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(54) Title: GLUT-1 AS A RECEPTOR FOR HTLV ENVELOPES AND ITS USES

(57) Abstract: The invention relates to the use of the ubiquitous vertebrate glucose transporter GLUT1, or of fragments or sequences derived thereof, for the *in vitro* diagnosis of cancers, when used as a tumor marker, or for the screening of compounds useful for the preparation of drugs for the prevention or the treatment of pathologies linked to an infection of an individual with a PTLV, or pathologies linked to an overexpression of GLUT1 on cell surfaces, or the *in vitro* detection of GLUT1 on cell surfaces. The invention also relates to pharmaceutical compositions containing GLUT1, or fragments or sequences derived thereof, and to their uses such as in the frame of the prevention or the treatment of pathologies linked to an infection of an individual with a PTLV.

GLUT-1 AS A RECEPTOR FOR HTLV ENVELOPES AND ITS USES

The invention relates to the use of the ubiquitous vertebrate glucose transporter GLUT1 represented by SEQ ID NO : 2, or of fragments or sequences derived thereof, for the *in vitro* diagnosis of cancers, when used as a tumor marker, or for the screening of compounds useful for the preparation of drugs for the prevention or the treatment of pathologies linked to an infection of an individual with a PTLV, or pathologies linked to an overexpression of GLUT1 on cell surfaces, or the *in vitro* detection of GLUT1 on cell surfaces. The invention also relates to pharmaceutical compositions containing GLUT1, or fragments or sequences derived thereof, and their uses such as in the frame of the prevention or the treatment of pathologies linked to an infection of an individual with a PTLV.

The human T-cell leukemia virus (HTLV) is associated with leukemia and neurological syndromes. The role of viral envelopes in HTLV physiopathology is unclear and the envelope receptor, found in all vertebrate cell lines, remains unidentified.

HTLV envelope glycoproteins induce syncytium formation *in vitro* but their physiopathological effects are unclear. All vertebrate cell lines express functional HTLV envelope receptors, including cells resistant to HTLV envelope-mediated syncytium formation. We found that expression of the HTLV receptor-binding domain decreased lactate production due to diminished glucose consumption whereas binding-defective envelope mutants did not alter glucose metabolism. Glucose starvation increased HTLV receptor expression, reminiscent of nutrient sensing responses. Accordingly, overexpression of GLUT-1, the ubiquitous vertebrate glucose transporter, specifically increased HTLV envelope binding and GLUT-1 colocalized with HTLV envelopes. Moreover, HTLV envelope binding was highest in human erythrocytes, where GLUT-1 is abundantly expressed and is the sole glucose transporter isoform. These results demonstrate that GLUT-1 is an HTLV envelope receptor, and that this ligand/receptor interaction likely participates in the immunological and neurological disorders associated with HTLV infection.

Thus, the invention relates to the use of the ubiquitous vertebrate glucose transporter GLUT1 represented by SEQ ID NO : 2, or of fragments or sequences derived thereof, said fragments or derived sequences being able to bind to the envelope proteins of the primate T-cell leukemia viruses (PTLV), or of cells expressing GLUT1, for:

- the screening of compounds useful for :

* the preparation of drugs for the prevention or the treatment of pathologies linked to an infection of an individual with a PTLV,

5 * the preparation of drugs for the prevention or the treatment of pathologies linked to an overexpression of GLUT1 on cell surfaces,

* the *in vitro* detection of GLUT1 on cell surfaces,

said compounds being selected for their ability to bind specifically to said GLUT1,

- the detection, concentration, and/or purification of PTLV or variants thereof, or of PTLV envelope proteins, or fragments thereof,

10 - the preparation of drugs for the prevention or the treatment of pathologies either linked to an infection of an individual or an animal with a PTLV, such as HTLV-1, HTLV-2, STLV-1, STLV-2, STLV-3, or their variants, or linked to the presence of PTLV SU-related sequences in such individuals or animals,

- the *in vitro* diagnosis of cancers, when used as a tumor marker.

15 For illustration purpose, screened compounds mentioned above can be selected for their ability to bind specifically to said GLUT1, or fragments of GLUT1, according to the following method using a EGFP-tagged GLUT1-binding component derived from PTLV RBD (receptor binding domain) as an example of such compound able to bind to GLUT1.

