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(54) **APOLIPOPROTEIN L- I VARIANTS AND THEIR USE**

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G01N 33/53	(2006.01)
C12Q 1/68	(2006.01)
C07K 16/12	(2006.01)
C12N 5/10	(2006.01)
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(57) **ABSTRACT**

An isolated human Apolipoprotein L-I corresponding to a wild type human Apolipoprotein sequence is modified by a deletion at its C-terminal end.

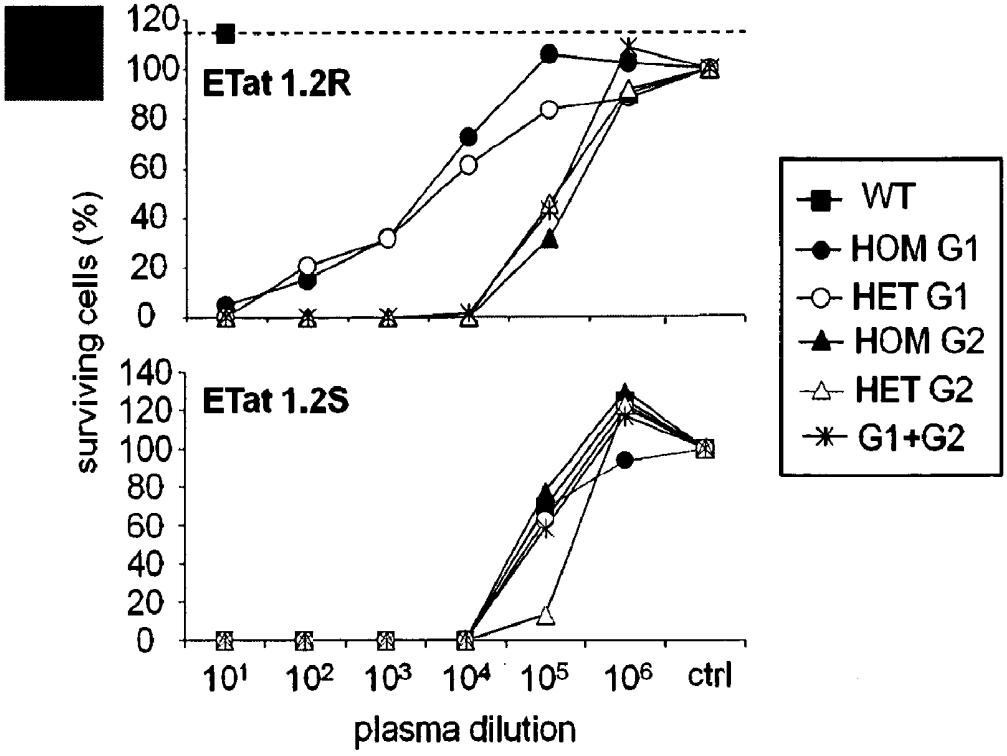
ETat 1.2R
ETat 1.2S
surviving cells (%)
plasma dilution
10¹ 10² 10³ 10⁴ 10⁵ 10⁶ ctrl
WT
HOM G1
HET G1
HOM G2
HET G2
G1+G2

Fig. 1

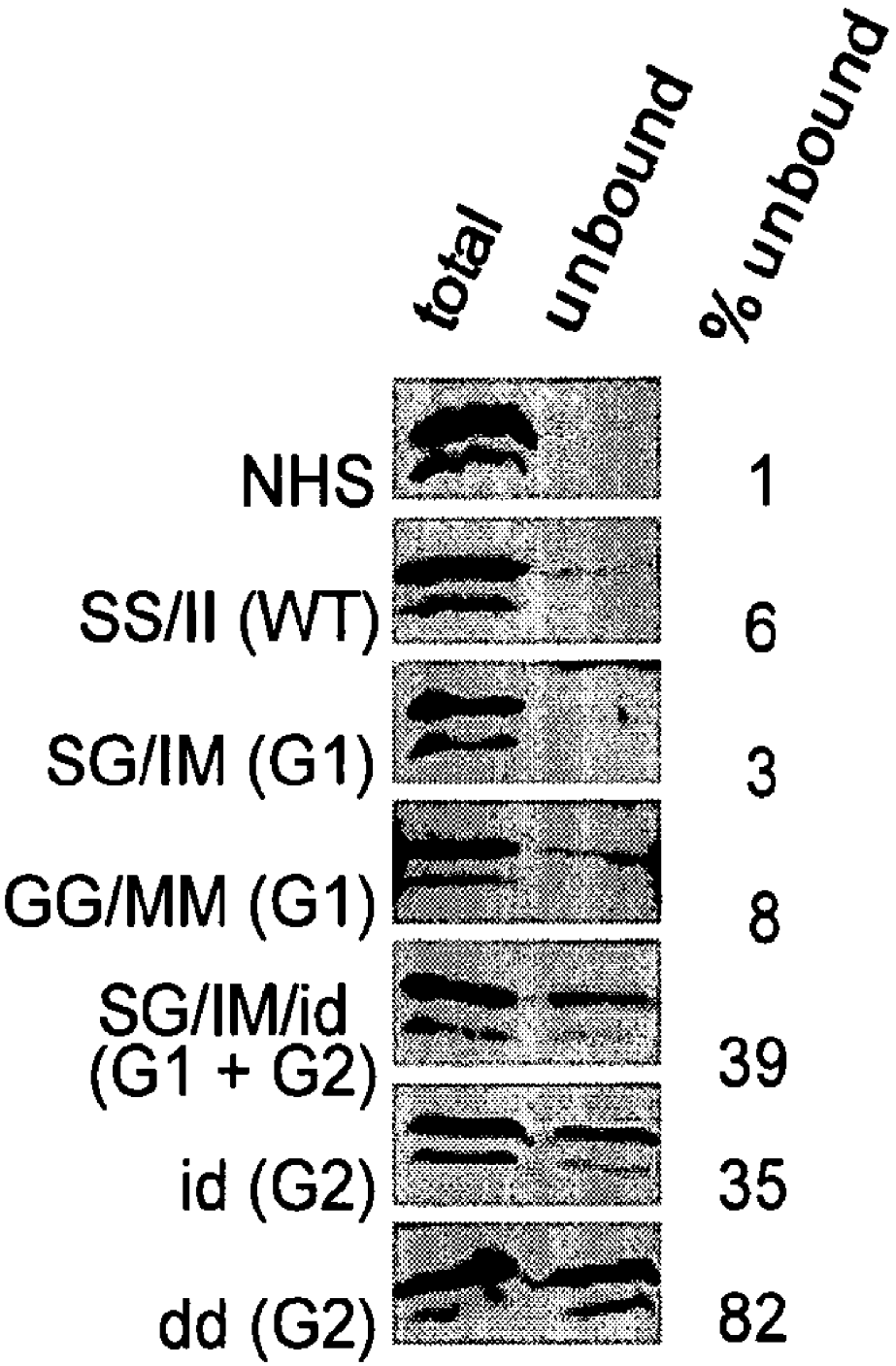
total
unbound
% unbound
NHS
1
SS/II (WT)
6
SG/IM (G1)
3
GG/MM (G1)
8
SG/IM/id (G1 + G2)
39
id (G2)
35
dd (G2)
82

Fig. 2

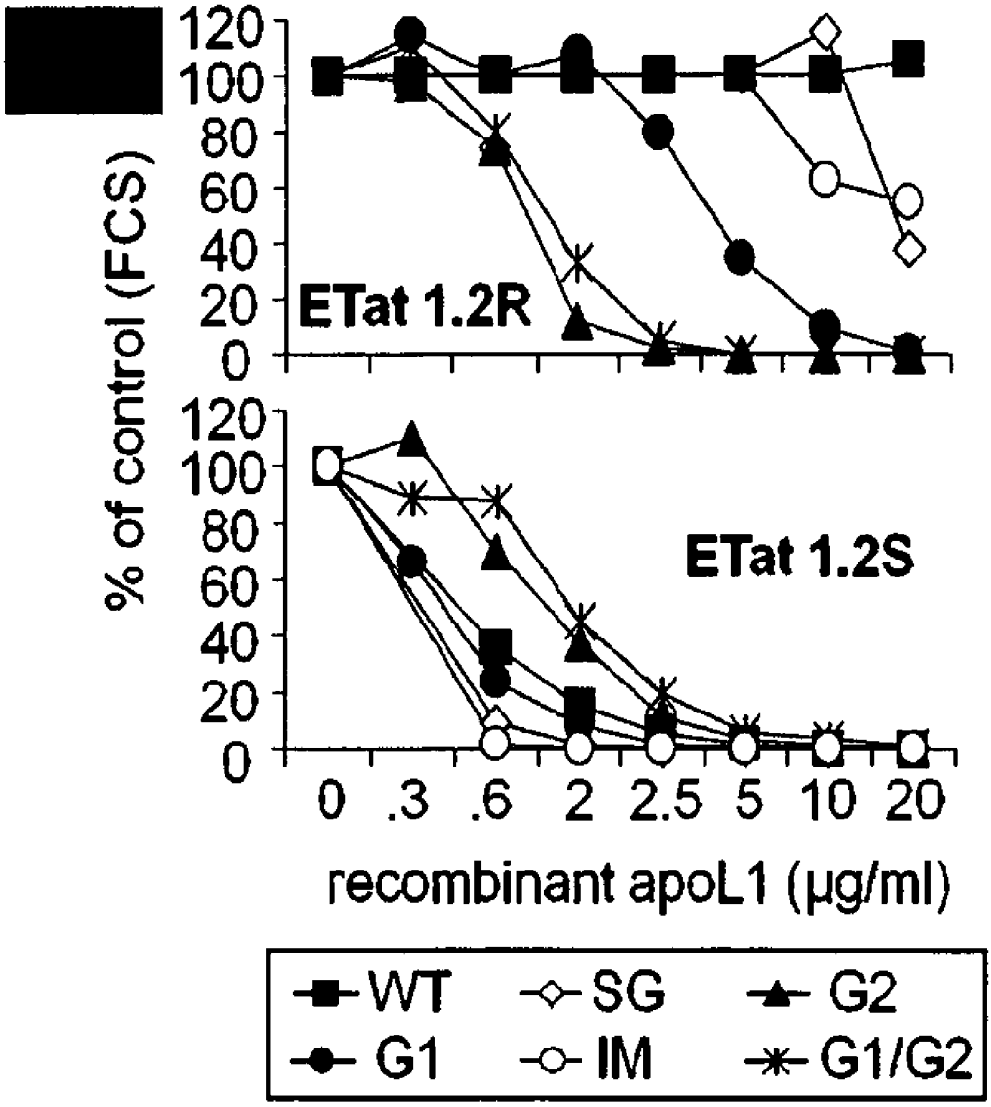
% of control (FCS)
120
100
80
60
40
20
0
ETat 1.2R
ETat 1.2S
0 .3 .6 2 2.5 5 10 20
recombinant apoL1 (µg/ml)
WT
SG
G2
G1
IM
G1/G2

