism, gene expression, protein synthesis, and non-metabolic processes such as cell growth and differentiation. The diverse effects of IR activation are mediated through a multicomponent signaling complex that assembles upon binding of insulin. Thus, the intrinsic protein-tyrosine kinase activity of IR results in autophosphorylation of several tyrosine residues followed by recruitment and phosphorylation of several intracellular protein substrates including IR substrate (IRS) proteins and Scr-homolgy-2 containing (Shc) proteins. This initiates the activation of two main signalling pathways: the phosphatidylinositol 3-kinase (PI3K)-AKT/protein kinase B (PKB) pathway, which is responsible for most of the metabolic actions, including translocation of the glucose transporter GLUT4 to the cell membrane and stimulation of glycogen synthesis, and the Ras-mitogen-activated protein kinase (MAPK) pathway, which regulates expression of some genes and cooperates with the (PI3K)-AKT pathway to control cell growth and differentiation (reviewed in 3-8).

[0004] The ability of insulin to stimulate glucose disposal vary continuously throughout a population of apparently healthy persons, and a difference of ≥ 600% exists between the most insulin-sensitive and the most insulin resistance persons. However, the third of the population that is the most insulin resistant is at a much greater risk of developing several abnormalities and clinical syndromes, including type 2 diabetes, cardio vascular diseases, hypertension, stroke, non-alcoholic fatty liver, polycystic ovary disease, and certain forms of cancer (reviewed in 9)
Individuals are said to be 'insulin resistant', because their tissues behave as if there was insufficient insulin in the bloodstream as reflected by decreased insulin response and glucose uptake in liver, adipose tissue, and skeletal muscle. The first response to insulin resistance is a compensatory production and secretion of insulin to compensate for the body's decreased sensitivity, leading to hyperinsulinaemia. Thus, high insulin levels and a decreased responsiveness of tissue to the clearance of glucose from the bloodstream characterize insulin resistance. Insulin resistance is the primary event leading to a series of metabolic changes including compensatory hyperinsulinemia, dyslipidemia, decompensation of pancreatic beta-cells, and hyperglycemia (reviewed in 6-8).

Type 2 diabetes and insulin resistance.

[0005] Type-2 diabetes (non-insulin-dependent diabetes) is a complex and heterogeneous disorder associated with an increased risk for mortality as well as morbidity. The incidence is steadily increasing and the disease presently affects more than 150 million people worldwide making it a major public concern. The disorder is a prototypic complex polygenic disease with a strong heritable component but is also heavily influenced by environmental factors such as e.g. obesity. The pathogenesis of type 2 diabetes involves progressive development of insulin resistance in liver and peripheral tissue accompanied by defective insulin secretion from pancreatic beta cells leading to overt hyperglycaemia (an abnormally high amount of glucose levels in blood). The first response to insulin resistance is a compensatory production and secretion of insulin to compensate for the body's decreased sensitivity, leading to hyperinsulinaemia and rendering the individual prediabetic. However, when the pancreas of an insulin resistant individual is unable to produce sufficient hormone to compensate for the increased demand, the β-cell mass will ultimately be exhausted and degenerate leading to hyperglycemia and overt type-2 diabetes (reviewed in 4 and 5). Thus, type 2 diabetes only develops in subjects that are unable to sustain the β-cell compensatory insulin response. These subjects have "susceptible" as opposed to "robust" islets - a condition determined by genetic and/or acquired factors, ex obesity (fig.4).

[0006] Identification of a peptide/protein that could restore glucose metabolism and treat insulin resistance hold great promise as new therapeutic targets in the potentially combined treatment of type 2 diabetes, metabolic syndrome and other diseases characterised by insulin resistance.

The SorCS1 receptor.

[0007] SorCS1 is one of five members of the mammalian Vps10p-domain (Vps10p-D) receptor family, which also comprises Sortilin, SorLA, SorCS2, and SorCS3. They are all type-1 transmembrane receptors sharing the characteristic structural feature of an N-terminal Vps10p-D with high homology to Vps10p, a sorting protein in yeast (10). At present the physiological function(s) of the receptor family is unclear, but recent findings indicate that both Sortilin and SorLA play a crucial role as regulators of neuronal survival and death (11,12). Interestingly, Sortilin has also been associated with insulin-regulated glucose up-take as it may facilitate translocation of the glucose transporter GLUT4 from an intracellular compartment to the plasma membrane (13,14).

[0008] SorCS1 is unique among the Vps10p-D receptors as it exists in several distinct splice variants, denoted SorCS1- a, b, c, c+, and d, that encode identical extracellular and transmembrane parts, and cytoplasmic domains that differ in length and sequence (10, 11). The present inventors, and others have found that SorCS1, in addition to in the nervous system, is expressed in adipose tissue, skeletal muscle and β-cells of the pancreas; all tissues involved in glucose metabolism. Moreover, each splice variant exhibit a distinct tissue distribution as well as subcellular expression pattern suggesting that the tail-variants might be implicated in different biological activities (15-17).

Summary of the invention

[0009] The present inventors have studied the effect of SorCS1 and its different splice variants on the treatment of insulin resistance in mice, and the effect of SorCS1 and the different splice variants on insulin receptor expression using cell studies, and consequently in a main aspect the present invention relates to a SorCS1-like agent for use in treating insulin resistance and/or a disease associated with insulin resistance in an individual, wherein said agent is capable of binding to the insulin receptor (IR) at a SorCS1 binding site and being capable of sensitization of an insulin receptor.

[0010] SorCS1 is one of five members of the mammalian Vps10p-domain (Vps10p-D) receptor family, which also comprises Sortilin, SorLA, SorCS2, and SorCS3 (Fig.1). Murine SorCS1 is unique among the Vps10p-D receptors as it exists in several distinct splice variants, denoted mSorCS1- a, b, c, c+, and d (Fig.2)

[0011] In brief, the investors have demonstrated that in knockout mice lacking all splice variants of mSorCS1 the old male mice are hyperinsulimic but prediabetic, whereas old SorCS1 knockout female mice are hyperglycaemic and hyperinsulimic, thus both becoming diabetic with age, as a consequence of insulin resistance in the transgenic mice. Furthermore, the investors have shown that murine SorCS1 binds the insulin receptor and that mSorCS1 regulates the expression of the insulin receptor.

[0012] Furthermore, the invention relates to a nucleic acid sequence encoding a polypeptide as defined above for use in the treatment of insulin resistance or diseases associated with insulin resistance in an individual, as well as a vector, a host cell and a packaging cell line comprising the nucleic acid for treatment purposes.

[0013] In a further aspect the invention relates to a pharmaceutical composition comprising one or more of the agent as defined above; or the isolated nucleic acid sequence as defined above; or the the expression vector as defined above; or a composition of host cells as defined above; or a packaging cell line as defined above, or a combination thereof.

[0014] Furthermore, in another aspect the present invention relates to a method of treatment of insulin resistance or diseases associated with insulin resistance, said method comprising administering to an individual in need thereof a therapeutically effective amount of the agent as defined above; or the isolated nucleic acid sequence as defined above; or the the expression vector as defined above; or a composition of host cells as defined above; or a packaging cell line as defined above, or a combination thereof.

[0015] In another aspect, the present invention relates to a method of upregulating an insulin receptor or a fragment or variant thereof, in a patient in need thereof, said method comprising administering to an individual in need thereof a therapeutically effective amount of the agent as defined above; or the isolated nucleic acid sequence as defined above; or the the expression vector as defined above; or a composition of host cells as defined above; or a packaging cell line as defined above, or a combination thereof.

[0016] Disclosed is a method comprising administering a Vps1 0p-domain receptor selected from the group consisting of:

1. a) SorCS1
2. b) SorCS2
3. c) SorCS3
4. d) Sortilin and
5. e) SorLA,

thus being useful in a method of treatment of insulin resistence or diseases associated with insulin resistance.

[0017] The diseases associated with insulin resistance are in particular selected from the group consisting of insulin resistance syndrome, Type 2 diabetes mellitus, impaired glucose tolerance, the metabolic syndrome, hyperglycemia, hyperinsulinemia, arteriosclerosis, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, dyslipidemia, obesity, central obesity, polycystic ovarian syndrome, hypercoagulability, hypertension, microalbuminuria, insulin resistance syndrome (IRS), Type 2 diabetes mellitus, impaired glucose tolerance, the metabolic syndrome, hyperglycemia, and hyperinsulinemia.

[0018] Disclosed is a kit in parts comprising:

- a pharmaceutical composition as defined herein,
- a medical instrument or other means for administering said pharmaceutical composition,
- instructions on how to use the kit in parts.

[0019] In a further aspect, the present invention relates to a screening method employing a transgenic knock-out mouse in which the endogenous Vps10p-domain receptor SorCS1 genes have been disrupted to abolish expression of a functional SorCS1 receptor, and wherein said mouse exhibits a reduced response to insulin relative to a non-transgenic control mouse. In a further important aspect, the invention relates to a method for screening for the ability of the SorCS1-like agent to reduce blood glucose levels, said method comprising the steps of:

1. a) providing a first and a second transgenic mouse;
2. b) administering to said first transgenic mouse a candidate agent, and
3. c) administering to said second transgenic mouse a physiological solution, and
4. d) taking blood samples from the mouse of b) and c) respectively, at predetermined time intervals, such as at 15 minutes, 30 minutes, 60 minutes, 2 and 4 hours, subsequent to administration of said agent, and
5. e) comparing blood glucose levels in the samples of d); wherein a reduction in blood glucose level of said first transgenic mouse administered said candidate agent relative to said second transgenic mouse not administered said candidate agent indicates that the candidate agent reduces blood glucose levels.

[0020] In a further important aspect, the invention relates to a method for screening for the ability of the SorCS1-like agent to reduce blood glucose levels, said method comprising the steps of:

1. a) providing a first and a second wild-type mouse; and
2. b) administering to said first mouse the agent of claim 1, and
3. c) administering to said second mouse a physiological solution, and
4. d) taking blood samples from the two mice of b) and c) respectively, at predetermined time intervals, such as at 15 minutes, 30 minutes, 60 minutes, 2 and 4 hours, subsequent to administration of said agent, and
5. e) comparing plasma glucose levels in the samples of d); wherein a reduction in blood glucose level of said first wild-type mouse administered said agent relative to said second wild type mouse not administered said candidate agent, indicates that the agent reduces blood glucose levels.

[0021] Disclosed is a transgenic mouse capable of encod soluble and/or full length SorCS1 in a tissue specific manner, upon activation of expression.

[0022] Disclosed is the use of an agent capable enhancing binding activity between SorCS1 or a fragment or variant thereof, and an insulin receptor for the treatment of insulin resistans and/or diseases associated with insulin resistance.

Brief description of the drawings

[0023]

Fig. 1. The Vps10p-domain receptor family. Their structural organization is indicated.

Fig. 2. **Splice** variants of **mSorCS1.** A) Organization of the murine SorCS1 gene leading to the generation of different cytoplasmic tails. B) Amino acid sequences of the mSorCS1 cytoplasmic domains.

Fig. 3. **Expression** of the different **mSorCS1 splice** variants. Fragments obtained by RT-PCR on mRNA from different tissue with specific primer pairs used to identify the extracellular part of SorCS1 (extra) or each of the five tail variants (a, b, c, c^+, and d).

Fig. 4. Generation of the **mSorCS1** knockout mouse. A) Strategy used to generate mSorCS1 knockout mice by homologous recombination in embryonic stem cells. B) Analysis of mSorCS1 mRNA expression, showing lack of transcription of all mSorCS1 splice variant. C) Western blot analysis of cortex showing lack of mSorCS1 protein in the mSorCS1 knockout (KO) mice.

Fig. 5 Average **blood** glucose in A) **male** and B) **female** mice at different age. Animals were fasted overnight (16h). Blood samples were obtained by retroorbital bleeding and plasma glucose was measured immediately on an automatic monitor.

Fig. 6. **Plasma insulin levels** in **female wild-type** and **SorCS1** knockout mice from 10 to 50 weeks of age. Animals were fasted overnight (16h). Blood samples were obtained by retroorbital bleeding and plasma insulin levels were determined using an ultrasensitive mouse insulin enzyme-linked immunosorbent assay kit.

Fig. 7. Glucose tolerance test in **SorCS1** knockout mice and **wild** type **littermates.** Mice 59 weeks of age were fasted overnight (16 h) and injected intraperitoneally with a bolus of glucose (2 mg/g body weight) in sterile saline. Blood samples were obtained by retroorbital bleeding at times 0, 15, 30, 60, and 120 min after injection, and plasma A) glucose and B) insulin levels were measured. Data are means ± SEM for four mice in each group.

Fig. 8. Elevated **levels** of fasting plasma glucose and insulin in wild type mice on Western type diet. Female A) + C) and male B) + D) wild type and SorCS1 knockout mice were fed a high calorie Western type diet (WD) from 10 weeks of age to 50 weeks of age. At 50 weeks of age the animals were fasted overnight (16h), blood samples were obtained by retroorbital bleeding and plasma glucose A) + B) and plasma insulin levels C) + D) were measured. Data are means ± SEM for 4 to 10 mice in each group.

Fig. 9. Abdominal adipose tissue in wild-type and knockout mice fed a western type diet.

Female A) and male B) wild type and SorCS1 knockout mice were fed a high calorie Western type diet (WD) from 10 weeks of age to 50 weeks of age. At the end of the study the animals were killed and the abdominal fat (adipose tissue) was separated and weighed. Data are means ± SEM for 4 to 10 mice in each group.

Fig. 10. Expression of IR, phosphorylated IR (pY-IR) and Glut4 in muscle and adipose tissue. Female SorCS1 knockout (-/-) mice and wild-type (+/+) control mice 50 weeks of age were fasted overnight, injected intraperitoneally with insulin (10 units/kg body weight) in sterile saline, and killed 15 min later. A) Adipose and B) muscle tissue (100 µg) were analysed by western blotting with anti-IR, anti-IR-pY, anti-Glut, and anti-actin as a loading control.

Fig. 11. Physical interaction between SorCS1 and insulin receptor. A) CHO cells transfected with the indicated receptors (only transient transfected with IR_A and IR_B) were stimulated with insulin and immunoprecipitated with IR, and analysed by western blotting using α-SorCS1-leu and α-IR, respectively. B) Surface plasmon resonance experiment (BIAcore) showing the direct interaction of soluble full-length extracellular part of SorCS1 with immobilized soluble insulin receptor (IR). The K_d is estimated to approximately 5 nM.

Fig. 12. Insulin receptor expression in CHO cells transfected with SorCS1. Cell lysat from CHO cells and CHO cells stably expressing mSorCS1-A, mSorCS1-B, mSorCS1-C, mSorCS1-D, and msol.SorCS1 (the extracellular part of SorCS1) were subjected to SDS-PAGE and Western blot analysis using anti-IR, anti-SorCS1-leu and anti-actin as a loading control.

Fig.13: Expression of IR and SorCS1 on the cell membrane. CHO cells and CHO cells stably expressing mSorCS1-B and mSorCS1-C were subjected to surface biotinylation followed by SDS-PAGE and Western blot analysis using anti-IR, anti-SorCS1-leu and anti-actin as a loading control. The Bio lanes contain biotinylated surface proteins, the Intra lanes contain intracellular proteins, and cell lysates (lysat) were used as input control.

Fig. 14: Development stages towards type 2 diabetes in human. Increases in blood glucose concentration during the development of T2D are illustrated on the graph (black line) showing the change from normal to pre-diabetic, before the onset of frank diabetes. Furthermore, the level of insulin during development of T2D is revealed on the same graph (dashed line), showing an increase of insulin during the pre-diabetic state as compensation to insulin resistance and a severe decline in insulin release at onset of frank diabetes as a consequence of β cell failure.

Fig. 15: Insulin immunostaining of pancreatic islets in wild-type and knockout mice 20 days of age. Pancreata were removed, fixed in paraformaldehyde, cryosectioned, and immunostained with anti-insulin antibody. Representative images are shown.

Figure 16: Alignment of SorCS1

Sequence alignment of SorCS1 from Human (homo sapiens), Chimpanzee (Pan troglodytes), Cow (Bos Taurus), Mouse (Mus musculus), Rat (Rattus norvegicus), Dog (Canis lupus familiaris) and Chicken (Gallus gallus) origin. The sequence identity is as demonstrated in table 2.

Table 2: Sequence identity to human SorCS1

Species	Protein (% identity)	DNA (% identity)
Human	100	100
Chimpanzee	99.6	99.4
Dog	97.6	92.5
Cow	92.9	89.8
Mouse	93.2	87.7
Rat	93.2	88.0
Chicken	85.3	79.7

Fig. 17: Decreased plasma glucose levels in female wild-type and SorCS1 knockout mice after hepatic overexpression of soluble SorCS1.

SorCS1 knockout or wild-type female mice were injected with an adenovirus for hepatic expression of soluble human SorCS1 or with a control virus encoding LacZ. At the day of injection (0d) as well as 7 days after virus administration (7d) plasma glucose was determined in mice fasted 16 hrs. The figure shows relative plasma glucose after normalization to the values obtained at day 0. (n=4). The figure shows that overexpression of soluble SorCS1 (the extracellular domain) reduces plasma glucose in both wild-type and SorCS1 knockout mice.

Fig. 18: Expression of IR, phosphorylated IR, and Glut4 in muscle and adipose tissue from SorCS1 knockout female mice over-expressing soluble SorCS1.

Female SorCS1 knockout (-/-) mice 40 weeks of age were injected with an adenoviral vector expressing either human soluble SorCS1 or LacZ as a control. Twelve days after virus injection, the mice were fasted overnight, injected intraperitoneally with insulin (10 units/kg body weight) in sterile saline, and killed 15 min later. 50 µg lysates from muscle (A) and adipose tissue (B) were analysed by western blotting with anti-IR, anti-IR-pY, and anti-Glut4. The figure shows that treatment with SorCS1-encoding virus increases IR expression, IR phosphorylation as well as Glut4 expression.

Fig. **19: Decreased plasma glucose and insulin levels in diabetic db/db female mice over-expressing soluble SorCS1.**

Obese type-2 diabetic female db/db mice 10 weeks of age were injected with adenovirus expressing either human soluble SorCS1 or LacZ as a control. At day 0 (d0) prior to virus infection and 7 days after (d7), blood samples from mice fasted overnight (16 hrs) were obtained by retroorbital bleeding and blood glucose (A) and plasma insulin (B) levels were measured. Data are means ± SEM for 5 mice in each group and are presented as relative values compared to day 0. Mice treated with SorCS1 virus, but not LacZ virus, exhibit increased insulin sensitivity as reflected by reduced plasma glucose and insulin levels. The increase in both plasma glucose and insulin from day 0 to 7 in the LacZ group reflects that the animals are in the process of developing diabetes.

Fig. 20: Glucose tolerance test in diabetic db/db female mice with over-expression of soluble SorCS1.

Fasted female db/db mice were 3 days post-infection with adenovira expressing either soluble SorCS1 or LacZ fasted injected intraperitoneally with a bolus of glucose (2mg/g body weight) in sterile saline. Blood samples were obtained by retroorbital bleeding at times 0, 15, 30, 90, and 150 min after injection, and blood glucose levels were measured. Values are means ± SEM for 5 mice in each group. The experiment shows that baseline blood glucose is restored at 150 min in mice that received the sol-

SorCS1 virus, whereas hyperglycemia is maintained in mice treated with LacZ-virus.

Fig. 21: Plasma glucose and insulin levels in diabetic db/db male mice over-expressing soluble SorCS1.

Obese male db/db mice 6 weeks of age were injected with adenovirus expressing either human soluble SorCS1 or LacZ as a control. At day 0 and 7, mice were fasted overnight (16h), blood samples were obtained by retroorbital bleeding and blood glucose (A) and plasma insulin (B) levels were measured. Data are means ± SEM for 5 mice in each group and are presented as relative change to day 0. The figure show that treatment with SorCS1 virus increases glucose sensitivity as plasma glucose decreases while insulin levels are similar to that of mice receiving LacZ virus. The increase in plasma insulin from day 0 to 7 in both groups reflects that the animals are in the process of developing diabetes. During the course of the experiment they can still compensate a reduction in insulin sensitivity by increasing insulin production.

Fig. 22: Subcellular localization of Glut4 in muscle tissue from db/db male mice over-expressing soluble SorCS1.

Light microsomes isolated by subcellular fractionation from muscle tissue of five db/db male mice after over-expression of soluble SorCS1 or lacZ were fractionated in a 0.8 M to 1.6 M sucrose velocity gradient. Gradient fractions were subjected to gel electrophoresis and blotted with a Glut4 antibody, thus identifying the location of Glut4 in the different fractions. The experiment shows that SorCS1 expression changes the subcellular localization of Glut4, in line an important role of SorCS1 in regulating glucose uptake.

Fig. 23: Analysis of SorCS1/IR contact sequences by SPOT analysiss.

1. A) Consecutive 16-mer amino acid peptides overlapping by three residues of the human insulin receptor were spotted on to filters. The filters were subsequently incubated with the radiolabelled extracellular domains of murine SorCS1, and binding was detected by autoradiography. Possible SorCS1 binding sites in the insulin receptor are indicated.
2. B) Consecutive 16-mer amino acid peptides overlapping by three residues of human SorCS1-a were spotted on to filters and probed for insulin receptor binding using his-tagged soluble receptor. Peptides capable of SorCS1-a binding were visualized by Western blotting using an antibody against the histidine tag. Possible binding sequences in SorCS1-a are indicated.

Fig. 24: Gene expression profiling of adipose tissue from SorCS1 knockout mice by PCR arrays.

The gene expression in SorCS1 knockout adipose tissue as compared to wild-type adipose tissue was examined for A) 84 genes related to the mouse insulin signalling pathway and B) 84 genes related to mouse lipoprotein signalling & cholesterol metabolism. Genes in the SorCS1 knockouts that are either 3 times higher or lower than that of wild-type mice are listed and their putative functions indicated.

Detailed description on the invention

Definitions

[0024] 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.

[0025] Adjuvant: Any substance whose admixture with an administered immunogenic determinant / antigen increases or otherwise modifies the immune response to said determinant.

[0026] Affinity: The interaction of most ligands with their binding sites can be characterized in terms of a binding affinity. In general, high affinity ligand binding results from greater intermolecular force between the ligand and its receptor while low affinity ligand binding involves less intermolecular force between the ligand and its receptor. In general, high affinity binding involves a longer residence time for the ligand at its receptor binding site than is the case for low affinity binding. High affinity binding of ligands to receptors is often physiologically important when some of the binding energy can be used to cause a conformational change in the receptor, resulting in altered behavior of an associated ion channel or enzyme.

[0027] A ligand that can bind to a receptor, alter the function of the receptor and trigger a physiological response is called an agonist for that receptor. Agonist binding to a receptor can be characterized both in terms of how much physiological response can be triggered and the concentration of the agonist that is required to produce the physiological response. High affinity ligand binding implies that a relatively low concentration of a ligand is adequate to maximally occupy a ligand binding site and trigger a physiological response. Low affinity binding implies that a relatively high concentration of a ligand is required before the binding site is maximally occupied and the maximum physiological response to the ligand is achieved. Ligand binding is often

characterized in terms of the concentration of ligand at which half of the receptor binding sites are occupied, known as the dissociation constant (k_d). Affinity is also the strength of binding between receptors and their ligands, for example between an antibody and its antigen.

[0028] Alcohol: A class of organic compounds containing one or more hydroxyl groups (OH). In this context a saturated or unsaturated, branched or unbranched hydrocarbon group sitting as a substituent on a larger molecule.

[0029] Alicyclic group: the term "alicyclic group" means a cyclic hydrocarbon group having properties resembling those of aliphatic groups.

[0030] Aliphatic group: in the context of the present invention, the term "aliphatic group" means a saturated or unsaturated linear or branched hydrocarbon group. This term is used to encompass alkyl, alkenyl, and alkynyl groups, for example.

[0031] Alkyl group: the term "alkyl group" means a saturated linear or branched hydrocarbon group including, for example, methyl, ethyl, isopropyl, t-butyl, heptyl, dodecyl, octadecyl, amyl, 2-ethylhexyl, and the like.

[0032] Alkenyl group: the term "alkenyl group" means an unsaturated, linear or branched hydrocarbon group with one or more carbon-carbon double bonds, such as a vinyl group.

[0033] Alkynyl group: the term "alkynyl group" means an unsaturated, linear or branched hydrocarbon group with one or more carbon-carbon triple bonds.

[0034] Amphiphil: substance containing both polar, water-soluble and nonpolar, water-insoluble groups.

[0035] Agonist: An agonist is a compound capable of increasing or effecting the activity of a receptor. Specifically, a Vps10p-domain receptor agonist is a compound capable of binding to one or more of binding sites of a Vps10p-domain receptor thereby inducing the same physiological response as a given endogenous agonist ligand compound.

[0036] Antagonist: An antagonist is in this case synonymous with an inhibitor. An antagonist is a compound capable of decreasing the activity of an effector such as a receptor. Specifically, a Vps10p-domain receptor antagonist is a compound capable of binding to one or more of binding sites of Vps10p-domain receptor thereby inhibiting binding of another ligand thus inhibiting a physiological resonse.

[0037] Antibody: The term "antibody" as referred to herein includes whole antibodies and any antigen binding fragment (*i.e.*, "antigen-binding portion") or single chain thereof. Polyclonal antibody: Polyclonal antibodies are a mixture of antibody molecules recognising a specific given antigen, hence polyclonal antibodies may recognise different epitopes within said antigen.

[0038] Aromatic group: the term "aromatic group" or "aryl group" means a mono- or polycyclic aromatic hydrocarbon group.

[0039] Binding: The term "binding" refers to a condition of proximity between chemical entities or compounds, or portions thereof. The binding may be non-covalent-wherein the juxtaposition is energetically favoured by hydrogen bonding or van der Waals or electrostatic interactions-or it may be covalent. The agents according to the invention are capable of binding to the insulin receptor. An assay for binding may be the Biocore assay discussed in relation to Figure 11B as well as the co.IP assay discussed in relation to Figure 11A.

[0040] Binding site: The term "binding site" or "binding pocket", as used herein, refers to a region of a molecule or molecular complex that, as a result of its shape, favourably associates with another molecule, molecular complex, chemical entity or compound. As used herein, the pocket comprises at least a deep cavity and, optionally a shallow cavity.

[0041] Bioreactive agent or biologically active or biological activity: The terms are as used herein refers to effect of any a substance which may be used in connection with an application that is therapeutic or otherwise useful according to this invention. The biological activity refers to the biological effect in vitro and/or in vivo. In the present context the biological activity of an agent is the capability of binding to the insulin receptor and/or enhancing binding of a SorCS1-like agent to the insulin receptor, and the biological activity includes sensitization of the insulin receptor. The bioactive agents may be neutral, positively or negatively charged. Suitable bioactive agents include, for example, prodrugs, diagnostic agents, therapeutic agents, pharmaceutical agents, drugs, oxygen delivery agents, blood substitutes, synthetic organic molecules, polypeptides, peptides, vitamins, steroids, steroid analogues and genetic determinants, including nucleosides, nucleotides and polynucleotides.

[0042] Cationic group: A chemical group capable of functioning as a proton donor when a compound comprising the chemical group is dissolved in a solvent, preferably when dissolved in water.

[0043] Complex: As used herein the term "complex" refers to the combination of a molecule or a protein, conservative analogues or truncations thereof bound to a chemical entity.

[0044] Cyclic group: the term "cyclic group" means a closed ring hydrocarbon group that is classified as an alicyclic group, aromatic group, or heterocyclic group.

[0045] Cycloalkenyl: means a monovalent unsaturated carbocyclic radical consisting of one, two or three rings, of three to eight carbons per ring, which can optionally be substituted with one or two substituents selected from the group consisting of hydroxy, cyano, lower alkenyl, lower alkoxy, lower haloalkoxy, alkenylthio, halo, haloalkenyl, hydroxyalkenyl, nitro, alkoxycarbonenyl, amino, alkenylamino, alkenylsulfonyl, arylsulfonyl, alkenylaminosulfonyl, arylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, alkenylaminocarbonyl, arylaminocarbonyl, alkenylcarbonylamino and arylcarbonylamino.

[0046] Cycloalkyl: means a monovalent saturated carbocyclic radical consisting of one, two or three rings, of three to eight carbons per ring, which can optionally be substituted with one or two substituents selected from the group consisting of hydroxy, cyano, lower alkyl, lower alkoxy, lower haloalkoxy, alkylthio, halo, haloalkyl, hydroxyalkyl, nitro, alkoxycarbonyl, amino, alkylamino, alkylsulfonyl, arylsulfonyl, alkylaminosulfonyl, arylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, alkylaminocarbonyl, arylaminocarbonyl, alkylcarbonylamino and arylcarbonylamino.

[0047] Electrostatic interaction: The term "electrostatic interaction" as used herein refers to any interaction occurring between charged components, molecules or ions, due to attractive forces when components of opposite electric charge are attracted to each other. Examples include, but are not limited to: ionic interactions, covalent interactions, interactions between a ion and a dipole (ion and polar molecule), interactions between two dipoles (partial charges of polar molecules), hydrogen bonds and London dispersion bonds (induced dipoles of polarizable molecules). Thus, for example, "ionic interaction" or "electrostatic interaction" refers to the attraction between a first, positively charged molecule and a second, negatively charged molecule. Ionic or electrostatic interactions include, for example, the attraction between a negatively charged bioactive agent.

[0048] Form a ring: means that the atoms mentioned are connected through a bond when the ring structure is formed.

[0049] Fragments: The polypeptide fragments, including any functional equivalents thereof, may comprise less than 500 amino acid residues, such as less than 450 amino acid residues, for example less than 400 amino acid residues, such as less than 350 amino acid residues, for example less than 300 amino acid residues, for example less than 250 amino acid residues, such as less than 240 amino acid residues, for example less than 225 amino acid residues, such as less than 200 amino acid residues, for example less than 180 amino acid residues, such as less than 160 amino acid residues, for example less than 150 amino acid residues, such as less than 140 amino acid residues, for example less than 130 amino acid residues, such as less than 120 amino acid residues, for example less than 110 amino acid residues, such as less than 100 amino acid residues, for example less than 90 amino acid residues, such as less than 85 amino acid residues, for example less than 80 amino acid residues, such as less than 75 amino acid residues, for example less than 70 amino acid residues, such as less than 65 amino acid residues, for example less than 60 amino acid residues, such as less than 55 amino acid residues, for example less than 50 amino acid residues, such as less than 45 amino acid residues, for example less than 40 amino acid residues, such as 35 amino acid residues, for example 30 amino acid residues, such as 25 amino acid residues, such as 20 amino acid residues, for example 15 amino acid residues, such as 10 amino acid residues, for example 5 contiguous amino acid residues of an amino acid sequence 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 and 51 or a variant thereof being at least 70% identical to said sequences. Also, the polypeptide fragments, including any functional equivalents thereof, may comprise more than 5 amino acid residues, such as more than 10 amino acid residues, for example more than 15 amino acid residues, such as more than 20 amino acid residues, for example more than 25 amino acid residues, for example more than 50 amino acid residues, such as more than 75 amino acid residues, for example more than 100 amino acid residues, such as more than 125 amino acid residues, for example more than 150 amino acid residues, such as more than 175 amino acid residues, for example more than 200 amino acid residues, such as more than 225 amino acid residues, for example more than 250 amino acid residues, such as more than 275 amino acid residues, for example more than 300 amino acid residues, such as more than 325 amino acid residues, for example more than 350 amino acid residues, such as more than 375 amino acid residues, for example more than 400 amino acid residues, such as more than 425 amino acid residues, for example more than 450 amino acid residues, such as more than 475 amino acid residues, for example more than 500 amino acid residues, such as more than 525 amino acid residues, for example more than 550 amino acid residues, such as more than 575 amino acid residues, for example more than

600 amino acid residues, such as 625 amino acid residues, for example 650 amino acid residues, such as 675 amino acid residues, such as 700 amino acid residues of an amino acid sequence 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 and 51 or a variant thereof being at least 70% identical to said sequences.

[0050] Functional equivalency: "Functional equivalency" is established by means of reference to the corresponding functionality of a predetermined fragment of the sequence.

[0051] Functional equivalents or variants of a SorCS1 polypeptide, or a fragment thereof will be understood to exhibit amino acid sequences gradually differing from the preferred predetermined SorCS1 polypeptide or the SorCS1 fragment sequence respectively, as the number and scope of insertions, deletions and substitutions including conservative substitutions increase, while retaining the biological activity of a SorCS1 polypeptide in this context. This difference is measured as a reduction in homology between the preferred predetermined sequence and the fragment or functional equivalent.

[0052] A functional variant obtained by substitution may well exhibit some form or degree of native SorCS1 activity, and yet be less homologous, if residues containing functionally similar amino acid side chains are substituted. Functionally similar in this respect refers to dominant characteristics of the side chains such as hydrophobic, basic, neutral or acidic, or the presence or absence of steric bulk. Accordingly, in one embodiment of the invention, the degree of identity is not a principal measure of a fragment being a variant or functional equivalent of a preferred predetermined fragment according to the present invention.

[0053] Gene "silencing": a process leading to reduced expression of endogenous genes. Gene silencing is preferably the result of post-transcriptional reduction of gene expression.

[0054] Group: (Moiety / substitution) as is well understood in this technical area, a large degree of substitution is not only tolerated, but is often advisable. Substitution is anticipated on the materials of the present invention. As a means of simplifying the discussion and recitation of certain terminology used throughout this application, the terms "group" and "moiety" are used to differentiate between chemical species that allow for substitution or that may be substituted and those that do not allow or may not be so substituted. Thus, when the term "group" is used to describe a chemical substituent, the described chemical material includes the unsubstituted group and that group with O, N, or S atoms, for example, in the chain as well as carbonyl groups or other conventional substitution. Where the term "moiety" is used to describe a chemical compound or substituent, only an unsubstituted chemical material is intended to be included. For example, the phrase "alkyl group" is intended to include not only pure open chain saturated hydrocarbon alkyl substituents, such as methyl, ethyl, propyl, t-butyl, and the like, but also alkyl substituents bearing further substituents known in the art, such as hydroxy, alkoxy, alkylsulfonyl, halogen atoms, cyano, nitro, amino, carboxyl, etc. Thus, "alkyl group" includes ether groups, haloalkyls, nitroalkyls, carboxyalkyls, hydroxyalkyls, sulfoalkyls, etc. On the other hand, the phrase "alkyl moiety" is limited to the inclusion of only pure open chain saturated hydrocarbon alkyl substituents, such as methyl, ethyl, propyl, t-butyl, and the like. The same definitions apply to "alkenyl group" and "alkenyl moiety"; to "alkynyl group" and "alkynyl moiety"; to "cyclic group" and "cyclic moiety; to "alicyclic group" and "alicyclic moiety"; to "aromatic group" or "aryl group" and to "aromatic moiety" or "aryl moiety"; as well as to "heterocyclic group" and "heterocyclic moiety".

[0055] Heterocyclic group: the term "heterocyclic group" means a closed ring hydrocarbon in which one or more of the atoms in the ring is an element other than carbon (e.g., nitrogen, oxygen, sulphur, etc.).

[0056] Heterocyclyl means a monovalent saturated cyclic radical, consisting of one to two rings, of three to eight atoms per ring, incorporating one or two ring heteroatoms (chosen from N, O or $S(O)_{0-2}$, and which can optionally be substituted with one or two substituents selected from the group consisting of hydroxyl, oxo, cyano, lower alkyl, lower alkoxy, lower haloalkoxy, alkylthio, halo, haloalkyl, hydroxyalkyl, nitro, alkoxycarbonyl, amino, alkylamino, alkylsulfonyl, arylsulfonyl, alkylaminosulfonyl, arylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, alkylaminofarbonyl, arylaminocarbonyl, alkylcarbonylamino, or arylcarbonylamino.

[0057] Heteroaryl means a monovalent aromatic cyclic radical having one to three rings, of four to eight atoms per ring, incorporating one or two heteroatoms (chosen from nitrogen, oxygen, or sulphur) within the ring which can optionally be substituted with one or two substituents selected from the group consisting of hydroxy, cyano, lower alkyl, lower alkoxy, lower haloalkoxy, alkylthio, halo, haloalkyl, hydroxyalkyl, nitro, alkoxycarbonyl, amino, alkylamino, alkylsulfonyl, arylsulfonyl, alkylaminosulfonyl, arylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, alkylaminocarbonyl, arylaminocarbonyl, alkylcarbonlamino and arylcarbonylamino.

[0058] Homology: The homology between amino acid sequences may be calculated using well known scoring matrices such as

any one of BLOSUM 30, BLOSUM 40, BLOSUM 45, BLOSUM 50, BLOSUM 55, BLOSUM 60, BLOSUM 62, BLOSUM 65, BLOSUM 70, BLOSUM 75, BLOSUM 80, BLOSUM 85, and BLOSUM 90.

[0059] Fragments sharing homology with fragments of SEQ ID NOs: 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 and 51, respectively, are preferably at least about 60 percent homologous, for example at least 65 percent homologous, for example at least 70 percent homologous, for example at least 75 percent homologous, for example at least 80 percent homologous, for example at least 85 percent homologous, for example at least 90 percent homologous, for example at least 92 percent homologous, such as at least 94 percent homologous, for example at least 95 percent homologous, such as at least 96 percent homologous, for example at least 97 percent homologous, such as at least 98 percent homologous, for example at least 99 percent homologous with said predetermined fragment sequences, respectively. According to one embodiment of the invention, the homology percentages refer to identity percentages.

[0060] A further suitably adaptable method for determining structure and function relationships of peptide fragments is described in US 6,013,478. Also, methods of assaying the binding of an amino acid sequence to a receptor moiety are known to the skilled artisan.

[0061] In addition to conservative substitutions introduced into any position of a preferred predetermined SorCS1 polypeptide, or a fragment thereof, it may also be desirable to introduce non-conservative substitutions in any one or more positions of such a SorCS1 polypeptide, or a fragment thereof.

[0062] A non-conservative substitution leading to the formation of a functionally equivalent fragment of a SorCS1 polypeptide, or a fragment thereof would for example i) differ substantially in polarity, for example a residue with a non-polar side chain (Ala, Leu, Pro, Trp, Val, Ile, Leu, Phe or Met) substituted for a residue with a polar side chain such as Gly, Ser, Thr, Cys, Tyr, Asn, or Gln or a charged amino acid such as Asp, Glu, Arg, or Lys, or substituting a charged or a polar residue for a non-polar one; and/or ii) differ substantially in its effect on polypeptide backbone orientation such as substitution of or for Pro or Gly by another residue; and/or iii) differ substantially in electric charge, for example substitution of a negatively charged residue such as Glu or Asp for a positively charged residue such as Lys, His or Arg (and vice versa); and/or iv) differ substantially in steric bulk, for example substitution of a bulky residue such as His, Trp, Phe or Tyr for one having a minor side chain, e.g. Ala, Gly or Ser (and vice versa).

[0063] Variants obtained by substitution of amino acids may in one preferred embodiment be made based upon the hydrophobicity and hydrophilicity values and the relative similarity of the amino acid side-chain substituents, including charge, size, and the like. Exemplary amino acid substitutions which take various of the foregoing characteristics into consideration are well known to those of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

[0064] In addition to the variants described herein, sterically similar variants may be formulated to mimic the key portions of the variant structure and that such compounds may also be used in the same manner as the variants of the invention. This may be achieved by techniques of modelling and chemical designing known to those of skill in the art.

[0065] Disclosed are functional variants comprising substituted amino acids having hydrophilic values or hydropathic indices that are within +/-4.9, for example within +/-4.7, such as within +/-4.5, for example within +/-4.3, such as within +/-4.1, for example within +/-3.9, such as within +/-3.7, for example within +/- 3.5, such as within +/-3.3, for example within +/- 3.1, such as within +/- 2.9, for example within +/- 2.7, such as within +/-2.5, for example within +/-2.3, such as within +/- 2.1, for example within +/- 2.0, such as within +/- 1.8, for example within +/- 1.6, such as within +/- 1.5, for example within +/- 1.4, such as within +/- 1.3 for example within +/- 1.2, such as within +/- 1.1, for example within +/-1.0, such as within +/- 0.9, for example within +/- 0.8, such as within +/- 0.7, for example within +/- 0.6, such as within +/- 0.5, for example within +/- 0.4, such as within +/- 0.3, for example within +/- 0.25, such as within +/- 0.2 of the value of the amino acid it has substituted.

[0066] The importance of the hydrophilic and hydropathic amino acid indices in conferring interactive biologic function on a protein is well understood in the art (Kyte & Doo-little, 1982 and Hopp, U.S. Pat. No. 4,554,101.

[0067] The amino acid hydropathic index values as used herein are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5); glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5) (Kyte & Doolittle, 1982).

[0068] The amino acid hydrophilicity values are: arginine (+3.0); lysine (+3.0); aspartate (+3.0.+-.1); glutamate (+3.0.+-.1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (-0.4); proline (-0.5.+-.1); alanine (-0.5); histidine (-0.5); cysteine (-1.0); methionine (-1.3); valine (-1.5); leucine (-1.8); isoleucine (-1.8); tyrosine (-2.3); phenylalanine (-2.5); tryptophan (-3.4) (U.S. 4,554,101).

[0069] In addition to the peptidyl compounds described herein, sterically similar compounds may be formulated to mimic the key portions of the peptide structure and that such compounds may also be used in the same manner as the peptides of the invention. This may be achieved by techniques of modelling and chemical designing known to those of skill in the art. For example, esterification and other alkylations may be employed to modify the amino terminus of, e.g., a di-arginine peptide backbone, to mimic a tetra peptide structure.

[0070] Peptides with N-terminal alkylations and C-terminal esterifications are also disclosed. Functional equivalents also comprise glycosylated and covalent or aggregative conjugates formed with the same or other SorCS1 polypeptides, or fragment thereof, including dimers or unrelated chemical moieties. Such functional equivalents are prepared by linkage of functionalities to groups which are found in fragment including at any one or both of the N- and C-termini, by means known in the art.

[0071] Functional equivalents may thus comprise fragments conjugated to aliphatic or acyl esters or amides of the carboxyl terminus, alkylamines or residues containing carboxyl side chains, e.g., conjugates to alkylamines at aspartic acid residues; O-acyl derivatives of hydroxyl group-containing residues and N-acyl derivatives of the amino terminal amino acid or amino-group containing residues, e.g. conjugates with fMet-Leu-Phe or immunogenic proteins. Derivatives of the acyl groups are selected from the group of alkyl-moieties (including C3 to C10 normal alkyl), thereby forming alkanoyl species, and carbocyclic or heterocyclic compounds, thereby forming aroyl species. The reactive groups preferably are difunctional compounds known per se for use in cross-linking proteins to insoluble matrices through reactive side groups.

[0072] Covalent or aggregative functional equivalents and derivatives thereof are useful as reagents in immunoassays or for affinity purification procedures. For example, a fragment of a SorCS1 polypeptide according to the present invention may be insolubilized by covalent bonding to cyanogen bromide-activated Sepharose by methods known per se or adsorbed to polyolefin surfaces, either with or without glutaraldehyde cross-linking, for use in an assay or purification of anti-SorCS1 activity modulator antibodies or cell surface receptors. Fragments may also be labelled with a detectable group, e.g., radioiodinated by the chloramine T procedure, covalently bound to rare earth chelates or conjugated to another fluorescent moiety for use in e.g. diagnostic assays.

[0073] Mutagenesis of a preferred predetermined SorCS1 polypeptide, or a fragment thereof, can be conducted by making amino acid insertions, usually on the order of about from 1 to 10 amino acid residues, preferably from about 1 to 5 amino acid residues, or deletions of from about from 1 to 10 residues, such as from about 2 to 5 residues.

[0074] In one embodiment the ligand of binding site 1, 2 or 3 is an oligopeptide synthesised by automated synthesis. Any of the commercially available solid-phase techniques may be employed, such as the Merrifield solid phase synthesis method, in which amino acids are sequentially added to a growing amino acid chain (see Merrifield, J. Am. Chem. Soc. 85:2149-2146, 1963).

[0075] Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Applied Biosystems, Inc. of Foster City, Calif., and may generally be operated according to the manufacturer's instructions. Solid phase synthesis will enable the incorporation of desirable amino acid substitutions into any fragment of SorCS1 according to the present invention. It will be understood that substitutions, deletions, insertions or any subcombination thereof may be combined to arrive at a final sequence of a functional equivalent. Insertions shall be understood to include amino-terminal and/or carboxyl-terminal fusions, e.g. with a hydrophobic or immunogenic protein or a carrier such as any polypeptide or scaffold structure capable as serving as a carrier.

[0076] Oligomers including dimers including homodimers and heterodimers of fragments of sortilin inhibitors are also provided.

[0077] SorCS1 polypeptides and fragments, functional equivalents and variants thereof can be produced as homodimers or heterodimers with other amino acid sequences or with native sortilin inhibitor sequences. Heterodimers include dimers containing immunoreactive sortilin inhibiting fragments as well as sortilin inhibiting fragments that need not have or exert any biological activity. SorCS1 polypeptides, or fragments and variants thereof may be synthesised both in vitro and in vivo. Methods for in vitro synthesis are well known, and methods being suitable or suitably adaptable to the synthesis in vivo of sortilin inhibitors are also described in the prior art. When synthesized in vivo, a host cell is transformed with vectors containing DNA encoding a sortilin peptide inhibitor or a fragment thereof. A vector is defined as a replicable nucleic acid construct. Vectors are used to mediate

expression of SorCS1 polypeptides, and/or fragments and variants. An expression vector is a replicable DNA construct in which a nucleic acid sequence encoding the predetermined sortilin inhibitting fragment, or any functional equivalent thereof that can be expressed in vivo, is operably linked to suitable control sequences capable of effecting the expression of the fragment or equivalent in a suitable host. Such control sequences are well known in the art. Both prokaryotic and eukaryotic cells may be used for synthesising ligands.

[0078] Cultures of cells derived from multicellular organisms however represent preferred host cells. In principle, any higher eukaryotic cell culture is workable, whether from vertebrate or invertebrate culture. Examples of useful host cell lines are VERO and HeLa cells, Chinese hamster ovary (CHO) cell lines, and WI38, BHK, COS-7, 293 and MDCK cell lines. Preferred host cells are eukaryotic cells known to synthesize endogenous sortilin inhibitors. Cultures of such host cells may be isolated and used as a source of the fragment, or used in therapeutic methods of treatment, including therapeutic methods aimed at promoting or inhibiting a growth state, or diagnostic methods carried out on the human or animal body.

[0079] Hydrophobic bond: The term "hydrogen bond" as used herein refers to an attractive force, or bridge, which may occur between a hydrogen atom which is bonded covalently to an electronegative atom, for example, oxygen, sulphur, or nitrogen, and another electronegative atom. The hydrogen bond may occur between a hydrogen atom in a first molecule and an electronegative atom in a second molecule (intermolecular hydrogen bonding). Also, the hydrogen bond may occur between a hydrogen atom and an electronegative atom which are both contained in a single molecule (intramolecular hydrogen bonding).

[0080] Hydrophobic interaction: The term "hydrophobic interaction" as used herein refers to any interaction occurring between essentially non-polar (hydrophobic) components located within attraction range of one another in a polar environment (e.g. water). As used herein, attraction range is on the scale of from 0.1 up to 2 nm. A particular type of hydrophobic interaction is exerted by "Van der Waal's forces", i.e. the attractive forces between non-polar molecules that are accounted for by quantum mechanics. Van der Waal's forces are generally associated with momentary dipole moments which are induced by neighbouring molecules and which involve changes in electron distribution.

[0081] Insulin: Insulin is a hormone that is produced by the beta cells of the pancreas. The insulin produced is released into the blood stream and is transported throughout the body. Insulin is an important hormone that has many actions within the body. Most of the actions of insulin are directed at metabolism (control) of carbohydrates (sugars and starches), lipids (fats), and proteins. Insulin also is important in regulating the cells of the body including their growth.

[0082] Insulin resistance: Insulin resistance (IR) is a condition in which the cells of the body become resistant to the effects of insulin, that is, the normal response to a given amount of insulin is reduced. As a result, higher levels of insulin are needed in order for insulin to have its effects. Insulin resistance precedes the development of type 2 diabetes, sometimes by several years. In individuals who will ultimately develop type 2 diabetes, it is believed that blood glucose and insulin levels are normal for many years; then at some point in time, insulin resistance develops. Accordingly, the treatment of the cause of insulin resistance is preferred over treatment of the symptoms of diabetes. The present invention is primarily aimed at providing a medicament for use in the treatment of insulin resistance.

[0083] In vitro/in vivo: the terms are used in their normal meaning.

[0084] Ligand: a substance, compound or biomolecule such as a protein including receptors, that is able to bind to and form a complex with (a second) biomolecule to serve a biological purpose. In a narrower sense, it is a signal triggering molecule binding to a site on a target protein, by intermolecular forces such as ionic bonds, hydrogen bonds and Van der Waals forces. The docking (association) is usually reversible (dissociation). Actual irreversible covalent binding between a ligand and its target molecule is rare in biological systems. As opposed to the meaning in metalorganic and inorganic chemistry, it is irrelevant, whether or not the ligand actually binds at a metal site, as it is the case in hemoglobin. Ligand binding to receptors may alter the chemical conformation, i.e. the three dimensional shape of the receptor protein. The conformational state of a receptor protein determines the functional state of a receptor. The tendency or strength of binding is called affinity. Ligands include substrates, inhibitors, activators, non-self receptors, co-receptors and neurotransmitters.

[0085] Pharmaceutical agent: The terms "pharmaceutical agent" or "drug" or "medicament" refer to any therapeutic or prophylactic use of an agent according to the invention, which agent may be used in the treatment (including the prevention, diagnosis, alleviation, or cure) of a malady, affliction, condition, disease or injury in a patient. Therapeutically useful genetic determinants, peptides, polypeptides and polynucleotides may be included within the meaning of the term pharmaceutical or drug. As defined herein, a "therapeutic agent", "pharmaceutical agent" or "drug" or "medicament" is a type of bioactive agent.

[0086] Pharmaceutical composition: or drug, medicament or agent refers to any chemical or biological material, compound, or

composition capable of inducing a desired therapeutic effect when properly administered to a patient. Some drugs are sold in an inactive form that is converted in vivo into a metabolite with pharmaceutical activity. For purposes of the present invention, the terms "pharmaceutical composition" and "medicament" preferably encompass an active agent as such or an inactive drug and the active metabolite.

[0087] Polypeptide: The term "polypeptide" as used herein refers to a molecule comprising at least two amino acids. The amino acids may be natural or synthetic. "Oligopeptides" are defined herein as being polypeptides of length not more than 100 amino acids. The term "polypeptide" is also intended to include proteins, i.e. functional biomolecules comprising at least one polypeptide; when comprising at least two polypeptides, these may form complexes, be covalently linked or may be non-covalently linked. The polypeptides in a protein can be glycosylated and/or lipidated and/or comprise prosthetic groups.

[0088] Polynucleotide: "Polynucleotide" as used herein refers to a molecule comprising at least two nucleic acids. The nucleic acids may be naturally occurring or modified, such as locked nucleic acids (LNA), or peptide nucleic acids (PNA). Polynucleotide as used herein generally pertains to

1. i) a polynucleotide comprising a predetermined coding sequence, or
2. ii) a polynucleotide encoding a predetermined amino acid sequence, or
3. iii) a polynucleotide encoding a fragment of a polypeptide encoded by polynucleotides (i) or (ii), wherein said fragment has at least one predetermined activity as specified herein; and
4. iv) a polynucleotide the complementary strand of which hybridizes under stringent conditions with a polynucleotide as defined in any one of (i), (ii) and (iii), and encodes a polypeptide, or a fragment thereof, having at least one predetermined activity as specified herein; and
5. v) a polynucleotide comprising a nucleotide sequence which is degenerate to the nucleotide sequence of polynucleotides (iii) or (iv);

or the complementary strand of such a polynucleotide.

[0089] Prediabetes: Prediabetes refers to the intermediate metabolic states between normal and diabetic glucose homeostasis. It comprises of two distinct states, those of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) or a combination of both but by itself is not diabetes. Thus, it is a condition in which blood glucose level is higher than normal, but not high enough to be classified as type 2 diabetes.

[0090] Purified antibody: The term a "purified antibody" is an antibody at least 60 weight percent of which is free from the polypeptides and naturally-occurring organic molecules with which it is naturally associated. Preferably, the preparation comprises antibody in an amount of at least 75 weight percent, more preferably at least 90 weight percent, and most preferably at least 99 weight percent.

[0091] Root mean square deviation: The term "root mean square deviation" (rmsd) is used as a mean of comparing two closely related structures and relates to a deviation in the distance between related atoms of the two structures after structurally minimizing this distance in an alignment. Related proteins with closely related structures will be characterized by relatively low RMSD values whereas larger differences will result in an increase of the RMSD value.

[0092] Sensitization of the insulin receptor: the term "sensitization of the insulin receptor" is used to explain that the agents according to the invention are preferred to be able to stabilise the insulin receptor, and preferably also to increase the amount of insulin receptors. Sensitization of the insulin receptor may be measured by administering an agent according to the invention and then performing a glucose tolerance test, as discussed in relation to Figure 20. Furthermore, the sensitization may be assessed by assessing the amount of insulin receptors before and after administration of the agent according to the invention, whereby an increase is indicative of sensitization of the insulin receptor. Also, the sensitization may be assessed by assessing the amount of activated insulin receptors, ie. phosphorylated insulin receptors. Furthermore, the sensitization may also be assessed by measuring the affinity between insulin and the insulin receptor, in that an increase in affinity is an indication of sensitization.

[0093] Sequence identity: Sequence identity is determined by utilising fragments of SorCS1 polypeptides comprising at least 25 contiguous amino acids and having an amino acid sequence which is at least 80%, such as 85%, for example 90%, such as 95%, for example 99% identical to the amino acid sequence of any 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 and 51 respectively, wherein the percent identity is determined with the algorithm GAP, BESTFIT, or FASTA in the Wisconsin Genetics Software Package Release 7.0, using default gap weights.

[0094] The following terms are used to describe the sequence relationships between two or more polynucleotides: "predetermined sequence", "comparison window", "sequence identity", "percentage of sequence identity", and "substantial identity".

[0095] Optimal alignment of sequences for aligning a comparison window may be conducted by the local homology algorithm of Smith and Waterman (1981) Adv. Appl. Math. 2: 482 , by the homology alignment algorithm of Needleman and Wunsch (1970) J. Mol. Biol. 48: 443, by the search for similarity method of Pearson and Lipman (1988) Proc. Natl. Acad. Sci. (U.S.A.) 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package Release 7.0, Genetics Computer Group, 575 Science Dr., Madison, Wis.), or by inspection, and the best alignment (i.e., resulting in the highest percentage of homology over the comparison window) generated by the various methods is selected.

[0096] As applied to polypeptides, a degree of identity of amino acid sequences is a function of the number of identical amino acids at positions shared by the amino acid sequences. A degree of homology or similarity of amino acid sequences is a function of the number of amino acids, i.e. structurally related, at positions shared by the amino acid sequences.

[0097] An "unrelated" or "non-homologous" sequence shares less than 40% identity, though preferably less than 25% identity, with one of the SorCS1 polypeptide sequences of the present invention. The term "substantial identity" means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 80 percent sequence identity, preferably at least 90 percent sequence identity, more preferably at least 95 percent sequence identity or more (e.g., 99 percent sequence identity). Preferably, residue positions which are not identical differ by conservative amino acid substitutions.

[0098] Conservative amino acid substitutions refer to the interchangeability of residues having similar side chains. For example, a group of amino acids having aliphatic side chains is glycine, alanine, valine, leucine, and isoleucine; a group of amino acids having aliphatic-hydroxyl side chains is serine and threonine, a group of amino acids having amide-containing side chains is asparagine and glutamine; a group of amino acids having aromatic side chains is phenylalanine, tyrosine, and tryptophan; a group of amino acids having basic side chains is lysine, arginine, and histidine; and a group of amino acids having sulphur-containing side chains is cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, and asparagine-glutamine.

[0099] Additionally, variants are also determined based on a predetermined number of conservative amino acid substitutions as defined herein below. Conservative amino acid substitution as used herein relates to the substitution of one amino acid (within a predetermined group of amino acids) for another amino acid (within the same group), wherein the amino acids exhibit similar or substantially similar characteristics.

[0100] Within the meaning of the term "conservative amino acid substitution" as applied herein, one amino acid may be substituted for another within the groups of amino acids indicated herein below:

1. i) Amino acids having polar side chains (Asp, Glu, Lys, Arg, His, Asn, Gln, Ser, Thr, Tyr, and Cys,)
2. ii) Amino acids having non-polar side chains (Gly, Ala, Val, Leu, Ile, Phe, Trp, Pro, and Met)
3. iii) Amino acids having aliphatic side chains (Gly, Ala Val, Leu, Ile)
4. iv) Amino acids having cyclic side chains (Phe, Tyr, Trp, His, Pro)
5. v) Amino acids having aromatic side chains (Phe, Tyr, Trp)
6. vi) Amino acids having acidic side chains (Asp, Glu)
7. vii) Amino acids having basic side chains (Lys, Arg, His)
8. viii) Amino acids having amide side chains (Asn, Gln)
9. ix) Amino acids having hydroxy side chains (Ser, Thr)
10. x) Amino acids having sulphur-containing side chains (Cys, Met),
11. xi) Neutral, weakly hydrophobic amino acids (Pro, Ala, Gly, Ser, Thr)
12. xii) Hydrophilic, acidic amino acids (Gln, Asn, Glu, Asp), and
13. xiii) Hydrophobic amino acids (Leu, Ile, Val)

[0101] Accordingly, a variant or a fragment thereof according to the invention may comprise, within the same variant of the sequence or fragments thereof, or among different variants of the sequence or fragments thereof, at least one substitution, such as a plurality of substitutions introduced independently of one another.

[0102] It is clear from the above outline that the same variant or fragment thereof may comprise more than one conservative amino acid substitution from more than one group of conservative amino acids as defined herein above.

[0103] The addition or deletion of at least one amino acid may be an addition or deletion of from preferably 2 to 250 amino acids, such as from 10 to 20 amino acids, for example from 20 to 30 amino acids, such as from 40 to 50 amino acids. However, additions or deletions of more than 50 amino acids, such as additions from 50 to 100 amino acids, addition of 100 to 150 amino acids, addition of 150-250 amino acids, are also disclosed.

[0104] The deletion and/or the addition may - independently of one another - be a deletion and/or an addition within a sequence and/or at the end of a sequence.

[0105] SorCS1-like agent: The expression "a SorCS1-like agent" as used herein refers to any agent capable of structurally imitating the Vps10p-domain receptor SorCS1 thus having the same or similar biological effect on the insulin receptor, as the effect demonstrated herein by the present inventors. Acordingly, as SorCS1-like agent may be a peptide, a polypeptide, a small organic molecule, siRNA, siDNA, nucleic acid molecules encoding a polypeptide. In a preferred embodiment, the SorCS1-like agent is a SorCS1 fragment, preferably human soluble SorCS1 (SEQ ID NO: 15) or a precursor thereof.

[0106] Substituted lower alkyl means a lower alkyl having one to three substituents selected from the group consisting of hydroxyl, alkoxy, amino, amido, carboxyl, acyl, halogen, cyano, nitro and thiol.

[0107] Treatment: The term "treatment" as used herein refers to a method involving therapy including surgery of a clinical condition in an individual including a human or animal body. The therapy may be ameliorating, curative or prophylactic, i.e. reducing mental and behavioural symptoms.

[0108] Variants: The term "variants" as used herein refers to amino acid sequence variants said variants preferably having at least 60% identity, for example at least 63% identity, such as at least 66% identity, for example at least 70% sequence identity, for example at least 72% sequence identity, for example at least 75% sequence identity, for example at least 80% sequence identity, such as at least 85% sequence identity, for example at least 90% sequence identity, such as at least 91% sequence identity, for example at least 91% sequence identity, such as at least 92% sequence identity, for example at least 93% sequence identity, such as at least 94% sequence identity, for example at least 95% sequence identity, such as at least 96% sequence identity, for example at least 97% sequence identity, such as at least 98% sequence identity, for example 99% sequence identity with any of the predetermined sequences.

[0109] The variants preferably include the fragments shown to bind to the insulin receptor, see for example Figure 23B and/or parts of the SorCS1 sequence conserved from one species to other, see for example Figure 13.

[0110] Up-regulation of expression: a process leading to increased expression of genes, preferably of endogenous genes.

Insulin resistance

[0111] Insulin resistance (IR) is a condition in which the cells of the body become resistant to the effects of insulin, that is, the normal response to a given amount of insulin is reduced. As a result, higher levels of insulin are needed in order for insulin to have its effects. The resistance is seen with both the body's own insulin (endogenous) and if insulin is given through injection (exogenous).

[0112] There are probably several causes of insulin resistance and as described herein above there is a strong genetic factor. Drug-induced IR may be a further cause. In addition, insulin resistance is seen often in the following conditions: the metabolic syndrome, obesity, pregnancy, infection or severe illness and stress during steroid use. Treatments of insulin resistance in these conditions are aspects of the present invention.

[0113] The relationship between insulin resistance and diabetes is as follows. Type 2 diabetes, is the type of diabetes that normally occurs later in life. Insulin resistance precedes the development of type 2 diabetes, sometimes by several years. In individuals who will ultimately develop type 2 diabetes, it is believed that blood glucose and insulin levels are normal for many years; then at some point in time, insulin resistance develops most likely caused by overweight/obesity, physical inactivity and/or a series of currently not yet well-defined genetic polymorphisms. Accordingly, the treatment of the cause of insulin resistance is preferred over treatment of the symptoms of diabetes. The present invention is primarily aimed at providing a medicament for use

in the treatment of insulin resistance.

[0114] As is well known by those skilled in the art, one of the actions of insulin is to cause the cells of the body, particularly hepatocytes and other cells of the liver, the muscle and fat cells, to remove and use glucose from the blood. In this way insulin controls the blood glucose level. Insulin has this effect on the cells by binding to insulin receptors on the cell surface and to allow influx of glucose into the cells, to be used as energy by the cell. With insulin resistance, the cells do not react appropriately to the insulin (they are resistant), and a signal is sent to the pancreas that more insulin needs to be produced, which in turn results in increased level of insulin in the blood resulting in an even stronger signal through the insulin receptors. In this manner the insulin resistance of the cells increases over time. As long as the pancreas is able to produce enough insulin to overcome this resistance, blood glucose levels remain normal. When the pancreas can no longer produce enough insulin, the blood glucose levels begin to rise, initially after meals when glucose levels are at their highest and more insulin is needed, but eventually in the fasting state as well. At this point, insulin resistance has resulted in a number of medical conditions, including type 2 diabetes, fatty liver, atherosclerosis wherein the latter in turn may result in coronary artery disease (angina pectoris and heart attack), stroke and peripheral vascular disease. A further medical condition associated with insulin resistance includes skin lesions, acanthosis nigricans (a cosmetic condition involving darkening of the skin in areas where there are creases such as the neck and arm pits). Further conditions associated with IR are skin tags, reproductive abnormalities in women, polycystic ovary disease, hyperandrogenism, high male hormone levels and growth abnormalities.

[0115] Growth abnormalities as a result of insulin resistance are caused by the high levels of circulating insulin that may be present in the blood. While insulin's effects on glucose metabolism may be impaired, it's effects on other mechanisms may be intact (or at least less impaired). Insulin, which is an anabolic, can exert effects on growth, through a medicator known as insulin-like growth factor -1. Patients may have actual linear growth and a noticeable coarsening of features. The increase incidence of skin tags mentioned above may be through this mechanism as well.

[0116] The ability of insulin to stimulate glucose disposal vary continuously throughout a population of apparently healthy persons, and a difference of ≥ 600% exists between the most insulin-sensitive and the most insulin resistance persons. Approximately 50% of this variability can be attributed to adiposisty (25%) and physical fitness (25%), with the remaining 50% likely of genetic origin. The third of the population that is the most insulin resistant is at a much greater risk of developing several abnormalities and clinical syndromes, including type 2 diabetes, cardio vascular diseases, hypertension, stroke, non-alcoholic fatty liver, polycystic ovary disease, and certain forms of cancer
Insulin resistance can be diagnosed by a physician who can identify individuals that are likely to have insulin resistance with a detailed patient history, patient physical examination, and laboratory testing utilizing the risk factors. Tests for diagnosing IR includes but are not limited to euglycemic insulin clamping and intravenous tolerance testing. However, these are expensive or complicated and are not necessary for managing patients.

[0117] In general clinical practice, glucose levels in conjunction with fasting insulin levels can give the physician a clue as to whether insulin resistance is present or not in patients without diabetes.

[0118] Insulin resistance can be treated by attempting to reduce the need for insulin, in combination with increasing the sensitivity of the cells to the action of insulin can be increased.

[0119] To decrease the need for insulin the individual suffering from insulin resistance can alter his/her diet, and particularly the intake of carbohydrates through the diet.

[0120] As described herein, the present invention addresses methods for sensitizing the cells (insulin receptors) to increase the action of insulin.

[0121] In one aspect the agent according to the present invention may be used to treat diseases and disorders associated with insulin resistance wherein said diseases and disorders are selected from the group consisting of insulin resistance syndrome, Type 2 diabetes mellitus, impaired glucose tolerance, the metabolic syndrome, hyperglycemia, hyperinsulinemia, arteriosclerosis, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, dyslipidemia, obesity, central obesity, polycystic ovarian syndrome, hypercoagulability, hypertension, microalbuminuria, and any combinations thereof.

[0122] Other conditions treatable by the present invention include but are not limited to insulin resistance syndrome (IRS), Type 2 diabetes mellitus, impaired glucose tolerance, the metabolic syndrome, hyperglycemia, and hyperinsulinemia.

Agent of the invention

[0123] The present inventors have found that SorCS1 physically interacts with the insulin receptor (Fig.11), and have furthermore shown by cell biological experiments that the expression of the insulin receptor is elevated in cells stably over-expressing soluble SorCS1 or the different SorCS1 splice variants (Fig.12), and the elevated amount of insulin receptor is still located on the cell surface (Fig.13).

[0124] Also, the inventors have found that overexpression of soluble SorCS1 in SorCS1 knockout mice as well as administration of SorCS1 decreases the plasma glucose level (Fig. 17) and increases expression and phosphorylation of the insulin receptor as well as the glucose transporter type 4 (Glut4) protein (Fig. 18). Moreover, overexpression of soluble SorCS1 in type 2 diabetic female mice decreases the plasma glucose and insulin levels (Fig. 19) and changes the subcellular localization of Glut4, which may consequently regulate glucose uptake.

[0125] Therefore, in a main aspect, the present invention relates to a SorCS1-like agent for use in the treatment of insulin resistance and/or a disease associated with insulin resistance in an individual, wherein said agent is capable of binding to the insulin receptor (IR) at a SorCS1 binding site and being capable of sensitization of an insulin receptor. The insulin receptor may be any insulin receptor, but preferably the insulin receptor is a human insulin receptor having the sequence of SEQ ID NO: 56.

[0126] The present inventors have found that SorCS1 binds to the insulin receptor through at least one binding site, and that one or more of the following parts of SorCS1 takes part in the binding:

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

[0127] Accordingly, the SorCS1-like agent preferably binds to a binding site on the insulin receptor, which binding site is characterised in that one or more of the shown parts of SorCS1 bind(s) to said binding site.

[0128] In a preferred embodiment the binding site on the insulin receptor comprises one or more of the sequences defined as follows:

SEQ ID NO: 56 aa 100-120

SEQ ID NO: 56 aa 127-150

SEQ ID NO: 56 aa 284-310

SEQ ID NO: 56 aa 362-379

SEQ ID NO: 56 aa 593-610

SEQ ID NO: 56 aa 629-652

SEQ ID NO: 56 aa 749-772.

[0129] In one preferred embodiment, the agent as defined herein above is selected from the group consisting of

1. a) an isolated SorCS1 polypeptide selected from the group consisting of

1. i) an amino acid sequence 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 and 51;
2. ii) a biologically active sequence variant of the amino acid sequence of a) wherein the variant has at least 70% sequence identity to said SEQ ID NO: 1; or
3. iii) a biologically active fragment of any of i or ii wherein said fragment comprises at least 5 contiguous amino acids of any of a) through b), and having at least 70% sequence identity to SEQ ID NO: 1 in a range of overlap of at least 5 amino acids wherein the biological activity is sensitization of an insulin receptor,

or a pharmaceutically acceptable salt thereof.

[0130] In one example, the polypeptide is a naturally occurring allelic variant of the sequence selected from the group consisting of SEQ ID NO: 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 and 51, and preferably the polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NOs: 5, 10, 15, 21, 27, 33, 37, 39, 43 and 47.

[0131] In a further example the polypeptide is a variant polypeptide described therein, wherein any amino acid specified in the selected sequence is altered to provide a conservative substitution as defined above. Accordingly, the polypeptide preferably has at least 70%, e.g. 75%, such as 80%, e.g. 85%, such as 90%, e.g. 95%, such as 98%, e.g. 99% sequence identity to a protein having a sequence 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 and 51.

[0132] In one example the polypeptide is glycosylated, such as a polypeptide being selected from the group consisting of SEQ ID NOs: 1, 2, 3, 4, 6, 7, 8, 9, 11, 12, 13, 14, wherein the polypeptide may be glycosylated in one or more of the following amino acid residue positions 184, 352, 433, 765, 776, 816, 847, 908 and 929, and/or 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, wherein the polypeptide may be glycosylated in one or more of the following amino acid residue positions 184, 352, 433, 765, 776, 816, 847, 908 and 929, and in another embodiment the glycosylated fragment has the sequence selected from the group consisting of SEQ ID NO: 5, 10 and 15, or the glycosylated polypeptide fragment has the sequence selected from the group consisting of SEQ ID NO: 21, 27 and 33.

[0133] In some embodiments, however, it is preferred that the polypeptide is deglycosylated.
The SorCS1-like agent may comprise a soluble fragment of a polypeptide as defined herein or a fragment of a variant, and accordingly, in one embodiment the polypeptide is a soluble polypeptide being a fragment of the sequences selected from the group consisting of SEQ ID NOs: 1, 2, 3, 4, 6, 7, 8, 9, 11, 12, 13, 14, or the polypeptide is a soluble polypeptide being a fragment of the sequences of claim 15.

[0134] It is preferred that the polypeptide is capable of forming at least one intramolecular cystine bridge, and more preferably that the polypeptide as defined herein above comprises a dimer of said polypeptide linked through at least one intermolecular cystine bridge.

[0135] In one embodiment the polypeptide according to the present invention 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.

Nucleic acid, vectors and host cells

[0136] Disclosed is a nucleic acid sequence capable of encoding the polypeptide as defined herein above, wherein the encoded polypeptide has at least 70%%, e.g. 75%, such as 80%, e.g. 85%, such as 90%, e.g. 95%, such as 98%, e.g. 99% sequence identity to a sequence 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 and 51 or to a fragment thereof.

[0137] Disclosed is a vector, said vector comprising at least one nucleic acid molecule as defined herein above, for use in the treatment of insulin resistance or diseases associated with insulin resistance in an individual.

[0138] The vector of the invention may further comprise a promoter which may be operably linked to the nucleic acid molecule of

the invention.

[0139] The promoter may be, but is not limited to the group consisting of: CMV, human UbiC, RSV, Tet-regulatable promoter, Mo-MLV-LTR, Mx1, EF-1alpha, PDGF beta and CaMK II.

[0140] The vector of the invention may be selected from the group consisting of vectors derived from the Retroviridae family including lentivirus, HIV, SIV, FIV, EAIV, CIV. Other vectors of the invention are selected from the group consisting of alphavirus, adenovirus, adeno associated virus, baculovirus, HSV, coronavirus, Bovine papilloma virus, Mo-MLV, preferably adeno associated virus.

[0141] In another preferred embodiment, the invention also relates to a host cell comprising the nucleic acid as described above, and even more preferred an isolated host cell of the invention is transformed or transduced with at least one vector as defined herein above, for use in the treatment of insulin resistance or diseases associated with insulin resistance in an individual.

[0142] The isolated host may be selected from the group consisting of Saccharomyces cerevisiae, E. coli, Aspergillus and Sf9 insect cells and of mammalian cells selected from the group consisting of human, feline, porcine, simian, canine, murine and rat cells, wherein the mammalian cell may be selected from, but is not limited to the group consisting of muscle cells, hepatocytes, adipocytes and cells of the pancreas such as α cells, β cells and δ cells.

[0143] In one embodiment the isolated host cell is selected from the group consisting of CHO, CHO-K1, HEI193T, HEK293, COS, PC12, HiB5, RN33b and BHK cells.

[0144] Disclosed is a packaging cell line as defined herein above, wherein said packaging cell line is capable of producing an infective virus particle for use in the treatment of insulin resistance or diseases associated with insulin resistance in an individual, said virus particle comprising a Retroviridae derived genome comprising a 5' retroviral LTR, a tRNA binding site, a packaging signal, a promoter operably linked to a polynucleotide sequence encoding the polypeptide as defined herein above, an origin of second strand DNA synthesis, and a 3' retroviral LTR.

[0145] In one example the genome of the packaging cell line is lentivirally derived and the LTRs are lentiviral.

[0146] As discussed above the SorCS1-like agent is any agent having the biological activity of SorCS1 in relation to the insulin receptor, ie. an agent which is capable a binding to the insulin receptor, and more preferably the agent is also capable of sensitizing the insulin receptor whereby it is possible to lower the blood glucose concentration in the individual being administered with the SorCS1-like agent by treating insulin resistance and diseases associated with insulin resistance. The agent may be any type of compound, such as polypeptides, antibodies as well as small organic molecules, wherein the antibody may be selected from the group consisting of: polyclonal antibodies, monoclonal antibodies, humanised antibodies, single chain antibodies, recombinant antibodies directed towards the insulin receptor.

[0147] Furthermore, as discussed herein administration of nucleic acids either naked, or in host cells or packaging cells, wherein the nucleic acid is capable of encoding the polypeptide as discussed herein, for the treatment of insulin resistance and diseases associated with insulin resistance is also an aspect of the invention.

Antibodies

[0148] As mentioned above, the agent may be an antibody, in particularly an antibody directed against the insulin receptor, or more preferred against one or more of the binding sites on the insulin receptor shown in Figure 23A.

[0149] Antibodies may furthermore be used as research toold for screening various aspects of the invention. Such methods are well known by those skilled in the art but is nevertheless described in further detail below. The antibodies for used for research tools are both antibodies directed towards the insulin receptor as well as directed towards the Vps10p-domain receptor, including SorCS1.

[0150] It is an aspect to provide antibodies or functional equivalents thereof specifically recognising and binding epitopes of the Vps10p-domain receptors and insulin receptors.

[0151] The antibody or functional equivalent thereof may be any antibody known in the art, for example a polyclonal or a

monoclonal antibody derived from a mammal or a synthetic antibody, such as a single chain antibody or hybrids comprising antibody fragments. Furthermore, the antibody may be mixtures of monoclonal antibodies or artificial polyclonal antibodies. In addition functional equivalents of antibodies may be antibody fragments, in particular epitope binding fragments. Furthermore, antibodies or functional equivalent thereof may be a small molecule mimicking an antibody. Naturally occurring antibodies are immunoglobulin molecules consisting of heavy and light chains. In preferred examples, the antibody is a monoclonal antibody.

[0152] The antibodies may also be recombinant antibodies. Recombinant antibodies are antibodies or fragments thereof or functional equivalents thereof produced using recombinant technology. For example recombinant antibodies may be produced using a synthetic library or by phage display. Recombinant antibodies may be produced according to any conventional method for example the methods outlined in "Recombinant Antibodies", Frank Breitling, Stefan Dübel, Jossey-Bass, September 1999.

[0153] The antibodies may also be bispecific antibodies, i.e. antibodies specifically recognising two different epitopes. Bispecific antibodies may in general be prepared starting from monoclonal antibodies, or from recombinant antibodies, for example by fusing two hybridoma's in order to combine their specificity, by Chemical crosslinking or using recombinant technologies. Antibodies according to the present invention may also be tri-specific antibodies.

[0154] Functional equivalents of antibodies may be a fragment of an antibody, preferably an antigen binding fragment or a variable region. Examples of antibody fragments useful with the present invention include Fab, Fab', $F(ab')_2$ and Fv fragments. Papain digestion of antibodies produces two identical antigen binding fragments, called the Fab fragment, each with a single antigen binding site, and a residual "Fc" fragment, so-called for its ability to crystallize readily. Pepsin treatment yields an $F(ab')_2$ fragment that has two antigen binding fragments which are capable of cross-linking antigen, and a residual other fragment (which is termed pFc'). Additional fragments can include diabodies, linear antibodies, single-chain antibody molecules, and multispecific antibodies formed from antibody fragments. As used herein, "functional fragment" with respect to antibodies, refers to Fv, F(ab) and $F(ab')_2$ fragments.

[0155] Preferred antibody fragments retain some or essential all the ability of an antibody to selectively binding with its antigen or receptor. Some preferred fragments are defined as follows:

1. (1) Fab is the fragment that contains a monovalent antigen-binding fragment of an antibody molecule. A Fab fragment can be produced by digestion of whole antibody with the enzyme papain to yield an intact light chain and a portion of one heavy chain.
2. (2) Fab' is the fragment of an antibody molecule and can be obtained by treating whole antibody with pepsin, followed by reduction, to yield an intact light chain and a portion of the heavy chain. Two Fab' fragments are obtained per antibody molecule. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxyl terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region.
3. (3) $(Fab')_2$ is the fragment of an antibody that can be obtained by treating whole antibody with the enzyme pepsin without subsequent reduction. $F(ab')_2$ is a dimer of two Fab' fragments held together by two disulfide bonds.
4. (4) Fv is the minimum antibody fragment that contains a complete antigen recognition and binding site. This region consists of a dimer of one heavy and one light chain variable domain in a tight, non-covalent association (V_H-V_L dimer). It is in this configuration that the three CDRs of each variable domain interact to define an antigen binding site on the surface of the V_H-V_L dimer. Collectively, the six CDRs confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

[0156] In one example the antibody is a single chain antibody ("SCA"), defined as a genetically engineered molecule containing the variable region of the light chain, the variable region of the heavy chain, linked by a suitable polypeptide linker as a genetically fused single chain molecule. Such single chain antibodies are also refered to as "single-chain Fv" or "scFv" antibody fragments. Generally, the Fv polypeptide further comprises a polypeptide linker between the VH and VL domains that enables the scFv to form the desired structure for antigen binding.

Procedures for making antibodies

[0157] Polyclonal and monoclonal antibodies directed against a specific antigen, or epitope of an antigen, can be produced according to standard procedures (see e.g. Antibodies - A laboratory Manual by Ed Harlow and David Lane, Cold Spring Harbor

Laboratory 1998, ISBN 0-87969-314-2). The procedure for subsequent generation of humanized antibodies or fragments thereof has also been described (e.g. A. M. Scott et al, Cancer Research 60:3254-3261, 2000; A. Nissim and Y. Chernajovsky, Handb. Exp. Pharmacol. 181:3-18, 2008; A. Mountain and J. R. Adair, Biotechnol. Genet. Eng. Rev. 10:1-142, 1992).

Humanised antibody framework

[0158] It is not always desirable to use non-human antibodies for human therapy, since the non-human "foreign" epitopes may elicit immune response in the individual to be treated. To eliminate or minimize the problems associated with non-human antibodies, it is desirable to engineer chimeric antibody derivatives, i.e., "humanized" antibody molecules that combine the non-human Fab variable region binding determinants with a human constant region (Fc). Such antibodies are characterized by equivalent antigen specificity and affinity of the monoclonal and polyclonal antibodies described above, and are less immunogenic when administered to humans, and therefore more likely to be tolerated by the individual to be treated.

[0159] Accordingly, in one example the binding polypeptide has a binding domain carried on a humanised antibody framework, also called a humanised antibody.

Human Antibodies

[0160] Human monoclonal antibodies can be produced by a variety of techniques, including conventional monoclonal antibody methodology, e.g., the standard somatic cell hybridization technique of Kohler and Milstein, Nature 256:495 (1975). Although somatic cell hybridization procedures are preferred, in principle, other techniques for producing monoclonal antibody can be employed, e.g., viral or oncogenic transformation of B-lymphocytes or phage display techniques using libraries of human antibody genes.

[0161] To generate fully human monoclonal antibodies to the epitopes of interest to the present invention, transgenic or transchromosomal mice containing human immunoglobulin genes (e.g., HCo12, HCo7 or KM mice) can be immunized with an enriched preparation of the antigen and/or cells expressing the epitopes of the receptor targets of the present invention, as described, for example, by Lonberg et al. (1994), supra; Fishwild et al. (1996), supra, and WO 98/24884. Alternatively, mice can be immunized with DNA encoding the CaOU-1 epitope. Preferably, the mice will be 6-16 weeks of age upon the first infusion.

Monovalent antibodies

[0162] The monospecific binding polypeptide may be monovalent, i.e. having only one binding domain.

[0163] For a monovalent antibody, the immunoglobulin constant domain amino acid residue sequences comprise the structural portions of an antibody molecule known in the art as CH1, CH2, CH3 and CH4. Preferred are those binding polypeptides which are known in the art as C_L. Preferrred C_L polypeptides are selected from the group consisting of C_{kappa} and C_{lambda}.

[0164] Furthermore, insofar as the constant domain can be either a heavy or light chain constant domain (C_H or C_L, respectively), a variety of monovalent binding polypeptide compositions are contemplated by the present invention. For example, light chain constant domains are capable of disulfide bridging to either another light chain constant domain, or to a heavy chain constant domain. In contrast, a heavy chain constant domain can form two independent disulfide bridges, allowing for the possibility of bridging to both another heavy chain and to a light chain, or to form polymers of heavy chains.