20 A EGFP-tagged Glut1-binding component derived from PTLV RBD is applied onto live or fixed suspension or attached cells. After washes with appropriate buffer, cells are incubated for 30 min at RT, washed and analyzed or quantified as attached on an appropriate support on a fluorescent microscope or as individual cell suspension on a fluorescent analysis cell sorter (FACS). Alternatively, a non-fluorescent GLUT1-binding component derived from PTLV RBD is applied as described above and revealed with a secondary fluorochrome-tagged reagent such as a fluorochrome-tagged secondary antibody directed against the PTLV RBD or 25 against a non fluorochrome tag attached to the said PTLV RBD component.

The invention relates more particularly to the use as defined above, of fragments of GLUT1 chosen among the followings :

- SEQ ID NO : 25 : NAPQKVIEFY

30 - SEQ ID NO : 26 : NQTWVHRYGESILPTTLTTLWS

- SEQ ID NO : 27 : KSFEMLILGR

- SEQ ID NO : 28 : DSIMGNKDL

- SEQ ID NO : 29 : YSTSIFEKAGVQQP

- SEQ ID NO : 30 : EQLPWMSYLS

- SEQ ID NO : 31 : QYVEQLC
- SEQ ID NO : 32 : IVGMCFQYVEQLC

These fragments of GLUT1 correspond to the predicted extracellular loops of human GLUT1 as described by Mueckler, M., and C. Makepeace. 1997. Identification of an amino acid residue that lies between the exofacial vestibule and exofacial substrate-binding site of the GLUT1 sugar permeation pathway. *J Biol Chem.* 272(48):30141-6.

The invention also concerns the use of compounds selected for their ability to bind specifically to GLUT1 as defined above, for the preparation of drugs for the prevention or the treatment of pathologies linked to an infection of an individual with a PTLV, such as pathologies corresponding to adult T cell leukemia (ATL), HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP), as well as other HTLV-associated syndromes such as large granular lymphocyte (LGL) leukaemia (Loughran, T. P., K. G. Hadlock, R. Perzova, T. C. Gentile, Q. Yang, S. K. Foun, and B. J. Poiesz. 1998. Epitope mapping of HTLV envelope seroreactivity in LGL leukaemia. *Br J Haematol.* 101(2):318-24.), uveitis (Mochizuki, M., A. Ono, E. Ikeda, N. Hikita, T. Watanabe, K. Yamaguchi, K. Sagawa, and K. Ito. 1996. HTLV-I uveitis. *J Acquir Immune Defic Syndr Hum Retrovirol.* 13 Suppl 1:S50-6.), infective dermatitis (La Grenade, L., R. A. Schwartz, and C. K. Janniger. 1996. Childhood dermatitis in the tropics: with special emphasis on infective dermatitis, a marker for infection with human T-cell leukemia virus-I. *Cutis.* 58(2):115-8.), arthropathies (Nishioka, K., T. Sumida, and T. Hasunuma. 1996. Human T lymphotropic virus type I in arthropathy and autoimmune disorders. *Arthritis Rheum.* 39(8):1410-8.), cutaneous T cell lymphoma (mycosis fungoides) (Hall, W. W., C. R. Liu, O. Schneewind, H. Takahashi, M. H. Kaplan, G. Roupe, and A. Vahlne. 1991. Deleted HTLV-I provirus in blood and cutaneous lesions of patients with mycosis fungoides. *Science.* 253(5017):317-20. 2. Zucker-Franklin, D., B. A. Pancake, M. Marmor, and P. M. Legler. 1997. Reexamination of human T cell lymphotropic virus (HTLV-I/II) prevalence. *Proc Natl Acad Sci U S A.* 94(12):6403-7), polymyositis (Saito M, Higuchi I, Saito A, Izumo S, Usuku K, Bangham CR, Osame M. Molecular analysis of T cell clonotypes in muscle-infiltrating lymphocytes from patients with human T lymphotropic virus type 1 polymyositis. *J Infect Dis.* 2002 Nov 1;186(9):1231-41), and potentially other idiopathic diseases in which PTLV or PTLV sequences may be involved.

The invention relates more particularly to the use for the preparation of drugs for the prevention or the treatment of pathologies linked to an infection of an individual with a PTLV, of compounds chosen among the followings :