Fig. 3

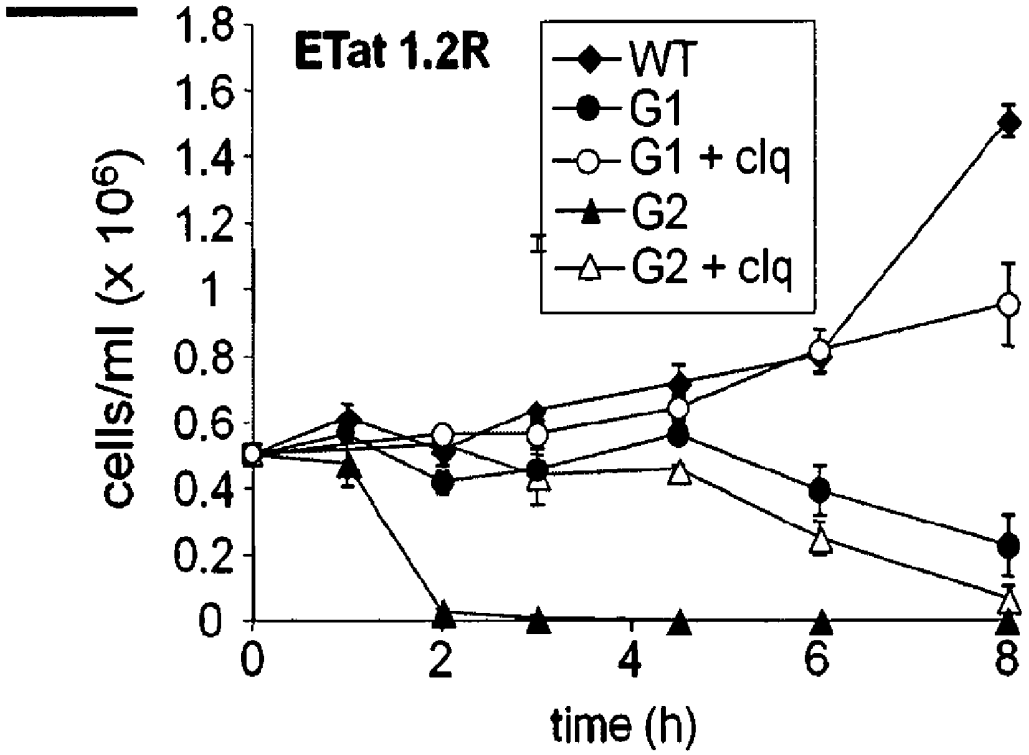
ETat 1.2R
WT
G1
G1 + clq
G2
G2 + clq
cells/ml (x 10^6)
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
2
4
6
8
time (h)

Fig. 4

Fig. 5

APOLIPOPROTEIN L- I VARIANTS AND THEIR USE

FIELD OF THE INVENTION

[0001] The present invention is in the field of Molecular Biology and is related to Apolipoprotein L-I variants sequence(s) (c-terminal mutant of Apolipoprotein L-I (apoL1)) and its/their pharmaceutical (therapeutical or prophylactic) use, especially for a treatment and/or a prevention of diseases induced in mammals, especially in human, preferably infections induced by *Trypanosoma*, especially African *Trypanosoma*, more particularly *Trypanosoma brucei rhodesiense* and/or *Trypanosoma brucei gambiense*.

BACKGROUND OF THE INVENTION AND STATE OF THE ART

[0002] Apolipoprotein L-I (apoL1) is a human-specific serum protein that kills *Trypanosoma brucei* through ionic pore formation in endosomal membranes of the parasite. The *T. brucei* subspecies *rhodesiense* and *gambiense* resist this lytic activity and can infect humans, causing sleeping sickness. In the case of *T. b. rhodesiense* resistance to lysis involves interaction of the Serum Resistance-Associated (SRA) protein with the C-terminal helix of apoL1.

[0003] Normal human serum (NHS) is able to kill *T. b. brucei*, but not *T. b. rhodesiense* and *T. b. gambiense*. The lytic factor was identified as being apoL1. This protein is associated with HDL particles that are efficiently taken up by the parasite through specific binding to a haptoglobin-hemoglobin surface receptor, due to the simultaneous presence of haptoglobin-related protein (Hpr) acting as a ligand in these particles. Trypanosome lysis results from anionic pore formation by apoL1 in the lysosomal membrane of the parasite. Resistance to lysis has only been studied in case of *T. b. rhodesiense*, where it was shown to depend on a parasite protein termed SRA. As synthesis of SRA only occurs after transcriptional activation of a given Variant Specific Glycoprotein (VSG) gene expression site from a repertoire of 10-20 candidates, *T. b. rhodesiense* clones can be either sensitive or resistant to NHS depending on which expression site is active. The mechanism by which SRA inhibits the activity of apoL1 is unclear. Direct coil-coiling interaction between the C-terminal α-helix of apoL1 and the N-terminal α-helix of SRA was demonstrated in vitro, but in vivo only evidence for tight co-localization between the two proteins was obtained. Total deletion of the C-terminal helix appeared to confer toxic activity to recombinant apoL1 on *T. b. rhodesiense*, suggesting that, in vivo, SRA neutralizes apoL1 through interaction with its C-terminal domain. However, the trypanolytic effect of this deleted apoL1 was weak and incomplete. Moreover, data obtained following transgenic expression of a similarly truncated apoL1 in mice suggested that its trypanolytic potential was lost in vivo.

AIMS OF THE INVENTION

[0004] The present invention aims to propose a new pharmaceutical composition comprising one or more Apolipoprotein variant(s) (in the form of an amino acid sequence, or a nucleotide sequence(s), a vector, a cell, a blood sample and/or particles including HDL particles) or an inhibitor of this Apolipoprotein that could be administrated to mammals, especially to humans to cure and/or prevent *Trypanosoma* infections (especially *T. b. rhodesiense*) and related diseases (possibly in the treatment and/or prevention of glomerulosclerosis including focal segmental glomerulosclerosis (FSGS) cause of idiopathic nephrotic syndrome, HIV associated nephropathy and hypertension associated end-stage kidney disease (ESKD) in these mammals, especially in humans.

SUMMARY OF THE INVENTION

[0005] The present invention is related to a (an isolated) human Apolipoprotein L-I sequence (variant) corresponding to this wild type human Apolipoprotein sequence (SEQ.ID.NO.1, SEQ.ID.NO.4 or SEQ.ID.NO.7) modified by (which comprises) a deletion of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 of its last C-terminal amino acids.

[0006] More preferably, the Apolipoprotein L-I sequence (variant) according to the invention is the wild type human Apolipoprotein sequence, but exhibiting N388/Y389 deletion (a deletion of two amino acids located at its last C-terminal amino acids).

[0007] Alternatively, the Apolipoprotein L-I sequence (variant) according to the invention is the wild type human Apolipoprotein sequence, but exhibiting S342G/I384M mutations.

[0008] Preferably, the human Apolipoprotein (variant) according to the invention presents a sequence which is selected from the group consisting of SEQ.ID.NO.2, SEQ.ID.NO.3, SEQ.ID.NO.5, SEQ.ID.NO.6, SEQ.ID.NO.8, and SEQ.ID.NO.9, being more preferably selected from the group consisting of SEQ.ID.NO.2, SEQ.ID.NO.5 and SEQ.ID.NO.8.

[0009] Another aspect of the present invention is related to an inhibitor, such as a (monoclonal) antibody or an specific hypervariable portion thereof, including nanobodies, specifically recognizing (and possibly neutralizing its function) a protein sequence of the invention, preferably selected from the group consisting of SEQ.ID.NO.2, SEQ.ID.NO.3, SEQ.ID.NO.5, SEQ.ID.NO.6, SEQ.ID.NO.8, and SEQ.ID.NO.9, being more preferably selected from the group consisting of SEQ.ID.NO.2, SEQ.ID.NO.5 and SEQ.ID.NO.8 (and preferably not recognizing SEQ.ID.NO.1, SEQ.ID.NO.4 or SEQ.ID.NO.7), and the (hybridoma) cell producing this inhibitor, preferably this (monoclonal) antibody or its portion.