[0165] The specification contemplates an isolated monovalent binding polypeptide wherein the constant chain domain C has a cysteine residue capable of forming at least one disulfide bridge, and where at least two monovalent polypeptides are covalently linked by said disulfide bridge.

[0166] The constant chain domain C can be either C_L or C_H. Where C is C_L, the C_L polypeptide is preferably selected from the group consisting of C_{kappa} and C_{lambda}.

[0167] The specification contemplates a binding polypeptide composition comprising a monovalent polypeptide as above except where C is C_L having a cysteine residue capable of forming a disulfide bridge, such that the composition contains two monovalent

polypeptides covalently linked by said disulfide bridge.

Multispecificity, including bispecificity

[0168] Disclosed are multispecific binding polypeptides, which have affinity for and are capable of binding at least two different entities. Multispecific binding polypeptides can include bispecific binding polypeptides.

[0169] In one example the multispecific molecule is a bispecific antibody (BsAb), which carries at least two different binding domains, where preferably at least one of which is of antibody origin.

[0170] A bispecific molecule can also be a single chain bispecific molecule, such as a single chain bispecific antibody, a single chain bispecific molecule comprising one single chain antibody and a binding domain, or a single chain bispecific molecule comprising two binding domains. Multispecific molecules can also be single chain molecules or may comprise at least two single chain molecules.

[0171] The multispecific, including bispecific, antibodies may be produced by any suitable manner known to the person skilled in the art.
The traditional approach to generate bispecific whole antibodies was to fuse two hybridoma cell lines each producing an antibody having the desired specificity. Because of the random association of immunoglobulin heavy and light chains, these hybrid hybridomas produce a mixture of up to 10 different heavy and light chain combinations, only one of which is the bispecific antibody. Therefore, these bispecific antibodies have to be purified with cumbersome procedures, which considerably decrease the yield of the desired product.

[0172] By using a bispecific or multispecific binding polypeptide according to the invention the invention offers several advantages as compared to monospecific/monovalent binding polypeptides.

[0173] While human monoclonal antibodies are preferred, other antibodies which can be employed in the bispecific or multispecific molecules of the invention are murine, chimeric and humanized monoclonal antibodies. Such murine, chimeric and humanized monoclonal antibodies can be prepared by methods known in the art.

[0174] The inventors of this application have raised antibodies against several parts of the Vps10p-domain receptors. The present disclosure is directed to antibodies against the unifying feature of this receptor family - the Vps10p domain. The below sequence alignment of the Vps10p-domain demonstrate the conservation within this receptor family.

Table 1: Antibodies against Vps10p-domain receptors

Receptor	Name	Antigen	Species	Western	IH/IC	Ref.
SorLA	SORLA goat	extracellular domain	goat	X	X	Schmidt et. al., J.Biol.Chem. 282:32956-67, 2007
	Hale SORLA	Cytoplasmic domain	rabbit	X		
	SORLA LA	Complemen t type repeat	rabbit	X		
	Sol SORLA	extracellular domain	rabbit	X	X	Andersen et al., PNAS 103:13461-6, 2005
	SORLA tail	Cytoplasmic domain	rabbit	X		
	SORLA VPS	VPS10p domain	rabbit	X		
	#606870	Peptide seq. in Vps10p-domain	rabbit	X		
	#642739	C-terminal	rabbit	X		
	#643739	Cytoplasmic tail	rabbit	X		
	20C11	Extracellular domain	mouse	X	X	

Receptor	Name	Antigen	Species	Western	IH/IC	Ref.
	AG4	Extracellular domain	mouse	X		
Sortilin	#5264	Extracellular domain	rabbit	X	X	Munck Petersen et al, EMBO J. 18 :595-604, 1999
	#5448	Cytoplasmic domain	rabbit	X	X	Jansen et al, Nature Neurosci. 10 :1449-1457,2007
	#5287	Cytoplasmic domain	rabbit	X		
	CP 96 334	propeptide	Rabbit	X		Munck Petersen et al, EMBO J. 18 :595-604, 1999
	SR 96 204					
	#5438	Vps10p	rabbit	X		
	Sortilin goat /Laika	Extracellular domain	goat	X		
	F9	Extracellular domain	mouse	X	X	
	F11	Extracellular domain	mouse	X	X	
	AF2934	Extracellular domain	goat	X	X	R&D Systems, Jansen et al, Nature Neurosci. 10 :1449-1457,2007
	AF3154	Extracellular domain	goat	X	X	R&D Systems; Jansen et al, Nature Neurosci. 10 :1449-1457,2007
	anti-NTR3	Extracellular domain	mouse	X	X	BD Transduction Laboratories,
	ANT-009	Extracellular domain	mouse	X	X	Alomone Labs ; Nykjaer et al, Nature427 :8 43-848, 2004
SorCS1	AF3457	Extracellular domain	goat	X	X	BD Transduction Laboratories
	SorCS1 goat	Extracellular domain	goat	X		
	L-SorCS1	Extracellular domain	rabbit	X	X	Hermey et al, J.Biol.Chem. 279:50221-50229, 2003
	Leu-SorCS1	Leucine-rich domain	rabbit	X	X	Hermey et al, J.Biol.Chem. 279:50221-50229, 2003
	#5466	Extracellular domain	rabbit	X	X	
	1D	Extracellular domain	mouse	X		
	4H	Extracellular domain	mouse	X		
	6B	Extracellular domain	mouse	X		
	4A	Extracellular domain	mouse	X		

Receptor	Name	Antigen	Species	Western	IH/IC	Ref.
SorCS2	AF4237	Extracellular domain	sheep	X		BD Transduction Laboratories
	SorCS2 goat	Extracellular domain	goat	X	X	
	#5422	Extracellular domain	rabbit	X	X	Hermey et al, Biochem. J., 395:285-93, 2006
	#5431	28 C-terminal amino acids	rabbit	X	X	
	SorCS2-prp	propeptide	rabbit	X		Schousboe Sjoegaard, Dissertation, Aarhus University, 2005
	M1	Extracellular domain	mouse		X	Roland Holst, Master of Science Thesis, Aarhus University, 2006
	M3	Extracellular domain	mouse		X	Roland Holst, Master of Science Thesis, Aarhus University, 2006
	M4	Extracellular domain	mouse		X	Roland Holst, Master of Science Thesis, Aarhus University, 2006
	M7	Extracellular domain	mouse		X	Roland Holst, Master of Science Thesis, Aarhus University, 2006
	M9	Extracellular domain	mouse		X	Roland Holst, Master of Science Thesis, Aarhus University, 2006
	M10	Extracellular domain	mouse		X	Roland Holst, Master of Science Thesis, Aarhus University, 2006
	M13	Extracellular domain	mouse	X		Roland Holst, Master of Science Thesis, Aarhus University, 2006
	M15	Extracellular domain	mouse		X	Roland Holst, Master of Science Thesis, Aarhus University, 2006
	M18	Extracellular domain	mouse	X	X	Roland Holst, Master of Science Thesis, Aarhus University, 2006
	M19	Extracellular domain	mouse	X	X	Roland Holst, Master of Science Thesis, Aarhus University, 2006
	S21	Extracellular domain	mouse	X		Roland Holst, Master of Science Thesis, Aarhus University, 2006
	SorCS2-GST-73aa	Extracellular domain	rabbit	X		
	SorCS2-GST-100aa	Extracellular domain	rabbit	X		
	SorCS2-GST-172aa	Extracellular domain	rabbit	X		
SorCS3	SorCS3-N	extracellular domain	rabbit	X		
	SorCS3-C	15 C-terminal aa	rabbit	X		

Receptor	Name	Antigen	Species	Western	IH/IC	Ref.
	Sort3 N Term	N-terminal domain	rabbit	X	X	Westergaard et al, FEBS Lett. 579:1172-6, 2005
	#5389					
	#5432	Extracellular domain	rabbit	X	X	
	MAB3067	Extracellular domain	mouse	X		BD Transduction Laboratories
	MAB30671	Extracellular domain	mouse	X		BD Transduction Laboratories
	AF3326	Extracellular domain	goat	X		BD Transduction Laboratories
	SorCS3 goat	Extracellular domain	goat	X		

Successful clinical use of antibodies

[0175] A number of therapeutic antibodies are in clinical use. Examples include Genentech's Rituxan, an antibody directed against the CD20 receptor (used in rheumatoid arthritis), Johnson & Johnson's Remicade, an antibody directed against TNF alpha receptor (in Psoriasis), Roche's Avastin, an anti-VEGF antibody used for treatment of colorectal and lung cancer, as well as Herceptin, an antibody against the receptor HRE2 used in breast cancer therapy.

[0176] Assessing binding to a receptor is routine work for the person skilled in the bio-technical field. In this regard it has to be mentioned that the Vps10p-domain receptor family were known at the priority date of this invention and binding assays involving.

[0177] In one example, the is an anti-Insulin Receptor polyclonal or monoclonal antibody.

Transgenic SorCS1 mice

[0178] The present inventors have found that SorCS1 is expressed in adipose tissue, skeletal muscle and β-cells of the pancreas; all tissues involved in glucose metabolism (Fig.3). In order to examine the function of SorCS1 and its different splice variants the investors generated a conditional knockout mouse using a new developed targeting strategy based on FLP recombination and an insertion technique called 'recombinase-mediated cassette exchange'. The model was used to generate a 'full' knockout mouse lacking all splice forms of SorCS1 whereby expression of all the splice variants have been disrupted (Fig.4). SorCS1 mice deficient in all splice variants ('full' knockout) show no gross abnormalities or signs of changed behaviour, they are fertile and they exhibit a normal life span (unpublished). However, the SorCS1 knockout mouse was phenotypically characterized with respect to glucose metabolism and development of type-2 diabetes, and preliminary results support an important role of the receptor in development of diabetes. Whereas blood glucose levels in fasting male mice at 17 and 50 weeks of age were similar to that of control littermates, female mice at the age of 50 weeks showed a dramatic elevation in blood glucose as compared to age-matched control mice (Fig.5). However, both genders exhibited elevated levels of insulin at 50 weeks of age (Fig.6 female only). In agreement, their pancreatic islets were up to 3-fold enlarged as determined by immunostaining for a β-cell marker (Fig. 15). The results indicate that old SorCS1 knockout male mice are hyperinsulimic but prediabetic, whereas old SorCS1 knockout female mice are hyperglycaemic and hyperinsulimic, thus becoming diabetic.

[0179] Furthermore, the investors have also found that both male and female SorCS1 knockout mice have normal body weight. The absence of obesity in the knockout mice makes it possible to dissociate the effect of obesity on the prediabetic or diabetic phenotype, which complicates analysis in several existing animal models of diabetes. However, because obesity is a significant risk factor for type-2 diabetes, SorCS1 deficient animals were also fed a high calorie Western type diet to study the impact of obesity on disease progression. Physiological measurements revealed increases in plasma glucose and insulin levels and in abdominal fat for the wild type mice on high calorie diet compared to wild type mice on normal diet (fig.8+9). In contrast, the SorCS1 knockout mice showed no significant changes on Western type diet compared to normal diet, thus showing no aggravation of the diabetic status. The lower amount of abdominal fat in the knockout mice on western diet compared to the wild type mice confirm the insulin resistance of the knockout mice as it leads to reduced uptake of glucose in the adipose tissue and

thereby less production of abdominal fat.

[0180] Accordingly, the present inventors have shown that the SorCS1 knockout mouse is a unique animal model for studying insulin resistance and diseases related to insulin resistance, in particularly diabetes because the SorCS1 knockout mouse develops the symptoms normally related to insulin resistance and diabetes, including the late symptoms of diabetes, such as neuropathic symptoms.

[0181] In addition, the inventors have shown that 50 weeks old male and female SorCS1-/-mice exhibit elevated amount of phosphorylated IR as compared to age-matched controls (Fig. 10) suggesting that SorCS1 may partake in insulin Signalling in peripheral tissues. Alternatively, a signal derived from SorCS1 that convert on the insulin signalling pathways may be missing, resulting in compensatory upregulation of phosphorylated IR. Since SorCS1 is also engaged in cellular sorting, the receptor may also regulate the subcellular distribution of IR.

[0182] Therefore, one important aspect of the present invention relates to a transgenic knock-out mouse in which the endogenous Vps10p-domain receptor SorCS1 genes have been disrupted to abolish expression of a functional SorCS1 receptor, and wherein said mouse exhibits a reduced response to insulin relative to a non-transgenic control mouse.

[0183] In a further embodiment the invention relates to the transgenic mouse as defined herein above, wherein said disruption comprises a deletion of the SorCS1 receptor gene nucleotide sequences encoding the start codon or a region of the mouse SorCS1 receptor from the extracellular domain, transmembrane domain, or the cytoplasmic domain.

[0184] In one aspect, the invention relates to a transgenic mouse capable of encoding soluble and/or full length SorCS1 in a tissue specific manner, upon activation of expression. The procedure for preparing said mouse is described in example 12. The tissue to be specifically activated may be selected from, but is not limited to, the group consisting of liver, muscle, pancreas and adipose tissue.

Methods of screening for agents of the invention

[0185] The present invention provides specific targets and methods for screening and evaluating further candidate agents as claimed including SorCS1 peptide and polypeptide fragments and mutant and variants thereof.

[0186] While the screening of a large number of peptides for a certain physiological activity may be a laborious undertaking, the exact disclosures of the assay herin to be carried out enables the skilled person to reproduce the present invention without undue burden of experimentation and without needing inventive skill.

[0187] For this purpose screening libraries of candidate agents outside the scope of protection are readily available for purchase on the market. Whether a library is a peptide library or a chemical library does not have any impact in the present situation since screening of chemical libraries is also routine work. In fact screening of chemical libraries is a service offered by commercial companies, and it is clear from their presentation material (See e.g. http://www.analyticon.com/) that they do not consider the screening work as such to be inventive.

[0188] Initially in the process of screening for SorCs1-like agents it is relevant to perform binding studies as discussed herein, in particularly in relation to the Figures and the Examples to verify that the agent binds to the insulin receptor. Furthermore, it may be relevant to show that the agent in fact also sensitizes the insulin receptor. As discussed above, this may be done indirectly by showing that administration of the SorCS1-like agent in fact reduces the blood glucose concentration by for example performing a glucose tolerance test (GTT), and preferably also showing that the insulin concentration is lowered, if it initially was increased. Furthermore, sensitisation of the insulin receptor may also be measured by measuring the amount of insulin receptor, since administration of soluble SorCS1 leads to an increase of insulin receptors.

[0189] Accordingly, in one embodiment the present invention relates to a method for screening for the ability of the SorCS1-like agent as defined herein above to reduce blood glucose levels, said method comprising the steps of

1. a) providing a first and a second transgenic mouse;
2. b) administering to said first transgenic mouse a candidate agent, and
3. c) administering to said second transgenic mouse a physiological solution, and
4. d) taking blood samples from the mouse of b) and c) respectively, at predetermined time intervals, such as at 15 minutes, 30 minutes, 60 minutes, 2 and 4 hours, subsequent to administration of said agent, and

5. e) comparing blood glucose levels in the samples of d); wherein a reduction in blood glucose level of said first transgenic mouse administered said candidate agent relative to said second transgenic mouse not administered said candidate agent indicates that the candidate agent reduces blood glucose levels.

[0190] In another embodiment, the invention relates to a method for screening for the ability of the SorCS1-like agent of the invention to reduce blood glucose levels, said method comprising the steps of

a) providing a first and a second wild-type mouse; and

f) administering to said first mouse the agent of claim 1, and

g) administering to said second mouse a physiological solution, and

h) taking blood samples from the two mice of b) and c) respectively, at predetermined time intervals, such as at 15 minutes, 30 minutes, 60 minutes, 2 and 4 hours, subsequent to administration of said agent, and

i) comparing plasma glucose levels in the samples of d); wherein a reduction in blood glucose level of said first wild-type mouse administered said agent relative to said second wild type mouse not administered said candidate agent, indicates that the agent reduces blood glucose levels.

Pharmaceutical composition and administration forms

[0191] The present invention also encompass pharmaceutical compositions comprising the agent as defined herein. In the present context the term agent and compound is considered synonyms when discussin the pharmaceutical composition.

[0192] The main routes of drug delivery according to this invention are parenteral, oral or enteral, and topical in order to introduce the agent into the blood stream to ultimately target the sites of the insulin receptors.

[0193] The agent may be administered to cross any mucosal membrane of an animal to which the biologically active substance is to be given, e.g. in the nose, vagina, eye, mouth, genital tract, lungs, gastrointestinal tract, or rectum, preferably the mucosa of the nose, or mouth.

[0194] The agents may be administered orally or enterally

[0195] Compounds of the invention may also be administered parenterally, that is by intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. Appropriate dosage forms for such administration may be prepared by conventional techniques. The compounds may also be administered by inhalation, which is by intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques.

[0196] The compounds according to the invention may be administered with at least one other compound, such as for example insulin. The compounds may be administered simultaneously, either as separate formulations or combined in a unit dosage form, or administered sequentially.

[0197] In one embodiment of the present invention, the dosage of the active ingredient of the pharmaceutical composition as defined herein above, is between 10 µg to 500 mg per kg body mass, such as between 20 µg and 400 mg, e.g. between 30 µg and 300 mg, such as between 40 µg and 200 mg, e.g. between 50 µg and 100 mg, such as between 60 µg and 90 µg, e.g. between 70 µg and 80 µg.

[0198] Furthermore, the dosage may be administered as a bolus administration or as a continuous administration. In relation to bolus administration the pharmaceutical composition may be administered at intervals of 30 minutes to 24 hours, such as at intervals of 1 to 6 hours. When the administration is continuous it is administered over an interval of time that normally is from 6 hours to 7 days. However, normally the dosage will be administered as a bolus 1-3 times per day.

[0199] In one important aspect the duration of the treatment is life long.

Formulations

[0200] Whilst it is possible for the compounds or salts of the present invention to be administered as the raw chemical, it is preferred to present them in the form of a pharmaceutical formulation. Accordingly, the present specification further provides a pharmaceutical formulation, for medicinal application, which comprises a compound of the present invention or a pharmaceutically acceptable salt thereof, as herein defined, and a pharmaceutically acceptable carrier therefore.

[0201] The agents of the present invention may be formulated into a wide variety dosage forms, suitable for the various administration forms discussed above.

[0202] The pharmaceutical compositions and dosage forms may comprise the agents of the invention or its pharmaceutically acceptable salt or a crystal form thereof as the active component.

[0203] Furthermore, the pharmaceutical compositions may comprises pharmaceutically acceptable carriers that can be either solid or liquid.

[0204] Solid form preparations are normally provided for oral or enteral administration, such as powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, wetting agents, tablet disintegrating agents, or an encapsulating material.

[0205] Preferably, the composition will be about 0.5% to 75% by weight of a compound or compounds of the invention, with the remainder consisting of suitable pharmaceutical excipients. For oral administration, such excipients include pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, gelatin, sucrose, magnesium carbonate, and the like.

[0206] In powders, the carrier is a finely divided solid which is a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. Powders and tablets preferably contain from one to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be as solid forms suitable for oral administration.

[0207] Drops may comprise sterile or non-sterile aqueous or oil solutions or suspensions, and may be prepared by dissolving the active ingredient in a suitable aqueous solution, optionally including a bactericidal and/or fungicidal agent and/or any other suitable preservative, and optionally including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container aseptically. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01 %). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

[0208] Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavours, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

[0209] Other forms suitable for oral administration include liquid form preparations including emulsions, syrups, elixirs, aqueous solutions, aqueous suspensions, toothpaste, gel dentrifrice, chewing gum, or solid form preparations which are intended to be converted shortly before use to liquid form preparations. Emulsions may be prepared in solutions in aqueous propylene glycol solutions or may contain emulsifying agents such as lecithin, sorbitan monooleate, or acacia. Aqueous solutions can be prepared

by dissolving the active component in water and adding suitable colorants, flavours, stabilizing and thickening agents. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well known suspending agents. Solid form preparations include solutions, suspensions, and emulsions, and may contain, in addition to the active component, colorants, flavours, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

[0210] The compounds of the present invention may be formulated for parenteral administration (e.g., by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, for example solutions in aqueous polyethylene glycol. Examples of oily or nonaqueous carriers, diluents, solvents or vehicles include propylene glycol, polyethylene glycol, vegetable oils (e.g., olive oil), and injectable organic esters (e.g., ethyl oleate), and may contain formulatory agents such as preserving, wetting, emulsifying or suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution for constitution before use with a suitable vehicle, e.g., sterile, pyrogen-free water.

[0211] Oils useful in parenteral formulations include petroleum, animal, vegetable, or synthetic oils. Specific examples of oils useful in such formulations include peanut, soybean, sesame, cottonseed, corn, olive, petrolatum, and mineral. Suitable fatty acids for use in parenteral formulations include oleic acid, stearic acid, and isostearic acid. Ethyl oleate and isopropyl myristate are examples of suitable fatty acid esters.

[0212] Suitable soaps for use in parenteral formulations include fatty alkali metal, ammonium, and triethanolamine salts, and suitable detergents include (a) cationic detergents such as, for example, dimethyl dialkyl ammonium halides, and alkyl pyridinium halides; (b) anionic detergents such as, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates, (c) nonionic detergents such as, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylenepolypropylene copolymers, (d) amphoteric detergents such as, for example, alkyl-.beta.-aminopropionates, and 2-alkyl-imidazoline quaternary ammonium salts, and (e) mixtures thereof.

[0213] The parenteral formulations typically will contain from about 0.5 to about 25% by weight of the active ingredient in solution. Preservatives and buffers may be used. In order to minimize or eliminate irritation at the site of injection, such compositions may contain one or more nonionic surfactants having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulations will typically range from about 5to about 15% by weight. Suitable surfactants include polyethylene sorbitan fatty acid esters, such as sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol. The parenteral formulations can be presented in unit-dose or multi-dose sealed containers, such as ampules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid excipient, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

[0214] The compounds of the invention can also be delivered topically for transdermal or transmucosal administration. Regions for topical administration include the skin surface and also mucous membrane tissues of the vagina, rectum, nose, mouth, and throat. Compositions for topical administration via the skin and mucous membranes should not give rise to signs of irritation, such as swelling or redness. Transdermal administration typically involves the delivery of a pharmaceutical agent for percutaneous passage of the drug into the systemic circulation of the patient. The skin sites include anatomic regions for transdermally administering the drug and include the forearm, abdomen, chest, back, buttock, mastoidal area, and the like.

[0215] The topical composition may include a pharmaceutically acceptable carrier adapted for topical administration. Thus, the composition may take the form of a suspension, solution, ointment, lotion, sexual lubricant, cream, foam, aerosol, spray, suppository, implant, inhalant, tablet, such as a sublingual tablet, capsule, dry powder, syrup, balm or lozenge, for example. Methods for preparing such compositions are well known in the pharmaceutical industry.

[0216] The compounds of the present invention may be formulated for topical administration to the epidermis as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also containing one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Formulations suitable for topical administration in the mouth include lozenges comprising active agents in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid

carrier.

[0217] Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or a macrogel. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or nonionic surfactant such as a sorbitan ester or a polyoxyethylene derivative thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

[0218] Lotions include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

[0219] Transdermal delivery may be accomplished by exposing a source of the complex to a patient's skin for an extended period of time. Transdermal patches have the added advantage of providing controlled delivery of a pharmaceutical agent-chemical modifier complex to the body. See Transdermal Drug Delivery: Developmental Issues and Research Initiatives, Hadgraft and Guy (eds.), Marcel Dekker, Inc., (1989); Controlled Drug Delivery: Fundamentals and Applications, Robinson and Lee (eds.), Marcel Dekker Inc., (1987); and Transdermal Delivery of Drugs, Vols. 1-3, Kydonieus and Berner (eds.), CRC Press, (1987). Such dosage forms can be made by dissolving, dispersing, or otherwise incorporating the pharmaceutical agent-chemical modifier complex in a proper medium, such as an elastomeric matrix material. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate-controlling membrane or dispersing the compound in a polymer matrix or gel.

[0220] For example, a simple adhesive patch can be prepared from a backing material and an acrylate adhesive. The pharmaceutical agent-chemical modifier complex and any enhancer are formulated into the adhesive casting solution and allowed to mix thoroughly. The solution is cast directly onto the backing material and the casting solvent is evaporated in an oven, leaving an adhesive film. The release liner can be attached to complete the system.

[0221] Foam matrix patches are similar in design and components to the liquid reservoir system, except that the gelled pharmaceutical agent-chemical modifier solution is constrained in a thin foam layer, typically a polyurethane. This foam layer is situated between the backing and the membrane which have been heat sealed at the periphery of the patch.

[0222] For passive delivery systems, the rate of release is typically controlled by a membrane placed between the reservoir and the skin, by diffusion from a monolithic device, or by the skin itself serving as a rate-controlling barrier in the delivery system. See U.S. Pat. Nos. 4,816,258; 4,927,408; 4,904,475; 4,588,580, 4,788,062; and the like. The rate of drug delivery will be dependent, in part, upon the nature of the membrane. For example, the rate of drug delivery across membranes within the body is generally higher than across dermal barriers. The rate at which the complex is delivered from the device to the membrane is most advantageously controlled by the use of rate-limiting membranes which are placed between the reservoir and the skin. Assuming that the skin is sufficiently permeable to the complex (i.e., absorption through the skin is greater than the rate of passage through the membrane), the membrane will serve to control the dosage rate experienced by the patient.

[0223] Suitable permeable membrane materials may be selected based on the desired degree of permeability, the nature of the complex, and the mechanical considerations related to constructing the device. Exemplary permeable membrane materials include a wide variety of natural and synthetic polymers, such as polydimethylsiloxanes (silicone rubbers), ethylenevinylacetate copolymer (EVA), polyurethanes, polyurethane-polyether copolymers, polyethylenes, polyamides, polyvinylchlorides (PVC), polypropylenes, polycarbonates, polytetrafluoroethylenes (PTFE), cellulosic materials, e.g., cellulose triacetate and cellulose nitrate/acetate, and hydrogels, e.g., 2-hydroxyethylmethacrylate (HEMA).

[0224] The compounds of the present invention may also be formulated for administration as suppositories. A low melting wax, such as a mixture of fatty acid glycerides or cocoa butter is first melted and the active component is dispersed homogeneously, for example, by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and to solidify.

[0225] The active compound may be formulated into a suppository comprising, for example, about 0.5% to about 50% of a compound of the invention, disposed in a polyethylene glycol (PEG) carrier (e.g., PEG 1000 [96%] and PEG 4000 [4%].

[0226] The compounds of the present invention may be formulated for vaginal administration. Pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

[0227] The compounds of the present invention may be formulated for nasal administration. The solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in a single or multidose form. In the latter case of a dropper or pipette this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray this may be achieved for example by means of a metering atomizing spray pump.

[0228] The compounds of the present invention may be formulated for aerosol administration, particularly to the respiratory tract and including intranasal administration. The compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. The active ingredient is provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by a metered valve. Alternatively the active ingredients may be provided in a form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidine (PVP). The powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of e.g., gelatin or blister packs from which the powder may be administered by means of an inhaler.

[0229] When desired, formulations can be prepared with enteric coatings adapted for sustained or controlled release administration of the active ingredient.

[0230] The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Pharmaceutically acceptable salts

[0231] Pharmaceutically acceptable salts of the instant compounds, where they can be prepared, are also disclosed.

[0232] These salts will be ones which are acceptable in their application to a pharmaceutical use. By that it is meant that the salt will retain the biological activity of the parent compound and the salt will not have untoward or deleterious effects in its application and use in treating diseases.

[0233] Pharmaceutically acceptable salts are prepared in a standard manner. If the parent compound is a base it is treated with an excess of an organic or inorganic acid in a suitable solvent. If the parent compound is an acid, it is treated with an inorganic or organic base in a suitable solvent.

[0234] The compounds of the invention may be administered in the form of an alkali metal or earth alkali metal salt thereof, concurrently, simultaneously, or together with a pharmaceutically acceptable carrier or diluent, especially and preferably in the form of a pharmaceutical composition thereof, whether by oral, rectal, or parenteral (including subcutaneous) route, in an effective amount.

[0235] Examples of pharmaceutically acceptable acid addition salts for use in the present inventive pharmaceutical composition include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric and sulfuric acids, and organic acids, such as tartaric, acetic, citric, malic, lactic, fumaric, benzoic, glycolic, gluconic, succinic, p-toluenesulphonic acids, and arylsulphonic, for example.

[0236] In one embodiment the pharmaceutical composition as defined herein above comprises a pharmaceutically acceptable carrier.

[0237] In one embodiment of the present invention the pH of the pharmaceutical composition as defined herein above is between pH 4 and pH 9.

Kit of parts

[0238] In one aspect the present specification relates to a kit in parts comprising:

- a pharmaceutical composition as defined herein above
- a medical instrument or other means for administering the medicament
- instructions on how to use the kit in parts.
- optionally a second active ingredient as defined herein above

[0239] The instrument as defined herein above is also called insulin pen described in US Patents Nos. 5,462,535, US 5,999,323 and US 5,984,906. The second ingredient may be any suitable active ingredient normally administered to individuals suffering from insulin resistance and diseases associated with insulin resistance such as insulin. By sensitizing the insulin receptor due to administration of a pharmaceutical composition as defined herein it is believed that the need for insulin is reduced.

Treatments

[0240] As discussed above the present specification also relates to the treatment of insulin resistance or diseases associated with insulin resistance, said method comprising administering to an individual in need thereof a therapeutically effective amount of the agent as defined above; or the isolated nucleic acid sequence as defined above; or the the expression vector as defined above; or a composition of host cells as defined above; or a packaging cell line as defined above, or a combination thereof.

[0241] The diseases associated with insulin resistance are in particular selected from the group consisting of insulin resistance syndrome, Type 2 diabetes mellitus, impaired glucose tolerance, the metabolic syndrome, hyperglycemia, hyperinsulinemia, arteriosclerosis, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, dyslipidemia, obesity, central obesity, polycystic ovarian syndrome, hypercoagulability, hypertension, microalbuminuria, insulin resistance syndrome (IRS), Type 2 diabetes mellitus, impaired glucose tolerance, the metabolic syndrome, hyperglycemia, and hyperinsulinemia.

[0242] The present inventors have found that administration of a SorCS1-like agent sensitizes the insulin receptor, in that it stabilises the insulin receptor, increases the amount of insulin receptors, and/or increases the amount of activated insulin receptors (phosphorylated insulin receptors are measured). Therefore, in another aspect, the present specification relates to a method of sensitizing an insulin receptor, said method comprising administering a Vps10p-domain receptor selected from the group consisting of:

f) SorCS1

g) SorCS2

h) SorCS3

i) Sortilin and

j) SorLA,

thus being useful in a method of treatment of insulin resistence or diseases associated with insulin resistance.

[0243] Furthermore, the inventors have found that when administering a SorCS1-like agent then the insulin receptors may be upregulated, and accordingly, the present specification relates to a method of upregulating an insulin receptor or a fragment or variant thereof, in a patient in need thereof, said method comprising administering to an individual in need thereof a therapeutically effective amount of the agent as defined above; or the isolated nucleic acid sequence as defined above; or the the expression vector as defined above; or a composition of host cells as defined above; or a packaging cell line as defined above, or a combination thereof.

[0244] Furthermore, it has been found that a SorCS1-like agent increases the insulin sensitivity, and accordingly the present invention also relates to a method for increasing insulin sensitivity comprising administering to an individual in need thereof a therapeutically effective amount of the agent as defined above; or the isolated nucleic acid sequence as defined above; or the the expression vector as defined above; or a composition of host cells as defined above; or a packaging cell line as defined above, or a combination thereof. This individual is typically an individual suffering from any of the diseases mentioned above, more likely an individual suffering from diabetes type 1 or type 2.

Detailed Description of the drawings

[0245]

Figure 1: The Vps10p-domain receptor family. Their structural organization is indicated.

Figure 2: Splice variants of mSorCS1. A) Organization of the murine SorCS1 gene leading to the generation of different cytoplasmic tails. The black boxes represent exon 23 and 24 with typical splice sites. In the composite internal/terminal exon 25 (grey) and 26 (white), the dotted line indicates a potential splice site. The alternative used terminal exons 25, 26, 27, and 28 are shown in white. B) Amino acid sequences of the mSorCS1 cytoplasmic domains. Dileucine motifs are underlined, SH3 domain-binding motifs are overlined, SH2 domain-binding motifs are underlined by dashed lines, and YXXØ motifs are overlined by dashed lines.

Figure 3: Expression of the different mSorCS1 splice variants. Expression of the extracellular part of SorCS1 (SorCS1.ex) and the five tail splice variants SorCS1-a, -b, -c, c^+ and -d were determined in tissue from adult mice by reverse transcription-PCR (RT-PCR) with specific primer pairs. The SorCS1.ex specific primers are spanning the exon 21 to 24 junctions giving a 390 bp product. The SorCS1-a specific primers are spanning the exon 21 to 25 junctions giving a 586 bp product. The SorCS1-b specific primers are spanning the exon 21 to 25 junctions and the exon 25 to 27 junctions giving a 621 bp product. The SorCS1-c specific primers are spanning the exon 21 to 26 junctions giving a 626bp product. The SorCS1-d specific primers are spanning the exon 21 to 25 junctions and the exon 25 to 28 junction giving a 636bp product. Total RNA preparations were made from hippocampus, liver, adipose tissue (fat), muscle, pancreas and testis isolated from wild type and hippocampus and liver from SorCS1-KO mice of about 8 weeks of age using the Versagene Total RNA purification Kit (Gentra Systems). Briefly, tissues were surgically removed and frozen on dry ice. Frozen tissue samples were disrupted and homogenized for up to 60 sec using a rotor stator (Ultra-Turrax, IKA-Werke) in 800 µl lysis buffer containing 5 mM Tris (2-carboxyethyl) phosphine (TCEP) and the total RNA was purified according to the manufacturers protocol for the kit. RT-PCR were performed with 0.75 µg to 1 µg total RNA from each sample using the TITANIUM One-step RT-PCR kit (Clontech). All reactions were performed in 50 µl volume containing 1 x One-step buffer (40 mM tricine, 20 mM KCl, 3 mM $MgCl_2$, 3.75µg/µl BSA), 0.2 mM of each dNTP, 25 µl Thermostabilizing reagent, 10 µl GC-melt, 20 µM Oligo(dT)primer, 20 units Recombinant RNase inhibitor, 1 x RT-TITANIUM™ Taq enzyme mix (all supplied with the kit) and 45 µM of each primer. PCR conditions were: 50°C for 1 hour, 94°C for 5 min, 35 cycles at 94°C for 30 sec, 64°C for 30 sec, 68°C for 1 min, and 68°C for 2 min.

Figure 4: Generation of the mSorCS1 knockout mouse. A) Strategy used to generate mSorCS1 knockout mice by homologous recombination in embryonic stem cells. A schematic representation of the wild-type murine SorCS1 locus (top), the targeting vector (middle), and the homologous recombinant genome (bottom) are shown. B) Analysis of mSorCS1 mRNA expression, showing lack of transcription of all mSorCS1 splice variant. Fragments are obtained by RT-PCR on mRNA from hippocampus of wild-type (WT) and SorCS1 knockout (KO) mice using specific primer pairs to identify the extracellular part of SorCS1 (ext) or each of the five tail variants (a, b, c, c^+, and d) (see fig.3). C) Western blot analysis of cortex showing lack of mSorCS1 protein in the mSorCS1 knockout (KO) mice. Proteins were extracted as lysates from cortex obtained at E14.5. The tissue was dissolved in 100 µl TNE-buffer (10 mM Tris-HCl, 150 mM NaCl, 1 mM EDTA, 1% nonidet P-40 (Sigma Aldrich) pH. 8) containing protease inhibitors (CompleteMini) by vigorous vortexing. After freezing ON at 20°C, the lysates were vortexed and centrifuged 10 min at 1000 x g. The lysates (supernatant) were transferred to a new tube and Bio-Rad Protein Assay measured the protein concentration. Lysates (200µg) were resolved on SDS-PAGE and transferred to nitrocellulose. The blot was then probed with a rabbit polyclonal antibody against the leucine-rich part of SorCS1 (α-hSorCS1-leu). Arrow indicates band of SorCS1. Neo; neomycin, TK; thymidine kinase, FRT/F3; Flp recombinase target sites.

Figure 5: Average blood glucose in A) male and B) female mice at different age. Animals were fasted overnight (16h). Wild type (wt) and SorCS1 knockout (KO) mice were anesthetized with diethyl ether, blood samples were obtained by retroorbital bleeding and plasma glucose was measured immediately on an automatic monitor (Ascensia Contour from Bayer). Statistically significant increases in blood glucose levels from knockout relative to wild type mice are indicated with stars. Error bars indicate SEM.

Figure 6: Plasma insulin levels in female wild-type and SorCS1 knockout mice from 10 to 50 weeks of age. Animals were fasted overnight (16h). Mice were anesthetized with diethyl ether, blood samples were obtained by retroorbital bleeding and plasma insulin levels were determined using an ultrasensitive mouse insulin enzyme-linked immunosorbent assay kit (DRG

Diagnostics, Marburg, Germany). Data are means ± SEM for 4 to 10 mice in each group. Statistically significant increases in blood glucose levels from knockout relative to wild type mice are indicated with stars.

Figure 7: Glucose tolerance test in SorCS1 knockout mice and wild type littermates. Female wild type (wt) and SorCS1 knockout (KO) mice 59 weeks of age were fasted overnight (16 h) and injected intraperitoneally with a bolus of D-glucose (Sigma) (2 mg/g body weight) in sterile saline. Mice were anesthetized with diethyl ether, blood samples were obtained by retroorbital bleeding at times 0, 15, 30, 60, and 120 min after injection, and plasma A) glucose and B) insulin levels were measured. Plasma glucose was measured immediately after sampling on an automatic monitor (Ascensia Contour from Bayer). Insulin levels were determined using an ultrasensitive mouse insulin enzyme-linked immunosorbent assay kit (DRG Diagnostics, Marburg, Germany). Data are means ± SEM for four mice in each group.

Figure 8: Elevated plasma glucose- and insulin levels in wild type mice on Western type diet. Female A) + C) and male B) + D) wild type (wt) and SorCS1 knockout (KO) mice were fed a high calorie Western type diet (WD) (24%protein, 41%carbonhydrate, 24%fat) (Research Diets. D12451) from 10 weeks of age to 50 weeks of age. At 50 weeks of age the animals were fasted overnight (16h), anesthetized with diethyl ether and blood samples were obtained by retroorbital bleeding. Plasma glucose levels A) + B) were measured immediately after sampling on an automatic monitor (Ascensia Contour from Bayer), whereas plasma insulin levels C) + D) were determined using an ultrasensitive mouse insulin enzyme-linked immunosorbent assay kit (DRG Diagnostics, Marburg, Germany). Data are means ± SEM for 4 to 10 mice in each group.

Figure 9: Abdominal adipose tissue in wild-type and knockout mice on western type diet.

Female A) and male B) wild type and SorCS1 knockout mice were fed a high calorie Western type diet (WD) (24%protein, 41%carbonhydrate, 24%fat) (Research Diets. D12451) from 10 weeks of age to 50 weeks of age. At the end of the study the animals were killed and the abdominal fat (adipose tissue) was separated and weighed. Data are means ± SEM for 4 to 10 mice in each group.

Figure 10: Expression of IR, phosphorylated IR (pY-IR) and Glut4 in muscle and adipose tissue. Female SorCS1 knockout (-/-) mice and wild-type (+/+) control mice 50 weeks of age were fasted overnight, injected intraperitoneally with insulin (Novorapid, Novo Nordisk A/S) (10 units/kg body weight) in sterile saline, and killed 15 min later. A) Adipose and B) muscle tissue were removed and homogenized in lysis buffer TNE-buffer (10 mM Tris-HCl, 150 mM NaCl, 1 mM EDTA, 1% nonidet P-40 (Sigma Aldrich) pH. 8) containing protease inhibitors (CompleteMini). The lysates were cleared by centrifugation 10 min at 1000 x g, and protein concentrations were determined by Bio-Rad Protein Assay. Equal amounts of total protein for different samples (100 µg) were separated on a 4-16% SDS-PAGE gel and transferred onto polyvinylidene difluoride (PVDF) membranes (Amersham Pharmacia). Membrane was analysed by western blotting with anti-IR (Santa Cruz Biotechnology, sc-711), anti-IR-pY (R&D systems, AF2507), anti-Glut4 (Abcam, ab654), and anti-β-actin (Sigma, AF5441) as a loading control. Bound antibodies were developed by SuperSignal West Pico reagent (Pierce) and a Fuji film LAS3000.

Figure 11: Physical interaction between SorCS1 and insulin receptor. A) CHO cells transfected with the indicated receptors (only transient transfected with IR_A and IR_B) were stimulated with insulin for 30 min followed by crosslinking with 5 nM DSP (Pierce) and subsequently lysed. The cell lysates was incubated with antibody against IR (Santa Cruz Biotechnology, sc-711) bound to Gammabind beads (GE Healthcare). The precipitated complexes were eluted from the washed beads with SDS loading buffer. The eluate was subjected to SDS-PAGE and Western blot analysis using α-SorCS1-leu and α-IR to reveale the presence of a SorCS1:IR complex. Crude lysates subjected to Western blot analysis using α-SorCS1-leu and α-IR were included to assess the transfection efficiency. B) Surface plasmon resonance experiment (BIAcore) showing the direct interaction of soluble full-length extracellular part of SorCS1 with immobilized soluble insulin receptor (IR) (R&D systems). The soluble SorCS1 concentrations used were 50 nM, 75 nM, and 150 nM. The K_d is estimated to approximately 5 nM.

Figure 12: Insulin receptor expression in CHO cells transfected with SorCS1. Chinese hamster ovary (CHO) cells stably transfected with the four murine SorCS1 splice variants (SorCS1-a,-b,-c,-d) and msol.SorCS1 (the extracellular part of SorCS1) were grown to confluency in serum-free HyQ-CCM5 CHO medium (HyClone) supplemented with antibiotics (50 U/ml penicillin/50 µg/ml streptomycin). The cells were washed with PBS and lysed in lysis-buffer (1% Triton X-100, 20 mM Tris-HCl, 10 mM EDTA, pH 8.0), supplemented with proteinase inhibitors (CompleteMini, Roche Molecular Biochemicals). Aliquots of the lysates, corresponding to 10 µg protein, were dissolved in SDS sample buffer and subjected to reducing SDS-PAGE using 4-16% acrylamide gels. For immunoblotting, proteins were electrophoretically transferred onto polyvinylidene difluoride (PVDF) membranes (Amersham Pharmacia) and probed with anti-IR (Santa Cruz Biotechnology, sc-711), anti-SorCS1-leu and anti-β-actin (Sigma, AF5441) as a loading control. Bound antibodies were developed by SuperSignal West Pico reagent (Pierce) and a Fuji film LAS3000.

Figure 13: Expression of IR and SorCS1 on the cell membrane. Cell surface expression of the insulin receptor and SorCS1 was determined by cell surface biotinylation. CHO cells and CHO cells stably expressing mSorCS1-B and mSorCS1-C were subjected to surface biotinylation using the membrane impermeable biotinylation reagent NHS-SS-biotin (Pierce). Cells were grown to confluency, following which cells were washed with phosphate-buffered saline (PBS). Biotinylation was carried out using 0.5 mg/ml NHS-SS-biotin in PBS for 90 min at 4 °C with gentle shaking. After labeling, cells were washed twice with ice-cold PBS to remove the residual NHS-SS-biotin. Subsequently, cells were solubilized in lysis buffer (10 mM Tris-HCl, 150 mM NaCl, 1 mM EDTA, 1% nonidet P-40 (Sigma Aldrich) pH. 8) containing protease inhibitors (CompleteMini) by gently shaking on ice for

approximately 10 min. The lysate were clarified by centrifugation at 14,000x*g* for 5 min at 4 °C, 20 µl of the cleared lysate was saved (lysate fraction) and the rest of the lysate was incubated overnight with 100 µl of streptavidin-agarose beads (Sigma) at 4 °C with gentle agitation. After incubation, the lysate/beads mixture was separated by centrifugation at 14,000x*g* for 5 min at 4 °C. The lysate fraction contains the intracellular proteins of the cells (Intra). The beads were washed twice with PBS and the captured biotinylated proteins (Bio) were eluted from the beads with 150 µl of SDS sample buffer. Finally, a portion of the biotinylated (Bio) (30 µl), the intracellular (Intra) (25 µl), and the crude lysates (Lysate) was subjected to SDS-PAGE and Western blot analysis using anti-IR (Santa Cruz Biotechnology, sc-711), anti-IR-pY (R&D systems, AF2507), anti-Glut4 (Abcam, ab654), and antic-β-actin (Sigma, AF5441) as a loading control. Bound antibodies were developed by SuperSignal West Pico reagent (Pierce) and a Fuji film LAS3000.

Figure 14: Development stages towards type 2 diabetes in human. Type 2 diabetes (T2D) develops in response to obesity in subjects that have underlying genetic and acquired predispositions to both insulin resistance and β cell dysfunction. Over time, islet β cell compensation for the insulin resistance fails, resulting in progressive decline in β cell function. As a consequence, subject's progress from normal glucose tolerance to impaired glucose tolerance (prediabetes) and finally to established T2D. Increases in blood glucose concentration during the development of T2D are illustrated on the graph (black line) showing the change from normal to pre-diabetic, before the onset of frank diabetes. Furthermore, the level of insulin during development of T2D is revealed on the same graph (dashed line), showing an increase of insulin during the pre-diabetic state as compensation to insulin resistance and a severe decline in insulin release at onset of frank diabetes as a consequence of β cell failure.

Figure 15: Insulin immunostaining of pancreatic islets in wild-type and knockout mice 20 days of age. Pancreata were removed and fixed with 4% paraformaldehyde, freshly prepared in PBS. Samples were embedded in Tissue-Tek (Sakura). Cryosections (10 µm) were obtained from several positions throughout the pancreas, and stored in -80ºC. For immunostaining, the slide were placed in PBS for 2x5 min, blocked in 0.2% hydrogen peroxid (H_2O_2) in methanol for 15 min at -20ºC, washed with PBS (1x5min) and PBS + 0.1% TritonX-100 (2x10 min) before preincubation with 10% fetal calf serum (FCS) in PBS for 30 min. Slides were subsequently rinsed in PBS (3x2 min) and incubated overnight at 4ºC in primary antibody guinea pig anti-insulin (I-8510, Sigma) diluted in PBS + 10% FCS (1:500). Slides were washed with PBS (3x15 min), incubated with secondary antibody Cy3-conjugated anti-guinea pig (706-165-148, Jackson ImmunoResearch) diluted in PBS + FCS (1:500) in the dark for 1 hr at RT, and subsequently washed in PBS (3x15min) and allowed to air-dry. Finally, the slides were mounted with Vectashield with DAPI (H-1200, Vector Labs) and analysed by confocal scanning laser microscopy (LMS 510, Carl Zeiss).

Figure 16: Alignment of SorCS1

Sequence alignment of SorCS1 from Human (homo sapiens), Chimpanzee (Pan troglodytes), Cow (Bos Taurus), Mouse (Mus musculus), Rat (Rattus norvegicus), Dog (Canis lupus familiaris) and Chicken (Gallus gallus) origin. The sequence identity is as demonstrated in table 2.

Table 2: Sequence identity to human SorCS1

Species	Protein (% identity)	DNA (% identity)
Human	100	100
Chimpanzee	99.6	99.4
Dog	97.6	92.5
Cow	92.9	89.8
Mouse	93.2	87.7
Rat	93.2	88.0
Chicken	85.3	79.7

Fig. 17: Decreased plasma glucose levels in female wild-type and SorCS1 knockout mice after hepatic overexpression of soluble SorCS1.

Wild-type and SorCS1 knockout female mice were injected with an adenovirus over-expressing soluble SorCS1. The recombinant adenovirus for expression of human soluble SorCS1 (hsol.SorCS1) was generated as follows:

pcDNA3.1/Zeo(-)/hsol.SorCS1 encoding the human soluble SorCS1 cDNA (amino acids 1-1100) was digested with Pme1 and Apa1 and the fragment encoding hsol.SorCS1 inserted into the shuttle plasmid pVQpacAd5CMVK-NpA (ViraQuest Inc, North Liberty, IA). ViraQuest Inc, North Liberty, IA, then used this shuttle plasmid for generation and propagation of adenovirus over-expressing hsol.

SorCS1. Female SorCS1 knockout and wild-type mice 40 weeks of age were fasted overnight. In the morning, on day 0, blood samples were obtained by retroorbital bleeding and plasma glucose was measured immediately on an automatic monitor (Ascentia Contour from Bayer). Then, the mice were injected in the tail vein with 2E9 pfu's of an adenoviral vector with either hsol.SorCS1 or LacZ as a negative control (from ViraQuest Inc, North Liberty, IA). On day 7, measurements of plasma glucose were repeated on overnight fasted mice to evaluate the effect of the SorCS1 and

LacZ protein. The data are means ± SEM for 3 mice in each group. Mice with over-expression of soluble SorCS1 exhibited a significant decrease in plasma glucose (≈40%) both in SorCS1 knockout mice and wild-type mice. This increase was not seen in the mice that received the control virus LacZ.

Fig. 18: Expression of IR, phosphorylated IR, and Glut4 in muscle and adipose tissue from SorCS1 knockout female mice over-expressing soluble SorCS1.

Female SorCS1 knockout (-/-) mice 40 weeks of age were injected with a adenoviral vector expressing either hsol.SorCS1 or LacZ as a negative control (see detailed protocol in Fib.17). On day 12 after virus injection, the mice were fasted overnight, injected intraperitoneally with insulin (Novorapid, Novo Nordisk A/S) (10 units/kg body weight) in sterile saline, and killed 15 min later. A) Muscle and B) adipose tissue were removed and homogenized in lysis buffer TNE-buffer (10mM Tris-HCl, 150 mM NaCl, 1mM EDTA, 1% nonidet P-40, pH. 8) containing protease inhibitors (Complete Mini, Roche) and phosphatase inhibitors (cocktail 1, Sigma Aldrich). The lysates were cleared by centrifugation 10 min at 10.000 x g, and protein concentration were determined by Bio-Rad Protein Assay. Equal amount of total protein (50 µg) for different samples were separated on a 4-12 % Bis-tris gel (Nupage, Invitrogen) and transferred onto polyvinylidene difluoride (PVDF) membranes (Amersham Pharmacia). Membranes were analysed by western blotting with anti-IR (Santa Cruz Biotechnology, sc-711), anti-IR-pY (R&D systems, AF2507) and anti-Glut4 (Abcam, ab654). Bound antibodies were developed by Super-Signal West Pico reagent (Pierce) and a Fuji film LAS3000. In both A) muscle and B) adipose tissue from SorCS1 knockout mice over-expressing soluble SorCS1 there are elevated amount of IR, phosphorylated IR (IR-pY) and glut4 compared to mice expressing the LacZ control protein, suggesting increased insulin sensitivity in mice which received the hsol.SorCS1 virus.

Fig. 19: Decreased plasma glucose and insulin levels in diabetic db/db female mice over-expressing soluble SorCS1.

To evaluate the effect of soluble SorCS1 in an obese mouse model that spontaneously develops type 2 diabetes we used the db/db mouse strain (BKS.Cg-*m*+/+Lpr^{db}/BomTac from Taconic). These mice lack the leptin receptor consequently the mice become obese and develop insulin resistance and finally severe diabetes at the age of 6-8 weeks. We injected adenovirus expressing either hsol.SorCS1 or LacZ as a control (as described in Fig. 17), to examine the effect on plasma glucose and insulin levels. In detail, db/db female mice 10 weeks of age were fasted overnight. In the morning, on day 0, the mice were anesthetized with diethyl ether and blood samples were obtained by retroorbital bleeding. A) Blood glucose was measured immediately on an automatic monitor (Ascentia Contour from Bayer), whereas B) plasma insulin levels were determined using an ultrasensitive mouse insulin enzyme-linked immunoabsorbent assay kit (DRG Diagnostics). Thereafter the mice were injected in the tail vein with 2E9 pfu's of an adenoviral vector with either hsol.SorCS1 or LacZ (from ViraQuest Inc, North Liberty, IA) as a negative control virus. On day 7, measurements of blood glucose and plasma insulin were repeated on overnight fasted mice to evaluate the effect of the SorCS1 and LacZ protein. Data are means ± SEM for 5 mice in each group. On day 7, db/db female mice with over-expression of soluble SorCS1 exhibited a significant decrease in blood glucose (≈35%) compared to the mice that received the control LacZ virus. Furthermore, on day 7 there was also a significant decrease in the plasma insulin levels in the db/db female mice over-expressing soluble SorCS1 compared to mice that express the control virus. Thus, over-expression of soluble SorCS1 improves the diabetic status in this type 2 diabetic mouse model.

Fig. 20: Glucose tolerance test in diabetic db/db female mice with over-expression of soluble SorCS1.

Female db/db mice injected with adenoviruses expressing either soluble SorCS1 or LacZ (see fig. 17) where on day 3 fasted over-night (16 hrs). On day 4 the mice were injected intraperitoneally with a bolus of glucose (2mg/g body weight) in sterile saline. The animals were anesthetized with diethyl ether and blood samples were obtained by retroorbital bleeding at times 0, 15, 30, 90, and 150 min after injection. Blood glucose levels were measured immediately after sampling on an automatic monitor (Ascentia Contour from Bayer). Data are means ± SEM for 5 mice in each group. The results show, that over-expression of soluble SorCS1 renders the mice more sensitive to insulin as the level of blood glucose returns to baseline after 150 min. By contrast, blood glucose in mice expressing LacZ stays elevated during the course of the experiments. In conclusion, db/db female mice with over-expression of soluble SorCS1 are less insulin resistant.

Fig. 21: Plasma glucose and insulin levels in diabetic db/db male mice over-expressing soluble SorCS1.

To evaluate the effect of soluble SorCS1 in an obese mouse model that spontaneously develops type 2 diabetes we used the db/db mouse strain (BKS.Cg-*m*+/+Lpr^{db}/BomTac from Taconic). These mice lack the leptin receptor consequently the mice become obese and develop insulin resistance and finally severe diabetes at the age of 6-8 weeks. We injected adenovirus expressing either hsol.SorCS1 or LacZ as a control (as described in Fig. 17), to examine the effect on plasma glucose and insulin levels. In detail, db/db male mice 6 weeks of age were fasted overnight. In the morning, on day 0, the mice were anesthetized with diethyl ether and blood samples were obtained by retroorbital bleeding. A) Blood glucose was measured immediately on an automatic monitor (Ascentia Contour from Bayer), whereas B) plasma insulin levels were determined using an ultrasensitive mouse insulin enzyme-linked immunoabsorbent assay kit (DRG Diagnostics). Thereafter the mice were injected in the tail vein with 2E9 pfu's of an adenoviral vector with either hsol.SorCS1 or LacZ (from ViraQuest Inc, North Liberty, IA) as a negative control virus. On day 7, measurements of blood glucose and plasma insulin were repeated on overnight fasted mice to evaluate the effect of the SorCS1 and LacZ protein. Data are means ± SEM for 5 mice in each group. On day 7, db/db male mice with over-

expression of soluble SorCS1 exhibited a significant decrease in blood glucose (≈35%) compared to the mice that received the control LacZ virus. Because the decline in glucose levels were not accounted by an increased insulin concentration as compared to LacZ treated animals, we conclude that over-expression of soluble SorCS1 improves the diabetic status in male type 2 diabetic db/db mice.

Fig. 22: Subcellular localization of Glut4 in muscle tissue from db/db male mice over-expressing soluble SorCS1.

To evaluate if over-expression of soluble SorCS1 might change the distribution of Glut4 we conducted subcellular fractionation on muscle tissue from db/db male mice over-expressing soluble SorCS1. In detail, db/db male mice 6 weeks of age were injected in the tail vein with a adenoviral vector expressing either hsol.SorCS1 or LacZ as a control as described in fig. 17. On day 7 after virus injection, the mice were fasted overnight, injected intraperitoneally with insulin (Novorapid, Novo Nordisk A/S) (10 units/kg body weight) in sterile saline, and killed 15 min later. Muscle tissue from 5 mice injected with the same virus was removed, pooled and transferred to 5 ml of HEPES-buffered sucrose (0.25 M sucrose, 1 mM EDTA, 20 mM HEPES-KOH, pH. 7.4), homogenized by 10 strokes up and down using a Teflon pestle, and centrifuged at 1000 x g for 10 min. Thus, heavy mitochondrial, light mitochondrial, and microsomal fraction were obtained by several round of centrifugation. First, the supernatant was centrifuged at 3.000 x g for 10 min, then the resulting supernatant was centrifuged at 16.000 x g for 10 min, and finally the resulting supernatant was centrifuged a 100.000 x g for 45 min giving a pellet containing the microsomal fraction. The microsomal fractions were resuspended in 0.5 ml HEPES-buffered solution and subjected to sucrose (velocity) gradient centrifugation. The 0.5 ml microsomal samples were loaded onto a 12 ml linear 0.8 M to 1.6 M sucrose gradient in 1 M HEPES, pH 7.2, and centrifuged 18 h in a swinging bucket rotor (SW41 Ti) at 84.000 x g. Each gradient was separated into 24 fractions starting from the top of the tube. Finally, gel electrophoresis and Western blotting analyzed the expression of Glut4 in the different fractions. The result shows that the sedimentation distribution of Glut4 in muscle tissue over-expressing SorCS1 is different from muscle tissue expressing the control protein lacZ. Thus, accumulation of glut4 shifted from fractions 2 - 4 after LacZ treatment to fractions 8-12 in the SorCS1 group. This indicate that over-expression of soluble SorCS1 might change the distribution of Glut4 and thereby modulate glucose uptake.

Fig. 23 A+B: Analysis of SorCS1/IR contact sequences by SPOT analysiss.

Co-immunoprecipitation and BIAcore (surface Plasmon resonance) experiments showed SorCS1 can physically associate with the insulin receptor. We here used SPOT synthesis analysis to identify linear amino acid sequences in either of the two receptors that may partake in the protein-protein interaction. In practice filters were spotted with consecutive 15-mer peptides overlapping by three amino acids from the N- to the C-terminus of SorCS1 (B) and IR (A), and the filters were subsequently probed with (A) ^{125}I-labelled soluble human SorCS1 or (B) histidine-tagged insulin receptor (R&D systems, no1544-IR/CF). The filters were then washed and bound proteins visualized. The binding assay was performed directly on the peptide membrane through immunodetection or radiography of bound protein. In detail, the membrane was washed 1 x 10 min in 96% ethanol, followed by 3 x 10 min washing with 1 x TBS (500 mM Tris-HCl, 1500 mM NaCl), pH.8.0 and 3 hrs incubation in membrane blocking buffer (BB; 1 x Blocking buffer (B6429, Sigma), 1 x TBS, 5% sucrose). The blocked IR-membrane was incubated overnight with ^{125}I-sol.SorCS1 (400.000 cpm/ml BB) and the SorCS1-membrane with his-IR (10 µg/ml BB). Both membrane were washed 3 x 10 min with 1 x TBS. A) Bound his-IR on the SorCS1 membrane was detected by immunodetection using primary anti-body against the histidine tag, α-histidine (Invitrogen) (Mouse monoclonal) followed by an HRP-tagged secondary anti-mouse antibody (Sigma). Bound antibody was visualized using the enhanced chemiluminescence (ECL) Western blotting Detection reagent (Amersham biosciences) and a Fuli film LAS1000). Bound radiolabelled SorCS1 to the IR-membrane was detected by radiography using an Fuji image plate, and after 12 hrs exposure subsequently developed using a Fujifilm FLA3000. A signal (SPOT) indicates that the ligand binds to a peptide. Overlapping linear binding epitopes are represented by signals from neighbouring spots. The SPOT's are framed on the membrane figures and key sequences corresponding to the SPOT's are indicated beneath the membrane.

Fig. 24 A+B: Gene expression profiling of adipose tissue from SorCS1 knockout mice by PCR arrays.

Using gene array analysis of adipose tissue from SorCS1 knockout wild-type adipose mice we tested expression of A) 84 genes related to the mouse insulin signalling pathway and B) 84 genes related to mouse lipoprotein signalling & cholesterol metabolism. In practice, first strand cDNA was synthesized from total RNA (Applied Biosystems) from SorCS1 knockout (-/-) and wild-type (+/+) adipose tissue from female mice 50 weeks of age (n = 3). Then superarray of A) Mouse Insulin Signalling Pathway (PAMM-030A RT2 Profiler PCR arrays) or B) the type Mouse Lipoprotein Signalling & Cholesterol Metabolism (PAMM-080-A RT2 Profiler PCR arrays) were processed using an ABI7900 platform (Applied Biosystems) and SYBR Green/Rox PCR (SABiosciences). AROS Applied Biotechnology, Aarhus, Denmark, did the expression analyses. Genes showing an expression more than 3 times up- or down-regulated in the SorCS1 knockout mice when compared to wild-type mice are listed in the upper tables and their known functions are indicated in the table below. Several genes in A and B show changed expression in the SorCS1 knockout mice compared to the wild-type mice indicating that insulin and cholesterol signalling pathways and metabolism are altered in SorCS1 knockout mice.

Examples

Example 1: Expression of mSorCS1 splice variants in tissues from mice

[0246] Expression of the extracellular part of SorCS1 (SorCS1.ex) and the five tail splice variants SorCS1-a, -b, -c, c^+ and -d were determined in various tissues from adult mice (see Fig. 3). The organization of the SorCS1 gene and the amino acid sequences of the cytoplasmic domains of the splice variants are shown in Figure 2A and 2B, respectively.

[0247] Expression of the extracellular part of SorCS1 (SorCS1.ex) and splice variants were determined by reverse transcription-PCR (RT-PCR) with specific primer pairs. The SorCS1.ex specific primers (SEQ ID NO: 57 and SEQ ID NO: 58) are spanning the exon 21 to 24 junctions giving a 390 bp product. The SorCS1-a specific primers (SEQ ID NO: 59 and SEQ ID NO: 60) are spanning the exon 21 to 25 junctions giving a 586 bp product. The SorCS1-b specific primers (SEQ ID NO: 61 and SEQ ID NO: 62) are spanning the exon 21 to 25 junctions and the exon 25 to 27 junctions giving a 621 bp product. The SorCS1-c (SEQ ID NO: 63 and SEQ ID NO: 64) specific primers are spanning the exon 21 to 26 junctions giving a 626bp product. The SorCS1-d specific primers (SEQ ID NO: 65 and SEQ ID NO: 66) are spanning the exon 21 to 25 junctions and the exon 25 to 28 junction giving a 636bp product. Total RNA preparations were made from hippocampus, liver, adipose tissue (fat), muscle, pancreas and testis isolated from wild type and hippocampus and liver from SorCS1-KO mice of about 8 weeks of age using the Versagene Total RNA purification Kit (Gentra Systems). Briefly, tissues were surgically removed and frozen on dry ice. Frozen tissue samples were disrupted and homogenized for up to 60 sec using a rotor stator (Ultra-Turrax, IKA-Werke) in 800 µl lysis buffer containing 5 mM Tris (2-carboxyethyl) phosphine (TCEP) and the total RNA was purified according to the manufacturers protocol for the kit. RT-PCR were performed with 0.75 µg to 1 µg total RNA from each sample using the TITANIUM One-step RT-PCR kit (Clontech). All reactions were performed in 50 µl volume containing 1 x One-step buffer (40 mM tricine, 20 mM KCl, 3 mM $MgCl_2$, 3.75µg/µl BSA), 0.2 mM of each dNTP, 25 µl Thermostabilizing reagent, 10 µl GC-melt, 20 µM Oligo(dT)primer, 20 units Recombinant RNase inhibitor, 1 x RT-TITANIUM™ Taq enzyme mix (all supplied with the kit) and 45 µM of each primer. PCR conditions were: 50°C for 1 hour, 94°C for 5 min, 35 cycles at 94°C for 30 sec, 64°C for 30 sec, 68°C for 1 min, and 68°C for 2 min.

Example 2: Generation of the mSorCS1 knockout mouse

[0248] To investigate the function of SorCS1 and its different splica variants, a conditional knockout mouse was generated by homologous recombination in embryonic stem cells. The homologous recombination was initiated by the site-specific FLP recombinase at a FRT-site, which results in "recombinase-mediated cassette exchange". The recombination event is illustrated in Fig. 4A, where the SorCS1 gene is "exchanged" with the Neo gene thereby generating a full knockout mouse where all SorCS1 splice variants are disrupted.

[0249] Expression of SorCS1 was tested in wild-type and SorCS1 knockout mice by RT-PCR on mRNA from hippocampus of wild-type (WT) and SorCS1 knockout (KO) mice using specific primer pairs to identify the extracellular part of SorCS1 (ext) or each of the five tail variants (a, b, c, c^+, and d). The results shown in Figure 4B reveal that transcription of all mSorCS1 splice variants are disrupted in the SorCS1 knockout mouse.

[0250] Western blot analysis of cortex revealed the lack of mSorCS1 protein in the mSorCS1 knockout (KO) mice (Fig. 4C). Proteins were extracted as lysates from cortex obtained at E14.5. The tissue was dissolved in 100 µl TNE-buffer (10 mM Tris-HCl, 150 mM NaCl, 1 mM EDTA, 1% nonidet P-40 (Sigma Aldrich) pH. 8) containing protease inhibitors (CompleteMini) by vigorous vortexing. After freezing ON at 20°C, the lysates were vortexed and centrifuged 10 min at 1000 x g. The lysates (supernatant) were transferred to a new tube and Bio-Rad Protein Assay measured the protein concentration. Lysates (200µg) were resolved on SDS-PAGE and transferred to nitrocellulose. The blot was then probed with a rabbit polyclonal antibody against the leucine-rich part of SorCS1 (α-hSorCS1-leu).

Example 3: Plasma glucose levels in SorCS1 knockout mice

[0251] Type 2 diabetes (T2D) develops in response to obesity in subjects that have underlying genetic and acquired predispositions to both insulin resistance and β cell dysfunction. Over time, islet β cell compensation for the insulin resistance fails, resulting in progressive decline in β cell function. As a consequence, subject's progress from normal glucose tolerance to impaired glucose tolerance (pre-diabetes) and finally to established T2D. Increases in blood glucose concentration during the development of T2D are illustrated on the graph (black line) showing the change from normal to pre-diabetic, before the onset of frank diabetes. Furthermore, the level of insulin during development of T2D is revealed on the same graph (dashed line), showing

an increase of insulin during the pre-diabetic state as compensation to insulin resistance and a severe decline in insulin release at onset of frank diabetes as a consequence of β cell failure (Fig. 14)

[0252] To examine the SorCS1 knockout mouse with respect to glucose metabolism, the plasma glucose levels were determined in male (Fig. 5A) and female mice (Fig. 5B) at different age. Animals were fasted overnight (16h). Mice were anesthetized with diethyl ether, blood samples were obtained by retroorbital bleeding and plasma glucose was measured immediately on an automatic monitor (Ascensia Contour from Bayer). The results in Figure 5B shows a statistically significant increase in plasma glucose levels of female SorCS1 knockout mice at an age of 23 and 50 weeks relative to wild type mice.

Example 4: Plasma insulin levels in female SorCS1 knockout mice

[0253] To further examine the SorCS1 knockout mouse with respect to glucose metabolism, the plasma insulin levels were determined in female SorCS1 knockout mice from 10 to 20 weeks of age (Fig. 6). Animals were fasted overnight (16h). Mice were anesthetized with diethyl ether, blood samples were obtained by retroorbital bleeding and plasma insulin levels were determined using an ultrasensitive mouse insulin enzyme-linked immunosorbent assay kit (DRG Diagnostics, Marburg, Germany). Data are means ± SEM for 4 to 10 mice in each group. In agreement with the results shown in Figure 5B, the results in Figure 6 shows a statistically significant increase plasma insulin levels of female SorCS1 knockout mice at an age of 23 and 50 weeks relative to wild type mice.

[0254] Insulin levels were further investigated by immunostaining of tissues from wild-type and SorCS1 knockout mice 20 days of age.

[0255] Pancreata were removed and fixed with 4% paraformaldehyde, freshly prepared in PBS. Samples were embedded in Tissue-Tek (Sakura). Cryosections (10 µm) were obtained from several positions throughout the pancreas, and stored in -80°C. For immunostaining, the slide were placed in PBS for 2x5 min, blocked in 0.2% hydrogen peroxid (H_2O_2) in methanol for 15 min at -20°C, washed with PBS (1x5min) and PBS + 0.1% TritonX-100 (2x10 min) before preincubation with 10% fetal calf serum (FCS) in PBS for 30 min. Thereafter rinsed in PBS (3x2 min) and incubated overnight at 4°C in primary antibody guinea pig anti-insulin (I-8510, Sigma) diluted in PBS + 10% FCS (1:500). Slides were washed with PBS (3x15 min), incubated with secondary antibody Cy3-conjugated anti-guinea pig (706-165-148, Jackson ImmunoResearch) diluted in PBS + FCS (1:500) in the dark for 1 hr at RT, and subsequently washed in PBS (3x15min) and allowed to air-dry. Finally, the slides were mounted with Vectashield with DAPI (H-1200, Vector Labs) and analysed by confocal scanning laser microscopy (LMS 510, Carl Zeiss). This data suggest that the pancreas strives to compensate the decreased insulin sensitivity by increasing the size of beta-cell islets and insulin production.

Example 5: Glucose tolerance test in female SorCS1 knockout mice

[0256] The glucose tolerance of female SorCS1 knockout mice was tested by measuring glucose and insulin levels at different time points after injection with glucose (Fig. 8) Female mice 59 weeks of age were fasted overnight (16 h) and injected intraperitoneally with a bolus of D-glucose (Sigma) (2 mg/g body weight) in sterile saline. Mice were anesthetized with diethyl ether, blood samples were obtained by retroorbital bleeding at times 0, 15, 30, 60, and 120 min after injection, and plasma glucose levels (Fig. 8A) and insulin levels (Fig. 8B) were measured. Plasma glucose levels were measured immediately after sampling on an automatic monitor (Ascensia Contour from Bayer). Insulin levels were determined using an ultrasensitive mouse insulin enzyme-linked immunosorbent assay kit (DRG Diagnostics, Marburg, Germany). The results in Fig. 7B show increased insulin levels in female SorCS1 knockout mice at all time points (0-120 min) after injection.

Example 6: Elevated levels of plasma glucose and insulin in wild type mice on Western type diet

[0257] Female (Fig. 8A+8C) and male (Fig. 8B+8D) wild type and SorCS1 knockout mice were fed a high calorie Western type diet (WD) (24%protein, 41%carbonhydrate, 24%fat) (Research Diets. D12451) from 10 weeks of age to 50 weeks of age. At 50 weeks of age the animals were fasted overnight (16h), anesthetized with diethyl ether and blood samples were obtained by retroorbital bleeding. Plasma glucose levels (Fig. 8A+8B) were measured immediately after sampling on an automatic monitor (Ascensia Contour from Bayer), whereas plasma insulin levels (Fig. 8C+8D) were determined using an ultrasensitive mouse insulin enzyme-linked immunosorbent assay kit (DRG Diagnostics, Marburg, Germany). The results depicted in Figure 6 shows

plasma glucose and insulin levels are elevated in wild type mice on Western type diet.

Example 7: Demonstration of increased insulin receptor phosphorylation in SorCS1 knockout mice.

[0258] Female SorCS1 knockout (-/-) mice and wild-type (+/+) control mice 40 and 50 weeks of age were fasted overnight, injected intraperitoneally with insulin (10 units/kg body weight) in sterile saline, and killed 15 min later. Muscle tissue were removed and homogenized in lysis buffer TNE-buffer (10 mM Tris-HCl, 150 mM NaCl, 1 mM EDTA, 1% nonidet P-40 (Sigma Aldrich), pH= 8.0 containing protease (CompleteMini, Roche) and phosphatase inhibitors (Cocktail 1, Sigma Aldrich). The lysates were cleared by centrifugation 10 min at 1000 x g, and protein concentration were determined by Bio-Rad Protein Assay. Equal amounts of total protein from different samples (100 µg) were separated on a 4-16% SDS-PAGE gel and transferred onto polyvinylidene difluoride (PVDF) membranes (Amersham Pharmacia). Membrane were subjected to Western blotting with anti-IR (Santa Cruz Biotechnology, sc-711), anti-IR-pY (R&D, AF 2507), and anti-β-actin (Sigma Aldrich, AF5441) as a loading control. Furthermore, tyrosine phosphorylation of IR were also analysed by immunoprecipitation with an anti-phosphotyrosine antibody (4G10). The immunoprecipitaion was conducted as follows. 100 µg protein from muscle tissue was incubated with Gammabind G-Sepharose beads (Amersham Bioscience) coated with anti-phosphotyrosine (4G10, Upstate/Millipore) overnight at 4°C. The beads were subsequently washed 4 x 5 min, and finally resuspended in reducing sample buffer (20 mM DTE, 2.5% SDS) and boiled. The supernatant of the bolied samples, containing precipitated proteins, were analyzed by Western blotting using anti-IR (Santa Cruz Biotechnology, sc-711). All bound antibodies were developed by Super Signal West Pico reagent (Pierce) and a Fuji film LAS3000. Figure 10 shows an increased expression of insulin receptor and a decreased phosphorylation of the insulin receptor in SorCS1 knockout mice aged 50 weeks suggesting that IR accumulates in a compartment in SorCS1 knockout mice thereby precluding the receptor from phosphorylation and activation. The results suggest that SorCS1 plays a role in insulin signalling and activation of the insulin receptor.

Example 8: Physical interaction between SorCS1 and insulin receptor

[0259] To examine the interaction between SorCS1 an the insulin receptor (IR), Chinese hamster ovary (CHO) cells stably transfected with the four murine SorCS1 splice variants (SorCS1-a,-b,-c,-d) and msol.SorCS1 (the extracellular part of SorCS1) were grown to confluency in serum-free HyQ-CCM5 CHO medium (HyClone) supplemented with antibiotics (50 U/ml penicillin/ 50 µg/ml streptomycin). The cells were washed with PBS and lysed in lysis-buffer (1% Triton X-100, 20 mM Tris-HCl, 10 mM EDTA, pH 8.0), supplemented with proteinase inhibitors (CompleteMini, Roche Molecular Biochemicals). Aliquots of the lysates, corresponding to 10 µg protein, were dissolved in SDS sample buffer and subjected to reducing SDS-PAGE using 4-16% acrylamide gels. For immunoblotting, proteins were electrophoretically transferred onto polyvinylidene difluoride (PVDF) membranes (Amersham Pharmacia) and probed with anti-IR (Santa Cruz Biotechnology, sc-711), anti-SorCS1-leu and anti-β-actin (Sigma, AF5441) as a loading control. Bound antibodies were developed by SuperSignal West Pico reagent (Pierce) and a Fuji film LAS3000. Cell lines stably transfected with the different splice variants of SorCS1 showed elevated expression of the IR compared to CHO cells with out SorCS1 expression (Fig.12). To identify the cellular localisation of the elevated amount of IR in the SorCS1 transfected cells surface biotinylation were conducted. CHO cells and CHO cells stably expressing mSorCS1-B and mSorCS1-C were subjected to surface biotinylation using the membrane impermeable biotinylation reagent NHS-SS-biotin (Pierce). Confluent cell monolayers were washed in phosphate-buffered saline (PBS) and biotinylation was carried out using 0.5 mg/ml NHS-SS-biotin in PBS for 90 min at 4 °C with gentle shaking. After labeling, cells were washed twice with ice-cold PBS to remove the residual NHS-SS-biotin. Subsequently, cells were solubilized in lysis buffer (10 mM Tris-HCl, 150 mM NaCl, 1 mM EDTA, 1% nonidet P-40 (Sigma Aldrich) pH. 8) containing protease inhibitors (CompleteMini) by gently shaking on ice for approximately 10 min. The lysate were clarified by centrifugation at 14,000x*g* for 5 min at 4 °C, 20 µl of the cleared lysate was saved (lysate fraction) and the rest of the lysate was incubated overnight with 100 µl of streptavidin-agarose beads (Sigma) at 4 °C with gentle agitation. After incubation, the lysate/beads mixture was separated by centrifugation at 14,000x*g* for 5 min at 4 °C. The lysate fraction contains the intracellular proteins of the cells (Intra). The beads were washed twice with PBS and the captured biotinylated proteins (Bio) were eluted from the beads with 150 µl of SDS sample buffer. Finally, a portion of the biotinylated (Bio) (30 µl), the intracellular (Intra) (25 µl), and the crude lysates (Lysate) was subjected to SDS-PAGE and Western blot analysis using anti-IR (Santa Cruz Biotechnology, sc-711), anti-IR-pY (R&D systems, AF2507), anti-Glut4 (Abcam, ab654), and anti-β-actin (Sigma, AF5441) as a loading control. The elevated amount of the insulin receptor in SorCS1-B and SorCS1-C cells were located on the cell surface (in the Bio fraction), co-localising with a portion of the SorCS1 proteins (Fig. 13), indicating that SorCS1 regulates the expression of IR by physical interaction and/or by lowering the turn over of the IR protein.

Example 9: Demonstration of SorCS1:IR complex formation.

[0260] To examine the potential physical interaction between SorCS1 and IR, CHO cell stably transfected with plasmids encoding SorCS1-B and -C and subsequently transiently transfected with IR_A and IR_B were used for immunoprecipitation. The cells were transfected with plasmids encoding IR_A and IR_B using the HiFect kit (Amaxa) according to the supplier's protocol. After two days of growth and at 80% confluency the cells were crosslinked with DSP (Peirce) and subsequently lysed. The cell lysates was incubated with antibody against IR (Santa Cruz Biotechnology, sc-711) bound to Gammabind beads (GE Healthcare). The precipitated complexes were eluted from the washed beads with SDS loading buffer and subjected to SDS-PAGE and Western blot analysis using anti-SorCS1-leu and anti-IR (Santa Cruz Biotechnology, sc-711). Western blot analysis revealed the presence of a SorCS1:IR complex (Fig. 11A). The direct interaction of the extracellular domains of SorCS1 and IR was also demonstrated using surface plasmon resonance (Biacore, Sweden) using CaHBS as standard running buffer (10 mM HEPES, pH 7.4, 140 mM NaCl, 2 mM $CaCl_2$, 1 mM EGTA, 0.005% tween-20). A biosensor chip from Biacore (CM5, cat.no. BR-1000-14) was activated using the NHS/EDC method as described by the supplier followed by coating with soluble IR (R&D systems, 28-956). Soluble SorCS1 showed strong binding to soluble insulin receptor with a K_d estimated to approximately 5 nM (Fig. 11 B).

Example 10: Analysis of SorCS1/IR contact sites based on SPOT synthesis.

[0261] The co-immunoprecipitation and the Biacore experiments showed protein interaction at whole molecular level. However, the SPOT synthesis method is used to identify the protein interaction at amino acid level using a protein-derived scan of overlapping peptides either from SorCS1 or IR, thereby identifying small SorCS1 peptide agonists. The SPOT synthesis maps linear epitopes (protein chain involved in interaction) using overlapping peptides derived from the entire primary sequence of either human SorCS1-a (Fig. 23A) or human IR-B (Fig. 23B). In detail, the SorCS1 and IR sequence is fragmented and synthesized on cellulose with short overlapping peptides (15 amino acids in length and shifted by 3 amino acid) from C-terminus to N-terminus, which is subsequently probed for binding to the respective partner protein, IR-protein (histidine-tagged) (R&D systems, no1544-IR/CF) and soluble mouse SorCS1 protein (I^{125}-tagged). The binding assay is performed directly on the peptide membrane through immunodetection or radiography of bound protein. In detail, the membrane is washed 1 x 10 min in 96% ethanol, followed by 3 x 10 min wash with 1 x TBS (500 mM Tris-HCl, 1500 mM NaCl), pH.8.0 and 3 hrs incubation in membrane blocking buffer (BB; 1 x Blocking buffer (B6429, Sigma), 1 x TBS, 5% sucrose). The blocked IR-membrane is incubated overnight with I^{125}-sol.SorCS1 (400.000 cpm/ml BB) and the SorCS1-membrane with his-IR (10 µg/ml BB). Both membrane are washed 3 x 10 min with 1 x TBS. In Fig. 23A, the bound protein on the SorCS1 membrane was detected by immunodetection using primary anti-body against the histidine tag, α-histidine (Invitrogen) (Mouse monoclonal) followed by an HRP-tagged secondary anti-mouse antibody (Sigma). Bound antibody was visualized by using the enhanced chemiluminescence (ECL) Western blotting Detection reagent (Amersham biosciences) and a Fuli film LAS1000. In Fig. 23B, the bound protein on the IR-membrane was detected by radiography as the membrane was exposed to a fuji image plate for 12 hrs, which was subsequently developed using a Fujifilm FLA3000. A specific signal (SPOT) indicates that the peptide interacts with the applied ligand. Linear binding epitopes are present in neighbouring peptides on the SPOT membrane and represent the binding site.

Example 11: Binding of specific peptides to either SorCS1 or IR

[0262] The SPOT analysis identified synthetic SorCS1 or IR candidate peptides binding to their ligand protein (IR and SorCS1). The binding was further confirmed by surface plasmon resonance (Biacore, Sweden) analysis (Fig. 11 B) using CaHBS as standard running buffer (10 mM HEPES, pH 7.4, 140 mM NaCl, 2 mM $CaCl_2$, 1 mM EGTA, 0.005% tween-20). A biosensor chip from Biacore (CM5, cat.no. BR-1000-14) was activated using the NHS/EDC method as described by the supplier followed by coating with soluble IR (R&D systems, 28-956). Full-length SorCS1 was tested for binding to IR by passage over the biosensor chip, showing a positive sigmoid binding curve, indicating direct interaction of soluble full-length extracellular part of SorCS1 with immobilized soluble insulin receptor (IR)

[0263] Example 6: Competition studies. The synthetic SorCS1 and IR peptides that bind to the ligands protein are used in competitions studies to establish their influence on the interaction between SorCS1 and IR in the SorCS1:IR complex. A biosensor chip from Biacore (CM5, cat.no. BR-1000-14) was activated using the NHS/EDC method as described by the supplier followed by coating with soluble IR (R&D systems, 28-956) or soluble SorCS1. The chips were incubated with samples of pure soluble SorCS1 or soluble IR (R&D systems, 28-956) (300nM, 40µl) in the absence of competing peptide to determine the maximal binding capacity set to represent 100% binding (see example 5). In subsequent experiments, a similar amount of soluble SorCS1 or IR are injected to the ligand ship, but in the presence of competing peptides at different concentrations to determine their ability to diminish or destroy the interaction between SorCS1 and IR.