- androgenic steroids (36: May JM, Danzo BJ. Photolabeling of the human erythrocyte glucose carrier with androgenic steroids. *Biochim Biophys Acta*. 1988 Aug 18;943(2):199-210),
- 5 - cytochalasin B, forskolin, dipyridamole, isobutylmethylxanthine (20: Hellwig B, Joost HG. Differentiation of erythrocyte-(GLUT1), liver-(GLUT2), and adipocyte-type (GLUT4) glucose transporters by binding of the inhibitory ligands cytochalasin B, forskolin, dipyridamole, and isobutylmethylxanthine. *Mol Pharmacol*. 1991 Sep;40(3):383-9),
 - ethanol (Krauss SW, Diamond I, Gordon AS. Selective inhibition by ethanol of the type 1 facilitative glucose transporter (GLUT1). *Mol Pharmacol*. 1994 Jun;45(6):1281-6),
- 10 - genistein (Vera JC, Reyes AM, Carcamo JG, Velasquez FV, Rivas CI, Zhang RH, Strobel P, Iribarren R, Scher HI, Slebe JC, et al. Genistein is a natural inhibitor of hexose and dehydroascorbic acid transport through the glucose transporter, GLUT1. *J Biol Chem*. 1996 Apr 12;271(15):8719-24),
 - cadmium (Lachaal M, Liu H, Kim S, Spangler RA, Jung CY. Cadmium increases GLUT1 substrate binding affinity in vitro while reducing its cytochalasin B binding affinity. *Biochemistry*. 1996 Nov 26;35 (47):14958-62),
 - barbiturate (el-Barbary A, Fenstermacher JD, Haspel HC. Barbiturate inhibition of GLUT-1 mediated hexose transport in human erythrocytes exhibits substrate dependence for equilibrium exchange but not unidirectional sugar flux. *Biochemistry*. 1996 Dec 3;35(48):15222-7),
 - dehydroascorbic acid (Rumsey SC, Kwon O, Xu GW, Burant CF, Simpson I, Levine M. Glucose transporter isoforms GLUT1 and GLUT3 transport dehydroascorbic acid. *J Biol Chem*. 1997 Jul 25;272(30):18982-9),
 - tricyclic antidepressants (Pinkofsky HB, Dwyer DS, Bradley RJ. The inhibition of GLUT1 glucose transport and cytochalasin B binding activity by tricyclic antidepressants. *Life Sci*. 2000;66(3):271-8.),
 - oestradiol, genistein and the anti-oestrogens, faslodex (ICI 182780), tamoxifen (Afzal I, Cunningham P, Naftalin RJ. Interactions of ATP, oestradiol, genistein and the anti-oestrogens, faslodex (ICI 182780) and tamoxifen, with the human erythrocyte glucose transporter, GLUT1. *Biochem J*. 2002 Aug 1;365(Pt 3):707-19),
 - gamma agonists of peroxisome proliferator-activated receptors (PPAR) such as thiazolidinedione (troglitazone, pioglitazone, rosiglitazone) ("TZDs modify astrocyte metabolism and mitochondrial function, which could be beneficial in neurological conditions where glucose availability is reduced" from Dello Russo C, Gavril'yuk V, Weinberg G,

Almeida A, Bolanos JP, Palmer J, Pelligrino D, Galea E, Feinstein DL.. Peroxisome proliferator-activated receptor gamma thiazolidinedione agonists increase glucose metabolism in astrocytes. *J Biol Chem.* 2003 Feb 21;278(8):5828-36).

5 The invention also relates to the use of compounds selected for their ability to bind specifically to GLUT1 as defined above, for the preparation of drugs for the prevention or the treatment of pathologies linked to an overexpression of GLUT1 on cell surfaces, such as :

- cancers, such as :

. squamous cell carcinoma (Kunkel M, Reichert TE, Benz P, Lehr HA, Jeong JH, Wieand S, Bartenstein P, Wagner W, Whiteside TL. *Cancer.* 2003 Feb 15;97(4):1015-24),

10 . hypopharyngeal carcinoma (Mineta H, Miura K, Takebayashi S, Misawa K, Araki K, Misawa Y, Ueda Y. *Anticancer Res.* 2002 Nov-Dec;22(6B):3489-94),

. breast cancer (Brown RS, Wahl RL. Overexpression of Glut-1 glucose transporter in human breast cancer. An immunohistochemical study. *Cancer.* 1993 Nov 15;72(10):2979-85),

15 . cervical carcinoma (Mendez LE, Manci N, Cantuaria G, Gomez-Marin O, Penalver M, Braunschweiger P, Nadji M. Expression of glucose transporter-1 in cervical cancer and its precursors. *Gynecol Oncol.* 2002 Aug;86(2):138-43),

20 . ovarian carcinoma (Cantuaria G, Fagotti A, Ferrandina G, Magalhaes A, Nadji M, Angioli R, Penalver M, Mancuso S, Scambia G. GLUT-1 expression in ovarian carcinoma: association with survival and response to chemotherapy. *Cancer.* 2001 Sep 1;92(5):1144-50),

. lung cancer (Ito T, Noguchi Y, Satoh S, Hayashi H, Inayama Y, Kitamura H. Expression of facilitative glucose transporter isoforms in lung carcinomas: its relation to histologic type, differentiation grade, and tumor stage. *Mod Pathol.* 1998 May;11(5):437-43.