[0010] Another aspect of the present invention is related to a polynucleotide sequence encoding the Apolipoprotein L-I according to the invention and a vector comprising the (amino acid sequence of) Apolipoprotein L-I of the invention or its corresponding (coding) polynucleotide sequence.

[0011] Another aspect of the present invention is related to a cell transformed by this amino acid or polynucleotide sequence according to the invention and/or expressing the (recombinant and modified) Apolipoprotein L-I according to the invention; this cell is preferably a (non human embryonic) mammal cell, possibly grown in vitro.

[0012] Another aspect of the present invention is related to a diagnostic kit comprising means and media to identify whether a subject (including a human patient) comprises in his genome (and is expressing) the ApoL-I according to the invention (being preferably SEQ.ID.NO.2, SEQ.ID.NO.3, SEQ.ID.NO.5, SEQ.ID.NO.6, SEQ.ID.NO.8, or SEQ.ID.NO.9 or, more preferably being SEQ.ID.NO.2, SEQ.ID.NO.5 or SEQ.ID.NO.8.).

[0013] In this diagnostic kit, the preferred means are selected from the group consisting of nucleotide probes (nucleotide sequence) or antibodies (including specific

hypervariable portions thereof or nanobodies) possibly present upon (fixed to a solid support to form) a micro-array or primers able to amplify corresponding sequences by genetic amplification means (PCR, LCR, etc) able to identify these Apolipoprotein L-I variants (of the invention), inhibitors or markers, such as antibodies or specific hypervariable portions thereof (including nanobodies), specifically recognizing these Apolipoprotein L-I variants (being preferably SEQ.ID.NO.2, SEQ.ID.NO.3, SEQ.ID.NO.5, SEQ.ID.NO.6, SEQ.ID.NO.8, or SEQ.ID.NO.9 or, more preferably being SEQ.ID.NO.2, SEQ.ID.NO.5 or SEQ.ID.NO.8. (and more preferably not recognizing Apolipoprotein L-I of SEQ.ID.NO.1, SEQ.ID.NO.4 and/or SEQ.ID.NO.7)) and *Trypanosoma brucei rhodesiense* culture (possibly in conjunction with the ApoL1 of the invention as positive control for lysis).

[0014] The preferred kit may further comprises recombinant SRA sequence fixed upon a solid support (possibly in conjunction with the ApoL1 of the invention as negative control for binding).

[0015] The present invention further discloses a diagnostic (method) comprising the step of:

[0016] extracting a (DNA or RNA) nucleotide sequence from a biological sample obtained from a patient;

[0017] identifying if this DNA or RNA sequence is a variant in Apolipoprotein L-I, preferably being a DNA or a RNA variant nucleotide sequence encoding a protein sequence being selected from the group consisting of SEQ.ID.NO.2, SEQ.ID.NO.3, SEQ.ID.NO.5, SEQ.ID.NO.6, SEQ.ID.NO.8, and SEQ.ID.NO.9, being more preferably selected from the group consisting of SEQ.ID.NO.2, SEQ.ID.NO.5 and SEQ.ID.NO.8;

[0018] deducing whether this patient is carrying the variance in Apolipoprotein L-I and possibly whether this patient is homozygote or heterozygote for ApoL1 variation.

[0019] Alternatively, a related diagnostic method comprises the step of:

[0020] analysing a blood sample for variant in Apolipoprotein L-I (being preferably a protein sequence being selected from the group consisting of SEQ.ID.NO.2, SEQ.ID.NO.3, SEQ.ID.NO.5, SEQ.ID.NO.6, SEQ.ID.NO.8, and SEQ.ID.NO.9, being more preferably selected from the group consisting of SEQ.ID.NO.2, SEQ.ID.NO.5 and SEQ.ID.NO.8) through binding to the specific antibodies, hyper variable portions thereof or nanobodies of the present invention;

[0021] deducing whether this patient is carrying the variance in Apolipoprotein L-I and possibly whether this patient is homozygote or heterozygote for ApoL1 variation.

[0022] Alternatively, a related diagnostic method comprises the step of:

[0023] analysing a blood sample for variant in Apolipoprotein L-I through its capacity to lysate a *Trypanosoma brucei rhodesiense* culture;

[0024] deducing whether this patient is carrying the variance in Apolipoprotein L-I.

[0025] Alternatively (but less preferably), a related diagnostic method comprises the step of:

[0026] analysing a blood sample for variant in Apolipoprotein L-I through its absence of binding to SRA;

[0027] deducing whether the patient is carrying the variance in Apolipoprotein L-I. This method can be combined with the others above-described preferred diagnostic methods of the present invention.

[0028] Another aspect of the present invention is related to a pharmaceutical composition (including a vaccine) comprising an adequate pharmaceutical carrier (or diluent and possibly one or more adequate adjuvant(s)) and a sufficient amount of an element selected from the group consisting of the Apolipoprotein L-I (amino acid sequence) according to the invention, the inhibitor (preferably the antibody or its portion) according to the invention, the polynucleotide according to the invention, the vector according to the invention or the cell (possibly in the form of a pharmaceutically-acceptable lysate or lyophilisate) according to the invention; preferably, this pharmaceutical composition (vaccine) is used in (for) a treatment and/or a prevention of diseases induced in mammals (by *Trypanosoma brucei*; more preferably by *Trypanosoma brucei rhodesiense*)), being preferably humans; and wherein the Apolipoprotein L-I of the invention is preferably capable impeding its interaction with the Serum Associated protein (SRA) and/or to act despite having interacted with SRA.

[0029] Another aspect of the invention is a composition comprising from 100 pg/ml to 10 μg/ml of the Apolipoprotein L-I of the invention (consisting preferably of SEQ.ID.NO.2, SEQ.ID.NO.3, SEQ.ID.NO.5, SEQ.ID.NO.6, SEQ.ID.NO.8, and SEQ.ID.NO.9, being more preferably selected from the group consisting of SEQ.ID.NO.2, SEQ.ID.NO.5 and SEQ.ID.NO.8).

[0030] A related aspect of the invention is a blood sample (preferably a serum) or extract thereof comprising the Apolipoprotein L-I of the invention (consisting of SEQ.ID.NO.2, SEQ.ID.NO.3, SEQ.ID.NO.5, SEQ.ID.NO.6, SEQ.ID.NO.8, and SEQ.ID.NO.9, being more preferably selected from the group consisting of SEQ.ID.NO.2, SEQ.ID.NO.5 and SEQ.ID.NO.8).

[0031] Preferably this blood sample or extract thereof is in the form of (HDL) particles.

[0032] Advantageously, this blood sample (serum or extract preferably in the form of (HDL) particles) is for use as a medicament.

[0033] Preferably, this blood sample (serum or extract, including in the form of (HDL) particles) is for use in the treatment or prevention of *Trypanosoma* infections.

[0034] Preferably this blood sample (serum or extract preferably in the form of (HDL) particles) is for use in (or for the manufacture of a medicament for) the treatment of *Trypanosoma brucei* infections.

[0035] More preferably, this blood sample (serum or extract, preferably in the form of (HDL) particles) is for use in (or for the manufacture of a medicament for) the treatment or prevention of *Trypanosoma brucei rhodesiense* infections.

[0036] Possibly, the Apolipoprotein L-I of the invention is obtained (and/or purified) from blood samples comprising it.

[0037] Alternatively, the Apolipoprotein L-I of the invention is obtained after in vitro fermentation using the transfected cells of the invention.

[0038] Another aspect of the present invention is related to a non-human genetically modified mammal, which is expressing the Apolipoprotein L-I according to the invention (being preferably selected from the group consisting of SEQ.ID.NO.2, SEQ.ID.NO.3, SEQ.ID.NO.5, SEQ.ID.NO.6, SEQ.ID.NO.8, and SEQ.ID.NO.9 and more preferably being from the group consisting of SEQ.ID.NO.2, SEQ.ID.NO.5 and SEQ.ID.NO.8) or which may comprise the polynucleotide, the vector or the cell according to the invention or

which may express the synthesis of the amino acid sequence of the Apolipoprotein L-I of the invention.

[0039] Preferably, this non-human genetically modified mammal is a genetically modified cattle, preferably genetically modified cow, which could be resistant or tolerant to infection(s) induced by *Trypanosoma* and non or slowly affected by the related diseases (NAGANA), preferably infection(s) and disease(s) induced by *Trypanosoma brucei brucei, Trypanosoma brucei rhodesiense, trypanosoma congolense, trypanosoma evansi* and/or *trypanosoma vivax.*

[0040] Alternatively, this non-human genetically modified mammal is a genetically modified rodent possibly used in research as a model for a disease (such as glomerulosclerosis), like a mouse or a rat.

[0041] A last aspect of the invention is related to the treatment or prevention of glomerulosclerosis, especially focal segmental glomerulosclerosis (FSGS).

[0042] Possibly, the present invention provides for the use of a (specific) inhibitor of the function of a the ApoL1 of the invention (preferably selected from the group consisting of SEQ.ID.NO.2, SEQ.ID.NO.3, SEQ.ID.NO.5, SEQ.ID.NO.6, SEQ.ID.NO.8, and SEQ.ID.NO.9, being more preferably selected from the group consisting of SEQ.ID.NO.2, SEQ. ID.NO.5 and SEQ.ID.NO.8) as a medicament.