Example 7: Competition Studies

[0264] The synthetic SorCS1 and IR peptides that bind to the ligands protein are used in competitions studies in cells to establish their influence on the interaction between SorCS1 and IR in the SorCS1:IR complex. A) CHO cell stably transfected with plasmids encoding the different splice variants of SorCS1 and subsequently transiently transfected with IR_A and IR_B were used for immunoprecipitation. The cells are transfected with plasmids encoding IR using the Hifect kit (Amaxa) according to the supplier's protocol. The cells are grown two days in media without or with competing synthetic SorCS1 or IR peptide in different concentrations and at 80% confluency the cells are crosslinked with DSP and subsequently lysed. The cell lysates was incubated with antibody against IR (Santa Cruz Biotechnology, sc-711) bound to Gammabind beads (GE Healthcare). The precipitated complexes are eluted from the washed beads with SDS loading buffer and subjected to SDS-PAGE and Western blot analysis using anti-SorCS1-leu and anti-IR (Santa Cruz Biotechnology, sc-711). Western blot analyses are used to reveal the presence or absence of a SorCS1:IR complex, and thereby establish the ability of the synthetic peptide to diminish or destroy the interaction between SorCS1 and IR. B) Expression of endogene IR in the absence or presence of synthetic SorCS1 peptide(s) is examined in CHO cells and CHO cells stably transfected with the four murine SorCS1 splice variants (SorCS1-a,-b,-c,-d) and msol.SorCS1 (the extracellular part of SorCS1). The cells are grown to 80% confluency in serum-free HyQ-CCM5 CHO medium (HyClone) and in serum-free HyQ-CCM5 CHO medium supplemented with different concentration of synthetic SorCC1 peptide. The cells were washed with PBS and lysed in lysis-buffer and aliquots of the lysates are subjected to reducing SDS-PAGE and Western blot analysis using anti-SorCS1-leu and anti-IR (Santa Cruz Biotechnology, sc-711). Western blot analyses are used to reveal the influence of the synthetic SorCS1 peptide on the expression of IR in cells without or with stably expression of SorCS1, and thereby establish the ability of the synthetic peptide to diminish or destroy the up-regulation of IR in cells expressing SorCS1.

Example 8: Administering of soluble SorCS1 or SorCS1 peptides for the treatment of insulin resistance.

[0265] The soluble domain of mouse SorCS1 peptide(s) able to bind to IR (see example 5) is expressed recombinantly at a large scale in a mammalian cell culture and is subsequently purified by for example immunoaffinity chromatography. The protein/peptid is administered by peritoneal, intraveneous, intramuscular or subcutaneous injection to e.g. SorCS1 knockout mice or another diabetic animal model showing insulin resistance (1 mg to 1 g/kg body weight each day or every week) in parallel with a wild type reference mouse. Good effect is obtained, and the same methods using human SorCS1 are applied for patient with insulin resistance.

Example 9: The application of DNA encoding soluble SorCS1 or SorCS1 peptides for the treatment of insulin resistance.

Gene Therapy in a clinical setting

[0266] Gene therapy is defined as the introduction of exogenous genetic material into cells or tissue in order to cure a disease or to avoid associated symptoms, in this case insulin resistance. The genetic material can be introduced into living cells/patients using different delivery methods/compounds: a) as naked therapeutic genetic molecules (DNA), where the genetic material itself is introduced directly into the tissue/patient (example 9), b) as specialized gene delivery vehicles, where the gene is inserted into different biological entities suited for gene delivery before introduction into the patient (example 10), and c) as virus, where the gene is inserted into a viral vector before introduction into the patient. Proteins might have a short life-time when introduced into the mouse or patient, so an additional treatment is applied were plasmid DNA encoding soluble SorCS1 or SorCS1 peptides are delivered to the SorCS1 knockout mice either by peritoneal injection, oral administration or injection directly into muscle or adipose tissue. The DNA encoding soluble SorCS1 or specific SorCS1 fragments are transcribed into protein in the organism restoring the level of SorCS1 and thereby treating the insulin resistance. The same method is used in humans lacking SorCS1 or showing insulin resistance treating the symptoms of the patient.

Example 10: The application of gene delivery vehicles containing soluble SorCS1 or specific SorCS1 fragments for the treatment of insulin resistance.

[0267] To overcome any limitations of using plasmid DNA or adenovirus for expression of SorCS1 (soluble or specific fragments) specialized gene delivery vehicles (GDVs) are used which improve delivery efficiency and cell specificity whilst protecting against immune recognition. Several different GDVs will be produced: A) Strains of bacteria with desirable properties are transformed with plasmid cargo containing SorCS1 and amplified to generate GDVs. B) the phagemid, a modified bacterial plasmid with phage sequence within, is used as the cargo of SorCS1 and transformed into bacteria. The bacteria is infected with a replication-defective helper phage that produces essential gene for the packing of the phagemid vector into bacteriophage GDVs. C) Virus surface proteins are produced in cell culture and purified as capsid monomers. The genetic cargo containing SorCS1 is then packaged into a virion as the monomers are transferred to a buffer that promotes assembly of the virion. D) Erythrocytes are harvested from the patient and lysed to produce erythrocyte ghosts. The ghosts are the loaded, through osmotic pressure, with the genetic cargo containing SorCS1 before being reintroduced into the patients. E) Patients-derived primary cells are harvested and stimulated to produce exosomes, which are then purified and loaded, by electroporation, with the genetic cargo containing SorCS1 before being reintroduced into the patient.

Example 12: The application of adenovirus expressing soluble SorCS1 or specific SorCS1 fragments for the treatment of insulin resistance.

[0268] Genetic material expressing soluble SorCS1 or specific peptides of SorCS1 is inserted into an adeno-associated viral vector. The adeno-associated viral vector is chosen because, unlike first-generation adenoviruses that contain a full complement of viral proteins, this vector encodes no viral proteins and has negligible toxicity. Furthermore, this virus gives prolonged and stable transgene (SorCS1) expression, which lower the need of repeated injection of virus to the patient. In detail, a DNA construct encoding either soluble SorCS1 or fragments of SorCS1 is inserted into an adeno-associated viral vector. The adeno-associated virus is together with a helper plasmid introduced into a cell culture and a large amount of adeno-associated virus produced. Finally, $1x10^{11}$ adeno-associated virus particles is injected into SorCS1 knockout mice. The viral-expressed SorCS1 cures the insulin resistance of the knockout mice and the same method is used to treat patients with insulin resistance.

Example 13: Generation of mouse overexpressing SorCS1

[0269] For tissue-specific induction of SorCS1 expression in the mouse, an expression construct containing a CAAG promoter (chicken beta-actin / minimal CMV) upstream of a lox-STOP-lox cassette, followed by the cDNA of full-length SorCS1 (all plice variants) or soluble SorCS1 is introduced by homologous recombination into the ROSA gene locus. To drive expression, the stop cassette is excised by cross-breeding with transgenic mice that express Cre-recombinase in a tissue specific manner. Alternatively, recombinant virus expressing Cre may be subjected to the mice containing the CAAG promoter (chicken beta-actin / minimal CMV), lox-STOP-lox cassette, followed by the cDNA of full-length SorCS1 (all plice variants) or soluble SorCS1 to induce expression of full-length or soluble SorCS1, respectively. Thus, liver expression is achieved by injecting Cre-expressing adenovirus into e.g. the tail vein.

[0270] This mouse may be used for, but is not limited to screening purposes for measuring glucose and insulin levels as well as insulin-receptor expression and phosphorylation (e.g. glucose tolerance and insulin strain) prior and subsequent to induction. In addition, the mouse may be crossbred with a SorCS1 knockout mouse, in order to study if SorCS1 overexpression can normalise or improve the phenotype.

Example 13: Decreased plasma glucose levels in mice overexpressing soluble SorCS1.

[0271] To examine the use of SorCS1 for treatment of insulin resistance, wild-type and SorCS1 knockout female mice were injected with an adenovirus over-expressing soluble SorCS1. The recombinant adenovirus for expression of human soluble SorCS1 (hsol.SorCS1) was generated as follows: pcDNA3.1/Zeo(-)/hsol.SorCS1 encoding the human soluble SorCS1 cDNA (amino acids 1-1100) was digested with Pme1 and Apa1 and the fragment encoding hsol.SorCS1 inserted into the shuttle plasmid pVQpacAd5CMVK-NpA (ViraQuest Inc, North Liberty, IA). ViraQuest Inc, North Liberty, IA, then used this shuttle plasmid for generation and propagation of adenovirus over-expressing hsol. SorCS1. Female SorCS1 knockout and wild-type mice 40 weeks of age were fasted overnight. In the morning, on day 0, blood samples were obtained by retroorbital bleeding and plasma glucose was measured immediately on an automatic monitor (Ascentia Contour from Bayer). The mice were subsequently injected in the tail vein with 2E9 pfu's of an adenoviral vector with either hsol.SorCS1 or LacZ as a negative control (from ViraQuest Inc, North Liberty, IA). On day 7, measurements of plasma glucose were repeated on overnight fasted mice to evaluate the effect of the

SorCS1 and LacZ protein. As shown in Fig. 17, wild-type and SorCS1 knockout mice, which over-expressed soluble SorCS1 protein, exhibited a significant decrease in plasma glucose levels (≈40%) both in. As expected, a significant decrease in glucose levels was not observed in mice that received the LacZ control virus.

Example 14: Expression and phosphorylation of IR and expression of Glut4 in SorCS1 knockout mice over-expressing soluble SorCS1.

[0272] To further examine the effect of SorCS1 on insulin resistance, the expression of insulin receptor (IR), phosphorylation of IR and the expression of glucose transporter type 4 (Glut4) was determined in mice overexpressing SorCS1. Female SorCS1 knockout (-/-) mice 40 weeks of age were injected with an adenoviral vector expressing either hsol.SorCS1 or LacZ as a negative control (see example 13). On day 12 after virus injection, the mice were fasted overnight, injected intraperitoneally with insulin (Novorapid, Novo Nordisk A/S) (10 units/kg body weight) in sterile saline, and killed 15 min later. Muscle and adipose tissue were removed and homogenized in lysis buffer TNE-buffer (10mM Tris-HCl, 150 mM NaCl, 1 mM EDTA, 1% nonidet P-40, pH. 8) containing protease inhibitors (Complete Mini, Roche) and phosphatase inhibitors (cocktail 1, Sigma Aldrich). The lysates were cleared by centrifugation 10 min at 10.000 x g, and protein concentration were determined by Bio-Rad Protein Assay. Equal amount of total protein (50 µg) for different samples were separated on a 4-12 % Bis-tris gel (Nupage, Invitrogen) and transferred onto polyvinylidene difluoride (PVDF) membranes (Amersham Pharmacia). Membranes were analysed by western blotting with anti-IR (Santa Cruz Biotechnology, sc-711), anti-IR-pY (R&D systems, AF2507) and anti-Glut4 (Abcam, ab654). Bound antibodies were developed by Super-Signal West Pico reagent (Pierce) and a Fuji film LAS3000. Elevated amounts of IR, phosphorylated IR (IR-pY) and glut4 were observed in both muscle (Fig. 18A) and adipose (Fig. 18B) tissue from SorCS1 knockout mice over-expressing soluble SorCS1 when compared to mice expressing the LacZ control protein, suggesting increased insulin sensitivity in mice overexpressing SorCS1.

Example 15: Decreased plasma glucose and insulin levels in diabetic db/db female mice over-expressing soluble SorCS1.

[0273] To evaluate the effect of soluble SorCS1 in an obese mouse model that spontaneously develops type 2 diabetes we used the db/db mouse strain (BKS.Cg-*m*+/+Lpr^{db}/BomTac from Taconic). These mice lack the leptin receptor consequently the mice become obese and develop insulin resistance and finally severe diabetes at the age of 6-8 weeks. To examine the effect on plasma glucose and insulin levels, mice were injected with adenovirus expressing either hsol.SorCS1 or LacZ as a control (see example 13). In detail, db/db female mice 10 weeks of age were fasted overnight. In the morning, on day 0, the mice were anesthetized with diethyl ether and blood samples were obtained by retroorbital bleeding. Blood glucose was measured immediately on an automatic monitor (Ascentia Contour from Bayer), whereas plasma insulin levels were determined using an ultrasensitive mouse insulin enzyme-linked immunoabsorbent assay kit (DRG Diagnostics). Thereafter the mice were injected in the tail vein with 2E9 pfu's of an adenoviral vector with either hsol.SorCS1 or LacZ (from ViraQuest Inc, North Liberty, IA) as a negative control virus. On day 7, measurements of blood glucose and plasma insulin were repeated on overnight fasted mice to evaluate the effect of the SorCS1 and LacZ protein. Data shown in Fig. 19 are means ± SEM for 5 mice in each group. On day 7, db/db female mice with over-expression of soluble SorCS1 exhibited a significant decrease in blood glucose (≈35%) compared to the mice that received the control LacZ virus (Fig. 19A). Furthermore, on day 7 there was also a significant decrease in the plasma insulin levels in the db/db female mice over-expressing soluble SorCS1 compared to mice that express the control virus (Fig. 19B). Thus, over-expression of soluble SorCS1 improves the diabetic status in the type 2 diabetic (db/db) mouse model.

Example 16: Glucose tolerance test in diabetic db/db female mice with over-expression of soluble SorCS1.

[0274] To examine the effect of SorCS1 on glucose tolerance, female db/db mice injected with adenoviruses expressing either soluble SorCS1 or LacZ (see exampple 13) where on day 3 fasted over-night (16 hrs). On day 4 the mice were injected intraperitoneally with a bolus of glucose (2mg/g body weight) in sterile saline. The animals were anesthetized with diethyl ether and blood samples were obtained by retroorbital bleeding at times 0, 15, 30, 90, and 150 minutes after injection. Blood glucose levels were measured immediately after sampling on an automatic monitor (Ascentia Contour from Bayer). Data shown in Fig. 20 are means ± SEM for 5 mice in each group. The results in Fig. 20 show that over-expression of soluble SorCS1 renders the mice more sensitive to insulin as the level of blood glucose becomes normal (i.e. the same as before glucose injection) after 150 min. By contrast, the blood glucose level in mice expressing the control protein LacZ remains elevated during the 150 minutes. In conclusion, these results show that db/db female mice over-expressing soluble SorCS1 are less insulin resistant.

Example 17: Plasma glucose and insulin levels in diabetic db/db male mice over-expressing soluble SorCS1.

[0275] To evaluate the effect of soluble SorCS1 in an obese mouse model that spontaneously develops type 2 diabetes, we used the db/db mouse strain (BKS.Cg-*m*+/+Lpr^{db}/BomTac from Taconic). Mice were injected with adenovirus expressing either hsol.SorCS1 or LacZ as a control (see example 13), to examine the effect on plasma glucose and insulin levels. In detail, db/db male mice 6 weeks of age were fasted overnight. In the morning, on day 0, the mice were anesthetized with diethyl ether and blood samples were obtained by retroorbital bleeding. Blood glucose was measured immediately on an automatic monitor (Ascentia Contour from Bayer), whereas plasma insulin levels were determined using an ultrasensitive mouse insulin enzyme-linked immunoabsorbent assay kit (DRG Diagnostics). The mice were subsequently injected in the tail vein with 2E9 pfu's of an adenoviral vector with either hsol.SorCS1 or LacZ (from ViraQuest Inc, North Liberty, IA) as a negative control. On day 7, measurements of blood glucose and plasma insulin were repeated on overnight fasted mice to evaluate the effect of the SorCS1 and LacZ protein. The data shown in Fig. 21 are means ± SEM for 5 mice in each group. On day 7, db/db male mice with over-expression of soluble SorCS1 exhibited a significant decrease in blood glucose (≈35%) compared to the mice that received the control LacZ virus (Fig. 21 A). Because the decline in glucose levels were not accounted by an increased insulin concentration in mice overexpressing SorCS1 (Fig. 21 B), we conclude that over-expression of soluble SorCS1 improves the diabetic status in male type 2 diabetic db/db mice.

Example 18: Subcellular localization of Glut4 in muscle tissue from db/db male mice over-expressing soluble SorCS1.

[0276] To evaluate if over-expression of soluble SorCS1 might change the distribution of Glut4 we conducted subcellular fractionation on muscle tissue from db/db male mice over-expressing soluble SorCS1. In detail, db/db male mice 6 weeks of age were injected in the tail vein with an adenoviral vector expressing either hsol.SorCS1 or LacZ as a control (see example 13). On day 7 after virus injection, the mice were fasted overnight, injected intraperitoneally with insulin (Novorapid, Novo Nordisk A/S) (10 units/kg body weight) in sterile saline, and killed 15 min later. Muscle tissue from 5 mice injected with the same virus was removed, pooled and transferred to 5 ml of HEPES-buffered sucrose (0.25 M sucrose, 1 mM EDTA, 20 mM HEPES-KOH, pH. 7.4), homogenized by 10 strokes up and down using a Teflon pestle, and centrifuged at 1000 x g for 10 min. Thus, heavy mitochondrial, light mitochondrial, and microsomal fraction were obtained by several round of centrifugation. First, the supernatant was centrifuged at 3.000 x g for 10 min, then the resulting supernatant was centrifuged at 16.000 x g for 10 min, and finally the resulting supernatant was centrifuged a 100.000 x g for 45 min giving a pellet containing the microsomal fraction. The microsomal fractions were resuspended in 0.5 ml HEPES-buffered solution and subjected to sucrose (velocity) gradient centrifugation. The 0.5 ml microsomal samples were loaded onto a 12 ml linear 0.8 M to 1.6 M sucrose gradient in 1 M HEPES, pH 7.2, and centrifuged 18 h in a swinging bucket rotor (SW41 Ti) at 84.000 x g. Each gradient was separated into 24 fractions starting from the top of the tube. Finally, gel electrophoresis and Western blotting analyzed the expression of Glut4 in the different fractions. The results in Fig. 22 show that the sedimentation distribution of Glut4 in muscle tissue over-expressing SorCS1 (lower panel) is different from muscle tissue expressing the control protein lacZ (upper panel). Thus, over-expression of soluble SorCS1 in db/db male mice may change the distribution of Glut4 and thereby modulate glucose uptake.

Example 19: Gene expression profiling of adipose tissue from SorCS1 knockout mice by PCR arrays.

[0277] To examine the gene expression profile of SorCS1 knockout mice, the expression of 84 genes related to the mouse insulin signalling pathway and 84 genes related to mouse lipoprotein signalling & cholesterol metabolism was determined using microarray analysis. The microarray analysis were performed using RNA from adipose tissue of SorCS1 knockout wild-type adipose mice. In practice, first strand cDNA was synthesized from total RNA (Applied Biosystems) from SorCS1 knockout (-/-) and wild-type (+/+) adipose tissue from female mice 50 weeks of age (n = 3). Then superarray of Mouse Insulin Signalling Pathway (PAMM-030A RT2 Profiler PCR arrays) or B) the type Mouse Lipoprotein Signalling & Cholesterol Metabolism (PAMM-080-A RT2 Profiler PCR arrays) were processed using an ABI7900 platform (Applied Biosystems) and SYBR Green/Rox PCR (SABiosciences). AROS Applied Biotechnology, Aarhus, Denmark, did the expression analyses. Genes showing an expression more than 3 times up- or down-regulated in the SorCS1 knockout mice when compared to wild-type mice are listed in the upper tables and their known functions are indicated in the table below. The data in Fig. 24 shows that the expression of several genes are changed expression in the SorCS1 knockout mice compared to the wild-type mice, indicating that insulin and cholesterol signalling pathways and metabolism are altered in SorCS1 knockout mice.

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[0278]

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Overview of sequences

[0279]

SEQ ID NO 1: Homo sapiens preproSorCS1b (Isoform 1)

SEQ ID NO 2: Homo sapiens preproSorCS1 (Isoform 2)

SEQ ID NO 3: Homo sapiens preproSorCS1c (Isoform 3)

SEQ ID NO 4: Homo sapiens preproSorCS1a (Isoform 4)

SEQ ID NO 5: Soluble Homo sapiens preproSorCS1

SEQ ID NO 6: Homo sapiens proSorCS1b (Isoform 1)

SEQ ID NO 7: Homo sapiens proSorCS1 (Isoform 2)

SEQ ID NO 8: Homo sapiens proSorCS1c (Isoform 3)

SEQ ID NO 9: Homo sapiens proSorCS1a (Isoform 4)

SEQ ID NO 10: Soluble Homo sapiens proSorCS1

SEQ ID NO 11: Homo sapiens mature SorCS1b (Isoform 1)

SEQ ID NO 12: Homo sapiens mature SorCS1 (Isoform 2)

SEQ ID NO 13: Homo sapiens mature SorCS1c (Isoform 3)

SEQ ID NO 14: Homo sapiens mature SorCS1a (Isoform 4)

SEQ ID NO 15: Soluble Homo sapiens mature SorCS1

SEQ ID NO 16: Mouse preproSorCS1b (isoform 1)

SEQ ID NO 17: Mouse preproSorCS1a (isoform 2)

SEQ ID NO 18: Mouse preproSorCS1c (isoform 3)

SEQ ID NO 19: Mouse preproSorCS1c+ (isoform 4)

SEQ ID NO 20: Mouse preproSorCS1d

SEQ ID NO 21: Soluble mouse preproSorCS1

SEQ ID NO 22: Mouse proSorCS1b (isoform 1)

SEQ ID NO 23: Mouse proSorCS1a (isoform 2)

SEQ ID NO 24: Mouse proSorCS1c (isoform 3)

SEQ ID NO 25: Mouse proSorCS1c+ (isoform 4)

SEQ ID NO 26: Mouse proSorCS1d

SEQ ID NO 27: Soluble mouse proSorCS1

SEQ ID NO 28: Mouse mature SorCS1b (isoform 1)

SEQ ID NO 29: Mouse mature SorCS1a (isoform 2)

SEQ ID NO 30: Mouse mature SorCS1c (isoform 3)

SEQ ID NO 31: Mouse mature SorCS1c+ (isoform 4)

SEQ ID NO 32: Mouse mature SorCS1d

SEQ ID NO 33: Soluble mouse mature SorCS1

SEQ ID NO 34: Chimpanzee preproSorCS1

SEQ ID NO 35: Chimpanzee proSorCS1

SEQ ID NO 36: Chimpanzee mature SorCS1

SEQ ID NO 37: Chimpanzee soluble SorCS1

SEQ ID NO 38: Dog mature SorCS1

SEQ ID NO 39: Dog soluble SorCS1

SEQ ID NO 40: Cow preproSorCS1

SEQ ID NO 41: Cow proSorCS1

SEQ ID NO 42: Cow mature SorCS1

SEQ ID NO 43: Cow soluble SorCS1

SEQ ID NO 44: Rat preproSorSC1

SEQ ID NO 45: Rat proSorCS1

SEQ ID NO 46: Rat mature SorCS1

SEQ ID NO 47: Rat soluble SorCS1

SEQ ID NO 48: Chicken preproSorCS1

SEQ ID NO 49: Chicken proSorCS1

SEQ ID NO 50: Chicken mature SorCS1

SEQ ID NO 51: Chicken soluble SorCS1

SEQ ID NO 52: Homo sapiens Sortilin

SEQ ID NO 53: Homo sapiens SorLA

SEQ ID NO 54: Homo sapiens SorCS2

SEQ ID NO 55: Homo sapiens SorCS3

SEQ ID NO 56: Homo sapiens Human Insulin Receptor (IR)

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SorCS1-a (ex25), reverse primer
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SEQ ID NO: 62
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SEQ ID NO: 63
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SEQUENCE LISTING

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Ile Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu
        835                 840                 845

Ser Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly Ile
    850                 855                 860

Phe Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala
865                 870                 875                 880

Val Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser
                885                 890                 895

Leu Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val
            900                 905                 910

Leu Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly
        915                 920                 925

Asn Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe Arg
```

```
    930                 935                 940

Phe Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly
945                 950                 955                 960

Asn Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe
                965                 970                 975

Arg Ser Leu Arg Leu Ser Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro
            980                 985                 990

Asp Ile Pro Glu Trp Arg Arg Asp  Ile Gly Arg Val Ile  Lys Lys Ser
        995                 1000                1005

Leu Val  Glu Ala Thr Gly Val  Pro Gly Gln His Ile  Leu Val Ala
    1010                1015                1020

Val Leu  Pro Gly Leu Pro Thr  Thr Ala Glu Leu Phe  Val Leu Pro
    1025                1030                1035

Tyr Gln  Asp Pro Ala Gly Glu  Asn Lys Arg Ser Thr  Asp Asp Leu
    1040                1045                1050

Glu Gln  Ile Ser Glu Leu Leu  Ile His Thr Leu Asn  Gln Asn Ser
    1055                1060                1065

Val His  Phe Glu Leu Lys Pro  Gly Val Arg Val Leu  Val His Ala
    1070                1075                1080

Ala His  Leu Thr Ala Ala Pro  Leu Val Asp Leu Thr  Pro Thr His
    1085                1090                1095

Ser Gly  Ser Ala Met Leu Met  Leu Leu Ser Val Val  Phe Val Gly
    1100                1105                1110

Leu Ala  Val Phe Val Ile Tyr  Lys Phe Lys Arg Arg  Val Ala Leu
    1115                1120                1125

Pro Ser  Pro Pro Ser Pro Ser  Thr Gln Pro Gly Asp  Ser Ser Leu
    1130                1135                1140

Arg Leu  Gln Arg Ala Arg His  Ala Thr Pro Pro Ser  Thr Pro Lys
    1145                1150                1155

Arg Gly  Ser Ala Gly Ala Gln  Tyr Ala Ile
    1160                1165
```

<210> 2

<211> 1197

<212> PRT

<213> Homo sapiens

<220>

<221> MISC_FEATURE

<222> (1)..(1197)

<223> preproSorCS1, Isoform 2

<400> 2

```
Met Gly Lys Val Gly Ala Gly Gly Gly Ser Gln Ala Arg Leu Ser Ala
1               5                   10                  15

Leu Leu Ala Gly Ala Gly Leu Leu Ile Leu Cys Ala Pro Gly Val Cys
            20                  25                  30

Gly Gly Gly Ser Cys Cys Pro Ser Pro His Pro Ser Ser Ala Pro Arg
        35                  40                  45

Ser Ala Ser Thr Pro Arg Gly Phe Ser His Gln Gly Arg Pro Gly Arg
    50                  55                  60

Ala Pro Ala Thr Pro Leu Pro Leu Val Val Arg Pro Leu Phe Ser Val
65                  70                  75                  80

Ala Pro Gly Asp Arg Ala Leu Ser Leu Glu Arg Ala Arg Gly Thr Gly
                85                  90                  95

Ala Ser Met Ala Val Ala Ala Arg Ser Gly Arg Arg Arg Arg Ser Gly
            100                 105                 110

Ala Asp Gln Glu Lys Ala Glu Arg Gly Glu Gly Ala Ser Arg Ser Pro
        115                 120                 125

Arg Gly Val Leu Arg Asp Gly Gly Gln Gln Glu Pro Gly Thr Arg Glu
    130                 135                 140

Arg Asp Pro Asp Lys Ala Thr Arg Phe Arg Met Glu Glu Leu Arg Leu
145                 150                 155                 160

Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala
                165                 170                 175

Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile Leu Thr
            180                 185                 190

Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp
        195                 200                 205

Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Val
    210                 215                 220
```

```
Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys
225                 230                 235                 240

Arg Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser Leu Leu
                245                 250                 255

Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe
            260                 265                 270

Tyr Ile Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu
        275                 280                 285

Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe Gly Arg
    290                 295                 300

Arg Trp Gln Leu Ile Gln Glu Gly Val Val Pro Asn Arg Phe Tyr Trp
305                 310                 315                 320

Ser Val Met Gly Ser Asn Lys Glu Pro Asp Leu Val His Leu Glu Ala
                325                 330                 335

Arg Thr Val Asp Gly His Ser His Tyr Leu Thr Cys Arg Met Gln Asn
            340                 345                 350

Cys Thr Glu Ala Asn Arg Gln Pro Phe Pro Gly Tyr Ile Asp Pro Asp
        355                 360                 365

Ser Leu Ile Val Gln Asp His Tyr Val Phe Val Gln Leu Thr Ser Gly
    370                 375                 380

Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn Ala Phe Ala Gln
385                 390                 395                 400

Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His Val Ile Ser
                405                 410                 415

Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln Asn
            420                 425                 430

Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe Thr
        435                 440                 445

Leu Ala Leu Glu Asn Val Gln Ser Ser Arg Gly Pro Glu Gly Asn Ile
    450                 455                 460

Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu Ala
465                 470                 475                 480
```

```
Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn Lys
                485                 490                 495

Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Thr Asp Leu Arg Gly
            500                 505                 510

Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His Leu His Leu
        515                 520                 525

Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala Ser Lys Asp
    530                 535                 540

Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Ser Glu Leu
545                 550                 555                 560

Ser Asp Thr Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn Thr
                565                 570                 575

Trp Arg Gln Ile Phe Glu Glu Glu His Ser Val Leu Tyr Leu Asp Gln
            580                 585                 590

Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro Ile Arg His
        595                 600                 605

Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr Ser Phe
    610                 615                 620

Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu Pro Gly Glu
625                 630                 635                 640

Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg Ser Glu
                645                 650                 655

Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp Arg Arg Cys
            660                 665                 670

Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln Gly Glu Ala
        675                 680                 685

Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu Arg
    690                 695                 700

Lys Cys Met Gln Gly Lys Tyr Ala Gly Ala Met Glu Ser Glu Pro Cys
705                 710                 715                 720

Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg His
                725                 730                 735
```

```
Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser Leu
            740                 745                 750

Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Thr Gly Tyr
        755                 760                 765

Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln Tyr
    770                 775                 780

Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu Arg
785                 790                 795                 800

Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn Val
                805                 810                 815

Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr Leu Ile
            820                 825                 830

Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu Ser
        835                 840                 845

Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly Ile Phe
    850                 855                 860

Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala Val
865                 870                 875                 880

Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser Leu
                885                 890                 895

Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val Leu
            900                 905                 910

Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly Asn
        915                 920                 925

Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe Arg Phe
    930                 935                 940

Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly Asn
945                 950                 955                 960

Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe Arg
                965                 970                 975

Ser Leu Arg Leu Ser Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro Asp
            980                 985                 990

Ile Pro Glu Trp Arg Arg Asp Ile  Gly Arg Val Ile Lys  Lys Ser Leu
```

```
        995                 1000                1005

Val Glu  Ala Thr Gly Val Pro  Gly Gln His Ile Leu  Val Ala Val
    1010                1015                1020

Leu Pro  Gly Leu Pro Thr Thr  Ala Glu Leu Phe Val  Leu Pro Tyr
    1025                1030                1035

Gln Asp  Pro Ala Gly Glu Asn  Lys Arg Ser Thr Asp  Asp Leu Glu
    1040                1045                1050

Gln Ile  Ser Glu Leu Leu Ile  His Thr Leu Asn Gln  Asn Ser Val
    1055                1060                1065

His Phe  Glu Leu Lys Pro Gly  Val Arg Val Leu Val  His Ala Ala
    1070                1075                1080

His Leu  Thr Ala Ala Pro Leu  Val Asp Leu Thr Pro  Thr His Ser
    1085                1090                1095

Gly Ser  Ala Met Leu Met Leu  Leu Ser Val Val Phe  Val Gly Leu
    1100                1105                1110

Ala Val  Phe Val Ile Tyr Lys  Phe Lys Arg Lys Ile  Pro Gly Ile
    1115                1120                1125

Asn Val  Tyr Ala Gln Met Gln  Asn Glu Lys Glu Gln  Glu Met Ile
    1130                1135                1140

Ser Pro  Val Ser His Ser Glu  Ser Arg Pro Asn Val  Pro Gln Thr
    1145                1150                1155

Glu Leu  Arg Arg Pro Gly Gln  Leu Ile Asp Glu Lys  Val Glu Ser
    1160                1165                1170

Gln Leu  Ile Gly Ser Ile Ser  Ile Val Ala Glu Asn  Gln Ser Thr
    1175                1180                1185

Lys Glu  Ile Pro Thr Tyr Val  Asn Val
    1190                1195
```

<210> 3

<211> 1179

<212> PRT

<213> Homo sapiens

<220>

<221> MISC_FEATURE

<222> (1)..(1179)

<223> preproSorCS1c, Isoform 3

<400> 3

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Met Gly Lys Val Gly Ala Gly Gly Gly Ser Gln Ala Arg Leu Ser Ala
1               5                   10                  15

Leu Leu Ala Gly Ala Gly Leu Leu Ile Leu Cys Ala Pro Gly Val Cys
            20                  25                  30

Gly Gly Gly Ser Cys Cys Pro Ser Pro His Pro Ser Ser Ala Pro Arg
        35                  40                  45

Ser Ala Ser Thr Pro Arg Gly Phe Ser His Gln Gly Arg Pro Gly Arg
    50                  55                  60

Ala Pro Ala Thr Pro Leu Pro Leu Val Val Arg Pro Leu Phe Ser Val
65                  70                  75                  80

Ala Pro Gly Asp Arg Ala Leu Ser Leu Glu Arg Ala Arg Gly Thr Gly
                85                  90                  95

Ala Ser Met Ala Val Ala Ala Arg Ser Gly Arg Arg Arg Arg Ser Gly
            100                 105                 110

Ala Asp Gln Glu Lys Ala Glu Arg Gly Glu Gly Ala Ser Arg Ser Pro
        115                 120                 125

Arg Gly Val Leu Arg Asp Gly Gly Gln Gln Glu Pro Gly Thr Arg Glu
    130                 135                 140

Arg Asp Pro Asp Lys Ala Thr Arg Phe Arg Met Glu Glu Leu Arg Leu
145                 150                 155                 160

Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala
                165                 170                 175

Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile Leu Thr
            180                 185                 190

Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp
        195                 200                 205

Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Val
    210                 215                 220

Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys
225                 230                 235                 240

Arg Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser Leu Leu
                245                 250                 255
```

```
Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe
            260                 265                 270

Tyr Ile Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu
        275                 280                 285

Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe Gly Arg
    290                 295                 300

Arg Trp Gln Leu Ile Gln Glu Gly Val Val Pro Asn Arg Phe Tyr Trp
305                 310                 315                 320

Ser Val Met Gly Ser Asn Lys Glu Pro Asp Leu Val His Leu Glu Ala
                325                 330                 335

Arg Thr Val Asp Gly His Ser His Tyr Leu Thr Cys Arg Met Gln Asn
            340                 345                 350

Cys Thr Glu Ala Asn Arg Asn Gln Pro Phe Pro Gly Tyr Ile Asp Pro
        355                 360                 365

Asp Ser Leu Ile Val Gln Asp His Tyr Val Phe Val Gln Leu Thr Ser
    370                 375                 380

Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn Ala Phe Ala
385                 390                 395                 400

Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His Val Ile
                405                 410                 415

Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln
            420                 425                 430

Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe
        435                 440                 445

Thr Leu Ala Leu Glu Asn Val Gln Ser Ser Arg Gly Pro Glu Gly Asn
    450                 455                 460

Ile Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu
465                 470                 475                 480

Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn
                485                 490                 495

Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Thr Asp Leu Arg
            500                 505                 510
```

```
Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His Leu His
        515                 520                 525

Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala Ser Lys
    530                 535                 540

Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Ser Glu
545                 550                 555                 560

Leu Ser Asp Thr Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn
                565                 570                 575

Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Val Leu Tyr Leu Asp
            580                 585                 590

Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro Ile Arg
        595                 600                 605

His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr Ser
    610                 615                 620

Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu Pro Gly
625                 630                 635                 640

Glu Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg Ser
                645                 650                 655

Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp Arg Arg
            660                 665                 670

Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln Gly Glu
        675                 680                 685

Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu
    690                 695                 700

Arg Lys Cys Met Gln Gly Lys Tyr Ala Gly Ala Met Glu Ser Glu Pro
705                 710                 715                 720

Cys Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg
                725                 730                 735

His Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser
            740                 745                 750

Leu Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Thr Gly
        755                 760                 765
```

```
Tyr Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln
    770                 775                 780

Tyr Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu
785                 790                 795                 800

Arg Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn
                805                 810                 815

Val Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr Leu
            820                 825                 830

Ile Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu
        835                 840                 845

Ser Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly Ile
    850                 855                 860

Phe Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala
865                 870                 875                 880

Val Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser
                885                 890                 895

Leu Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val
            900                 905                 910

Leu Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly
        915                 920                 925

Asn Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe Arg
    930                 935                 940

Phe Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly
945                 950                 955                 960

Asn Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe
                965                 970                 975

Arg Ser Leu Arg Leu Ser Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro
            980                 985                 990

Asp Ile Pro Glu Trp Arg Arg Asp  Ile Gly Arg Val Ile  Lys Lys Ser
        995                 1000                1005

Leu Val  Glu Ala Thr Gly Val  Pro Gly Gln His Ile  Leu Val Ala
    1010                1015                1020

Val Leu  Pro Gly Leu Pro Thr  Thr Ala Glu Leu Phe  Val Leu Pro
```

```
    1025                1030                1035

Tyr Gln  Asp Pro Ala Gly Glu  Asn Lys Arg Ser Thr  Asp Asp Leu
    1040                1045                1050

Glu Gln  Ile Ser Glu Leu Leu  Ile His Thr Leu Asn  Gln Asn Ser
    1055                1060                1065

Val His  Phe Glu Leu Lys Pro  Gly Val Arg Val Leu  Val His Ala
    1070                1075                1080

Ala His  Leu Thr Ala Ala Pro  Leu Val Asp Leu Thr  Pro Thr His
    1085                1090                1095

Ser Gly  Ser Ala Met Leu Met  Leu Leu Ser Val Val  Phe Val Gly
    1100                1105                1110

Leu Ala  Val Phe Val Ile Tyr  Lys Phe Lys Arg Lys  Ile Pro Gly
    1115                1120                1125

Ile Asn  Val Tyr Ala Gln Met  Gln Asn Glu Lys Glu  Gln Glu Met
    1130                1135                1140

Ile Ser  Pro Val Ser His Ser  Glu Ser Arg Pro Asn  Val Pro Gln
    1145                1150                1155

Thr Glu  Leu Arg Arg Pro Gly  Gln Leu Ile Asp Glu  Lys Val Glu
    1160                1165                1170

Ser Gln  Leu Ile Gly Lys
    1175
```

<210> 4

<211> 1159

<212> PRT

<213> Homo sapiens

<220>

<221> MISC_FEATURE

<222> (1)..(1159)

<223> preproSorCS1a, Isoform 4

<400> 4

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Met Gly Lys Val Gly Ala Gly Gly Gly Ser Gln Ala Arg Leu Ser Ala
1               5                   10                  15

Leu Leu Ala Gly Ala Gly Leu Leu Ile Leu Cys Ala Pro Gly Val Cys
            20                  25                  30

Gly Gly Gly Ser Cys Cys Pro Ser Pro His Pro Ser Ser Ala Pro Arg
```

```
        35                  40                  45

Ser Ala Ser Thr Pro Arg Gly Phe Ser His Gln Gly Arg Pro Gly Arg
    50                  55                  60

Ala Pro Ala Thr Pro Leu Pro Leu Val Val Arg Pro Leu Phe Ser Val
65                  70                  75                  80

Ala Pro Gly Asp Arg Ala Leu Ser Leu Glu Arg Ala Arg Gly Thr Gly
                85                  90                  95

Ala Ser Met Ala Val Ala Ala Arg Ser Gly Arg Arg Arg Arg Ser Gly
            100                 105                 110

Ala Asp Gln Glu Lys Ala Glu Arg Gly Glu Gly Ala Ser Arg Ser Pro
        115                 120                 125

Arg Gly Val Leu Arg Asp Gly Gly Gln Gln Glu Pro Gly Thr Arg Glu
    130                 135                 140

Arg Asp Pro Asp Lys Ala Thr Arg Phe Arg Met Glu Glu Leu Arg Leu
145                 150                 155                 160

Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala
                165                 170                 175

Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile Leu Thr
            180                 185                 190

Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp
        195                 200                 205

Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Val
    210                 215                 220

Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys
225                 230                 235                 240

Arg Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser Leu Leu
                245                 250                 255

Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe
            260                 265                 270

Tyr Ile Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu
        275                 280                 285

Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe Gly Arg
    290                 295                 300
```

```
Arg Trp Gln Leu Ile Gln Glu Gly Val Val Pro Asn Arg Phe Tyr Trp
305                 310                 315                 320

Ser Val Met Gly Ser Asn Lys Glu Pro Asp Leu Val His Leu Glu Ala
                325                 330                 335

Arg Thr Val Asp Gly His Ser His Tyr Leu Thr Cys Arg Met Gln Asn
            340                 345                 350

Cys Thr Glu Ala Asn Arg Asn Gln Pro Phe Pro Gly Tyr Ile Asp Pro
        355                 360                 365

Asp Ser Leu Ile Val Gln Asp His Tyr Val Phe Val Gln Leu Thr Ser
    370                 375                 380

Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn Ala Phe Ala
385                 390                 395                 400

Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His Val Ile
                405                 410                 415

Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln
            420                 425                 430

Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe
        435                 440                 445

Thr Leu Ala Leu Glu Asn Val Gln Ser Ser Arg Gly Pro Glu Gly Asn
    450                 455                 460

Ile Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu
465                 470                 475                 480

Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn
                485                 490                 495

Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Thr Asp Leu Arg
            500                 505                 510

Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His Leu His
        515                 520                 525

Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala Ser Lys
    530                 535                 540

Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Ser Glu
545                 550                 555                 560
```

```
Leu Ser Asp Thr Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn
                565                 570                 575

Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Val Leu Tyr Leu Asp
            580                 585                 590

Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro Ile Arg
        595                 600                 605

His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr Ser
    610                 615                 620

Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu Pro Gly
625                 630                 635                 640

Glu Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg Ser
                645                 650                 655

Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp Arg Arg
            660                 665                 670

Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln Gly Glu
        675                 680                 685

Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu
    690                 695                 700

Arg Lys Cys Met Gln Gly Lys Tyr Ala Gly Ala Met Glu Ser Glu Pro
705                 710                 715                 720

Cys Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg
                725                 730                 735

His Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser
            740                 745                 750

Leu Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Thr Gly
        755                 760                 765

Tyr Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln
    770                 775                 780

Tyr Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu
785                 790                 795                 800

Arg Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn
                805                 810                 815
```

```
Val Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr Leu
            820                 825                 830

Ile Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu
        835                 840                 845

Ser Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly Ile
    850                 855                 860

Phe Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala
865                 870                 875                 880

Val Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser
                885                 890                 895

Leu Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val
            900                 905                 910

Leu Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly
        915                 920                 925

Asn Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe Arg
    930                 935                 940

Phe Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly
945                 950                 955                 960

Asn Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe
                965                 970                 975

Arg Ser Leu Arg Leu Ser Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro
            980                 985                 990

Asp Ile Pro Glu Trp Arg Arg Asp  Ile Gly Arg Val Ile  Lys Lys Ser
        995                 1000                1005

Leu Val  Glu Ala Thr Gly Val  Pro Gly Gln His Ile  Leu Val Ala
    1010                1015                1020

Val Leu  Pro Gly Leu Pro Thr  Thr Ala Glu Leu Phe  Val Leu Pro
    1025                1030                1035

Tyr Gln  Asp Pro Ala Gly Glu  Asn Lys Arg Ser Thr  Asp Asp Leu
    1040                1045                1050

Glu Gln  Ile Ser Glu Leu Leu  Ile His Thr Leu Asn  Gln Asn Ser
    1055                1060                1065

Val His  Phe Glu Leu Lys Pro  Gly Val Arg Val Leu  Val His Ala

    1070                1075                1080

Ala His  Leu Thr Ala Ala Pro  Leu Val Asp Leu Thr  Pro Thr His
    1085                1090                1095

Ser Gly  Ser Ala Met Leu Met  Leu Leu Ser Val Val  Phe Val Gly
    1100                1105                1110

Leu Ala  Val Phe Val Ile Tyr  Lys Phe Lys Arg Cys  Val Ser Leu
    1115                1120                1125

Tyr Pro  Arg Ser Pro Thr Pro  Asp Leu Phe Leu Leu  Pro Asp Arg
    1130                1135                1140

Phe Arg  Ser Met Cys Tyr Ser  Asp Val His Ser Ser  Asp Gly Phe
    1145                1150                1155

Tyr
```

<210> 5

<211> 1100

<212> PRT

<213> Homo sapiens

<220>

<221> MISC_FEATURE
<222> (1)..(1100)
<223> Soluble preproSorCS1

<400> 5

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Met Gly Lys Val Gly Ala Gly Gly Gly Ser Gln Ala Arg Leu Ser Ala
1               5                   10                  15

Leu Leu Ala Gly Ala Gly Leu Leu Ile Leu Cys Ala Pro Gly Val Cys
            20                  25                  30

Gly Gly Gly Ser Cys Cys Pro Ser Pro His Pro Ser Ser Ala Pro Arg
        35                  40                  45

Ser Ala Ser Thr Pro Arg Gly Phe Ser His Gln Gly Arg Pro Gly Arg
    50                  55                  60

Ala Pro Ala Thr Pro Leu Pro Leu Val Val Arg Pro Leu Phe Ser Val
65                  70                  75                  80

Ala Pro Gly Asp Arg Ala Leu Ser Leu Glu Arg Ala Arg Gly Thr Gly
                85                  90                  95

Ala Ser Met Ala Val Ala Ala Arg Ser Gly Arg Arg Arg Arg Ser Gly

            100                 105                 110

Ala Asp Gln Glu Lys Ala Glu Arg Gly Glu Gly Ala Ser Arg Ser Pro
        115                 120                 125

Arg Gly Val Leu Arg Asp Gly Gly Gln Gln Glu Pro Gly Thr Arg Glu
    130                 135                 140

Arg Asp Pro Asp Lys Ala Thr Arg Phe Arg Met Glu Glu Leu Arg Leu
145                 150                 155                 160

Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala
                165                 170                 175

Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile Leu Thr
            180                 185                 190

Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp
        195                 200                 205

Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Val
    210                 215                 220

Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys
225                 230                 235                 240

Arg Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser Leu Leu
                245                 250                 255

Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe
            260                 265                 270

Tyr Ile Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu
        275                 280                 285

Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe Gly Arg
    290                 295                 300

Arg Trp Gln Leu Ile Gln Glu Gly Val Val Pro Asn Arg Phe Tyr Trp
305                 310                 315                 320

Ser Val Met Gly Ser Asn Lys Glu Pro Asp Leu Val His Leu Glu Ala
                325                 330                 335

Arg Thr Val Asp Gly His Ser His Tyr Leu Thr Cys Arg Met Gln Asn
            340                 345                 350

Cys Thr Glu Ala Asn Arg Asn Gln Pro Phe Pro Gly Tyr Ile Asp Pro
        355                 360                 365
```

```
Asp Ser Leu Ile Val Gln Asp His Tyr Val Phe Val Gln Leu Thr Ser
    370                 375                 380

Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn Ala Phe Ala
385                 390                 395                 400

Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His Val Ile
                405                 410                 415

Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln
            420                 425                 430

Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe
        435                 440                 445

Thr Leu Ala Leu Glu Asn Val Gln Ser Ser Arg Gly Pro Glu Gly Asn
    450                 455                 460

Ile Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu
465                 470                 475                 480

Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn
                485                 490                 495

Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Thr Asp Leu Arg
            500                 505                 510

Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His Leu His
        515                 520                 525

Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala Ser Lys
    530                 535                 540

Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Ser Glu
545                 550                 555                 560

Leu Ser Asp Thr Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn
                565                 570                 575

Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Val Leu Tyr Leu Asp
            580                 585                 590

Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro Ile Arg
        595                 600                 605

His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr Ser
    610                 615                 620
```

```
Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu Pro Gly
625                 630                 635                 640

Glu Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg Ser
                645                 650                 655

Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp Arg Arg
            660                 665                 670

Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln Gly Glu
        675                 680                 685

Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu
    690                 695                 700

Arg Lys Cys Met Gln Gly Lys Tyr Ala Gly Ala Met Glu Ser Glu Pro
705                 710                 715                 720

Cys Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg
                725                 730                 735

His Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser
            740                 745                 750

Leu Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Thr Gly
        755                 760                 765

Tyr Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln
    770                 775                 780

Tyr Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu
785                 790                 795                 800

Arg Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn
                805                 810                 815

Val Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr Leu
            820                 825                 830

Ile Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu
        835                 840                 845

Ser Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly Ile
    850                 855                 860

Phe Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala
865                 870                 875                 880
```

```
Val Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser
                885                 890                 895

Leu Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val
            900                 905                 910

Leu Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly
        915                 920                 925

Asn Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe Arg
    930                 935                 940

Phe Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly
945                 950                 955                 960

Asn Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe
                965                 970                 975

Arg Ser Leu Arg Leu Ser Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro
            980                 985                 990

Asp Ile Pro Glu Trp Arg Arg Asp  Ile Gly Arg Val Ile  Lys Lys Ser
        995                 1000                1005

Leu Val  Glu Ala Thr Gly Val  Pro Gly Gln His Ile  Leu Val Ala
    1010                1015                1020

Val Leu  Pro Gly Leu Pro Thr  Thr Ala Glu Leu Phe  Val Leu Pro
    1025                1030                1035

Tyr Gln  Asp Pro Ala Gly Glu  Asn Lys Arg Ser Thr  Asp Asp Leu
    1040                1045                1050

Glu Gln  Ile Ser Glu Leu Leu  Ile His Thr Leu Asn  Gln Asn Ser
    1055                1060                1065

Val His  Phe Glu Leu Lys Pro  Gly Val Arg Val Leu  Val His Ala
    1070                1075                1080

Ala His  Leu Thr Ala Ala Pro  Leu Val Asp Leu Thr  Pro Thr His
    1085                1090                1095

Ser Gly
    1100
```

<210> 6

<211> 1134

<212> PRT

<213> Homo sapiens

<220>

<221> MISC_FEATURE

<222> (1)..(1134)

<223> proSorCS1b, Isoform 1

<400> 6

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Gly Gly Ser Cys Cys Pro Ser Pro His Pro Ser Ser Ala Pro Arg Ser
1               5                  10                  15

Ala Ser Thr Pro Arg Gly Phe Ser His Gln Gly Arg Pro Gly Arg Ala
            20                  25                  30

Pro Ala Thr Pro Leu Pro Leu Val Val Arg Pro Leu Phe Ser Val Ala
        35                  40                  45

Pro Gly Asp Arg Ala Leu Ser Leu Glu Arg Ala Arg Gly Thr Gly Ala
    50                  55                  60

Ser Met Ala Val Ala Ala Arg Ser Gly Arg Arg Arg Arg Ser Gly Ala
65                  70                  75                  80

Asp Gln Glu Lys Ala Glu Arg Gly Glu Gly Ala Ser Arg Ser Pro Arg
                85                  90                  95

Gly Val Leu Arg Asp Gly Gly Gln Gln Glu Pro Gly Thr Arg Glu Arg
            100                 105                 110

Asp Pro Asp Lys Ala Thr Arg Phe Arg Met Glu Glu Leu Arg Leu Thr
        115                 120                 125

Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala Met
    130                 135                 140

Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile Leu Thr Lys
145                 150                 155                 160

Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp Arg
                165                 170                 175

Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Val Gly
            180                 185                 190

Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys Arg
        195                 200                 205

Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser Leu Leu Ile
    210                 215                 220

Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe Tyr
```

```
225                 230                 235                 240

Ile Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu Ala
                245                 250                 255

Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe Gly Arg Arg
            260                 265                 270

Trp Gln Leu Ile Gln Glu Gly Val Val Pro Asn Arg Phe Tyr Trp Ser
        275                 280                 285

Val Met Gly Ser Asn Lys Glu Pro Asp Leu Val His Leu Glu Ala Arg
    290                 295                 300

Thr Val Asp Gly His Ser His Tyr Leu Thr Cys Arg Met Gln Asn Cys
305                 310                 315                 320

Thr Glu Ala Asn Arg Asn Gln Pro Phe Pro Gly Tyr Ile Asp Pro Asp
                325                 330                 335

Ser Leu Ile Val Gln Asp His Tyr Val Phe Val Gln Leu Thr Ser Gly
            340                 345                 350

Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn Ala Phe Ala Gln
        355                 360                 365

Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His Val Ile Ser
    370                 375                 380

Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln Asn
385                 390                 395                 400

Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe Thr
                405                 410                 415

Leu Ala Leu Glu Asn Val Gln Ser Ser Arg Gly Pro Glu Gly Asn Ile
            420                 425                 430

Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu Ala
        435                 440                 445

Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn Lys
    450                 455                 460

Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Thr Asp Leu Arg Gly
465                 470                 475                 480

Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His Leu His Leu
                485                 490                 495
```

```
Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala Ser Lys Asp
            500                 505                 510

Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Ser Glu Leu
        515                 520                 525

Ser Asp Thr Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn Thr
    530                 535                 540

Trp Arg Gln Ile Phe Glu Glu Glu His Ser Val Leu Tyr Leu Asp Gln
545                 550                 555                 560

Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro Ile Arg His
                565                 570                 575

Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr Ser Phe
            580                 585                 590

Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu Pro Gly Glu
        595                 600                 605

Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg Ser Glu
    610                 615                 620

Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp Arg Arg Cys
625                 630                 635                 640

Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln Gly Glu Ala
                645                 650                 655

Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu Arg
            660                 665                 670

Lys Cys Met Gln Gly Lys Tyr Ala Gly Ala Met Glu Ser Glu Pro Cys
        675                 680                 685

Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg His
    690                 695                 700

Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser Leu
705                 710                 715                 720

Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Thr Gly Tyr
                725                 730                 735

Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln Tyr
            740                 745                 750
```

```
Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu Arg
        755                 760                 765

Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn Val
    770                 775                 780

Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr Leu Ile
785                 790                 795                 800

Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu Ser
                805                 810                 815

Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly Ile Phe
            820                 825                 830

Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala Val
        835                 840                 845

Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser Leu
    850                 855                 860

Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val Leu
865                 870                 875                 880

Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly Asn
                885                 890                 895

Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe Arg Phe
            900                 905                 910

Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly Asn
        915                 920                 925

Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe Arg
    930                 935                 940

Ser Leu Arg Leu Ser Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro Asp
945                 950                 955                 960

Ile Pro Glu Trp Arg Arg Asp Ile Gly Arg Val Ile Lys Lys Ser Leu
                965                 970                 975

Val Glu Ala Thr Gly Val Pro Gly Gln His Ile Leu Val Ala Val Leu
            980                 985                 990

Pro Gly Pro Thr Thr Ala Glu Leu  Phe Val Leu Pro Tyr  Gln Asp Pro
        995                 1000                1005

Ala Gly  Glu Asn Lys Arg Ser  Thr Asp Asp Leu Glu  Gln Ile Ser
    1010                1015                1020

Glu Leu  Leu Ile His Thr Leu  Asn Gln Asn Ser Val  His Phe Glu
    1025                1030                1035

Leu Lys  Pro Gly Val Arg Val  Leu Val His Ala Ala  His Leu Thr
    1040                1045                1050

Ala Ala  Pro Leu Val Asp Leu  Thr Pro Thr His Ser  Gly Ser Ala
    1055                1060                1065

Met Leu  Met Leu Leu Ser Val  Val Phe Val Gly Leu  Ala Val Phe
    1070                1075                1080

Val Ile  Tyr Lys Phe Lys Arg  Arg Val Ala Leu Pro  Ser Pro Pro
    1085                1090                1095

Ser Pro  Ser Thr Gln Pro Gly  Asp Ser Ser Leu Arg  Leu Gln Arg
    1100                1105                1110

Ala Arg  His Ala Thr Pro Pro  Ser Thr Pro Lys Arg  Gly Ser Ala
    1115                1120                1125

Gly Ala  Gln Tyr Ala Ile
    1130
```

<210> 7
<211> 1164
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (1)..(1164)
<223> proSorCS1, Isoform 2

<400> 7

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Gly Gly Ser Cys Cys Pro Ser Pro His Pro Ser Ser Ala Pro Arg Ser
1               5                  10                  15

Ala Ser Thr Pro Arg Gly Phe Ser His Gln Gly Arg Pro Gly Arg Ala
            20                  25                  30

Pro Ala Thr Pro Leu Pro Leu Val Val Arg Pro Leu Phe Ser Val Ala
        35                  40                  45

Pro Gly Asp Arg Ala Leu Ser Leu Glu Arg Ala Arg Gly Thr Gly Ala
    50                  55                  60

Ser Met Ala Val Ala Ala Arg Ser Gly Arg Arg Arg Arg Ser Gly Ala
65                  70                  75                  80

Asp Gln Glu Lys Ala Glu Arg Gly Glu Gly Ala Ser Arg Ser Pro Arg
                85                  90                  95

Gly Val Leu Arg Asp Gly Gly Gln Gln Glu Pro Gly Thr Arg Glu Arg
            100                 105                 110

Asp Pro Asp Lys Ala Thr Arg Phe Arg Met Glu Glu Leu Arg Leu Thr
        115                 120                 125

Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala Met
    130                 135                 140

Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile Leu Thr Lys
145                 150                 155                 160

Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp Arg
                165                 170                 175

Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Val Gly
            180                 185                 190

Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys Arg
        195                 200                 205

Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser Leu Leu Ile
    210                 215                 220

Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe Tyr
225                 230                 235                 240

Ile Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu Ala
                245                 250                 255

Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe Gly Arg Arg
            260                 265                 270

Trp Gln Leu Ile Gln Glu Gly Val Val Pro Asn Arg Phe Tyr Trp Ser
        275                 280                 285

Val Met Gly Ser Asn Lys Glu Pro Asp Leu Val His Leu Glu Ala Arg
    290                 295                 300

Thr Val Asp Gly His Ser His Tyr Leu Thr Cys Arg Met Gln Asn Cys
305                 310                 315                 320

Thr Glu Ala Asn Arg Gln Pro Phe Pro Gly Tyr Ile Asp Pro Asp Ser
```

```
                325                 330                 335

Leu Ile Val Gln Asp His Tyr Val Phe Val Gln Leu Thr Ser Gly Gly
            340                 345                 350

Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn Ala Phe Ala Gln Met
        355                 360                 365

Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His Val Ile Ser Thr
    370                 375                 380

Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln Asn Asp
385                 390                 395                 400

Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe Thr Leu
                405                 410                 415

Ala Leu Glu Asn Val Gln Ser Ser Arg Gly Pro Glu Gly Asn Ile Met
            420                 425                 430

Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu Ala Asn
        435                 440                 445

Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn Lys Gly
    450                 455                 460

Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Thr Asp Leu Arg Gly Asp
465                 470                 475                 480

Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His Leu His Leu Lys
                485                 490                 495

Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala Ser Lys Asp Thr
            500                 505                 510

Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Ser Glu Leu Ser
        515                 520                 525

Asp Thr Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn Thr Trp
    530                 535                 540

Arg Gln Ile Phe Glu Glu Glu His Ser Val Leu Tyr Leu Asp Gln Gly
545                 550                 555                 560

Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro Ile Arg His Leu
                565                 570                 575

Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr Ser Phe Thr
            580                 585                 590
```

```
Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu Pro Gly Glu Glu
        595                 600                 605

Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg Ser Glu Trp
    610                 615                 620

Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp Arg Arg Cys Ala
625                 630                 635                 640

Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln Gly Glu Ala Cys
                645                 650                 655

Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu Arg Lys
            660                 665                 670

Cys Met Gln Gly Lys Tyr Ala Gly Ala Met Glu Ser Glu Pro Cys Val
        675                 680                 685

Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg His Ser
    690                 695                 700

Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser Leu Ser
705                 710                 715                 720

Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Thr Gly Tyr Arg
                725                 730                 735

Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln Tyr Thr
            740                 745                 750

Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu Arg Ile
        755                 760                 765

Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn Val Thr
    770                 775                 780

Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr Leu Ile Gln
785                 790                 795                 800

Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu Ser Ser
                805                 810                 815

Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly Ile Phe Arg
            820                 825                 830

Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala Val Leu
        835                 840                 845
```

```
Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser Leu Pro
    850                 855                 860

Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val Leu Trp
865                 870                 875                 880

Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly Asn Asn
                885                 890                 895

Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe Arg Phe Thr
            900                 905                 910

Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly Asn Ala
        915                 920                 925

Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe Arg Ser
    930                 935                 940

Leu Arg Leu Ser Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro Asp Ile
945                 950                 955                 960

Pro Glu Trp Arg Arg Asp Ile Gly Arg Val Ile Lys Lys Ser Leu Val
                965                 970                 975

Glu Ala Thr Gly Val Pro Gly Gln His Ile Leu Val Ala Val Leu Pro
            980                 985                 990

Gly Leu Pro Thr Thr Ala Glu Leu  Phe Val Leu Pro Tyr  Gln Asp Pro
        995                 1000                1005

Ala Gly  Glu Asn Lys Arg Ser  Thr Asp Asp Leu Glu  Gln Ile Ser
    1010                1015                1020

Glu Leu  Leu Ile His Thr Leu  Asn Gln Asn Ser Val  His Phe Glu
    1025                1030                1035

Leu Lys  Pro Gly Val Arg Val  Leu Val His Ala Ala  His Leu Thr
    1040                1045                1050

Ala Ala  Pro Leu Val Asp Leu  Thr Pro Thr His Ser  Gly Ser Ala
    1055                1060                1065

Met Leu  Met Leu Leu Ser Val  Val Phe Val Gly Leu  Ala Val Phe
    1070                1075                1080

Val Ile  Tyr Lys Phe Lys Arg  Lys Ile Pro Gly Ile  Asn Val Tyr
    1085                1090                1095

Ala Gln  Met Gln Asn Glu Lys  Glu Gln Glu Met Ile  Ser Pro Val
    1100                1105                1110

Ser His  Ser Glu Ser Arg Pro  Asn Val Pro Gln Thr  Glu Leu Arg
    1115                1120                1125

Arg Pro  Gly Gln Leu Ile Asp  Glu Lys Val Glu Ser  Gln Leu Ile
    1130                1135                1140

Gly Ser  Ile Ser Ile Val Ala  Glu Asn Gln Ser Thr  Lys Glu Ile
    1145                1150                1155

Pro Thr  Tyr Val Asn Val
    1160
```

<210> 8

<211> 1146

<212> PRT

<213> Homo sapiens

<220>

<221> MISC_FEATURE

<222> (1)..(1146)

<223> proSorCS1c, Isoform 3

<400> 8

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Gly Gly Ser Cys Cys Pro Ser Pro His Pro Ser Ser Ala Pro Arg Ser
1               5                   10                  15

Ala Ser Thr Pro Arg Gly Phe Ser His Gln Gly Arg Pro Gly Arg Ala
            20                  25                  30

Pro Ala Thr Pro Leu Pro Leu Val Val Arg Pro Leu Phe Ser Val Ala
        35                  40                  45

Pro Gly Asp Arg Ala Leu Ser Leu Glu Arg Ala Arg Gly Thr Gly Ala
    50                  55                  60

Ser Met Ala Val Ala Ala Arg Ser Gly Arg Arg Arg Arg Ser Gly Ala
65                  70                  75                  80

Asp Gln Glu Lys Ala Glu Arg Gly Glu Gly Ala Ser Arg Ser Pro Arg
                85                  90                  95

Gly Val Leu Arg Asp Gly Gly Gln Gln Glu Pro Gly Thr Arg Glu Arg
            100                 105                 110

Asp Pro Asp Lys Ala Thr Arg Phe Arg Met Glu Glu Leu Arg Leu Thr
        115                 120                 125

Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala Met
    130                 135                 140

Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile Leu Thr Lys
145                 150                 155                 160

Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp Arg
                165                 170                 175

Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Val Gly
            180                 185                 190

Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys Arg
        195                 200                 205

Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser Leu Leu Ile
    210                 215                 220

Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe Tyr
225                 230                 235                 240

Ile Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu Ala
                245                 250                 255

Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe Gly Arg Arg
            260                 265                 270

Trp Gln Leu Ile Gln Glu Gly Val Val Pro Asn Arg Phe Tyr Trp Ser
        275                 280                 285

Val Met Gly Ser Asn Lys Glu Pro Asp Leu Val His Leu Glu Ala Arg
    290                 295                 300

Thr Val Asp Gly His Ser His Tyr Leu Thr Cys Arg Met Gln Asn Cys
305                 310                 315                 320

Thr Glu Ala Asn Arg Asn Gln Pro Phe Pro Gly Tyr Ile Asp Pro Asp
                325                 330                 335

Ser Leu Ile Val Gln Asp His Tyr Val Phe Val Gln Leu Thr Ser Gly
            340                 345                 350

Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn Ala Phe Ala Gln
        355                 360                 365

Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His Val Ile Ser
    370                 375                 380

Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln Asn
```

```
385                 390                 395                 400

Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe Thr
                405                 410                 415

Leu Ala Leu Glu Asn Val Gln Ser Ser Arg Gly Pro Glu Gly Asn Ile
            420                 425                 430

Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu Ala
        435                 440                 445

Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn Lys
    450                 455                 460

Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Thr Asp Leu Arg Gly
465                 470                 475                 480

Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His Leu His Leu
                485                 490                 495

Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala Ser Lys Asp
            500                 505                 510

Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Ser Glu Leu
        515                 520                 525

Ser Asp Thr Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn Thr
    530                 535                 540

Trp Arg Gln Ile Phe Glu Glu Glu His Ser Val Leu Tyr Leu Asp Gln
545                 550                 555                 560

Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro Ile Arg His
                565                 570                 575

Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr Ser Phe
            580                 585                 590

Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu Pro Gly Glu
        595                 600                 605

Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg Ser Glu
    610                 615                 620

Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp Arg Arg Cys
625                 630                 635                 640

Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln Gly Glu Ala
                645                 650                 655
```

```
Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu Arg
            660                 665                 670

Lys Cys Met Gln Gly Lys Tyr Ala Gly Ala Met Glu Ser Glu Pro Cys
        675                 680                 685

Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg His
    690                 695                 700

Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser Leu
705                 710                 715                 720

Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Thr Gly Tyr
                725                 730                 735

Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln Tyr
            740                 745                 750

Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu Arg
        755                 760                 765

Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn Val
    770                 775                 780

Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr Leu Ile
785                 790                 795                 800

Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu Ser
                805                 810                 815

Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly Ile Phe
            820                 825                 830

Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala Val
        835                 840                 845

Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser Leu
    850                 855                 860

Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val Leu
865                 870                 875                 880

Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly Asn
                885                 890                 895

Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe Arg Phe
            900                 905                 910
```

```
Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly Asn
        915                 920                 925

Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe Arg
    930                 935                 940

Ser Leu Arg Leu Ser Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro Asp
945                 950                 955                 960

Ile Pro Glu Trp Arg Arg Asp Ile Gly Arg Val Ile Lys Lys Ser Leu
                965                 970                 975

Val Glu Ala Thr Gly Val Pro Gly Gln His Ile Leu Val Ala Val Leu
            980                 985                 990

Pro Gly Leu Pro Thr Thr Ala Glu  Leu Phe Val Leu Pro  Tyr Gln Asp
        995                 1000                1005

Pro Ala  Gly Glu Asn Lys Arg  Ser Thr Asp Asp Leu  Glu Gln Ile
    1010                1015                1020

Ser Glu  Leu Leu Ile His Thr  Leu Asn Gln Asn Ser  Val His Phe
    1025                1030                1035

Glu Leu  Lys Pro Gly Val Arg  Val Leu Val His Ala  Ala His Leu
    1040                1045                1050

Thr Ala  Ala Pro Leu Val Asp  Leu Thr Pro Thr His  Ser Gly Ser
    1055                1060                1065

Ala Met  Leu Met Leu Leu Ser  Val Val Phe Val Gly  Leu Ala Val
    1070                1075                1080

Phe Val  Ile Tyr Lys Phe Lys  Arg Lys Ile Pro Gly  Ile Asn Val
    1085                1090                1095

Tyr Ala  Gln Met Gln Asn Glu  Lys Glu Gln Glu Met  Ile Ser Pro
    1100                1105                1110

Val Ser  His Ser Glu Ser Arg  Pro Asn Val Pro Gln  Thr Glu Leu
    1115                1120                1125

Arg Arg  Pro Gly Gln Leu Ile  Asp Glu Lys Val Glu  Ser Gln Leu
    1130                1135                1140

Ile Gly  Lys
    1145
```

<210> 9

<211> 1125

<212> PRT

<213> Homo sapiens

<220>

<221> MISC_FEATURE

<222> (1)..(1125)

<223> proSorCS1a, Isoform 4

<400> 9

```
Gly Gly Ser Cys Cys Pro Ser Pro His Pro Ser Ser Ala Pro Arg Ser
1               5                  10                  15

Ala Ser Thr Pro Arg Gly Phe Ser His Gln Gly Arg Pro Gly Arg Ala
            20                  25                  30

Pro Ala Thr Pro Leu Pro Leu Val Val Arg Pro Leu Phe Ser Val Ala
        35                  40                  45

Pro Gly Asp Arg Ala Leu Ser Leu Glu Arg Ala Arg Gly Thr Gly Ala
    50                  55                  60

Ser Met Ala Val Ala Ala Arg Ser Gly Arg Arg Arg Arg Ser Gly Ala
65                  70                  75                  80

Asp Gln Glu Lys Ala Glu Arg Gly Glu Gly Ala Ser Arg Ser Pro Arg
                85                  90                  95

Gly Val Leu Arg Asp Gly Gly Gln Gln Glu Pro Gly Thr Arg Glu Arg
            100                 105                 110

Asp Pro Asp Lys Ala Thr Arg Phe Arg Met Glu Glu Leu Arg Leu Thr
        115                 120                 125

Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala Met
    130                 135                 140

Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile Leu Thr Lys
145                 150                 155                 160

Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp Arg
                165                 170                 175

Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Val Gly
            180                 185                 190

Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys Arg
        195                 200                 205
```

```
Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser Leu Leu Ile
    210                 215                 220

Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe Tyr
225                 230                 235                 240

Ile Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu Ala
                245                 250                 255

Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe Gly Arg Arg
            260                 265                 270

Trp Gln Leu Ile Gln Glu Gly Val Val Pro Asn Arg Phe Tyr Trp Ser
        275                 280                 285

Val Met Gly Ser Asn Lys Glu Pro Asp Leu Val His Leu Glu Ala Arg
    290                 295                 300

Thr Val Asp Gly His Ser His Tyr Leu Thr Cys Arg Met Gln Asn Cys
305                 310                 315                 320

Thr Glu Ala Asn Arg Asn Gln Pro Phe Pro Gly Tyr Ile Asp Pro Asp
                325                 330                 335

Ser Leu Ile Val Gln Asp His Tyr Val Phe Val Gln Leu Thr Ser Gly
            340                 345                 350

Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn Ala Phe Ala Gln
        355                 360                 365

Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His Val Ile Ser
    370                 375                 380

Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln Asn
385                 390                 395                 400

Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe Thr
                405                 410                 415

Leu Ala Leu Glu Asn Val Gln Ser Ser Arg Gly Pro Glu Gly Asn Ile
            420                 425                 430

Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu Ala
        435                 440                 445

Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn Lys
    450                 455                 460

Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Thr Asp Leu Arg Gly
```

```
465                 470                 475                 480

Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His Leu His Leu
                485                 490                 495

Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ala Ser Lys Asp Thr
            500                 505                 510

Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Ser Glu Leu Ser
        515                 520                 525

Asp Thr Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn Thr Trp
    530                 535                 540

Arg Gln Ile Phe Glu Glu Glu His Ser Val Leu Tyr Leu Asp Gln Gly
545                 550                 555                 560

Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro Ile Arg His Leu
                565                 570                 575

Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr Ser Phe Thr
            580                 585                 590

Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu Pro Gly Glu Glu
        595                 600                 605

Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg Ser Glu Trp
    610                 615                 620

Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp Arg Arg Cys Ala
625                 630                 635                 640

Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln Gly Glu Ala Cys
                645                 650                 655

Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu Arg Lys
            660                 665                 670

Cys Met Gln Gly Lys Tyr Ala Gly Ala Met Glu Ser Glu Pro Cys Val
        675                 680                 685

Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg His Ser
    690                 695                 700

Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser Leu Ser
705                 710                 715                 720

Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Thr Gly Tyr Arg
                725                 730                 735
```

```
Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln Tyr Thr
            740                 745                 750

Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu Arg Ile
        755                 760                 765

Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn Val Thr
    770                 775                 780

Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr Leu Ile Gln
785                 790                 795                 800

Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu Ser Ser
                805                 810                 815

Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly Ile Phe Arg
            820                 825                 830

Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala Val Leu
        835                 840                 845

Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser Leu Pro
    850                 855                 860

Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val Leu Trp
865                 870                 875                 880

Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly Asn Asn
                885                 890                 895

Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe Arg Phe Thr
            900                 905                 910

Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly Asn Ala
        915                 920                 925

Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe Arg Ser
    930                 935                 940

Leu Arg Leu Ser Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro Asp Ile
945                 950                 955                 960

Pro Glu Trp Arg Arg Asp Ile Gly Arg Val Ile Lys Lys Ser Leu Val
                965                 970                 975

Glu Ala Thr Gly Val Pro Gly Gln His Ile Leu Val Ala Val Leu Pro
            980                 985                 990

Gly Leu Pro Thr Thr Ala Glu Leu  Phe Val Leu Pro Tyr  Gln Asp Pro
        995                 1000                1005

Ala Gly  Glu Asn Lys Arg Ser  Thr Asp Asp Leu Glu  Gln Ile Ser
    1010                1015                1020

Glu Leu  Leu Ile His Thr Leu  Asn Gln Asn Ser Val  His Phe Glu
    1025                1030                1035

Leu Lys  Pro Gly Val Arg Val  Leu Val His Ala Ala  His Leu Thr
    1040                1045                1050

Ala Ala  Pro Leu Val Asp Leu  Thr Pro Thr His Ser  Gly Ser Ala
    1055                1060                1065

Met Leu  Met Leu Leu Ser Val  Val Phe Val Gly Leu  Ala Val Phe
    1070                1075                1080

Val Ile  Tyr Lys Phe Lys Arg  Cys Val Ser Leu Tyr  Pro Arg Ser
    1085                1090                1095

Pro Thr  Pro Asp Leu Phe Leu  Leu Pro Asp Arg Phe  Arg Ser Met
    1100                1105                1110

Cys Tyr  Ser Asp Val His Ser  Ser Asp Gly Phe Tyr
    1115                1120                1125
```

<210> 10
<211> 1046
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (1)..(1046)
<223> Soluble proSorCS1

<400> 10

```
Gly Phe Ser His Gln Gly Arg Pro Gly Arg Ala Pro Ala Thr Pro Leu
1               5                   10                  15

Pro Leu Val Val Arg Pro Leu Phe Ser Val Ala Pro Gly Asp Arg Ala
            20                  25                  30

Leu Ser Leu Glu Arg Ala Arg Gly Thr Gly Ala Ser Met Ala Val Ala
        35                  40                  45

Ala Arg Ser Gly Arg Arg Arg Arg Ser Gly Ala Asp Gln Glu Lys Ala
    50                  55                  60

Glu Arg Gly Glu Gly Ala Ser Arg Ser Pro Arg Gly Val Leu Arg Asp
65                  70                  75                  80

Gly Gly Gln Gln Glu Pro Gly Thr Arg Glu Arg Asp Pro Asp Lys Ala
                85                  90                  95

Thr Arg Phe Arg Met Glu Glu Leu Arg Leu Thr Ser Thr Thr Phe Ala
            100                 105                 110

Leu Thr Gly Asp Ser Ala His Asn Gln Ala Met Val His Trp Ser Gly
        115                 120                 125

His Asn Ser Ser Val Ile Leu Ile Leu Thr Lys Leu Tyr Asp Tyr Asn
    130                 135                 140

Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp Arg Ser Thr Asp Tyr Gly
145                 150                 155                 160

Thr Thr Tyr Glu Lys Leu Asn Asp Lys Val Gly Leu Lys Thr Ile Leu
                165                 170                 175

Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys Arg Lys Ile Met Leu Leu
            180                 185                 190

Thr Asp Pro Glu Ile Glu Ser Ser Leu Leu Ile Ser Ser Asp Glu Gly
        195                 200                 205

Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe Tyr Ile Gln Ser Leu Leu
    210                 215                 220

Phe His Pro Lys Gln Glu Asp Trp Ile Leu Ala Tyr Ser Gln Asp Gln
225                 230                 235                 240

Lys Leu Tyr Ser Ser Ala Glu Phe Gly Arg Arg Trp Gln Leu Ile Gln
                245                 250                 255

Glu Gly Val Val Pro Asn Arg Phe Tyr Trp Ser Val Met Gly Ser Asn
            260                 265                 270

Lys Glu Pro Asp Leu Val His Leu Glu Ala Arg Thr Val Asp Gly His
        275                 280                 285

Ser His Tyr Leu Thr Cys Arg Met Gln Asn Cys Thr Glu Ala Asn Arg
    290                 295                 300

Asn Gln Pro Phe Pro Gly Tyr Ile Asp Pro Asp Ser Leu Ile Val Gln
305                 310                 315                 320
```

```
Asp His Tyr Val Phe Val Gln Leu Thr Ser Gly Gly Arg Pro His Tyr
                325                 330                 335

Tyr Val Ser Tyr Arg Arg Asn Ala Phe Ala Gln Met Lys Leu Pro Lys
            340                 345                 350

Tyr Ala Leu Pro Lys Asp Met His Val Ile Ser Thr Asp Glu Asn Gln
        355                 360                 365

Val Phe Ala Ala Val Gln Glu Trp Asn Gln Asn Asp Thr Tyr Asn Leu
    370                 375                 380

Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe Thr Leu Ala Leu Glu Asn
385                 390                 395                 400

Val Gln Ser Ser Arg Gly Pro Glu Gly Asn Ile Met Ile Asp Leu Tyr
                405                 410                 415

Glu Val Ala Gly Ile Lys Gly Met Phe Leu Ala Asn Lys Lys Ile Asp
            420                 425                 430

Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn Lys Gly Arg Asp Trp Arg
        435                 440                 445

Leu Leu Gln Ala Pro Asp Thr Asp Leu Arg Gly Asp Pro Val His Cys
    450                 455                 460

Leu Leu Pro Tyr Cys Ser Leu His Leu His Leu Lys Val Ser Glu Asn
465                 470                 475                 480

Pro Tyr Thr Ser Gly Ile Ile Ala Ser Lys Asp Thr Ala Pro Ser Ile
                485                 490                 495

Ile Val Ala Ser Gly Asn Ile Gly Ser Glu Leu Ser Asp Thr Asp Ile
            500                 505                 510

Ser Met Phe Val Ser Ser Asp Ala Gly Asn Thr Trp Arg Gln Ile Phe
        515                 520                 525

Glu Glu Glu His Ser Val Leu Tyr Leu Asp Gln Gly Gly Val Leu Val
    530                 535                 540

Ala Met Lys His Thr Ser Leu Pro Ile Arg His Leu Trp Leu Ser Phe
545                 550                 555                 560

Asp Glu Gly Arg Ser Trp Ser Lys Tyr Ser Phe Thr Ser Ile Pro Leu
                565                 570                 575

Phe Val Asp Gly Val Leu Gly Glu Pro Gly Glu Glu Thr Leu Ile Met
```

```
           580                 585                 590

Thr Val Phe Gly His Phe Ser His Arg Ser Glu Trp Gln Leu Val Lys
        595                 600                 605

Val Asp Tyr Lys Ser Ile Phe Asp Arg Arg Cys Ala Glu Glu Asp Tyr
    610                 615                 620

Arg Pro Trp Gln Leu His Ser Gln Gly Glu Ala Cys Ile Met Gly Ala
625                 630                 635                 640

Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu Arg Lys Cys Met Gln Gly
                645                 650                 655

Lys Tyr Ala Gly Ala Met Glu Ser Glu Pro Cys Val Cys Thr Glu Ala
            660                 665                 670

Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg His Ser Asn Gly Gln Cys
        675                 680                 685

Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser Leu Ser Lys Asp Cys Ser
    690                 695                 700

Leu Gly Gln Ser Tyr Leu Asn Ser Thr Gly Tyr Arg Lys Val Val Ser
705                 710                 715                 720

Asn Asn Cys Thr Asp Gly Val Arg Glu Gln Tyr Thr Ala Lys Pro Gln
                725                 730                 735

Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu Arg Ile Val Thr Ala Asp
            740                 745                 750

Gly Lys Leu Thr Ala Glu Gln Gly His Asn Val Thr Leu Met Val Gln
        755                 760                 765

Leu Glu Glu Gly Asp Val Gln Arg Thr Leu Ile Gln Val Asp Phe Gly
    770                 775                 780

Asp Gly Ile Ala Val Ser Tyr Val Asn Leu Ser Ser Met Glu Asp Gly
785                 790                 795                 800

Ile Lys His Val Tyr Gln Asn Val Gly Ile Phe Arg Val Thr Val Gln
                805                 810                 815

Val Asp Asn Ser Leu Gly Ser Asp Ser Ala Val Leu Tyr Leu His Val
            820                 825                 830

Thr Cys Pro Leu Glu His Val His Leu Ser Leu Pro Phe Val Thr Thr
        835                 840                 845
```

```
Lys Asn Lys Glu Val Asn Ala Thr Ala Val Leu Trp Pro Ser Gln Val
    850                 855                 860

Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly Asn Asn Thr Glu Pro Leu
865                 870                 875                 880

Ile Thr Leu Glu Gly Ser Ile Ser Phe Arg Phe Thr Ser Glu Gly Met
                885                 890                 895

Asn Thr Ile Thr Val Gln Val Ser Ala Gly Asn Ala Ile Leu Gln Asp
            900                 905                 910

Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe Arg Ser Leu Arg Leu Ser
        915                 920                 925

Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro Asp Ile Pro Glu Trp Arg
    930                 935                 940

Arg Asp Ile Gly Arg Val Ile Lys Lys Ser Leu Val Glu Ala Thr Gly
945                 950                 955                 960

Val Pro Gly Gln His Ile Leu Val Ala Val Leu Pro Gly Leu Pro Thr
                965                 970                 975

Thr Ala Glu Leu Phe Val Leu Pro Tyr Gln Asp Pro Ala Gly Glu Asn
            980                 985                 990

Lys Arg Ser Thr Asp Asp Leu Glu  Gln Ile Ser Glu Leu  Leu Ile His
        995                 1000                1005

Thr Leu  Asn Gln Asn Ser Val  His Phe Glu Leu Lys  Pro Gly Val
    1010                1015                1020

Arg Val  Leu Val His Ala Ala  His Leu Thr Ala Ala  Pro Leu Val
    1025                1030                1035

Asp Leu  Thr Pro Thr His Ser  Gly
    1040                1045
```

<210> 11

<211> 1058

<212> PRT

<213> Homo sapiens

<220>

<221> MISC_FEATURE

<222> (1)..(1058)

<223> Mature SorCS1b, Isoform 1

<400> 11

```
Ser Gly Ala Asp Gln Glu Lys Ala Glu Arg Gly Glu Gly Ala Ser Arg
1               5                  10                  15

Ser Pro Arg Gly Val Leu Arg Asp Gly Gly Gln Gln Glu Pro Gly Thr
            20                  25                  30

Arg Glu Arg Asp Pro Asp Lys Ala Thr Arg Phe Arg Met Glu Glu Leu
        35                  40                  45

Arg Leu Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn
    50                  55                  60

Gln Ala Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile
65                  70                  75                  80

Leu Thr Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser
                85                  90                  95

Leu Trp Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp
            100                 105                 110

Lys Val Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr
        115                 120                 125

Asn Lys Arg Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser
    130                 135                 140

Leu Leu Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu
145                 150                 155                 160

Asn Phe Tyr Ile Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp
                165                 170                 175

Ile Leu Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe
            180                 185                 190

Gly Arg Arg Trp Gln Leu Ile Gln Glu Gly Val Val Pro Asn Arg Phe
        195                 200                 205

Tyr Trp Ser Val Met Gly Ser Asn Lys Glu Pro Asp Leu Val His Leu
    210                 215                 220

Glu Ala Arg Thr Val Asp Gly His Ser His Tyr Leu Thr Cys Arg Met
225                 230                 235                 240

Gln Asn Cys Thr Glu Ala Asn Arg Asn Gln Pro Phe Pro Gly Tyr Ile
                245                 250                 255
```

```
Asp Pro Asp Ser Leu Ile Val Gln Asp His Tyr Val Phe Val Gln Leu
            260                 265                 270

Thr Ser Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn Ala
        275                 280                 285

Phe Ala Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His
    290                 295                 300

Val Ile Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp
305                 310                 315                 320

Asn Gln Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val
                325                 330                 335

Tyr Phe Thr Leu Ala Leu Glu Asn Val Gln Ser Ser Arg Gly Pro Glu
            340                 345                 350

Gly Asn Ile Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met
        355                 360                 365

Phe Leu Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr
    370                 375                 380

Tyr Asn Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Thr Asp
385                 390                 395                 400

Leu Arg Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His
                405                 410                 415

Leu His Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala
            420                 425                 430

Ser Lys Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly
        435                 440                 445

Ser Glu Leu Ser Asp Thr Asp Ile Ser Met Phe Val Ser Ser Asp Ala
    450                 455                 460

Gly Asn Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Val Leu Tyr
465                 470                 475                 480

Leu Asp Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro
                485                 490                 495

Ile Arg His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys
            500                 505                 510
```

```
Tyr Ser Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu
        515                 520                 525

Pro Gly Glu Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His
    530                 535                 540

Arg Ser Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp
545                 550                 555                 560

Arg Arg Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln
                565                 570                 575

Gly Glu Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys
            580                 585                 590

Ser Glu Arg Lys Cys Met Gln Gly Lys Tyr Ala Gly Ala Met Glu Ser
        595                 600                 605

Glu Pro Cys Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr
    610                 615                 620

Glu Arg His Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro
625                 630                 635                 640

Ser Ser Leu Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser
                645                 650                 655

Thr Gly Tyr Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg
            660                 665                 670

Glu Gln Tyr Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg
        675                 680                 685

Gly Leu Arg Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly
    690                 695                 700

His Asn Val Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg
705                 710                 715                 720

Thr Leu Ile Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val
                725                 730                 735

Asn Leu Ser Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val
            740                 745                 750

Gly Ile Phe Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp
        755                 760                 765

Ser Ala Val Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His
```

```
    770                 775                 780

Leu Ser Leu Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr
785                 790                 795                 800

Ala Val Leu Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp
                805                 810                 815

Tyr Gly Asn Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser
            820                 825                 830

Phe Arg Phe Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser
        835                 840                 845

Ala Gly Asn Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu
    850                 855                 860

Glu Phe Arg Ser Leu Arg Leu Ser Phe Ser Pro Asn Leu Asp Asp Tyr
865                 870                 875                 880

Asn Pro Asp Ile Pro Glu Trp Arg Arg Asp Ile Gly Arg Val Ile Lys
                885                 890                 895

Lys Ser Leu Val Glu Ala Thr Gly Val Pro Gly Gln His Ile Leu Val
            900                 905                 910

Ala Val Leu Pro Gly Leu Pro Thr Thr Ala Glu Leu Phe Val Leu Pro
        915                 920                 925

Tyr Gln Asp Pro Ala Gly Glu Asn Lys Arg Ser Thr Asp Asp Leu Glu
    930                 935                 940

Gln Ile Ser Glu Leu Leu Ile His Thr Leu Asn Gln Asn Ser Val His
945                 950                 955                 960

Phe Glu Leu Lys Pro Gly Val Arg Val Leu Val His Ala Ala His Leu
                965                 970                 975

Thr Ala Ala Pro Leu Val Asp Leu Thr Pro Thr His Ser Gly Ser Ala
            980                 985                 990

Met Leu Met Leu Leu Ser Val Val  Phe Val Gly Leu Ala  Val Phe Val
        995                 1000                1005

Ile Tyr  Lys Phe Lys Arg Arg  Val Ala Leu Pro Ser  Pro Pro Ser
    1010                1015                1020

Pro Ser  Thr Gln Pro Gly Asp  Ser Ser Leu Arg Leu  Gln Arg Ala
    1025                1030                1035

Arg His  Ala Thr Pro Pro Ser  Thr Pro Lys Arg Gly  Ser Ala Gly
    1040                1045                1050

Ala Gln  Tyr Ala Ile
    1055
```

<210> 12

<211> 1087

<212> PRT

<213> Homo sapiens

<220>

<221> MISC_FEATURE

<222> (1)..(1087)

<223> Mature SorCS1, Isoform 2

<400> 12

```
Ser Gly Ala Asp Gln Glu Lys Ala Glu Arg Gly Glu Gly Ala Ser Arg
1               5                  10                  15

Ser Pro Arg Gly Val Leu Arg Asp Gly Gly Gln Gln Glu Pro Gly Thr
            20                  25                  30

Arg Glu Arg Asp Pro Asp Lys Ala Thr Arg Phe Arg Met Glu Glu Leu
        35                  40                  45

Arg Leu Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn
    50                  55                  60

Gln Ala Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile
65                  70                  75                  80

Leu Thr Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser
                85                  90                  95

Leu Trp Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp
            100                 105                 110

Lys Val Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr
        115                 120                 125

Asn Lys Arg Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser
    130                 135                 140

Leu Leu Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu
145                 150                 155                 160

Asn Phe Tyr Ile Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp
                165                 170                 175
```

```
Ile Leu Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe
            180                 185                 190

Gly Arg Arg Trp Gln Leu Ile Gln Glu Gly Val Val Pro Asn Arg Phe
        195                 200                 205

Tyr Trp Ser Val Met Gly Ser Asn Lys Glu Pro Asp Leu Val His Leu
    210                 215                 220

Glu Ala Arg Thr Val Asp Gly His Ser His Tyr Leu Thr Cys Arg Met
225                 230                 235                 240

Gln Asn Cys Thr Glu Ala Asn Arg Gln Pro Phe Pro Gly Tyr Ile Asp
                245                 250                 255

Pro Asp Ser Leu Ile Val Gln Asp His Tyr Val Phe Val Gln Leu Thr
            260                 265                 270

Ser Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn Ala Phe
        275                 280                 285

Ala Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His Val
    290                 295                 300

Ile Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp Asn
305                 310                 315                 320

Gln Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr
                325                 330                 335

Phe Thr Leu Ala Leu Glu Asn Val Gln Ser Ser Arg Gly Pro Glu Gly
            340                 345                 350

Asn Ile Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe
        355                 360                 365

Leu Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr
    370                 375                 380

Asn Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Thr Asp Leu
385                 390                 395                 400

Arg Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His Leu
                405                 410                 415

His Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala Ser
            420                 425                 430
```

```
Lys Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Ser
        435                 440                 445

Glu Leu Ser Asp Thr Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly
    450                 455                 460

Asn Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Val Leu Tyr Leu
465                 470                 475                 480

Asp Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro Ile
                485                 490                 495

Arg His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr
            500                 505                 510

Ser Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu Pro
        515                 520                 525

Gly Glu Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg
    530                 535                 540

Ser Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp Arg
545                 550                 555                 560

Arg Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln Gly
                565                 570                 575

Glu Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser
            580                 585                 590

Glu Arg Lys Cys Met Gln Gly Lys Tyr Ala Gly Ala Met Glu Ser Glu
        595                 600                 605

Pro Cys Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu
    610                 615                 620

Arg His Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser
625                 630                 635                 640

Ser Leu Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Thr
                645                 650                 655

Gly Tyr Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu
            660                 665                 670

Gln Tyr Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly
        675                 680                 685
```

```
Leu Arg Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His
    690                 695                 700

Asn Val Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr
705                 710                 715                 720

Leu Ile Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn
                725                 730                 735

Leu Ser Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly
            740                 745                 750

Ile Phe Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser
        755                 760                 765

Ala Val Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu
    770                 775                 780

Ser Leu Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala
785                 790                 795                 800

Val Leu Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr
                805                 810                 815

Gly Asn Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe
            820                 825                 830

Arg Phe Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala
        835                 840                 845

Gly Asn Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu
    850                 855                 860

Phe Arg Ser Leu Arg Leu Ser Phe Ser Pro Asn Leu Asp Asp Tyr Asn
865                 870                 875                 880

Pro Asp Ile Pro Glu Trp Arg Arg Asp Ile Gly Arg Val Ile Lys Lys
                885                 890                 895

Ser Leu Val Glu Ala Thr Gly Val Pro Gly Gln His Ile Leu Val Ala
            900                 905                 910

Val Leu Pro Gly Leu Pro Thr Thr Ala Glu Leu Phe Val Leu Pro Tyr
        915                 920                 925

Gln Asp Pro Ala Gly Glu Asn Lys Arg Ser Thr Asp Asp Leu Glu Gln
    930                 935                 940

Ile Ser Glu Leu Leu Ile His Thr Leu Asn Gln Asn Ser Val His Phe
```

```
945                 950                 955                 960

Glu Leu Lys Pro Gly Val Arg Val Leu Val His Ala Ala His Leu Thr
                965                 970                 975

Ala Ala Pro Leu Val Asp Leu Thr Pro Thr His Ser Gly Ser Ala Met
            980                 985                 990

Leu Met Leu Leu Ser Val Val Phe  Val Gly Leu Ala Val  Phe Val Ile
        995                 1000                1005

Tyr Lys  Phe Lys Arg Lys Ile  Pro Gly Ile Asn Val  Tyr Ala Gln
    1010                1015                1020

Met Gln  Asn Glu Lys Glu Gln  Glu Met Ile Ser Pro  Val Ser His
    1025                1030                1035

Ser Glu  Ser Arg Pro Asn Val  Pro Gln Thr Glu Leu  Arg Arg Pro
    1040                1045                1050

Gly Gln  Leu Ile Asp Glu Lys  Val Glu Ser Gln Leu  Ile Gly Ser
    1055                1060                1065

Ile Ser  Ile Val Ala Glu Asn  Gln Ser Thr Lys Glu  Ile Pro Thr
    1070                1075                1080

Tyr Val  Asn Val
    1085
```

<210> 13

<211> 1069

<212> PRT

<213> Homo sapiens

<220>

<221> MISC_FEATURE

<222> (1)..(1069)

<223> Mature SorCS1c, Isoform 3

<400> 13

```
Ser Gly Ala Asp Gln Glu Lys Ala Glu Arg Gly Glu Gly Ala Ser Arg
1               5                   10                  15

Ser Pro Arg Gly Val Leu Arg Asp Gly Gly Gln Gln Glu Pro Gly Thr
            20                  25                  30

Arg Glu Arg Asp Pro Asp Lys Ala Thr Arg Phe Arg Met Glu Glu Leu
        35                  40                  45

Arg Leu Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn
```

```
    50                  55                  60

Gln Ala Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile
65                  70                  75                  80

Leu Thr Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser
                85                  90                  95

Leu Trp Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp
            100                 105                 110

Lys Val Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr
        115                 120                 125

Asn Lys Arg Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser
    130                 135                 140

Leu Leu Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu
145                 150                 155                 160

Asn Phe Tyr Ile Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp
                165                 170                 175

Ile Leu Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe
            180                 185                 190

Gly Arg Arg Trp Gln Leu Ile Gln Glu Gly Val Val Pro Asn Arg Phe
        195                 200                 205

Tyr Trp Ser Val Met Gly Ser Asn Lys Glu Pro Asp Leu Val His Leu
    210                 215                 220

Glu Ala Arg Thr Val Asp Gly His Ser His Tyr Leu Thr Cys Arg Met
225                 230                 235                 240

Gln Asn Cys Thr Glu Ala Asn Arg Asn Gln Pro Phe Pro Gly Tyr Ile
                245                 250                 255

Asp Pro Asp Ser Leu Ile Val Gln Asp His Tyr Val Phe Val Gln Leu
            260                 265                 270

Thr Ser Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn Ala
        275                 280                 285

Phe Ala Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His
    290                 295                 300

Val Ile Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp
305                 310                 315                 320
```

```
Asn Gln Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val
                325                 330                 335

Tyr Phe Thr Leu Ala Leu Glu Asn Val Gln Ser Ser Arg Gly Pro Glu
            340                 345                 350

Gly Asn Ile Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met
        355                 360                 365

Phe Leu Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr
    370                 375                 380

Tyr Asn Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Thr Asp
385                 390                 395                 400

Leu Arg Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His
                405                 410                 415

Leu His Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala
            420                 425                 430

Ser Lys Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly
        435                 440                 445

Ser Glu Leu Ser Asp Thr Asp Ile Ser Met Phe Val Ser Ser Asp Ala
    450                 455                 460

Gly Asn Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Val Leu Tyr
465                 470                 475                 480

Leu Asp Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro
                485                 490                 495

Ile Arg His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys
            500                 505                 510

Tyr Ser Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu
        515                 520                 525

Pro Gly Glu Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His
    530                 535                 540

Arg Ser Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp
545                 550                 555                 560

Arg Arg Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln
                565                 570                 575
```

```
Gly Glu Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys
            580                 585                 590

Ser Glu Arg Lys Cys Met Gln Gly Lys Tyr Ala Gly Ala Met Glu Ser
        595                 600                 605

Glu Pro Cys Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr
    610                 615                 620

Glu Arg His Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro
625                 630                 635                 640

Ser Ser Leu Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser
                645                 650                 655

Thr Gly Tyr Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg
            660                 665                 670

Glu Gln Tyr Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg
        675                 680                 685

Gly Leu Arg Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly
    690                 695                 700

His Asn Val Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg
705                 710                 715                 720

Thr Leu Ile Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val
                725                 730                 735

Asn Leu Ser Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val
            740                 745                 750

Gly Ile Phe Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp
        755                 760                 765

Ser Ala Val Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His
    770                 775                 780

Leu Ser Leu Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr
785                 790                 795                 800

Ala Val Leu Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp
                805                 810                 815

Tyr Gly Asn Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser
            820                 825                 830
```

```
Phe Arg Phe Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser
        835                 840                 845

Ala Gly Asn Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu
    850                 855                 860

Glu Phe Arg Ser Leu Arg Leu Ser Phe Ser Pro Asn Leu Asp Asp Tyr
865                 870                 875                 880

Asn Pro Asp Ile Pro Glu Trp Arg Arg Asp Ile Gly Arg Val Ile Lys
                885                 890                 895

Lys Ser Leu Val Glu Ala Thr Gly Val Pro Gly Gln His Ile Leu Val
            900                 905                 910

Ala Val Leu Pro Gly Leu Pro Thr Thr Ala Glu Leu Phe Val Leu Pro
        915                 920                 925

Tyr Gln Asp Pro Ala Gly Glu Asn Lys Arg Ser Thr Asp Asp Leu Glu
    930                 935                 940

Gln Ile Ser Glu Leu Leu Ile His Thr Leu Asn Gln Asn Ser Val His
945                 950                 955                 960

Phe Glu Leu Lys Pro Gly Val Arg Val Leu Val His Ala Ala His Leu
                965                 970                 975

Thr Ala Ala Pro Leu Val Asp Leu Thr Pro Thr His Ser Gly Ser Ala
            980                 985                 990

Met Leu Met Leu Leu Ser Val Val  Phe Val Gly Leu Ala  Val Phe Val
        995                 1000                1005

Ile Tyr  Lys Phe Lys Arg Lys  Ile Pro Gly Ile Asn  Val Tyr Ala
    1010                1015                1020

Gln Met  Gln Asn Glu Lys Glu  Gln Glu Met Ile Ser  Pro Val Ser
    1025                1030                1035

His Ser  Glu Ser Arg Pro Asn  Val Pro Gln Thr Glu  Leu Arg Arg
    1040                1045                1050

Pro Gly  Gln Leu Ile Asp Glu  Lys Val Glu Ser Gln  Leu Ile Gly
    1055                1060                1065

Lys
```

<210> 14

<211> 1048

<212> PRT

<213> Homo sapiens

<220>

<221> MISC_FEATURE

<222> (1)..(1048)

<223> Mature SorCS1a, Isoform 4

<400> 14

```
Ser Gly Ala Asp Gln Glu Lys Ala Glu Arg Gly Glu Gly Ala Ser Arg
1               5                  10                  15

Ser Pro Arg Gly Val Leu Arg Asp Gly Gly Gln Gln Glu Pro Gly Thr
            20                  25                  30

Arg Glu Arg Asp Pro Asp Lys Ala Thr Arg Phe Arg Met Glu Glu Leu
        35                  40                  45

Arg Leu Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn
    50                  55                  60

Gln Ala Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile
65                  70                  75                  80

Leu Thr Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser
                85                  90                  95

Leu Trp Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp
            100                 105                 110

Lys Val Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr
        115                 120                 125

Asn Lys Arg Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser
    130                 135                 140

Leu Leu Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu
145                 150                 155                 160

Asn Phe Tyr Ile Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp
                165                 170                 175

Ile Leu Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe
            180                 185                 190

Gly Arg Arg Trp Gln Leu Ile Gln Glu Gly Val Val Pro Asn Arg Phe
        195                 200                 205

Tyr Trp Ser Val Met Gly Ser Asn Lys Glu Pro Asp Leu Val His Leu
```

```
    210                 215                 220

Glu Ala Arg Thr Val Asp Gly His Ser His Tyr Leu Thr Cys Arg Met
225                 230                 235                 240

Gln Asn Cys Thr Glu Ala Asn Arg Asn Gln Pro Phe Pro Gly Tyr Ile
                245                 250                 255

Asp Pro Asp Ser Leu Ile Val Gln Asp His Tyr Val Phe Val Gln Leu
            260                 265                 270

Thr Ser Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn Ala
        275                 280                 285

Phe Ala Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His
    290                 295                 300

Val Ile Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp
305                 310                 315                 320

Asn Gln Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val
                325                 330                 335

Tyr Phe Thr Leu Ala Leu Glu Asn Val Gln Ser Ser Arg Gly Pro Glu
            340                 345                 350

Gly Asn Ile Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met
        355                 360                 365

Phe Leu Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr
    370                 375                 380

Tyr Asn Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Thr Asp
385                 390                 395                 400

Leu Arg Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His
                405                 410                 415

Leu His Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ala Ser
            420                 425                 430

Lys Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Ser
        435                 440                 445

Glu Leu Ser Asp Thr Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly
    450                 455                 460

Asn Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Val Leu Tyr Leu
465                 470                 475                 480
```

```
Asp Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro Ile
                485                 490                 495

Arg His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr
            500                 505                 510

Ser Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu Pro
        515                 520                 525

Gly Glu Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg
    530                 535                 540

Ser Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp Arg
545                 550                 555                 560

Arg Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln Gly
                565                 570                 575

Glu Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser
            580                 585                 590

Glu Arg Lys Cys Met Gln Gly Lys Tyr Ala Gly Ala Met Glu Ser Glu
        595                 600                 605

Pro Cys Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu
    610                 615                 620

Arg His Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser
625                 630                 635                 640

Ser Leu Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Thr
                645                 650                 655

Gly Tyr Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu
            660                 665                 670

Gln Tyr Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly
        675                 680                 685

Leu Arg Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His
    690                 695                 700

Asn Val Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr
705                 710                 715                 720

Leu Ile Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn
                725                 730                 735
```

```
Leu Ser Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly
            740                 745                 750

Ile Phe Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser
        755                 760                 765

Ala Val Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu
    770                 775                 780

Ser Leu Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala
785                 790                 795                 800

Val Leu Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr
                805                 810                 815

Gly Asn Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe
            820                 825                 830

Arg Phe Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala
        835                 840                 845

Gly Asn Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu
    850                 855                 860

Phe Arg Ser Leu Arg Leu Ser Phe Ser Pro Asn Leu Asp Asp Tyr Asn
865                 870                 875                 880

Pro Asp Ile Pro Glu Trp Arg Arg Asp Ile Gly Arg Val Ile Lys Lys
                885                 890                 895

Ser Leu Val Glu Ala Thr Gly Val Pro Gly Gln His Ile Leu Val Ala
            900                 905                 910

Val Leu Pro Gly Leu Pro Thr Thr Ala Glu Leu Phe Val Leu Pro Tyr
        915                 920                 925

Gln Asp Pro Ala Gly Glu Asn Lys Arg Ser Thr Asp Asp Leu Glu Gln
    930                 935                 940

Ile Ser Glu Leu Leu Ile His Thr Leu Asn Gln Asn Ser Val His Phe
945                 950                 955                 960

Glu Leu Lys Pro Gly Val Arg Val Leu Val His Ala Ala His Leu Thr
                965                 970                 975

Ala Ala Pro Leu Val Asp Leu Thr Pro Thr His Ser Gly Ser Ala Met
            980                 985                 990

Leu Met Leu Leu Ser Val Val Phe  Val Gly Leu Ala Val  Phe Val Ile
        995                 1000                1005

Tyr Lys  Phe Lys Arg Cys Val  Ser Leu Tyr Pro Arg  Ser Pro Thr
    1010                1015                1020

Pro Asp  Leu Phe Leu Leu Pro  Asp Arg Phe Arg Ser  Met Cys Tyr
    1025                1030                1035

Ser Asp  Val His Ser Ser Asp  Gly Phe Tyr
    1040                1045
```

<210> 15

<211> 990

<212> PRT

<213> Homo sapiens

<220>

<221> MISC_FEATURE

<222> (1)..(990)

<223> Soluble mature SorCS1

<400> 15

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Ser Gly Ala Asp Gln Glu Lys Ala Glu Arg Gly Glu Gly Ala Ser Arg
1               5                  10                  15

Ser Pro Arg Gly Val Leu Arg Asp Gly Gly Gln Gln Glu Pro Gly Thr
            20                  25                  30

Arg Glu Arg Asp Pro Asp Lys Ala Thr Arg Phe Arg Met Glu Glu Leu
        35                  40                  45

Arg Leu Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn
    50                  55                  60

Gln Ala Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile
65                  70                  75                  80

Leu Thr Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser
                85                  90                  95

Leu Trp Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp
            100                 105                 110

Lys Val Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr
        115                 120                 125

Asn Lys Arg Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser
    130                 135                 140

Leu Leu Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu
145                 150                 155                 160

Asn Phe Tyr Ile Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp
                165                 170                 175

Ile Leu Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe
            180                 185                 190

Gly Arg Arg Trp Gln Leu Ile Gln Glu Gly Val Val Pro Asn Arg Phe
        195                 200                 205

Tyr Trp Ser Val Met Gly Ser Asn Lys Glu Pro Asp Leu Val His Leu
    210                 215                 220

Glu Ala Arg Thr Val Asp Gly His Ser His Tyr Leu Thr Cys Arg Met
225                 230                 235                 240

Gln Asn Cys Thr Glu Ala Asn Arg Asn Gln Pro Phe Pro Gly Tyr Ile
                245                 250                 255

Asp Pro Asp Ser Leu Ile Val Gln Asp His Tyr Val Phe Val Gln Leu
            260                 265                 270

Thr Ser Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn Ala
        275                 280                 285

Phe Ala Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His
    290                 295                 300

Val Ile Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp
305                 310                 315                 320

Asn Gln Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val
                325                 330                 335

Tyr Phe Thr Leu Ala Leu Glu Asn Val Gln Ser Ser Arg Gly Pro Glu
            340                 345                 350

Gly Asn Ile Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met
        355                 360                 365

Phe Leu Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr
    370                 375                 380

Tyr Asn Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Thr Asp
385                 390                 395                 400

Leu Arg Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His
```

```
                405                 410                 415

Leu His Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala
            420                 425                 430

Ser Lys Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly
        435                 440                 445

Ser Glu Leu Ser Asp Thr Asp Ile Ser Met Phe Val Ser Ser Asp Ala
    450                 455                 460

Gly Asn Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Val Leu Tyr
465                 470                 475                 480

Leu Asp Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro
                485                 490                 495

Ile Arg His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys
            500                 505                 510

Tyr Ser Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu
        515                 520                 525

Pro Gly Glu Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His
    530                 535                 540

Arg Ser Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp
545                 550                 555                 560

Arg Arg Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln
                565                 570                 575

Gly Glu Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys
            580                 585                 590

Ser Glu Arg Lys Cys Met Gln Gly Lys Tyr Ala Gly Ala Met Glu Ser
        595                 600                 605

Glu Pro Cys Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr
    610                 615                 620

Glu Arg His Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro
625                 630                 635                 640

Ser Ser Leu Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser
                645                 650                 655

Thr Gly Tyr Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg
            660                 665                 670
```

```
Glu Gln Tyr Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg
        675                 680                 685

Gly Leu Arg Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly
    690                 695                 700

His Asn Val Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg
705                 710                 715                 720

Thr Leu Ile Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val
                725                 730                 735

Asn Leu Ser Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val
            740                 745                 750

Gly Ile Phe Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp
        755                 760                 765

Ser Ala Val Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His
    770                 775                 780

Leu Ser Leu Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr
785                 790                 795                 800

Ala Val Leu Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp
                805                 810                 815

Tyr Gly Asn Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser
            820                 825                 830

Phe Arg Phe Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser
        835                 840                 845

Ala Gly Asn Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu
    850                 855                 860

Glu Phe Arg Ser Leu Arg Leu Ser Phe Ser Pro Asn Leu Asp Asp Tyr
865                 870                 875                 880

Asn Pro Asp Ile Pro Glu Trp Arg Arg Asp Ile Gly Arg Val Ile Lys
                885                 890                 895

Lys Ser Leu Val Glu Ala Thr Gly Val Pro Gly Gln His Ile Leu Val
            900                 905                 910

Ala Val Leu Pro Gly Leu Pro Thr Thr Ala Glu Leu Phe Val Leu Pro
        915                 920                 925

Tyr Gln Asp Pro Ala Gly Glu Asn Lys Arg Ser Thr Asp Asp Leu Glu
    930                 935                 940

Gln Ile Ser Glu Leu Leu Ile His Thr Leu Asn Gln Asn Ser Val His
945                 950                 955                 960

Phe Glu Leu Lys Pro Gly Val Arg Val Leu Val His Ala Ala His Leu
                965                 970                 975

Thr Ala Ala Pro Leu Val Asp Leu Thr Pro Thr His Ser Gly
            980                 985                 990
```

<210> 16

<211> 1167

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

<222> (1)..(1167)

<223> preproSorCS1b, isoform 1

<400> 16

```
Met Gly Lys Val Gly Ala Gly Asp Gly Ser Ser Ala Gly Leu Ser Ala
1               5                   10                  15

Leu Leu Ala Gly Ala Gly Leu Leu Met Leu Leu Ala Pro Gly Val Cys
            20                  25                  30

Ser Ser Leu Ser Cys Cys Pro Pro Gln His Pro Ser Ser Thr Pro Arg
        35                  40                  45

Arg Thr Leu Thr Pro Arg Gly Phe Pro His Pro Gly Pro Leu Gly Arg
    50                  55                  60

Ala Pro Ala Thr Pro Pro Pro Leu Phe Met Arg Pro Leu Phe Ala Val
65                  70                  75                  80

Ala Pro Gly Asp Arg Ala Leu Phe Leu Glu Arg Ala Gly Gly Ser Arg
                85                  90                  95

Val Ser Val Ala Thr Ala Ala Arg Ser Gly Arg Arg Arg Arg Ser Gly
            100                 105                 110

Thr Glu Pro Glu Lys Ile Glu Pro Gly Glu Gly Ala Ser Arg Ser Arg
        115                 120                 125

Arg Asp Met Leu Lys Asp Gly Gly Gln Gln Gly Leu Gly Thr Gly Ala
    130                 135                 140

Arg Asp Pro Gly Lys Ala Thr Arg Phe Arg Met Glu Glu Leu Arg Leu
145                 150                 155                 160

Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala
                165                 170                 175

Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile Leu Thr
            180                 185                 190

Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp
        195                 200                 205

Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Val
    210                 215                 220

Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys
225                 230                 235                 240

Cys Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser Leu Leu
                245                 250                 255

Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe
            260                 265                 270

Tyr Leu Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu
        275                 280                 285

Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe Gly Arg
    290                 295                 300

Arg Trp Gln Leu Ile Gln Glu Ser Val Val Pro Asn Arg Phe Tyr Trp
305                 310                 315                 320

Ser Val Met Gly Ser Ser Lys Glu Pro Asp Leu Val His Leu Glu Ala
                325                 330                 335

Arg Thr Val Asp Gly His Ser Ile Tyr Leu Thr Cys Arg Met Gln Asn
            340                 345                 350

Cys Thr Glu Ala Asn Arg Asn Lys Pro Phe Pro Gly Tyr Ile Asp Pro
        355                 360                 365

Asp Ser Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu Thr Ser
    370                 375                 380

Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Ser Pro Phe Ala
385                 390                 395                 400
```

```
Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His Val Ile
                405                 410                 415

Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln
            420                 425                 430

Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe
        435                 440                 445

Thr Leu Ala Leu Glu Asn Val Arg Ser Ser Arg Gly Pro Glu Gly Asn
    450                 455                 460

Val Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu
465                 470                 475                 480

Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn
                485                 490                 495

Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Ala Asp Leu Arg
            500                 505                 510

Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His Leu His
        515                 520                 525

Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala Ser Arg
    530                 535                 540

Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Ser Glu
545                 550                 555                 560

Leu Ser Asp Ser Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn
                565                 570                 575

Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Ile Leu Tyr Leu Asp
            580                 585                 590

Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro Ile Arg
        595                 600                 605

His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr Ser
    610                 615                 620

Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu Pro Gly
625                 630                 635                 640

Glu Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg Ser
                645                 650                 655

Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp Arg Arg
```

```
           660                 665                 670

Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln Gly Glu
        675                 680                 685

Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu
    690                 695                 700

Arg Lys Cys Met Gln Lys Tyr Ala Gly Ala Met Glu Ser Glu Pro Cys
705                 710                 715                 720

Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg His
                725                 730                 735

Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser Leu
            740                 745                 750

Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Ala Gly Tyr
        755                 760                 765

Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln Tyr
    770                 775                 780

Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu Arg
785                 790                 795                 800

Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn Val
                805                 810                 815

Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr Leu Ile
            820                 825                 830

Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu Ser
        835                 840                 845

Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly Ile Phe
    850                 855                 860

Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala Val
865                 870                 875                 880

Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser Leu
                885                 890                 895

Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val Leu
            900                 905                 910

Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly Asn
        915                 920                 925
```

```
Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe Lys Phe
    930                 935                 940

Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly Asn
945                 950                 955                 960

Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe Arg
                965                 970                 975

Ser Leu Arg Leu Ala Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro Asp
            980                 985                 990

Ile Pro Glu Trp Arg Arg Asp Ile  Ser Arg Val Ile Lys  Lys Ser Leu
        995                 1000                1005

Val Glu  Ala Thr Gly Ile Pro  Ser Gln His Ile Leu  Val Ala Val
    1010                1015                1020

Leu Pro  Gly Leu Pro Thr Ala  Ala Glu Leu Phe Val  Leu Pro Tyr
    1025                1030                1035

Gln Asp  Gly Thr Arg Glu Asn  Lys Arg Ser Pro Glu  Asp Leu Glu
    1040                1045                1050

Gln Ile  Ser Glu Val Leu Ile  His Lys Leu Asn Gln  Asn Leu Val
    1055                1060                1065

His Phe  Glu Leu Lys Pro Gly  Val Gln Val Leu Val  His Ala Ala
    1070                1075                1080

His Leu  Thr Ala Ala Pro Leu  Val Asp Leu Thr Pro  Thr His Ser
    1085                1090                1095

Gly Ser  Ala Met Leu Met Leu  Leu Ser Val Val Phe  Val Gly Leu
    1100                1105                1110

Ala Val  Phe Val Ile Tyr Lys  Phe Lys Arg Arg Val  Ala Leu Pro
    1115                1120                1125

Ser Pro  Pro Ser Pro Ser Ala  Gln Pro Gly Asp Ser  Ser Leu Arg
    1130                1135                1140

Leu Gln  Arg Pro Arg Pro Ala  Thr Pro Pro Ser Ser  Pro Lys Arg
    1145                1150                1155

Gly Ser  Ala Gly Ala Gln Phe  Ala Ile
    1160                1165
```

<210> 17

<211> 1147

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

<222> (1)..(1147)

<223> preproSorCS1b, isoform 2

<400> 17

```
Met Gly Lys Val Gly Ala Gly Asp Gly Ser Ser Ala Gly Leu Ser Ala
1               5                   10                  15

Leu Leu Ala Gly Ala Gly Leu Leu Met Leu Leu Ala Pro Gly Val Cys
            20                  25                  30

Ser Ser Leu Ser Cys Cys Pro Pro Gln His Pro Ser Ser Thr Pro Arg
        35                  40                  45

Arg Thr Leu Thr Pro Arg Gly Phe Pro His Pro Gly Pro Leu Gly Arg
    50                  55                  60

Ala Pro Ala Thr Pro Pro Pro Leu Phe Met Arg Pro Leu Phe Ala Val
65                  70                  75                  80

Ala Pro Gly Asp Arg Ala Leu Phe Leu Glu Arg Ala Gly Gly Ser Arg
                85                  90                  95

Val Ser Val Ala Thr Ala Ala Arg Ser Gly Arg Arg Arg Arg Ser Gly
            100                 105                 110

Thr Glu Pro Glu Lys Ile Glu Pro Gly Glu Gly Ala Ser Arg Ser Arg
        115                 120                 125

Arg Asp Met Leu Lys Asp Gly Gly Gln Gln Gly Leu Gly Thr Gly Ala
    130                 135                 140

Arg Asp Pro Gly Lys Ala Thr Arg Phe Arg Met Glu Glu Leu Arg Leu
145                 150                 155                 160

Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala
                165                 170                 175

Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile Leu Thr
            180                 185                 190

Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp
        195                 200                 205
```

```
Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Val
    210                 215                 220

Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys
225                 230                 235                 240

Cys Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser Leu Leu
                245                 250                 255

Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe
            260                 265                 270

Tyr Leu Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu
        275                 280                 285

Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe Gly Arg
    290                 295                 300

Arg Trp Gln Leu Ile Gln Glu Ser Val Val Pro Asn Arg Phe Tyr Trp
305                 310                 315                 320

Ser Val Met Gly Ser Ser Lys Glu Pro Asp Leu Val His Leu Glu Ala
                325                 330                 335

Arg Thr Val Asp Gly His Ser Ile Tyr Leu Thr Cys Arg Met Gln Asn
            340                 345                 350

Cys Thr Glu Ala Asn Arg Asn Lys Pro Phe Pro Gly Tyr Ile Asp Pro
        355                 360                 365

Asp Ser Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu Thr Ser
    370                 375                 380

Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Ser Pro Phe Ala
385                 390                 395                 400

Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His Val Ile
                405                 410                 415

Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln
            420                 425                 430

Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe
        435                 440                 445

Thr Leu Ala Leu Glu Asn Val Arg Ser Ser Arg Gly Pro Glu Gly Asn
    450                 455                 460
```

```
Val Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu
465                 470                 475                 480

Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn
                485                 490                 495

Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Ala Asp Leu Arg
            500                 505                 510

Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His Leu His
        515                 520                 525

Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala Ser Arg
    530                 535                 540

Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Ser Glu
545                 550                 555                 560

Leu Ser Asp Ser Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn
                565                 570                 575

Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Ile Leu Tyr Leu Asp
            580                 585                 590

Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro Ile Arg
        595                 600                 605

His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr Ser
    610                 615                 620

Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu Pro Gly
625                 630                 635                 640

Glu Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg Ser
                645                 650                 655

Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp Arg Arg
            660                 665                 670

Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln Gly Glu
        675                 680                 685

Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu
    690                 695                 700

Arg Lys Cys Met Gln Lys Tyr Ala Gly Ala Met Glu Ser Glu Pro Cys
705                 710                 715                 720

Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg His
```

```
                725                 730                 735

Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser Leu
            740                 745                 750

Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Ala Gly Tyr
        755                 760                 765

Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln Tyr
    770                 775                 780

Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu Arg
785                 790                 795                 800

Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn Val
                805                 810                 815

Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr Leu Ile
            820                 825                 830

Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu Ser
        835                 840                 845

Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly Ile Phe
    850                 855                 860

Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala Val
865                 870                 875                 880

Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser Leu
                885                 890                 895

Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val Leu
            900                 905                 910

Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly Asn
        915                 920                 925

Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe Lys Phe
    930                 935                 940

Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly Asn
945                 950                 955                 960

Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe Arg
                965                 970                 975

Ser Leu Arg Leu Ala Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro Asp
            980                 985                 990
```

```
Ile Pro Glu Trp Arg Arg Asp Ile  Ser Arg Val Ile Lys  Lys Ser Leu
        995                 1000                1005

Val Glu  Ala Thr Gly Ile Pro  Ser Gln His Ile Leu  Val Ala Val
    1010                1015                1020

Leu Pro  Gly Leu Pro Thr Ala  Ala Glu Leu Phe Val  Leu Pro Tyr
    1025                1030                1035

Gln Asp  Gly Thr Arg Glu Asn  Lys Arg Ser Pro Glu  Asp Leu Glu
    1040                1045                1050

Gln Ile  Ser Glu Val Leu Ile  His Lys Leu Asn Gln  Asn Leu Val
    1055                1060                1065

His Phe  Glu Leu Lys Pro Gly  Val Gln Val Leu Val  His Ala Ala
    1070                1075                1080

His Leu  Thr Ala Ala Pro Leu  Val Asp Leu Thr Pro  Thr His Ser
    1085                1090                1095

Gly Ser  Ala Met Leu Met Leu  Leu Ser Val Val Phe  Val Gly Leu
    1100                1105                1110

Ala Val  Phe Val Ile Tyr Lys  Phe Lys Arg Cys Val  Phe Leu Leu
    1115                1120                1125

Leu Pro  Ser Tyr Pro Arg Pro  Pro Pro Pro Ser Ser  Phe Cys Gln
    1130                1135                1140

Val Gln  Lys Gln
    1145
```

<210> 18

<211> 1178

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

<222> (1)..(1178)

<223> preproSorCS1c, isoform 3

<400> 18

```
Met Gly Lys Val Gly Ala Gly Asp Gly Ser Ser Ala Gly Leu Ser Ala
1               5                  10                  15

Leu Leu Ala Gly Ala Gly Leu Leu Met Leu Leu Ala Pro Gly Val Cys
            20                  25                  30
```

```
Ser Ser Leu Ser Cys Cys Pro Pro Gln His Pro Ser Ser Thr Pro Arg
        35                  40                  45

Arg Thr Leu Thr Pro Arg Gly Phe Pro His Pro Gly Pro Leu Gly Arg
    50                  55                  60

Ala Pro Ala Thr Pro Pro Pro Leu Phe Met Arg Pro Leu Phe Ala Val
65                  70                  75                  80

Ala Pro Gly Asp Arg Ala Leu Phe Leu Glu Arg Ala Gly Gly Ser Arg
                85                  90                  95

Val Ser Val Ala Thr Ala Ala Arg Ser Gly Arg Arg Arg Arg Ser Gly
            100                 105                 110

Thr Glu Pro Glu Lys Ile Glu Pro Gly Glu Gly Ala Ser Arg Ser Arg
        115                 120                 125

Arg Asp Met Leu Lys Asp Gly Gly Gln Gln Gly Leu Gly Thr Gly Ala
    130                 135                 140

Arg Asp Pro Gly Lys Ala Thr Arg Phe Arg Met Glu Glu Leu Arg Leu
145                 150                 155                 160

Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala
                165                 170                 175

Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile Leu Thr
            180                 185                 190

Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp
        195                 200                 205

Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Val
    210                 215                 220

Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys
225                 230                 235                 240

Cys Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser Leu Leu
                245                 250                 255

Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe
            260                 265                 270

Tyr Leu Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu
        275                 280                 285
```

```
Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe Gly Arg
    290                 295                 300

Arg Trp Gln Leu Ile Gln Glu Ser Val Val Pro Asn Arg Phe Tyr Trp
305                 310                 315                 320

Ser Val Met Gly Ser Ser Lys Glu Pro Asp Leu Val His Leu Glu Ala
                325                 330                 335

Arg Thr Val Asp Gly His Ser Ile Tyr Leu Thr Cys Arg Met Gln Asn
            340                 345                 350

Cys Thr Glu Ala Asn Arg Asn Lys Pro Phe Pro Gly Tyr Ile Asp Pro
        355                 360                 365

Asp Ser Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu Thr Ser
    370                 375                 380

Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Ser Pro Phe Ala
385                 390                 395                 400

Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His Val Ile
                405                 410                 415

Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln
            420                 425                 430

Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe
        435                 440                 445

Thr Leu Ala Leu Glu Asn Val Arg Ser Ser Arg Gly Pro Glu Gly Asn
    450                 455                 460

Val Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu
465                 470                 475                 480

Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn
                485                 490                 495

Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Ala Asp Leu Arg
            500                 505                 510

Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His Leu His
        515                 520                 525

Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala Ser Arg
    530                 535                 540
```

```
Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Ser Glu
545                 550                 555                 560

Leu Ser Asp Ser Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn
                565                 570                 575

Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Ile Leu Tyr Leu Asp
            580                 585                 590

Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro Ile Arg
        595                 600                 605

His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr Ser
    610                 615                 620

Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu Pro Gly
625                 630                 635                 640

Glu Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg Ser
                645                 650                 655

Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp Arg Arg
            660                 665                 670

Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln Gly Glu
        675                 680                 685

Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu
    690                 695                 700

Arg Lys Cys Met Gln Lys Tyr Ala Gly Ala Met Glu Ser Glu Pro Cys
705                 710                 715                 720

Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg His
                725                 730                 735

Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser Leu
            740                 745                 750

Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Ala Gly Tyr
        755                 760                 765

Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln Tyr
    770                 775                 780

Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu Arg
785                 790                 795                 800

Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn Val
```

```
               805                 810                 815

Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr Leu Ile
            820                 825                 830

Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu Ser
        835                 840                 845

Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly Ile Phe
    850                 855                 860

Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala Val
865                 870                 875                 880

Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser Leu
                885                 890                 895

Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val Leu
            900                 905                 910

Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly Asn
        915                 920                 925

Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe Lys Phe
    930                 935                 940

Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly Asn
945                 950                 955                 960

Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe Arg
                965                 970                 975

Ser Leu Arg Leu Ala Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro Asp
            980                 985                 990

Ile Pro Glu Trp Arg Arg Asp Ile  Ser Arg Val Ile Lys  Lys Ser Leu
        995                 1000                1005

Val Glu  Ala Thr Gly Ile Pro  Ser Gln His Ile Leu  Val Ala Val
    1010                1015                1020

Leu Pro  Gly Leu Pro Thr Ala  Ala Glu Leu Phe Val  Leu Pro Tyr
    1025                1030                1035

Gln Asp  Gly Thr Arg Glu Asn  Lys Arg Ser Pro Glu  Asp Leu Glu
    1040                1045                1050

Gln Ile  Ser Glu Val Leu Ile  His Lys Leu Asn Gln  Asn Leu Val
    1055                1060                1065

His Phe  Glu Leu Lys Pro Gly  Val Gln Val Leu Val  His Ala Ala
    1070                1075                1080

His Leu  Thr Ala Ala Pro Leu  Val Asp Leu Thr Pro  Thr His Ser
    1085                1090                1095

Gly Ser  Ala Met Leu Met Leu  Leu Ser Val Val Phe  Val Gly Leu
    1100                1105                1110

Ala Val  Phe Val Ile Tyr Lys  Phe Lys Arg Lys Ile  Pro Gly Ile
    1115                1120                1125

Asn Val  Tyr Ala Gln Met Gln  Asn Glu Lys Glu Gln  Glu Leu Ile
    1130                1135                1140

Asn Pro  Val Ser His Ser Glu  Ser Arg Pro Ser Val  Pro His Pro
    1145                1150                1155

Asp Leu  Arg Arg Pro Gly Gln  Leu Val Asp Glu Lys  Val Glu Ser
    1160                1165                1170

Gln Leu  Leu Gly Lys
    1175
```

<210> 19

<211> 1178

<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(1178)
<223> preproSorCS1c+, isoform 4

<400> 19

```
Met Gly Lys Val Gly Ala Gly Asp Gly Ser Ser Ala Gly Leu Ser Ala
1               5                   10                  15

Leu Leu Ala Gly Ala Gly Leu Leu Met Leu Leu Ala Pro Gly Val Cys
            20                  25                  30

Ser Ser Leu Ser Cys Cys Pro Pro Gln His Pro Ser Ser Thr Pro Arg
        35                  40                  45

Arg Thr Leu Thr Pro Arg Gly Phe Pro His Pro Gly Pro Leu Gly Arg
    50                  55                  60

Ala Pro Ala Thr Pro Pro Pro Leu Phe Met Arg Pro Leu Phe Ala Val
65                  70                  75                  80

Ala Pro Gly Asp Arg Ala Leu Phe Leu Glu Arg Ala Gly Gly Ser Arg
                85                  90                  95

Val Ser Val Ala Thr Ala Ala Arg Ser Gly Arg Arg Arg Arg Ser Gly
            100                 105                 110

Thr Glu Pro Glu Lys Ile Glu Pro Gly Glu Gly Ala Ser Arg Ser Arg
        115                 120                 125

Arg Asp Met Leu Lys Asp Gly Gly Gln Gln Gly Leu Gly Thr Gly Ala
    130                 135                 140

Arg Asp Pro Gly Lys Ala Thr Arg Phe Arg Met Glu Glu Leu Arg Leu
145                 150                 155                 160

Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala
                165                 170                 175

Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile Leu Thr
            180                 185                 190

Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp
        195                 200                 205

Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Val
    210                 215                 220

Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys
225                 230                 235                 240

Cys Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser Leu Leu
                245                 250                 255

Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe
            260                 265                 270

Tyr Leu Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu
        275                 280                 285

Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe Gly Arg
    290                 295                 300

Arg Trp Gln Leu Ile Gln Glu Ser Val Val Pro Asn Arg Phe Tyr Trp
305                 310                 315                 320

Ser Val Met Gly Ser Ser Lys Glu Pro Asp Leu Val His Leu Glu Ala
                325                 330                 335
```

```
Arg Thr Val Asp Gly His Ser Ile Tyr Leu Thr Cys Arg Met Gln Asn
            340                 345                 350

Cys Thr Glu Ala Asn Arg Asn Lys Pro Phe Pro Gly Tyr Ile Asp Pro
        355                 360                 365

Asp Ser Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu Thr Ser
    370                 375                 380

Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Ser Pro Phe Ala
385                 390                 395                 400

Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His Val Ile
                405                 410                 415

Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln
            420                 425                 430

Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe
        435                 440                 445

Thr Leu Ala Leu Glu Asn Val Arg Ser Ser Arg Gly Pro Glu Gly Asn
    450                 455                 460

Val Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu
465                 470                 475                 480

Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn
                485                 490                 495

Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Ala Asp Leu Arg
            500                 505                 510

Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His Leu His
        515                 520                 525

Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala Ser Arg
    530                 535                 540

Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Ser Glu
545                 550                 555                 560

Leu Ser Asp Ser Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn
                565                 570                 575

Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Ile Leu Tyr Leu Asp
            580                 585                 590
```

```
Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro Ile Arg
        595                 600                 605

His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr Ser
    610                 615                 620

Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu Pro Gly
625                 630                 635                 640

Glu Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg Ser
                645                 650                 655

Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp Arg Arg
            660                 665                 670

Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln Gly Glu
        675                 680                 685

Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu
    690                 695                 700

Arg Lys Cys Met Gln Lys Tyr Ala Gly Ala Met Glu Ser Glu Pro Cys
705                 710                 715                 720

Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg His
                725                 730                 735

Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser Leu
            740                 745                 750

Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Ala Gly Tyr
        755                 760                 765

Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln Tyr
    770                 775                 780

Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu Arg
785                 790                 795                 800

Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn Val
                805                 810                 815

Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr Leu Ile
            820                 825                 830

Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu Ser
        835                 840                 845

Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly Ile Phe
```

```
    850                 855                 860

Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala Val
865                 870                 875                 880

Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser Leu
                885                 890                 895

Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val Leu
            900                 905                 910

Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly Asn
        915                 920                 925

Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe Lys Phe
    930                 935                 940

Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly Asn
945                 950                 955                 960

Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe Arg
                965                 970                 975

Ser Leu Arg Leu Ala Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro Asp
            980                 985                 990

Ile Pro Glu Trp Arg Arg Asp Ile  Ser Arg Val Ile Lys  Lys Ser Leu
        995                 1000                1005

Val Glu  Ala Thr Gly Ile Pro  Ser Gln His Ile Leu  Val Ala Val
    1010                1015                1020

Leu Pro  Gly Leu Pro Thr Ala  Ala Glu Leu Phe Val  Leu Pro Tyr
    1025                1030                1035

Gln Asp  Gly Thr Arg Glu Asn  Lys Arg Ser Pro Glu  Asp Leu Glu
    1040                1045                1050

Gln Ile  Ser Glu Val Leu Ile  His Lys Leu Asn Gln  Asn Leu Val
    1055                1060                1065

His Phe  Glu Leu Lys Pro Gly  Val Gln Val Leu Val  His Ala Ala
    1070                1075                1080

His Leu  Thr Ala Ala Pro Leu  Val Asp Leu Thr Pro  Thr His Ser
    1085                1090                1095

Gly Ser  Ala Met Leu Met Leu  Leu Ser Val Val Phe  Val Gly Leu
    1100                1105                1110

Ala Val  Phe Val Ile Tyr Lys  Phe Lys Arg Lys Ile  Pro Gly Ile
    1115                1120                1125

Asn Val  Tyr Ala Gln Met Gln  Asn Glu Lys Glu Gln  Glu Leu Ile
    1130                1135                1140

Asn Pro  Val Ser His Ser Glu  Ser Arg Ser Ser Val  Pro His Pro
    1145                1150                1155

Asp Leu  Arg Arg Pro Gly Gln  Leu Val Asp Glu Lys  Val Glu Ser
    1160                1165                1170

Gln Leu  Leu Gly Glu
    1175
```

<210> 20

<211> 1191

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

<222> (1)..(1191)

<223> preproSorCS1d

<400> 20

```
Met Gly Lys Val Gly Ala Gly Asp Gly Ser Ser Ala Gly Leu Ser Ala
1               5                   10                  15

Leu Leu Ala Gly Ala Gly Leu Leu Met Leu Leu Ala Pro Gly Val Cys
            20                  25                  30

Ser Ser Leu Ser Cys Cys Pro Pro Gln His Pro Ser Ser Thr Pro Arg
        35                  40                  45

Arg Thr Leu Thr Pro Arg Gly Phe Pro His Pro Gly Pro Leu Gly Arg
    50                  55                  60

Ala Pro Ala Thr Pro Pro Pro Leu Phe Met Arg Pro Leu Phe Ala Val
65                  70                  75                  80

Ala Pro Gly Asp Arg Ala Leu Phe Leu Glu Arg Ala Gly Gly Ser Arg
                85                  90                  95

Val Ser Val Ala Thr Ala Ala Arg Ser Gly Arg Arg Arg Arg Ser Gly
            100                 105                 110

Thr Glu Pro Glu Lys Ile Glu Pro Gly Glu Gly Ala Ser Arg Ser Arg
        115                 120                 125

Arg Asp Met Leu Lys Asp Gly Gly Gln Gln Gly Leu Gly Thr Gly Ala
    130                 135                 140

Arg Asp Pro Gly Lys Ala Thr Arg Phe Arg Met Glu Glu Leu Arg Leu
145                 150                 155                 160

Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala
                165                 170                 175

Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile Leu Thr
            180                 185                 190

Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp
        195                 200                 205

Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Val
    210                 215                 220

Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys
225                 230                 235                 240

Cys Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser Leu Leu
                245                 250                 255

Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe
            260                 265                 270

Tyr Leu Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu
        275                 280                 285

Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe Gly Arg
    290                 295                 300

Arg Trp Gln Leu Ile Gln Glu Ser Val Val Pro Asn Arg Phe Tyr Trp
305                 310                 315                 320

Ser Val Met Gly Ser Ser Lys Glu Pro Asp Leu Val His Leu Glu Ala
                325                 330                 335

Arg Thr Val Asp Gly His Ser Ile Tyr Leu Thr Cys Arg Met Gln Asn
            340                 345                 350

Cys Thr Glu Ala Asn Arg Asn Lys Pro Phe Pro Gly Tyr Ile Asp Pro
        355                 360                 365

Asp Ser Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu Thr Ser
    370                 375                 380
```

```
Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Ser Pro Phe Ala
385                 390                 395                 400

Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His Val Ile
                405                 410                 415

Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln
            420                 425                 430

Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe
        435                 440                 445

Thr Leu Ala Leu Glu Asn Val Arg Ser Ser Arg Gly Pro Glu Gly Asn
    450                 455                 460

Val Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu
465                 470                 475                 480

Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn
                485                 490                 495

Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Ala Asp Leu Arg
            500                 505                 510

Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His Leu His
        515                 520                 525

Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala Ser Arg
    530                 535                 540

Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Ser Glu
545                 550                 555                 560

Leu Ser Asp Ser Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn
                565                 570                 575

Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Ile Leu Tyr Leu Asp
            580                 585                 590

Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro Ile Arg
        595                 600                 605

His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr Ser
    610                 615                 620

Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu Pro Gly
625                 630                 635                 640
```

```
Glu Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg Ser
                645                 650                 655

Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp Arg Arg
            660                 665                 670

Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln Gly Glu
        675                 680                 685

Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu
    690                 695                 700

Arg Lys Cys Met Gln Lys Tyr Ala Gly Ala Met Glu Ser Glu Pro Cys
705                 710                 715                 720

Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg His
                725                 730                 735

Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser Leu
            740                 745                 750

Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Ala Gly Tyr
        755                 760                 765

Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln Tyr
    770                 775                 780

Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu Arg
785                 790                 795                 800

Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn Val
                805                 810                 815

Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr Leu Ile
            820                 825                 830

Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu Ser
        835                 840                 845

Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly Ile Phe
    850                 855                 860

Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala Val
865                 870                 875                 880

Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser Leu
                885                 890                 895

Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val Leu
```

```
            900                 905                 910

Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly Asn
        915                 920                 925

Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe Lys Phe
    930                 935                 940

Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly Asn
945                 950                 955                 960

Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe Arg
                965                 970                 975

Ser Leu Arg Leu Ala Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro Asp
            980                 985                 990

Ile Pro Glu Trp Arg Arg Asp Ile  Ser Arg Val Ile Lys  Lys Ser Leu
        995                 1000                1005

Val Glu  Ala Thr Gly Ile Pro  Ser Gln His Ile Leu  Val Ala Val
    1010                1015                1020

Leu Pro  Gly Leu Pro Thr Ala  Ala Glu Leu Phe Val  Leu Pro Tyr
    1025                1030                1035

Gln Asp  Gly Thr Arg Glu Asn  Lys Arg Ser Pro Glu  Asp Leu Glu
    1040                1045                1050

Gln Ile  Ser Glu Val Leu Ile  His Lys Leu Asn Gln  Asn Leu Val
    1055                1060                1065

His Phe  Glu Leu Lys Pro Gly  Val Gln Val Leu Val  His Ala Ala
    1070                1075                1080

His Leu  Thr Ala Ala Pro Leu  Val Asp Leu Thr Pro  Thr His Ser
    1085                1090                1095

Gly Ser  Ala Met Leu Met Leu  Leu Ser Val Val Phe  Val Gly Leu
    1100                1105                1110

Ala Val  Phe Val Ile Tyr Lys  Phe Lys Arg Gly Trp  Arg Asp Arg
    1115                1120                1125

Ser Ala  Val Lys Asn Ile Gly  Cys Ser Cys Arg Gly  Pro Gly Phe
    1130                1135                1140

Asn Ser  Gln His Gln Gln Gly  Gly Ser Gln Ala Ser  Val Thr Ser
    1145                1150                1155

Val Pro  Arg Asp Pro Ser Pro  Ser Ser Asp Leu His  Gly His Gln
    1160                1165                1170

Glu His  Thr Trp Cys Thr Asp  Ile His Pro Gly Lys  Thr Pro Ile
    1175                1180                1185

His Ile  Lys
    1190
```

<210> 21

<211> 1099

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

<222> (1)..(1099)

<223> Soluble preproSorCS1

<400> 21

```
Met Gly Lys Val Gly Ala Gly Asp Gly Ser Ser Ala Gly Leu Ser Ala
1               5                   10                  15

Leu Leu Ala Gly Ala Gly Leu Leu Met Leu Leu Ala Pro Gly Val Cys
            20                  25                  30

Ser Ser Leu Ser Cys Cys Pro Pro Gln His Pro Ser Ser Thr Pro Arg
        35                  40                  45

Arg Thr Leu Thr Pro Arg Gly Phe Pro His Pro Gly Pro Leu Gly Arg
    50                  55                  60

Ala Pro Ala Thr Pro Pro Pro Leu Phe Met Arg Pro Leu Phe Ala Val
65                  70                  75                  80

Ala Pro Gly Asp Arg Ala Leu Phe Leu Glu Arg Ala Gly Gly Ser Arg
                85                  90                  95

Val Ser Val Ala Thr Ala Ala Arg Ser Gly Arg Arg Arg Arg Ser Gly
            100                 105                 110

Thr Glu Pro Glu Lys Ile Glu Pro Gly Glu Gly Ala Ser Arg Ser Arg
        115                 120                 125

Arg Asp Met Leu Lys Asp Gly Gly Gln Gln Gly Leu Gly Thr Gly Ala
    130                 135                 140

Arg Asp Pro Gly Lys Ala Thr Arg Phe Arg Met Glu Glu Leu Arg Leu
145                 150                 155                 160
```

```
Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala
                165                 170                 175

Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile Leu Thr
            180                 185                 190

Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp
        195                 200                 205

Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Val
    210                 215                 220

Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys
225                 230                 235                 240

Cys Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser Leu Leu
                245                 250                 255

Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe
            260                 265                 270

Tyr Leu Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu
        275                 280                 285

Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe Gly Arg
    290                 295                 300

Arg Trp Gln Leu Ile Gln Glu Ser Val Val Pro Asn Arg Phe Tyr Trp
305                 310                 315                 320

Ser Val Met Gly Ser Ser Lys Glu Pro Asp Leu Val His Leu Glu Ala
                325                 330                 335

Arg Thr Val Asp Gly His Ser Ile Tyr Leu Thr Cys Arg Met Gln Asn
            340                 345                 350

Cys Thr Glu Ala Asn Arg Asn Lys Pro Phe Pro Gly Tyr Ile Asp Pro
        355                 360                 365

Asp Ser Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu Thr Ser
    370                 375                 380

Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Ser Pro Phe Ala
385                 390                 395                 400

Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His Val Ile
                405                 410                 415
```

```
Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln
            420                 425                 430

Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe
        435                 440                 445

Thr Leu Ala Leu Glu Asn Val Arg Ser Ser Arg Gly Pro Glu Gly Asn
    450                 455                 460

Val Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu
465                 470                 475                 480

Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn
                485                 490                 495

Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Ala Asp Leu Arg
            500                 505                 510

Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His Leu His
        515                 520                 525

Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala Ser Arg
    530                 535                 540

Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Ser Glu
545                 550                 555                 560

Leu Ser Asp Ser Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn
                565                 570                 575

Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Ile Leu Tyr Leu Asp
            580                 585                 590

Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro Ile Arg
        595                 600                 605

His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr Ser
    610                 615                 620

Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu Pro Gly
625                 630                 635                 640

Glu Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg Ser
                645                 650                 655

Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp Arg Arg
            660                 665                 670
```

```
Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln Gly Glu
        675                 680                 685

Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu
    690                 695                 700

Arg Lys Cys Met Gln Lys Tyr Ala Gly Ala Met Glu Ser Glu Pro Cys
705                 710                 715                 720

Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg His
                725                 730                 735

Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser Leu
            740                 745                 750

Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Ala Gly Tyr
        755                 760                 765

Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln Tyr
    770                 775                 780

Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu Arg
785                 790                 795                 800

Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn Val
                805                 810                 815

Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr Leu Ile
            820                 825                 830

Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu Ser
        835                 840                 845

Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly Ile Phe
    850                 855                 860

Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala Val
865                 870                 875                 880

Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser Leu
                885                 890                 895

Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val Leu
            900                 905                 910

Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly Asn
        915                 920                 925

Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe Lys Phe
```

```
    930                 935                 940

Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly Asn
945                 950                 955                 960

Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe Arg
                965                 970                 975

Ser Leu Arg Leu Ala Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro Asp
            980                 985                 990

Ile Pro Glu Trp Arg Arg Asp Ile  Ser Arg Val Ile Lys  Lys Ser Leu
        995                 1000                1005

Val Glu  Ala Thr Gly Ile Pro  Ser Gln His Ile Leu  Val Ala Val
    1010                1015                1020

Leu Pro  Gly Leu Pro Thr Ala  Ala Glu Leu Phe Val  Leu Pro Tyr
    1025                1030                1035

Gln Asp  Gly Thr Arg Glu Asn  Lys Arg Ser Pro Glu  Asp Leu Glu
    1040                1045                1050

Gln Ile  Ser Glu Val Leu Ile  His Lys Leu Asn Gln  Asn Leu Val
    1055                1060                1065

His Phe  Glu Leu Lys Pro Gly  Val Gln Val Leu Val  His Ala Ala
    1070                1075                1080

His Leu  Thr Ala Ala Pro Leu  Val Asp Leu Thr Pro  Thr His Ser
    1085                1090                1095

Gly
```

<210> 22

<211> 1134

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

<222> (1)..(1134)

<223> proSorCS1b (isoform 1)

<400> 22

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Ser Leu Ser Cys Cys Pro Pro Gln His Pro Ser Ser Thr Pro Arg Arg
1               5                   10                  15

Thr Leu Thr Pro Arg Gly Phe Pro His Pro Gly Pro Leu Gly Arg Ala
```

```
            20                  25                  30

Pro Ala Thr Pro Pro Pro Leu Phe Met Arg Pro Leu Phe Ala Val Ala
        35                  40                  45

Pro Gly Asp Arg Ala Leu Phe Leu Glu Arg Ala Gly Gly Ser Arg Val
    50                  55                  60

Ser Val Ala Thr Ala Ala Arg Ser Gly Arg Arg Arg Arg Ser Gly Thr
65                  70                  75                  80

Glu Pro Glu Lys Ile Glu Pro Gly Glu Gly Ala Ser Arg Ser Arg Arg
                85                  90                  95

Asp Met Leu Lys Asp Gly Gly Gln Gln Gly Leu Gly Thr Gly Ala Arg
            100                 105                 110

Asp Pro Gly Lys Ala Thr Arg Phe Arg Met Glu Glu Leu Arg Leu Thr
        115                 120                 125

Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala Met
    130                 135                 140

Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile Leu Thr Lys
145                 150                 155                 160

Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp Arg
                165                 170                 175

Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Val Gly
            180                 185                 190

Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys Cys
        195                 200                 205

Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser Leu Leu Ile
    210                 215                 220

Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe Tyr
225                 230                 235                 240

Leu Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu Ala
                245                 250                 255

Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe Gly Arg Arg
            260                 265                 270

Trp Gln Leu Ile Gln Glu Ser Val Val Pro Asn Arg Phe Tyr Trp Ser
        275                 280                 285
```

```
Val Met Gly Ser Ser Lys Glu Pro Asp Leu Val His Leu Glu Ala Arg
    290                 295                 300

Thr Val Asp Gly His Ser Ile Tyr Leu Thr Cys Arg Met Gln Asn Cys
305                 310                 315                 320

Thr Glu Ala Asn Arg Asn Lys Pro Phe Pro Gly Tyr Ile Asp Pro Asp
                325                 330                 335

Ser Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu Thr Ser Gly
            340                 345                 350

Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Ser Pro Phe Ala Gln
        355                 360                 365

Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His Val Ile Ser
    370                 375                 380

Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln Asn
385                 390                 395                 400

Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe Thr
                405                 410                 415

Leu Ala Leu Glu Asn Val Arg Ser Ser Arg Gly Pro Glu Gly Asn Val
            420                 425                 430

Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu Ala
        435                 440                 445

Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn Lys
    450                 455                 460

Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Ala Asp Leu Arg Gly
465                 470                 475                 480

Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His Leu His Leu
                485                 490                 495

Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala Ser Arg Asp
            500                 505                 510

Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Ser Glu Leu
        515                 520                 525

Ser Asp Ser Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn Thr
    530                 535                 540
```

```
Trp Arg Gln Ile Phe Glu Glu Glu His Ser Ile Leu Tyr Leu Asp Gln
545                 550                 555                 560

Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro Ile Arg His
                565                 570                 575

Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr Ser Phe
            580                 585                 590

Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu Pro Gly Glu
        595                 600                 605

Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg Ser Glu
    610                 615                 620

Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp Arg Arg Cys
625                 630                 635                 640

Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln Gly Glu Ala
                645                 650                 655

Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu Arg
            660                 665                 670

Lys Cys Met Gln Lys Tyr Ala Gly Ala Met Glu Ser Glu Pro Cys Val
        675                 680                 685

Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg His Ser
    690                 695                 700

Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser Leu Ser
705                 710                 715                 720

Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Ala Gly Tyr Arg
                725                 730                 735

Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln Tyr Thr
            740                 745                 750

Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu Arg Ile
        755                 760                 765

Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn Val Thr
    770                 775                 780

Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr Leu Ile Gln
785                 790                 795                 800
```

```
Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu Ser Ser
                805                 810                 815

Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly Ile Phe Arg
            820                 825                 830

Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala Val Leu
        835                 840                 845

Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser Leu Pro
    850                 855                 860

Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val Leu Trp
865                 870                 875                 880

Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly Asn Asn
                885                 890                 895

Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe Lys Phe Thr
            900                 905                 910

Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly Asn Ala
        915                 920                 925

Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe Arg Ser
    930                 935                 940

Leu Arg Leu Ala Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro Asp Ile
945                 950                 955                 960

Pro Glu Trp Arg Arg Asp Ile Ser Arg Val Ile Lys Lys Ser Leu Val
                965                 970                 975

Glu Ala Thr Gly Ile Pro Ser Gln His Ile Leu Val Ala Val Leu Pro
            980                 985                 990

Gly Leu Pro Thr Ala Ala Glu Leu  Phe Val Leu Pro Tyr  Gln Asp Gly
        995                 1000                1005

Thr Arg  Glu Asn Lys Arg Ser  Pro Glu Asp Leu Glu  Gln Ile Ser
    1010                1015                1020

Glu Val  Leu Ile His Lys Leu  Asn Gln Asn Leu Val  His Phe Glu
    1025                1030                1035

Leu Lys  Pro Gly Val Gln Val  Leu Val His Ala Ala  His Leu Thr
    1040                1045                1050

Ala Ala  Pro Leu Val Asp Leu  Thr Pro Thr His Ser  Gly Ser Ala

    1055                1060                1065

Met Leu  Met Leu Leu Ser Val  Val Phe Val Gly Leu  Ala Val Phe
    1070                1075                1080

Val Ile  Tyr Lys Phe Lys Arg  Arg Val Ala Leu Pro  Ser Pro Pro
    1085                1090                1095

Ser Pro  Ser Ala Gln Pro Gly  Asp Ser Ser Leu Arg  Leu Gln Arg
    1100                1105                1110

Pro Arg  Pro Ala Thr Pro Pro  Ser Ser Pro Lys Arg  Gly Ser Ala
    1115                1120                1125

Gly Ala  Gln Phe Ala Ile
    1130
```

<210> 23

<211> 1114

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

<222> (1)..(1114)

<223> proSorCS1a, isoform 2

<400> 23

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Ser Leu Ser Cys Cys Pro Pro Gln His Pro Ser Ser Thr Pro Arg Arg
1               5                  10                  15

Thr Leu Thr Pro Arg Gly Phe Pro His Pro Gly Pro Leu Gly Arg Ala
            20                  25                  30

Pro Ala Thr Pro Pro Pro Leu Phe Met Arg Pro Leu Phe Ala Val Ala
        35                  40                  45

Pro Gly Asp Arg Ala Leu Phe Leu Glu Arg Ala Gly Gly Ser Arg Val
    50                  55                  60

Ser Val Ala Thr Ala Ala Arg Ser Gly Arg Arg Arg Arg Ser Gly Thr
65                  70                  75                  80

Glu Pro Glu Lys Ile Glu Pro Gly Glu Gly Ala Ser Arg Ser Arg Arg
                85                  90                  95

Asp Met Leu Lys Asp Gly Gly Gln Gln Gly Leu Gly Thr Gly Ala Arg
            100                 105                 110

Asp Pro Gly Lys Ala Thr Arg Phe Arg Met Glu Glu Leu Arg Leu Thr

        115                 120                 125

Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala Met
    130                 135                 140

Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile Leu Thr Lys
145                 150                 155                 160

Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp Arg
                165                 170                 175

Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Val Gly
            180                 185                 190

Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys Cys
        195                 200                 205

Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser Leu Leu Ile
    210                 215                 220

Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe Tyr
225                 230                 235                 240

Leu Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu Ala
                245                 250                 255

Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe Gly Arg Arg
            260                 265                 270

Trp Gln Leu Ile Gln Glu Ser Val Val Pro Asn Arg Phe Tyr Trp Ser
        275                 280                 285

Val Met Gly Ser Ser Lys Glu Pro Asp Leu Val His Leu Glu Ala Arg
    290                 295                 300

Thr Val Asp Gly His Ser Ile Tyr Leu Thr Cys Arg Met Gln Asn Cys
305                 310                 315                 320

Thr Glu Ala Asn Arg Asn Lys Pro Phe Pro Gly Tyr Ile Asp Pro Asp
                325                 330                 335

Ser Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu Thr Ser Gly
            340                 345                 350

Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Ser Pro Phe Ala Gln
        355                 360                 365

Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His Val Ile Ser
    370                 375                 380
```

```
Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln Asn
385                 390                 395                 400

Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe Thr
                405                 410                 415

Leu Ala Leu Glu Asn Val Arg Ser Ser Arg Gly Pro Glu Gly Asn Val
            420                 425                 430

Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu Ala
        435                 440                 445

Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn Lys
    450                 455                 460

Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Ala Asp Leu Arg Gly
465                 470                 475                 480

Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His Leu His Leu
                485                 490                 495

Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala Ser Arg Asp
            500                 505                 510

Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Ser Glu Leu
        515                 520                 525

Ser Asp Ser Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn Thr
    530                 535                 540

Trp Arg Gln Ile Phe Glu Glu Glu His Ser Ile Leu Tyr Leu Asp Gln
545                 550                 555                 560

Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro Ile Arg His
                565                 570                 575

Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr Ser Phe
            580                 585                 590

Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu Pro Gly Glu
        595                 600                 605

Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg Ser Glu
    610                 615                 620

Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp Arg Arg Cys
625                 630                 635                 640
```

```
Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln Gly Glu Ala
                645                 650                 655

Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu Arg
            660                 665                 670

Lys Cys Met Gln Lys Tyr Ala Gly Ala Met Glu Ser Glu Pro Cys Val
        675                 680                 685

Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg His Ser
    690                 695                 700

Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser Leu Ser
705                 710                 715                 720

Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Ala Gly Tyr Arg
                725                 730                 735

Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln Tyr Thr
            740                 745                 750

Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu Arg Ile
        755                 760                 765

Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn Val Thr
    770                 775                 780

Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr Leu Ile Gln
785                 790                 795                 800

Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu Ser Ser
                805                 810                 815

Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly Ile Phe Arg
            820                 825                 830

Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala Val Leu
        835                 840                 845

Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser Leu Pro
    850                 855                 860

Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val Leu Trp
865                 870                 875                 880

Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly Asn Asn
                885                 890                 895
```

```
Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe Lys Phe Thr
            900                 905                 910

Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly Asn Ala
        915                 920                 925

Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe Arg Ser
    930                 935                 940

Leu Arg Leu Ala Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro Asp Ile
945                 950                 955                 960

Pro Glu Trp Arg Arg Asp Ile Ser Arg Val Ile Lys Lys Ser Leu Val
                965                 970                 975

Glu Ala Thr Gly Ile Pro Ser Gln His Ile Leu Val Ala Val Leu Pro
            980                 985                 990

Gly Leu Pro Thr Ala Ala Glu Leu  Phe Val Leu Pro Tyr  Gln Asp Gly
        995                 1000                1005

Thr Arg  Glu Asn Lys Arg Ser  Pro Glu Asp Leu Glu  Gln Ile Ser
    1010                1015                1020

Glu Val  Leu Ile His Lys Leu  Asn Gln Asn Leu Val  His Phe Glu
    1025                1030                1035

Leu Lys  Pro Gly Val Gln Val  Leu Val His Ala Ala  His Leu Thr
    1040                1045                1050

Ala Ala  Pro Leu Val Asp Leu  Thr Pro Thr His Ser  Gly Ser Ala
    1055                1060                1065

Met Leu  Met Leu Leu Ser Val  Val Phe Val Gly Leu  Ala Val Phe
    1070                1075                1080

Val Ile  Tyr Lys Phe Lys Arg  Cys Val Phe Leu Leu  Leu Pro Ser
    1085                1090                1095

Tyr Pro  Arg Pro Pro Pro Pro  Ser Ser Phe Cys Gln  Val Gln Lys
    1100                1105                1110

Gln
```

<210> 24

<211> 1145

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

<222> (1)..(1145)

<223> proSorCS1c, isoform 3

<400> 24

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Ser Leu Ser Cys Cys Pro Pro Gln His Pro Ser Ser Thr Pro Arg Arg
1               5                  10                  15

Thr Leu Thr Pro Arg Gly Phe Pro His Pro Gly Pro Leu Gly Arg Ala
            20                  25                  30

Pro Ala Thr Pro Pro Pro Leu Phe Met Arg Pro Leu Phe Ala Val Ala
        35                  40                  45

Pro Gly Asp Arg Ala Leu Phe Leu Glu Arg Ala Gly Gly Ser Arg Val
    50                  55                  60

Ser Val Ala Thr Ala Ala Arg Ser Gly Arg Arg Arg Arg Ser Gly Thr
65                  70                  75                  80

Glu Pro Glu Lys Ile Glu Pro Gly Glu Gly Ala Ser Arg Ser Arg Arg
                85                  90                  95

Asp Met Leu Lys Asp Gly Gly Gln Gln Gly Leu Gly Thr Gly Ala Arg
            100                 105                 110

Asp Pro Gly Lys Ala Thr Arg Phe Arg Met Glu Glu Leu Arg Leu Thr
        115                 120                 125

Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala Met
    130                 135                 140

Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile Leu Thr Lys
145                 150                 155                 160

Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp Arg
                165                 170                 175

Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Val Gly
            180                 185                 190

Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys Cys
        195                 200                 205

Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser Leu Leu Ile
    210                 215                 220

Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe Tyr
```

```
225                 230                 235                 240

Leu Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu Ala
                245                 250                 255

Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe Gly Arg Arg
            260                 265                 270

Trp Gln Leu Ile Gln Glu Ser Val Val Pro Asn Arg Phe Tyr Trp Ser
        275                 280                 285

Val Met Gly Ser Ser Lys Glu Pro Asp Leu Val His Leu Glu Ala Arg
    290                 295                 300

Thr Val Asp Gly His Ser Ile Tyr Leu Thr Cys Arg Met Gln Asn Cys
305                 310                 315                 320

Thr Glu Ala Asn Arg Asn Lys Pro Phe Pro Gly Tyr Ile Asp Pro Asp
                325                 330                 335

Ser Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu Thr Ser Gly
            340                 345                 350

Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Ser Pro Phe Ala Gln
        355                 360                 365

Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His Val Ile Ser
    370                 375                 380

Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln Asn
385                 390                 395                 400

Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe Thr
                405                 410                 415

Leu Ala Leu Glu Asn Val Arg Ser Ser Arg Gly Pro Glu Gly Asn Val
            420                 425                 430

Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu Ala
        435                 440                 445

Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn Lys
    450                 455                 460

Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Ala Asp Leu Arg Gly
465                 470                 475                 480

Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His Leu His Leu
                485                 490                 495
```

```
Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala Ser Arg Asp
            500                 505                 510

Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Ser Glu Leu
        515                 520                 525

Ser Asp Ser Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn Thr
    530                 535                 540

Trp Arg Gln Ile Phe Glu Glu Glu His Ser Ile Leu Tyr Leu Asp Gln
545                 550                 555                 560

Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro Ile Arg His
                565                 570                 575

Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr Ser Phe
            580                 585                 590

Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu Pro Gly Glu
        595                 600                 605

Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg Ser Glu
    610                 615                 620

Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp Arg Arg Cys
625                 630                 635                 640

Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln Gly Glu Ala
                645                 650                 655

Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu Arg
            660                 665                 670

Lys Cys Met Gln Lys Tyr Ala Gly Ala Met Glu Ser Glu Pro Cys Val
        675                 680                 685

Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg His Ser
    690                 695                 700

Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser Leu Ser
705                 710                 715                 720

Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Ala Gly Tyr Arg
                725                 730                 735

Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln Tyr Thr
            740                 745                 750
```

```
Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu Arg Ile
        755                 760                 765

Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn Val Thr
    770                 775                 780

Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr Leu Ile Gln
785                 790                 795                 800

Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu Ser Ser
                805                 810                 815

Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly Ile Phe Arg
            820                 825                 830

Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala Val Leu
        835                 840                 845

Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser Leu Pro
    850                 855                 860

Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val Leu Trp
865                 870                 875                 880

Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly Asn Asn
                885                 890                 895

Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe Lys Phe Thr
            900                 905                 910

Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly Asn Ala
        915                 920                 925

Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe Arg Ser
    930                 935                 940

Leu Arg Leu Ala Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro Asp Ile
945                 950                 955                 960

Pro Glu Trp Arg Arg Asp Ile Ser Arg Val Ile Lys Lys Ser Leu Val
                965                 970                 975

Glu Ala Thr Gly Ile Pro Ser Gln His Ile Leu Val Ala Val Leu Pro
            980                 985                 990

Gly Leu Pro Thr Ala Ala Glu Leu  Phe Val Leu Pro Tyr  Gln Asp Gly
        995                 1000                1005
```

```
Thr Arg  Glu Asn Lys Arg Ser  Pro Glu Asp Leu Glu  Gln Ile Ser
    1010                1015                1020

Glu Val  Leu Ile His Lys Leu  Asn Gln Asn Leu Val  His Phe Glu
    1025                1030                1035

Leu Lys  Pro Gly Val Gln Val  Leu Val His Ala Ala  His Leu Thr
    1040                1045                1050

Ala Ala  Pro Leu Val Asp Leu  Thr Pro Thr His Ser  Gly Ser Ala
    1055                1060                1065

Met Leu  Met Leu Leu Ser Val  Val Phe Val Gly Leu  Ala Val Phe
    1070                1075                1080

Val Ile  Tyr Lys Phe Lys Arg  Lys Ile Pro Gly Ile  Asn Val Tyr
    1085                1090                1095

Ala Gln  Met Gln Asn Glu Lys  Glu Gln Glu Leu Ile  Asn Pro Val
    1100                1105                1110

Ser His  Ser Glu Ser Arg Pro  Ser Val Pro His Pro  Asp Leu Arg
    1115                1120                1125

Arg Pro  Gly Gln Leu Val Asp  Glu Lys Val Glu Ser  Gln Leu Leu
    1130                1135                1140