25 Younes M, Brown RW, Stephenson M, Gondo M, Cagle PT. Overexpression of Glut1 and Glut3 in stage I nonsmall cell lung carcinoma is associated with poor survival. *Cancer.* 1997 Sep 15;80(6):1046-51),

. pancreatic cancer (Reske SN, Grillenberger KG, Glatting G, Port M, Hildebrandt M, Gansauge F, Beger HG. Overexpression of glucose transporter 1 and increased FDG uptake in pancreatic carcinoma. *J Nucl Med.* 1997 Sep;38(9):1344-8),

. insulinoma (1: Boden G, Murer E, Mozzoli M. Glucose transporter proteins in human insulinoma. *Ann Intern Med.* 1994 Jul 15;121(2):109-12,

- inflammatory conditions,

- immune or auto-immune diseases, such as :

- . autoimmune myocarditis (Tokita N, Hasegawa S, Tsujimura E, Yutani K, Izumi T, Nishimura T. Serial changes in 14C-deoxyglucose and 201Tl uptake in autoimmune myocarditis in rats. *J Nucl Med.* 2001 Feb;42(2):285-91),
- 5 . in the frame of CD28 T-cell activation (Frauwirth KA, Riley JL, Harris MH, Parry RV, Rathmell JC, Plas DR, Elstrom RL, June CH, Thompson CB. The CD28 signaling pathway regulates glucose metabolism. *Immunity.* 2002 Jun;16(6):769-77),
- 10 . in the frame of immunomodulation (Moriguchi S, Kato M, Sakai K, Yamamoto S, Shimizu E. Decreased mitogen response of splenic lymphocytes in obese Zucker rats is associated with the decreased expression of glucose transporter 1 (GLUT-1). *Am J Clin Nutr.* 1998 Jun;67(6):1124-9),
- 15 - disorders of the central nervous system, such as facilitated glucose transporter protein type 1 (GLUT1) deficiency syndrome (review in Klepper J, Voit T. *Eur J Pediatr.* 2002 Jun;161(6):295-304.)
- The invention relates more particularly to the use for the preparation of drugs for the prevention or the treatment of pathologies linked to an overexpression of GLUT1 on cell surfaces, of compounds chosen among the followings :
- 20 - polypeptides compounds corresponding to the envelope proteins of PTLV, or fragments or sequences derived thereof, said fragments or derived sequences being able to bind to GLUT1,
- 25 - glucose or derivatives such as galactose, 2-fluorodeoxyglucose, 2-deoxyglucose, 3-O-methylglucose
- androgenic steroids, cytochalasin B, forskolin, dipyridamole, isobutylmethylxanthine, ethanol, genistein, cadmium, barbiturate, dehydroascorbic acid, tricyclic antidepressants, oestradiol, anti-oestrogens, faslodex (ICI 182780), tamoxifen, gamma agonists of peroxisome proliferator-activated receptors (PPAR) such as thiazolidinedione, troglitazone, pioglitazone, rosiglitazone, as mentioned above.
- 30 The invention relates more particularly to the use of polypeptides corresponding to the envelope proteins of PTLV, or fragments or sequences derived thereof, said polypeptides being selected for their ability to bind specifically to the ubiquitous vertebrate glucose transporter GLUT1 represented by SEQ ID NO : 2, or of nucleotide sequences encoding said polypeptides, for the preparation of drugs for the prevention or the treatment of pathologies linked to an overexpression of GLUT1 on cell surfaces, and the *in vitro* diagnosis of said pathologies.

The invention concerns more particularly the use as defined above, of polypeptides able to bind to at least one of the above mentioned fragments of GLUT1 corresponding to SEQ ID NO : 25, SEQ ID NO : 26, SEQ ID NO : 27, SEQ ID NO : 28, SEQ ID NO : 29, SEQ ID NO: 30, SEQ ID NO : 31, and SEQ ID NO : 32.

5 The invention concerns more particularly the use as defined above, of polypeptides able to bind to at least the fragment of GLUT1 corresponding to SEQ ID NO : 32.