[0043] Preferably, the present invention provides for the use of a (specific) inhibitor (preferably an (monoclonal) antibody, a specific hypervariable portion thereof or a nanobody) of the function of a protein sequence selected from the group consisting of SEQ.ID.NO.2, SEQ.ID.NO.3, SEQ.ID.NO.5, SEQ.ID.NO.6, SEQ.ID.NO.8, and SEQ.ID.NO.9, being more preferably selected from the group consisting of SEQ. ID.NO.2, SEQ.ID.NO.5 and SEQ.ID.NO.8 for the treatment and/or the prevention of glomerulosclerosis.

[0044] Advantageously, the present invention provides for the use of antibodies (including specific hypervariable portions thereof or nanobodies) specifically recognizing (and preferably neutralizing its function) a protein sequence selected from the group consisting of SEQ.ID.NO.2, SEQ. ID.NO.3, SEQ.ID.NO.5, SEQ.ID.NO.6, SEQ.ID.NO.8, and SEQ.ID.NO.9, being more preferably selected from the group consisting of SEQ.ID.NO.2, SEQ.ID.NO.5 and SEQ. ID.NO.8 for use as a medicament.

[0045] Preferably, the specific inhibitor (more preferably a neutralizing (monoclonal) antibody (including specific hypervariable portions thereof or nanobodies) is for use in the treatment of glomerulosclerosis, including focal segmental glomerulosclerosis (FSGS), in patients expressing the Apolipoprotein L-I of the present invention (consisting of SEQ. ID.NO.2, SEQ.ID.NO.3, SEQ.ID.NO.5, SEQ.ID.NO.6, SEQ.ID.NO.8, and SEQ.ID.NO.9, being more preferably selected from the group consisting of SEQ.ID.NO.2, SEQ. ID.NO.5 and SEQ.ID.NO.8) and more preferably not expressing SEQ.ID.NO.1, SEQ.ID.NO.4 or SEQ.ID.NO.7.

[0046] Advantageously, the present invention provides for drugs to reduce blood pressure (antihypertensive) and/or blood cholesterol content for use in (or for the manufacture of a medicament for) a treatment and/or for a prevention of glomerulosclerosis (including Focal segmental glomerulosclerosis (FSGS)) cause of idiopathic nephrotic syndrome, HIV associated Nephropathy and hypertension-associated end-stage kidney disease (ESKD) mostly observed in African Americans) for patients expressing the Apolipoprotein L-I of the present invention (preferably consisting of SEQ.ID.NO.2, SEQ.ID.NO.3, SEQ.ID.NO.5, SEQ.ID.NO.6, SEQ.ID.NO.8, and SEQ.ID.NO.9, being more preferably selected from the group consisting of SEQ.ID.NO.2, SEQ.ID.NO.5 and SEQ. ID.NO.8) and more preferably not expressing SEQ.ID.NO.1, SEQ.ID.NO.4 or SEQ.ID.NO.7.

[0047] Preferably, the drugs to reduce blood pressure (antihypertensive) according to the invention are selected from the group consisting of: angiotensin-converting inhibitors (such as captopril, enalapril, fosinopril (Monopril®), lisinopril (Zestril®), quinapril and ramipril (Altace®)), angiotensin II receptor antagonists (such as telmisartan (Micardis, Pritor), irbesartan (Avapro), losartan (Cozaar®), valsartan (Diovan®), candesartan (Amias®), olmesartan (Benicar®, Olmetec®), calcium channel blockers (such as nifedipine (Adalat®) amlodipine (Norvasc®), diltiazem, verapamil, diuretics (such as bendroflumethiazide, chlorthalidone, hydrochlorothiazide) or a mixture thereof.

[0048] Preferably, the drugs to reduce blood cholesterol levels according to the invention are selected from the group consisting of statins (most prominently rosuvastatin, atorvastatin, simvastatin, or pravastatin), cholesterol absorption inhibitors (ezetimibe), fibrates (gemfibrozil, bezafibrate, fenofibrate or ciprofibrate), vitamin B3 (niacin), bile acid sequestrants (colestipol, cholestyramine) or a mixture thereof.

[0049] Alternatively, blood cholesterol levels can be reduced by appropriate diet, such as cholesterol-reduced feed and/or fat (especially saturated and/or trans)-reduced feed.

[0050] The present invention will be described in more details in the following detailed description of the invention in reference to the enclosed figures presented as non limited illustrations of the present invention.

SHORT DESCRIPTION OF THE FIGURES

[0051] FIG. **1**: Trypanolytic potential of apoL1 variants on NHS-resistant (ETat 1.2R; SRA+: upper panel) and NHS-sensitive (ETat 1.2S; SRA−: lower panel) *T. brucei* ETat 1.2 clones and titration of trypanolytic activity in plasma samples after overnight incubation (100%=control incubation in fetal calf serum without plasma; hom, het=homozygous and heterozygous mutations, respectively; G1 stands for S342G/I384M mutation, while G2 stands for N388/Y389 deletion).

[0052] FIG. **2**: ApoL1 content of various plasma samples before and after affinity chromatography through SRA column (NHS=normal human serum; WT=wild type apoL1 ; S=serine 342; G=glycine 342; I=isoleucine 384; M=methionin384; i=insertion of N388/Y389; d=deletion of N388/Y389).

[0053] FIG. **3**: Trypanolytic activity of several recombinant apoL1 variants after overnight incubation (FCS=fetal calf serum) on resistant (R) and sensitive (S) clones of *Trypanosoma brucei.*

[0054] FIG. **4**:. Kinetics of trypanolysis of resistant *T. brucei rhodesiense* by 20 μg/ml recombinant apoL1 variants, in the presence or absence of 25 μM chloroquine (clq).

[0055] FIG. **5**: Phenotype of ETat1.2R trypanosomes (*T. brucei rhodesiense*) incubated with various recombinant apoL1 (20 pg/ml; 1h30 and 6h incubation, for G1 and G2 respectively; the arrows point to the swelling lysosome).

DETAILED DESCRIPTION OF THE INVENTION

[0056] The serum protein apolipoprotein L-I (apoL1) is responsible for human innate immunity against *Trypanosoma brucei brucei*, because this protein kills the parasite by gen-

erating ionic pores in the lysosomal membrane. Two *T. brucei* subspecies (*T. b. rhodesiense* and *T. b. gambiense*) can resist apoL1 and therefore, infect humans and cause sleeping sickness. In *T. b. rhodesiense* resistance to human serum is linked to interaction of the Serum Resistance-Associated protein with the C-terminal region of apoL1. Mutations targeted to this region reduced its interaction with SRA, while preserving the activity of the ionic pore-forming domain. The inventors identified variants that did not bind to SRA, but acquired the ability to efficiently kill *T. b. rhodesiense*.

[0057] However, the inventors previously showed that mutants they produced in the L370-L392 leucine zipper lost in vitro trypanolytic activity. Mutants in the conserved G361-5364 motif still interacted with SRA, but lost trypanolytic potential in some cases.

[0058] The inventors analyzed the effects of various naturally-occurring (as well as artificial ones) deletions and mutations in the C-terminal domain of apoL1 on the trypanolytic potential of this protein against *T. b. brucei* and *T. b. rhodesiense*.

[0059] The inventors further treated patients suffering from *Trypanosoma* infection (*Trypanosoma b. rhodesiense*) with blood samples (serum or HDL fractions) obtained from patients expressing ApoL1 variants (being homozygotes or heterozygotes).

[0060] The inventors observed that *Trypanosoma* were killed in vivo, even when using elevated dilutions of these blood samples, resulting into the prevention of sleeping sickness in patients infected with *b. rhodesiense*. The inventors further noticed no renal toxicity, despite the injection of this variant of ApoL1 protein.

[0061] The inventors then screened from patients that carry variants of ApoL1 (patients that express the ApoL1 of the invention, being heterozygotes or, more preferably, homozygotes) and treat them in order to prevent (treat) the renal symptom associated with these variant.

[0062] In addition, rodent expressing the ApoL1 of the present invention were investigated for their renal pathologies and for the development of corresponding treatments.

Material and Method

[0063] Unless stated otherwise, the experiments, including *Trypanaosoma* culture and the tests of human sera for their lytic activities, were carried-out in a manner similar to the ones already published: Locordier L. et al., 2009; C-terminal mutants of apolipoprotein L-I efficiently kill both *Trypanosoma brucei brucei* and *Trypanosoma brucei rhodesiense*; PLoS Pathog. 2009 December; 5(12):e1000685.

[0064] The sera obtained from patients with variant ApoL1 were diluted from 1000 to 100000 times and showed lytic activity even at these high dilutions.

[0065] More precisely, the inventors tested the variants of ApoL1 at concentrations ranging from 80 pg/ml to 20 μg/ml and observed in every case a lytic activity for every sera comprising SEQ.ID.NO.2 and for the majority of sera comprising SEQ.ID.NO.3.

[0066] The inventors used preferably the ApoL1 of the invention at about 10 ng/ml to about 20 μg/ml and still more preferably at about 2 μg/ml to about 10 μg/ml.