Gly Lys
    1145
```

<210> 25

<211> 1144

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

<222> (1)..(1144)

<223> proSorCS1c+, isoform 4

<400> 25

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Ser Leu Ser Cys Cys Pro Pro Gln His Pro Ser Ser Thr Pro Arg Arg
1               5                   10                  15

Thr Leu Thr Pro Arg Gly Phe Pro His Pro Gly Pro Leu Gly Arg Ala
            20                  25                  30

Pro Ala Thr Pro Pro Pro Leu Phe Met Arg Pro Leu Phe Ala Val Ala
        35                  40                  45
```

```
Pro Gly Asp Arg Ala Leu Phe Leu Glu Arg Ala Gly Gly Ser Arg Val
    50                  55                  60

Ser Val Ala Thr Ala Ala Arg Ser Gly Arg Arg Arg Arg Ser Gly Thr
65                  70                  75                  80

Glu Pro Glu Lys Ile Glu Pro Gly Glu Gly Ala Ser Arg Ser Arg Arg
                85                  90                  95

Asp Met Leu Lys Asp Gly Gly Gln Gln Gly Leu Gly Thr Gly Ala Arg
            100                 105                 110

Asp Pro Gly Lys Ala Thr Arg Phe Arg Met Glu Glu Leu Arg Leu Thr
        115                 120                 125

Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala Met
    130                 135                 140

Val Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile Leu Thr Lys Leu
145                 150                 155                 160

Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp Arg Ser
                165                 170                 175

Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Val Gly Leu
            180                 185                 190

Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys Cys Lys
        195                 200                 205

Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser Leu Leu Ile Ser
    210                 215                 220

Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe Tyr Leu
225                 230                 235                 240

Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu Ala Tyr
                245                 250                 255

Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe Gly Arg Arg Trp
            260                 265                 270

Gln Leu Ile Gln Glu Ser Val Val Pro Asn Arg Phe Tyr Trp Ser Val
        275                 280                 285

Met Gly Ser Ser Lys Glu Pro Asp Leu Val His Leu Glu Ala Arg Thr
    290                 295                 300

Val Asp Gly His Ser Ile Tyr Leu Thr Cys Arg Met Gln Asn Cys Thr
```

```
305                 310                 315                 320

Glu Ala Asn Arg Asn Lys Pro Phe Pro Gly Tyr Ile Asp Pro Asp Ser
                325                 330                 335

Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu Thr Ser Gly Gly
            340                 345                 350

Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Ser Pro Phe Ala Gln Met
        355                 360                 365

Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His Val Ile Ser Thr
    370                 375                 380

Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln Asn Asp
385                 390                 395                 400

Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe Thr Leu
                405                 410                 415

Ala Leu Glu Asn Val Arg Ser Ser Arg Gly Pro Glu Gly Asn Val Met
            420                 425                 430

Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu Ala Asn
        435                 440                 445

Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn Lys Gly
    450                 455                 460

Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Ala Asp Leu Arg Gly Asp
465                 470                 475                 480

Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His Leu His Leu Lys
                485                 490                 495

Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala Ser Arg Asp Thr
            500                 505                 510

Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Ser Glu Leu Ser
        515                 520                 525

Asp Ser Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn Thr Trp
    530                 535                 540

Arg Gln Ile Phe Glu Glu Glu His Ser Ile Leu Tyr Leu Asp Gln Gly
545                 550                 555                 560

Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro Ile Arg His Leu
                565                 570                 575
```

```
Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr Ser Phe Thr
            580                 585                 590

Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu Pro Gly Glu Glu
        595                 600                 605

Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg Ser Glu Trp
    610                 615                 620

Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp Arg Arg Cys Ala
625                 630                 635                 640

Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln Gly Glu Ala Cys
                645                 650                 655

Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu Arg Lys
            660                 665                 670

Cys Met Gln Lys Tyr Ala Gly Ala Met Glu Ser Glu Pro Cys Val Cys
        675                 680                 685

Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg His Ser Asn
    690                 695                 700

Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser Leu Ser Lys
705                 710                 715                 720

Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Ala Gly Tyr Arg Lys
                725                 730                 735

Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln Tyr Thr Ala
            740                 745                 750

Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu Arg Ile Val
        755                 760                 765

Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn Val Thr Leu
    770                 775                 780

Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr Leu Ile Gln Val
785                 790                 795                 800

Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu Ser Ser Met
                805                 810                 815

Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly Ile Phe Arg Val
            820                 825                 830
```

```
Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala Val Leu Tyr
        835                 840                 845

Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser Leu Pro Phe
    850                 855                 860

Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val Leu Trp Pro
865                 870                 875                 880

Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly Asn Asn Thr
                885                 890                 895

Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe Lys Phe Thr Ser
            900                 905                 910

Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly Asn Ala Ile
        915                 920                 925

Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe Arg Ser Leu
    930                 935                 940

Arg Leu Ala Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro Asp Ile Pro
945                 950                 955                 960

Glu Trp Arg Arg Asp Ile Ser Arg Val Ile Lys Lys Ser Leu Val Glu
                965                 970                 975

Ala Thr Gly Ile Pro Ser Gln His Ile Leu Val Ala Val Leu Pro Gly
            980                 985                 990

Leu Pro Thr Ala Ala Glu Leu Phe  Val Leu Pro Tyr Gln  Asp Gly Thr
        995                 1000                1005

Arg Glu  Asn Lys Arg Ser Pro  Glu Asp Leu Glu Gln  Ile Ser Glu
    1010                1015                1020

Val Leu  Ile His Lys Leu Asn  Gln Asn Leu Val His  Phe Glu Leu
    1025                1030                1035

Lys Pro  Gly Val Gln Val Leu  Val His Ala Ala His  Leu Thr Ala
    1040                1045                1050

Ala Pro  Leu Val Asp Leu Thr  Pro Thr His Ser Gly  Ser Ala Met
    1055                1060                1065

Leu Met  Leu Leu Ser Val Val  Phe Val Gly Leu Ala  Val Phe Val
    1070                1075                1080

Ile Tyr  Lys Phe Lys Arg Lys  Ile Pro Gly Ile Asn  Val Tyr Ala
    1085                1090                1095

Gln Met  Gln Asn Glu Lys Glu  Gln Glu Leu Ile Asn  Pro Val Ser
    1100                1105                1110

His Ser  Glu Ser Arg Ser Ser  Val Pro His Pro Asp  Leu Arg Arg
    1115                1120                1125

Pro Gly  Gln Leu Val Asp Glu  Lys Val Glu Ser Gln  Leu Leu Gly
    1130                1135                1140

Glu
```

<210> 26

<211> 1158

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

<222> (1)..(1158)

<223> proSorCS1d

<400> 26

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Ser Leu Ser Cys Cys Pro Pro Gln His Pro Ser Ser Thr Pro Arg Arg
1               5                   10                  15

Thr Leu Thr Pro Arg Gly Phe Pro His Pro Gly Pro Leu Gly Arg Ala
            20                  25                  30

Pro Ala Thr Pro Pro Pro Leu Phe Met Arg Pro Leu Phe Ala Val Ala
        35                  40                  45

Pro Gly Asp Arg Ala Leu Phe Leu Glu Arg Ala Gly Gly Ser Arg Val
    50                  55                  60

Ser Val Ala Thr Ala Ala Arg Ser Gly Arg Arg Arg Arg Ser Gly Thr
65                  70                  75                  80

Glu Pro Glu Lys Ile Glu Pro Gly Glu Gly Ala Ser Arg Ser Arg Arg
                85                  90                  95

Asp Met Leu Lys Asp Gly Gly Gln Gln Gly Leu Gly Thr Gly Ala Arg
            100                 105                 110

Asp Pro Gly Lys Ala Thr Arg Phe Arg Met Glu Glu Leu Arg Leu Thr
        115                 120                 125

Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala Met
    130                 135                 140

Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile Leu Thr Lys
145                 150                 155                 160

Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp Arg
                165                 170                 175

Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Val Gly
            180                 185                 190

Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys Cys
        195                 200                 205

Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser Leu Leu Ile
    210                 215                 220

Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe Tyr
225                 230                 235                 240

Leu Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu Ala
                245                 250                 255

Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe Gly Arg Arg
            260                 265                 270

Trp Gln Leu Ile Gln Glu Ser Val Val Pro Asn Arg Phe Tyr Trp Ser
        275                 280                 285

Val Met Gly Ser Ser Lys Glu Pro Asp Leu Val His Leu Glu Ala Arg
    290                 295                 300

Thr Val Asp Gly His Ser Ile Tyr Leu Thr Cys Arg Met Gln Asn Cys
305                 310                 315                 320

Thr Glu Ala Asn Arg Asn Lys Pro Phe Pro Gly Tyr Ile Asp Pro Asp
                325                 330                 335

Ser Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu Thr Ser Gly
            340                 345                 350

Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Ser Pro Phe Ala Gln
        355                 360                 365

Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His Val Ile Ser
    370                 375                 380

Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln Asn
```

```
385                 390                 395                 400

Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe Thr
                405                 410                 415

Leu Ala Leu Glu Asn Val Arg Ser Ser Arg Gly Pro Glu Gly Asn Val
            420                 425                 430

Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu Ala
        435                 440                 445

Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn Lys
    450                 455                 460

Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Ala Asp Leu Arg Gly
465                 470                 475                 480

Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His Leu His Leu
                485                 490                 495

Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala Ser Arg Asp
            500                 505                 510

Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Ser Glu Leu
        515                 520                 525

Ser Asp Ser Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn Thr
    530                 535                 540

Trp Arg Gln Ile Phe Glu Glu Glu His Ser Ile Leu Tyr Leu Asp Gln
545                 550                 555                 560

Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro Ile Arg His
                565                 570                 575

Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr Ser Phe
            580                 585                 590

Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu Pro Gly Glu
        595                 600                 605

Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg Ser Glu
    610                 615                 620

Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp Arg Arg Cys
625                 630                 635                 640

Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln Gly Glu Ala
                645                 650                 655
```

```
Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu Arg
            660                 665                 670

Lys Cys Met Gln Lys Tyr Ala Gly Ala Met Glu Ser Glu Pro Cys Val
        675                 680                 685

Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg His Ser
    690                 695                 700

Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser Leu Ser
705                 710                 715                 720

Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Ala Gly Tyr Arg
                725                 730                 735

Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln Tyr Thr
            740                 745                 750

Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu Arg Ile
        755                 760                 765

Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn Val Thr
    770                 775                 780

Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr Leu Ile Gln
785                 790                 795                 800

Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu Ser Ser
                805                 810                 815

Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly Ile Phe Arg
            820                 825                 830

Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala Val Leu
        835                 840                 845

Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser Leu Pro
    850                 855                 860

Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val Leu Trp
865                 870                 875                 880

Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly Asn Asn
                885                 890                 895

Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe Lys Phe Thr
            900                 905                 910
```

```
Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly Asn Ala
        915                 920                 925

Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe Arg Ser
    930                 935                 940

Leu Arg Leu Ala Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro Asp Ile
945                 950                 955                 960

Pro Glu Trp Arg Arg Asp Ile Ser Arg Val Ile Lys Lys Ser Leu Val
                965                 970                 975

Glu Ala Thr Gly Ile Pro Ser Gln His Ile Leu Val Ala Val Leu Pro
            980                 985                 990

Gly Leu Pro Thr Ala Ala Glu Leu  Phe Val Leu Pro Tyr  Gln Asp Gly
        995                 1000                1005

Thr Arg  Glu Asn Lys Arg Ser  Pro Glu Asp Leu Glu  Gln Ile Ser
    1010                1015                1020

Glu Val  Leu Ile His Lys Leu  Asn Gln Asn Leu Val  His Phe Glu
    1025                1030                1035

Leu Lys  Pro Gly Val Gln Val  Leu Val His Ala Ala  His Leu Thr
    1040                1045                1050

Ala Ala  Pro Leu Val Asp Leu  Thr Pro Thr His Ser  Gly Ser Ala
    1055                1060                1065

Met Leu  Met Leu Leu Ser Val  Val Phe Val Gly Leu  Ala Val Phe
    1070                1075                1080

Val Ile  Tyr Lys Phe Lys Arg  Gly Trp Arg Asp Arg  Ser Ala Val
    1085                1090                1095

Lys Asn  Ile Gly Cys Ser Cys  Arg Gly Pro Gly Phe  Asn Ser Gln
    1100                1105                1110

His Gln  Gln Gly Gly Ser Gln  Ala Ser Val Thr Ser  Val Pro Arg
    1115                1120                1125

Asp Pro  Ser Pro Ser Ser Asp  Leu His Gly His Gln  Glu His Thr
    1130                1135                1140

Trp Cys  Thr Asp Ile His Pro  Gly Lys Thr Pro Ile  His Ile Lys
    1145                1150                1155
```

<210> 27

<211> 1066

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

<222> (1)..(1066)

<223> Soluble proSorCS1

<400> 27

```
Ser Leu Ser Cys Cys Pro Pro Gln His Pro Ser Ser Thr Pro Arg Arg
1               5                  10                  15

Thr Leu Thr Pro Arg Gly Phe Pro His Pro Gly Pro Leu Gly Arg Ala
            20                  25                  30

Pro Ala Thr Pro Pro Pro Leu Phe Met Arg Pro Leu Phe Ala Val Ala
        35                  40                  45

Pro Gly Asp Arg Ala Leu Phe Leu Glu Arg Ala Gly Gly Ser Arg Val
    50                  55                  60

Ser Val Ala Thr Ala Ala Arg Ser Gly Arg Arg Arg Arg Ser Gly Thr
65                  70                  75                  80

Glu Pro Glu Lys Ile Glu Pro Gly Glu Gly Ala Ser Arg Ser Arg Arg
                85                  90                  95

Asp Met Leu Lys Asp Gly Gly Gln Gln Gly Leu Gly Thr Gly Ala Arg
            100                 105                 110

Asp Pro Gly Lys Ala Thr Arg Phe Arg Met Glu Glu Leu Arg Leu Thr
        115                 120                 125

Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala Met
    130                 135                 140

Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile Leu Thr Lys
145                 150                 155                 160

Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp Arg
                165                 170                 175

Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Val Gly
            180                 185                 190

Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys Cys
        195                 200                 205
```

```
Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser Leu Leu Ile
    210                 215                 220

Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe Tyr
225                 230                 235                 240

Leu Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu Ala
                245                 250                 255

Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe Gly Arg Arg
            260                 265                 270

Trp Gln Leu Ile Gln Glu Ser Val Val Pro Asn Arg Phe Tyr Trp Ser
        275                 280                 285

Val Met Gly Ser Ser Lys Glu Pro Asp Leu Val His Leu Glu Ala Arg
    290                 295                 300

Thr Val Asp Gly His Ser Ile Tyr Leu Thr Cys Arg Met Gln Asn Cys
305                 310                 315                 320

Thr Glu Ala Asn Arg Asn Lys Pro Phe Pro Gly Tyr Ile Asp Pro Asp
                325                 330                 335

Ser Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu Thr Ser Gly
            340                 345                 350

Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Ser Pro Phe Ala Gln
        355                 360                 365

Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His Val Ile Ser
    370                 375                 380

Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln Asn
385                 390                 395                 400

Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe Thr
                405                 410                 415

Leu Ala Leu Glu Asn Val Arg Ser Ser Arg Gly Pro Glu Gly Asn Val
            420                 425                 430

Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu Ala
        435                 440                 445

Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn Lys
    450                 455                 460

Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Ala Asp Leu Arg Gly
```

```
465                 470                 475                 480

Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His Leu His Leu
                485                 490                 495

Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala Ser Arg Asp
            500                 505                 510

Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Ser Glu Leu
        515                 520                 525

Ser Asp Ser Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn Thr
    530                 535                 540

Trp Arg Gln Ile Phe Glu Glu Glu His Ser Ile Leu Tyr Leu Asp Gln
545                 550                 555                 560

Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro Ile Arg His
                565                 570                 575

Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr Ser Phe
            580                 585                 590

Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu Pro Gly Glu
        595                 600                 605

Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg Ser Glu
    610                 615                 620

Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp Arg Arg Cys
625                 630                 635                 640

Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln Gly Glu Ala
                645                 650                 655

Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu Arg
            660                 665                 670

Lys Cys Met Gln Lys Tyr Ala Gly Ala Met Glu Ser Glu Pro Cys Val
        675                 680                 685

Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg His Ser
    690                 695                 700

Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser Leu Ser
705                 710                 715                 720

Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Ala Gly Tyr Arg
                725                 730                 735
```

```
Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln Tyr Thr
            740                 745                 750

Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu Arg Ile
        755                 760                 765

Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn Val Thr
    770                 775                 780

Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr Leu Ile Gln
785                 790                 795                 800

Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu Ser Ser
                805                 810                 815

Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly Ile Phe Arg
            820                 825                 830

Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala Val Leu
        835                 840                 845

Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser Leu Pro
    850                 855                 860

Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val Leu Trp
865                 870                 875                 880

Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly Asn Asn
                885                 890                 895

Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe Lys Phe Thr
            900                 905                 910

Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly Asn Ala
        915                 920                 925

Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe Arg Ser
    930                 935                 940

Leu Arg Leu Ala Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro Asp Ile
945                 950                 955                 960

Pro Glu Trp Arg Arg Asp Ile Ser Arg Val Ile Lys Lys Ser Leu Val
                965                 970                 975

Glu Ala Thr Gly Ile Pro Ser Gln His Ile Leu Val Ala Val Leu Pro
            980                 985                 990

Gly Leu Pro Thr Ala Ala Glu Leu  Phe Val Leu Pro Tyr  Gln Asp Gly
        995                 1000                1005

Thr Arg  Glu Asn Lys Arg Ser  Pro Glu Asp Leu Glu  Gln Ile Ser
    1010                1015                1020

Glu Val  Leu Ile His Lys Leu  Asn Gln Asn Leu Val  His Phe Glu
    1025                1030                1035

Leu Lys  Pro Gly Val Gln Val  Leu Val His Ala Ala  His Leu Thr
    1040                1045                1050

Ala Ala  Pro Leu Val Asp Leu  Thr Pro Thr His Ser  Gly
    1055                1060                1065
```

<210> 28

<211> 1057

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

<222> (1)..(1057)

<223> mature SorCS1b, isoform 1

<400> 28

```
Ser Gly Thr Glu Pro Glu Lys Ile Glu Pro Gly Glu Gly Ala Ser Arg
1               5                  10                  15

Ser Arg Arg Asp Met Leu Lys Asp Gly Gly Gln Gln Gly Leu Gly Thr
            20                  25                  30

Gly Ala Arg Asp Pro Gly Lys Ala Thr Arg Phe Arg Met Glu Glu Leu
        35                  40                  45

Arg Leu Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn
    50                  55                  60

Gln Ala Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile
65                  70                  75                  80

Leu Thr Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser
                85                  90                  95

Leu Trp Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp
            100                 105                 110

Lys Val Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr
        115                 120                 125

Asn Lys Cys Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser
    130                 135                 140

Leu Leu Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu
145                 150                 155                 160

Asn Phe Tyr Leu Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp
                165                 170                 175

Ile Leu Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe
            180                 185                 190

Gly Arg Arg Trp Gln Leu Ile Gln Glu Ser Val Val Pro Asn Arg Phe
        195                 200                 205

Tyr Trp Ser Val Met Gly Ser Ser Lys Glu Pro Asp Leu Val His Leu
    210                 215                 220

Glu Ala Arg Thr Val Asp Gly His Ser Ile Tyr Leu Thr Cys Arg Met
225                 230                 235                 240

Gln Asn Cys Thr Glu Ala Asn Arg Asn Lys Pro Phe Pro Gly Tyr Ile
                245                 250                 255

Asp Pro Asp Ser Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu
            260                 265                 270

Thr Ser Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Ser Pro
        275                 280                 285

Phe Ala Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His
    290                 295                 300

Val Ile Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp
305                 310                 315                 320

Asn Gln Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val
                325                 330                 335

Tyr Phe Thr Leu Ala Leu Glu Asn Val Arg Ser Ser Arg Gly Pro Glu
            340                 345                 350

Gly Asn Val Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met
        355                 360                 365

Phe Leu Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr
    370                 375                 380
```

```
Tyr Asn Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Ala Asp
385                 390                 395                 400

Leu Arg Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His
                405                 410                 415

Leu His Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala
            420                 425                 430

Ser Arg Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly
        435                 440                 445

Ser Glu Leu Ser Asp Ser Asp Ile Ser Met Phe Val Ser Ser Asp Ala
    450                 455                 460

Gly Asn Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Ile Leu Tyr
465                 470                 475                 480

Leu Asp Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro
                485                 490                 495

Ile Arg His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys
            500                 505                 510

Tyr Ser Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu
        515                 520                 525

Pro Gly Glu Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His
    530                 535                 540

Arg Ser Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp
545                 550                 555                 560

Arg Arg Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln
                565                 570                 575

Gly Glu Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys
            580                 585                 590

Ser Glu Arg Lys Cys Met Gln Lys Tyr Ala Gly Ala Met Glu Ser Glu
        595                 600                 605

Pro Cys Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu
    610                 615                 620

Arg His Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser
625                 630                 635                 640

Ser Leu Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Ala
```

```
                645                 650                 655

Gly Tyr Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu
            660                 665                 670

Gln Tyr Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly
        675                 680                 685

Leu Arg Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His
    690                 695                 700

Asn Val Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr
705                 710                 715                 720

Leu Ile Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn
                725                 730                 735

Leu Ser Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly
            740                 745                 750

Ile Phe Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser
        755                 760                 765

Ala Val Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu
    770                 775                 780

Ser Leu Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala
785                 790                 795                 800

Val Leu Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr
                805                 810                 815

Gly Asn Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe
            820                 825                 830

Lys Phe Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala
        835                 840                 845

Gly Asn Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu
    850                 855                 860

Phe Arg Ser Leu Arg Leu Ala Phe Ser Pro Asn Leu Asp Asp Tyr Asn
865                 870                 875                 880

Pro Asp Ile Pro Glu Trp Arg Arg Asp Ile Ser Arg Val Ile Lys Lys
                885                 890                 895

Ser Leu Val Glu Ala Thr Gly Ile Pro Ser Gln His Ile Leu Val Ala
            900                 905                 910
```

```
Val Leu Pro Gly Leu Pro Thr Ala Ala Glu Leu Phe Val Leu Pro Tyr
        915                 920                 925

Gln Asp Gly Thr Arg Glu Asn Lys Arg Ser Pro Glu Asp Leu Glu Gln
    930                 935                 940

Ile Ser Glu Val Leu Ile His Lys Leu Asn Gln Asn Leu Val His Phe
945                 950                 955                 960

Glu Leu Lys Pro Gly Val Gln Val Leu Val His Ala Ala His Leu Thr
                965                 970                 975

Ala Ala Pro Leu Val Asp Leu Thr Pro Thr His Ser Gly Ser Ala Met
            980                 985                 990

Leu Met Leu Leu Ser Val Val Phe  Val Gly Leu Ala Val  Phe Val Ile
        995                 1000                1005

Tyr Lys  Phe Lys Arg Arg Val  Ala Leu Pro Ser Pro  Pro Ser Pro
    1010                1015                1020

Ser Ala  Gln Pro Gly Asp Ser  Ser Leu Arg Leu Gln  Arg Pro Arg
    1025                1030                1035

Pro Ala  Thr Pro Pro Ser Ser  Pro Lys Arg Gly Ser  Ala Gly Ala
    1040                1045                1050

Gln Phe  Ala Ile
    1055
```

<210> 29

<211> 1037

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

<222> (1)..(1037)

<223> mature SorCS1a, isoform 2

<400> 29

```
Ser Gly Thr Glu Pro Glu Lys Ile Glu Pro Gly Glu Gly Ala Ser Arg
1               5                   10                  15

Ser Arg Arg Asp Met Leu Lys Asp Gly Gly Gln Gln Gly Leu Gly Thr
            20                  25                  30

Gly Ala Arg Asp Pro Gly Lys Ala Thr Arg Phe Arg Met Glu Glu Leu
        35                  40                  45
```

```
Arg Leu Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn
    50                  55                  60

Gln Ala Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile
65                  70                  75                  80

Leu Thr Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser
                85                  90                  95

Leu Trp Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp
            100                 105                 110

Lys Val Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr
        115                 120                 125

Asn Lys Cys Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser
    130                 135                 140

Leu Leu Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu
145                 150                 155                 160

Asn Phe Tyr Leu Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp
                165                 170                 175

Ile Leu Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe
            180                 185                 190

Gly Arg Arg Trp Gln Leu Ile Gln Glu Ser Val Val Pro Asn Arg Phe
        195                 200                 205

Tyr Trp Ser Val Met Gly Ser Ser Lys Glu Pro Asp Leu Val His Leu
    210                 215                 220

Glu Ala Arg Thr Val Asp Gly His Ser Ile Tyr Leu Thr Cys Arg Met
225                 230                 235                 240

Gln Asn Cys Thr Glu Ala Asn Arg Asn Lys Pro Phe Pro Gly Tyr Ile
                245                 250                 255

Asp Pro Asp Ser Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu
            260                 265                 270

Thr Ser Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Ser Pro
        275                 280                 285

Phe Ala Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His
    290                 295                 300
```

```
Val Ile Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp
305                 310                 315                 320

Asn Gln Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val
                325                 330                 335

Tyr Phe Thr Leu Ala Leu Glu Asn Val Arg Ser Ser Arg Gly Pro Glu
            340                 345                 350

Gly Asn Val Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met
        355                 360                 365

Phe Leu Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr
    370                 375                 380

Tyr Asn Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Ala Asp
385                 390                 395                 400

Leu Arg Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His
                405                 410                 415

Leu His Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala
            420                 425                 430

Ser Arg Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly
        435                 440                 445

Ser Glu Leu Ser Asp Ser Asp Ile Ser Met Phe Val Ser Ser Asp Ala
    450                 455                 460

Gly Asn Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Ile Leu Tyr
465                 470                 475                 480

Leu Asp Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro
                485                 490                 495

Ile Arg His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys
            500                 505                 510

Tyr Ser Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu
        515                 520                 525

Pro Gly Glu Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His
    530                 535                 540

Arg Ser Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp
545                 550                 555                 560
```

```
Arg Arg Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln
                565                 570                 575

Gly Glu Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys
            580                 585                 590

Ser Glu Arg Lys Cys Met Gln Lys Tyr Ala Gly Ala Met Glu Ser Glu
        595                 600                 605

Pro Cys Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu
    610                 615                 620

Arg His Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser
625                 630                 635                 640

Ser Leu Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Ala
                645                 650                 655

Gly Tyr Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu
            660                 665                 670

Gln Tyr Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly
        675                 680                 685

Leu Arg Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His
    690                 695                 700

Asn Val Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr
705                 710                 715                 720

Leu Ile Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn
                725                 730                 735

Leu Ser Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly
            740                 745                 750

Ile Phe Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser
        755                 760                 765

Ala Val Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu
    770                 775                 780

Ser Leu Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala
785                 790                 795                 800

Val Leu Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr
                805                 810                 815

Gly Asn Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe
```

```
            820                 825                 830

Lys Phe Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala
        835                 840                 845

Gly Asn Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu
    850                 855                 860

Phe Arg Ser Leu Arg Leu Ala Phe Ser Pro Asn Leu Asp Asp Tyr Asn
865                 870                 875                 880

Pro Asp Ile Pro Glu Trp Arg Arg Asp Ile Ser Arg Val Ile Lys Lys
                885                 890                 895

Ser Leu Val Glu Ala Thr Gly Ile Pro Ser Gln His Ile Leu Val Ala
            900                 905                 910

Val Leu Pro Gly Leu Pro Thr Ala Ala Glu Leu Phe Val Leu Pro Tyr
        915                 920                 925

Gln Asp Gly Thr Arg Glu Asn Lys Arg Ser Pro Glu Asp Leu Glu Gln
    930                 935                 940

Ile Ser Glu Val Leu Ile His Lys Leu Asn Gln Asn Leu Val His Phe
945                 950                 955                 960

Glu Leu Lys Pro Gly Val Gln Val Leu Val His Ala Ala His Leu Thr
                965                 970                 975

Ala Ala Pro Leu Val Asp Leu Thr Pro Thr His Ser Gly Ser Ala Met
            980                 985                 990

Leu Met Leu Leu Ser Val Val Phe  Val Gly Leu Ala Val  Phe Val Ile
        995                 1000                1005

Tyr Lys  Phe Lys Arg Cys Val  Phe Leu Leu Leu Pro  Ser Tyr Pro
    1010                1015                1020

Arg Pro  Pro Pro Pro Ser Ser  Phe Cys Gln Val Gln  Lys Gln
    1025                1030                1035
```

<210> 30

<211> 1068

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

<222> (1)..(1068)

<223> mature SorCS1c, isoform 3

<400> 30

```
Ser Gly Thr Glu Pro Glu Lys Ile Glu Pro Gly Glu Gly Ala Ser Arg
1               5                  10                  15

Ser Arg Arg Asp Met Leu Lys Asp Gly Gly Gln Gln Gly Leu Gly Thr
            20                  25                  30

Gly Ala Arg Asp Pro Gly Lys Ala Thr Arg Phe Arg Met Glu Glu Leu
        35                  40                  45

Arg Leu Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn
    50                  55                  60

Gln Ala Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile
65                  70                  75                  80

Leu Thr Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser
                85                  90                  95

Leu Trp Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp
            100                 105                 110

Lys Val Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr
        115                 120                 125

Asn Lys Cys Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser
    130                 135                 140

Leu Leu Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu
145                 150                 155                 160

Asn Phe Tyr Leu Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp
                165                 170                 175

Ile Leu Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe
            180                 185                 190

Gly Arg Arg Trp Gln Leu Ile Gln Glu Ser Val Val Pro Asn Arg Phe
        195                 200                 205

Tyr Trp Ser Val Met Gly Ser Ser Lys Glu Pro Asp Leu Val His Leu
    210                 215                 220

Glu Ala Arg Thr Val Asp Gly His Ser Ile Tyr Leu Thr Cys Arg Met
225                 230                 235                 240

Gln Asn Cys Thr Glu Ala Asn Arg Asn Lys Pro Phe Pro Gly Tyr Ile
                245                 250                 255
```

```
Asp Pro Asp Ser Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu
            260                 265                 270

Thr Ser Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Ser Pro
        275                 280                 285

Phe Ala Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His
    290                 295                 300

Val Ile Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp
305                 310                 315                 320

Asn Gln Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val
                325                 330                 335

Tyr Phe Thr Leu Ala Leu Glu Asn Val Arg Ser Ser Arg Gly Pro Glu
            340                 345                 350

Gly Asn Val Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met
        355                 360                 365

Phe Leu Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr
    370                 375                 380

Tyr Asn Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Ala Asp
385                 390                 395                 400

Leu Arg Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His
                405                 410                 415

Leu His Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala
            420                 425                 430

Ser Arg Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly
        435                 440                 445

Ser Glu Leu Ser Asp Ser Asp Ile Ser Met Phe Val Ser Ser Asp Ala
    450                 455                 460

Gly Asn Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Ile Leu Tyr
465                 470                 475                 480

Leu Asp Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro
                485                 490                 495

Ile Arg His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys
            500                 505                 510
```

```
Tyr Ser Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu
        515                 520                 525

Pro Gly Glu Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His
    530                 535                 540

Arg Ser Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp
545                 550                 555                 560

Arg Arg Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln
                565                 570                 575

Gly Glu Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys
            580                 585                 590

Ser Glu Arg Lys Cys Met Gln Lys Tyr Ala Gly Ala Met Glu Ser Glu
        595                 600                 605

Pro Cys Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu
    610                 615                 620

Arg His Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser
625                 630                 635                 640

Ser Leu Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Ala
                645                 650                 655

Gly Tyr Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu
            660                 665                 670

Gln Tyr Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly
        675                 680                 685

Leu Arg Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His
    690                 695                 700

Asn Val Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr
705                 710                 715                 720

Leu Ile Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn
                725                 730                 735

Leu Ser Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly
            740                 745                 750

Ile Phe Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser
        755                 760                 765
```

```
Ala Val Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu
    770                 775                 780

Ser Leu Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala
785                 790                 795                 800

Val Leu Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr
                805                 810                 815

Gly Asn Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe
            820                 825                 830

Lys Phe Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala
        835                 840                 845

Gly Asn Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu
    850                 855                 860

Phe Arg Ser Leu Arg Leu Ala Phe Ser Pro Asn Leu Asp Asp Tyr Asn
865                 870                 875                 880

Pro Asp Ile Pro Glu Trp Arg Arg Asp Ile Ser Arg Val Ile Lys Lys
                885                 890                 895

Ser Leu Val Glu Ala Thr Gly Ile Pro Ser Gln His Ile Leu Val Ala
            900                 905                 910

Val Leu Pro Gly Leu Pro Thr Ala Ala Glu Leu Phe Val Leu Pro Tyr
        915                 920                 925

Gln Asp Gly Thr Arg Glu Asn Lys Arg Ser Pro Glu Asp Leu Glu Gln
    930                 935                 940

Ile Ser Glu Val Leu Ile His Lys Leu Asn Gln Asn Leu Val His Phe
945                 950                 955                 960

Glu Leu Lys Pro Gly Val Gln Val Leu Val His Ala Ala His Leu Thr
                965                 970                 975

Ala Ala Pro Leu Val Asp Leu Thr Pro Thr His Ser Gly Ser Ala Met
            980                 985                 990

Leu Met Leu Leu Ser Val Val Phe  Val Gly Leu Ala Val  Phe Val Ile
        995                 1000                1005

Tyr Lys  Phe Lys Arg Lys Ile  Pro Gly Ile Asn Val  Tyr Ala Gln
    1010                1015                1020

Met Gln  Asn Glu Lys Glu Gln  Glu Leu Ile Asn Pro  Val Ser His

    1025                1030                1035

Ser Glu  Ser Arg Pro Ser Val  Pro His Pro Asp Leu  Arg Arg Pro
    1040                1045                1050

Gly Gln  Leu Val Asp Glu Lys  Val Glu Ser Gln Leu  Leu Gly Lys
    1055                1060                1065
```

<210> 31

<211> 1068

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

<222> (1)..(1068)

<223> mature SorCS1c+, isoform 4

<400> 31

```
Ser Gly Thr Glu Pro Glu Lys Ile Glu Pro Gly Glu Gly Ala Ser Arg
1               5                  10                  15

Ser Arg Arg Asp Met Leu Lys Asp Gly Gly Gln Gln Gly Leu Gly Thr
            20                  25                  30

Gly Ala Arg Asp Pro Gly Lys Ala Thr Arg Phe Arg Met Glu Glu Leu
        35                  40                  45

Arg Leu Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn
    50                  55                  60

Gln Ala Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile
65                  70                  75                  80

Leu Thr Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser
                85                  90                  95

Leu Trp Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp
            100                 105                 110

Lys Val Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr
        115                 120                 125

Asn Lys Cys Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser
    130                 135                 140

Leu Leu Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu
145                 150                 155                 160

Asn Phe Tyr Leu Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp
```

```
                165                 170                 175

Ile Leu Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe
            180                 185                 190

Gly Arg Arg Trp Gln Leu Ile Gln Glu Ser Val Val Pro Asn Arg Phe
        195                 200                 205

Tyr Trp Ser Val Met Gly Ser Ser Lys Glu Pro Asp Leu Val His Leu
    210                 215                 220

Glu Ala Arg Thr Val Asp Gly His Ser Ile Tyr Leu Thr Cys Arg Met
225                 230                 235                 240

Gln Asn Cys Thr Glu Ala Asn Arg Asn Lys Pro Phe Pro Gly Tyr Ile
                245                 250                 255

Asp Pro Asp Ser Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu
            260                 265                 270

Thr Ser Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Ser Pro
        275                 280                 285

Phe Ala Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His
    290                 295                 300

Val Ile Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp
305                 310                 315                 320

Asn Gln Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val
                325                 330                 335

Tyr Phe Thr Leu Ala Leu Glu Asn Val Arg Ser Ser Arg Gly Pro Glu
            340                 345                 350

Gly Asn Val Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met
        355                 360                 365

Phe Leu Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr
    370                 375                 380

Tyr Asn Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Ala Asp
385                 390                 395                 400

Leu Arg Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His
                405                 410                 415

Leu His Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala
            420                 425                 430
```

```
Ser Arg Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly
        435                 440                 445

Ser Glu Leu Ser Asp Ser Asp Ile Ser Met Phe Val Ser Ser Asp Ala
    450                 455                 460

Gly Asn Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Ile Leu Tyr
465                 470                 475                 480

Leu Asp Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro
                485                 490                 495

Ile Arg His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys
            500                 505                 510

Tyr Ser Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu
        515                 520                 525

Pro Gly Glu Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His
    530                 535                 540

Arg Ser Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp
545                 550                 555                 560

Arg Arg Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln
                565                 570                 575

Gly Glu Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys
            580                 585                 590

Ser Glu Arg Lys Cys Met Gln Lys Tyr Ala Gly Ala Met Glu Ser Glu
        595                 600                 605

Pro Cys Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu
    610                 615                 620

Arg His Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser
625                 630                 635                 640

Ser Leu Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Ala
                645                 650                 655

Gly Tyr Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu
            660                 665                 670

Gln Tyr Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly
        675                 680                 685
```

```
Leu Arg Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His
    690                 695                 700

Asn Val Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr
705                 710                 715                 720

Leu Ile Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn
                725                 730                 735

Leu Ser Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly
            740                 745                 750

Ile Phe Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser
        755                 760                 765

Ala Val Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu
    770                 775                 780

Ser Leu Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala
785                 790                 795                 800

Val Leu Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr
                805                 810                 815

Gly Asn Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe
            820                 825                 830

Lys Phe Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala
        835                 840                 845

Gly Asn Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu
    850                 855                 860

Phe Arg Ser Leu Arg Leu Ala Phe Ser Pro Asn Leu Asp Asp Tyr Asn
865                 870                 875                 880

Pro Asp Ile Pro Glu Trp Arg Arg Asp Ile Ser Arg Val Ile Lys Lys
                885                 890                 895

Ser Leu Val Glu Ala Thr Gly Ile Pro Ser Gln His Ile Leu Val Ala
            900                 905                 910

Val Leu Pro Gly Leu Pro Thr Ala Ala Glu Leu Phe Val Leu Pro Tyr
        915                 920                 925

Gln Asp Gly Thr Arg Glu Asn Lys Arg Ser Pro Glu Asp Leu Glu Gln
    930                 935                 940

Ile Ser Glu Val Leu Ile His Lys Leu Asn Gln Asn Leu Val His Phe
945                 950                 955                 960

Glu Leu Lys Pro Gly Val Gln Val Leu Val His Ala Ala His Leu Thr
                965                 970                 975

Ala Ala Pro Leu Val Asp Leu Thr Pro Thr His Ser Gly Ser Ala Met
            980                 985                 990

Leu Met Leu Leu Ser Val Val Phe  Val Gly Leu Ala Val  Phe Val Ile
        995                 1000                1005

Tyr Lys  Phe Lys Arg Lys Ile  Pro Gly Ile Asn Val  Tyr Ala Gln
    1010                1015                1020

Met Gln  Asn Glu Lys Glu Gln  Glu Leu Ile Asn Pro  Val Ser His
    1025                1030                1035

Ser Glu  Ser Arg Ser Ser Val  Pro His Pro Asp Leu  Arg Arg Pro
    1040                1045                1050

Gly Gln  Leu Val Asp Glu Lys  Val Glu Ser Gln Leu  Leu Gly Glu
    1055                1060                1065
```

<210> 32

<211> 1081

<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(1081)
<223> mature SorCS1d

<400> 32

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Ser Gly Thr Glu Pro Glu Lys Ile Glu Pro Gly Glu Gly Ala Ser Arg
1               5                   10                  15

Ser Arg Arg Asp Met Leu Lys Asp Gly Gly Gln Gln Gly Leu Gly Thr
            20                  25                  30

Gly Ala Arg Asp Pro Gly Lys Ala Thr Arg Phe Arg Met Glu Glu Leu
        35                  40                  45

Arg Leu Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn
    50                  55                  60

Gln Ala Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile
65                  70                  75                  80

Leu Thr Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser
                85                  90                  95

Leu Trp Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp
            100                 105                 110

Lys Val Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr
        115                 120                 125

Asn Lys Cys Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser
    130                 135                 140

Leu Leu Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu
145                 150                 155                 160

Asn Phe Tyr Leu Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp
                165                 170                 175

Ile Leu Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe
            180                 185                 190

Gly Arg Arg Trp Gln Leu Ile Gln Glu Ser Val Val Pro Asn Arg Phe
        195                 200                 205

Tyr Trp Ser Val Met Gly Ser Ser Lys Glu Pro Asp Leu Val His Leu
    210                 215                 220

Glu Ala Arg Thr Val Asp Gly His Ser Ile Tyr Leu Thr Cys Arg Met
225                 230                 235                 240

Gln Asn Cys Thr Glu Ala Asn Arg Asn Lys Pro Phe Pro Gly Tyr Ile
                245                 250                 255

Asp Pro Asp Ser Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu
            260                 265                 270

Thr Ser Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Ser Pro
        275                 280                 285

Phe Ala Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His
    290                 295                 300

Val Ile Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp
305                 310                 315                 320

Asn Gln Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val
                325                 330                 335

Tyr Phe Thr Leu Ala Leu Glu Asn Val Arg Ser Ser Arg Gly Pro Glu
```

```
            340                 345                 350

Gly Asn Val Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met
        355                 360                 365

Phe Leu Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr
    370                 375                 380

Tyr Asn Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Ala Asp
385                 390                 395                 400

Leu Arg Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His
                405                 410                 415

Leu His Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala
            420                 425                 430

Ser Arg Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly
        435                 440                 445

Ser Glu Leu Ser Asp Ser Asp Ile Ser Met Phe Val Ser Ser Asp Ala
    450                 455                 460

Gly Asn Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Ile Leu Tyr
465                 470                 475                 480

Leu Asp Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro
                485                 490                 495

Ile Arg His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys
            500                 505                 510

Tyr Ser Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu
        515                 520                 525

Pro Gly Glu Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His
    530                 535                 540

Arg Ser Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp
545                 550                 555                 560

Arg Arg Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln
                565                 570                 575

Gly Glu Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys
            580                 585                 590

Ser Glu Arg Lys Cys Met Gln Lys Tyr Ala Gly Ala Met Glu Ser Glu
        595                 600                 605
```

```
Pro Cys Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu
    610                 615                 620

Arg His Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser
625                 630                 635                 640

Ser Leu Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Ala
                645                 650                 655

Gly Tyr Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu
            660                 665                 670

Gln Tyr Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly
        675                 680                 685

Leu Arg Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His
    690                 695                 700

Asn Val Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr
705                 710                 715                 720

Leu Ile Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn
                725                 730                 735

Leu Ser Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly
            740                 745                 750

Ile Phe Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser
        755                 760                 765

Ala Val Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu
    770                 775                 780

Ser Leu Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala
785                 790                 795                 800

Val Leu Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr
                805                 810                 815

Gly Asn Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe
            820                 825                 830

Lys Phe Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala
        835                 840                 845

Gly Asn Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu
    850                 855                 860
```

```
Phe Arg Ser Leu Arg Leu Ala Phe Ser Pro Asn Leu Asp Asp Tyr Asn
865                 870                 875                 880

Pro Asp Ile Pro Glu Trp Arg Arg Asp Ile Ser Arg Val Ile Lys Lys
                885                 890                 895

Ser Leu Val Glu Ala Thr Gly Ile Pro Ser Gln His Ile Leu Val Ala
            900                 905                 910

Val Leu Pro Gly Leu Pro Thr Ala Ala Glu Leu Phe Val Leu Pro Tyr
        915                 920                 925

Gln Asp Gly Thr Arg Glu Asn Lys Arg Ser Pro Glu Asp Leu Glu Gln
    930                 935                 940

Ile Ser Glu Val Leu Ile His Lys Leu Asn Gln Asn Leu Val His Phe
945                 950                 955                 960

Glu Leu Lys Pro Gly Val Gln Val Leu Val His Ala Ala His Leu Thr
                965                 970                 975

Ala Ala Pro Leu Val Asp Leu Thr Pro Thr His Ser Gly Ser Ala Met
            980                 985                 990

Leu Met Leu Leu Ser Val Val Phe  Val Gly Leu Ala Val  Phe Val Ile
        995                 1000                1005

Tyr Lys  Phe Lys Arg Gly Trp  Arg Asp Arg Ser Ala  Val Lys Asn
    1010                1015                1020

Ile Gly  Cys Ser Cys Arg Gly  Pro Gly Phe Asn Ser  Gln His Gln
    1025                1030                1035

Gln Gly  Gly Ser Gln Ala Ser  Val Thr Ser Val Pro  Arg Asp Pro
    1040                1045                1050

Ser Pro  Ser Ser Asp Leu His  Gly His Gln Glu His  Thr Trp Cys
    1055                1060                1065

Thr Asp  Ile His Pro Gly Lys  Thr Pro Ile His Ile  Lys
    1070                1075                1080
```

<210> 33

<211> 989

<212> PRT

<213> Mus musculus

<220>

<221> MISC_FEATURE

<222> (1)..(989)

<223> Soluble mature SorCS1

<400> 33

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Ser Gly Thr Glu Pro Glu Lys Ile Glu Pro Gly Glu Gly Ala Ser Arg
1               5                  10                  15

Ser Arg Arg Asp Met Leu Lys Asp Gly Gly Gln Gln Gly Leu Gly Thr
            20                  25                  30

Gly Ala Arg Asp Pro Gly Lys Ala Thr Arg Phe Arg Met Glu Glu Leu
        35                  40                  45

Arg Leu Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn
    50                  55                  60

Gln Ala Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile
65                  70                  75                  80

Leu Thr Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser
                85                  90                  95

Leu Trp Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp
            100                 105                 110

Lys Val Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr
        115                 120                 125

Asn Lys Cys Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser
    130                 135                 140

Leu Leu Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu
145                 150                 155                 160

Asn Phe Tyr Leu Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp
                165                 170                 175

Ile Leu Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe
            180                 185                 190

Gly Arg Arg Trp Gln Leu Ile Gln Glu Ser Val Val Pro Asn Arg Phe
        195                 200                 205

Tyr Trp Ser Val Met Gly Ser Ser Lys Glu Pro Asp Leu Val His Leu
    210                 215                 220

Glu Ala Arg Thr Val Asp Gly His Ser Ile Tyr Leu Thr Cys Arg Met
225                 230                 235                 240
```

```
Gln Asn Cys Thr Glu Ala Asn Arg Asn Lys Pro Phe Pro Gly Tyr Ile
                245                 250                 255

Asp Pro Asp Ser Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu
            260                 265                 270

Thr Ser Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Ser Pro
        275                 280                 285

Phe Ala Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His
    290                 295                 300

Val Ile Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp
305                 310                 315                 320

Asn Gln Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val
                325                 330                 335

Tyr Phe Thr Leu Ala Leu Glu Asn Val Arg Ser Ser Arg Gly Pro Glu
            340                 345                 350

Gly Asn Val Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met
        355                 360                 365

Phe Leu Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr
    370                 375                 380

Tyr Asn Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Ala Asp
385                 390                 395                 400

Leu Arg Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His
                405                 410                 415

Leu His Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala
            420                 425                 430

Ser Arg Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly
        435                 440                 445

Ser Glu Leu Ser Asp Ser Asp Ile Ser Met Phe Val Ser Ser Asp Ala
    450                 455                 460

Gly Asn Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Ile Leu Tyr
465                 470                 475                 480

Leu Asp Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro
                485                 490                 495

Ile Arg His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys
```

```
           500                 505                 510

Tyr Ser Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu
        515                 520                 525

Pro Gly Glu Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His
    530                 535                 540

Arg Ser Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp
545                 550                 555                 560

Arg Arg Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln
                565                 570                 575

Gly Glu Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys
            580                 585                 590

Ser Glu Arg Lys Cys Met Gln Lys Tyr Ala Gly Ala Met Glu Ser Glu
        595                 600                 605

Pro Cys Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu
    610                 615                 620

Arg His Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser
625                 630                 635                 640

Ser Leu Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Ala
                645                 650                 655

Gly Tyr Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu
            660                 665                 670

Gln Tyr Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly
        675                 680                 685

Leu Arg Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His
    690                 695                 700

Asn Val Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr
705                 710                 715                 720

Leu Ile Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn
                725                 730                 735

Leu Ser Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly
            740                 745                 750

Ile Phe Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser
        755                 760                 765
```

```
Ala Val Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu
    770                 775                 780

Ser Leu Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala
785                 790                 795                 800

Val Leu Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr
                805                 810                 815

Gly Asn Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe
            820                 825                 830

Lys Phe Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala
        835                 840                 845

Gly Asn Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu
    850                 855                 860

Phe Arg Ser Leu Arg Leu Ala Phe Ser Pro Asn Leu Asp Asp Tyr Asn
865                 870                 875                 880

Pro Asp Ile Pro Glu Trp Arg Arg Asp Ile Ser Arg Val Ile Lys Lys
                885                 890                 895

Ser Leu Val Glu Ala Thr Gly Ile Pro Ser Gln His Ile Leu Val Ala
            900                 905                 910

Val Leu Pro Gly Leu Pro Thr Ala Ala Glu Leu Phe Val Leu Pro Tyr
        915                 920                 925

Gln Asp Gly Thr Arg Glu Asn Lys Arg Ser Pro Glu Asp Leu Glu Gln
    930                 935                 940

Ile Ser Glu Val Leu Ile His Lys Leu Asn Gln Asn Leu Val His Phe
945                 950                 955                 960

Glu Leu Lys Pro Gly Val Gln Val Leu Val His Ala Ala His Leu Thr
                965                 970                 975

Ala Ala Pro Leu Val Asp Leu Thr Pro Thr His Ser Gly
            980                 985
```

<210> 34

<211> 1361

<212> PRT

<213> Pan troglodytes

<220>

<221> MISC_FEATURE

<222> (1)..(1361)

<223> preproSorCS1

<400> 34

```
Met Thr Gly Arg Phe Pro Pro Arg Asn Arg Lys Leu Pro Thr His Arg
1               5                   10                  15

Pro Leu Arg Glu Pro Gly Val Asp Arg Pro Arg Gly Gln Gly Ala Arg
            20                  25                  30

Thr Gln Arg Trp Asp Pro Arg Pro Arg Gly Arg Arg Val Gly Gly Gly
        35                  40                  45

Glu Arg Arg Gly Glu Ala Ala Ala Ala Pro Ala Arg Pro Arg Gly Ser
    50                  55                  60

Arg Arg Arg Arg Leu Gln Arg Pro Glu Thr Arg Ala Arg Ala Arg Ser
65                  70                  75                  80

Ala Ser Asp Phe Ser Ser Ala Pro Pro Pro Arg Gly Gly Gly Ser Leu
                85                  90                  95

Arg Pro Asp Pro Arg Ser Ala Gln Ala Gln Pro Gly Arg Ala Ala Ala
            100                 105                 110

Thr Cys Pro Ala Pro Pro Pro Pro Ala Pro Thr Ala Ala Gln Leu Gly
        115                 120                 125

Trp Ser Trp Gly Pro Glu Arg Arg Pro Pro Thr Ala Ala Ser Ala Glu
    130                 135                 140

Leu Arg Ala Ala Thr Phe Val Leu Gly Pro Leu Ser Pro Leu Leu Phe
145                 150                 155                 160

Ala Pro Ala Met Gly Lys Val Gly Ala Gly Gly Gly Ser Gln Ala Arg
                165                 170                 175

Leu Ser Ala Leu Leu Ala Gly Ala Gly Leu Leu Val Leu Cys Ala Pro
            180                 185                 190

Gly Val Cys Gly Gly Gly Ser Cys Cys Pro Pro Pro His Pro Ser Ser
        195                 200                 205

Ala Pro Arg Ser Ala Ser Thr Pro Arg Gly Phe Ser His Gln Gly Arg
    210                 215                 220

Pro Gly Arg Ala Pro Ala Thr Pro Leu Pro Leu Val Val Arg Pro Leu
225                 230                 235                 240
```

```
Phe Ser Val Ala Pro Gly Asp Arg Ala Leu Ser Leu Glu Arg Ala Arg
                245                 250                 255

Gly Thr Gly Ala Ser Met Ala Val Ala Ala Arg Ser Gly Arg Arg Arg
            260                 265                 270

Arg Ser Gly Ala Asp Gln Glu Lys Ala Glu Arg Gly Glu Gly Ala Ser
        275                 280                 285

Arg Ser Pro Arg Gly Val Leu Arg Asp Gly Gly Gln Gln Glu Pro Gly
    290                 295                 300

Thr Leu Glu Arg Asp Pro Asp Lys Ala Thr Arg Phe Arg Met Glu Glu
305                 310                 315                 320

Leu Arg Leu Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His
                325                 330                 335

Asn Gln Ala Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu
            340                 345                 350

Ile Leu Thr Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser
        355                 360                 365

Ser Leu Trp Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn
    370                 375                 380

Asp Lys Val Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro
385                 390                 395                 400

Thr Asn Lys Arg Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser
                405                 410                 415

Ser Leu Leu Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg
            420                 425                 430

Leu Asn Phe Tyr Ile Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp
        435                 440                 445

Trp Ile Leu Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu
    450                 455                 460

Phe Gly Arg Arg Trp Gln Leu Ile Gln Glu Gly Val Val Pro Asn Arg
465                 470                 475                 480

Phe Tyr Trp Ser Val Met Gly Ser Asn Lys Glu Pro Asp Leu Val His
                485                 490                 495
```

```
Leu Glu Ala Arg Thr Val Asp Gly His Ser His Tyr Leu Thr Cys Arg
            500                 505                 510

Met Gln Asn Cys Thr Glu Ala Asn Arg Asn Gln Pro Phe Pro Gly Tyr
        515                 520                 525

Ile Asp Pro Asp Ser Leu Ile Val Gln Asp His Tyr Val Phe Val Gln
    530                 535                 540

Leu Thr Ser Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn
545                 550                 555                 560

Ala Phe Ala Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met
                565                 570                 575

His Val Ile Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu
            580                 585                 590

Trp Asn Gln Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly
        595                 600                 605

Val Tyr Phe Thr Leu Ala Leu Glu Asn Val Gln Ser Ser Arg Gly Pro
    610                 615                 620

Glu Gly Asn Ile Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly
625                 630                 635                 640

Met Phe Leu Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile
                645                 650                 655

Thr Tyr Asn Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Thr
            660                 665                 670

Asp Leu Arg Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu
        675                 680                 685

His Leu His Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile
    690                 695                 700

Ala Ser Lys Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile
705                 710                 715                 720

Gly Ser Glu Leu Ser Asp Thr Asp Ile Ser Met Phe Val Ser Ser Asp
                725                 730                 735

Ala Gly Asn Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Val Leu
            740                 745                 750

Tyr Leu Asp Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu
```

```
        755                 760                 765

Pro Ile Arg His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser
    770                 775                 780

Lys Tyr Ser Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly
785                 790                 795                 800

Glu Pro Gly Glu Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser
                805                 810                 815

His Arg Ser Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe
            820                 825                 830

Asp Arg Arg Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser
        835                 840                 845

Gln Gly Glu Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg
    850                 855                 860

Lys Ser Glu Arg Lys Cys Met Gln Gly Lys Tyr Ala Gly Ala Met Glu
865                 870                 875                 880

Ser Glu Pro Cys Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly
                885                 890                 895

Tyr Glu Arg His Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn
            900                 905                 910

Pro Ser Ser Leu Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn
        915                 920                 925

Ser Thr Gly Tyr Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val
    930                 935                 940

Arg Glu Gln Tyr Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro
945                 950                 955                 960

Arg Gly Leu Arg Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln
                965                 970                 975

Gly His Asn Val Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln
            980                 985                 990

Arg Thr Leu Ile Gln Val Asp Phe  Gly Asp Gly Ile Ala  Val Ser Tyr
        995                 1000                1005

Val Asn  Leu Ser Ser Met Glu  Asp Gly Ile Lys His  Val Tyr Gln
    1010                1015                1020
```

```
Asn Val  Gly Ile Phe Arg Val  Thr Val Gln Val Asp  Asn Ser Leu
    1025                1030                1035

Gly Ser  Asp Ser Ala Val Leu  Tyr Leu His Val Thr  Cys Pro Leu
    1040                1045                1050

Glu His  Val His Leu Ser Leu  Pro Phe Val Thr Thr  Lys Asn Lys
    1055                1060                1065

Glu Val  Asn Ala Thr Ala Val  Leu Trp Pro Ser Gln  Val Gly Thr
    1070                1075                1080

Leu Thr  Tyr Val Trp Trp Tyr  Gly Asn Asn Thr Glu  Pro Leu Ile
    1085                1090                1095

Thr Leu  Glu Gly Ser Ile Ser  Phe Arg Phe Thr Ser  Glu Gly Met
    1100                1105                1110

Asn Thr  Ile Thr Val Gln Val  Ser Ala Gly Asn Ala  Ile Leu Gln
    1115                1120                1125

Asp Thr  Lys Thr Ile Ala Val  Tyr Glu Glu Phe Arg  Ser Leu Arg
    1130                1135                1140

Leu Ser  Phe Ser Pro Asn Leu  Asp Asp Tyr Asn Pro  Asp Ile Pro
    1145                1150                1155

Glu Trp  Arg Arg Asp Ile Gly  Arg Val Ile Lys Lys  Ser Leu Val
    1160                1165                1170

Glu Ala  Thr Gly Val Pro Gly  Gln His Ile Leu Val  Ala Val Leu
    1175                1180                1185

Pro Gly  Leu Pro Thr Thr Ala  Glu Leu Phe Val Leu  Pro Tyr Gln
    1190                1195                1200

Asp Pro  Ala Gly Glu Asn Lys  Arg Ser Thr Asp Asp  Leu Glu Gln
    1205                1210                1215

Ile Ser  Glu Leu Leu Ile His  Thr Leu Asn Gln Asn  Ser Val His
    1220                1225                1230

Phe Glu  Leu Lys Pro Gly Val  Arg Val Leu Val His  Ala Ala His
    1235                1240                1245

Leu Thr  Ala Ala Pro Leu Val  Asp Leu Thr Pro Thr  His Ser Gly
    1250                1255                1260

Ser Ala  Met Leu Met Leu Leu  Ser Val Val Phe Val  Gly Leu Ala
    1265                1270                1275

Val Phe  Val Ile Tyr Lys Phe  Lys Arg Lys Ile Pro  Gly Ile Asn
    1280                1285                1290

Val Tyr  Ala Gln Met Gln Asn  Glu Lys Glu Gln Glu  Met Ile Ser
    1295                1300                1305

Pro Val  Ser His Phe Glu Ser  Arg Pro Ser Val Pro  Gln Thr Glu
    1310                1315                1320

Leu Arg  Arg Pro Gly Gln Leu  Ile Asp Glu Lys Val  Glu Ser Gln
    1325                1330                1335

Leu Ile  Gly Ser Ile Ser Ile  Val Ala Glu Asn Gln  Ser Thr Lys
    1340                1345                1350

Glu Ile  Pro Thr Tyr Val Asn  Val
    1355                1360
```

<210> 35

<211> 1165

<212> PRT

<213> Pan troglodytes

<220>
<221> MISC_FEATURE
<222> (1)..(1165)
<223> proSorCS1

<400> 35

```
Gly Gly Ser Cys Cys Pro Pro Pro His Pro Ser Ser Ala Pro Arg Ser
1               5                  10                  15

Ala Ser Thr Pro Arg Gly Phe Ser His Gln Gly Arg Pro Gly Arg Ala
            20                  25                  30

Pro Ala Thr Pro Leu Pro Leu Val Val Arg Pro Leu Phe Ser Val Ala
        35                  40                  45

Pro Gly Asp Arg Ala Leu Ser Leu Glu Arg Ala Arg Gly Thr Gly Ala
    50                  55                  60

Ser Met Ala Val Ala Ala Arg Ser Gly Arg Arg Arg Arg Ser Gly Ala
65                  70                  75                  80

Asp Gln Glu Lys Ala Glu Arg Gly Glu Gly Ala Ser Arg Ser Pro Arg
                85                  90                  95

Gly Val Leu Arg Asp Gly Gly Gln Gln Glu Pro Gly Thr Leu Glu Arg
            100                 105                 110

Asp Pro Asp Lys Ala Thr Arg Phe Arg Met Glu Glu Leu Arg Leu Thr
        115                 120                 125

Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala Met
    130                 135                 140

Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile Leu Thr Lys
145                 150                 155                 160

Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp Arg
                165                 170                 175

Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Val Gly
            180                 185                 190

Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys Arg
        195                 200                 205

Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser Leu Leu Ile
    210                 215                 220

Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe Tyr
225                 230                 235                 240

Ile Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu Ala
                245                 250                 255

Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe Gly Arg Arg
            260                 265                 270

Trp Gln Leu Ile Gln Glu Gly Val Val Pro Asn Arg Phe Tyr Trp Ser
        275                 280                 285

Val Met Gly Ser Asn Lys Glu Pro Asp Leu Val His Leu Glu Ala Arg
    290                 295                 300

Thr Val Asp Gly His Ser His Tyr Leu Thr Cys Arg Met Gln Asn Cys
305                 310                 315                 320

Thr Glu Ala Asn Arg Asn Gln Pro Phe Pro Gly Tyr Ile Asp Pro Asp
                325                 330                 335

Ser Leu Ile Val Gln Asp His Tyr Val Phe Val Gln Leu Thr Ser Gly
            340                 345                 350
```

```
Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn Ala Phe Ala Gln
        355                 360                 365

Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His Val Ile Ser
    370                 375                 380

Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln Asn
385                 390                 395                 400

Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe Thr
                405                 410                 415

Leu Ala Leu Glu Asn Val Gln Ser Ser Arg Gly Pro Glu Gly Asn Ile
            420                 425                 430

Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu Ala
        435                 440                 445

Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn Lys
    450                 455                 460

Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Thr Asp Leu Arg Gly
465                 470                 475                 480

Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His Leu His Leu
                485                 490                 495

Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala Ser Lys Asp
            500                 505                 510

Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Ser Glu Leu
        515                 520                 525

Ser Asp Thr Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn Thr
    530                 535                 540

Trp Arg Gln Ile Phe Glu Glu Glu His Ser Val Leu Tyr Leu Asp Gln
545                 550                 555                 560

Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro Ile Arg His
                565                 570                 575

Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr Ser Phe
            580                 585                 590

Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu Pro Gly Glu
        595                 600                 605

Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg Ser Glu
```

```
    610                 615                 620

Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp Arg Arg Cys
625                 630                 635                 640

Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln Gly Glu Ala
                645                 650                 655

Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu Arg
            660                 665                 670

Lys Cys Met Gln Gly Lys Tyr Ala Gly Ala Met Glu Ser Glu Pro Cys
        675                 680                 685

Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg His
    690                 695                 700

Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser Leu
705                 710                 715                 720

Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Thr Gly Tyr
                725                 730                 735

Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln Tyr
            740                 745                 750

Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu Arg
        755                 760                 765

Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn Val
    770                 775                 780

Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr Leu Ile
785                 790                 795                 800

Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu Ser
                805                 810                 815

Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly Ile Phe
            820                 825                 830

Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala Val
        835                 840                 845

Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser Leu
    850                 855                 860

Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val Leu
865                 870                 875                 880
```

```
Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly Asn
                885                 890                 895

Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe Arg Phe
            900                 905                 910

Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly Asn
        915                 920                 925

Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe Arg
    930                 935                 940

Ser Leu Arg Leu Ser Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro Asp
945                 950                 955                 960

Ile Pro Glu Trp Arg Arg Asp Ile Gly Arg Val Ile Lys Lys Ser Leu
                965                 970                 975

Val Glu Ala Thr Gly Val Pro Gly Gln His Ile Leu Val Ala Val Leu
            980                 985                 990

Pro Gly Leu Pro Thr Thr Ala Glu  Leu Phe Val Leu Pro  Tyr Gln Asp
        995                 1000                1005

Pro Ala  Gly Glu Asn Lys Arg  Ser Thr Asp Asp Leu  Glu Gln Ile
    1010                1015                1020

Ser Glu  Leu Leu Ile His Thr  Leu Asn Gln Asn Ser  Val His Phe
    1025                1030                1035

Glu Leu  Lys Pro Gly Val Arg  Val Leu Val His Ala  Ala His Leu
    1040                1045                1050

Thr Ala  Ala Pro Leu Val Asp  Leu Thr Pro Thr His  Ser Gly Ser
    1055                1060                1065

Ala Met  Leu Met Leu Leu Ser  Val Val Phe Val Gly  Leu Ala Val
    1070                1075                1080

Phe Val  Ile Tyr Lys Phe Lys  Arg Lys Ile Pro Gly  Ile Asn Val
    1085                1090                1095

Tyr Ala  Gln Met Gln Asn Glu  Lys Glu Gln Glu Met  Ile Ser Pro
    1100                1105                1110

Val Ser  His Phe Glu Ser Arg  Pro Ser Val Pro Gln  Thr Glu Leu
    1115                1120                1125

Arg Arg  Pro Gly Gln Leu Ile  Asp Glu Lys Val Glu  Ser Gln Leu
    1130                1135                1140

Ile Gly  Ser Ile Ser Ile Val  Ala Glu Asn Gln Ser  Thr Lys Glu
    1145                1150                1155

Ile Pro  Thr Tyr Val Asn Val
    1160                1165
```

<210> 36

<211> 1088

<212> PRT

<213> Pan troglodytes

<220>

<221> MISC_FEATURE

<222> (1)..(1088)

<223> mature SorCS1

<400> 36

```
Ser Gly Ala Asp Gln Glu Lys Ala Glu Arg Gly Glu Gly Ala Ser Arg
1               5                  10                  15

Ser Pro Arg Gly Val Leu Arg Asp Gly Gly Gln Gln Glu Pro Gly Thr
            20                  25                  30

Leu Glu Arg Asp Pro Asp Lys Ala Thr Arg Phe Arg Met Glu Glu Leu
        35                  40                  45

Arg Leu Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn
    50                  55                  60

Gln Ala Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile
65                  70                  75                  80

Leu Thr Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser
                85                  90                  95

Leu Trp Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp
            100                 105                 110

Lys Val Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr
        115                 120                 125

Asn Lys Arg Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser
    130                 135                 140

Leu Leu Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu
145                 150                 155                 160
```

```
Asn Phe Tyr Ile Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp
                165                 170                 175

Ile Leu Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe
            180                 185                 190

Gly Arg Arg Trp Gln Leu Ile Gln Glu Gly Val Val Pro Asn Arg Phe
        195                 200                 205

Tyr Trp Ser Val Met Gly Ser Asn Lys Glu Pro Asp Leu Val His Leu
    210                 215                 220

Glu Ala Arg Thr Val Asp Gly His Ser His Tyr Leu Thr Cys Arg Met
225                 230                 235                 240

Gln Asn Cys Thr Glu Ala Asn Arg Asn Gln Pro Phe Pro Gly Tyr Ile
                245                 250                 255

Asp Pro Asp Ser Leu Ile Val Gln Asp His Tyr Val Phe Val Gln Leu
            260                 265                 270

Thr Ser Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn Ala
        275                 280                 285

Phe Ala Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His
    290                 295                 300

Val Ile Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp
305                 310                 315                 320

Asn Gln Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val
                325                 330                 335

Tyr Phe Thr Leu Ala Leu Glu Asn Val Gln Ser Ser Arg Gly Pro Glu
            340                 345                 350

Gly Asn Ile Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met
        355                 360                 365

Phe Leu Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr
    370                 375                 380

Tyr Asn Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Thr Asp
385                 390                 395                 400

Leu Arg Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His
                405                 410                 415
```

```
Leu His Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala
            420                 425                 430

Ser Lys Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly
        435                 440                 445

Ser Glu Leu Ser Asp Thr Asp Ile Ser Met Phe Val Ser Ser Asp Ala
    450                 455                 460

Gly Asn Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Val Leu Tyr
465                 470                 475                 480

Leu Asp Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro
                485                 490                 495

Ile Arg His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys
            500                 505                 510

Tyr Ser Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu
        515                 520                 525

Pro Gly Glu Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His
    530                 535                 540

Arg Ser Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp
545                 550                 555                 560

Arg Arg Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln
                565                 570                 575

Gly Glu Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys
            580                 585                 590

Ser Glu Arg Lys Cys Met Gln Gly Lys Tyr Ala Gly Ala Met Glu Ser
        595                 600                 605

Glu Pro Cys Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr
    610                 615                 620

Glu Arg His Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro
625                 630                 635                 640

Ser Ser Leu Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser
                645                 650                 655

Thr Gly Tyr Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg
            660                 665                 670

Glu Gln Tyr Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg
```

```
        675                 680                 685

Gly Leu Arg Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly
    690                 695                 700

His Asn Val Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg
705                 710                 715                 720

Thr Leu Ile Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val
                725                 730                 735

Asn Leu Ser Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val
            740                 745                 750

Gly Ile Phe Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp
        755                 760                 765

Ser Ala Val Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His
    770                 775                 780

Leu Ser Leu Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr
785                 790                 795                 800

Ala Val Leu Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp
                805                 810                 815

Tyr Gly Asn Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser
            820                 825                 830

Phe Arg Phe Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser
        835                 840                 845

Ala Gly Asn Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu
    850                 855                 860

Glu Phe Arg Ser Leu Arg Leu Ser Phe Ser Pro Asn Leu Asp Asp Tyr
865                 870                 875                 880

Asn Pro Asp Ile Pro Glu Trp Arg Arg Asp Ile Gly Arg Val Ile Lys
                885                 890                 895

Lys Ser Leu Val Glu Ala Thr Gly Val Pro Gly Gln His Ile Leu Val
            900                 905                 910

Ala Val Leu Pro Gly Leu Pro Thr Thr Ala Glu Leu Phe Val Leu Pro
        915                 920                 925

Tyr Gln Asp Pro Ala Gly Glu Asn Lys Arg Ser Thr Asp Asp Leu Glu
    930                 935                 940
```

```
Gln Ile Ser Glu Leu Leu Ile His Thr Leu Asn Gln Asn Ser Val His
945                 950                 955                 960

Phe Glu Leu Lys Pro Gly Val Arg Val Leu Val His Ala Ala His Leu
                965                 970                 975

Thr Ala Ala Pro Leu Val Asp Leu Thr Pro Thr His Ser Gly Ser Ala
            980                 985                 990

Met Leu Met Leu Leu Ser Val Val  Phe Val Gly Leu Ala  Val Phe Val
        995                 1000                1005

Ile Tyr  Lys Phe Lys Arg Lys  Ile Pro Gly Ile Asn  Val Tyr Ala
    1010                1015                1020

Gln Met  Gln Asn Glu Lys Glu  Gln Glu Met Ile Ser  Pro Val Ser
    1025                1030                1035

His Phe  Glu Ser Arg Pro Ser  Val Pro Gln Thr Glu  Leu Arg Arg
    1040                1045                1050

Pro Gly  Gln Leu Ile Asp Glu  Lys Val Glu Ser Gln  Leu Ile Gly
    1055                1060                1065

Ser Ile  Ser Ile Val Ala Glu  Asn Gln Ser Thr Lys  Glu Ile Pro
    1070                1075                1080

Thr Tyr  Val Asn Val
    1085
```

<210> 37

<211> 990

<212> PRT

<213> Pan troglodytes

<220>

<221> MISC_FEATURE

<222> (1)..(990)

<223> soluble SorCS1

<400> 37

```
Ser Gly Ala Asp Gln Glu Lys Ala Glu Arg Gly Glu Gly Ala Ser Arg
1               5                   10                  15

Ser Pro Arg Gly Val Leu Arg Asp Gly Gly Gln Gln Glu Pro Gly Thr
            20                  25                  30

Leu Glu Arg Asp Pro Asp Lys Ala Thr Arg Phe Arg Met Glu Glu Leu
        35                  40                  45
```

```
Arg Leu Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn
    50                  55                  60

Gln Ala Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile
65                  70                  75                  80

Leu Thr Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser
                85                  90                  95

Leu Trp Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp
            100                 105                 110

Lys Val Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr
        115                 120                 125

Asn Lys Arg Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser
    130                 135                 140

Leu Leu Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu
145                 150                 155                 160

Asn Phe Tyr Ile Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp
                165                 170                 175

Ile Leu Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe
            180                 185                 190

Gly Arg Arg Trp Gln Leu Ile Gln Glu Gly Val Val Pro Asn Arg Phe
        195                 200                 205

Tyr Trp Ser Val Met Gly Ser Asn Lys Glu Pro Asp Leu Val His Leu
    210                 215                 220

Glu Ala Arg Thr Val Asp Gly His Ser His Tyr Leu Thr Cys Arg Met
225                 230                 235                 240

Gln Asn Cys Thr Glu Ala Asn Arg Asn Gln Pro Phe Pro Gly Tyr Ile
                245                 250                 255

Asp Pro Asp Ser Leu Ile Val Gln Asp His Tyr Val Phe Val Gln Leu
            260                 265                 270

Thr Ser Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn Ala
        275                 280                 285

Phe Ala Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His
    290                 295                 300
```

```
Val Ile Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp
305                 310                 315                 320

Asn Gln Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val
                325                 330                 335

Tyr Phe Thr Leu Ala Leu Glu Asn Val Gln Ser Ser Arg Gly Pro Glu
            340                 345                 350

Gly Asn Ile Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met
        355                 360                 365

Phe Leu Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr
    370                 375                 380

Tyr Asn Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Thr Asp
385                 390                 395                 400

Leu Arg Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His
                405                 410                 415

Leu His Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala
            420                 425                 430

Ser Lys Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly
        435                 440                 445

Ser Glu Leu Ser Asp Thr Asp Ile Ser Met Phe Val Ser Ser Asp Ala
    450                 455                 460

Gly Asn Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Val Leu Tyr
465                 470                 475                 480

Leu Asp Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro
                485                 490                 495

Ile Arg His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys
            500                 505                 510

Tyr Ser Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu
        515                 520                 525

Pro Gly Glu Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His
    530                 535                 540

Arg Ser Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp
545                 550                 555                 560
```

```
Arg Arg Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln
                565                 570                 575

Gly Glu Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys
            580                 585                 590

Ser Glu Arg Lys Cys Met Gln Gly Lys Tyr Ala Gly Ala Met Glu Ser
        595                 600                 605

Glu Pro Cys Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr
    610                 615                 620

Glu Arg His Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro
625                 630                 635                 640

Ser Ser Leu Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser
                645                 650                 655

Thr Gly Tyr Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg
            660                 665                 670

Glu Gln Tyr Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg
        675                 680                 685

Gly Leu Arg Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly
    690                 695                 700

His Asn Val Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg
705                 710                 715                 720

Thr Leu Ile Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val
                725                 730                 735

Asn Leu Ser Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val
            740                 745                 750

Gly Ile Phe Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp
        755                 760                 765

Ser Ala Val Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His
    770                 775                 780

Leu Ser Leu Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr
785                 790                 795                 800

Ala Val Leu Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp
                805                 810                 815

Tyr Gly Asn Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser
```

```
            820                 825                 830

Phe Arg Phe Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser
        835                 840                 845

Ala Gly Asn Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu
    850                 855                 860

Glu Phe Arg Ser Leu Arg Leu Ser Phe Ser Pro Asn Leu Asp Asp Tyr
865                 870                 875                 880

Asn Pro Asp Ile Pro Glu Trp Arg Arg Asp Ile Gly Arg Val Ile Lys
                885                 890                 895

Lys Ser Leu Val Glu Ala Thr Gly Val Pro Gly Gln His Ile Leu Val
            900                 905                 910

Ala Val Leu Pro Gly Leu Pro Thr Thr Ala Glu Leu Phe Val Leu Pro
        915                 920                 925

Tyr Gln Asp Pro Ala Gly Glu Asn Lys Arg Ser Thr Asp Asp Leu Glu
    930                 935                 940

Gln Ile Ser Glu Leu Leu Ile His Thr Leu Asn Gln Asn Ser Val His
945                 950                 955                 960

Phe Glu Leu Lys Pro Gly Val Arg Val Leu Val His Ala Ala His Leu
                965                 970                 975

Thr Ala Ala Pro Leu Val Asp Leu Thr Pro Thr His Ser Gly
            980                 985                 990
```

<210> 38

<211> 997

<212> PRT

<213> Canis lupus familiaris

<220>

<221> MISC_FEATURE

<222> (1)..(997)

<223> mature SorCS1

<400> 38

```
Met Arg Lys Val Ser Glu Ile Met Val Leu Arg Ser Trp His Ser Val
1               5                   10                  15

Ile Leu Ile Leu Thr Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr
            20                  25                  30

Glu Ser Ser Leu Trp Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys
```

```
        35                  40                  45

Leu Asn Asp Lys Val Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val
    50                  55                  60

Cys Pro Thr Asn Lys Arg Lys Ile Met Leu Leu Thr Asp Pro Glu Ile
65                  70                  75                  80

Glu Ser Ser Leu Leu Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys
                85                  90                  95

Tyr Arg Leu Asn Phe Tyr Ile Gln Ser Leu Leu Phe His Pro Lys Gln
            100                 105                 110

Glu Asp Trp Ile Leu Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser
        115                 120                 125

Ala Glu Phe Gly Arg Arg Trp Gln Leu Ile Gln Glu Gly Val Val Pro
    130                 135                 140

Asn Arg Phe Tyr Trp Ser Val Met Gly Ser Asn Lys Glu Pro Asp Leu
145                 150                 155                 160

Val His Leu Glu Ala Arg Thr Val Asp Gly His Ser Gln Tyr Leu Thr
                165                 170                 175

Cys Arg Met Gln Asn Cys Thr Glu Ala Asn Arg Asn Lys Pro Phe Pro
            180                 185                 190

Gly Tyr Ile Asp Pro Asp Ser Leu Ile Val Gln Asp Asp Tyr Val Phe
        195                 200                 205

Val Gln Leu Thr Ser Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg
    210                 215                 220

Arg Asn Ala Phe Ala Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys
225                 230                 235                 240

Asp Met His Val Ile Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val
                245                 250                 255

Gln Glu Trp Asn Gln Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr
            260                 265                 270

Arg Gly Val Tyr Phe Thr Leu Ala Leu Glu Asn Val Gln Ser Ser Arg
        275                 280                 285

Gly Pro Glu Gly Asn Ile Met Ile Asp Leu Tyr Glu Val Ala Gly Ile
    290                 295                 300
```

```
Lys Gly Met Phe Leu Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr
305                 310                 315                 320

Phe Ile Thr Tyr Asn Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro
                325                 330                 335

Asp Thr Asp Leu Arg Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys
            340                 345                 350

Ser Leu His Leu His Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly
        355                 360                 365

Ile Ile Ala Ser Arg Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly
    370                 375                 380

Asn Ile Gly Ser Glu Leu Ser Asp Ser Asp Ile Ser Met Phe Val Ser
385                 390                 395                 400

Ser Asp Ala Gly Asn Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser
                405                 410                 415

Val Leu Tyr Leu Asp Gln Gly Gly Val Leu Val Ala Met Lys His Thr
            420                 425                 430

Ser Leu Pro Ile Arg His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser
        435                 440                 445

Trp Ser Lys Tyr Ser Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val
    450                 455                 460

Leu Gly Glu Pro Gly Glu Glu Thr Leu Ile Met Thr Val Phe Gly His
465                 470                 475                 480

Phe Ser His Arg Ser Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser
                485                 490                 495

Ile Phe Asp Arg Arg Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu
            500                 505                 510

His Ser Gln Gly Glu Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys
        515                 520                 525

Lys Arg Lys Ser Glu Arg Lys Cys Met Gln Gly Lys Tyr Ala Gly Ala
    530                 535                 540

Met Glu Ser Glu Pro Cys Val Cys Thr Glu Ala Asp Phe Asp Cys Asp
545                 550                 555                 560
```

```
Tyr Gly Tyr Glu Arg His Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp
                565                 570                 575

Phe Asn Pro Ser Ser Leu Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr
            580                 585                 590

Leu Asn Ser Thr Gly Tyr Arg Lys Val Val Ser Asn Asn Cys Thr Asp
        595                 600                 605

Gly Val Arg Glu Gln Tyr Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys
    610                 615                 620

Ala Pro Arg Gly Leu Arg Ile Val Thr Ala Asp Gly Lys Leu Thr Ala
625                 630                 635                 640

Glu Gln Gly His Asn Val Thr Leu Met Val Gln Leu Glu Glu Gly Asp
                645                 650                 655

Val Gln Arg Thr Leu Ile Gln Val Asp Phe Gly Asp Gly Ile Ala Val
            660                 665                 670

Ser Tyr Val Asn Leu Ser Ser Met Glu Asp Gly Ile Lys His Val Tyr
        675                 680                 685

His Asn Val Gly Ile Phe Arg Val Thr Val Gln Val Asp Asn Ser Leu
    690                 695                 700

Gly Ser Asp Ser Ala Val Leu Tyr Leu His Val Thr Cys Pro Leu Glu
705                 710                 715                 720

His Val His Leu Ser Leu Pro Phe Val Thr Thr Lys Asn Lys Glu Val
                725                 730                 735

Asn Ala Thr Ala Val Leu Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr
            740                 745                 750

Val Trp Trp Tyr Gly Asn Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly
        755                 760                 765

Ser Ile Ser Phe Lys Phe Thr Ser Glu Gly Met Asn Thr Ile Thr Val
    770                 775                 780

Gln Val Ser Ala Gly Asn Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala
785                 790                 795                 800

Val Tyr Glu Glu Phe Arg Ser Leu Arg Leu Ser Phe Ser Pro Asn Leu
                805                 810                 815
```

```
Asp Asp Tyr Asn Pro Asp Ile Pro Glu Trp Arg Arg Asp Ile Ser Arg
            820                 825                 830

Val Ile Lys Lys Ser Leu Val Glu Ala Thr Gly Val Pro Gly Gln His
        835                 840                 845

Ile Leu Val Ala Val Leu Pro Gly Leu Pro Thr Ala Ala Glu Leu Phe
    850                 855                 860

Val Leu Pro Tyr Gln Asp Pro Thr Gly Glu Asn Lys Arg Ser Ala Glu
865                 870                 875                 880

Asp Leu Glu Gln Ile Ser Glu Leu Leu Ile His Lys Leu Asn Gln Asn
                885                 890                 895

Ser Val His Phe Glu Leu Lys Pro Gly Val Gln Ile Leu Val His Ala
            900                 905                 910

Ala His Leu Thr Ala Ala Pro Leu Val Asp Leu Thr Pro Thr His Ser
        915                 920                 925

Gly Ser Ala Met Leu Met Leu Leu Ser Val Val Phe Val Gly Leu Ala
    930                 935                 940

Val Phe Val Ile Tyr Lys Phe Lys Arg Arg Val Ala Leu Pro Ser Pro
945                 950                 955                 960

Pro Ser Pro Ser Thr Gln Pro Gly Asp Ser Ser Leu Arg Leu Gln Arg
                965                 970                 975

Ala Arg His Ala Thr Pro Pro Ser Thr Pro Lys Arg Gly Ser Ala Gly
            980                 985                 990

Ala Gln Phe Ala Ile
        995
```

<210> 39

<211> 929

<212> PRT

<213> Canis lupus familiaris

<220>

<221> MISC_FEATURE

<222> (1) .. (929)

<223> soluble SorCS1

<400> 39

```
Met Arg Lys Val Ser Glu Ile Met Val Leu Arg Ser Trp His Ser Val
1               5                   10                  15
```

```
Ile Leu Ile Leu Thr Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr
            20                  25                  30

Glu Ser Ser Leu Trp Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys
        35                  40                  45

Leu Asn Asp Lys Val Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val
    50                  55                  60

Cys Pro Thr Asn Lys Arg Lys Ile Met Leu Leu Thr Asp Pro Glu Ile
65                  70                  75                  80

Glu Ser Ser Leu Leu Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys
                85                  90                  95

Tyr Arg Leu Asn Phe Tyr Ile Gln Ser Leu Leu Phe His Pro Lys Gln
            100                 105                 110