The invention concerns more particularly the use as defined above, of GLUT1 binding polypeptides mentioned above chosen among the followings :

10 - the envelope protein of HTLV-1 corresponding to SEQ ID NO : 4, or of HTLV-2 corresponding to SEQ ID NO : 6, or of STLV-1 corresponding to SEQ ID NO : 8, or of STLV-2 corresponding to SEQ ID NO : 10, or of STLV-3 corresponding to SEQ ID NO : 12,

15 - fragments of the envelope proteins of PTLV, said fragments corresponding to polypeptides delimited in their N-terminal extremity by the amino acid located in position 1 to 90, or in position 75 to 90, and in their C-terminal extremity by the amino acid located in position 135 to 245, or in position 135 to 150, of said envelope proteins of PTLV, such as SEQ ID NO : 4, 6, 8, 10, 12,

20 - fragments of the envelope proteins of PTLV, said fragments corresponding to the following polypeptides :

25 * the polypeptide delimited in its N-terminal extremity by the amino acid located in position 83 to 89, and in its C-terminal extremity by the amino acid located in position 139 to 145, of the envelope protein of the strain MT-2 of HTLV-1 corresponding to SEQ ID NO : 4,

30 * the polypeptide delimited in its N-terminal extremity by the amino acid located in position 79 to 85, and in its C-terminal extremity by the amino acid located in position 135 to 141, of the envelope protein of the strain NRA of HTLV-2 corresponding to SEQ ID NO : 6,

* the polypeptide delimited in its N-terminal extremity by the amino acid located in position 83 to 89, and in its C-terminal extremity by the amino acid located in position 139 to 145, of the envelope protein of STLV-1 corresponding to SEQ ID NO : 8,

* the polypeptide delimited in its N-terminal extremity by the amino acid located in position 79 to 85, and in its C-terminal extremity by the amino acid located in position 135 to 141, of the envelope protein of STLV-2 corresponding to SEQ ID NO : 10,

* the polypeptide delimited in its N-terminal extremity by the amino acid located in position 82 to 88, and in its C-terminal extremity by the amino acid located in position 138 to 144, of the envelope protein of STLV-3 corresponding to SEQ ID NO : 12,

* the polypeptide corresponding to the envelope protein of a variant of HTLV-1, said polypeptide having the following sequence SEQ ID NO : 14,

5 I K K P N P N G G G Y Y L A S Y S D
 P C S L K C P Y L G C Q S W T C P Y
 T G A V S S P Y W K F Q Q D V

* the polypeptide corresponding to the envelope protein of a variant of HTLV-1, said polypeptide having the following sequence SEQ ID NO : 16,

10 V K K P N R N G G G Y Y L A S Y S D
 P C S L K C P Y L G C Q S W T C P Y
 T G A V S S P Y W K F Q Q D V

* the polypeptide corresponding to the envelope protein of a variant of HTLV-1, said polypeptide having the following sequence SEQ ID NO : 18,

15 I K K P N R N G G G Y Y L A S Y S D
 P C S L K C P Y L G C Q S W T C P Y
 T G A V S S P Y W K F Q Q D V

* the polypeptide corresponding to the envelope protein of a variant of HTLV-1, said polypeptide having the following sequence SEQ ID NO : 20,

20 I K K P N R N G G G Y Y L A S Y S D
 P C S L K C P Y L G C Q S W T C P Y
 T G P V S S P Y W K F Q Q D V

* the polypeptide corresponding to the envelope protein of a variant of HTLV-1, said polypeptide having the following sequence SEQ ID NO : 22,

25 I K K P N R N G G G Y H S A S Y S D P
 C S L K C P Y L G C Q S W T C P Y A G
 A V S S P Y W K F Q Q D V N F T Q E V

* the polypeptide corresponding to the envelope protein of a variant of HTLV-2, said polypeptide having the following sequence SEQ ID NO : 24,

30 I R K P N R Q G L G Y Y S P S Y N D
 P C S L Q C P Y L G S Q S W T C P Y
 T A P V S T P S W N F H S D V

The invention concerns more particularly the use mentioned above of GLUT1 binding polypeptides as defined above, characterized in that the treated or detected pathologies are the followings :

- solid tumors, such as brain tumors, squamous cell carcinoma, hypopharyngeal carcinoma, breast cancer, cervical carcinoma, ovarian carcinoma, pancreatic cancer, insulinoma,

- inflammatory conditions, such as multiple sclerosis, rheumatoid arthritis,

5 - immune or auto-immune diseases, such as autoimmune myocarditis, or in the frame of CD28 T-cell activation, or in the frame of immunomodulation, or systemic lupus erythematosus,

- disorders of the central nervous system, such as facilitated glucose transporter protein type 1 (GLUT1) deficiency syndrome.