SEQUENCE LISTING

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<211> LENGTH: 398
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

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        35                  40                  45

Ser Lys Pro Leu Gly Asp Trp Ala Ala Gly Thr Met Asp Pro Glu Ser
    50                  55                  60

Ser Ile Phe Ile Glu Asp Ala Ile Lys Tyr Phe Lys Glu Lys Val Ser
65                  70                  75                  80

Thr Gln Asn Leu Leu Leu Leu Leu Thr Asp Asn Glu Ala Trp Asn Gly
                85                  90                  95

Phe Val Ala Ala Ala Glu Leu Pro Arg Asn Glu Ala Asp Glu Leu Arg
            100                 105                 110

Lys Ala Leu Asp Asn Leu Ala Arg Gln Met Ile Met Lys Asp Lys Asn
        115                 120                 125
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Trp His Asp Lys Gly Gln Gln Tyr Arg Asn Trp Phe Leu Lys Glu Phe
    130                 135                 140

Pro Arg Leu Lys Ser Lys Leu Glu Asp Asn Ile Arg Arg Leu Arg Ala
145                 150                 155                 160

Leu Ala Asp Gly Val Gln Lys Val His Lys Gly Thr Thr Ile Ala Asn
                165                 170                 175

Val Val Ser Gly Ser Leu Ser Ile Ser Ser Gly Ile Leu Thr Leu Val
            180                 185                 190

Gly Met Gly Leu Ala Pro Phe Thr Glu Gly Gly Ser Leu Val Leu Leu
        195                 200                 205

Glu Pro Gly Met Glu Leu Gly Ile Thr Ala Ala Leu Thr Gly Ile Thr
    210                 215                 220

Ser Ser Thr Ile Asp Tyr Gly Lys Lys Trp Trp Thr Gln Ala Gln Ala
225                 230                 235                 240

His Asp Leu Val Ile Lys Ser Leu Asp Lys Leu Lys Glu Val Lys Glu
                245                 250                 255

Phe Leu Gly Glu Asn Ile Ser Asn Phe Leu Ser Leu Ala Gly Asn Thr
            260                 265                 270

Tyr Gln Leu Thr Arg Gly Ile Gly Lys Asp Ile Arg Ala Leu Arg Arg
        275                 280                 285

Ala Arg Ala Asn Leu Gln Ser Val Pro His Ala Ser Ala Ser Arg Pro
    290                 295                 300

Arg Val Thr Glu Pro Ile Ser Ala Glu Ser Gly Glu Gln Val Glu Arg
305                 310                 315                 320

Val Asn Glu Pro Ser Ile Leu Glu Met Ser Arg Gly Val Lys Leu Thr
                325                 330                 335

Asp Val Ala Pro Val Ser Phe Phe Leu Val Leu Asp Val Val Tyr Leu
            340                 345                 350

Val Tyr Glu Ser Lys His Leu His Glu Gly Ala Lys Ser Glu Thr Ala
        355                 360                 365

Glu Glu Leu Lys Lys Val Ala Gln Glu Leu Glu Glu Lys Leu Asn Ile
    370                 375                 380

Leu Asn Asn Asn Tyr Lys Ile Leu Gln Ala Asp Gln Glu Leu
385                 390                 395


<210> SEQ ID NO 2
<211> LENGTH: 396
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(396)
<223> OTHER INFORMATION: Apo L 1 variant

<400> SEQUENCE: 2

Met Glu Gly Ala Ala Leu Leu Arg Val Ser Val Leu Cys Ile Trp Met
1               5                   10                  15

Ser Ala Leu Phe Leu Gly Val Arg Val Arg Ala Glu Glu Ala Gly Ala
            20                  25                  30

Arg Val Gln Gln Asn Val Pro Ser Gly Thr Asp Thr Gly Asp Pro Gln
        35                  40                  45

Ser Lys Pro Leu Gly Asp Trp Ala Ala Gly Thr Met Asp Pro Glu Ser
    50                  55                  60

Ser Ile Phe Ile Glu Asp Ala Ile Lys Tyr Phe Lys Glu Lys Val Ser
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65                  70                  75                  80

Thr Gln Asn Leu Leu Leu Leu Leu Thr Asp Asn Glu Ala Trp Asn Gly
                85                  90                  95

Phe Val Ala Ala Ala Glu Leu Pro Arg Asn Glu Ala Asp Glu Leu Arg
            100                 105                 110

Lys Ala Leu Asp Asn Leu Ala Arg Gln Met Ile Met Lys Asp Lys Asn
        115                 120                 125

Trp His Asp Lys Gly Gln Gln Tyr Arg Asn Trp Phe Leu Lys Glu Phe
    130                 135                 140

Pro Arg Leu Lys Ser Lys Leu Glu Asp Asn Ile Arg Arg Leu Arg Ala
145                 150                 155                 160

Leu Ala Asp Gly Val Gln Lys Val His Lys Gly Thr Thr Ile Ala Asn
                165                 170                 175

Val Val Ser Gly Ser Leu Ser Ile Ser Ser Gly Ile Leu Thr Leu Val
            180                 185                 190

Gly Met Gly Leu Ala Pro Phe Thr Glu Gly Gly Ser Leu Val Leu Leu
        195                 200                 205

Glu Pro Gly Met Glu Leu Gly Ile Thr Ala Ala Leu Thr Gly Ile Thr
    210                 215                 220

Ser Ser Thr Ile Asp Tyr Gly Lys Lys Trp Trp Thr Gln Ala Gln Ala
225                 230                 235                 240

His Asp Leu Val Ile Lys Ser Leu Asp Lys Leu Lys Glu Val Lys Glu
                245                 250                 255

Phe Leu Gly Glu Asn Ile Ser Asn Phe Leu Ser Leu Ala Gly Asn Thr
            260                 265                 270

Tyr Gln Leu Thr Arg Gly Ile Gly Lys Asp Ile Arg Ala Leu Arg Arg
        275                 280                 285

Ala Arg Ala Asn Leu Gln Ser Val Pro His Ala Ser Ala Ser Arg Pro
    290                 295                 300

Arg Val Thr Glu Pro Ile Ser Ala Glu Ser Gly Glu Gln Val Glu Arg
305                 310                 315                 320

Val Asn Glu Pro Ser Ile Leu Glu Met Ser Arg Gly Val Lys Leu Thr
                325                 330                 335

Asp Val Ala Pro Val Ser Phe Phe Leu Val Leu Asp Val Val Tyr Leu
            340                 345                 350

Val Tyr Glu Ser Lys His Leu His Glu Gly Ala Lys Ser Glu Thr Ala
        355                 360                 365

Glu Glu Leu Lys Lys Val Ala Gln Glu Leu Glu Glu Lys Leu Asn Ile
    370                 375                 380

Leu Asn Asn Lys Ile Leu Gln Ala Asp Gln Glu Leu
385                 390                 395


<210> SEQ ID NO 3
<211> LENGTH: 398
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(398)
<223> OTHER INFORMATION: Apo L 1 Variant

<400> SEQUENCE: 3

Met Glu Gly Ala Ala Leu Leu Arg Val Ser Val Leu Cys Ile Trp Met
1               5                   10                  15
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```
Ser Ala Leu Phe Leu Gly Val Arg Val Arg Ala Glu Glu Ala Gly Ala
            20                  25                  30

Arg Val Gln Gln Asn Val Pro Ser Gly Thr Asp Thr Gly Asp Pro Gln
        35                  40                  45

Ser Lys Pro Leu Gly Asp Trp Ala Ala Gly Thr Met Asp Pro Glu Ser
    50                  55                  60

Ser Ile Phe Ile Glu Asp Ala Ile Lys Tyr Phe Lys Glu Lys Val Ser
65                  70                  75                  80

Thr Gln Asn Leu Leu Leu Leu Leu Thr Asp Asn Glu Ala Trp Asn Gly
                85                  90                  95

Phe Val Ala Ala Ala Glu Leu Pro Arg Asn Glu Ala Asp Glu Leu Arg
            100                 105                 110

Lys Ala Leu Asp Asn Leu Ala Arg Gln Met Ile Met Lys Asp Lys Asn
        115                 120                 125

Trp His Asp Lys Gly Gln Gln Tyr Arg Asn Trp Phe Leu Lys Glu Phe
    130                 135                 140

Pro Arg Leu Lys Ser Lys Leu Glu Asp Asn Ile Arg Arg Leu Arg Ala
145                 150                 155                 160

Leu Ala Asp Gly Val Gln Lys Val His Lys Gly Thr Thr Ile Ala Asn
                165                 170                 175

Val Val Ser Gly Ser Leu Ser Ile Ser Ser Gly Ile Leu Thr Leu Val
            180                 185                 190

Gly Met Gly Leu Ala Pro Phe Thr Glu Gly Gly Ser Leu Val Leu Leu
        195                 200                 205

Glu Pro Gly Met Glu Leu Gly Ile Thr Ala Ala Leu Thr Gly Ile Thr
    210                 215                 220

Ser Ser Thr Ile Asp Tyr Gly Lys Lys Trp Trp Thr Gln Ala Gln Ala
225                 230                 235                 240

His Asp Leu Val Ile Lys Ser Leu Asp Lys Leu Lys Glu Val Lys Glu
                245                 250                 255

Phe Leu Gly Glu Asn Ile Ser Asn Phe Leu Ser Leu Ala Gly Asn Thr
            260                 265                 270

Tyr Gln Leu Thr Arg Gly Ile Gly Lys Asp Ile Arg Ala Leu Arg Arg
        275                 280                 285

Ala Arg Ala Asn Leu Gln Ser Val Pro His Ala Ser Ala Ser Arg Pro
    290                 295                 300

Arg Val Thr Glu Pro Ile Ser Ala Glu Ser Gly Glu Gln Val Glu Arg
305                 310                 315                 320