Glu Asp Trp Ile Leu Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser
        115                 120                 125

Ala Glu Phe Gly Arg Arg Trp Gln Leu Ile Gln Glu Gly Val Val Pro
    130                 135                 140

Asn Arg Phe Tyr Trp Ser Val Met Gly Ser Asn Lys Glu Pro Asp Leu
145                 150                 155                 160

Val His Leu Glu Ala Arg Thr Val Asp Gly His Ser Gln Tyr Leu Thr
                165                 170                 175

Cys Arg Met Gln Asn Cys Thr Glu Ala Asn Arg Asn Lys Pro Phe Pro
            180                 185                 190

Gly Tyr Ile Asp Pro Asp Ser Leu Ile Val Gln Asp Asp Tyr Val Phe
        195                 200                 205

Val Gln Leu Thr Ser Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg
    210                 215                 220

Arg Asn Ala Phe Ala Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys
225                 230                 235                 240

Asp Met His Val Ile Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val
                245                 250                 255

Gln Glu Trp Asn Gln Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr
            260                 265                 270

Arg Gly Val Tyr Phe Thr Leu Ala Leu Glu Asn Val Gln Ser Ser Arg
```

```
        275                 280                 285

Gly Pro Glu Gly Asn Ile Met Ile Asp Leu Tyr Glu Val Ala Gly Ile
    290                 295                 300

Lys Gly Met Phe Leu Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr
305                 310                 315                 320

Phe Ile Thr Tyr Asn Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro
                325                 330                 335

Asp Thr Asp Leu Arg Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys
            340                 345                 350

Ser Leu His Leu His Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly
        355                 360                 365

Ile Ile Ala Ser Arg Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly
    370                 375                 380

Asn Ile Gly Ser Glu Leu Ser Asp Ser Asp Ile Ser Met Phe Val Ser
385                 390                 395                 400

Ser Asp Ala Gly Asn Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser
                405                 410                 415

Val Leu Tyr Leu Asp Gln Gly Gly Val Leu Val Ala Met Lys His Thr
            420                 425                 430

Ser Leu Pro Ile Arg His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser
        435                 440                 445

Trp Ser Lys Tyr Ser Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val
    450                 455                 460

Leu Gly Glu Pro Gly Glu Glu Thr Leu Ile Met Thr Val Phe Gly His
465                 470                 475                 480

Phe Ser His Arg Ser Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser
                485                 490                 495

Ile Phe Asp Arg Arg Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu
            500                 505                 510

His Ser Gln Gly Glu Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys
        515                 520                 525

Lys Arg Lys Ser Glu Arg Lys Cys Met Gln Gly Lys Tyr Ala Gly Ala
    530                 535                 540
```

```
Met Glu Ser Glu Pro Cys Val Cys Thr Glu Ala Asp Phe Asp Cys Asp
545                 550                 555                 560

Tyr Gly Tyr Glu Arg His Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp
                565                 570                 575

Phe Asn Pro Ser Ser Leu Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr
            580                 585                 590

Leu Asn Ser Thr Gly Tyr Arg Lys Val Val Ser Asn Asn Cys Thr Asp
        595                 600                 605

Gly Val Arg Glu Gln Tyr Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys
    610                 615                 620

Ala Pro Arg Gly Leu Arg Ile Val Thr Ala Asp Gly Lys Leu Thr Ala
625                 630                 635                 640

Glu Gln Gly His Asn Val Thr Leu Met Val Gln Leu Glu Glu Gly Asp
                645                 650                 655

Val Gln Arg Thr Leu Ile Gln Val Asp Phe Gly Asp Gly Ile Ala Val
            660                 665                 670

Ser Tyr Val Asn Leu Ser Ser Met Glu Asp Gly Ile Lys His Val Tyr
        675                 680                 685

His Asn Val Gly Ile Phe Arg Val Thr Val Gln Val Asp Asn Ser Leu
    690                 695                 700

Gly Ser Asp Ser Ala Val Leu Tyr Leu His Val Thr Cys Pro Leu Glu
705                 710                 715                 720

His Val His Leu Ser Leu Pro Phe Val Thr Thr Lys Asn Lys Glu Val
                725                 730                 735

Asn Ala Thr Ala Val Leu Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr
            740                 745                 750

Val Trp Trp Tyr Gly Asn Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly
        755                 760                 765

Ser Ile Ser Phe Lys Phe Thr Ser Glu Gly Met Asn Thr Ile Thr Val
    770                 775                 780

Gln Val Ser Ala Gly Asn Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala
785                 790                 795                 800

Val Tyr Glu Glu Phe Arg Ser Leu Arg Leu Ser Phe Ser Pro Asn Leu
                805                 810                 815

Asp Asp Tyr Asn Pro Asp Ile Pro Glu Trp Arg Arg Asp Ile Ser Arg
            820                 825                 830

Val Ile Lys Lys Ser Leu Val Glu Ala Thr Gly Val Pro Gly Gln His
        835                 840                 845

Ile Leu Val Ala Val Leu Pro Gly Leu Pro Thr Ala Ala Glu Leu Phe
    850                 855                 860

Val Leu Pro Tyr Gln Asp Pro Thr Gly Glu Asn Lys Arg Ser Ala Glu
865                 870                 875                 880

Asp Leu Glu Gln Ile Ser Glu Leu Leu Ile His Lys Leu Asn Gln Asn
                885                 890                 895

Ser Val His Phe Glu Leu Lys Pro Gly Val Gln Ile Leu Val His Ala
            900                 905                 910

Ala His Leu Thr Ala Ala Pro Leu Val Asp Leu Thr Pro Thr His Ser
        915                 920                 925

Gly
```

<210> 40
<211> 1196
<212> PRT
<213> Bos taurus

<220>
<221> MISC_FEATURE
<222> (1)..(1196)
<223> preproSorCS1

<400> 40

```
Met Gly Lys Val Gly Ala Gly Gly Val Ser Pro Ala Gly Leu Ser Ala
1               5                   10                  15

Leu Leu Ala Gly Ala Gly Leu Leu Val Leu Cys Ala Pro Gly Ser Cys
            20                  25                  30

Gly Gly Gly Ser Cys Cys Pro Pro Arg His Pro Ser Ala Ala Pro Arg
        35                  40                  45

Trp Ala Pro Thr Pro Gly Gly Leu Pro His Gln Gly Pro Arg Gly Arg
    50                  55                  60

Ala Pro Ala Thr Pro Leu Pro Gln Leu Gly Arg Pro Leu Phe Ala Val
65                  70                  75                  80

Ala Pro Gly Asp Arg Ala Leu Ser Leu Glu Arg Ala Pro Gly Thr Gly
                85                  90                  95

Ala Ser Val Ala Val Ala Pro Arg Ser Gly Arg Lys Arg Arg Ser Gly
            100                 105                 110

Glu Asp Gln Glu Lys Ala Glu Arg Gly Glu Gly Thr Ser Arg Ser Pro
        115                 120                 125

Arg Gly Val Leu Arg Asp Arg Gly Gln Leu Glu Pro Gly Thr Leu Glu
    130                 135                 140

Arg Asp Pro Asp Lys Ala Thr Arg Phe Arg Leu Glu Glu Leu Lys Leu
145                 150                 155                 160

Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala
                165                 170                 175

Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile Leu Thr
            180                 185                 190

Lys Leu Phe Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp
        195                 200                 205

Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Val
    210                 215                 220

Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys
225                 230                 235                 240

Arg Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser Leu Leu
                245                 250                 255

Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe
            260                 265                 270

Tyr Ile Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu
        275                 280                 285

Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe Gly Arg
    290                 295                 300

Arg Trp Gln Leu Ile Gln Glu Ala Val Val Pro Asn Arg Phe Tyr Trp
305                 310                 315                 320
```

```
Ser Val Met Gly Ser Asn Lys Glu Pro Asp Leu Val His Leu Glu Ala
                325                 330                 335

Arg Thr Val Asp Gly His Ser Gln Tyr Leu Thr Cys Arg Met Gln Asn
            340                 345                 350

Cys Thr Glu Ala Asn Arg Asn Lys Pro Phe Pro Gly Tyr Ile Asp Pro
        355                 360                 365

Asp Ser Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu Thr Ser
    370                 375                 380

Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn Ala Phe Ala
385                 390                 395                 400

Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His Val Ile
                405                 410                 415

Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln
            420                 425                 430

Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe
        435                 440                 445

Thr Leu Ala Leu Glu Asn Val Gln Ser Ser Arg Gly Pro Glu Gly Asn
    450                 455                 460

Val Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu
465                 470                 475                 480

Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn
                485                 490                 495

Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Thr Asp Leu Arg
            500                 505                 510

Gly Asp Pro Val His Cys Val Leu Pro Tyr Cys Ser Leu His Leu His
        515                 520                 525

Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala Ser Arg
    530                 535                 540

Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Ser Glu
545                 550                 555                 560

Leu Ser Asp Ser Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn
                565                 570                 575

Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Val Leu Tyr Leu Asp
```

```
           580                 585                 590

Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro Ile Arg
        595                 600                 605

His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr Ser
    610                 615                 620

Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu Pro Gly
625                 630                 635                 640

Glu Glu Thr Leu Ile Met Thr Leu Leu Asp His Ser His Ser Asp Trp
                645                 650                 655

Leu Val Thr Ala Leu Gln Pro Cys Cys Leu Phe Leu Leu Gly Asn Glu
            660                 665                 670

Trp Glu Asp Lys Ile Ala Trp Lys Pro Gln Asp Gln Gly Glu Ala Cys
        675                 680                 685

Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu Arg Lys
    690                 695                 700

Cys Met Gln Gly Lys Tyr Ala Gly Ala Met Glu Ser Glu Pro Cys Val
705                 710                 715                 720

Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg His Ser
                725                 730                 735

Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser Leu Ser
            740                 745                 750

Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Thr Gly Tyr Arg
        755                 760                 765

Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln Tyr Thr
    770                 775                 780

Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu Arg Ile
785                 790                 795                 800

Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn Val Thr
                805                 810                 815

Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr Leu Ile Gln
            820                 825                 830

Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu Ser Ser
        835                 840                 845
```

```
Met Glu Asp Gly Ile Lys His Val Tyr His Asn Val Gly Ile Phe Arg
    850                 855                 860

Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala Val Leu
865                 870                 875                 880

Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser Leu Pro
                885                 890                 895

Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val Leu Trp
            900                 905                 910

Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly Asn Asn
        915                 920                 925

Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ala Phe Lys Phe Thr
    930                 935                 940

Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly Asn Ala
945                 950                 955                 960

Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe Arg Ser
                965                 970                 975

Leu Arg Leu Ser Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro Asp Ile
            980                 985                 990

Pro Glu Trp Arg Arg Asp Val Ser  Arg Val Ile Lys Lys  Ala Leu Val
        995                 1000                1005

Glu Ala  Thr Gly Val Pro Gly  Gln His Ile Leu Val  Ala Val Leu
    1010                1015                1020

Pro Gly  Leu Pro Thr Ala Ala  Glu Leu Phe Val Leu  Pro His Gln
    1025                1030                1035

Asp Pro  Thr Gly Glu Asn Lys  Arg Pro Ala Glu Asp  Leu Glu Gln
    1040                1045                1050

Ile Ser  Glu Leu Met Ile His  Lys Leu Asn Gln Asn  Ser Val His
    1055                1060                1065

Phe Glu  Leu Lys Pro Gly Val  Gln Val Leu Val His  Ala Ala His
    1070                1075                1080

Leu Thr  Ala Ala Pro Leu Val  Asp Leu Thr Pro Thr  His Ser Gly
    1085                1090                1095

Ser Ala  Met Leu Met Leu Leu  Ser Val Val Phe Val  Gly Leu Ala
    1100                1105                1110

Val Phe  Val Ile Tyr Lys Phe  Lys Arg Lys Ile Pro  Gly Ile Asn
    1115                1120                1125

Val Tyr  Ala Gln Met Gln Asn  Glu Lys Glu Gln Glu  Met Val Ser
    1130                1135                1140

Arg Val  Ser His Pro Glu Ser  Arg Pro Tyr Val Pro  Gln Thr Glu
    1145                1150                1155

Leu Arg  Arg Pro Gly Gln Leu  Ile Asp Glu Lys Val  Glu Ser Gln
    1160                1165                1170

Leu Ile  Gly Ser Ile Ser Ile  Val Ala Glu Asn Gln  Ser Thr Lys
    1175                1180                1185

Glu Ile  Pro Thr Tyr Val Asn  Val
    1190                1195
```

<210> 41

<211> 1163

<212> PRT

<213> Bos taurus

<220>
<221> MISC_FEATURE
<222> (1)..(1163)
<223> proSorCS1

<400> 41

```
Gly Gly Ser Cys Cys Pro Pro Arg His Pro Ser Ala Ala Pro Arg Trp
1               5                  10                  15

Ala Pro Thr Pro Gly Gly Leu Pro His Gln Gly Pro Arg Gly Arg Ala
            20                  25                  30

Pro Ala Thr Pro Leu Pro Gln Leu Gly Arg Pro Leu Phe Ala Val Ala
        35                  40                  45

Pro Gly Asp Arg Ala Leu Ser Leu Glu Arg Ala Pro Gly Thr Gly Ala
    50                  55                  60

Ser Val Ala Val Ala Pro Arg Ser Gly Arg Lys Arg Arg Ser Gly Glu
65                  70                  75                  80

Asp Gln Glu Lys Ala Glu Arg Gly Glu Gly Thr Ser Arg Ser Pro Arg
                85                  90                  95

Gly Val Leu Arg Asp Arg Gly Gln Leu Glu Pro Gly Thr Leu Glu Arg
            100                 105                 110

Asp Pro Asp Lys Ala Thr Arg Phe Arg Leu Glu Glu Leu Lys Leu Thr
        115                 120                 125

Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala Met
    130                 135                 140

Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile Leu Thr Lys
145                 150                 155                 160

Leu Phe Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp Arg
                165                 170                 175

Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Val Gly
            180                 185                 190

Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys Arg
        195                 200                 205

Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser Leu Leu Ile
    210                 215                 220

Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe Tyr
225                 230                 235                 240

Ile Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu Ala
                245                 250                 255

Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe Gly Arg Arg
            260                 265                 270

Trp Gln Leu Ile Gln Glu Ala Val Val Pro Asn Arg Phe Tyr Trp Ser
        275                 280                 285

Val Met Gly Ser Asn Lys Glu Pro Asp Leu Val His Leu Glu Ala Arg
    290                 295                 300

Thr Val Asp Gly His Ser Gln Tyr Leu Thr Cys Arg Met Gln Asn Cys
305                 310                 315                 320

Thr Glu Ala Asn Arg Asn Lys Pro Phe Pro Gly Tyr Ile Asp Pro Asp
                325                 330                 335

Ser Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu Thr Ser Gly
            340                 345                 350
```

```
Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn Ala Phe Ala Gln
        355                 360                 365

Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His Val Ile Ser
    370                 375                 380

Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln Asn
385                 390                 395                 400

Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe Thr
                405                 410                 415

Leu Ala Leu Glu Asn Val Gln Ser Ser Arg Gly Pro Glu Gly Asn Val
            420                 425                 430

Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu Ala
        435                 440                 445

Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn Lys
    450                 455                 460

Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Thr Asp Leu Arg Gly
465                 470                 475                 480

Asp Pro Val His Cys Val Leu Pro Tyr Cys Ser Leu His Leu His Leu
                485                 490                 495

Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala Ser Arg Asp
            500                 505                 510

Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Ser Glu Leu
        515                 520                 525

Ser Asp Ser Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn Thr
    530                 535                 540

Trp Arg Gln Ile Phe Glu Glu Glu His Ser Val Leu Tyr Leu Asp Gln
545                 550                 555                 560

Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro Ile Arg His
                565                 570                 575

Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr Ser Phe
            580                 585                 590

Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu Pro Gly Glu
        595                 600                 605

Glu Thr Leu Ile Met Thr Leu Leu Asp His Ser His Ser Asp Trp Leu
```

```
    610                 615                 620

Val Thr Ala Leu Gln Pro Cys Cys Leu Phe Leu Leu Gly Asn Glu Trp
625                 630                 635                 640

Glu Asp Lys Ile Ala Trp Lys Pro Gln Asp Gln Gly Glu Ala Cys Ile
                645                 650                 655

Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu Arg Lys Cys
            660                 665                 670

Met Gln Gly Lys Tyr Ala Gly Ala Met Glu Ser Glu Pro Cys Val Cys
        675                 680                 685

Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg His Ser Asn
    690                 695                 700

Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser Leu Ser Lys
705                 710                 715                 720

Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Thr Gly Tyr Arg Lys
                725                 730                 735

Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln Tyr Thr Ala
            740                 745                 750

Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu Arg Ile Val
        755                 760                 765

Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn Val Thr Leu
    770                 775                 780

Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr Leu Ile Gln Val
785                 790                 795                 800

Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu Ser Ser Met
                805                 810                 815

Glu Asp Gly Ile Lys His Val Tyr His Asn Val Gly Ile Phe Arg Val
            820                 825                 830

Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala Val Leu Tyr
        835                 840                 845

Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser Leu Pro Phe
    850                 855                 860

Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val Leu Trp Pro
865                 870                 875                 880
```

```
Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly Asn Asn Thr
                885                 890                 895

Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ala Phe Lys Phe Thr Ser
            900                 905                 910

Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly Asn Ala Ile
        915                 920                 925

Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe Arg Ser Leu
    930                 935                 940

Arg Leu Ser Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro Asp Ile Pro
945                 950                 955                 960

Glu Trp Arg Arg Asp Val Ser Arg Val Ile Lys Lys Ala Leu Val Glu
                965                 970                 975

Ala Thr Gly Val Pro Gly Gln His Ile Leu Val Ala Val Leu Pro Gly
            980                 985                 990

Leu Pro Thr Ala Ala Glu Leu Phe  Val Leu Pro His Gln  Asp Pro Thr
        995                 1000                1005

Gly Glu  Asn Lys Arg Pro Ala  Glu Asp Leu Glu Gln  Ile Ser Glu
    1010                1015                1020

Leu Met  Ile His Lys Leu Asn  Gln Asn Ser Val His  Phe Glu Leu
    1025                1030                1035

Lys Pro  Gly Val Gln Val Leu  Val His Ala Ala His  Leu Thr Ala
    1040                1045                1050

Ala Pro  Leu Val Asp Leu Thr  Pro Thr His Ser Gly  Ser Ala Met
    1055                1060                1065

Leu Met  Leu Leu Ser Val Val  Phe Val Gly Leu Ala  Val Phe Val
    1070                1075                1080

Ile Tyr  Lys Phe Lys Arg Lys  Ile Pro Gly Ile Asn  Val Tyr Ala
    1085                1090                1095

Gln Met  Gln Asn Glu Lys Glu  Gln Glu Met Val Ser  Arg Val Ser
    1100                1105                1110

His Pro  Glu Ser Arg Pro Tyr  Val Pro Gln Thr Glu  Leu Arg Arg
    1115                1120                1125

Pro Gly  Gln Leu Ile Asp Glu  Lys Val Glu Ser Gln  Leu Ile Gly
    1130                1135                1140

Ser Ile  Ser Ile Val Ala Glu  Asn Gln Ser Thr Lys  Glu Ile Pro
    1145                1150                1155

Thr Tyr  Val Asn Val
    1160
```

<210> 42
<211> 1086
<212> PRT
<213> Bos taurus

<220>
<221> MISC_FEATURE
<222> (1)..(1086)
<223> mature SorCS1

<400> 42

```
Ser Gly Glu Asp Gln Glu Lys Ala Glu Arg Gly Glu Gly Thr Ser Arg
1               5                  10                  15

Ser Pro Arg Gly Val Leu Arg Asp Arg Gly Gln Leu Glu Pro Gly Thr
            20                  25                  30

Leu Glu Arg Asp Pro Asp Lys Ala Thr Arg Phe Arg Leu Glu Glu Leu
        35                  40                  45

Lys Leu Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn
    50                  55                  60

Gln Ala Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile
65                  70                  75                  80

Leu Thr Lys Leu Phe Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser
                85                  90                  95

Leu Trp Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp
            100                 105                 110

Lys Val Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr
        115                 120                 125

Asn Lys Arg Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser
    130                 135                 140

Leu Leu Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu
145                 150                 155                 160
```

```
Asn Phe Tyr Ile Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp
                165                 170                 175

Ile Leu Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe
            180                 185                 190

Gly Arg Arg Trp Gln Leu Ile Gln Glu Ala Val Val Pro Asn Arg Phe
        195                 200                 205

Tyr Trp Ser Val Met Gly Ser Asn Lys Glu Pro Asp Leu Val His Leu
    210                 215                 220

Glu Ala Arg Thr Val Asp Gly His Ser Gln Tyr Leu Thr Cys Arg Met
225                 230                 235                 240

Gln Asn Cys Thr Glu Ala Asn Arg Asn Lys Pro Phe Pro Gly Tyr Ile
                245                 250                 255

Asp Pro Asp Ser Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu
            260                 265                 270

Thr Ser Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn Ala
        275                 280                 285

Phe Ala Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His
    290                 295                 300

Val Ile Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp
305                 310                 315                 320

Asn Gln Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val
                325                 330                 335

Tyr Phe Thr Leu Ala Leu Glu Asn Val Gln Ser Ser Arg Gly Pro Glu
            340                 345                 350

Gly Asn Val Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met
        355                 360                 365

Phe Leu Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr
    370                 375                 380

Tyr Asn Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Thr Asp
385                 390                 395                 400

Leu Arg Gly Asp Pro Val His Cys Val Leu Pro Tyr Cys Ser Leu His
                405                 410                 415
```

```
Leu His Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala
            420                 425                 430

Ser Arg Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly
        435                 440                 445

Ser Glu Leu Ser Asp Ser Asp Ile Ser Met Phe Val Ser Ser Asp Ala
    450                 455                 460

Gly Asn Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Val Leu Tyr
465                 470                 475                 480

Leu Asp Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro
                485                 490                 495

Ile Arg His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys
            500                 505                 510

Tyr Ser Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu
        515                 520                 525

Pro Gly Glu Glu Thr Leu Ile Met Thr Leu Leu Asp His Ser His Ser
    530                 535                 540

Asp Trp Leu Val Thr Ala Leu Gln Pro Cys Cys Leu Phe Leu Leu Gly
545                 550                 555                 560

Asn Glu Trp Glu Asp Lys Ile Ala Trp Lys Pro Gln Asp Gln Gly Glu
                565                 570                 575

Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu
            580                 585                 590

Arg Lys Cys Met Gln Gly Lys Tyr Ala Gly Ala Met Glu Ser Glu Pro
        595                 600                 605

Cys Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg
    610                 615                 620

His Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser
625                 630                 635                 640

Leu Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Thr Gly
                645                 650                 655

Tyr Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln
            660                 665                 670

Tyr Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu
```

```
        675                 680                 685

Arg Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn
    690                 695                 700

Val Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr Leu
705                 710                 715                 720

Ile Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu
                725                 730                 735

Ser Ser Met Glu Asp Gly Ile Lys His Val Tyr His Asn Val Gly Ile
            740                 745                 750

Phe Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala
        755                 760                 765

Val Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser
    770                 775                 780

Leu Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val
785                 790                 795                 800

Leu Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly
                805                 810                 815

Asn Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ala Phe Lys
            820                 825                 830

Phe Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly
        835                 840                 845

Asn Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe
    850                 855                 860

Arg Ser Leu Arg Leu Ser Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro
865                 870                 875                 880

Asp Ile Pro Glu Trp Arg Arg Asp Val Ser Arg Val Ile Lys Lys Ala
                885                 890                 895

Leu Val Glu Ala Thr Gly Val Pro Gly Gln His Ile Leu Val Ala Val
            900                 905                 910

Leu Pro Gly Leu Pro Thr Ala Ala Glu Leu Phe Val Leu Pro His Gln
        915                 920                 925

Asp Pro Thr Gly Glu Asn Lys Arg Pro Ala Glu Asp Leu Glu Gln Ile
    930                 935                 940
```

```
Ser Glu Leu Met Ile His Lys Leu Asn Gln Asn Ser Val His Phe Glu
945                 950                 955                 960

Leu Lys Pro Gly Val Gln Val Leu Val His Ala Ala His Leu Thr Ala
                965                 970                 975

Ala Pro Leu Val Asp Leu Thr Pro Thr His Ser Gly Ser Ala Met Leu
            980                 985                 990

Met Leu Leu Ser Val Val Phe Val  Gly Leu Ala Val Phe  Val Ile Tyr
        995                 1000                1005

Lys Phe  Lys Arg Lys Ile Pro  Gly Ile Asn Val Tyr  Ala Gln Met
    1010                1015                1020

Gln Asn  Glu Lys Glu Gln Glu  Met Val Ser Arg Val  Ser His Pro
    1025                1030                1035

Glu Ser  Arg Pro Tyr Val Pro  Gln Thr Glu Leu Arg  Arg Pro Gly
    1040                1045                1050

Gln Leu  Ile Asp Glu Lys Val  Glu Ser Gln Leu Ile  Gly Ser Ile
    1055                1060                1065

Ser Ile  Val Ala Glu Asn Gln  Ser Thr Lys Glu Ile  Pro Thr Tyr
    1070                1075                1080

Val Asn  Val
    1085
```

<210> 43

<211> 988

<212> PRT

<213> Bos taurus

<220>

<221> MISC_FEATURE

<222> (1)..(988)

<223> soluble SorCS1

<400> 43

```
Ser Gly Glu Asp Gln Glu Lys Ala Glu Arg Gly Glu Gly Thr Ser Arg
1               5                   10                  15

Ser Pro Arg Gly Val Leu Arg Asp Arg Gly Gln Leu Glu Pro Gly Thr
            20                  25                  30

Leu Glu Arg Asp Pro Asp Lys Ala Thr Arg Phe Arg Leu Glu Glu Leu
        35                  40                  45
```

```
Lys Leu Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn
    50                  55                  60

Gln Ala Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile
65                  70                  75                  80

Leu Thr Lys Leu Phe Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser
                85                  90                  95

Leu Trp Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp
            100                 105                 110

Lys Val Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr
        115                 120                 125

Asn Lys Arg Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser
    130                 135                 140

Leu Leu Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu
145                 150                 155                 160

Asn Phe Tyr Ile Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp
                165                 170                 175

Ile Leu Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe
            180                 185                 190

Gly Arg Arg Trp Gln Leu Ile Gln Glu Ala Val Val Pro Asn Arg Phe
        195                 200                 205

Tyr Trp Ser Val Met Gly Ser Asn Lys Glu Pro Asp Leu Val His Leu
    210                 215                 220

Glu Ala Arg Thr Val Asp Gly His Ser Gln Tyr Leu Thr Cys Arg Met
225                 230                 235                 240

Gln Asn Cys Thr Glu Ala Asn Arg Asn Lys Pro Phe Pro Gly Tyr Ile
                245                 250                 255

Asp Pro Asp Ser Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu
            260                 265                 270

Thr Ser Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn Ala
        275                 280                 285

Phe Ala Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His
    290                 295                 300
```

```
Val Ile Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp
305                 310                 315                 320

Asn Gln Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val
                325                 330                 335

Tyr Phe Thr Leu Ala Leu Glu Asn Val Gln Ser Ser Arg Gly Pro Glu
            340                 345                 350

Gly Asn Val Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met
        355                 360                 365

Phe Leu Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr
    370                 375                 380

Tyr Asn Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Thr Asp
385                 390                 395                 400

Leu Arg Gly Asp Pro Val His Cys Val Leu Pro Tyr Cys Ser Leu His
                405                 410                 415

Leu His Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala
            420                 425                 430

Ser Arg Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly
        435                 440                 445

Ser Glu Leu Ser Asp Ser Asp Ile Ser Met Phe Val Ser Ser Asp Ala
    450                 455                 460

Gly Asn Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Val Leu Tyr
465                 470                 475                 480

Leu Asp Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro
                485                 490                 495

Ile Arg His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys
            500                 505                 510

Tyr Ser Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu
        515                 520                 525

Pro Gly Glu Glu Thr Leu Ile Met Thr Leu Leu Asp His Ser His Ser
    530                 535                 540

Asp Trp Leu Val Thr Ala Leu Gln Pro Cys Cys Leu Phe Leu Leu Gly
545                 550                 555                 560
```

```
Asn Glu Trp Glu Asp Lys Ile Ala Trp Lys Pro Gln Asp Gln Gly Glu
                565                 570                 575

Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu
            580                 585                 590

Arg Lys Cys Met Gln Gly Lys Tyr Ala Gly Ala Met Glu Ser Glu Pro
        595                 600                 605

Cys Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg
    610                 615                 620

His Ser Asn Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser
625                 630                 635                 640

Leu Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Thr Gly
                645                 650                 655

Tyr Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln
            660                 665                 670

Tyr Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu
        675                 680                 685

Arg Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn
    690                 695                 700

Val Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr Leu
705                 710                 715                 720

Ile Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu
                725                 730                 735

Ser Ser Met Glu Asp Gly Ile Lys His Val Tyr His Asn Val Gly Ile
            740                 745                 750

Phe Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala
        755                 760                 765

Val Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser
    770                 775                 780

Leu Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val
785                 790                 795                 800

Leu Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly
                805                 810                 815

Asn Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ala Phe Lys
```

```
            820                 825                 830

Phe Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly
        835                 840                 845

Asn Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe
    850                 855                 860

Arg Ser Leu Arg Leu Ser Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro
865                 870                 875                 880

Asp Ile Pro Glu Trp Arg Arg Asp Val Ser Arg Val Ile Lys Lys Ala
                885                 890                 895

Leu Val Glu Ala Thr Gly Val Pro Gly Gln His Ile Leu Val Ala Val
            900                 905                 910

Leu Pro Gly Leu Pro Thr Ala Ala Glu Leu Phe Val Leu Pro His Gln
        915                 920                 925

Asp Pro Thr Gly Glu Asn Lys Arg Pro Ala Glu Asp Leu Glu Gln Ile
    930                 935                 940

Ser Glu Leu Met Ile His Lys Leu Asn Gln Asn Ser Val His Phe Glu
945                 950                 955                 960

Leu Lys Pro Gly Val Gln Val Leu Val His Ala Ala His Leu Thr Ala
                965                 970                 975

Ala Pro Leu Val Asp Leu Thr Pro Thr His Ser Gly
            980                 985
```

<210> 44

<211> 1369

<212> PRT

<213> Rattus norvegicus

<220>

<221> MISC_FEATURE

<222> (1)..(1369)

<223> preproSorCS1

<400> 44

```
Met Arg Ala Gln Val Phe Leu Gln Gln Ser Gly Leu Ser Glu Lys Lys
1               5                   10                  15

His Thr Asp Gly Ile Pro Thr Val Pro Ser Ile Asn Val Ile Pro Glu
            20                  25                  30

Arg Ser Lys Glu Leu Leu Val Pro Arg Gly Arg Val Leu Trp Leu Leu
```

```
        35                  40                  45

Ala Gly Thr Leu Arg Ser Leu Gly Arg Val Gly Asp Ser Thr Ala Arg
    50                  55                  60

Ala Arg Leu Pro Val His Ser Ala Ala Arg Arg Arg Asp Ala Ala Pro
65                  70                  75                  80

Gly Ala Leu Ala Glu Pro Ala Leu Pro Pro Ala Ser Pro Arg Arg Arg
                85                  90                  95

Arg Arg Arg Trp Leu Ala Ala Pro Ser Gln Pro Ala Arg Ser Ser Gln
            100                 105                 110

Ala Gln Pro Gly Arg Ala Ala Gly Thr Cys Pro Ala Pro Pro Pro Arg
        115                 120                 125

Ala Pro Pro Pro Pro Asn Leu Asp Gly Val Val Val Leu Ser Ala His
    130                 135                 140

Pro Ala Ala Val Ser Pro Val Pro Arg Ser Ala Ala Cys Leu Arg Phe
145                 150                 155                 160

Gly Thr Pro Ser Pro Leu Leu Ser Ala Pro Glu Met Gly Lys Val Gly
                165                 170                 175

Ala Gly Asp Gly Ser Ser Ala Ala Leu Ser Ala Leu Leu Thr Gly Ala
            180                 185                 190

Gly Leu Leu Met Leu Leu Ala Pro Gly Ile Cys Ser Ser Leu Ser Cys
        195                 200                 205

Cys Pro Pro Gln His Pro Ser Ser Thr Pro Arg Trp Thr Leu Thr Pro
    210                 215                 220

Arg Gly Phe Ser Tyr Pro Gly Pro Leu Gly Arg Ala Pro Ala Thr Pro
225                 230                 235                 240

Pro Pro Leu Phe Met Arg Pro Leu Phe Ala Val Ala Pro Gly Asp Arg
                245                 250                 255

Ala Leu Phe Leu Glu Arg Ala Gly Gly Ser Arg Val Ser Val Ala Thr
            260                 265                 270

Ala Ser Arg Ser Gly Arg Arg Arg Arg Ser Gly Met Asp Pro Glu Lys
        275                 280                 285

Thr Glu Pro Gly Glu Gly Thr Ser Arg Ser Arg Arg Asp Met Leu Arg
    290                 295                 300
```

```
Asp Gly Gly Gln Gln Gly Pro Gly Thr Gly Ala Arg Asp Pro Asp Lys
305                 310                 315                 320

Ala Thr Arg Phe Arg Met Glu Glu Leu Arg Leu Thr Ser Thr Thr Phe
                325                 330                 335

Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala Met Val His Trp Ser
            340                 345                 350

Gly His Asn Ser Ser Val Ile Leu Ile Leu Thr Lys Leu Tyr Asp Tyr
        355                 360                 365

Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp Arg Ser Thr Asp Tyr
    370                 375                 380

Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Val Gly Leu Lys Thr Ile
385                 390                 395                 400

Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys Arg Lys Ile Met Leu
                405                 410                 415

Leu Thr Asp Pro Glu Ile Glu Ser Ser Leu Leu Ile Ser Ser Asp Glu
            420                 425                 430

Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe Tyr Ile Gln Ser Leu
        435                 440                 445

Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu Ala Tyr Ser Gln Asp
    450                 455                 460

Gln Lys Leu Tyr Ser Ser Ala Glu Phe Gly Arg Arg Trp Gln Leu Ile
465                 470                 475                 480

Gln Glu Ala Val Val Pro Asn Arg Phe Tyr Trp Ser Val Leu Gly Ser
                485                 490                 495

Asn Lys Glu Pro Asp Leu Val His Leu Glu Ala Arg Thr Val Asp Gly
            500                 505                 510

His Ser Ile Tyr Leu Thr Cys Arg Met Gln Asn Cys Thr Glu Ala Asn
        515                 520                 525

Arg Asn Lys Pro Phe Pro Gly Tyr Ile Asp Pro Asp Ser Leu Ile Val
    530                 535                 540

Gln Asp Asp Tyr Val Phe Val Gln Leu Thr Ser Gly Gly Arg Pro His
545                 550                 555                 560
```

```
Tyr Tyr Val Ser Tyr Arg Arg Asn Pro Phe Ala Gln Met Lys Leu Pro
                565                 570                 575

Lys Tyr Ala Leu Pro Lys Asp Met His Val Ile Ser Thr Asp Glu Asn
            580                 585                 590

Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln Asn Asp Thr Tyr Asn
        595                 600                 605

Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe Thr Leu Ala Leu Glu
    610                 615                 620

Asn Val Gln Ser Ser Arg Gly Pro Glu Gly Asn Val Met Ile Asp Leu
625                 630                 635                 640

Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu Ala Asn Lys Lys Ile
                645                 650                 655

Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn Lys Gly Arg Asp Trp
            660                 665                 670

Arg Leu Leu Gln Ala Pro Asp Ala Asp Leu Arg Gly Asp Pro Val His
        675                 680                 685

Cys Leu Leu Pro Tyr Cys Ser Leu His Leu His Leu Lys Val Ser Glu
    690                 695                 700

Asn Pro Tyr Thr Ser Gly Ile Ile Ala Ser Arg Asp Thr Ala Pro Ser
705                 710                 715                 720

Ile Ile Val Ala Ser Gly Asn Ile Gly Ser Glu Leu Ser Asp Ser Asp
                725                 730                 735

Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn Thr Trp Arg Gln Ile
            740                 745                 750

Phe Glu Glu Glu His Ser Ile Leu Tyr Leu Asp Gln Gly Gly Val Leu
        755                 760                 765

Val Ala Met Lys His Thr Ser Leu Pro Ile Arg His Leu Trp Leu Ser
    770                 775                 780

Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr Ser Phe Thr Ser Ile Pro
785                 790                 795                 800

Leu Phe Val Asp Gly Val Leu Gly Glu Pro Gly Glu Glu Thr Leu Ile
                805                 810                 815
```

```
Met Thr Val Phe Gly His Phe Ser His Arg Ser Glu Trp Gln Leu Val
            820                 825                 830

Lys Val Asp Tyr Lys Ser Ile Phe Asp Arg Arg Cys Ala Glu Glu Asp
        835                 840                 845

Tyr Arg Pro Trp Gln Leu His Ser Gln Gly Glu Ala Cys Ile Met Gly
    850                 855                 860

Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu Arg Lys Cys Met Gln
865                 870                 875                 880

Gly Thr Tyr Ala Gly Ala Met Glu Ser Glu Pro Cys Val Cys Thr Glu
                885                 890                 895

Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg His Ser Ser Gly Gln
            900                 905                 910

Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser Leu Ser Lys Asp Cys
        915                 920                 925

Ser Leu Gly Gln Ser Tyr Leu Asn Ser Thr Gly Tyr Arg Lys Val Val
    930                 935                 940

Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln Tyr Thr Ala Lys Pro
945                 950                 955                 960

Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu Arg Ile Val Thr Ala
                965                 970                 975

Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn Val Thr Leu Met Val
            980                 985                 990

Gln Leu Glu Glu Gly Asp Val Gln  Arg Thr Leu Ile Gln  Val Asp Phe
        995                 1000                1005

Gly Asp  Gly Ile Ala Val Ser  Tyr Val Asn Leu Ser  Ser Met Glu
    1010                1015                1020

Asp Gly  Ile Lys His Val Tyr  Gln Asn Val Gly Ile  Phe Arg Val
    1025                1030                1035

Thr Val  Gln Val Asp Asn Ser  Leu Gly Ser Asp Ser  Ala Val Leu
    1040                1045                1050

Tyr Leu  His Val Thr Cys Pro  Leu Glu His Val His  Leu Ser Leu
    1055                1060                1065

Pro Phe  Val Thr Thr Lys Asn  Lys Glu Val Asn Ala  Thr Ala Val
```

```
    1070                1075                1080

Leu Trp  Pro Ser Gln Val Gly  Thr Leu Thr Tyr Val  Trp Trp Tyr
    1085                1090                1095

Gly Asn  Asn Thr Glu Pro Leu  Ile Thr Leu Glu Gly  Ser Ile Ser
    1100                1105                1110

Phe Lys  Phe Thr Ser Glu Gly  Met Asn Thr Ile Thr  Val Gln Val
    1115                1120                1125

Ser Ala  Gly Asn Ala Ile Leu  Gln Asp Thr Lys Thr  Ile Ala Val
    1130                1135                1140

Tyr Glu  Glu Phe Arg Ser Leu  Arg Leu Ala Phe Ser  Pro Asn Leu
    1145                1150                1155

Asp Asp  Tyr Asn Pro Asp Ile  Pro Glu Trp Arg Arg  Asp Ile Ser
    1160                1165                1170

Arg Val  Ile Lys Lys Ser Leu  Val Glu Ala Thr Gly  Ile Pro Ser
    1175                1180                1185

Gln His  Ile Leu Val Ala Val  Leu Pro Gly Leu Pro  Thr Ala Ala
    1190                1195                1200

Glu Leu  Phe Val Leu Pro Tyr  Gln Asp Gly Ala Arg  Glu Asn Lys
    1205                1210                1215

Arg Ser  Pro Glu Asp Leu Glu  Gln Ile Ser Glu Val  Leu Ile His
    1220                1225                1230

Lys Leu  Asn Gln Asn Leu Val  His Phe Glu Leu Lys  Pro Gly Val
    1235                1240                1245

Gln Val  Leu Val His Ala Ala  His Leu Thr Ala Ala  Pro Leu Val
    1250                1255                1260

Asp Leu  Thr Pro Thr His Ser  Gly Ser Ala Met Leu  Met Leu Leu
    1265                1270                1275

Ser Val  Val Phe Val Gly Leu  Ala Val Phe Val Ile  Tyr Lys Phe
    1280                1285                1290

Lys Arg  Lys Ile Pro Gly Ile  Asn Val Tyr Ala Gln  Met Gln Asn
    1295                1300                1305

Glu Lys  Glu Gln Glu Leu Ile  Asn Pro Val Ser His  Thr Glu Ser
    1310                1315                1320

Arg Pro  Thr Ala Pro His Pro  Asp Leu Arg Arg Pro  Gly Gln Leu
    1325                1330                1335

Val Asp  Glu Lys Val Glu Ser  His Leu Leu Gly Ser  Ile Ser Ile
    1340                1345                1350

Val Ala  Glu Asn Gln Ser Thr  Lys Glu Ile Pro Thr  Tyr Val Asn
    1355                1360                1365

Val
```

<210> 45
<211> 1165
<212> PRT
<213> Rattus norvegicus

<220>
<221> MISC_FEATURE
<222> (1)..(1165)
<223> proSorCS1

<400> 45

```
Ser Leu Ser Cys Cys Pro Pro Gln His Pro Ser Ser Thr Pro Arg Trp
1               5                  10                  15

Thr Leu Thr Pro Arg Gly Phe Ser Tyr Pro Gly Pro Leu Gly Arg Ala
            20                  25                  30

Pro Ala Thr Pro Pro Pro Leu Phe Met Arg Pro Leu Phe Ala Val Ala
        35                  40                  45

Pro Gly Asp Arg Ala Leu Phe Leu Glu Arg Ala Gly Gly Ser Arg Val
    50                  55                  60

Ser Val Ala Thr Ala Ser Arg Ser Gly Arg Arg Arg Arg Ser Gly Met
65                  70                  75                  80

Asp Pro Glu Lys Thr Glu Pro Gly Glu Gly Thr Ser Arg Ser Arg Arg
                85                  90                  95

Asp Met Leu Arg Asp Gly Gly Gln Gln Gly Pro Gly Thr Gly Ala Arg
            100                 105                 110

Asp Pro Asp Lys Ala Thr Arg Phe Arg Met Glu Glu Leu Arg Leu Thr
        115                 120                 125

Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala Met
    130                 135                 140

Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile Leu Thr Lys
145                 150                 155                 160

Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp Arg
                165                 170                 175

Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Val Gly
            180                 185                 190

Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys Arg
        195                 200                 205

Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser Leu Leu Ile
    210                 215                 220

Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe Tyr
225                 230                 235                 240

Ile Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu Ala
                245                 250                 255

Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe Gly Arg Arg
            260                 265                 270

Trp Gln Leu Ile Gln Glu Ala Val Val Pro Asn Arg Phe Tyr Trp Ser
        275                 280                 285

Val Leu Gly Ser Asn Lys Glu Pro Asp Leu Val His Leu Glu Ala Arg
    290                 295                 300

Thr Val Asp Gly His Ser Ile Tyr Leu Thr Cys Arg Met Gln Asn Cys
305                 310                 315                 320

Thr Glu Ala Asn Arg Asn Lys Pro Phe Pro Gly Tyr Ile Asp Pro Asp
                325                 330                 335

Ser Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu Thr Ser Gly
            340                 345                 350

Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn Pro Phe Ala Gln
        355                 360                 365

Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His Val Ile Ser
    370                 375                 380

Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln Asn
385                 390                 395                 400
```

```
Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe Thr
                405                 410                 415

Leu Ala Leu Glu Asn Val Gln Ser Ser Arg Gly Pro Glu Gly Asn Val
            420                 425                 430

Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu Ala
        435                 440                 445

Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn Lys
    450                 455                 460

Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Ala Asp Leu Arg Gly
465                 470                 475                 480

Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His Leu His Leu
                485                 490                 495

Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala Ser Arg Asp
            500                 505                 510

Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Ser Glu Leu
        515                 520                 525

Ser Asp Ser Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn Thr
    530                 535                 540

Trp Arg Gln Ile Phe Glu Glu Glu His Ser Ile Leu Tyr Leu Asp Gln
545                 550                 555                 560

Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro Ile Arg His
                565                 570                 575

Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys Tyr Ser Phe
            580                 585                 590

Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu Pro Gly Glu
        595                 600                 605

Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg Ser Glu
    610                 615                 620

Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp Arg Arg Cys
625                 630                 635                 640

Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln Gly Glu Ala
                645                 650                 655
```

```
Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys Ser Glu Arg
            660                 665                 670

Lys Cys Met Gln Gly Thr Tyr Ala Gly Ala Met Glu Ser Glu Pro Cys
        675                 680                 685

Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg His
    690                 695                 700

Ser Ser Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro Ser Ser Leu
705                 710                 715                 720

Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Thr Gly Tyr
                725                 730                 735

Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln Tyr
            740                 745                 750

Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg Gly Leu Arg
        755                 760                 765

Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn Val
    770                 775                 780

Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg Thr Leu Ile
785                 790                 795                 800

Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val Asn Leu Ser
                805                 810                 815

Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val Gly Ile Phe
            820                 825                 830

Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp Ser Ala Val
        835                 840                 845

Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser Leu
    850                 855                 860

Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val Leu
865                 870                 875                 880

Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Tyr Gly Asn
                885                 890                 895

Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser Phe Lys Phe
            900                 905                 910

Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly Asn
```

```
        915                 920                 925

Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Glu Phe Arg
    930                 935                 940

Ser Leu Arg Leu Ala Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro Asp
945                 950                 955                 960

Ile Pro Glu Trp Arg Arg Asp Ile Ser Arg Val Ile Lys Lys Ser Leu
                965                 970                 975

Val Glu Ala Thr Gly Ile Pro Ser Gln His Ile Leu Val Ala Val Leu
            980                 985                 990

Pro Gly Leu Pro Thr Ala Ala Glu  Leu Phe Val Leu Pro  Tyr Gln Asp
        995                 1000                1005

Gly Ala  Arg Glu Asn Lys Arg  Ser Pro Glu Asp Leu  Glu Gln Ile
    1010                1015                1020

Ser Glu  Val Leu Ile His Lys  Leu Asn Gln Asn Leu  Val His Phe
    1025                1030                1035

Glu Leu  Lys Pro Gly Val Gln  Val Leu Val His Ala  Ala His Leu
    1040                1045                1050

Thr Ala  Ala Pro Leu Val Asp  Leu Thr Pro Thr His  Ser Gly Ser
    1055                1060                1065

Ala Met  Leu Met Leu Leu Ser  Val Val Phe Val Gly  Leu Ala Val
    1070                1075                1080

Phe Val  Ile Tyr Lys Phe Lys  Arg Lys Ile Pro Gly  Ile Asn Val
    1085                1090                1095

Tyr Ala  Gln Met Gln Asn Glu  Lys Glu Gln Glu Leu  Ile Asn Pro
    1100                1105                1110

Val Ser  His Thr Glu Ser Arg  Pro Thr Ala Pro His  Pro Asp Leu
    1115                1120                1125

Arg Arg  Pro Gly Gln Leu Val  Asp Glu Lys Val Glu  Ser His Leu
    1130                1135                1140

Leu Gly  Ser Ile Ser Ile Val  Ala Glu Asn Gln Ser  Thr Lys Glu
    1145                1150                1155

Ile Pro  Thr Tyr Val Asn Val
    1160                1165
```

<210> 46
<211> 1088
<212> PRT
<213> Rattus norvegicus

<220>
<221> MISC_FEATURE
<222> (1)..(1088)
<223> mature SorCS1

<400> 46

```
Ser Gly Met Asp Pro Glu Lys Thr Glu Pro Gly Glu Gly Thr Ser Arg
1               5                  10                  15

Ser Arg Arg Asp Met Leu Arg Asp Gly Gly Gln Gln Gly Pro Gly Thr
            20                  25                  30

Gly Ala Arg Asp Pro Asp Lys Ala Thr Arg Phe Arg Met Glu Glu Leu
        35                  40                  45

Arg Leu Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn
    50                  55                  60

Gln Ala Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile
65                  70                  75                  80

Leu Thr Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser
                85                  90                  95

Leu Trp Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp
            100                 105                 110

Lys Val Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr
        115                 120                 125

Asn Lys Arg Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser
    130                 135                 140

Leu Leu Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu
145                 150                 155                 160

Asn Phe Tyr Ile Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp
                165                 170                 175

Ile Leu Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe
            180                 185                 190

Gly Arg Arg Trp Gln Leu Ile Gln Glu Ala Val Val Pro Asn Arg Phe
        195                 200                 205
```

```
Tyr Trp Ser Val Leu Gly Ser Asn Lys Glu Pro Asp Leu Val His Leu
    210                 215                 220

Glu Ala Arg Thr Val Asp Gly His Ser Ile Tyr Leu Thr Cys Arg Met
225                 230                 235                 240

Gln Asn Cys Thr Glu Ala Asn Arg Asn Lys Pro Phe Pro Gly Tyr Ile
                245                 250                 255

Asp Pro Asp Ser Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu
            260                 265                 270

Thr Ser Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn Pro
        275                 280                 285

Phe Ala Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His
    290                 295                 300

Val Ile Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp
305                 310                 315                 320

Asn Gln Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val
                325                 330                 335

Tyr Phe Thr Leu Ala Leu Glu Asn Val Gln Ser Ser Arg Gly Pro Glu
            340                 345                 350

Gly Asn Val Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met
        355                 360                 365

Phe Leu Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr
    370                 375                 380

Tyr Asn Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Ala Asp
385                 390                 395                 400

Leu Arg Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His
                405                 410                 415

Leu His Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala
            420                 425                 430

Ser Arg Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly
        435                 440                 445

Ser Glu Leu Ser Asp Ser Asp Ile Ser Met Phe Val Ser Ser Asp Ala
    450                 455                 460
```

```
Gly Asn Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Ile Leu Tyr
465                 470                 475                 480

Leu Asp Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro
                485                 490                 495

Ile Arg His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys
            500                 505                 510

Tyr Ser Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu
        515                 520                 525

Pro Gly Glu Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His
    530                 535                 540

Arg Ser Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp
545                 550                 555                 560

Arg Arg Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln
                565                 570                 575

Gly Glu Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys
            580                 585                 590

Ser Glu Arg Lys Cys Met Gln Gly Thr Tyr Ala Gly Ala Met Glu Ser
        595                 600                 605

Glu Pro Cys Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr
    610                 615                 620

Glu Arg His Ser Ser Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro
625                 630                 635                 640

Ser Ser Leu Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser
                645                 650                 655

Thr Gly Tyr Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg
            660                 665                 670

Glu Gln Tyr Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg
        675                 680                 685

Gly Leu Arg Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly
    690                 695                 700

His Asn Val Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg
705                 710                 715                 720
```

```
Thr Leu Ile Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val
                725                 730                 735

Asn Leu Ser Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val
            740                 745                 750

Gly Ile Phe Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp
        755                 760                 765

Ser Ala Val Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His
    770                 775                 780

Leu Ser Leu Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr
785                 790                 795                 800

Ala Val Leu Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp
                805                 810                 815

Tyr Gly Asn Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser
            820                 825                 830

Phe Lys Phe Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser
        835                 840                 845

Ala Gly Asn Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu
    850                 855                 860

Glu Phe Arg Ser Leu Arg Leu Ala Phe Ser Pro Asn Leu Asp Asp Tyr
865                 870                 875                 880

Asn Pro Asp Ile Pro Glu Trp Arg Arg Asp Ile Ser Arg Val Ile Lys
                885                 890                 895

Lys Ser Leu Val Glu Ala Thr Gly Ile Pro Ser Gln His Ile Leu Val
            900                 905                 910

Ala Val Leu Pro Gly Leu Pro Thr Ala Ala Glu Leu Phe Val Leu Pro
        915                 920                 925

Tyr Gln Asp Gly Ala Arg Glu Asn Lys Arg Ser Pro Glu Asp Leu Glu
    930                 935                 940

Gln Ile Ser Glu Val Leu Ile His Lys Leu Asn Gln Asn Leu Val His
945                 950                 955                 960

Phe Glu Leu Lys Pro Gly Val Gln Val Leu Val His Ala Ala His Leu
                965                 970                 975

Thr Ala Ala Pro Leu Val Asp Leu Thr Pro Thr His Ser Gly Ser Ala

            980                 985                 990

Met Leu Met Leu Leu Ser Val Val  Phe Val Gly Leu Ala  Val Phe Val
        995                 1000                1005

Ile Tyr  Lys Phe Lys Arg Lys  Ile Pro Gly Ile Asn  Val Tyr Ala
    1010                1015                1020

Gln Met  Gln Asn Glu Lys Glu  Gln Glu Leu Ile Asn  Pro Val Ser
    1025                1030                1035

His Thr  Glu Ser Arg Pro Thr  Ala Pro His Pro Asp  Leu Arg Arg
    1040                1045                1050

Pro Gly  Gln Leu Val Asp Glu  Lys Val Glu Ser His  Leu Leu Gly
    1055                1060                1065

Ser Ile  Ser Ile Val Ala Glu  Asn Gln Ser Thr Lys  Glu Ile Pro
    1070                1075                1080

Thr Tyr  Val Asn Val
    1085
```

<210> 47

<211> 990

<212> PRT

<213> Rattus norvegicus

<220>

<221> MISC_FEATURE

<222> (1)..(990)

<223> soluble SorCS1

<400> 47

```
Ser Gly Met Asp Pro Glu Lys Thr Glu Pro Gly Glu Gly Thr Ser Arg
1               5                   10                  15

Ser Arg Arg Asp Met Leu Arg Asp Gly Gly Gln Gln Gly Pro Gly Thr
            20                  25                  30

Gly Ala Arg Asp Pro Asp Lys Ala Thr Arg Phe Arg Met Glu Glu Leu
        35                  40                  45

Arg Leu Thr Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn
    50                  55                  60

Gln Ala Met Val His Trp Ser Gly His Asn Ser Ser Val Ile Leu Ile
65                  70                  75                  80

Leu Thr Lys Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser
```

```
                85                  90                  95

Leu Trp Arg Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp
            100                 105                 110

Lys Val Gly Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr
        115                 120                 125

Asn Lys Arg Lys Ile Met Leu Leu Thr Asp Pro Glu Ile Glu Ser Ser
    130                 135                 140

Leu Leu Ile Ser Ser Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu
145                 150                 155                 160

Asn Phe Tyr Ile Gln Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp
                165                 170                 175

Ile Leu Ala Tyr Ser Gln Asp Gln Lys Leu Tyr Ser Ser Ala Glu Phe
            180                 185                 190

Gly Arg Arg Trp Gln Leu Ile Gln Glu Ala Val Val Pro Asn Arg Phe
        195                 200                 205

Tyr Trp Ser Val Leu Gly Ser Asn Lys Glu Pro Asp Leu Val His Leu
    210                 215                 220

Glu Ala Arg Thr Val Asp Gly His Ser Ile Tyr Leu Thr Cys Arg Met
225                 230                 235                 240

Gln Asn Cys Thr Glu Ala Asn Arg Asn Lys Pro Phe Pro Gly Tyr Ile
                245                 250                 255

Asp Pro Asp Ser Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu
            260                 265                 270

Thr Ser Gly Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn Pro
        275                 280                 285

Phe Ala Gln Met Lys Leu Pro Lys Tyr Ala Leu Pro Lys Asp Met His
    290                 295                 300

Val Ile Ser Thr Asp Glu Asn Gln Val Phe Ala Ala Val Gln Glu Trp
305                 310                 315                 320

Asn Gln Asn Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val
                325                 330                 335

Tyr Phe Thr Leu Ala Leu Glu Asn Val Gln Ser Ser Arg Gly Pro Glu
            340                 345                 350
```

```
Gly Asn Val Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met
        355                 360                 365

Phe Leu Ala Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr
    370                 375                 380

Tyr Asn Lys Gly Arg Asp Trp Arg Leu Leu Gln Ala Pro Asp Ala Asp
385                 390                 395                 400

Leu Arg Gly Asp Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His
                405                 410                 415

Leu His Leu Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Ile Ile Ala
            420                 425                 430

Ser Arg Asp Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly
        435                 440                 445

Ser Glu Leu Ser Asp Ser Asp Ile Ser Met Phe Val Ser Ser Asp Ala
    450                 455                 460

Gly Asn Thr Trp Arg Gln Ile Phe Glu Glu Glu His Ser Ile Leu Tyr
465                 470                 475                 480

Leu Asp Gln Gly Gly Val Leu Val Ala Met Lys His Thr Ser Leu Pro
                485                 490                 495

Ile Arg His Leu Trp Leu Ser Phe Asp Glu Gly Arg Ser Trp Ser Lys
            500                 505                 510

Tyr Ser Phe Thr Ser Ile Pro Leu Phe Val Asp Gly Val Leu Gly Glu
        515                 520                 525

Pro Gly Glu Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His
    530                 535                 540

Arg Ser Glu Trp Gln Leu Val Lys Val Asp Tyr Lys Ser Ile Phe Asp
545                 550                 555                 560

Arg Arg Cys Ala Glu Glu Asp Tyr Arg Pro Trp Gln Leu His Ser Gln
                565                 570                 575

Gly Glu Ala Cys Ile Met Gly Ala Lys Arg Ile Tyr Lys Lys Arg Lys
            580                 585                 590

Ser Glu Arg Lys Cys Met Gln Gly Thr Tyr Ala Gly Ala Met Glu Ser
        595                 600                 605
```

```
Glu Pro Cys Val Cys Thr Glu Ala Asp Phe Asp Cys Asp Tyr Gly Tyr
    610                 615                 620

Glu Arg His Ser Ser Gly Gln Cys Leu Pro Ala Phe Trp Phe Asn Pro
625                 630                 635                 640

Ser Ser Leu Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser
                645                 650                 655

Thr Gly Tyr Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg
            660                 665                 670

Glu Gln Tyr Thr Ala Lys Pro Gln Lys Cys Pro Gly Lys Ala Pro Arg
        675                 680                 685

Gly Leu Arg Ile Val Thr Ala Asp Gly Lys Leu Thr Ala Glu Gln Gly
    690                 695                 700

His Asn Val Thr Leu Met Val Gln Leu Glu Glu Gly Asp Val Gln Arg
705                 710                 715                 720

Thr Leu Ile Gln Val Asp Phe Gly Asp Gly Ile Ala Val Ser Tyr Val
                725                 730                 735

Asn Leu Ser Ser Met Glu Asp Gly Ile Lys His Val Tyr Gln Asn Val
            740                 745                 750

Gly Ile Phe Arg Val Thr Val Gln Val Asp Asn Ser Leu Gly Ser Asp
        755                 760                 765

Ser Ala Val Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His
    770                 775                 780

Leu Ser Leu Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr
785                 790                 795                 800

Ala Val Leu Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp
                805                 810                 815

Tyr Gly Asn Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Ser
            820                 825                 830

Phe Lys Phe Thr Ser Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser
        835                 840                 845

Ala Gly Asn Ala Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu
    850                 855                 860

Glu Phe Arg Ser Leu Arg Leu Ala Phe Ser Pro Asn Leu Asp Asp Tyr
865                 870                 875                 880

Asn Pro Asp Ile Pro Glu Trp Arg Arg Asp Ile Ser Arg Val Ile Lys
                885                 890                 895

Lys Ser Leu Val Glu Ala Thr Gly Ile Pro Ser Gln His Ile Leu Val
            900                 905                 910

Ala Val Leu Pro Gly Leu Pro Thr Ala Ala Glu Leu Phe Val Leu Pro
        915                 920                 925

Tyr Gln Asp Gly Ala Arg Glu Asn Lys Arg Ser Pro Glu Asp Leu Glu
    930                 935                 940

Gln Ile Ser Glu Val Leu Ile His Lys Leu Asn Gln Asn Leu Val His
945                 950                 955                 960

Phe Glu Leu Lys Pro Gly Val Gln Val Leu Val His Ala Ala His Leu
                965                 970                 975

Thr Ala Ala Pro Leu Val Asp Leu Thr Pro Thr His Ser Gly
            980                 985                 990
```

<210> 48

<211> 1258

<212> PRT
<213> Gallus gallus

<220>
<221> MISC_FEATURE
<222> (1)..(1258)
<223> preproSorCS1

<400> 48

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Met Glu Lys Val Ala Gly Trp Tyr Pro Ala Trp His Val Ala Leu Leu
1               5                   10                  15

Tyr Trp Thr Trp Leu Phe Leu Phe Thr Phe Gly Phe Thr Gly Ala Glu
            20                  25                  30

Ile Thr Cys Arg Ser Cys His Ser Gln Val Asn Pro Gln Gln Gln His
        35                  40                  45

Pro Gln Gln Gly Leu Pro Met His Leu Lys Thr Asp Arg Gly Glu Lys
    50                  55                  60

Glu Arg Trp Arg Ile Pro Gly Glu Gln Gly Gly Glu Arg Gly Arg Gly
65                  70                  75                  80

Ala Gly Met Asp Thr Glu Asp Ala Glu Leu Gln Ala Pro Phe Asp Pro
                85                  90                  95

Ala Leu Ala Gly Thr Lys Phe Ser Gly Trp Glu Thr Arg Ser Trp Ala
            100                 105                 110

Ser Glu Pro Glu Lys Ala Pro Gly Asp Ser Arg Pro Gly Ala Ala Ala
        115                 120                 125

Ala Pro Thr Gly Glu Tyr Pro Gln Arg Gly Gln Ala Gly Gly Arg Arg
    130                 135                 140

Asn Ser Ala Arg Arg Arg Arg Gly Arg Ser Pro Arg Gly Thr Ala Gly
145                 150                 155                 160

Pro Gly Gly Ala Ala Gly Arg Glu Pro Gly Gly Ser Gly Ala Ala Arg
                165                 170                 175

Phe Gly Leu Glu Glu Leu Arg Leu Gly Ser Thr Thr Phe Ala Leu Thr
            180                 185                 190

Gly Asp Ser Ala His Asn Gln Ala Met Val His Trp Ser Gly Gln Asn
        195                 200                 205

Ser Ser Val Ile Leu Ile Leu Thr Lys Leu Tyr Asp Tyr Asn Leu Gly
    210                 215                 220

Ser Ile Thr Glu Ser Ser Leu Trp Arg Ser Thr Asp Tyr Gly Thr Thr
225                 230                 235                 240

Tyr Glu Lys Leu Asn Asp Lys Ile Gly Leu Lys Thr Ile Leu Ser Tyr
                245                 250                 255

Leu Tyr Val Cys Pro Thr Asn Lys Arg Lys Ile Met Leu Leu Thr Asp
            260                 265                 270

Pro Glu Val Glu Ser Ser Leu Leu Ile Ser Thr Asp Glu Gly Ala Thr
        275                 280                 285

Tyr Gln Lys Tyr Arg Leu Asn Phe Tyr Ile His Ser Leu Leu Phe His
    290                 295                 300

Pro Lys Gln Glu Asp Trp Ile Leu Ala Tyr Ser Gln Asp Gln Lys Leu
305                 310                 315                 320

Phe Ser Ser Val Glu Phe Gly Arg Arg Trp Leu Leu Leu His Glu Gly
                325                 330                 335

Val Ala Pro Asn Arg Phe Tyr Trp Ser Met Met Val Ser Gly Arg Glu
```

```
            340                 345                 350

Pro Asp Leu Val His Leu Glu Ala Lys Thr Val Asp Gly His Ala Gln
        355                 360                 365

Tyr Ile Thr Cys Lys Met Gln Asn Cys Ser Glu Ala Ser Gln Asn Lys
    370                 375                 380

Pro Phe Pro Gly Tyr Ile Asp His Asn Ser Leu Ile Val Gln Asp Asp
385                 390                 395                 400

Tyr Val Phe Val Gln Leu Thr Ser Gly Gly Arg Pro His Tyr Tyr Val
                405                 410                 415

Ser Tyr Arg Arg Asn Ala Phe Thr Pro Ile Lys Leu Pro Lys Tyr Ser
            420                 425                 430

Leu Pro Lys Asp Met His Val Ile Ser Thr Asp Glu Ser Gln Val Phe
        435                 440                 445

Ala Ala Val Gln Glu Trp Asn Gln Asn Asp Thr Tyr Asn Leu Tyr Ile
    450                 455                 460

Ser Asp Thr Arg Gly Val Tyr Phe Thr Leu Ala Leu Glu Asn Val Lys
465                 470                 475                 480

Ser Ser Gln Gly Leu Asp Gly Asn Val Met Ile Asp Leu Tyr Glu Val
                485                 490                 495

Ala Gly Ile Lys Gly Met Phe Leu Ala Asn Lys Lys Ile Asp Asn Gln
            500                 505                 510

Val Lys Thr Phe Ile Thr Tyr Asn Lys Gly Arg Asp Trp Asn Leu Leu
        515                 520                 525

Gln Ala Pro Asp Thr Asp Leu Lys Gly Asn Pro Val His Cys Leu Leu
    530                 535                 540

Pro Tyr Cys Ser Leu His Leu His Leu Lys Val Ser Glu Asn Pro Tyr
545                 550                 555                 560

Thr Ser Gly Asn Ile Ala Ser Arg Asp Thr Ala Pro Ser Ile Ile Val
                565                 570                 575

Ala Ser Gly Asn Ile Gly Pro Glu Leu Ser Asp Asn Asp Ile Ser Met
            580                 585                 590

Phe Val Ser Ser Asp Ala Gly Asn Thr Trp Arg Gln Ile Phe Glu Glu
        595                 600                 605
```

```
Glu His Ser Val Leu Tyr Leu Asp Gln Gly Gly Val Leu Val Ala Ile
    610                 615                 620

Lys His Thr Ser Leu Pro Ile Arg His Leu Trp Leu Ser Phe Asp Glu
625                 630                 635                 640

Gly Lys Ser Trp Ser Lys Tyr Ser Phe Thr Ser Leu Pro Leu Phe Val
                645                 650                 655

Asp Gly Ile Leu Gly Glu Pro Gly Glu Glu Thr Leu Ile Met Thr Val
            660                 665                 670

Phe Gly His Phe Ser His Arg Ser Glu Trp Gln Leu Val Lys Ile Asp
        675                 680                 685

Tyr Lys Ser Ile Phe Asp Arg Arg Cys Ala Glu Glu Asp Tyr Trp Thr
    690                 695                 700

Trp Gln Leu His Ser Gln Gly Glu Ala Cys Ile Met Gly Ala Lys Arg
705                 710                 715                 720

Ile Tyr Arg Lys Arg Lys Ser Glu Lys Lys Cys Met Gln Gly Lys Tyr
                725                 730                 735

Ala Gly Ala Met Thr Ser Glu Pro Cys Val Cys Thr Asp Ala Asp Phe
            740                 745                 750

Asp Cys Asp Tyr Gly Tyr Glu Arg His Arg Asn Gly Gln Cys Leu Pro
        755                 760                 765

Ala Phe Trp Tyr Asn Pro Ser Ser Leu Ser Lys Asp Cys Ser Leu Gly
    770                 775                 780

Gln Ser Tyr Leu Asn Ser Thr Gly Tyr Arg Lys Val Val Ser Asn Asn
785                 790                 795                 800

Cys Thr Asp Gly Val Arg Glu Gln Tyr Thr Ala Lys Pro Gln Gln Cys
                805                 810                 815

Pro Gly Lys Ala Pro Gln Gly Leu Arg Ile Ile Thr Ser Asp Gly Lys
            820                 825                 830

Leu Thr Ala Glu Gln Gly His Asn Val Thr Phe Leu Val Gln Leu Glu
        835                 840                 845

Glu Gly Asp Leu Gln Arg Ser Leu Ile Gln Val Asp Phe Gly Asp Gly
    850                 855                 860
```

```
Thr Ala Val Ser Tyr Ala Asn Leu Ser Ser Thr Glu Asp Gly Ile Lys
865                 870                 875                 880

His Thr Tyr Gln Asn Val Gly Ile Phe Arg Val Thr Val Leu Val Glu
                885                 890                 895

Asn Ser Leu Gly Ser Asp Asn Ala Val Leu Tyr Leu His Val Thr Cys
            900                 905                 910

Pro Leu Glu His Val His Leu Ser Leu Pro Phe Val Thr Thr Lys Asn
        915                 920                 925

Lys Glu Val Asn Ala Thr Ala Val Leu Trp Pro Ser Gln Val Gly Thr
    930                 935                 940

Leu Thr Tyr Val Trp Trp Phe Gly Asn Asn Thr Glu Pro Leu Ile Thr
945                 950                 955                 960

Leu Glu Gly Ser Ile Thr Phe Thr Phe Ser Val Glu Gly Met Asn Thr
                965                 970                 975

Ile Thr Val Gln Val Ser Ala Gly Asn Thr Ile Leu Gln Asp Thr Lys
            980                 985                 990

Thr Ile Ala Val Tyr Glu Gln Phe  Arg Ser Leu Arg Leu  Ser Phe Ser
        995                 1000                1005

Pro Asn  Leu Asp Asp Tyr Asn  Pro Asp Ile Pro Glu  Trp Arg Arg
    1010                1015                1020

Asp Ile  Ser Arg Val Val Lys  Arg Ala Leu Val Glu  Ala Thr Gly
    1025                1030                1035

Ile Ser  Ser Lys His Ile Leu  Val Ala Val Leu Pro  Gly Leu Pro
    1040                1045                1050

Thr Ser  Ala Glu Leu Phe Ile  Leu Pro Tyr Gln Asp  Ala Thr Gly
    1055                1060                1065

Gly Asn  Lys Arg Thr Glu Asp  Leu Glu Gln Ile Ser  Glu Ile Leu
    1070                1075                1080

Ile Gln  Lys Leu Asn Gln Asn  Phe Val His Phe Glu  Leu Lys Pro
    1085                1090                1095

Gly Val  Arg Val Leu Val His  Ala Ala His Leu Thr  Ala Ala Pro
    1100                1105                1110
```

```
Leu Val  Asp Leu Thr Pro Ser  His Ser Gly Ser Ala  Met Leu Met
    1115                1120                1125

Leu Leu  Ser Val Val Phe Val  Gly Leu Ala Val Phe  Val Ile Tyr
    1130                1135                1140

Lys Phe  Lys Arg Lys Ile Pro  Gly Leu Asn Ile Tyr  Ala Gln Met
    1145                1150                1155

Gln Asn  Glu Lys Asp Gln Glu  Met Val Ser Pro Val  Ser Gln Arg
    1160                1165                1170

Glu Ser  Ile Pro Asn Val Pro  Gln Ser Glu Leu Met  Ser Pro Glu
    1175                1180                1185

Gln Leu  Val Asp Glu Lys Leu  Asp Val Gln Pro Ile  Glu Gln Pro
    1190                1195                1200

Gln Ala  Thr Val Gln Asn Pro  Arg Lys Gly Asn Ala  Ala Lys Val
    1205                1210                1215

Val Trp  Thr Glu Asp Phe Gln  Lys Ala Cys Gly Ser  Pro Arg Gly
    1220                1225                1230

Phe Lys  Pro Arg Pro Gly Ala  Glu Val Phe Pro Gln  Leu Leu Ser
    1235                1240                1245

Pro Arg  Ala Gln Lys Lys Ser  Leu Pro Met
    1250                1255
```

<210> 49

<211> 1200

<212> PRT

<213> Gallus gallus

<220>

<221> MISC_FEATURE

<222> (1)..(1200)

<223> proSorCS1

<400> 49

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Thr Asp Arg Gly Glu Lys Glu Arg Trp Arg Ile Pro Gly Glu Gln Gly
1               5                   10                  15

Gly Glu Arg Gly Arg Gly Ala Gly Met Asp Thr Glu Asp Ala Glu Leu
            20                  25                  30

Gln Ala Pro Phe Asp Pro Ala Leu Ala Gly Thr Lys Phe Ser Gly Trp
        35                  40                  45
```

```
Glu Thr Arg Ser Trp Ala Ser Glu Pro Glu Lys Ala Pro Gly Asp Ser
    50                  55                  60

Arg Pro Gly Ala Ala Ala Ala Pro Thr Gly Glu Tyr Pro Gln Arg Gly
65                  70                  75                  80

Gln Ala Gly Gly Arg Arg Asn Ser Ala Arg Arg Arg Arg Gly Arg Ser
                85                  90                  95

Pro Arg Gly Thr Ala Gly Pro Gly Gly Ala Ala Gly Arg Glu Pro Gly
            100                 105                 110

Gly Ser Gly Ala Ala Arg Phe Gly Leu Glu Glu Leu Arg Leu Gly Ser
        115                 120                 125

Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala Met Val
    130                 135                 140

His Trp Ser Gly Gln Asn Ser Ser Val Ile Leu Ile Leu Thr Lys Leu
145                 150                 155                 160

Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp Arg Ser
                165                 170                 175

Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Ile Gly Leu
            180                 185                 190

Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys Arg Lys
        195                 200                 205

Ile Met Leu Leu Thr Asp Pro Glu Val Glu Ser Ser Leu Leu Ile Ser
    210                 215                 220

Thr Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe Tyr Ile
225                 230                 235                 240

His Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu Ala Tyr
                245                 250                 255

Ser Gln Asp Gln Lys Leu Phe Ser Ser Val Glu Phe Gly Arg Arg Trp
            260                 265                 270

Leu Leu Leu His Glu Gly Val Ala Pro Asn Arg Phe Tyr Trp Ser Met
        275                 280                 285

Met Val Ser Gly Arg Glu Pro Asp Leu Val His Leu Glu Ala Lys Thr
    290                 295                 300

Val Asp Gly His Ala Gln Tyr Ile Thr Cys Lys Met Gln Asn Cys Ser
```

```
305                 310                 315                 320

Glu Ala Ser Gln Asn Lys Pro Phe Pro Gly Tyr Ile Asp His Asn Ser
                325                 330                 335

Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu Thr Ser Gly Gly
            340                 345                 350

Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn Ala Phe Thr Pro Ile
        355                 360                 365

Lys Leu Pro Lys Tyr Ser Leu Pro Lys Asp Met His Val Ile Ser Thr
    370                 375                 380

Asp Glu Ser Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln Asn Asp
385                 390                 395                 400

Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe Thr Leu
                405                 410                 415

Ala Leu Glu Asn Val Lys Ser Ser Gln Gly Leu Asp Gly Asn Val Met
            420                 425                 430

Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu Ala Asn
        435                 440                 445

Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn Lys Gly
    450                 455                 460

Arg Asp Trp Asn Leu Leu Gln Ala Pro Asp Thr Asp Leu Lys Gly Asn
465                 470                 475                 480

Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His Leu His Leu Lys
                485                 490                 495

Val Ser Glu Asn Pro Tyr Thr Ser Gly Asn Ile Ala Ser Arg Asp Thr
            500                 505                 510

Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Pro Glu Leu Ser
        515                 520                 525

Asp Asn Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn Thr Trp
    530                 535                 540

Arg Gln Ile Phe Glu Glu Glu His Ser Val Leu Tyr Leu Asp Gln Gly
545                 550                 555                 560

Gly Val Leu Val Ala Ile Lys His Thr Ser Leu Pro Ile Arg His Leu
                565                 570                 575
```

```
Trp Leu Ser Phe Asp Glu Gly Lys Ser Trp Ser Lys Tyr Ser Phe Thr
            580                 585                 590

Ser Leu Pro Leu Phe Val Asp Gly Ile Leu Gly Glu Pro Gly Glu Glu
        595                 600                 605

Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg Ser Glu Trp
    610                 615                 620

Gln Leu Val Lys Ile Asp Tyr Lys Ser Ile Phe Asp Arg Arg Cys Ala
625                 630                 635                 640

Glu Glu Asp Tyr Trp Thr Trp Gln Leu His Ser Gln Gly Glu Ala Cys
                645                 650                 655

Ile Met Gly Ala Lys Arg Ile Tyr Arg Lys Arg Lys Ser Glu Lys Lys
            660                 665                 670

Cys Met Gln Gly Lys Tyr Ala Gly Ala Met Thr Ser Glu Pro Cys Val
        675                 680                 685

Cys Thr Asp Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg His Arg
    690                 695                 700

Asn Gly Gln Cys Leu Pro Ala Phe Trp Tyr Asn Pro Ser Ser Leu Ser
705                 710                 715                 720

Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Thr Gly Tyr Arg
                725                 730                 735

Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln Tyr Thr
            740                 745                 750

Ala Lys Pro Gln Gln Cys Pro Gly Lys Ala Pro Gln Gly Leu Arg Ile
        755                 760                 765

Ile Thr Ser Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn Val Thr
    770                 775                 780

Phe Leu Val Gln Leu Glu Glu Gly Asp Leu Gln Arg Ser Leu Ile Gln
785                 790                 795                 800

Val Asp Phe Gly Asp Gly Thr Ala Val Ser Tyr Ala Asn Leu Ser Ser
                805                 810                 815

Thr Glu Asp Gly Ile Lys His Thr Tyr Gln Asn Val Gly Ile Phe Arg
            820                 825                 830
```

```
Val Thr Val Leu Val Glu Asn Ser Leu Gly Ser Asp Asn Ala Val Leu
        835                 840                 845

Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser Leu Pro
    850                 855                 860

Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val Leu Trp
865                 870                 875                 880

Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Phe Gly Asn Asn
                885                 890                 895

Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Thr Phe Thr Phe Ser
            900                 905                 910

Val Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly Asn Thr
        915                 920                 925

Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Gln Phe Arg Ser
    930                 935                 940

Leu Arg Leu Ser Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro Asp Ile
945                 950                 955                 960

Pro Glu Trp Arg Arg Asp Ile Ser Arg Val Val Lys Arg Ala Leu Val
                965                 970                 975

Glu Ala Thr Gly Ile Ser Ser Lys His Ile Leu Val Ala Val Leu Pro
            980                 985                 990

Gly Leu Pro Thr Ser Ala Glu Leu  Phe Ile Leu Pro Tyr  Gln Asp Ala
        995                 1000                1005

Thr Gly  Gly Asn Lys Arg Thr  Glu Asp Leu Glu Gln  Ile Ser Glu
    1010                1015                1020

Ile Leu  Ile Gln Lys Leu Asn  Gln Asn Phe Val His  Phe Glu Leu
    1025                1030                1035

Lys Pro  Gly Val Arg Val Leu  Val His Ala Ala His  Leu Thr Ala
    1040                1045                1050

Ala Pro  Leu Val Asp Leu Thr  Pro Ser His Ser Gly  Ser Ala Met
    1055                1060                1065

Leu Met  Leu Leu Ser Val Val  Phe Val Gly Leu Ala  Val Phe Val
    1070                1075                1080

Ile Tyr  Lys Phe Lys Arg Lys  Ile Pro Gly Leu Asn  Ile Tyr Ala
    1085                1090                1095

Gln Met  Gln Asn Glu Lys Asp  Gln Glu Met Val Ser  Pro Val Ser
    1100                1105                1110

Gln Arg  Glu Ser Ile Pro Asn  Val Pro Gln Ser Glu  Leu Met Ser
    1115                1120                1125

Pro Glu  Gln Leu Val Asp Glu  Lys Leu Asp Val Gln  Pro Ile Glu
    1130                1135                1140

Gln Pro  Gln Ala Thr Val Gln  Asn Pro Arg Lys Gly  Asn Ala Ala
    1145                1150                1155

Lys Val  Val Trp Thr Glu Asp  Phe Gln Lys Ala Cys  Gly Ser Pro
    1160                1165                1170

Arg Gly  Phe Lys Pro Arg Pro  Gly Ala Glu Val Phe  Pro Gln Leu
    1175                1180                1185