10 The invention relates more particularly to the use of compounds selected for their ability to bind specifically to GLUT1 as mentioned above, and more particularly GLUT1 binding polypeptides as defined above, for the *in vitro* detection of GLUT1 on cell surfaces in the frame of processes for the *in vitro* diagnosis of pathologies linked to an overexpression of GLUT1 on cell surfaces, such as pathologies defined above, said processes comprising the

15 following steps :

- contacting a biological sample (such as tumor biopsies or cells or tissue manifesting or with a suspected aberrant GLUT1 expression profile) from an individual with a compound, and more particularly a GLUT1 binding polypeptide, as defined above, said compound, or GLUT1 binding polypeptide, being optionally labeled, or susceptible to be recognized by a

20 labeled molecule,

- determining the level of said compound, or GLUT1 binding polypeptide, bound to the cells contained in the biological sample and comparison with the level of binding of said compound, or GLUT1 binding polypeptide, to cells contained in the biological sample from an healthy individual.

25 The invention concerns more particularly the use of compounds as defined above for the *in vitro* diagnosis of cancers, characterized in that the compounds used are chosen among the compounds defined above selected for their ability to bind specifically to GLUT1.

The invention relates more particularly to the use as defined above, of GLUT1 binding polypeptides, or of nucleotide sequences encoding said polypeptides, for the preparation of

30 drug vectors containing at their surface said polypeptides, said vectors being useful for targeting GLUT1 overexpressing cells for the prevention or the treatment of pathologies linked to an overexpression of GLUT1 on cell surfaces, said vectors containing molecules active against said pathologies, or containing genes in the frame of gene therapy of these pathologies.

The invention relates more particularly to the use as defined above, of GLUT1 binding polypeptides, or of nucleotide sequences encoding said polypeptides, for the preparation of drug vectors containing at their surface GLUT1 binding polypeptides, said vectors being useful for targeting GLUT1 overexpressing tumor cells, or cells involved in the inflammatory mechanism, or activated cells of the immune system, or cells of the central nervous system, for the prevention or the treatment of related pathologies as defined above.

5 The invention concerns more particularly the use of GLUT1 binding polypeptides, or of nucleotide sequences encoding said polypeptides, for the preparation of drug vectors as defined above, wherein the molecules active against the pathologies are antitumor molecules, 10 or molecules against inflammatory conditions, immune or auto-immune diseases, or disorders of the central nervous system.

15 The invention also relates to the use of nucleotide sequences encoding polypeptides compounds selected for their ability to bind specifically to GLUT1 as defined above, such as nucleotide sequences encoding the polypeptides defined above, or fragments thereof, for the preparation, by substitution of one or several nucleotides of said nucleotide sequences, of mutant nucleotide sequences encoding corresponding mutant polypeptides unable to bind to GLUT1.

The invention also concerns the use of mutant polypeptides unable to bind to GLUT1 as defined above :

20 - as a negative control in the frame of the screening of compounds able to bind specifically to the non mutated corresponding polypeptides, and thus liable to be used in the frame of the preparation of drugs for the prevention or the treatment of pathologies linked to an infection of an individual with a PTLV,

25 - for the preparation of drugs for the prevention or the treatment of pathologies linked to an infection of an individual with a PTLV.

The invention relates more particularly to the use as defined above, of mutant polypeptides corresponding to the polypeptides defined above, wherein :

- D in position 106 and/or Y in position 114 of the envelope protein of HTLV-1 corresponding to SEQ ID NO : 4,

30 - D in position 102 and/or Y in position 110 or of HTLV-2 corresponding to SEQ ID NO : 6,

- D in position 106 and/or Y in position 114 or of STLV-1 corresponding to SEQ ID NO : 8,

- D in position 102 and/or Y in position 110 or of STLV-2 corresponding to SEQ ID NO : 10,

- D in position 105 and/or Y in position 113 or of STLV-3 corresponding to SEQ ID NO : 12,

5 - D in position 18 and/or Y in position 26 of the polypeptides corresponding to SEQ ID NO : 14, 16, 18, 20, 22, and 24,

are substituted by another aminoacid, natural or not, such as mutant polypeptides corresponding to the polypeptides mentioned above wherein said D and/or A residues are substituted by A.

10 The invention also relates to the use of mutant nucleotide sequences encoding corresponding mutant polypeptides unable to bind to GLUT1 as defined above, for the preparation of transgenic mammal cells expressing said mutant polypeptides, said cells having a negative transdominant effect with regard to PTLV, thus preventing infection and dissemination of this latter in the organism.