Val Asn Glu Pro Ser Ile Leu Glu Met Ser Arg Gly Val Lys Leu Thr
                325                 330                 335

Asp Val Ala Pro Val Gly Phe Phe Leu Val Leu Asp Val Val Tyr Leu
            340                 345                 350

Val Tyr Glu Ser Lys His Leu His Glu Gly Ala Lys Ser Glu Thr Ala
        355                 360                 365

Glu Glu Leu Lys Lys Val Ala Gln Glu Leu Glu Glu Lys Leu Asn Met
    370                 375                 380

Leu Asn Asn Asn Tyr Lys Ile Leu Gln Ala Asp Gln Glu Leu
385                 390                 395
```

<210> SEQ ID NO 4
<211> LENGTH: 398

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<223> OTHER INFORMATION: NP 003652.2

<400> SEQUENCE: 4

Met Glu Gly Ala Ala Leu Leu Arg Val Ser Val Leu Cys Ile Trp Met
1 5 10 15

Ser Ala Leu Phe Leu Gly Val Gly Val Arg Ala Glu Glu Ala Gly Ala
            20 25 30

Arg Val Gln Gln Asn Val Pro Ser Gly Thr Asp Thr Gly Asp Pro Gln
        35 40 45

Ser Lys Pro Leu Gly Asp Trp Ala Ala Gly Thr Met Asp Pro Glu Ser
    50 55 60

Ser Ile Phe Ile Glu Asp Ala Ile Lys Tyr Phe Lys Glu Lys Val Ser
65 70 75 80

Thr Gln Asn Leu Leu Leu Leu Leu Thr Asp Asn Glu Ala Trp Asn Gly
                85 90 95

Phe Val Ala Ala Ala Glu Leu Pro Arg Asn Glu Ala Asp Glu Leu Arg
            100 105 110

Lys Ala Leu Asp Asn Leu Ala Arg Gln Met Ile Met Lys Asp Lys Asn
        115 120 125

Trp His Asp Lys Gly Gln Gln Tyr Arg Asn Trp Phe Leu Lys Glu Phe
    130 135 140

Pro Arg Leu Lys Ser Glu Leu Glu Asp Asn Ile Arg Arg Leu Arg Ala
145 150 155 160

Leu Ala Asp Gly Val Gln Lys Val His Lys Gly Thr Thr Ile Ala Asn
                165 170 175

Val Val Ser Gly Ser Leu Ser Ile Ser Ser Gly Ile Leu Thr Leu Val
            180 185 190

Gly Met Gly Leu Ala Pro Phe Thr Glu Gly Gly Ser Leu Val Leu Leu
        195 200 205

Glu Pro Gly Met Glu Leu Gly Ile Thr Ala Ala Leu Thr Gly Ile Thr
    210 215 220

Ser Ser Thr Met Asp Tyr Gly Lys Lys Trp Trp Thr Gln Ala Gln Ala
225 230 235 240

His Asp Leu Val Ile Lys Ser Leu Asp Lys Leu Lys Glu Val Arg Glu
                245 250 255

Phe Leu Gly Glu Asn Ile Ser Asn Phe Leu Ser Leu Ala Gly Asn Thr
            260 265 270

Tyr Gln Leu Thr Arg Gly Ile Gly Lys Asp Ile Arg Ala Leu Arg Arg
        275 280 285

Ala Arg Ala Asn Leu Gln Ser Val Pro His Ala Ser Ala Ser Arg Pro
    290 295 300

Arg Val Thr Glu Pro Ile Ser Ala Glu Ser Gly Glu Gln Val Glu Arg
305 310 315 320

Val Asn Glu Pro Ser Ile Leu Glu Met Ser Arg Gly Val Lys Leu Thr
                325 330 335

Asp Val Ala Pro Val Ser Phe Phe Leu Val Leu Asp Val Val Tyr Leu
            340 345 350

Val Tyr Glu Ser Lys His Leu His Glu Gly Ala Lys Ser Glu Thr Ala
        355 360 365

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Glu Glu Leu Lys Lys Val Ala Gln Glu Leu Glu Glu Lys Leu Asn Ile
    370                 375                 380

Leu Asn Asn Asn Tyr Lys Ile Leu Gln Ala Asp Gln Glu Leu
385                 390                 395


<210> SEQ ID NO 5
<211> LENGTH: 396
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(396)
<223> OTHER INFORMATION: Apo L 1 Variant

<400> SEQUENCE: 5

Met Glu Gly Ala Ala Leu Leu Arg Val Ser Val Leu Cys Ile Trp Met
1               5                   10                  15

Ser Ala Leu Phe Leu Gly Val Gly Val Arg Ala Glu Glu Ala Gly Ala
            20                  25                  30

Arg Val Gln Gln Asn Val Pro Ser Gly Thr Asp Thr Gly Asp Pro Gln
        35                  40                  45

Ser Lys Pro Leu Gly Asp Trp Ala Ala Gly Thr Met Asp Pro Glu Ser
    50                  55                  60

Ser Ile Phe Ile Glu Asp Ala Ile Lys Tyr Phe Lys Glu Lys Val Ser
65                  70                  75                  80

Thr Gln Asn Leu Leu Leu Leu Leu Thr Asp Asn Glu Ala Trp Asn Gly
                85                  90                  95

Phe Val Ala Ala Ala Glu Leu Pro Arg Asn Glu Ala Asp Glu Leu Arg
            100                 105                 110

Lys Ala Leu Asp Asn Leu Ala Arg Gln Met Ile Met Lys Asp Lys Asn
        115                 120                 125

Trp His Asp Lys Gly Gln Gln Tyr Arg Asn Trp Phe Leu Lys Glu Phe
    130                 135                 140

Pro Arg Leu Lys Ser Glu Leu Glu Asp Asn Ile Arg Arg Leu Arg Ala
145                 150                 155                 160

Leu Ala Asp Gly Val Gln Lys Val His Lys Gly Thr Thr Ile Ala Asn
                165                 170                 175

Val Val Ser Gly Ser Leu Ser Ile Ser Ser Gly Ile Leu Thr Leu Val
            180                 185                 190

Gly Met Gly Leu Ala Pro Phe Thr Glu Gly Gly Ser Leu Val Leu Leu
        195                 200                 205

Glu Pro Gly Met Glu Leu Gly Ile Thr Ala Ala Leu Thr Gly Ile Thr
    210                 215                 220

Ser Ser Thr Met Asp Tyr Gly Lys Lys Trp Trp Thr Gln Ala Gln Ala
225                 230                 235                 240

His Asp Leu Val Ile Lys Ser Leu Asp Lys Leu Lys Glu Val Arg Glu
                245                 250                 255

Phe Leu Gly Glu Asn Ile Ser Asn Phe Leu Ser Leu Ala Gly Asn Thr
            260                 265                 270

Tyr Gln Leu Thr Arg Gly Ile Gly Lys Asp Ile Arg Ala Leu Arg Arg
        275                 280                 285

Ala Arg Ala Asn Leu Gln Ser Val Pro His Ala Ser Ala Ser Arg Pro
    290                 295                 300
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Arg Val Thr Glu Pro Ile Ser Ala Glu Ser Gly Glu Gln Val Glu Arg
305                 310                 315                 320

Val Asn Glu Pro Ser Ile Leu Glu Met Ser Arg Gly Val Lys Leu Thr
                325                 330                 335

Asp Val Ala Pro Val Ser Phe Phe Leu Val Leu Asp Val Val Tyr Leu
            340                 345                 350

Val Tyr Glu Ser Lys His Leu His Glu Gly Ala Lys Ser Glu Thr Ala
        355                 360                 365

Glu Glu Leu Lys Lys Val Ala Gln Glu Leu Glu Glu Lys Leu Asn Ile
    370                 375                 380

Leu Asn Asn Lys Ile Leu Gln Ala Asp Gln Glu Leu
385                 390                 395


<210> SEQ ID NO 6
<211> LENGTH: 398
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(398)
<223> OTHER INFORMATION: Apo L 1 Variant

<400> SEQUENCE: 6

Met Glu Gly Ala Ala Leu Leu Arg Val Ser Val Leu Cys Ile Trp Met
1               5                   10                  15

Ser Ala Leu Phe Leu Gly Val Gly Val Arg Ala Glu Glu Ala Gly Ala
            20                  25                  30

Arg Val Gln Gln Asn Val Pro Ser Gly Thr Asp Thr Gly Asp Pro Gln
        35                  40                  45

Ser Lys Pro Leu Gly Asp Trp Ala Ala Gly Thr Met Asp Pro Glu Ser
    50                  55                  60

Ser Ile Phe Ile Glu Asp Ala Ile Lys Tyr Phe Lys Glu Lys Val Ser
65                  70                  75                  80

Thr Gln Asn Leu Leu Leu Leu Leu Thr Asp Asn Glu Ala Trp Asn Gly
                85                  90                  95

Phe Val Ala Ala Ala Glu Leu Pro Arg Asn Glu Ala Asp Glu Leu Arg
            100                 105                 110

Lys Ala Leu Asp Asn Leu Ala Arg Gln Met Ile Met Lys Asp Lys Asn
        115                 120                 125

Trp His Asp Lys Gly Gln Gln Tyr Arg Asn Trp Phe Leu Lys Glu Phe
    130                 135                 140

Pro Arg Leu Lys Ser Glu Leu Glu Asp Asn Ile Arg Arg Leu Arg Ala
145                 150                 155                 160

Leu Ala Asp Gly Val Gln Lys Val His Lys Gly Thr Thr Ile Ala Asn
                165                 170                 175

Val Val Ser Gly Ser Leu Ser Ile Ser Ser Gly Ile Leu Thr Leu Val
            180                 185                 190

Gly Met Gly Leu Ala Pro Phe Thr Glu Gly Gly Ser Leu Val Leu Leu
        195                 200                 205

Glu Pro Gly Met Glu Leu Gly Ile Thr Ala Ala Leu Thr Gly Ile Thr
    210                 215                 220

Ser Ser Thr Met Asp Tyr Gly Lys Lys Trp Trp Thr Gln Ala Gln Ala
225                 230                 235                 240

His Asp Leu Val Ile Lys Ser Leu Asp Lys Leu Lys Glu Val Arg Glu
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               245                 250                 255

Phe Leu Gly Glu Asn Ile Ser Asn Phe Leu Ser Leu Ala Gly Asn Thr
            260                 265                 270

Tyr Gln Leu Thr Arg Gly Ile Gly Lys Asp Ile Arg Ala Leu Arg Arg
        275                 280                 285

Ala Arg Ala Asn Leu Gln Ser Val Pro His Ala Ser Ala Ser Arg Pro
    290                 295                 300

Arg Val Thr Glu Pro Ile Ser Ala Glu Ser Gly Glu Gln Val Glu Arg
305                 310                 315                 320

Val Asn Glu Pro Ser Ile Leu Glu Met Ser Arg Gly Val Lys Leu Thr
                325                 330                 335

Asp Val Ala Pro Val Gly Phe Phe Leu Val Leu Asp Val Val Tyr Leu
            340                 345                 350

Val Tyr Glu Ser Lys His Leu His Glu Gly Ala Lys Ser Glu Thr Ala
        355                 360                 365

Glu Glu Leu Lys Lys Val Ala Gln Glu Leu Glu Glu Lys Leu Asn Met
    370                 375                 380

Leu Asn Asn Asn Tyr Lys Ile Leu Gln Ala Asp Gln Glu Leu
385                 390                 395


<210> SEQ ID NO 7
<211> LENGTH: 398
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

Met Glu Gly Ala Ala Leu Leu Arg Val Ser Val Leu Cys Ile Trp Met
1               5                   10                  15

Ser Ala Leu Phe Leu Gly Val Arg Val Arg Ala Glu Glu Ala Gly Ala
            20                  25                  30

Arg Val Gln Gln Asn Val Pro Ser Gly Thr Asp Thr Gly Asp Pro Gln
        35                  40                  45

Ser Lys Pro Leu Gly Asp Trp Ala Ala Gly Thr Met Asp Pro Glu Ser
    50                  55                  60

Ser Ile Phe Ile Glu Asp Ala Ile Lys Tyr Phe Lys Glu Lys Val Ser
65                  70                  75                  80

Ile Gln Asn Leu Leu Leu Leu Leu Thr Asp Asn Glu Ala Trp Asn Gly
                85                  90                  95

Phe Val Ala Ala Ala Glu Leu Pro Arg Asn Glu Ala Asp Glu Leu Arg
            100                 105                 110

Lys Ala Leu Asp Asn Leu Ala Arg Gln Met Ile Met Lys Asp Lys Asn
        115                 120                 125

Trp His Asp Lys Gly Gln Gln Tyr Arg Asn Trp Phe Leu Lys Glu Phe
    130                 135                 140

Pro Arg Leu Lys Ser Lys Leu Glu Asp Asn Ile Arg Arg Leu Arg Ala
145                 150                 155                 160

Leu Ala Asp Gly Val Gln Lys Val His Lys Gly Thr Thr Ile Ala Asn
                165                 170                 175

Val Val Ser Gly Ser Leu Ser Ile Ser Ser Gly Ile Leu Thr Leu Val
            180                 185                 190

Gly Met Gly Leu Ala Pro Phe Thr Glu Gly Gly Ser Leu Val Leu Leu
        195                 200                 205
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```
Glu Pro Gly Met Glu Leu Gly Ile Thr Ala Ala Leu Thr Gly Ile Thr
    210                 215                 220

Ser Ser Thr Ile Asp Tyr Gly Lys Lys Trp Trp Thr Gln Ala Gln Ala
225                 230                 235                 240

His Asp Leu Val Ile Lys Ser Leu Asp Lys Leu Lys Glu Val Lys Glu
                245                 250                 255

Phe Leu Gly Glu Asn Ile Ser Asn Phe Leu Ser Leu Ala Gly Asn Thr
            260                 265                 270

Tyr Gln Leu Thr Arg Gly Ile Gly Lys Asp Ile Arg Ala Leu Arg Arg
        275                 280                 285

Ala Arg Ala Asn Leu Gln Ser Val Pro His Ala Ser Ala Ser Arg Pro
    290                 295                 300

Arg Val Thr Glu Pro Ile Ser Ala Glu Ser Gly Glu Gln Val Glu Arg
305                 310                 315                 320

Val Asn Glu Pro Ser Ile Leu Glu Met Ser Arg Gly Val Lys Leu Thr
                325                 330                 335

Asp Val Ala Pro Val Ser Phe Phe Leu Val Leu Asp Val Val Tyr Leu
            340                 345                 350

Val Tyr Glu Ser Lys His Leu His Glu Gly Ala Lys Ser Glu Thr Ala
        355                 360                 365

Glu Glu Leu Lys Lys Val Ala Gln Glu Leu Glu Glu Lys Leu Asn Ile
    370                 375                 380

Leu Asn Asn Asn Tyr Lys Ile Leu Gln Ala Asp Gln Glu Leu
385                 390                 395


<210> SEQ ID NO 8
<211> LENGTH: 396
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(396)
<223> OTHER INFORMATION: Apo L 1 Variant

<400> SEQUENCE: 8

Met Glu Gly Ala Ala Leu Leu Arg Val Ser Val Leu Cys Ile Trp Met
1               5                   10                  15

Ser Ala Leu Phe Leu Gly Val Arg Val Arg Ala Glu Glu Ala Gly Ala
            20                  25                  30

Arg Val Gln Gln Asn Val Pro Ser Gly Thr Asp Thr Gly Asp Pro Gln
        35                  40                  45

Ser Lys Pro Leu Gly Asp Trp Ala Ala Gly Thr Met Asp Pro Glu Ser
    50                  55                  60

Ser Ile Phe Ile Glu Asp Ala Ile Lys Tyr Phe Lys Glu Lys Val Ser
65                  70                  75                  80

Ile Gln Asn Leu Leu Leu Leu Leu Thr Asp Asn Glu Ala Trp Asn Gly
                85                  90                  95

Phe Val Ala Ala Ala Glu Leu Pro Arg Asn Glu Ala Asp Glu Leu Arg
            100                 105                 110

Lys Ala Leu Asp Asn Leu Ala Arg Gln Met Ile Met Lys Asp Lys Asn
        115                 120                 125

Trp His Asp Lys Gly Gln Gln Tyr Arg Asn Trp Phe Leu Lys Glu Phe
    130                 135                 140

Pro Arg Leu Lys Ser Lys Leu Glu Asp Asn Ile Arg Arg Leu Arg Ala
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-continued