Leu Ser  Pro Arg Ala Gln Lys  Lys Ser Leu Pro Met
    1190                1195                1200
```

<210> 50

<211> 1121

<212> PRT
<213> Gallus gallus

<220>
<221> MISC_FEATURE
<222> (1)..(1121)
<223> mature SorCS1

<400> 50

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Gly Gln Ala Gly Gly Arg Arg Asn Ser Ala Arg Arg Arg Arg Gly Arg
1               5                   10                  15

Ser Pro Arg Gly Thr Ala Gly Pro Gly Gly Ala Ala Gly Arg Glu Pro
            20                  25                  30

Gly Gly Ser Gly Ala Ala Arg Phe Gly Leu Glu Glu Leu Arg Leu Gly
        35                  40                  45

Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala Met
    50                  55                  60

Val His Trp Ser Gly Gln Asn Ser Ser Val Ile Leu Ile Leu Thr Lys
65                  70                  75                  80

Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp Arg
                85                  90                  95

Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Ile Gly
            100                 105                 110

Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys Arg
        115                 120                 125

Lys Ile Met Leu Leu Thr Asp Pro Glu Val Glu Ser Ser Leu Leu Ile
    130                 135                 140

Ser Thr Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe Tyr
145                 150                 155                 160

Ile His Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu Ala
                165                 170                 175

Tyr Ser Gln Asp Gln Lys Leu Phe Ser Ser Val Glu Phe Gly Arg Arg
            180                 185                 190

Trp Leu Leu Leu His Glu Gly Val Ala Pro Asn Arg Phe Tyr Trp Ser
        195                 200                 205

Met Met Val Ser Gly Arg Glu Pro Asp Leu Val His Leu Glu Ala Lys
    210                 215                 220

Thr Val Asp Gly His Ala Gln Tyr Ile Thr Cys Lys Met Gln Asn Cys
225                 230                 235                 240

Ser Glu Ala Ser Gln Asn Lys Pro Phe Pro Gly Tyr Ile Asp His Asn
                245                 250                 255

Ser Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu Thr Ser Gly
            260                 265                 270

Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn Ala Phe Thr Pro
        275                 280                 285

Ile Lys Leu Pro Lys Tyr Ser Leu Pro Lys Asp Met His Val Ile Ser
    290                 295                 300

Thr Asp Glu Ser Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln Asn
305                 310                 315                 320

Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe Thr
                325                 330                 335

Leu Ala Leu Glu Asn Val Lys Ser Ser Gln Gly Leu Asp Gly Asn Val
```

```
            340                 345                 350

Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu Ala
        355                 360                 365

Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn Lys
    370                 375                 380

Gly Arg Asp Trp Asn Leu Leu Gln Ala Pro Asp Thr Asp Leu Lys Gly
385                 390                 395                 400

Asn Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His Leu His Leu
                405                 410                 415

Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Asn Ile Ala Ser Arg Asp
            420                 425                 430

Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Pro Glu Leu
        435                 440                 445

Ser Asp Asn Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn Thr
    450                 455                 460

Trp Arg Gln Ile Phe Glu Glu Glu His Ser Val Leu Tyr Leu Asp Gln
465                 470                 475                 480

Gly Gly Val Leu Val Ala Ile Lys His Thr Ser Leu Pro Ile Arg His
                485                 490                 495

Leu Trp Leu Ser Phe Asp Glu Gly Lys Ser Trp Ser Lys Tyr Ser Phe
            500                 505                 510

Thr Ser Leu Pro Leu Phe Val Asp Gly Ile Leu Gly Glu Pro Gly Glu
        515                 520                 525

Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg Ser Glu
    530                 535                 540

Trp Gln Leu Val Lys Ile Asp Tyr Lys Ser Ile Phe Asp Arg Arg Cys
545                 550                 555                 560

Ala Glu Glu Asp Tyr Trp Thr Trp Gln Leu His Ser Gln Gly Glu Ala
                565                 570                 575

Cys Ile Met Gly Ala Lys Arg Ile Tyr Arg Lys Arg Lys Ser Glu Lys
            580                 585                 590

Lys Cys Met Gln Gly Lys Tyr Ala Gly Ala Met Thr Ser Glu Pro Cys
        595                 600                 605
```

```
Val Cys Thr Asp Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg His
    610                 615                 620

Arg Asn Gly Gln Cys Leu Pro Ala Phe Trp Tyr Asn Pro Ser Ser Leu
625                 630                 635                 640

Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Thr Gly Tyr
                645                 650                 655

Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln Tyr
            660                 665                 670

Thr Ala Lys Pro Gln Gln Cys Pro Gly Lys Ala Pro Gln Gly Leu Arg
        675                 680                 685

Ile Ile Thr Ser Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn Val
    690                 695                 700

Thr Phe Leu Val Gln Leu Glu Glu Gly Asp Leu Gln Arg Ser Leu Ile
705                 710                 715                 720

Gln Val Asp Phe Gly Asp Gly Thr Ala Val Ser Tyr Ala Asn Leu Ser
                725                 730                 735

Ser Thr Glu Asp Gly Ile Lys His Thr Tyr Gln Asn Val Gly Ile Phe
            740                 745                 750

Arg Val Thr Val Leu Val Glu Asn Ser Leu Gly Ser Asp Asn Ala Val
        755                 760                 765

Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser Leu
    770                 775                 780

Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val Leu
785                 790                 795                 800

Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Phe Gly Asn
                805                 810                 815

Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Thr Phe Thr Phe
            820                 825                 830

Ser Val Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly Asn
        835                 840                 845

Thr Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Gln Phe Arg
    850                 855                 860
```

```
Ser Leu Arg Leu Ser Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro Asp
865                 870                 875                 880

Ile Pro Glu Trp Arg Arg Asp Ile Ser Arg Val Val Lys Arg Ala Leu
                885                 890                 895

Val Glu Ala Thr Gly Ile Ser Ser Lys His Ile Leu Val Ala Val Leu
            900                 905                 910

Pro Gly Leu Pro Thr Ser Ala Glu Leu Phe Ile Leu Pro Tyr Gln Asp
        915                 920                 925

Ala Thr Gly Gly Asn Lys Arg Thr Glu Asp Leu Glu Gln Ile Ser Glu
    930                 935                 940

Ile Leu Ile Gln Lys Leu Asn Gln Asn Phe Val His Phe Glu Leu Lys
945                 950                 955                 960

Pro Gly Val Arg Val Leu Val His Ala Ala His Leu Thr Ala Ala Pro
                965                 970                 975

Leu Val Asp Leu Thr Pro Ser His Ser Gly Ser Ala Met Leu Met Leu
            980                 985                 990

Leu Ser Val Val Phe Val Gly Leu  Ala Val Phe Val Ile  Tyr Lys Phe
        995                 1000                1005

Lys Arg  Lys Ile Pro Gly Leu  Asn Ile Tyr Ala Gln  Met Gln Asn
    1010                1015                1020

Glu Lys  Asp Gln Glu Met Val  Ser Pro Val Ser Gln  Arg Glu Ser
    1025                1030                1035

Ile Pro  Asn Val Pro Gln Ser  Glu Leu Met Ser Pro  Glu Gln Leu
    1040                1045                1050

Val Asp  Glu Lys Leu Asp Val  Gln Pro Ile Glu Gln  Pro Gln Ala
    1055                1060                1065

Thr Val  Gln Asn Pro Arg Lys  Gly Asn Ala Ala Lys  Val Val Trp
    1070                1075                1080

Thr Glu  Asp Phe Gln Lys Ala  Cys Gly Ser Pro Arg  Gly Phe Lys
    1085                1090                1095

Pro Arg  Pro Gly Ala Glu Val  Phe Pro Gln Leu Leu  Ser Pro Arg
    1100                1105                1110


Ala Gln  Lys Lys Ser Leu Pro  Met
    1115                1120
```

<210> 51

<211> 986

<212> PRT

<213> Gallus gallus

<220>

<221> MISC_FEATURE

<222> (1)..(986)

<223> soluble SorCS1

<400> 51

```
Gly Gln Ala Gly Gly Arg Arg Asn Ser Ala Arg Arg Arg Arg Gly Arg
1               5                   10                  15

Ser Pro Arg Gly Thr Ala Gly Pro Gly Gly Ala Ala Gly Arg Glu Pro
            20                  25                  30

Gly Gly Ser Gly Ala Ala Arg Phe Gly Leu Glu Glu Leu Arg Leu Gly
        35                  40                  45

Ser Thr Thr Phe Ala Leu Thr Gly Asp Ser Ala His Asn Gln Ala Met
    50                  55                  60

Val His Trp Ser Gly Gln Asn Ser Ser Val Ile Leu Ile Leu Thr Lys
65                  70                  75                  80

Leu Tyr Asp Tyr Asn Leu Gly Ser Ile Thr Glu Ser Ser Leu Trp Arg
                85                  90                  95

Ser Thr Asp Tyr Gly Thr Thr Tyr Glu Lys Leu Asn Asp Lys Ile Gly
            100                 105                 110

Leu Lys Thr Ile Leu Ser Tyr Leu Tyr Val Cys Pro Thr Asn Lys Arg
        115                 120                 125

Lys Ile Met Leu Leu Thr Asp Pro Glu Val Glu Ser Ser Leu Leu Ile
    130                 135                 140

Ser Thr Asp Glu Gly Ala Thr Tyr Gln Lys Tyr Arg Leu Asn Phe Tyr
145                 150                 155                 160

Ile His Ser Leu Leu Phe His Pro Lys Gln Glu Asp Trp Ile Leu Ala
                165                 170                 175

Tyr Ser Gln Asp Gln Lys Leu Phe Ser Ser Val Glu Phe Gly Arg Arg
            180                 185                 190
```

```
Trp Leu Leu Leu His Glu Gly Val Ala Pro Asn Arg Phe Tyr Trp Ser
        195                 200                 205

Met Met Val Ser Gly Arg Glu Pro Asp Leu Val His Leu Glu Ala Lys
    210                 215                 220

Thr Val Asp Gly His Ala Gln Tyr Ile Thr Cys Lys Met Gln Asn Cys
225                 230                 235                 240

Ser Glu Ala Ser Gln Asn Lys Pro Phe Pro Gly Tyr Ile Asp His Asn
                245                 250                 255

Ser Leu Ile Val Gln Asp Asp Tyr Val Phe Val Gln Leu Thr Ser Gly
            260                 265                 270

Gly Arg Pro His Tyr Tyr Val Ser Tyr Arg Arg Asn Ala Phe Thr Pro
        275                 280                 285

Ile Lys Leu Pro Lys Tyr Ser Leu Pro Lys Asp Met His Val Ile Ser
    290                 295                 300

Thr Asp Glu Ser Gln Val Phe Ala Ala Val Gln Glu Trp Asn Gln Asn
305                 310                 315                 320

Asp Thr Tyr Asn Leu Tyr Ile Ser Asp Thr Arg Gly Val Tyr Phe Thr
                325                 330                 335

Leu Ala Leu Glu Asn Val Lys Ser Ser Gln Gly Leu Asp Gly Asn Val
            340                 345                 350

Met Ile Asp Leu Tyr Glu Val Ala Gly Ile Lys Gly Met Phe Leu Ala
        355                 360                 365

Asn Lys Lys Ile Asp Asn Gln Val Lys Thr Phe Ile Thr Tyr Asn Lys
    370                 375                 380

Gly Arg Asp Trp Asn Leu Leu Gln Ala Pro Asp Thr Asp Leu Lys Gly
385                 390                 395                 400

Asn Pro Val His Cys Leu Leu Pro Tyr Cys Ser Leu His Leu His Leu
                405                 410                 415

Lys Val Ser Glu Asn Pro Tyr Thr Ser Gly Asn Ile Ala Ser Arg Asp
            420                 425                 430

Thr Ala Pro Ser Ile Ile Val Ala Ser Gly Asn Ile Gly Pro Glu Leu
        435                 440                 445

Ser Asp Asn Asp Ile Ser Met Phe Val Ser Ser Asp Ala Gly Asn Thr
```

```
    450                 455                 460

Trp Arg Gln Ile Phe Glu Glu Glu His Ser Val Leu Tyr Leu Asp Gln
465                 470                 475                 480

Gly Gly Val Leu Val Ala Ile Lys His Thr Ser Leu Pro Ile Arg His
                485                 490                 495

Leu Trp Leu Ser Phe Asp Glu Gly Lys Ser Trp Ser Lys Tyr Ser Phe
            500                 505                 510

Thr Ser Leu Pro Leu Phe Val Asp Gly Ile Leu Gly Glu Pro Gly Glu
        515                 520                 525

Glu Thr Leu Ile Met Thr Val Phe Gly His Phe Ser His Arg Ser Glu
    530                 535                 540

Trp Gln Leu Val Lys Ile Asp Tyr Lys Ser Ile Phe Asp Arg Arg Cys
545                 550                 555                 560

Ala Glu Glu Asp Tyr Trp Thr Trp Gln Leu His Ser Gln Gly Glu Ala
                565                 570                 575

Cys Ile Met Gly Ala Lys Arg Ile Tyr Arg Lys Arg Lys Ser Glu Lys
            580                 585                 590

Lys Cys Met Gln Gly Lys Tyr Ala Gly Ala Met Thr Ser Glu Pro Cys
        595                 600                 605

Val Cys Thr Asp Ala Asp Phe Asp Cys Asp Tyr Gly Tyr Glu Arg His
    610                 615                 620

Arg Asn Gly Gln Cys Leu Pro Ala Phe Trp Tyr Asn Pro Ser Ser Leu
625                 630                 635                 640

Ser Lys Asp Cys Ser Leu Gly Gln Ser Tyr Leu Asn Ser Thr Gly Tyr
                645                 650                 655

Arg Lys Val Val Ser Asn Asn Cys Thr Asp Gly Val Arg Glu Gln Tyr
            660                 665                 670

Thr Ala Lys Pro Gln Gln Cys Pro Gly Lys Ala Pro Gln Gly Leu Arg
        675                 680                 685

Ile Ile Thr Ser Asp Gly Lys Leu Thr Ala Glu Gln Gly His Asn Val
    690                 695                 700

Thr Phe Leu Val Gln Leu Glu Glu Gly Asp Leu Gln Arg Ser Leu Ile
705                 710                 715                 720
```

```
Gln Val Asp Phe Gly Asp Gly Thr Ala Val Ser Tyr Ala Asn Leu Ser
                725                 730                 735

Ser Thr Glu Asp Gly Ile Lys His Thr Tyr Gln Asn Val Gly Ile Phe
            740                 745                 750

Arg Val Thr Val Leu Val Glu Asn Ser Leu Gly Ser Asp Asn Ala Val
        755                 760                 765

Leu Tyr Leu His Val Thr Cys Pro Leu Glu His Val His Leu Ser Leu
    770                 775                 780

Pro Phe Val Thr Thr Lys Asn Lys Glu Val Asn Ala Thr Ala Val Leu
785                 790                 795                 800

Trp Pro Ser Gln Val Gly Thr Leu Thr Tyr Val Trp Trp Phe Gly Asn
                805                 810                 815

Asn Thr Glu Pro Leu Ile Thr Leu Glu Gly Ser Ile Thr Phe Thr Phe
            820                 825                 830

Ser Val Glu Gly Met Asn Thr Ile Thr Val Gln Val Ser Ala Gly Asn
        835                 840                 845

Thr Ile Leu Gln Asp Thr Lys Thr Ile Ala Val Tyr Glu Gln Phe Arg
    850                 855                 860

Ser Leu Arg Leu Ser Phe Ser Pro Asn Leu Asp Asp Tyr Asn Pro Asp
865                 870                 875                 880

Ile Pro Glu Trp Arg Arg Asp Ile Ser Arg Val Val Lys Arg Ala Leu
                885                 890                 895

Val Glu Ala Thr Gly Ile Ser Ser Lys His Ile Leu Val Ala Val Leu
            900                 905                 910

Pro Gly Leu Pro Thr Ser Ala Glu Leu Phe Ile Leu Pro Tyr Gln Asp
        915                 920                 925

Ala Thr Gly Gly Asn Lys Arg Thr Glu Asp Leu Glu Gln Ile Ser Glu
    930                 935                 940

Ile Leu Ile Gln Lys Leu Asn Gln Asn Phe Val His Phe Glu Leu Lys
945                 950                 955                 960

Pro Gly Val Arg Val Leu Val His Ala Ala His Leu Thr Ala Ala Pro
                965                 970                 975

Leu Val Asp Leu Thr Pro Ser His Ser Gly
            980                 985
```

<210> 52

<211> 831

<212> PRT

<213> Homo sapiens

<220>

<221> MISC_FEATURE

<222> (1)..(831)

<223> preproSortilin

<400> 52

```
Met Glu Arg Pro Trp Gly Ala Ala Asp Gly Leu Ser Arg Trp Pro His
1               5                  10                  15

Gly Leu Gly Leu Leu Leu Leu Leu Gln Leu Leu Pro Pro Ser Thr Leu
            20                  25                  30

Ser Gln Asp Arg Leu Asp Ala Pro Pro Pro Pro Ala Ala Pro Leu Pro
        35                  40                  45

Arg Trp Ser Gly Pro Ile Gly Val Ser Trp Gly Leu Arg Ala Ala Ala
    50                  55                  60

Ala Gly Gly Ala Phe Pro Arg Gly Gly Arg Trp Arg Arg Ser Ala Pro
65                  70                  75                  80

Gly Glu Asp Glu Glu Cys Gly Arg Val Arg Asp Phe Val Ala Lys Leu
                85                  90                  95

Ala Asn Asn Thr His Gln His Val Phe Asp Asp Leu Arg Gly Ser Val
            100                 105                 110

Ser Leu Ser Trp Val Gly Asp Ser Thr Gly Val Ile Leu Val Leu Thr
        115                 120                 125

Thr Phe His Val Pro Leu Val Ile Met Thr Phe Gly Gln Ser Lys Leu
    130                 135                 140

Tyr Arg Ser Glu Asp Tyr Gly Lys Asn Phe Lys Asp Ile Thr Asp Leu
145                 150                 155                 160

Ile Asn Asn Thr Phe Ile Arg Thr Glu Phe Gly Met Ala Ile Gly Pro
                165                 170                 175

Glu Asn Ser Gly Lys Val Val Leu Thr Ala Glu Val Ser Gly Gly Ser
            180                 185                 190
```

```
Arg Gly Gly Arg Ile Phe Arg Ser Ser Asp Phe Ala Lys Asn Phe Val
        195                 200                 205

Gln Thr Asp Leu Pro Phe His Pro Leu Thr Gln Met Met Tyr Ser Pro
    210                 215                 220

Gln Asn Ser Asp Tyr Leu Leu Ala Leu Ser Thr Glu Asn Gly Leu Trp
225                 230                 235                 240

Val Ser Lys Asn Phe Gly Gly Lys Trp Glu Glu Ile His Lys Ala Val
                245                 250                 255

Cys Leu Ala Lys Trp Gly Ser Asp Asn Thr Ile Phe Phe Thr Thr Tyr
            260                 265                 270

Ala Asn Gly Ser Cys Lys Ala Asp Leu Gly Ala Leu Glu Leu Trp Arg
        275                 280                 285

Thr Ser Asp Leu Gly Lys Ser Phe Lys Thr Ile Gly Val Lys Ile Tyr
    290                 295                 300

Ser Phe Gly Leu Gly Gly Arg Phe Leu Phe Ala Ser Val Met Ala Asp
305                 310                 315                 320

Lys Asp Thr Thr Arg Arg Ile His Val Ser Thr Asp Gln Gly Asp Thr
                325                 330                 335

Trp Ser Met Ala Gln Leu Pro Ser Val Gly Gln Glu Gln Phe Tyr Ser
            340                 345                 350

Ile Leu Ala Ala Asn Asp Asp Met Val Phe Met His Val Asp Glu Pro
        355                 360                 365

Gly Asp Thr Gly Phe Gly Thr Ile Phe Thr Ser Asp Asp Arg Gly Ile
    370                 375                 380

Val Tyr Ser Lys Ser Leu Asp Arg His Leu Tyr Thr Thr Thr Gly Gly
385                 390                 395                 400

Glu Thr Asp Phe Thr Asn Val Thr Ser Leu Arg Gly Val Tyr Ile Thr
                405                 410                 415

Ser Val Leu Ser Glu Asp Asn Ser Ile Gln Thr Met Ile Thr Phe Asp
            420                 425                 430

Gln Gly Gly Arg Trp Thr His Leu Arg Lys Pro Glu Asn Ser Glu Cys
        435                 440                 445
```

```
Asp Ala Thr Ala Lys Asn Lys Asn Glu Cys Ser Leu His Ile His Ala
    450                 455                 460

Ser Tyr Ser Ile Ser Gln Lys Leu Asn Val Pro Met Ala Pro Leu Ser
465                 470                 475                 480

Glu Pro Asn Ala Val Gly Ile Val Ile Ala His Gly Ser Val Gly Asp
                485                 490                 495

Ala Ile Ser Val Met Val Pro Asp Val Tyr Ile Ser Asp Asp Gly Gly
            500                 505                 510

Tyr Ser Trp Thr Lys Met Leu Glu Gly Pro His Tyr Tyr Thr Ile Leu
        515                 520                 525

Asp Ser Gly Gly Ile Ile Val Ala Ile Glu His Ser Ser Arg Pro Ile
    530                 535                 540

Asn Val Ile Lys Phe Ser Thr Asp Glu Gly Gln Cys Trp Gln Thr Tyr
545                 550                 555                 560

Thr Phe Thr Arg Asp Pro Ile Tyr Phe Thr Gly Leu Ala Ser Glu Pro
                565                 570                 575

Gly Ala Arg Ser Met Asn Ile Ser Ile Trp Gly Phe Thr Glu Ser Phe
            580                 585                 590

Leu Thr Ser Gln Trp Val Ser Tyr Thr Ile Asp Phe Lys Asp Ile Leu
        595                 600                 605

Glu Arg Asn Cys Glu Glu Lys Asp Tyr Thr Ile Trp Leu Ala His Ser
    610                 615                 620

Thr Asp Pro Glu Asp Tyr Glu Asp Gly Cys Ile Leu Gly Tyr Lys Glu
625                 630                 635                 640

Gln Phe Leu Arg Leu Arg Lys Ser Ser Val Cys Gln Asn Gly Arg Asp
                645                 650                 655

Tyr Val Val Thr Lys Gln Pro Ser Ile Cys Leu Cys Ser Leu Glu Asp
            660                 665                 670

Phe Leu Cys Asp Phe Gly Tyr Tyr Arg Pro Glu Asn Asp Ser Lys Cys
        675                 680                 685

Val Glu Gln Pro Glu Leu Lys Gly His Asp Leu Glu Phe Cys Leu Tyr
    690                 695                 700

Gly Arg Glu Glu His Leu Thr Thr Asn Gly Tyr Arg Lys Ile Pro Gly

705                 710                 715                 720

Asp Lys Cys Gln Gly Gly Val Asn Pro Val Arg Glu Val Lys Asp Leu
                725                 730                 735

Lys Lys Lys Cys Thr Ser Asn Phe Leu Ser Pro Glu Lys Gln Asn Ser
            740                 745                 750

Lys Ser Asn Ser Val Pro Ile Ile Leu Ala Ile Val Gly Leu Met Leu
        755                 760                 765

Val Thr Val Val Ala Gly Val Leu Ile Val Lys Lys Tyr Val Cys Gly
    770                 775                 780

Gly Arg Phe Leu Val His Arg Tyr Ser Val Leu Gln Gln His Ala Glu
785                 790                 795                 800

Ala Asn Gly Val Asp Gly Val Asp Ala Leu Asp Thr Ala Ser His Thr
                805                 810                 815

Asn Lys Ser Gly Tyr His Asp Asp Ser Asp Glu Asp Leu Leu Glu
            820                 825                 830
```

<210> 53

<211> 2214

<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (1)..(2214)
<223> preproSorLA

<400> 53

```
Met Ala Thr Arg Ser Ser Arg Arg Glu Ser Arg Leu Pro Phe Leu Phe
1               5                   10                  15

Thr Leu Val Ala Leu Leu Pro Pro Gly Ala Leu Cys Glu Val Trp Thr
            20                  25                  30

Gln Arg Leu His Gly Gly Ser Ala Pro Leu Pro Gln Asp Arg Gly Phe
        35                  40                  45

Leu Val Val Gln Gly Asp Pro Arg Glu Leu Arg Leu Trp Ala Arg Gly
    50                  55                  60

Asp Ala Arg Gly Ala Ser Arg Ala Asp Glu Lys Pro Leu Arg Arg Lys
65                  70                  75                  80

Arg Ser Ala Ala Leu Gln Pro Glu Pro Ile Lys Val Tyr Gly Gln Val
```

```
                85                  90                  95

Ser Leu Asn Asp Ser His Asn Gln Met Val Val His Trp Ala Gly Glu
            100                 105                 110

Lys Ser Asn Val Ile Val Ala Leu Ala Arg Asp Ser Leu Ala Leu Ala
        115                 120                 125

Arg Pro Lys Ser Ser Asp Val Tyr Val Ser Tyr Asp Tyr Gly Lys Ser
    130                 135                 140

Phe Lys Lys Ile Ser Asp Lys Leu Asn Phe Gly Leu Gly Asn Arg Ser
145                 150                 155                 160

Glu Ala Val Ile Ala Gln Phe Tyr His Ser Pro Ala Asp Asn Lys Arg
                165                 170                 175

Tyr Ile Phe Ala Asp Ala Tyr Ala Gln Tyr Leu Trp Ile Thr Phe Asp
            180                 185                 190

Phe Cys Asn Thr Leu Gln Gly Phe Ser Ile Pro Phe Arg Ala Ala Asp
        195                 200                 205

Leu Leu Leu His Ser Lys Ala Ser Asn Leu Leu Leu Gly Phe Asp Arg
    210                 215                 220

Ser His Pro Asn Lys Gln Leu Trp Lys Ser Asp Asp Phe Gly Gln Thr
225                 230                 235                 240

Trp Ile Met Ile Gln Glu His Val Lys Ser Phe Ser Trp Gly Ile Asp
                245                 250                 255

Pro Tyr Asp Lys Pro Asn Thr Ile Tyr Ile Glu Arg His Glu Pro Ser
            260                 265                 270

Gly Tyr Ser Thr Val Phe Arg Ser Thr Asp Phe Phe Gln Ser Arg Glu
        275                 280                 285

Asn Gln Glu Val Ile Leu Glu Glu Val Arg Asp Phe Gln Leu Arg Asp
    290                 295                 300

Lys Tyr Met Phe Ala Thr Lys Val Val His Leu Leu Gly Ser Glu Gln
305                 310                 315                 320

Gln Ser Ser Val Gln Leu Trp Val Ser Phe Gly Arg Lys Pro Met Arg
                325                 330                 335

Ala Ala Gln Phe Val Thr Arg His Pro Ile Asn Glu Tyr Tyr Ile Ala
            340                 345                 350
```

```
Asp Ala Ser Glu Asp Gln Val Phe Val Cys Val Ser His Ser Asn Asn
        355                 360                 365

Arg Thr Asn Leu Tyr Ile Ser Glu Ala Glu Gly Leu Lys Phe Ser Leu
    370                 375                 380

Ser Leu Glu Asn Val Leu Tyr Tyr Ser Pro Gly Gly Ala Gly Ser Asp
385                 390                 395                 400

Thr Leu Val Arg Tyr Phe Ala Asn Glu Pro Phe Ala Asp Phe His Arg
                405                 410                 415

Val Glu Gly Leu Gln Gly Val Tyr Ile Ala Thr Leu Ile Asn Gly Ser
            420                 425                 430

Met Asn Glu Glu Asn Met Arg Ser Val Ile Thr Phe Asp Lys Gly Gly
        435                 440                 445

Thr Trp Glu Phe Leu Gln Ala Pro Ala Phe Thr Gly Tyr Gly Glu Lys
    450                 455                 460

Ile Asn Cys Glu Leu Ser Gln Gly Cys Ser Leu His Leu Ala Gln Arg
465                 470                 475                 480

Leu Ser Gln Leu Leu Asn Leu Gln Leu Arg Arg Met Pro Ile Leu Ser
                485                 490                 495

Lys Glu Ser Ala Pro Gly Leu Ile Ile Ala Thr Gly Ser Val Gly Lys
            500                 505                 510

Asn Leu Ala Ser Lys Thr Asn Val Tyr Ile Ser Ser Ser Ala Gly Ala
        515                 520                 525

Arg Trp Arg Glu Ala Leu Pro Gly Pro His Tyr Tyr Thr Trp Gly Asp
    530                 535                 540

His Gly Gly Ile Ile Thr Ala Ile Ala Gln Gly Met Glu Thr Asn Glu
545                 550                 555                 560

Leu Lys Tyr Ser Thr Asn Glu Gly Glu Thr Trp Lys Thr Phe Ile Phe
                565                 570                 575

Ser Glu Lys Pro Val Phe Val Tyr Gly Leu Leu Thr Glu Pro Gly Glu
            580                 585                 590

Lys Ser Thr Val Phe Thr Ile Phe Gly Ser Asn Lys Glu Asn Val His
        595                 600                 605
```

```
Ser Trp Leu Ile Leu Gln Val Asn Ala Thr Asp Ala Leu Gly Val Pro
    610                 615                 620

Cys Thr Glu Asn Asp Tyr Lys Leu Trp Ser Pro Ser Asp Glu Arg Gly
625                 630                 635                 640

Asn Glu Cys Leu Leu Gly His Lys Thr Val Phe Lys Arg Arg Thr Pro
                645                 650                 655

His Ala Thr Cys Phe Asn Gly Glu Asp Phe Asp Arg Pro Val Val Val
            660                 665                 670

Ser Asn Cys Ser Cys Thr Arg Glu Asp Tyr Glu Cys Asp Phe Gly Phe
        675                 680                 685

Lys Met Ser Glu Asp Leu Ser Leu Glu Val Cys Val Pro Asp Pro Glu
    690                 695                 700

Phe Ser Gly Lys Ser Tyr Ser Pro Pro Val Pro Cys Pro Val Gly Ser
705                 710                 715                 720

Thr Tyr Arg Arg Thr Arg Gly Tyr Arg Lys Ile Ser Gly Asp Thr Cys
                725                 730                 735

Ser Gly Gly Asp Val Glu Ala Arg Leu Glu Gly Glu Leu Val Pro Cys
            740                 745                 750

Pro Leu Ala Glu Glu Asn Glu Phe Ile Leu Tyr Ala Val Arg Lys Ser
        755                 760                 765

Ile Tyr Arg Tyr Asp Leu Ala Ser Gly Ala Thr Glu Gln Leu Pro Leu
    770                 775                 780

Thr Gly Leu Arg Ala Ala Val Ala Leu Asp Phe Asp Tyr Glu His Asn
785                 790                 795                 800

Cys Leu Tyr Trp Ser Asp Leu Ala Leu Asp Val Ile Gln Arg Leu Cys
                805                 810                 815

Leu Asn Gly Ser Thr Gly Gln Glu Val Ile Ile Asn Ser Gly Leu Glu
            820                 825                 830

Thr Val Glu Ala Leu Ala Phe Glu Pro Leu Ser Gln Leu Leu Tyr Trp
        835                 840                 845

Val Asp Ala Gly Phe Lys Lys Ile Glu Val Ala Asn Pro Asp Gly Asp
    850                 855                 860
```

```
Phe Arg Leu Thr Ile Val Asn Ser Ser Val Leu Asp Arg Pro Arg Ala
865                 870                 875                 880

Leu Val Leu Val Pro Gln Glu Gly Val Met Phe Trp Thr Asp Trp Gly
                885                 890                 895

Asp Leu Lys Pro Gly Ile Tyr Arg Ser Asn Met Asp Gly Ser Ala Ala
            900                 905                 910

Tyr His Leu Val Ser Glu Asp Val Lys Trp Pro Asn Gly Ile Ser Val
        915                 920                 925

Asp Asp Gln Trp Ile Tyr Trp Thr Asp Ala Tyr Leu Glu Cys Ile Glu
    930                 935                 940

Arg Ile Thr Phe Ser Gly Gln Gln Arg Ser Val Ile Leu Asp Asn Leu
945                 950                 955                 960

Pro His Pro Tyr Ala Ile Ala Val Phe Lys Asn Glu Ile Tyr Trp Asp
                965                 970                 975

Asp Trp Ser Gln Leu Ser Ile Phe Arg Ala Ser Lys Tyr Ser Gly Ser
            980                 985                 990

Gln Met Glu Ile Leu Ala Asn Gln  Leu Thr Gly Leu Met  Asp Met Lys
        995                 1000                1005

Ile Phe  Tyr Lys Gly Lys Asn  Thr Gly Ser Asn Ala  Cys Val Pro
    1010                1015                1020

Arg Pro  Cys Ser Leu Leu Cys  Leu Pro Lys Ala Asn  Asn Ser Arg
    1025                1030                1035

Ser Cys  Arg Cys Pro Glu Asp  Val Ser Ser Ser Val  Leu Pro Ser
    1040                1045                1050

Gly Asp  Leu Met Cys Asp Cys  Pro Gln Gly Tyr Gln  Leu Lys Asn
    1055                1060                1065

Asn Thr  Cys Val Lys Glu Glu  Asn Thr Cys Leu Arg  Asn Gln Tyr
    1070                1075                1080

Arg Cys  Ser Asn Gly Asn Cys  Ile Asn Ser Ile Trp  Trp Cys Asp
    1085                1090                1095

Phe Asp  Asn Asp Cys Gly Asp  Met Ser Asp Glu Arg  Asn Cys Pro
    1100                1105                1110

Thr Thr  Ile Cys Asp Leu Asp  Thr Gln Phe Arg Cys  Gln Glu Ser
```

```
    1115                1120                1125

Gly Thr  Cys Ile Pro Leu Ser  Tyr Lys Cys Asp Leu  Glu Asp Asp
    1130                1135                1140

Cys Gly  Asp Asn Ser Asp Glu  Ser His Cys Glu Met  His Gln Cys
    1145                1150                1155

Arg Ser  Asp Glu Tyr Asn Cys  Ser Ser Gly Met Cys  Ile Arg Ser
    1160                1165                1170

Ser Trp  Val Cys Asp Gly Asp  Asn Asp Cys Arg Asp  Trp Ser Asp
    1175                1180                1185

Glu Ala  Asn Cys Thr Ala Ile  Tyr His Thr Cys Glu  Ala Ser Asn
    1190                1195                1200

Phe Gln  Cys Arg Asn Gly His  Cys Ile Pro Gln Arg  Trp Ala Cys
    1205                1210                1215

Asp Gly  Asp Thr Asp Cys Gln  Asp Gly Ser Asp Glu  Asp Pro Val
    1220                1225                1230

Asn Cys  Glu Lys Lys Cys Asn  Gly Phe Arg Cys Pro  Asn Gly Thr
    1235                1240                1245

Cys Ile  Pro Ser Ser Lys His  Cys Asp Gly Leu Arg  Asp Cys Ser
    1250                1255                1260

Asp Gly  Ser Asp Glu Gln His  Cys Glu Pro Leu Cys  Thr His Phe
    1265                1270                1275

Met Asp  Phe Val Cys Lys Asn  Arg Gln Gln Cys Leu  Phe His Ser
    1280                1285                1290

Met Val  Cys Asp Gly Ile Ile  Gln Cys Arg Asp Gly  Ser Asp Glu
    1295                1300                1305

Asp Ala  Ala Phe Ala Gly Cys  Ser Gln Asp Pro Glu  Phe His Lys
    1310                1315                1320

Val Cys  Asp Glu Phe Gly Phe  Gln Cys Gln Asn Gly  Val Cys Ile
    1325                1330                1335

Ser Leu  Ile Trp Lys Cys Asp  Gly Met Asp Asp Cys  Gly Asp Tyr
    1340                1345                1350

Ser Asp  Glu Ala Asn Cys Glu  Asn Pro Thr Glu Ala  Pro Asn Cys
    1355                1360                1365
```

```
Ser Arg  Tyr Phe Gln Phe Arg  Cys Glu Asn Gly His  Cys Ile Pro
    1370                 1375                 1380

Asn Arg  Trp Lys Cys Asp Arg  Glu Asn Asp Cys Gly  Asp Trp Ser
    1385                 1390                 1395

Asp Glu  Lys Asp Cys Gly Asp  Ser His Ile Leu Pro  Phe Ser Thr
    1400                 1405                 1410

Pro Gly  Pro Ser Thr Cys Leu  Pro Asn Tyr Tyr Arg  Cys Ser Ser
    1415                 1420                 1425

Gly Thr  Cys Val Met Asp Thr  Trp Val Cys Asp Gly  Tyr Arg Asp
    1430                 1435                 1440

Cys Ala  Asp Gly Ser Asp Glu  Glu Ala Cys Pro Leu  Leu Ala Asn
    1445                 1450                 1455

Val Thr  Ala Ala Ser Thr Pro  Thr Gln Leu Gly Arg  Cys Asp Arg
    1460                 1465                 1470

Phe Glu  Phe Glu Cys His Gln  Pro Lys Thr Cys Ile  Pro Asn Trp
    1475                 1480                 1485

Lys Arg  Cys Asp Gly His Gln  Asp Cys Gln Asp Gly  Arg Asp Glu
    1490                 1495                 1500

Ala Asn  Cys Pro Thr His Ser  Thr Leu Thr Cys Met  Ser Arg Glu
    1505                 1510                 1515

Phe Gln  Cys Glu Asp Gly Glu  Ala Cys Ile Val Leu  Ser Glu Arg
    1520                 1525                 1530

Cys Asp  Gly Phe Leu Asp Cys  Ser Asp Glu Ser Asp  Glu Lys Ala
    1535                 1540                 1545

Cys Ser  Asp Glu Leu Thr Val  Tyr Lys Val Gln Asn  Leu Gln Trp
    1550                 1555                 1560

Thr Ala  Asp Phe Ser Gly Asp  Val Thr Leu Thr Trp  Met Arg Pro
    1565                 1570                 1575

Lys Lys  Met Pro Ser Ala Ser  Cys Val Tyr Asn Val  Tyr Tyr Arg
    1580                 1585                 1590

Val Val  Gly Glu Ser Ile Trp  Lys Thr Leu Glu Thr  His Ser Asn
    1595                 1600                 1605
```

```
Lys Thr  Asn Thr Val Leu Lys  Val Leu Lys Pro Asp  Thr Thr Tyr
    1610                 1615                 1620

Gln Val  Lys Val Gln Val Gln  Cys Leu Ser Lys Ala  His Asn Thr
    1625                 1630                 1635

Asn Asp  Phe Val Thr Leu Arg  Thr Pro Glu Gly Leu  Pro Asp Ala
    1640                 1645                 1650

Pro Arg  Asn Leu Gln Leu Ser  Leu Pro Arg Glu Ala  Glu Gly Val
    1655                 1660                 1665

Ile Val  Gly His Trp Ala Pro  Pro Ile His Thr His  Gly Leu Ile
    1670                 1675                 1680

Arg Glu  Tyr Ile Val Glu Tyr  Ser Arg Ser Gly Ser  Lys Met Trp
    1685                 1690                 1695

Ala Ser  Gln Arg Ala Ala Ser  Asn Phe Thr Glu Ile  Lys Asn Leu
    1700                 1705                 1710

Leu Val  Asn Thr Leu Tyr Thr  Val Arg Val Ala Ala  Val Thr Ser
    1715                 1720                 1725

Arg Gly  Ile Gly Asn Trp Ser  Asp Ser Lys Ser Ile  Thr Thr Ile
    1730                 1735                 1740

Lys Gly  Lys Val Ile Pro Pro  Pro Asp Ile His Ile  Asp Ser Tyr
    1745                 1750                 1755

Gly Glu  Asn Tyr Leu Ser Phe  Thr Leu Thr Met Glu  Ser Asp Ile
    1760                 1765                 1770

Lys Val  Asn Gly Tyr Val Val  Asn Leu Phe Trp Ala  Phe Asp Thr
    1775                 1780                 1785

His Lys  Gln Glu Arg Arg Thr  Leu Asn Phe Arg Gly  Ser Ile Leu
    1790                 1795                 1800

Ser His  Lys Val Gly Asn Leu  Thr Ala His Thr Ser  Tyr Glu Ile
    1805                 1810                 1815

Ser Ala  Trp Ala Lys Thr Asp  Leu Gly Asp Ser Pro  Leu Ala Phe
    1820                 1825                 1830

Glu His  Val Met Thr Arg Gly  Val Arg Pro Pro Ala  Pro Ser Leu
    1835                 1840                 1845
```

```
Lys Ala  Lys Ala Ile Asn Gln  Thr Ala Val Glu Cys  Thr Trp Thr
    1850                1855                1860

Gly Pro  Arg Asn Val Val Tyr  Gly Ile Phe Tyr Ala  Thr Ser Phe
    1865                1870                1875

Leu Asp  Leu Tyr Arg Asn Pro  Lys Ser Leu Thr Thr  Ser Leu His
    1880                1885                1890

Asn Lys  Thr Val Ile Val Ser  Lys Asp Glu Gln Tyr  Leu Phe Leu
    1895                1900                1905

Val Arg  Val Val Val Pro Tyr  Gln Gly Pro Ser Ser  Asp Tyr Val
    1910                1915                1920

Val Val  Lys Met Ile Pro Asp  Ser Arg Leu Pro Pro  Arg His Leu
    1925                1930                1935

His Val  Val His Thr Gly Lys  Thr Ser Val Val Ile  Lys Trp Glu
    1940                1945                1950

Ser Pro  Tyr Asp Ser Pro Asp  Gln Asp Leu Leu Tyr  Ala Ile Ala
    1955                1960                1965

Val Lys  Asp Leu Ile Arg Lys  Thr Asp Arg Ser Tyr  Lys Val Lys
    1970                1975                1980

Ser Arg  Asn Ser Thr Val Glu  Tyr Thr Leu Asn Lys  Leu Glu Pro
    1985                1990                1995

Gly Gly  Lys Tyr His Ile Ile  Val Gln Leu Gly Asn  Met Ser Lys
    2000                2005                2010

Asp Ser  Ser Ile Lys Ile Thr  Thr Val Ser Leu Ser  Ala Pro Asp
    2015                2020                2025

Ala Leu  Lys Ile Ile Thr Glu  Asn Asp His Val Leu  Leu Phe Trp
    2030                2035                2040

Lys Ser  Leu Ala Leu Lys Glu  Lys His Phe Asn Glu  Ser Arg Gly
    2045                2050                2055

Tyr Glu  Ile His Met Phe Asp  Ser Ala Met Asn Ile  Thr Ala Tyr
    2060                2065                2070

Leu Gly  Asn Thr Thr Asp Asn  Phe Phe Lys Ile Ser  Asn Leu Lys
    2075                2080                2085

Met Gly  His Asn Tyr Thr Phe  Thr Val Gln Ala Arg  Cys Leu Phe

    2090                2095                2100

Gly Asn  Gln Ile Cys Gly Glu  Pro Ala Ile Leu Leu  Tyr Asp Glu
    2105                2110                2115

Leu Gly  Ser Gly Ala Asp Ala  Ser Ala Thr Gln Ala  Ala Arg Ser
    2120                2125                2130

Thr Asp  Val Ala Ala Val Val  Val Pro Ile Leu Phe  Leu Ile Leu
    2135                2140                2145

Leu Ser  Leu Gly Val Gly Phe  Ala Ile Leu Tyr Thr  Lys His Arg
    2150                2155                2160

Arg Leu  Gln Ser Ser Phe Thr  Ala Phe Ala Asn Ser  His Tyr Ser
    2165                2170                2175

Ser Arg  Leu Gly Ser Ala Ile  Phe Ser Ser Gly Asp  Asp Leu Gly
    2180                2185                2190

Glu Asp  Asp Glu Asp Ala Pro  Met Ile Thr Gly Phe  Ser Asp Asp
    2195                2200                2205

Val Pro  Met Val Ile Ala
    2210
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<210> 54
<211> 1159
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (1)..(1159)
<223> preproSorCS2

<400> 54

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Met Ala His Arg Gly Pro Ser Arg Ala Ser Lys Gly Pro Gly Pro Thr
1               5                  10                  15

Ala Arg Ala Pro Ser Pro Gly Ala Pro Pro Pro Pro Arg Ser Pro Arg
            20                  25                  30

Ser Arg Pro Leu Leu Leu Leu Leu Leu Leu Leu Gly Ala Cys Gly Ala
        35                  40                  45

Ala Gly Arg Ser Pro Glu Pro Gly Arg Leu Gly Pro His Ala Gln Leu
    50                  55                  60

Thr Arg Val Pro Arg Ser Pro Pro Ala Gly Arg Ala Glu Pro Gly Gly

65                  70                  75                  80

Gly Glu Asp Arg Gln Ala Arg Gly Thr Glu Pro Gly Ala Pro Gly Pro
                85                  90                  95

Ser Pro Gly Pro Ala Pro Gly Pro Gly Glu Asp Gly Ala Pro Ala Ala
            100                 105                 110

Gly Tyr Arg Arg Trp Glu Arg Ala Ala Pro Leu Ala Gly Val Ala Ser
        115                 120                 125

Arg Ala Gln Val Ser Leu Ile Ser Thr Ser Phe Val Leu Lys Gly Asp
    130                 135                 140

Ala Thr His Asn Gln Ala Met Val His Trp Thr Gly Glu Asn Ser Ser
145                 150                 155                 160

Val Ile Leu Ile Leu Thr Lys Tyr Tyr His Ala Asp Met Gly Lys Val
                165                 170                 175

Leu Glu Ser Ser Leu Trp Arg Ser Ser Asp Phe Gly Thr Ser Tyr Thr
            180                 185                 190

Lys Leu Thr Leu Gln Pro Gly Val Thr Thr Val Ile Asp Asn Phe Tyr
        195                 200                 205

Ile Cys Pro Thr Asn Lys Arg Lys Val Ile Leu Val Ser Ser Ser Leu
    210                 215                 220

Ser Asp Arg Asp Gln Ser Leu Phe Leu Ser Ala Asp Glu Gly Ala Thr
225                 230                 235                 240

Phe Gln Lys Gln Pro Ile Pro Phe Phe Val Glu Thr Leu Ile Phe His
                245                 250                 255

Pro Lys Glu Glu Asp Lys Val Leu Ala Tyr Thr Lys Glu Ser Lys Leu
            260                 265                 270

Tyr Val Ser Ser Asp Leu Gly Lys Lys Trp Thr Leu Leu Gln Glu Arg
        275                 280                 285

Val Thr Lys Asp His Val Phe Trp Ser Val Ser Gly Val Asp Ala Asp
    290                 295                 300

Pro Asp Leu Val His Val Glu Ala Gln Asp Leu Gly Gly Asp Phe Arg
305                 310                 315                 320

Tyr Val Thr Cys Ala Ile His Asn Cys Ser Glu Lys Met Leu Thr Ala
                325                 330                 335
```

```
Pro Phe Ala Gly Pro Ile Asp His Gly Ser Leu Thr Val Gln Asp Asp
            340                 345                 350

Tyr Ile Phe Phe Lys Ala Thr Ser Ala Asn Gln Thr Lys Tyr Tyr Val
        355                 360                 365

Ser Tyr Arg Arg Asn Glu Phe Val Leu Met Lys Leu Pro Lys Tyr Ala
    370                 375                 380

Leu Pro Lys Asp Leu Gln Ile Ile Ser Thr Asp Glu Ser Gln Val Phe
385                 390                 395                 400

Val Ala Val Gln Glu Trp Tyr Gln Met Asp Thr Tyr Asn Leu Tyr Gln
                405                 410                 415

Ser Asp Pro Arg Gly Val Arg Tyr Ala Leu Val Leu Gln Asp Val Arg
            420                 425                 430

Ser Ser Arg Gln Ala Glu Glu Ser Val Leu Ile Asp Ile Leu Glu Val
        435                 440                 445

Arg Gly Val Lys Gly Val Phe Leu Ala Asn Gln Lys Ile Asp Gly Lys
    450                 455                 460

Val Met Thr Leu Ile Thr Tyr Asn Lys Gly Arg Asp Trp Asp Tyr Leu
465                 470                 475                 480

Arg Pro Pro Ser Met Asp Met Asn Gly Lys Pro Thr Asn Cys Lys Pro
                485                 490                 495

Pro Asp Cys His Leu His Leu His Leu Arg Trp Ala Asp Asn Pro Tyr
            500                 505                 510

Val Ser Gly Thr Val His Thr Lys Asp Thr Ala Pro Gly Leu Ile Met
        515                 520                 525

Gly Ala Gly Asn Leu Gly Ser Gln Leu Val Glu Tyr Lys Glu Glu Met
    530                 535                 540

Tyr Ile Thr Ser Asp Cys Gly His Thr Trp Arg Gln Val Phe Glu Glu
545                 550                 555                 560

Glu His His Ile Leu Tyr Leu Asp His Gly Gly Val Ile Val Ala Ile
                565                 570                 575

Lys Asp Thr Ser Ile Pro Leu Lys Ile Leu Lys Phe Ser Val Asp Glu
            580                 585                 590
```

```
Gly Leu Thr Trp Ser Thr His Asn Phe Thr Ser Thr Ser Val Phe Val
        595                 600                 605

Asp Gly Leu Leu Ser Glu Pro Gly Asp Glu Thr Leu Val Met Thr Val
    610                 615                 620

Phe Gly His Ile Ser Phe Arg Ser Asp Trp Glu Leu Val Lys Val Asp
625                 630                 635                 640

Phe Arg Pro Ser Phe Ser Arg Gln Cys Gly Glu Glu Asp Tyr Ser Ser
                645                 650                 655

Trp Glu Leu Ser Asn Leu Gln Gly Asp Arg Cys Ile Met Gly Gln Gln
            660                 665                 670

Arg Ser Phe Arg Lys Arg Lys Ser Thr Ser Trp Cys Ile Lys Gly Arg
        675                 680                 685

Ser Phe Thr Ser Ala Leu Thr Ser Arg Val Cys Glu Cys Arg Asp Ser
    690                 695                 700

Asp Phe Leu Cys Asp Tyr Gly Phe Glu Arg Ser Pro Ser Ser Glu Ser
705                 710                 715                 720

Ser Thr Asn Lys Cys Ser Ala Asn Phe Trp Phe Asn Pro Leu Ser Pro
                725                 730                 735

Pro Asp Asp Cys Ala Leu Gly Gln Thr Tyr Thr Ser Ser Leu Gly Tyr
            740                 745                 750

Arg Lys Val Val Ser Asn Val Cys Glu Gly Gly Val Asp Met Gln Gln
        755                 760                 765

Ser Gln Val Gln Leu Gln Cys Pro Leu Thr Pro Pro Arg Gly Leu Gln
    770                 775                 780

Val Ser Ile Gln Gly Glu Ala Val Ala Val Arg Pro Gly Glu Asp Val
785                 790                 795                 800

Leu Phe Val Val Arg Gln Glu Gln Gly Asp Val Leu Thr Thr Lys Tyr
                805                 810                 815

Gln Val Asp Leu Gly Asp Gly Phe Lys Ala Met Tyr Val Asn Leu Thr
            820                 825                 830

Leu Thr Gly Glu Pro Ile Arg His Arg Tyr Glu Ser Pro Gly Ile Tyr
        835                 840                 845
```

```
Arg Val Ser Val Arg Ala Glu Asn Thr Ala Gly His Asp Glu Ala Val
    850                 855                 860

Leu Phe Val Gln Val Asn Ser Pro Leu Gln Ala Leu Tyr Leu Glu Val
865                 870                 875                 880

Val Pro Val Ile Gly Leu Asn Gln Glu Val Asn Leu Thr Ala Val Leu
                885                 890                 895

Leu Pro Leu Asn Pro Asn Leu Thr Val Phe Tyr Trp Trp Ile Gly His
            900                 905                 910

Ser Leu Gln Pro Leu Leu Ser Leu Asp Asn Ser Val Thr Thr Arg Phe
        915                 920                 925

Ser Asp Thr Gly Asp Val Arg Val Thr Val Gln Ala Ala Cys Gly Asn
    930                 935                 940

Ser Val Leu Gln Asp Ser Arg Val Leu Arg Val Leu Asp Gln Phe Gln
945                 950                 955                 960

Val Met Pro Leu Gln Phe Ser Lys Glu Leu Asp Ala Tyr Asn Pro Asn
                965                 970                 975

Thr Pro Glu Trp Arg Glu Asp Val Gly Leu Val Val Thr Arg Leu Leu
            980                 985                 990

Ser Lys Glu Thr Ser Val Pro Gln  Glu Leu Leu Val Thr  Val Val Lys
        995                 1000                1005

Pro Gly  Leu Pro Thr Leu Ala  Asp Leu Tyr Val Leu  Leu Pro Pro
    1010                1015                1020

Pro Arg  Pro Thr Arg Lys Arg  Ser Leu Ser Ser Asp  Lys Arg Leu
    1025                1030                1035

Ala Ala  Ile Gln Gln Val Leu  Asn Ala Gln Lys Ile  Ser Phe Leu
    1040                1045                1050

Leu Arg  Gly Gly Val Arg Val  Leu Val Ala Leu Arg  Asp Thr Gly
    1055                1060                1065

Thr Gly  Ala Glu Gln Leu Gly  Gly Gly Gly Gly Tyr  Trp Ala Val
    1070                1075                1080

Val Val  Leu Phe Val Ile Gly  Leu Phe Ala Ala Gly  Ala Phe Ile
    1085                1090                1095

Leu Tyr  Lys Phe Lys Arg Lys  Arg Pro Gly Arg Thr  Val Tyr Ala

    1100                1105                1110

Gln Met  His Asn Glu Lys Glu  Gln Glu Met Thr Ser  Pro Val Ser
    1115                1120                1125

His Ser  Glu Asp Val Gln Gly  Ala Val Gln Gly Asn  His Ser Gly
    1130                1135                1140

Val Val  Leu Ser Ile Asn Ser  Arg Glu Met His Ser  Tyr Leu Val
    1145                1150                1155

Ser
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<210> 55
<211> 1222
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (1)..(1222)
<223> preproSorCS3

<400> 55

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Met Glu Ala Ala Arg Thr Glu Arg Pro Ala Gly Arg Pro Gly Ala Pro
1               5                  10                  15

Leu Val Arg Thr Gly Leu Leu Leu Leu Ser Thr Trp Val Leu Ala Gly
            20                  25                  30

Ala Glu Ile Thr Trp Asp Ala Thr Gly Gly Pro Gly Arg Pro Ala Ala
        35                  40                  45

Pro Ala Ser Arg Pro Pro Ala Leu Ser Pro Leu Ser Pro Arg Ala Val
    50                  55                  60

Ala Ser Gln Trp Pro Glu Glu Leu Ala Ser Ala Arg Arg Ala Ala Val
65                  70                  75                  80

Leu Gly Arg Arg Ala Gly Pro Glu Leu Leu Pro Gln Gln Gly Gly Gly
                85                  90                  95

Arg Gly Gly Glu Met Gln Val Glu Ala Gly Gly Thr Ser Pro Ala Gly
            100                 105                 110

Glu Arg Arg Gly Arg Gly Ile Pro Ala Pro Ala Lys Leu Gly Gly Ala
        115                 120                 125

Arg Arg Ser Arg Arg Ala Gln Pro Pro Ile Thr Gln Glu Arg Gly Asp

    130                 135                 140

Ala Trp Ala Thr Ala Pro Ala Asp Gly Ser Arg Gly Ser Arg Pro Leu
145                 150                 155                 160

Ala Lys Gly Ser Arg Glu Glu Val Lys Ala Pro Arg Ala Gly Gly Ser
                165                 170                 175

Ala Ala Glu Asp Leu Arg Leu Pro Ser Thr Ser Phe Ala Leu Thr Gly
            180                 185                 190

Asp Ser Ala His Asn Gln Ala Met Val His Trp Ser Gly His Asn Ser
        195                 200                 205

Ser Val Ile Leu Ile Leu Thr Lys Leu Tyr Asp Phe Asn Leu Gly Ser
    210                 215                 220

Val Thr Glu Ser Ser Leu Trp Arg Ser Thr Asp Tyr Gly Thr Thr Tyr
225                 230                 235                 240

Glu Lys Leu Asn Asp Lys Val Gly Leu Lys Thr Val Leu Ser Tyr Leu
                245                 250                 255

Tyr Val Asn Pro Thr Asn Lys Arg Lys Ile Met Leu Leu Ser Asp Pro
            260                 265                 270

Glu Met Glu Ser Ser Ile Leu Ile Ser Ser Asp Glu Gly Ala Thr Tyr
        275                 280                 285

Gln Lys Tyr Arg Leu Thr Phe Tyr Ile Gln Ser Leu Leu Phe His Pro
    290                 295                 300

Lys Gln Glu Asp Trp Val Leu Ala Tyr Ser Leu Asp Gln Lys Leu Tyr
305                 310                 315                 320

Ser Ser Met Asp Phe Gly Arg Arg Trp Gln Leu Met His Glu Arg Ile
                325                 330                 335

Thr Pro Asn Arg Phe Tyr Trp Ser Val Ala Gly Leu Asp Lys Glu Ala
            340                 345                 350

Asp Leu Val His Met Glu Val Arg Thr Thr Asp Gly Tyr Ala His Tyr
        355                 360                 365

Leu Thr Cys Arg Ile Gln Glu Cys Ala Glu Thr Thr Arg Ser Gly Pro
    370                 375                 380

Phe Ala Arg Ser Ile Asp Ile Ser Ser Leu Val Val Gln Asp Glu Tyr
385                 390                 395                 400
```

```
Ile Phe Ile Gln Val Thr Thr Ser Gly Arg Ala Ser Tyr Tyr Val Ser
                405                 410                 415

Tyr Arg Arg Glu Ala Phe Ala Gln Ile Lys Leu Pro Lys Tyr Ser Leu
            420                 425                 430

Pro Lys Asp Met His Ile Ile Ser Thr Asp Glu Asn Gln Val Phe Ala
        435                 440                 445

Ala Val Gln Glu Trp Asn Gln Asn Asp Thr Tyr Asn Leu Tyr Ile Ser
    450                 455                 460

Asp Thr Arg Gly Ile Tyr Phe Thr Leu Ala Met Glu Asn Ile Lys Ser
465                 470                 475                 480

Ser Arg Gly Leu Met Gly Asn Ile Ile Ile Glu Leu Tyr Glu Val Ala
                485                 490                 495

Gly Ile Lys Gly Ile Phe Leu Ala Asn Lys Lys Val Asp Asp Gln Val
            500                 505                 510

Lys Thr Tyr Ile Thr Tyr Asn Lys Gly Arg Asp Trp Arg Leu Leu Gln
        515                 520                 525

Ala Pro Asp Val Asp Leu Arg Gly Ser Pro Val His Cys Leu Leu Pro
    530                 535                 540

Phe Cys Ser Leu His Leu His Leu Gln Leu Ser Glu Asn Pro Tyr Ser
545                 550                 555                 560

Ser Gly Arg Ile Ser Ser Lys Glu Thr Ala Pro Gly Leu Val Val Ala
                565                 570                 575

Thr Gly Asn Ile Gly Pro Glu Leu Ser Tyr Thr Asp Ile Gly Val Phe
            580                 585                 590

Ile Ser Ser Asp Gly Gly Asn Thr Trp Arg Gln Ile Phe Asp Glu Glu
        595                 600                 605

Tyr Asn Val Trp Phe Leu Asp Trp Gly Gly Ala Leu Val Ala Met Lys
    610                 615                 620

His Thr Pro Leu Pro Val Arg His Leu Trp Val Ser Phe Asp Glu Gly
625                 630                 635                 640

His Ser Trp Asp Lys Tyr Gly Phe Thr Ser Val Pro Leu Phe Val Asp
                645                 650                 655
```

```
Gly Ala Leu Val Glu Ala Gly Met Glu Thr His Ile Met Thr Val Phe
            660                 665                 670

Gly His Phe Ser Leu Arg Ser Glu Trp Gln Leu Val Lys Val Asp Tyr
        675                 680                 685

Lys Ser Ile Phe Ser Arg His Cys Thr Lys Glu Asp Tyr Gln Thr Trp
    690                 695                 700

His Leu Leu Asn Gln Gly Glu Pro Cys Val Met Gly Glu Arg Lys Ile
705                 710                 715                 720

Phe Lys Lys Arg Lys Pro Gly Ala Gln Cys Ala Leu Gly Arg Asp His
                725                 730                 735

Ser Gly Ser Val Val Ser Glu Pro Cys Val Cys Ala Asn Trp Asp Phe
            740                 745                 750

Glu Cys Asp Tyr Gly Tyr Glu Arg His Gly Glu Ser Gln Cys Val Pro
        755                 760                 765

Ala Phe Trp Tyr Asn Pro Ala Ser Pro Ser Lys Asp Cys Ser Leu Gly
    770                 775                 780

Gln Ser Tyr Leu Asn Ser Thr Gly Tyr Arg Arg Ile Val Ser Asn Asn
785                 790                 795                 800

Cys Thr Asp Gly Leu Arg Glu Lys Tyr Thr Ala Lys Ala Gln Met Cys
                805                 810                 815

Pro Gly Lys Ala Pro Arg Gly Leu His Val Val Thr Thr Asp Gly Arg
            820                 825                 830

Leu Val Ala Glu Gln Gly His Asn Ala Thr Phe Ile Ile Leu Met Glu
        835                 840                 845

Glu Gly Asp Leu Gln Arg Thr Asn Ile Gln Leu Asp Phe Gly Asp Gly
    850                 855                 860

Ile Ala Val Ser Tyr Ala Asn Phe Ser Pro Ile Glu Asp Gly Ile Lys
865                 870                 875                 880

His Val Tyr Lys Ser Ala Gly Ile Phe Gln Val Thr Ala Tyr Ala Glu
                885                 890                 895

Asn Asn Leu Gly Ser Asp Thr Ala Val Leu Phe Leu His Val Val Cys
            900                 905                 910
```

```
Pro Val Glu His Val His Leu Arg Val Pro Phe Val Ala Ile Arg Asn
        915                 920                 925

Lys Glu Val Asn Ile Ser Ala Val Val Trp Pro Ser Gln Leu Gly Thr
    930                 935                 940

Leu Thr Tyr Phe Trp Trp Phe Gly Asn Ser Thr Lys Pro Leu Ile Thr
945                 950                 955                 960

Leu Asp Ser Ser Ile Ser Phe Thr Phe Leu Ala Glu Gly Thr Asp Thr
                965                 970                 975

Ile Thr Val Gln Val Ala Ala Gly Asn Ala Leu Ile Gln Asp Thr Lys
            980                 985                 990

Glu Ile Ala Val His Glu Tyr Phe  Gln Ser Gln Leu Leu  Ser Phe Ser
        995                 1000                1005

Pro Asn  Leu Asp Tyr His Asn  Pro Asp Ile Pro Glu  Trp Arg Lys
    1010                1015                1020

Asp Ile  Gly Asn Val Ile Lys  Arg Ala Leu Val Lys  Val Thr Ser
    1025                1030                1035

Val Pro  Glu Asp Gln Ile Leu  Ile Ala Val Phe Pro  Gly Leu Pro
    1040                1045                1050

Thr Ser  Ala Glu Leu Phe Ile  Leu Pro Pro Lys Asn  Leu Thr Glu
    1055                1060                1065

Arg Arg  Lys Gly Asn Glu Gly  Asp Leu Glu Gln Ile  Val Glu Thr
    1070                1075                1080

Leu Phe  Asn Ala Leu Asn Gln  Asn Leu Val Gln Phe  Glu Leu Lys
    1085                1090                1095

Pro Gly  Val Gln Val Ile Val  Tyr Val Thr Gln Leu  Thr Leu Ala
    1100                1105                1110

Pro Leu  Val Asp Ser Ser Ala  Gly His Ser Ser Ser  Ala Met Leu
    1115                1120                1125

Met Leu  Leu Ser Val Val Phe  Val Gly Leu Ala Val  Phe Leu Ile
    1130                1135                1140

Tyr Lys  Phe Lys Arg Lys Ile  Pro Trp Ile Asn Ile  Tyr Ala Gln
    1145                1150                1155

Val Gln  His Asp Lys Glu Gln  Glu Met Ile Gly Ser  Val Ser Gln

    1160                1165                1170

Ser Glu  Asn Ala Pro Lys Ile  Thr Leu Ser Asp Phe  Thr Glu Pro
    1175                1180                1185

Glu Glu  Leu Leu Asp Lys Glu  Leu Asp Thr Arg Val  Ile Gly Gly
    1190                1195                1200

Ile Ala  Thr Ile Ala Asn Ser  Glu Ser Thr Lys Glu  Ile Pro Asn
    1205                1210                1215

Cys Thr  Ser Val
    1220
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<210> 56

<211> 1382

<212> PRT

<213> Homo sapiens

Human Insulin Receptor

<400> 56

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Met Gly Thr Gly Gly Arg Arg Gly Ala Ala Ala Ala Pro Leu Leu Val
1               5                  10                  15

Ala Val Ala Ala Leu Leu Leu Gly Ala Ala Gly His Leu Tyr Pro Gly
            20                  25                  30

Glu Val Cys Pro Gly Met Asp Ile Arg Asn Asn Leu Thr Arg Leu His
        35                  40                  45

Glu Leu Glu Asn Cys Ser Val Ile Glu Gly His Leu Gln Ile Leu Leu
    50                  55                  60

Met Phe Lys Thr Arg Pro Glu Asp Phe Arg Asp Leu Ser Phe Pro Lys
65                  70                  75                  80

Leu Ile Met Ile Thr Asp Tyr Leu Leu Leu Phe Arg Val Tyr Gly Leu
                85                  90                  95

Glu Ser Leu Lys Asp Leu Phe Pro Asn Leu Thr Val Ile Arg Gly Ser
            100                 105                 110

Arg Leu Phe Phe Asn Tyr Ala Leu Val Ile Phe Glu Met Val His Leu
        115                 120                 125

Lys Glu Leu Gly Leu Tyr Asn Leu Met Asn Ile Thr Arg Gly Ser Val
    130                 135                 140

Arg Ile Glu Lys Asn Asn Glu Leu Cys Tyr Leu Ala Thr Ile Asp Trp
145                 150                 155                 160
```

```
Ser Arg Ile Leu Asp Ser Val Glu Asp Asn Tyr Ile Val Leu Asn Lys
                165                 170                 175

Asp Asp Asn Glu Glu Cys Gly Asp Ile Cys Pro Gly Thr Ala Lys Gly
            180                 185                 190

Lys Thr Asn Cys Pro Ala Thr Val Ile Asn Gly Gln Phe Val Glu Arg
        195                 200                 205

Cys Trp Thr His Ser His Cys Gln Lys Val Cys Pro Thr Ile Cys Lys
    210                 215                 220

Ser His Gly Cys Thr Ala Glu Gly Leu Cys Cys His Ser Glu Cys Leu
225                 230                 235                 240

Gly Asn Cys Ser Gln Pro Asp Asp Pro Thr Lys Cys Val Ala Cys Arg
                245                 250                 255

Asn Phe Tyr Leu Asp Gly Arg Cys Val Glu Thr Cys Pro Pro Pro Tyr
            260                 265                 270

Tyr His Phe Gln Asp Trp Arg Cys Val Asn Phe Ser Phe Cys Gln Asp
        275                 280                 285

Leu His His Lys Cys Lys Asn Ser Arg Arg Gln Gly Cys His Gln Tyr
    290                 295                 300

Val Ile His Asn Asn Lys Cys Ile Pro Glu Cys Pro Ser Gly Tyr Thr
305                 310                 315                 320

Met Asn Ser Ser Asn Leu Leu Cys Thr Pro Cys Leu Gly Pro Cys Pro
                325                 330                 335

Lys Val Cys His Leu Leu Glu Gly Glu Lys Thr Ile Asp Ser Val Thr
            340                 345                 350

Ser Ala Gln Glu Leu Arg Gly Cys Thr Val Ile Asn Gly Ser Leu Ile
        355                 360                 365

Ile Asn Ile Arg Gly Gly Asn Asn Leu Ala Ala Glu Leu Glu Ala Asn
    370                 375                 380

Leu Gly Leu Ile Glu Glu Ile Ser Gly Tyr Leu Lys Ile Arg Arg Ser
385                 390                 395                 400

Tyr Ala Leu Val Ser Leu Ser Phe Phe Arg Lys Leu Arg Leu Ile Arg
                405                 410                 415
```

```
Gly Glu Thr Leu Glu Ile Gly Asn Tyr Ser Phe Tyr Ala Leu Asp Asn
            420                 425                 430

Gln Asn Leu Arg Gln Leu Trp Asp Trp Ser Lys His Asn Leu Thr Ile
        435                 440                 445

Thr Gln Gly Lys Leu Phe Phe His Tyr Asn Pro Lys Leu Cys Leu Ser
    450                 455                 460

Glu Ile His Lys Met Glu Glu Val Ser Gly Thr Lys Gly Arg Gln Glu
465                 470                 475                 480

Arg Asn Asp Ile Ala Leu Lys Thr Asn Gly Asp Gln Ala Ser Cys Glu
                485                 490                 495

Asn Glu Leu Leu Lys Phe Ser Tyr Ile Arg Thr Ser Phe Asp Lys Ile
            500                 505                 510

Leu Leu Arg Trp Glu Pro Tyr Trp Pro Pro Asp Phe Arg Asp Leu Leu
        515                 520                 525

Gly Phe Met Leu Phe Tyr Lys Glu Ala Pro Tyr Gln Asn Val Thr Glu
    530                 535                 540

Phe Asp Gly Gln Asp Ala Cys Gly Ser Asn Ser Trp Thr Val Val Asp
545                 550                 555                 560

Ile Asp Pro Pro Leu Arg Ser Asn Asp Pro Lys Ser Gln Asn His Pro
                565                 570                 575

Gly Trp Leu Met Arg Gly Leu Lys Pro Trp Thr Gln Tyr Ala Ile Phe
            580                 585                 590

Val Lys Thr Leu Val Thr Phe Ser Asp Glu Arg Arg Thr Tyr Gly Ala
        595                 600                 605

Lys Ser Asp Ile Ile Tyr Val Gln Thr Asp Ala Thr Asn Pro Ser Val
    610                 615                 620

Pro Leu Asp Pro Ile Ser Val Ser Asn Ser Ser Ser Gln Ile Ile Leu
625                 630                 635                 640

Lys Trp Lys Pro Pro Ser Asp Pro Asn Gly Asn Ile Thr His Tyr Leu
                645                 650                 655

Val Phe Trp Glu Arg Gln Ala Glu Asp Ser Glu Leu Phe Glu Leu Asp
            660                 665                 670
```

```
Tyr Cys Leu Lys Gly Leu Lys Leu Pro Ser Arg Thr Trp Ser Pro Pro
        675                 680                 685

Phe Glu Ser Glu Asp Ser Gln Lys His Asn Gln Ser Glu Tyr Glu Asp
    690                 695                 700

Ser Ala Gly Glu Cys Cys Ser Cys Pro Lys Thr Asp Ser Gln Ile Leu
705                 710                 715                 720

Lys Glu Leu Glu Glu Ser Ser Phe Arg Lys Thr Phe Glu Asp Tyr Leu
                725                 730                 735

His Asn Val Val Phe Val Pro Arg Lys Thr Ser Ser Gly Thr Gly Ala
            740                 745                 750

Glu Asp Pro Arg Pro Ser Arg Lys Arg Arg Ser Leu Gly Asp Val Gly
        755                 760                 765

Asn Val Thr Val Ala Val Pro Thr Val Ala Ala Phe Pro Asn Thr Ser
    770                 775                 780

Ser Thr Ser Val Pro Thr Ser Pro Glu Glu His Arg Pro Phe Glu Lys
785                 790                 795                 800

Val Val Asn Lys Glu Ser Leu Val Ile Ser Gly Leu Arg His Phe Thr
                805                 810                 815

Gly Tyr Arg Ile Glu Leu Gln Ala Cys Asn Gln Asp Thr Pro Glu Glu
            820                 825                 830

Arg Cys Ser Val Ala Ala Tyr Val Ser Ala Arg Thr Met Pro Glu Ala
        835                 840                 845

Lys Ala Asp Asp Ile Val Gly Pro Val Thr His Glu Ile Phe Glu Asn
    850                 855                 860

Asn Val Val His Leu Met Trp Gln Glu Pro Lys Glu Pro Asn Gly Leu
865                 870                 875                 880

Ile Val Leu Tyr Glu Val Ser Tyr Arg Arg Tyr Gly Asp Glu Glu Leu
                885                 890                 895

His Leu Cys Val Ser Arg Lys His Phe Ala Leu Glu Arg Gly Cys Arg
            900                 905                 910

Leu Arg Gly Leu Ser Pro Gly Asn Tyr Ser Val Arg Ile Arg Ala Thr
        915                 920                 925

Ser Leu Ala Gly Asn Gly Ser Trp Thr Glu Pro Thr Tyr Phe Tyr Val
```

```
    930                 935                 940

Thr Asp Tyr Leu Asp Val Pro Ser Asn Ile Ala Lys Ile Ile Ile Gly
945                 950                 955                 960

Pro Leu Ile Phe Val Phe Leu Phe Ser Val Val Ile Gly Ser Ile Tyr
                965                 970                 975

Leu Phe Leu Arg Lys Arg Gln Pro Asp Gly Pro Leu Gly Pro Leu Tyr
            980                 985                 990

Ala Ser Ser Asn Pro Glu Tyr Leu  Ser Ala Ser Asp Val  Phe Pro Cys
        995                 1000                1005

Ser Val  Tyr Val Pro Asp Glu  Trp Glu Val Ser Arg  Glu Lys Ile
    1010                1015                1020

Thr Leu  Leu Arg Glu Leu Gly  Gln Gly Ser Phe Gly  Met Val Tyr
    1025                1030                1035

Glu Gly  Asn Ala Arg Asp Ile  Ile Lys Gly Glu Ala  Glu Thr Arg
    1040                1045                1050

Val Ala  Val Lys Thr Val Asn  Glu Ser Ala Ser Leu  Arg Glu Arg
    1055                1060                1065

Ile Glu  Phe Leu Asn Glu Ala  Ser Val Met Lys Gly  Phe Thr Cys
    1070                1075                1080

His His  Val Val Arg Leu Leu  Gly Val Val Ser Lys  Gly Gln Pro
    1085                1090                1095

Thr Leu  Val Val Met Glu Leu  Met Ala His Gly Asp  Leu Lys Ser
    1100                1105                1110

Tyr Leu  Arg Ser Leu Arg Pro  Glu Ala Glu Asn Asn  Pro Gly Arg
    1115                1120                1125

Pro Pro  Pro Thr Leu Gln Glu  Met Ile Gln Met Ala  Ala Glu Ile
    1130                1135                1140

Ala Asp  Gly Met Ala Tyr Leu  Asn Ala Lys Lys Phe  Val His Arg
    1145                1150                1155

Asp Leu  Ala Ala Arg Asn Cys  Met Val Ala His Asp  Phe Thr Val
    1160                1165                1170

Lys Ile  Gly Asp Phe Gly Met  Thr Arg Asp Ile Tyr  Glu Thr Asp
    1175                1180                1185
```

```
Tyr Tyr  Arg Lys Gly Gly Lys  Gly Leu Leu Pro Val  Arg Trp Met
    1190                 1195                 1200

Ala Pro  Glu Ser Leu Lys Asp  Gly Val Phe Thr Thr  Ser Ser Asp
    1205                 1210                 1215

Met Trp  Ser Phe Gly Val Val  Leu Trp Glu Ile Thr  Ser Leu Ala
    1220                 1225                 1230

Glu Gln  Pro Tyr Gln Gly Leu  Ser Asn Glu Gln Val  Leu Lys Phe
    1235                 1240                 1245

Val Met  Asp Gly Gly Tyr Leu  Asp Gln Pro Asp Asn  Cys Pro Glu
    1250                 1255                 1260

Arg Val  Thr Asp Leu Met Arg  Met Cys Trp Gln Phe  Asn Pro Lys
    1265                 1270                 1275

Met Arg  Pro Thr Phe Leu Glu  Ile Val Asn Leu Leu  Lys Asp Asp
    1280                 1285                 1290

Leu His  Pro Ser Phe Pro Glu  Val Ser Phe Phe His  Ser Glu Glu
    1295                 1300                 1305

Asn Lys  Ala Pro Glu Ser Glu  Glu Leu Glu Met Glu  Phe Glu Asp
    1310                 1315                 1320

Met Glu  Asn Val Pro Leu Asp  Arg Ser Ser His Cys  Gln Arg Glu
    1325                 1330                 1335

Glu Ala  Gly Gly Arg Asp Gly  Gly Ser Ser Leu Gly  Phe Lys Arg
    1340                 1345                 1350

Ser Tyr  Glu Glu His Ile Pro  Tyr Thr His Met Asn  Gly Gly Lys
    1355                 1360                 1365

Lys Asn  Gly Arg Ile Leu Thr  Leu Pro Arg Ser Asn  Pro Ser
    1370                 1375                 1380
```

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PATENTKRAV

1. SorCS1-lignende middel til anvendelse til behandling af insulinresistens og/eller en sygdom, som er forbundet med insulinresistens, i et individ, hvor midlet er valgt fra gruppen bestående af:

a) et isoleret opløseligt SorCS1-polypeptid, som er valgt fra gruppen bestående af

i) en aminosyresekvens bestående af SEQ ID NO: 5, 10, 15, 21, 27 og 33;

ii) en biologisk aktiv sekvensvariant eller naturligt forekommende allelvariant af aminosyresekvensen i i), hvor varianten har mindst 70% sekvensidentitet med SEQ ID NO: 5, 10, 15, 21, 27 og 33; eller

iii) et biologisk aktivt fragment omfattende en aminosyresekvens, som er valgt fra gruppen bestående af:

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 og SEQ ID NO: 1 aa 763-783, SEQ ID NO: 1 aa 859-876 eller en variant af dette fragment, hvor varianten har mindst 70% sekvensidentitet med 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 og SEQ ID NO: 1 aa 763-783, SEQ ID NO: 1 aa 859-876;

hvor det isolerede opløselige SorCS1-polypeptid er i stand til at binde til insulinreceptoren ved et SorCS1-bindingssted og er i stand til at sensibilisere en insulinreceptor, og

hvor den biologiske aktivitet er sensibilisering af en insulinreceptor,

b) en nukleinsyresekvens, som koder for et polypeptid som defineret i a);

c) en ekspressionsvektor, som omfatter det i b) definerede nukleinsyremolekyle,

d) en isoleret værtscelle, som er transformeret eller transduceret med nukleinsyren ifølge b) eller vektoren ifølge c).

2. Middel til anvendelse ifølge krav 1, hvor midlet er et polypeptid, hvor polypeptidet er i stand til at danne en dimer af polypeptidet, som er bundet via mindst én intermolekylær cystinbro.

3. Middel til anvendelse ifølge et hvilket som helst af de foregående krav, hvor en hvilken som helst aminosyre, som er specificeret i den udvalgte sekvens, ændres for at tilvejebringe en konservativ substitution.

4. Middel til anvendelse ifølge et hvilket som helst af de foregående krav, hvor midlet er et polypeptid, hvor polypeptidet har mindst 75%, fortrinsvis mindst 80%, mere foretrukket mindst 85%, mere foretrukket mindst 90%, mere foretrukket mindst 95%, mere foretrukket mindst 98%, mest foretrukket mindst 99% sekvensidentitet med et protein, som har en sekvens, der er valgt fra gruppen bestående af SEQ ID NO: 5, 10, 15, 21, 27 og 33.

5. Middel til anvendelse ifølge et hvilket som helst af de foregående krav, hvor midlet er et polypeptid, hvor polypeptidet er glycosyleret.

6. Middel til anvendelse ifølge et hvilket som helst af de foregående krav, hvor midlet er et polypeptid, som desuden omfatter et affinitetstag såsom et polyhis-tag, et GST-tag, et HA-tag, et Flag-tag, et C-myc-tag, et HSV-tag, et V5-tag, et maltosebindingsprotein-tag, et cellulosebindingsdomæne-tag.

7. Middel til anvendelse ifølge krav 1, hvor vektoren omfatter en promotor, som er operativt bundet til nukleinsyremolekylet, hvor promotoren er valgt fra gruppen bestående af: CMV, human UbiC, RSV, Tet-regulerbar promotor, Mo-MLV-LTR, Mx1, EF-1alfa, PDGF beta og CaMK II.

8. Middel til anvendelse ifølge krav 1 og 7, hvor vektoren er valgt fra gruppen bestående af vektorer stammende fra Retroviridae-familien, herunder lentivirus, HIV, SIV, FIV, EAIV, CIV; alfavirus, adenovirus, adenoassocieret virus, baculovirus, HSV, coronavirus, Bovint papillomvirus, Mo-MLV, fortrinsvis adenoassocieret virus.

9. Middel til anvendelse ifølge krav 1, hvor cellen er valgt blandt: Saccharomyces cerevisiae, E. coli, Aspergillus og Sf9-insektceller, og pattedyrceller såsom menneske-, kat-

te-, svine-, abe-, hunde-, muse- og rotteceller, herunder muskelceller, hepatocytter, adipocytter og celler fra pancreas såsom α-celler, β-celler, δ-celler; CHO-, CHO-K1-, HEI193T-, HEK293-, COS-, HiB5-, RN33b- og BHK-celler.

10. Middel til anvendelse ifølge et hvilket som helst af de foregående krav, hvor den sygdom, der er forbundet med insulinresistens, er valgt fra gruppen bestående af insulinresistenssyndrom, Type 2 diabetes mellitus, svækket glukosetolerance, metabolisk syndrom, hyperglykæmi, hyperinsulinæmi, arteriosklerose, hypercholesterolæmi, hypertriglyceridæmi, hyperlipidæmi, dyslipidæmi, fedme, central fedme, polycystisk ovariesyndrom, mikroalbuminuri, hyperkoagulabilitet og hypertension og hvilke som helst kombinationer deraf.

11. Middel til anvendelse ifølge et hvilket som helst af de foregående krav, hvor midlet er i stand til at binde til insulinreceptoren ved et SorCS1-bindingssted og er i stand til at sensibilisere insulinreceptoren.

12. Fremgangsmåde til screening for evnen hos SorCS1-midlet ifølge krav 1 til at reducere blodglukoseniveauer, hvilken fremgangsmåde omfatter følgende trin:

a) der tilvejebringes en første og en anden transgen mus, i hvilken de endogene Vps10p-domænereceptor-SorCS1-gener er blevet afbrudt for at ophæve ekspression af en funktionel SorCS1-receptor, og hvor musen udviser et reduceret respons på insulin i forhold til en ikke-transgen kontrolmus;
b) kandidatmidlet administreres til den første transgene mus, og
c) en fysiologisk opløsning administreres til den anden transgene mus, og
d) der tages blodprøver fra henholdsvis musen fra b) og c) med forudbestemte tidsintervaller, såsom 15 minutter, 30 minutter, 60 minutter, 2 og 4 timer efter administration af midlet, og
e) blodglukoseniveauer sammenlignes i prøverne fra d), hvor en reduktion i blodglukoseniveau hos den første transgene mus, som har fået administreret kandidatmidlet, i forhold til den anden transgene mus, som ikke har fået administreret kandidatmidlet, indikerer, at kandidatmidlet reducerer blodglukoseniveauer.