15 The invention also concerns pharmaceutical compositions containing GLUT1 represented by SEQ ID NO : 2, or fragments or sequences derived thereof, said fragments or derived sequences being able to bind to the envelope proteins of the primate T-cell leukemia viruses (PTLV), in association with a pharmaceutically acceptable carrier.

20 The invention relates more particularly to pharmaceutical compositions containing mutant polypeptides corresponding to the polypeptides defined above, wherein :

- D in position 106 and/or Y in position 114 of the envelope protein of HTLV-1 corresponding to SEQ ID NO : 4,

- D in position 102 and/or Y in position 110 or of HTLV-2 corresponding to SEQ ID NO : 6,

25 - D in position 105 and/or Y in position 113 or of STLV-3 corresponding to SEQ ID NO : 12,

- D in position 18 and/or Y in position 26, of the polypeptides corresponding to SEQ ID NO : 14, 16, 18, 20, 22, and 24,

30 are substituted by another aminoacid, natural or not, such as mutant polypeptides corresponding to the polypeptides mentioned above wherein said D and/or A residues are substituted by A,

in association with a pharmaceutically acceptable carrier.

The invention also concerns transgenic mammal cells expressing mutant polypeptides unable to bind to GLUT1 as defined above, said cells having a negative transdominant effect

with regard to PTLV, thus preventing infection and dissemination of this latter in the organism.

The invention relates more particularly to pharmaceutical compositions containing transgenic mammal cells as defined above, in association with a pharmaceutically acceptable carrier.

The invention also concerns therapeutic vectors useful for targeting GLUT1 overexpressing cells in pathologies linked to an overexpression of GLUT1 on cell surfaces, such as defined above, said vectors containing at their surface GLUT1 binding polypeptides chosen among those defined above, and containing molecules active against said pathologies, as defined above, or containing genes in the frame of gene therapy.

The invention relates more particularly to pharmaceutical compositions containing therapeutic vectors as described above, in association with a pharmaceutically acceptable carrier.

The invention also relates to a method for the screening of compounds useful for :

* the preparation of drugs for the prevention or the treatment of pathologies linked to an infection of an individual with a PTLV,

* the preparation of drugs for the prevention or the treatment of pathologies linked to an overexpression of GLUT1 on cell surfaces,

* the *in vitro* detection of GLUT1 on cell surfaces,

said method comprising :

- the contacting of GLUT1 represented by SEQ ID NO : 2, or of fragments or sequences derived thereof, said fragments or derived sequences being able to bind to the envelope proteins of the primate T-cell leukemia viruses (PTLV), or of cells expressing GLUT1, with compounds to be tested,

- the selection of compounds able to bind specifically to GLUT1, or fragments or sequences derived thereof, as for example according to the method mentioned above.

The invention relates more particularly to a method for the screening of compounds useful for the prevention or the treatment of pathologies linked to an overexpression of GLUT1 on cell surfaces, and the *in vitro* diagnosis of said pathologies, comprising the steps described above:

The invention also concerns a method for the *in vitro* diagnosis pathologies linked to an overexpression of GLUT1 on cell surfaces, characterized in that it comprises :

- contacting a biological sample (such as biopsies or cells or tissue manifesting or with a suspected aberrant GLUT1 expression profile) from an individual with compounds, and more

particularly polypeptides, selected for their ability to bind specifically to GLUT1 as defined above, said compounds or polypeptides being optionally labeled, or susceptible to be recognized by a labeled molecule,

5 - determining the level of said compounds or polypeptides bound to the cells contained in the biological sample and comparison with the level of binding of said compound to cells contained in the biological sample from an healthy individual.

The invention relates more particularly to a method as defined above for the *in vitro* diagnosis of pathologies mentioned above.

10 The invention also concerns a kit for the *in vitro* diagnosis of pathologies linked to an overexpression of GLUT1 on cell surfaces as described above, comprising compounds, and more particularly polypeptides, selected for their ability to bind specifically to GLUT1 as defined above, said compounds or polypeptides being optionally labeled, and, if necessary reagents for the detection of the binding of said compounds or polypeptides to GLUT1 initially present on cell surfaces in the biological sample.

15 The invention is further illustrated with the detailed description hereafter of the determination of GLUT1 as a specific receptor for PTLV RBD.