```
145                 150                 155                 160

Leu Ala Asp Gly Val Gln Lys Val His Lys Gly Thr Thr Ile Ala Asn
                165                 170                 175

Val Val Ser Gly Ser Leu Ser Ile Ser Ser Gly Ile Leu Thr Leu Val
            180                 185                 190

Gly Met Gly Leu Ala Pro Phe Thr Glu Gly Gly Ser Leu Val Leu Leu
        195                 200                 205

Glu Pro Gly Met Glu Leu Gly Ile Thr Ala Ala Leu Thr Gly Ile Thr
    210                 215                 220

Ser Ser Thr Ile Asp Tyr Gly Lys Lys Trp Trp Thr Gln Ala Gln Ala
225                 230                 235                 240

His Asp Leu Val Ile Lys Ser Leu Asp Lys Leu Lys Glu Val Lys Glu
                245                 250                 255

Phe Leu Gly Glu Asn Ile Ser Asn Phe Leu Ser Leu Ala Gly Asn Thr
            260                 265                 270

Tyr Gln Leu Thr Arg Gly Ile Gly Lys Asp Ile Arg Ala Leu Arg Arg
        275                 280                 285

Ala Arg Ala Asn Leu Gln Ser Val Pro His Ala Ser Ala Ser Arg Pro
    290                 295                 300

Arg Val Thr Glu Pro Ile Ser Ala Glu Ser Gly Glu Gln Val Glu Arg
305                 310                 315                 320

Val Asn Glu Pro Ser Ile Leu Glu Met Ser Arg Gly Val Lys Leu Thr
                325                 330                 335

Asp Val Ala Pro Val Ser Phe Phe Leu Val Leu Asp Val Val Tyr Leu
            340                 345                 350

Val Tyr Glu Ser Lys His Leu His Glu Gly Ala Lys Ser Glu Thr Ala
        355                 360                 365

Glu Glu Leu Lys Lys Val Ala Gln Glu Leu Glu Glu Lys Leu Asn Ile
    370                 375                 380

Leu Asn Asn Lys Ile Leu Gln Ala Asp Gln Glu Leu
385                 390                 395


<210> SEQ ID NO 9
<211> LENGTH: 398
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(398)
<223> OTHER INFORMATION: Apo L 1 variant

<400> SEQUENCE: 9

Met Glu Gly Ala Ala Leu Leu Arg Val Ser Val Leu Cys Ile Trp Met
1               5                   10                  15