DRAWINGS

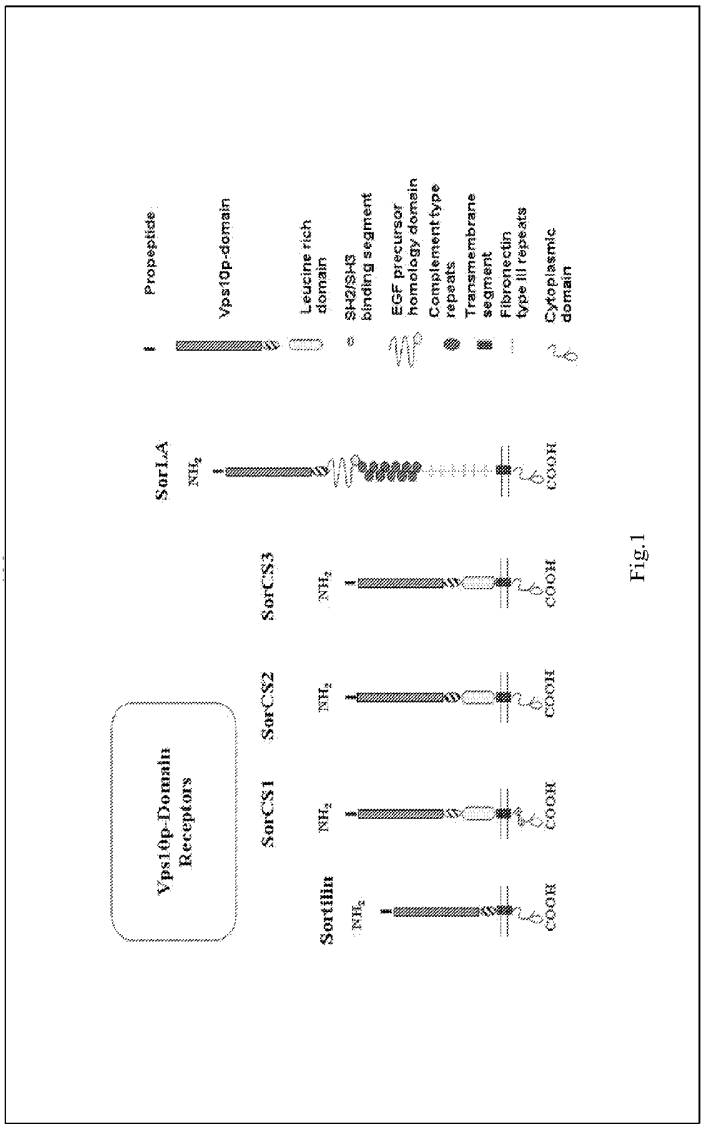


Fig.1

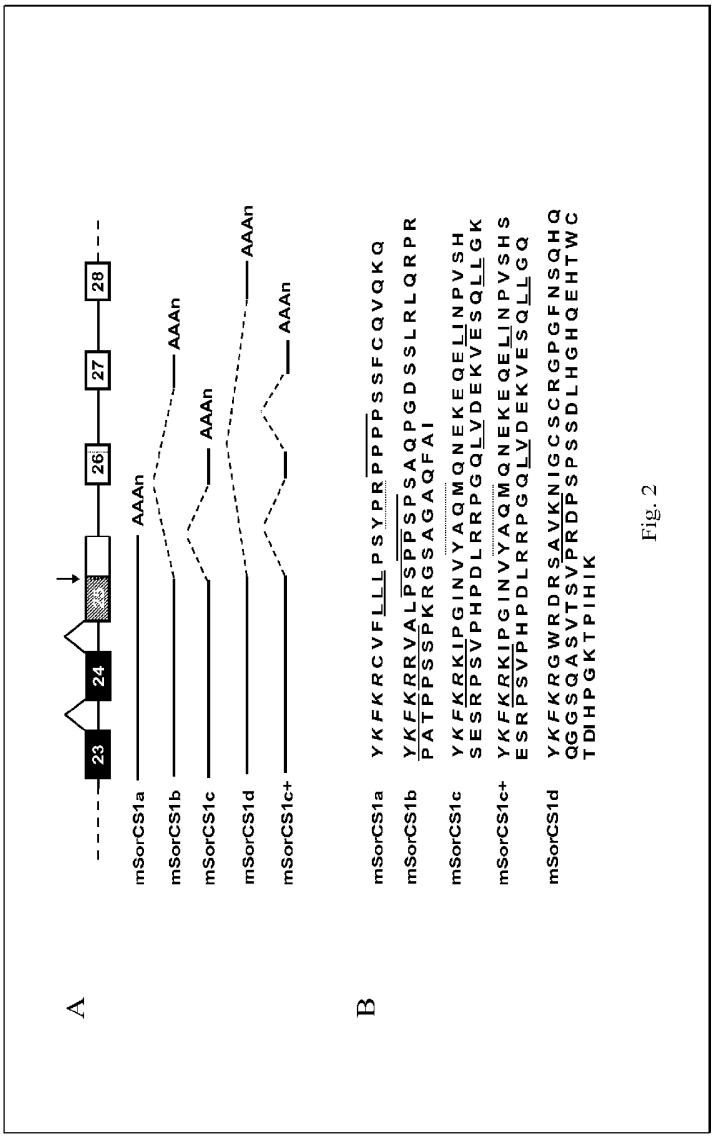

A
23
24
25
26
27
28
mSorCS1a
mSorCS1b
mSorCS1c
mSorCS1d
mSorCS1c+
AAAn
B
mSorCS1a YKFKRCVFLLLPSYPRPPPPSSFCQVQKQ
mSorCS1b YKFKRRVALPSPPSPSAQPGDSSLRLQRPR
PATPPSSPKRGSAGAQFAI
mSorCS1c YKFKRKIPGINVYAQMQNEKEQELINPVSH
SESRPSVPHPDLRRPGQLVDEKVESQLLGK
mSorCS1c+ YKFKRKIPGINVYAQMQNEKEQELINPVSHS
ESRPSVPHPDLRRPGQLVDEKVESQLLGQ
mSorCS1d YKFKRGWRDRSAVKNIGCSCRGPGFNSQHQ
QGGSQASVTSVPRDPSPSSDLHGHQEHTWC
TDIHPGKTPIHIK

Fig. 2

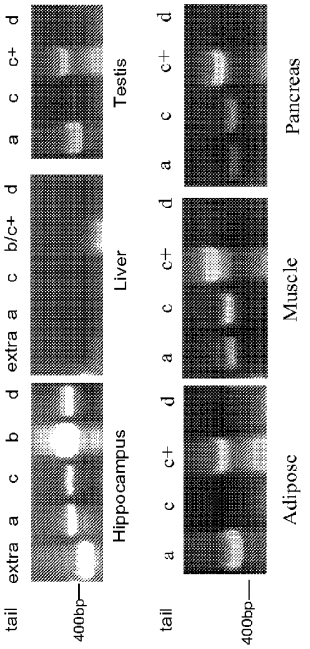

tail
extra a c b d extra a c b/c+ d a c c+ d
400bp
Hippocampus
Liver
Testis
tail
a c c+ d a c c+ d a c c+ d
400bp
Adiposc
Muscle
Pancreas

Fig. 3

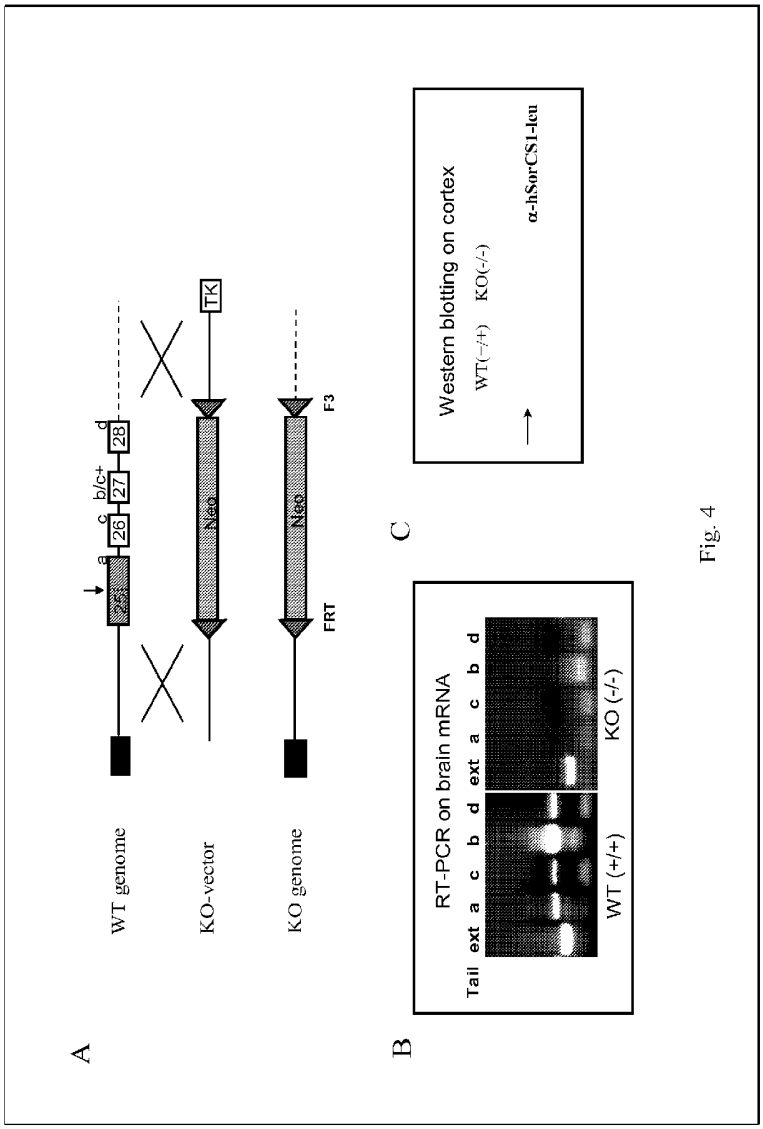

A
WT genome
KO-vector
KO genome
a
b/c+
c
d
26
27
28
Neo
TK
FRT
F3
B
RT-PCR on brain mRNA
Tail ext a c b d ext a c b d
WT (+/+)
KO (-/-)
C
Western blotting on cortex
WT(-/+) KO(-/-)
α-hSorCS1-leu

Fig. 4

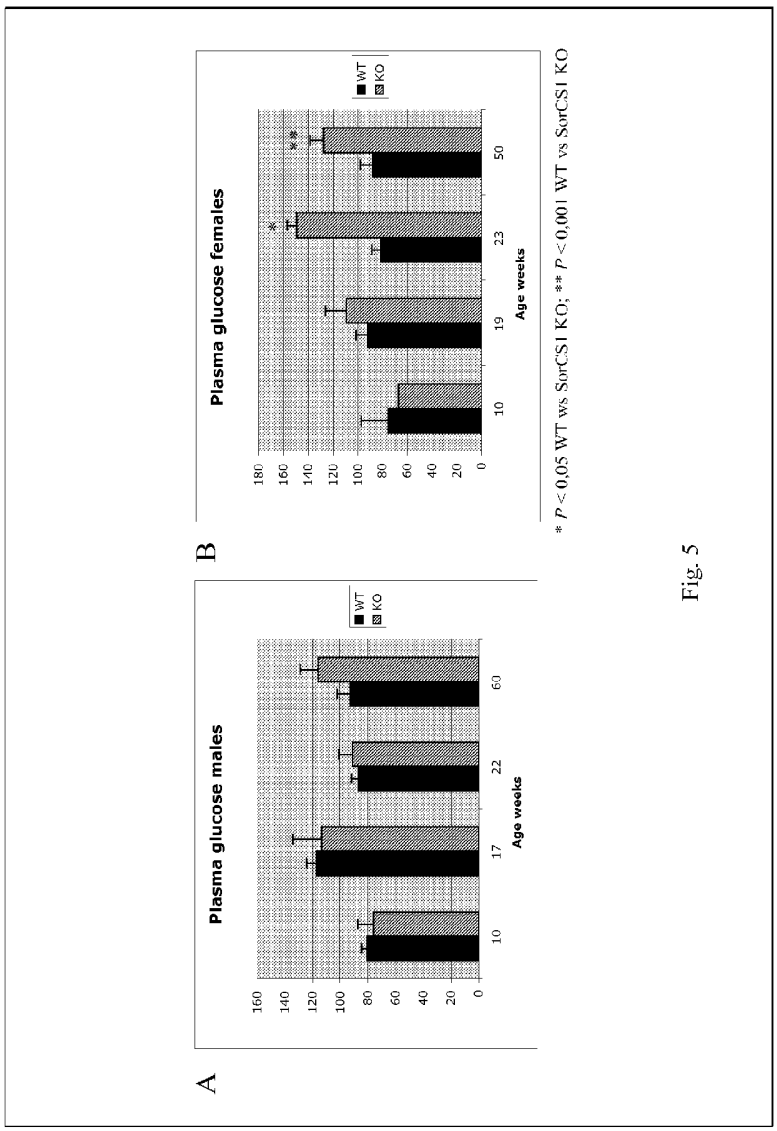
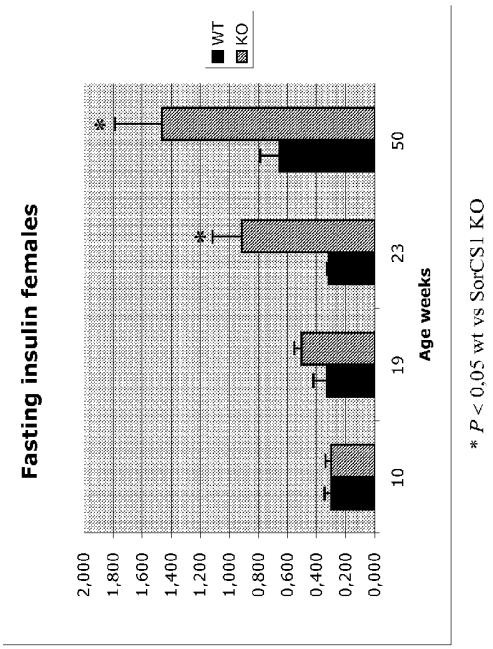

A
Plasma glucose males
WT
KO
Age weeks
0
20
40
60
80
100
120
140
160
10
17
22
60
B
Plasma glucose females
WT
KO
Age weeks
0
20
40
60
80
100
120
140
160
180
10
19
23
50
* $P < 0,05$ WT vs SorCS1 KO; ** $P < 0,001$ WT vs SorCS1 KO

Fig. 5



* $P < 0,05$ wt vs SorCS1 KO

Fig. 6

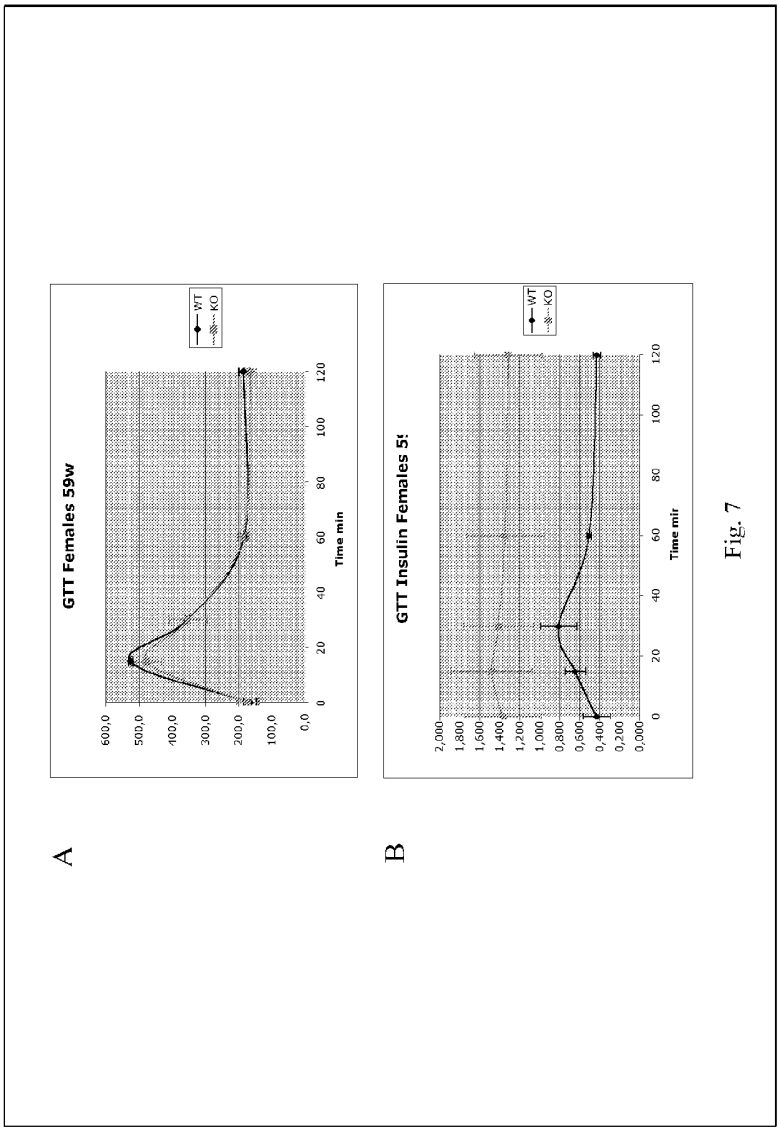

A
GTT Females 59w
WT
KO
600,0
500,0
400,0
300,0
200,0
100,0
0,0
0
20
40
60
80
100
120
Time min
B
GTT Insulin Females 5!
WT
KO
2,000
1,800
1,600
1,400
1,200
1,000
0,800
0,600
0,400
0,200
0,000
0
20
40
60
80
100
120
Time mir

Fig. 7

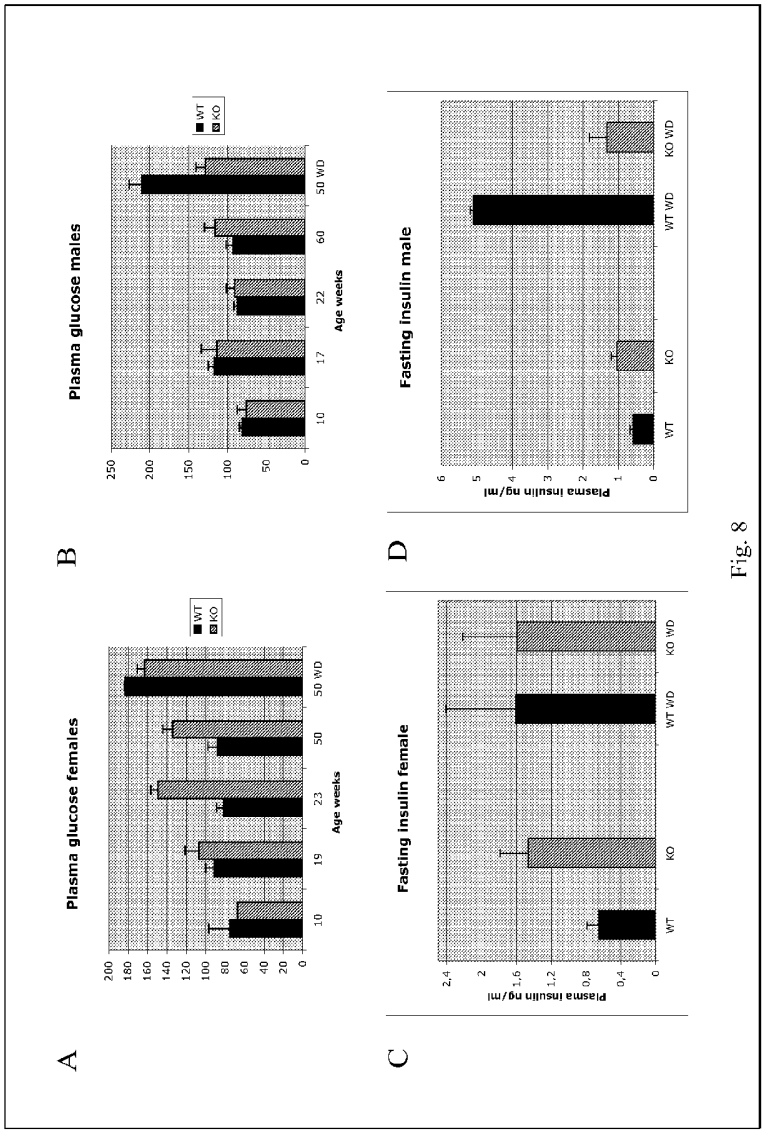

A
Plasma glucose females
WT
KO
Age weeks
10
19
23
50
50 WD
B
Plasma glucose males
WT
KO
Age weeks
10
17
22
60
50 WD
C
Fasting insulin female
Plasma insulin ng/ml
WT
KO
WT WD
KO WD
D
Fasting insulin male
Plasma insulin ng/ml
WT
KO
WT WD
KO WD

Fig. 8

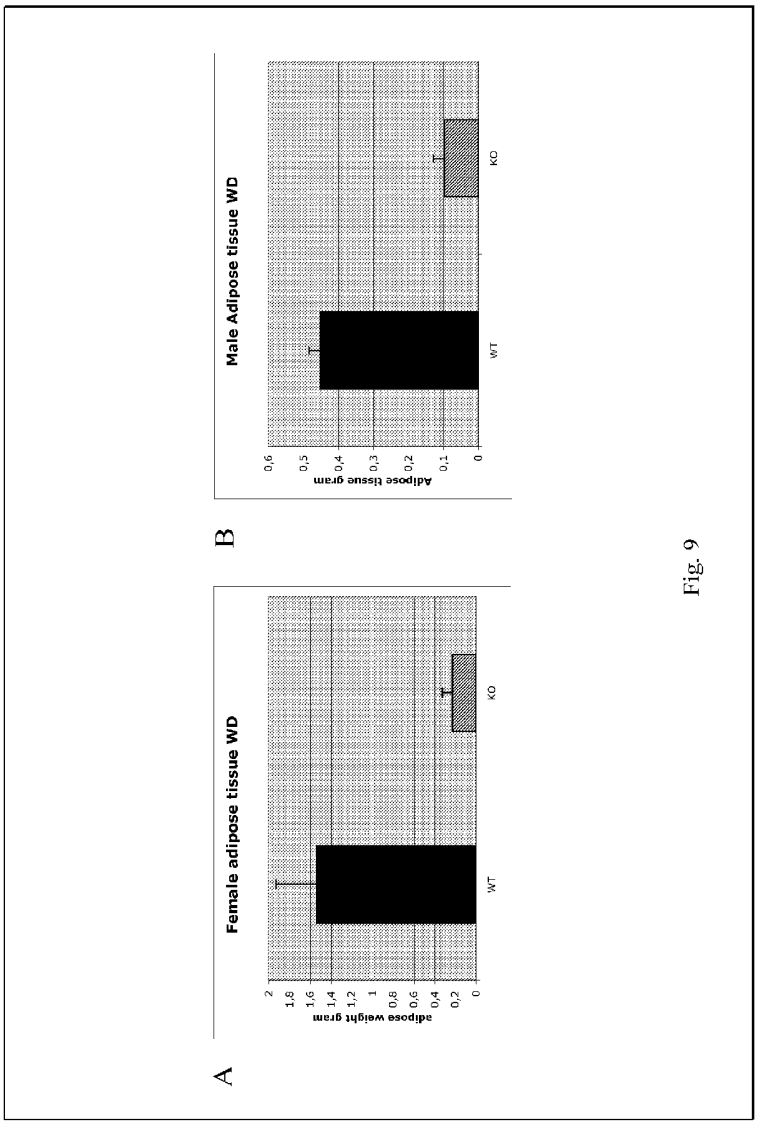

A
Female adipose tissue WD
adipose weight gram
2
1,8
1,6
1,4
1,2
1
0,8
0,6
0,4
0,2
0
WT
KO
B
Male Adipose tissue WD
Adipose tissue gram
0,6
0,5
0,4
0,3
0,2
0,1
0
WT
KO

Fig. 9

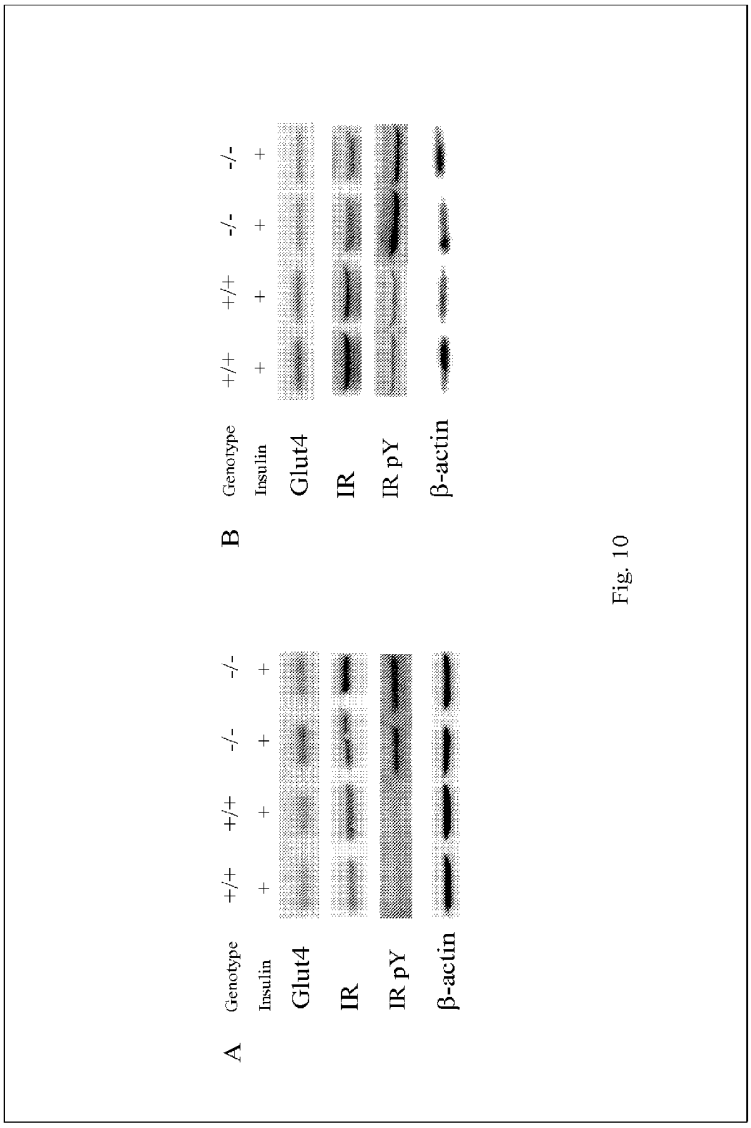

A
Genotype
Insulin
Glut4
IR
IR pY
β-actin
+/+
+/+
-/-
-/-
+
+
+
+
B
Genotype
Insulin
Glut4
IR
IR pY
β-actin
+/+
+/+
-/-
-/-
+
+
+
+

Fig. 10

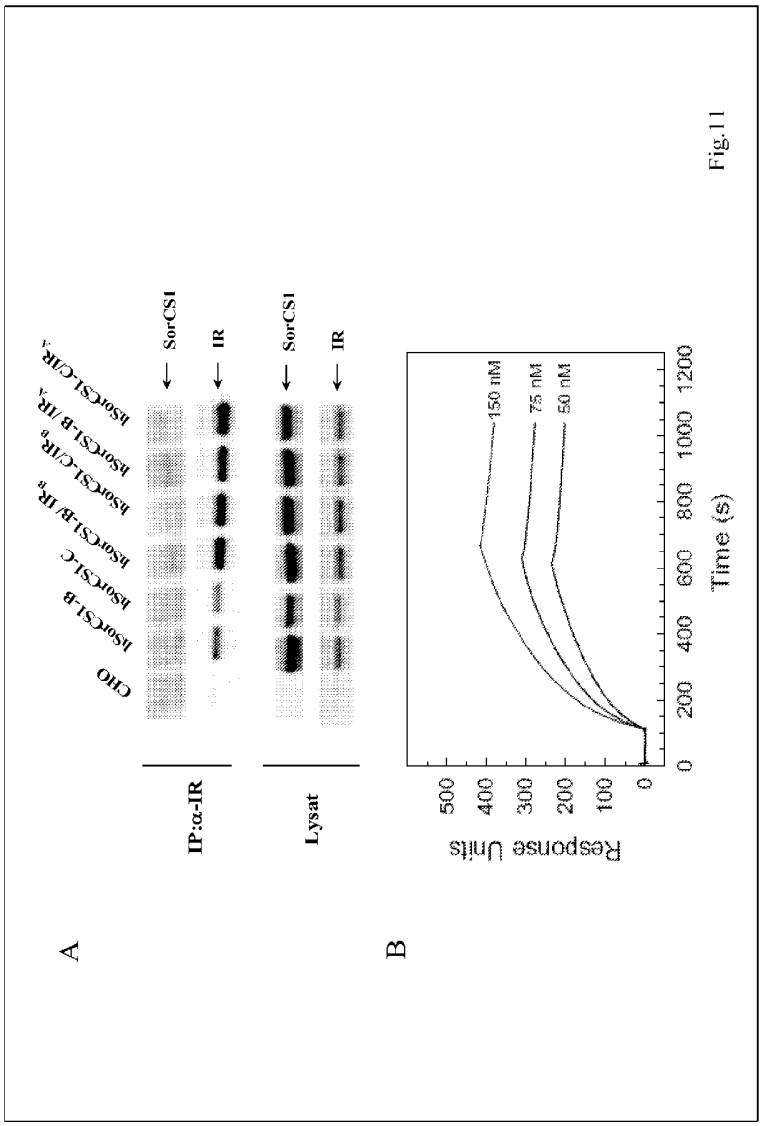

A
IP:α-IR
Lysat
SorCS1
IR
CHO
hSorCS1-B
hSorCS1-C
hSorCS1-B/IR$_B$
hSorCS1-C/IR$_B$
hSorCS1-B/IR$_A$
hSorCS1-C/IR$_A$
B
Response Units
Time (s)
150 nM
75 nM
50 nM
0
100
200
300
400
500
0
200
400
600
800
1000
1200

Fig.11

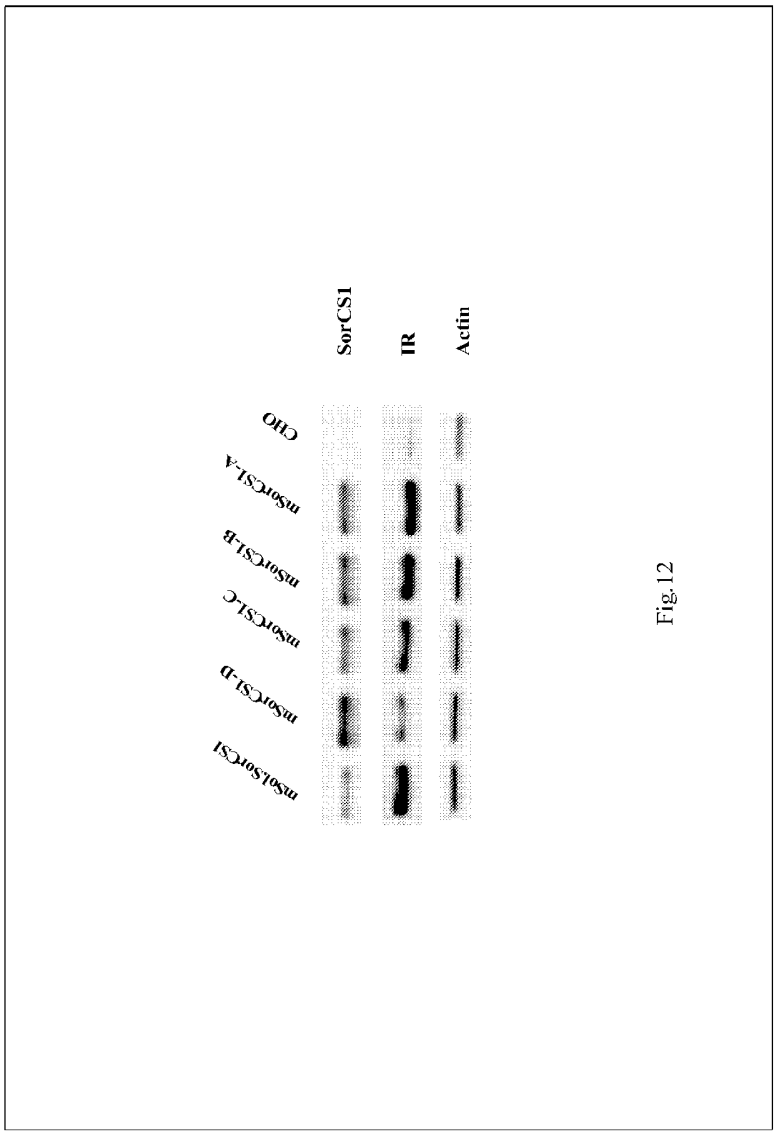

SorCS1
IR
Actin
CHO
mSorCS1-A
mSorCS1-B
mSorCS1-C
mSorCS1-D
mSolSorCS1

Fig.12

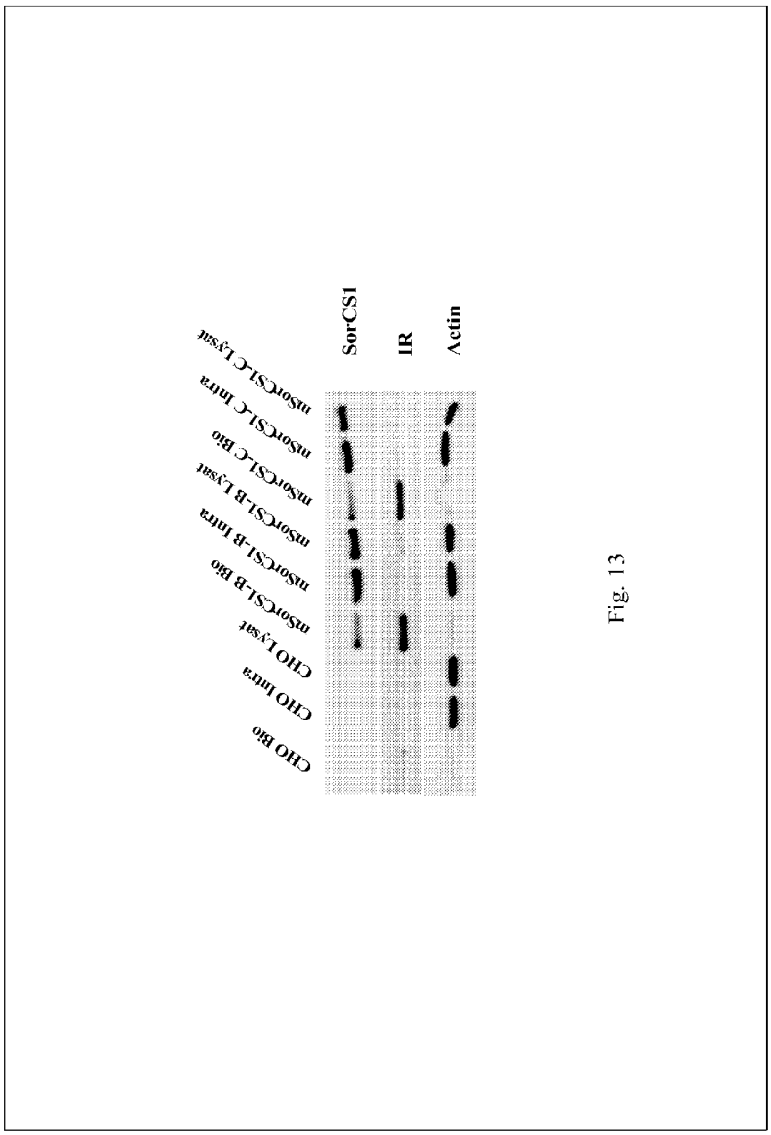

SorCS1
IR
Actin
hSorCS1-C Lysat
hSorCS1-C Intra
hSorCS1-C Bio
hSorCS1-B Lysat
hSorCS1-B Intra
hSorCS1-B Bio
CHO Lysat
CHO Intra
CHO Bio

Fig. 13

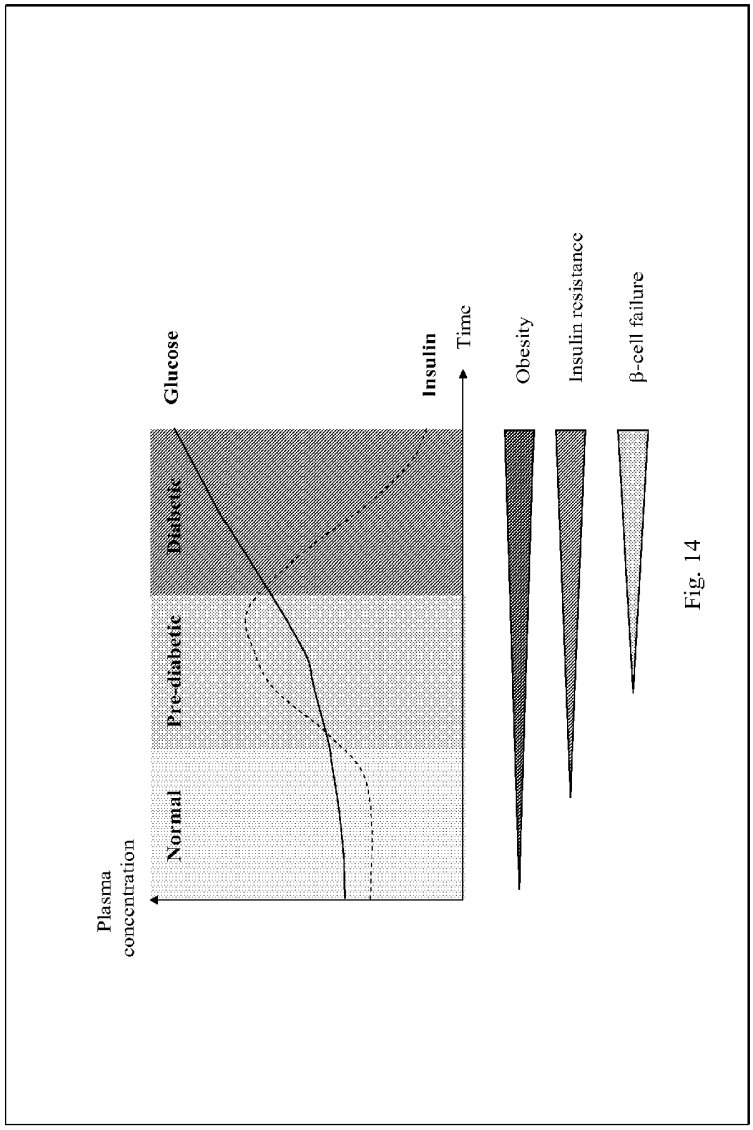

Plasma concentration
Normal
Pre-diabetic
Diabetic
Glucose
Insulin
Time
Obesity
Insulin resistance
β-cell failure

Fig. 14

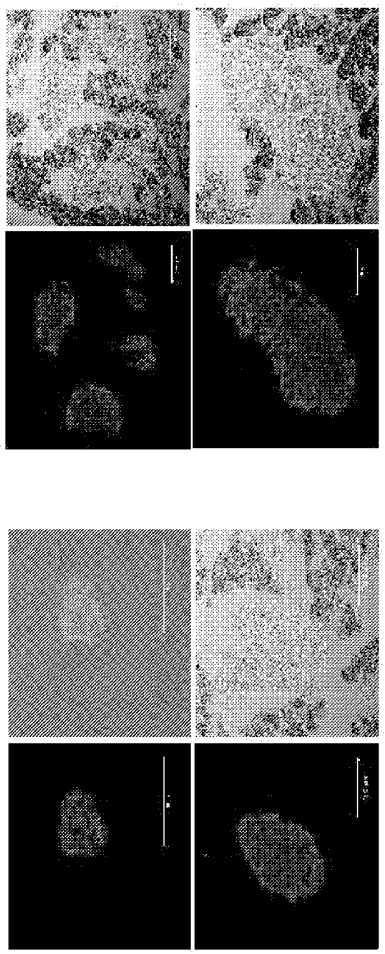


Fig. 15

Alignment of the SorCS1 protein from different species

Sequence 1: gi|61743975|ref|NP_001013049.1	1198 aa	Human (homo sapiens)
Sequence 2: gi|114632730|ref|XP_508026.2|	1361 aa	Chimpanzee (Pan troglodytes)
Sequence 3: gi|119917739|ref|XP_001253082.	1196 aa	Cow (Bos Taurus)
Sequence 4: gi|12025518|ref|NP_067352.1|	1167 aa	Mouse (Mus musculus)
Sequence 5: gi|109460253|ref|XP_220080.4|	1369 aa	Rat (Rattus norvegicus)
Sequence 6: gi|73998824|ref|XP_535010.2|	997 aa	Dog (Canis lupus familiaris)
Sequence 7: gi|118093020|ref|XP_421750.2|	1258 aa	Chicken (Gallus gallus)

```
Human (homo sapiens)                ------------------------------------------------------------
Chimpanzee (Pan troglodytes)        -------MTGRFPPRNRKLPTHRPLRRPGVDRPRGQGARTQRWDPRPRG 42
Cow (Bos taurus)                    ------------------------------------------------------------
Mouse (Mus musculus)                ------------------------------------------------------------
Rat (Rattus norvegicus)             MRAQVFLQQSGLSEKKHTDGIPTVPSINVIPERSKELIVPRGRVLWLIAG 50
Dog (Canis lupus familiaris)        ------------------------------------------------------------
Chicken (Gallus gallus)             ------------------------------------------------------------

Human (homo sapiens)                ------------------------------------------------------------
Chimpanzee (Pan troglodytes)        RRVGGGRRRGEAAAAPARPRGSRRRRLQRPSTRARARSASDFSSAPPPRG 92
Cow (Bos taurus)                    ------------------------------------------------------------
Mouse (Mus musculus)                ------------------------------------------------------------
Rat (Rattus norvegicus)             TLRSLGRVGDSTARARLFVHSAARRRDAAPGALAEPALPPASPRRRRRRW 100
Dog (Canis lupus familiaris)        ------------------------------------------------------------
Chicken (Gallus gallus)             ------------------------------------------------------------

Human (homo sapiens)                ------------------------------------------------------------
Chimpanzee (Pan troglodytes)        GGSLRPDPRSAQAQPGRAAATCPAPPPEAPTAAQLGWSWGPERRPTAAS 142
Cow (Bos taurus)                    ------------------------------------------------------------
Mouse (Mus musculus)                ------------------------------------------------------------
Rat (Rattus norvegicus)             LAAPSQPARSSQAQPGRAAGTCPAPPPAPPPPNLDGVVVLSAHPAAVSP 150
Dog (Canis lupus familiaris)        ------------------------------------------------------------
Chicken (Gallus gallus)             ----------------------------------------MEKV 4
```

Fig. 16

```
Human (homo sapiens)          ----------MGKVGAGGGSQARLSAILAGAGLLILCAP 29
Chimpanzee (Pan troglodytes)  AELRAATFVLGPLSPLLFAPAMGKVGAGGGSQARLSAILAGAGLIVLCAP 192
Cow (Bos taurus)              ----------MGKVGAGGVSPAGLSAILAGAGLIVLCAP 29
Mouse (Mus musculus)          ----------MGKVGAGDGSSAGLSAILAGAGLIMLAP 29
Rat (Rattus norvegicus)       VPRSAACLRFGTPSPLLSAPEMGKVGAGDGSSAALSAILTGAGLIMLAP 200
Dog (Canis lupus familiaris)  ----------
Chicken (Gallus gallus)       AGWYPAWHVALLYWTWLFLFTFGFTGAEITCRSCHSQVNPQQQHPQQGLP 54

Human (homo sapiens)          GVCGGGSCCPSPHPSSAPRSASTPRGFSHQGRPGRAPATPLPLVVRPLFS 79
Chimpanzee (Pan troglodytes)  GVCGGGSCCPPPHPSSAPRSASTPRGFSHQGRPGRAPATPLPLVVRPLFS 242
Cow (Bos taurus)              GSCGGGSCCPPRHPSAAPRWAPTPGGLPHQGPRGRAPATPLPQLGRPLFA 79
Mouse (Mus musculus)          GVCSSLSCCPPQHPSSTPRTLTPRGFPHPGPLGRAPATPPPLFMRPLFA 79
Rat (Rattus norvegicus)       GICSSLSCCPPQHPSSTPRWTLTPRGFSYPGPLGRAPATPPPLFMRPLFA 250
Dog (Canis lupus familiaris)  ----------
Chicken (Gallus gallus)       MHLKTDRGEKERWRIFGSQGGERGRGAGMDTEDAELQAPFDPALAGTKFS 104

Human (homo sapiens)          -VAPGDRALSLERARGTGASMAVAARSGRR-RRSGADQEKAERGEGASRS 127
Chimpanzee (Pan troglodytes)  -VAPGDRALSLERARGTGASMAVAARSGRR-RRSGADQEKAERGEGASRS 290
Cow (Bos taurus)              -VAPGDRALSLERAPGTGASVAVAPRSGRK-RRSGEDQEKAERGEGTSRS 127
Mouse (Mus musculus)          -VAPGDRALFLERAGGSRVSVATAARSGRR-RRSGTEPEKIEPGEGASRS 127
Rat (Rattus norvegicus)       -VAPGDRALFLERAGGSRVSVATASRSGRR-RRSGMDPEKTEPGEGTSRS 298
Dog (Canis lupus familiaris)  ----------
Chicken (Gallus gallus)       GWETRSWASEPEKAPGDSRPGAAAAPTGEYPQRGQAGGRRNSARRRRGRS 154

Human (homo sapiens)          PRGVLRDGGQQPGTRERDPDKATRFRMEELRLTSTTFALTGDSAHNQAM 177
Chimpanzee (Pan troglodytes)  PRGVLRDGGQQPGTLERDPDKATRFRMEELRLTSTTFALTGDSAHNQAM 340
Cow (Bos taurus)              PRGVLRDRGQLEPGTLERDPDKATRFRLEELKLTSTTFALTGDSAHNQAM 177
Mouse (Mus musculus)          RRDMLKDGGQQGLGTGARDPGKATRFRMEELRLTSTTFALTGDSAHNQAM 177
Rat (Rattus norvegicus)       RRDMLRDGGQQGFGTGARDPDKATRFRMEELRLTSTTFALTGDSAHNQAM 348
Dog (Canis lupus familiaris)  ----------MRKVS----------EIM 8
Chicken (Gallus gallus)       PRGTAGPGGAAG---REPGGSGAARFGLEELRLGSTTFALTGDSAHNQAM 201
                                          :: *           : *
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Fig. 16, continued

```
Human (homo sapiens)          VHWSGHNSSVILILTKLYDYNLGSITESSLWRSTDYGTTYEKLNDKVGLK 227
Chimpanzee (Pan troglodytes)  VHWSGHNSSVILILTKLYDYNLGSITESSLWRSTDYGTTYEKLNDKVGLK 390
Cow (Bos taurus)              VHWSGHNSSVILILTKLFDYNLGSITESSLWRSTDYGTTYEKLNDKVGLK 227
Mouse (Mus musculus)          VHWSGHNSSVILILTKLYDYNLGSITESSLWRSTDYGTTYEKLNDKVGLK 227
Rat (Rattus norvegicus)       VHWSGHNSSVILILTKLYDYNLGSITESSLWRSTDYGTTYEKLNDKVGLK 398
Dog (Canis lupus familiaris)  VLRSWH--SVILILTKLYDYNLGSITESSLWRSTDYGTTYEKLNDKVGLK 56
Chicken (Gallus gallus)       VHWSGQNSSVILILTKLYDYNLGSITESSLWRSTDYGTTYEKLNDKIGLK 251
                              *  * :  ********:**********************************:***

Human (homo sapiens)          TILSYLYVCPTNKRKIMLLTDPEIESSLLISSDEGATYQKYRLNFYIQSL 277
Chimpanzee (Pan troglodytes)  TILSYLYVCPTNKRKIMLLTDPEIESSLLISSDEGATYQKYRLNFYIQSL 440
Cow (Bos taurus)              TILSYLYVCPTNKRKIMLLTDPEIESSLLISSDEGATYQKYRLNFYIQSL 277
Mouse (Mus musculus)          TILSYLYVCPTNKCKIMLLTDPEIESSLLISSDEGATYQKYRLNFYLQSL 277
Rat (Rattus norvegicus)       TILSYLYVCPTNKRKIMLLTDPEIESSLLISSDEGATYQKYRLNFYIQSL 448
Dog (Canis lupus familiaris)  TILSYLYVCPTNKRKIMLLTDPEIESSLLISSDEGATYQKYRLNFYIQSL 106
Chicken (Gallus gallus)       TILSYLYVCPTNKRKIMLLTDPEVESSLLISTDEGATYQKYRLNFYIHSL 301
                              ********** ********** **********:**********:**********:;:**

Human (homo sapiens)          LFHPKQEDWILAYSQDQKLYSSAEFGRRWQLIQEGVVPNRFYWSVMGSNK 327
Chimpanzee (Pan troglodytes)  LFHPKQEDWILAYSQDQKLYSSAEFGRRWQLIQEGVVPNRFYWSVMGSNK 490
Cow (Bos taurus)              LFHPKQEDWILAYSQDQKLYSSAEFGRRWQLIQEAVVPNRFYWSVMGSNK 327
Mouse (Mus musculus)          LFHPKQEDWILAYSQDQKLYSSAEFGRRWQLIQESVVPNRFYWSVMGSSK 327
Rat (Rattus norvegicus)       LFHPKQEDWILAYSQDQKLYSSAEFGRRWQLIQEAVVPNRFYWSVLGSNK 498
Dog (Canis lupus familiaris)  LFHPKQEDWILAYSQDQKLYSSAEFGRRWQLIQEGVVPNRFYWSVMGSNK 156
Chicken (Gallus gallus)       LFHPKQEDWILAYSQDQKLFSSVEFGRRWLLLHEGVAPNRFYWSMMVSGR 351
                              ********************:**.****** *::*.*.*******:: *.:

Human (homo sapiens)          EFDLVHLEARTVDGHSHYLTCRMQNCTEANRNQFFPGYIDPDSLIVQDHY 377
Chimpanzee (Pan troglodytes)  EFDLVHLEARTVDGHSHYLTCRMQNCTEANRNQFFPGYIDPDSLIVQDHY 540
Cow (Bos taurus)              EFDLVHLEARTVDGHSQYLTCRMQNCTEANRNKFFPGYIDPDSLIVQDDY 377
Mouse (Mus musculus)          EFDLVHLEARTVDGHSIYLTCRMQNCTEANRNKFFPGYIDPDSLIVQDDY 377
Rat (Rattus norvegicus)       EFDLVHLEARTVDGHSIYLTCRMQNCTEANRNKFFPGYIDPDSLIVQDDY 548
Dog (Canis lupus familiaris)  EFDLVHLEARTVDGHSQYLTCRMQNCTEANRNKFFPGYIDPDSLIVQDDY 206
Chicken (Gallus gallus)       EFDLVHLEAKTVDGHAQYITCKMQNCSEASQNKFFPGYIDHNSLIVQDDY 401
                              *********:*****: *:**:****:**.:*:*******  :******.*
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Fig. 16, continued

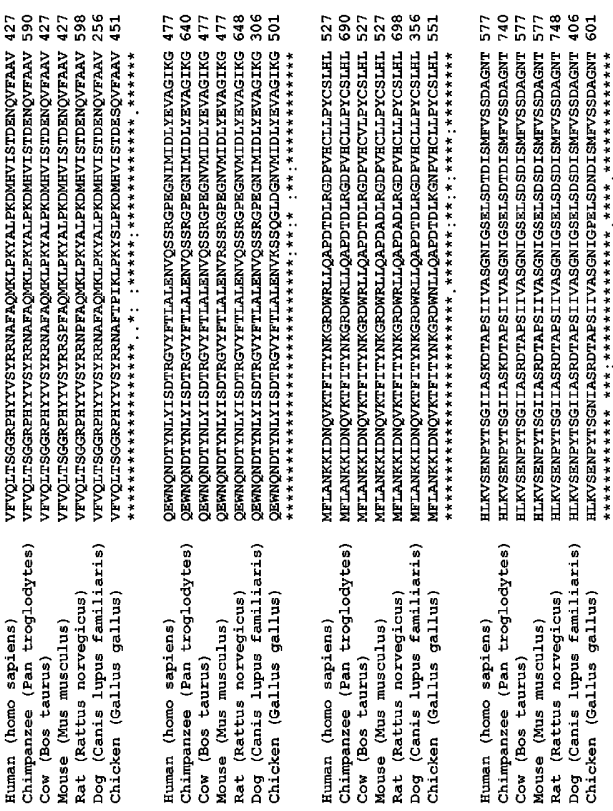


Fig. 16, continued

```
Human (homo sapiens)              WRQIFEEEHSVLYLDQGGVLVAMKHTSLPIRHLWLSFDEGRSWSKYSFTS 627
Chimpanzee (Pan troglodytes)      WRQIFEEEHSVLYLDQGGVLVAMKHTSLPIRHLWLSFDEGRSWSKYSFTS 790
Cow (Bos taurus)                  WRQIFEEEHSVLYLDQGGVLVAMKHTSLPIRHLWLSFDEGRSWSKYSFTS 627
Mouse (Mus musculus)              WRQIFEEEHSILYLDQGGVLVAMKHTSLPIRHLWLSFDEGRSWSKYSFTS 627
Rat (Rattus norvegicus)           WRQIFEEEHSILYLDQGGVLVAMKHTSLPIRHLWLSFDEGRSWSKYSFTS 798
Dog (Canis lupus familiaris)      WRQIFEEEHSVLYLDQGGVLVAMKHTSLPIRHLWLSFDEGRSWSKYSFTS 456
Chicken (Gallus gallus)           WRQIFEEEHSVLYLDQGGVLVAIKHTSLPIRHLWLSFDEGKSWSKYSFTS 651
                                  ********** *********** ***************** ********

Human (homo sapiens)              IPLFVDGVLGEPGETLIMTVFGHFSHRSEWQLVKVDYKSIFDRRCAEED 677
Chimpanzee (Pan troglodytes)      IPLFVDGVLGEPGETLIMTVFGHFSHRSEWQLVKVDYKSIFDRRCAEED 840
Cow (Bos taurus)                  IPLFVDGVLGEPGETLIMTLLDHS--HSDWLVTALQPCCLFLLGNEWED 675
Mouse (Mus musculus)              IPLFVDGVLGEPGETLIMTVFGHFSHRSEWQLVKVDYKSIFDRRCAEED 677
Rat (Rattus norvegicus)           IPLFVDGVLGEPGETLIMTVFGHFSHRSEWQLVKVDYKSIFDRRCAEED 848
Dog (Canis lupus familiaris)      IPLFVDGVLGEPGETLIMTVFGHFSHRSEWQLVKVDYKSIFDRRCAEED 506
Chicken (Gallus gallus)           LPLFVDGILGEPGETLIMTVFGHFSHRSEWQLVKIDYKSIFDRRCAEED 701
                                  :****** ********** ::.*  :*:* :. ::  .:*     **

Human (homo sapiens)              YRFWQLHSQGEACIMGAKRIYKKRKSERKCMQGKYAGAMESEPCVCTEAD 727
Chimpanzee (Pan troglodytes)      YRFWQLHSQGEACIMGAKRIYKKRKSERKCMQGKYAGAMESEPCVCTEAD 890
Cow (Bos taurus)                  KIAWKFQDQGEACIMGAKRIYKKRKSERKCMQGKYAGAMESEPCVCTEAD 725
Mouse (Mus musculus)              YRFWQLHSQGEACIMGAKRIYKKRKSERKCMQ-KYAGAMESEPCVCTEAD 726
Rat (Rattus norvegicus)           YRFWQLHSQGEACIMGAKRIYKKRKSERKCMQGTYAGAMESEPCVCTEAD 898
Dog (Canis lupus familiaris)      YRFWQLHSQGEACIMGAKRIYKKRKSERKCMQGKYAGAMESEPCVCTEAD 556
Chicken (Gallus gallus)           YWTWQLHSQGEACIMGAKRIYKKRKSEKKCMQGKYAGAMTSEPCVCTDAD 751
                                  .*: :.:********** ;*****;**** .***** *******:**

Human (homo sapiens)              FDCDYGYERHSNGQCLPAFWFNPSSLSKDCSLGQSYINSTGYRKVVSNNC 777
Chimpanzee (Pan troglodytes)      FDCDYGYERHSNGQCLPAFWFNPSSLSKDCSLGQSYINSTGYRKVVSNNC 940
Cow (Bos taurus)                  FDCDYGYERHSNGQCLPAFWFNPSSLSKDCSLGQSYINSTGYRKVVSNNC 775
Mouse (Mus musculus)              FDCDYGYERHSNGQCLPAFWFNPSSLSKDCSLGQSYINSAGYRKVVSNNC 776
Rat (Rattus norvegicus)           FDCDYGYERHSSGQCLPAFWFNPSSLSKDCSLGQSYLNSTGYRKVVSNNC 948
Dog (Canis lupus familiaris)      FDCDYGYERHSNGQCLPAFWFNPSSLSKDCSLGQSYINSTGYRKVVSNNC 606
Chicken (Gallus gallus)           FDCDYGYERHRNGQCLPAFWYNPSSLSKDCSLGQSYINSTGYRKVVSNNC 801
                                  ********** .********:*:********************:********
```

Fig. 16, continued

```
Human (homo sapiens)          TDGVREQYTAKFQKCPGKAPRGLRIVTADGKLTAEQGHNVTLMVQLEEGD 827
Chimpanzee (Pan troglodytes)  TDGVREQYTAKFQKCPGKAPRGLRIVTADGKLTAEQGHNVTLMVQLEEGD 990
Cow (Bos taurus)              TDGVREQYTAKFQKCPGKAPRGLRIVTADGKLTAEQGHNVTLMVQLEEGD 825
Mouse (Mus musculus)          TDGVRSQYTAKFQKCPGKAPRGLRIVTADGKLTAEQGHNVTLMVQLEEGD 826
Rat (Rattus norvegicus)       TDGVREQYTAKFQKCPGKAPRGLRIVTADGKLTAEQGHNVTLMVQLEEGD 998
Dog (Canis lupus familiaris)  TDGVREQYTAKFQKCPGKAPRGLRIVTADGKLTAEQGHNVTLMVQLEEGD 656
Chicken (Gallus gallus)       TDGVREQYTAKFQQCPGKAPQGLRITSDGKLTAEQGHNVTFLVQLEEGD 851
                              ********************:*******************::******

Human (homo sapiens)          VQRTLIQVDFGDGIAVSYVNLSSMEDGIKHVYQNVGIFRVTVQVDNSLGS 877
Chimpanzee (Pan troglodytes)  VQRTLIQVDFGDGIAVSYVNLSSMEDGIKHVYQNVGIFRVTVQVDNSLGS 1040
Cow (Bos taurus)              VQRTLIQVDFGDGIAVSYVNLSSMEDGIKHVYHNVGIFRVTVQVDNSLGS 875
Mouse (Mus musculus)          VQRTLIQVDFGDGIAVSYVNLSSMEDGIKHVYQNVGIFRVTVQVDNSLGS 876
Rat (Rattus norvegicus)       VQRTLIQVDFGDGIAVSYVNLSSMEDGIKHVYQNVGIFRVTVQVDNSLGS 1048
Dog (Canis lupus familiaris)  VQRTLIQVDFGDGIAVSYVNLSSMEDGIKHVYHNVGIFRVTVQVDNSLGS 706
Chicken (Gallus gallus)       LQRSLIQVDFGDGTAVSYANLSSTEDGIKHTYQNVGIFRVTVLVENSLGS 901
                              :**:********** ****.**** ******.*:*********** *:*****

Human (homo sapiens)          DSAVLYLHVTCPLEHVHLSLPFVTTKNKEVNATAVLWPSQVGTLTVWWY 927
Chimpanzee (Pan troglodytes)  DSAVLYLHVTCPLEHVHLSLPFVTTKNKEVNATAVLWPSQVGTLITVWWY 1090
Cow (Bos taurus)              DSAVIYLHVTCPLEHVHLSLPFVTTKNKEVNATAVLWPSQVGTLTVVWWY 925
Mouse (Mus musculus)          DSAVLYLHVTCPLEHVHLSLPFVTTKNKEVNATAVLWPSQVGTLTVVWWY 926
Rat (Rattus norvegicus)       DSAVLYLHVTCPLEHVHLSLPFVTTKNKEVNATAVLWPSQVGTLTVVWWY 1098
Dog (Canis lupus familiaris)  DSAVLYLHVTCPLEHVHLSLPFVTTKNKEVNATAVLWPSQVGTLTVVWWY 756
Chicken (Gallus gallus)       DNAVIYLHVTCPLEHVHLSLPFVTTKNKEVNATAVLWPSQVGTLTVVWWF 951
                              *.**********************************************:

Human (homo sapiens)          GNNTEPLITLEGSISFRFTSEGMNTITVQVSAGNAILQDTKTIAVTEEFR 977
Chimpanzee (Pan troglodytes)  GNNTEPLITLEGSISFRFTSEGMNTITVQVSAGNAILQDTKTIAVTEEFR 1140
Cow (Bos taurus)              GNNTEPLITLEGSIAFKFTSEGMNTITVQVSAGNAILQDTKTIAVTEEFR 975
Mouse (Mus musculus)          GNNTEPLITLEGSISFKFTSEGMNTITVQVSAGNAILQDTKTIAVTEEFR 976
Rat (Rattus norvegicus)       GNNTEPLITLEGSISFKFTSEGMNTITVQVSAGNAILQDTKTIAVTEEFR 1148
Dog (Canis lupus familiaris)  GNNTEPLITLEGSISFKFTSEGMNTITVQVSAGNAILQDTKTIAVTEEFR 806
Chicken (Gallus gallus)       GNNTEPLITLEGSITFTSVEGMNTITVQVSAGNTILQDTKTIAVTEQFR 1001
                              ********************:* *: **********************:**
```

Fig. 16, continued

```
Human (homo sapiens)          SLRLSFSPNLDDYNPDIPEWRRDIGRVIKKSLVEATGVFGQHILVAVLPG 1027
Chimpanzee (Pan troglodytes)  SLRLSFSPNLDDYNPDIPEWRRDIGRVIKKSLVEATGVFGQHILVAVLPG 1190
Cow (Bos taurus)              SLRLSFSPNLDDYNPDIPEWRRDVSRVIKKALVEATGVFGQHILVAVLPG 1025
Mouse (Mus musculus)          SLRLAFSPNLDDYNPDIPEWRRDISRVIKKSLVEATGIFSQHILVAVLPG 1026
Rat (Rattus norvegicus)       SLRLAFSPNLDDYNPDIPEWRRDISRVIKKSLVEATGIFSQHILVAVLPG 1198
Dog (Canis lupus familiaris)  SLRLSFSPNLDDYNPDIPEWRRDISRVIKKSLVEATGVFGQHILVAVLPG 856
Chicken (Gallus gallus)       SLRLSFSPNLDDYNPDIPEWRRDISRVVKRALVEATGISSKHILVAVLPG 1051
                              ****:**********************:.**:*::******:..:********

Human (homo sapiens)          LPTTAELFVLPYQDPAGENKKRSTDDLEQISELLIHTTNQNSVHFELKPGV 1077
Chimpanzee (Pan troglodytes)  LPTTAELFVLPYQDPAGENKKRSTDDLEQISELLIHTTNQNSVHFELKPGV 1240
Cow (Bos taurus)              LPTAAELFVLPHQDPTGENKRPAEDLEQISELMIHKLNQNSVHFELKPGV 1075
Mouse (Mus musculus)          LPTAAELFVLPYQDGTRENKKRSPEDLEQISEVLIHKLNQNLVHFELKPGV 1076
Rat (Rattus norvegicus)       LPTAAELFVLPYQDGARENKKRSPEDLEQISEVLIHKLNQNLVHFELKPGV 1248
Dog (Canis lupus familiaris)  LPTAAELFVLPYQDPTGENKKRSAEDLEQISELLIHKLNQNSVHFELKPGV 906
Chicken (Gallus gallus)       LPTSAELFILPYQDATGGNKR-TEDLEQISEILIQKLNQNFVHFELKPGV 1100
                              ***:****:**:**  :  ***  .:********::*:.**** *********

Human (homo sapiens)          RVLVHAAHLTAAPLVDLTPTHSGSAMLMLSVVFVGLAVFVIYKFKRKIP 1127
Chimpanzee (Pan troglodytes)  RVLVHAAHLTAAPLVDLTPTHSGSAMLMLSVVFVGLAVFVIYKFKRKIP 1290
Cow (Bos taurus)              QVLVHAAHLTAAPLVDLTPTHSGSAMLMLSVVFVGLAVFVIYKFKRKIP 1125
Mouse (Mus musculus)          QVLVHAAHLTAAPLVDLTPTHSGSAMLMLSVVFVGLAVFVIYKFKRKVA 1126
Rat (Rattus norvegicus)       QVLVHAAHLTAAPLVDLTPTHSGSAMLMLSVVFVGLAVFVIYKFKRKIP 1298
Dog (Canis lupus familiaris)  QILVHAAHLTAAPLVDLTPTHSGSAMLMLSVVFVGLAVFVIYKFKRKVA 956
Chicken (Gallus gallus)       RVLVHAAHLTAAPLVDLTPSHSGSAMLMLSVVFVGLAVFVIYKFKRKIP 1150
                              ::**********************:**********************::.

Human (homo sapiens)          GINVYAQMQNEKEQEMISFVSHSESRFNVFQTELRRFGQLIDEKVESQLI 1177
Chimpanzee (Pan troglodytes)  GINVYAQMQNEKEQEMISFVSHFESRFSVFQTELRRFGQLIDEKVESQLI 1340
Cow (Bos taurus)              GINVYAQMQNEKEQEMVSRVSHFESRFYVFQTELRRFGQLIDEKVESQLI 1175
Mouse (Mus musculus)          LFSPPSPSAQPGDSSLR----LQRPRPATPPSPKRGSAGAQFAI----- 1167
Rat (Rattus norvegicus)       GINVYAQMQNEKEQELINFVSHTESRFTAPHPDLRRFGQLVDEKVESHLL 1348
Dog (Canis lupus familiaris)  LFSPFSPSTQFGDSSLR----LQRARHATPPSTFKRGSAGAQFAI----- 997
Chicken (Gallus gallus)       GLNIYAQMQNEKDQEMVSFVSQRSSIFNVFQSELMSFEQLVDEKLDVQFI 1200
                                    .  :   :  :.::        ..   .* .          :  :
```

Fig. 16, continued

```
Human (homo sapiens)          GSISIVAENQSTKEIPTYVNV---------------------------------- 1198
Chimpanzee (Pan troglodytes)  GSISIVAENQSTKEIPTYVNV---------------------------------- 1361
Cow (Bos taurus)              GSISIVAENQSTKEIPTYVNV---------------------------------- 1196
Mouse (Mus musculus)          ---------------------------------------------------------
Rat (Rattus norvegicus)       GSISIVAENQSTKEIPTYVNV---------------------------------- 1369
Dog (Canis lupus familiaris)  ---------------------------------------------------------
Chicken (Gallus gallus)       EQPQATVQNPRKGNAAKVVWTEDFQKACGSPRGFKPRPGAEVFPQLLSPR 1250

Human (homo sapiens)          --------
Chimpanzee (Pan troglodytes)  --------
Cow (Bos taurus)              --------
Mouse (Mus musculus)          --------
Rat (Rattus norvegicus)       --------
Dog (Canis lupus familiaris)  --------
Chicken (Gallus gallus)       AQKKSLPM 1258
```

Fig. 16, continued

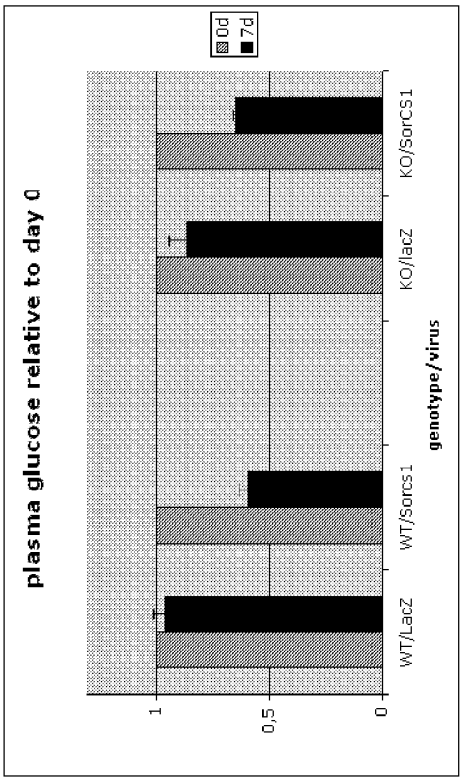

plasma glucose relative to day 0
0d
7d
1
0,5
0
WT/LacZ
WT/Sorcs1
KO/lacZ
KO/SorCS1
genotype/virus

Fig. 17

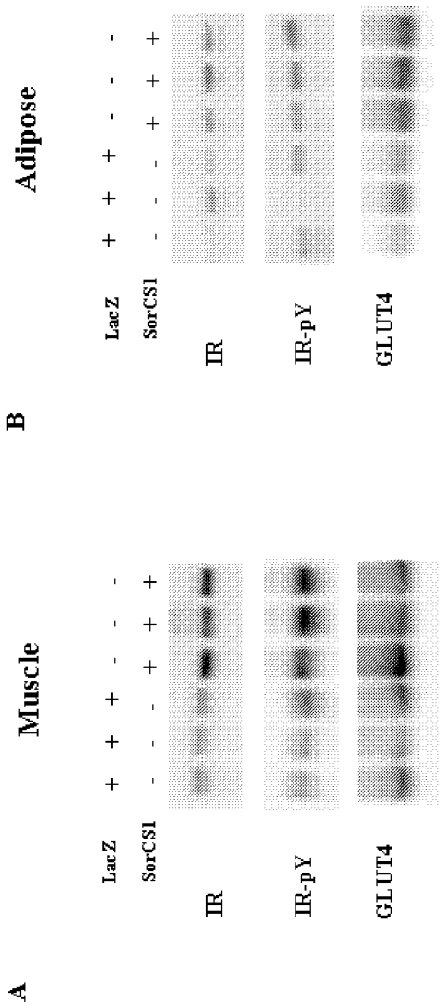

A
Muscle
LacZ + + + - - -
SorCS1 - - - + + +
IR
IR-pY
GLUT4
B
Adipose
LacZ + + + - - -
SorCS1 - - - + + +
IR
IR-pY
GLUT4

Fig. 18

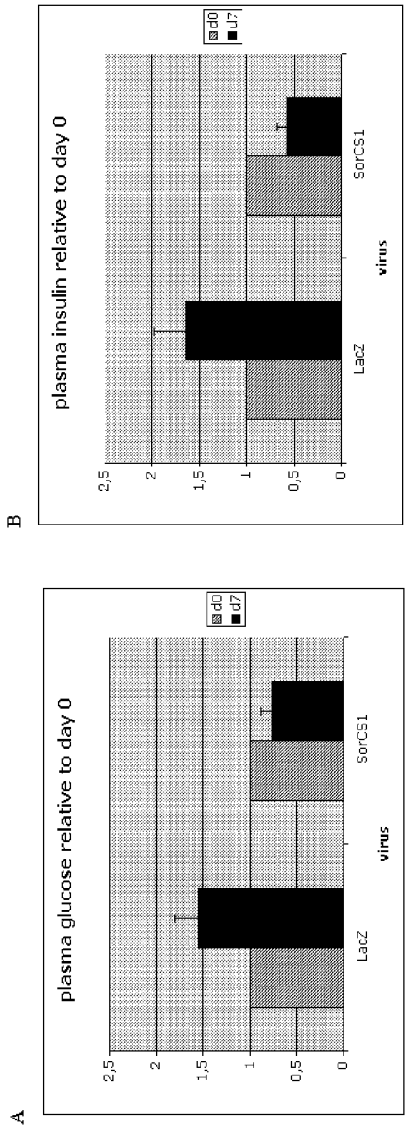

A
plasma glucose relative to day 0
d0
d7
2,5
2
1,5
1
0,5
0
LacZ
SorCS1
virus
B
plasma insulin relative to day 0
d0
d7
2,5
2
1,5
1
0,5
0
LacZ
SorCS1
virus

Fig. 19

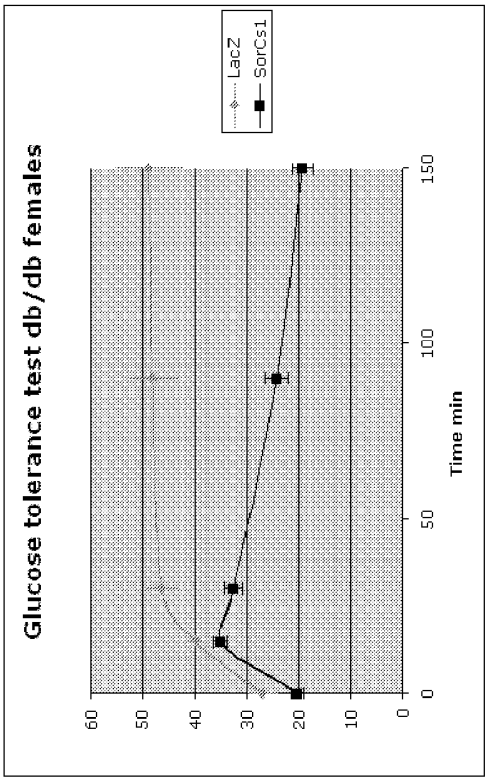

Glucose tolerance test db/db females
LacZ
SorCs1
60
50
40
30
20
10
0
0
50
100
150
Time min

Fig. 20

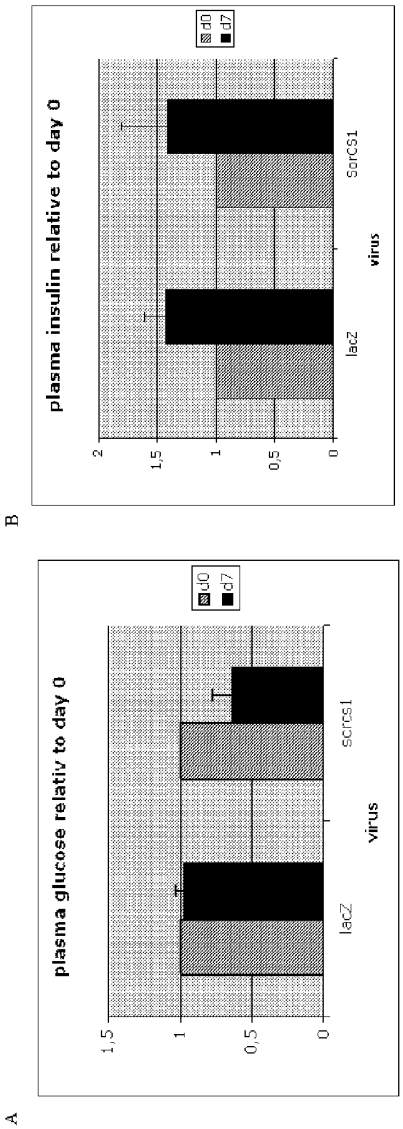

A
plasma glucose relativ to day 0
d0
d7
1,5
1
0,5
0
lacZ
scrs1
virus
B
plasma insulin relative to day 0
d0
d7
2
1,5
1
0,5
0
lacZ
SorCS1
virus

Fig. 21

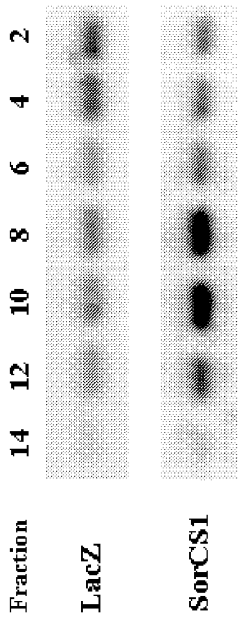
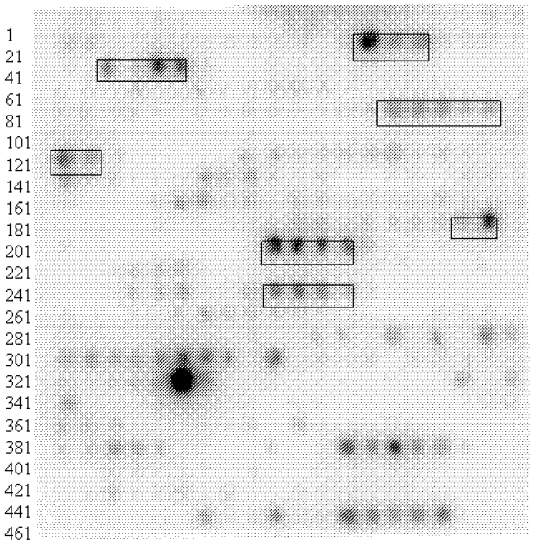


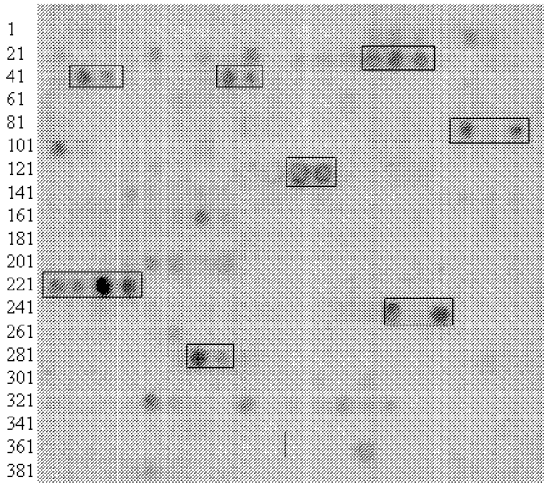
Fig. 22



34-36: KDLFPNLTVIRGSRLFFNYAL (aa 100-120)
43-46: HLKELGLYNLMNITRGSVRIEKNN (aa 127-150)
95-99: SFCQDLHHKCKNSRRQGCHQYVIHNNK (aa 284-310)
121-122: VINGSLIINIRGGNNLAA (aa 362-379)
198-199: VKTLVTFSDERRTYGAKS (aa 593-610)
210-213: ISVSNSSSQIILKWKPPSDPNGNI (aa 629-652)
250-253: GTGAEDPRPSRKRRSLGDVGNVTV (aa 749-772)

Fig. 23A

Human IR-his on hSorCS1-a



35-37: ARSGRRRRSGADQEKAERGEG (aa 103-124)
42-43: ASRSPRGVLRDGGQQEPG (aa 125-143)
48-49: TRERDPDKATRFRMEELR (aa 144-162)
99-100: QDQKLYSSAEFGRRWQLIQEG (aa197-218)
131-132: YVSYRRNAFAQMKLPKYA (aa 391-409)
221-224: VKVDYKSIFDRRCAEEDYRPWQLH (aa 661-684)
255-257: YLNSTGYRKVVSNNCTDGVRE (aa 763-783)
287-288: YQNGIFRVTVQVDNSLG (aa 859-876)

Fig. 23B

Insulin signalling

(adipose tissue SorCS1 KO >< wildtype)

Gene	Fold regulation	p-value
Aebp1 (AE binding protein 1)	-5.93	0.406
Dok1(docking protein 1)	7.24	0.188
Igf1r (insulin-like growth factor 1 receptor)	3.30	0.00008
Irs2 (Insulin receptor substrate 2)	-2.95	0.100
Pik3cb (phosphoinositide-3-kinase, catalytic, beta polypeptide)	-5.65	0.196
Ucp1 (uncoupling protein 1)	-25.35	0.085

Gene	Function
Aebp1	A transcriptional repressor with carboxypeptidase activity. Binds promotor of adipose P2 gene.
Dok1	A member of the IRS family. Function as a scaffolding protein that recruits signalling molecules (ras-GTP, Nck)
Igf1r	Binds IGF1 with high affinity. Has tyrosine kinase activity. Plays a critical role in transformation events.
Irs2	A cytoplasmic signaling molecule that mediates effects of insulin, insulin-like growth factor 1, and other cytokines by acting as a molecular adaptor between diverse receptor tyrosine kinases and downstream effectors.
Pik3cb	PI3k phosphorylate the inositol ring in inositol lipids. Is a participant in signalling pathways regulating cell growth.
Ucp1	Plays a role in heat production by uncoupling oxidative phosphorylation from the respiratory chain

Fig. 24A

Lipoprotein signalling and Cholesterol metabolism
(Adipose tissue SorCS1 KO >< wildtype)

Gene	Fold reg.	p-value
Akr1d1(aldo-keto reductase family1, member D1)	8.06	0.042
Colec12 (collectin sub-family member 12)	3.12	0.046
Dhcr7 (7-dehydrocholestrol reductase)	3.82	0.040
Hmgcs2 (3-hydroxy-3-methylglutaryl-Coenzyme A synthase 2)	6.01	0.013
Lcat (Lecithin cholesterol acyltransferase)	3.37	0.008
Ldlr (Low density protein receptor)	3.44	0.014
Mvd (mevalonate (diphospho) decarboxylase)	3.48	0.039
Nr1h4 (Nuclear receptor subfamily 1, group H, member 4)	3.49	0.041
Osbpl5 (Oxysterol binding protein-like 5)	3.61	0.048
Prkag2 (Protein kinase, AMP-activated, gamma 2 non-catalytic)	5.27	0.007
Soat1 (Sterol O-acyltransferase 1)	11.75	0.020
Vldlr (very low density lipoprotein receptor)	4.53	0.018

Gene	Function
Akr1d1	Catalysis of the 5-beta-reduction of bile acid intermediates and steroid hormones.
Colec12	A scavenger receptor binding to carbohydrate antigens on microorganisms and oxidized phospholipids of oxidatively damaged or apoptotic cells.
Dhcr7	A penultimate enzyme of sterol biosynthesis that converts 7-dehydro cholesterol to cholesterol
Hmgcs2	Mediates the first reaction in ketogenesis, a metabolic pathway that provides lipid-derived energy during carbohydrate deprivation
Lcat	An extracellular cholesterol esterifying enzyme. The esterification of cholesterol is required for cholesterol transport.
Ldlr	A cell surface protein involved in receptor mediated endocytosis of specific ligands eg. LDL
Mvd	Catalyzes the conversion of mevalonate pyrophosphate into isopentyl pyrophosphate – one of the early steps in cholesterol biosynthesis
Nr1h4	Regulates the expression of various transport proteins and biosynthetic enzymes crucial to the physiological maintenance of cholesterol and bile acid homeostasis.
Osbpl5	An intracellular lipid receptor – a member of the oxy sterol-binding protein family.
Prkag2	Subunit of AMPK an important energy-sensing enzyme that monitors cellular energy status and functions by inactivating key enzymes involved in regulating de novo biosynthesis of fatty acid and cholesterol
Soat1	Forms cholesterol esters from cholesterol. Accumulation of cholesterol esters as cytoplasmic lipid droplets is a characteristic feature of early stages of atherosclerotic plaques
Vldlr	Mediates cholesterol uptake possible in collaboration with ldl

Fig. 24B

DK/EP 2440233 T3