Ser Ala Leu Phe Leu Gly Val Arg Val Arg Ala Glu Glu Ala Gly Ala
            20                  25                  30

Arg Val Gln Gln Asn Val Pro Ser Gly Thr Asp Thr Gly Asp Pro Gln
        35                  40                  45

Ser Lys Pro Leu Gly Asp Trp Ala Ala Gly Thr Met Asp Pro Glu Ser
    50                  55                  60

Ser Ile Phe Ile Glu Asp Ala Ile Lys Tyr Phe Lys Glu Lys Val Ser
65                  70                  75                  80

Ile Gln Asn Leu Leu Leu Leu Leu Thr Asp Asn Glu Ala Trp Asn Gly
                85                  90                  95
```

-continued

```
Phe Val Ala Ala Ala Glu Leu Pro Arg Asn Glu Ala Asp Glu Leu Arg
            100                 105                 110

Lys Ala Leu Asp Asn Leu Ala Arg Gln Met Ile Met Lys Asp Lys Asn
        115                 120                 125

Trp His Asp Lys Gly Gln Gln Tyr Arg Asn Trp Phe Leu Lys Glu Phe
    130                 135                 140

Pro Arg Leu Lys Ser Lys Leu Glu Asp Asn Ile Arg Arg Leu Arg Ala
145                 150                 155                 160

Leu Ala Asp Gly Val Gln Lys Val His Lys Gly Thr Thr Ile Ala Asn
                165                 170                 175

Val Val Ser Gly Ser Leu Ser Ile Ser Ser Gly Ile Leu Thr Leu Val
            180                 185                 190

Gly Met Gly Leu Ala Pro Phe Thr Glu Gly Gly Ser Leu Val Leu Leu
        195                 200                 205

Glu Pro Gly Met Glu Leu Gly Ile Thr Ala Ala Leu Thr Gly Ile Thr
    210                 215                 220

Ser Ser Thr Ile Asp Tyr Gly Lys Lys Trp Trp Thr Gln Ala Gln Ala
225                 230                 235                 240

His Asp Leu Val Ile Lys Ser Leu Asp Lys Leu Lys Glu Val Lys Glu
                245                 250                 255

Phe Leu Gly Glu Asn Ile Ser Asn Phe Leu Ser Leu Ala Gly Asn Thr
            260                 265                 270

Tyr Gln Leu Thr Arg Gly Ile Gly Lys Asp Ile Arg Ala Leu Arg Arg
        275                 280                 285

Ala Arg Ala Asn Leu Gln Ser Val Pro His Ala Ser Ala Ser Arg Pro
    290                 295                 300

Arg Val Thr Glu Pro Ile Ser Ala Glu Ser Gly Glu Gln Val Glu Arg
305                 310                 315                 320

Val Asn Glu Pro Ser Ile Leu Glu Met Ser Arg Gly Val Lys Leu Thr
                325                 330                 335

Asp Val Ala Pro Val Gly Phe Phe Leu Val Leu Asp Val Val Tyr Leu
            340                 345                 350

Val Tyr Glu Ser Lys His Leu His Glu Gly Ala Lys Ser Glu Thr Ala
        355                 360                 365

Glu Glu Leu Lys Lys Val Ala Gln Glu Leu Glu Glu Lys Leu Asn Met
    370                 375                 380

Leu Asn Asn Asn Tyr Lys Ile Leu Gln Ala Asp Gln Glu Leu
385                 390                 395
```

1.-**24**. (canceled)

25. An isolated human Apolipoprotein L-I corresponding to the wild-type human Apolipoprotein sequence (SEQ.ID. NO.1, SEQ.ID.NO.4 or SEQ.ID.NO.7) modified by a deletion of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 of its last C-terminal amino acids.

26. An isolated human Apolipoprotein L-I, which is selected from the group consisting of SEQ.ID.NO.3, SEQ. ID.NO.6, and SEQ.ID.NO.9.

27. The Apolipoprotein L-I according to claim **25**, which is selected from the group consisting of SEQ.ID.NO.2, SEQ. ID.NO.5 and SEQ.ID.NO.8.

28. A blood sample or blood extract comprising the Apolipoprotein L-I according to claim **25**.

29. The blood sample of claim **28** being a serum.

30. The blood sample extract of claim **28** being an HDL particle.

31. A polynucleotide encoding the Apolipoprotein L-I according to claim **25**.

32. A vector comprising Apolipoprotein L-I according to claim **25** or the polynucleotide encoding the Apolipoprotein L-I according to claim **25**.

33. A cell transformed by a vector comprising Apolipoprotein L-I according to claim **25** or the polynucleotide encoding the Apolipoprotein L-I according to claim **25** and/or expressing the Apolipoprotein L-I.

34. A pharmaceutical composition comprising an adequate pharmaceutical carrier or diluent and a sufficient amount of

the Apolipoprotein L-I according to claim **25**, a blood sample or a blood sample extract comprising the Apolipoprotein L-I, the polynucleotide encoding the Apolipoprotein L-I, a vector comprising the Apolipoprotein L-I or the polynucleotide encoding the Apolipoprotein L-I, or the cell comprising Apolipoprotein L-I or the polynucleotide encoding the Apolipoprotein L-I and/or expressing the Apolipoprotein L-I.

35. The pharmaceutical composition according to the claim **34** for use in the treatment and/or the prevention of diseases induced in human by *Trypanosoma brucei*.

36. The pharmaceutical composition according to the claim **34** for use in the treatment and/or the prevention of diseases induced in human by *Trypanosoma brucei rhodesiense*.

37. A method of treatment and/or prevention of a disease related to infection by trypanosoma affecting a mammal, which comprises the step of administrating a sufficient amount of the pharmaceutical composition of claim **34** to the mammal to reduce and/or suppress the symptoms of the disease in the mammal.

38. The Method of claim **37**, wherein the mammal is a human.

39. A diagnostic kit comprising:

nucleotide probes able to identify Apolipoprotein L-I variants; or antibodies specifically recognizing Apolipoprotein L-I variants according to claim **25**, and/or

Trypanosoma brucei rhodesiense culture

and

means to identify whether a subject is expressing the Apolipoprotein L-I.

40. The kit of claim **39** further comprising recombinant SRA bound on a solid support.

41. A kit comprising

nucleotide probes able to identify Apolipoprotein L-I variants; or

antibodies specifically recognizing Apolipoprotein L-I variants according to claim **25**, and/or

Trypanosoma brucei rhodesiense culture

and

means to identify whether a subject is expressing the Apolipoprotein L-I, the Apolipoprotein L-I.

42. An Antibody (preferably a monoclonal antibody) or a specific hypervariable portion thereof specifically recognizing Apolipoprotein L-I according to claim **25** and not recognizing Apolipoprotein L-I of SEQ.ID.NO.1, SEQ.ID.NO.4 and/or SEQ.ID.NO.7.

43. An inhibitor directed to the protein according to claim **25**, for use in the treatment and/or the prevention of glomerulosclerosis.

44. A Blood-lowering cholesterol and/or antihypertensive for use in the treatment and/or for the prevention of glomerulosclerosis in patients expressing the Apolipoprotein L-I according to claim **25**.

45. A pharmaceutical compound selected from the group consisting of angiotensin-converting inhibitors, angiotensin II receptor antagonists, calcium channel blockers, diuretics, statins, cholesterol absorption inhibitors, vitamin B3 and bile acid sequestrants for use in the treatment and/or for the prevention of glomerulosclerosis in patients expressing the Apolipoprotein L-I according to claim **25**.

46. A non-human genetically modified mammal, which is expressing the Apolipoprotein L-I according to claim **25**.

47. The non-human genetically modified mammal of claim **46**, wherein the mammal is a rodent.

48. The non-human genetically modified mammal of claim **46**, wherein the mammal is a cattle.

* * * * *

专利名称(译)	载脂蛋白l-i变体及其用途		
公开(公告)号	US20120128682A1	公开(公告)日	2012-05-24
申请号	US13/388645	申请日	2010-08-18
申请(专利权)人(译)	布鲁塞尔自由大学		
当前申请(专利权)人(译)	布鲁塞尔自由大学		
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发明人	PAYS, ETIENNE LECORDIER, LAURENCE VANHOLLEBEKE, BENOLT		
IPC分类号	A61K39/395 C07H21/04 C12N15/63 A61K38/00 A61K31/7088 A61P3/06 A61P33/00 C12Q1/04 G01N33/53 C12Q1/68 C07K16/12 C12N5/10 C07K16/18 A01K67/027 A61K35/14 A61K35/16 C07K14/775		
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外部链接	Espacenet USPTO		

摘要(译)

对应于野生型人载脂蛋白序列的分离的人载脂蛋白L-I通过其C末端的缺失进行修饰。

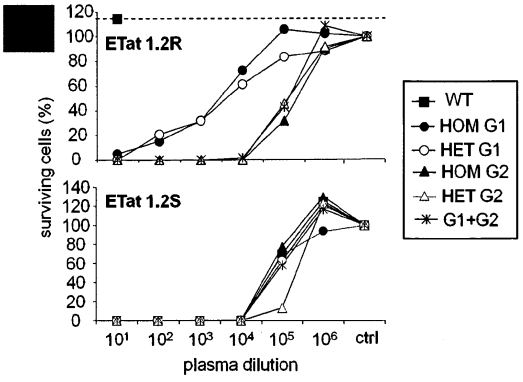

Fig. 1