20 The human T-cell leukemia virus (HTLV) type 1 and 2 are present in all areas of the world as endemic or sporadic infectious agents [Slattery, 1999]. The etiological role of HTLV-1 in adult T cell leukemia (ATL) and tropical spastic paraparesis/HTLV-associated myelopathy (TSP/HAM) has been well established [Poiesz, 1980; Yoshida, 1982; Gessain, 1985; Osame, 1986]. The apparently restricted tropism of HTLV to T lymphocytes in infected patients[Cavrois, 1996 ; Hanon, 2000] contrasts with the ability of the viral-encoded envelope glycoprotein (Env) to bind to and direct entry into all vertebrate cell types tested in vitro[Sutton, 1996 ; Trejo, 2000; Kim, 2003]. Retroviral infections depend on early 25 interactions between Env and cellular receptors. Identification of cellular receptors and coreceptors for other retroviral envelopes have helped to elucidate certain aspects of retrovirus physiopathology as well as their transmission and spreading within organisms and populations[Berger, 1999; Clapham, 2001; Weiss, 2002]. However, no clear association between HTLV Env and HTLV-associated diseases has been established and the identity of 30 the receptor(s) for HTLV-1 and HTLV-2 Env has remained elusive.

Numerous cell surface components have been shown to play a role in HTLV Env-mediated syncytia formation [Niyogi, 2001; Daenke, 1999; Hildreth, 1997]. Nevertheless, HTLV Env-dependent cell membrane fusion and syncytia formation appear to be distinct from receptor binding per se [Denesvre, 1996; Daenke, 2000; Kim, 2000; Kim, 2003]. The

search for HTLV Env receptor has been hindered in part by its ubiquitous presence [Sutton, 1996; Trejo, 2000; Jassal, 2001; Kim, 2003]. Additionally, the induction of rampant syncytium formation in cell culture upon expression of HTLV Env [Hoshino, 1983; Nagy, 1983] has prevented efficient and persistent Env expression. Based on our observation that the 5 HTLV Env amino terminal domain shares striking structural and functional homology with that of murine leukemia viruses (MLV), we defined HTLV Env receptor-binding domain (RBD) and derived HTLV Env-based tools that overcome the problem of syncytia formation [Kim, 2000; Kim, 2003]. We were thus able to follow specific interactions between the Env RBD and a primary HTLV receptor. Using these tools, we have previously shown that the 10 HTLV receptor is expressed on the surface on T lymphocytes, the major HTLV reservoir in vivo, only following T cell receptor activation[Manel, 2003].

Here we describe striking metabolic alterations in cell cultures following expression of HTLV envelopes as well as HTLV receptor binding domains. These alterations are characterized by a defect in the acidification of the cell culture medium associated with a 15 decreased lactate production and a decline in glucose consumption and uptake. These observations as well as the knowledge that Env receptors for the related MLV and most of the gammaretrovirus belong to the family of multiple-membrane spanning transporters[Overbaugh, 2001] prompted us to test ubiquitous lactate and glucose transport-associated molecules as receptors for HTLV Env. We show that the ubiquitous GLUT-1 20 glucose transporter, present in all vertebrates, is an essential and specific component of the receptor for HTLV. Moreover, interaction of GLUT-1 with the entire HTLV-1 and HTLV-2 envelopes as well as the truncated HTLV-1 and HTLV-2 RBDs alters glucose metabolism.

HTLV envelopes alter lactate metabolism

25 Cell proliferation in standard culture media is accompanied by acidification of the milieu that translates into a color change from red to yellow tones in the presence of the phenol-red pH indicator. Upon transfection of either highly syncytial HTLV-1 and HTLV-2 envelopes, or a non-syncytial chimeric envelope that harbors the HTLV-1 RBD in a MLV Env backbone (H₁₈₃FEnv), culture medium did not readily acidify, and harbored red tones for 30 several days post-transfection (fig 1a). Moreover, expression of truncated soluble HTLV RBD proteins fused with either GFP, -HA, or -rFc tags also inhibited medium acidification. In contrast, no envelope construct that lacked HTLV RBD, including different MLV group envelopes, feline, porcine, lentiviral and Jaagsiekte retroviral Envs, as well as VSV-G and Ebola glycoproteins, had this effect. The lack of acidification associated with HTLV-1 or

HTLV-2 Env expression was not an indirect consequence of their syncytial activity, since (i) medium acidification was observed in cells expressing a syncytial amphotropic-MLV Env (A-MLV devoid of the R peptide) (fig 1a) and (ii) medium acidification was blocked when HTLV Env was expressed in cells that are resistant to HTLV-Env mediated syncytia formation (NIH3T3 TK⁻ cells)[Kim, 2003].

Decrease of pH in cell culture is primarily due to extracellular accumulation of lactate [Warburg, 1956]. Lactate is the major byproduct of anaerobic glycolysis *in vitro* and its excretion is mediated by an H⁺/lactate symporter [Halestrap, 1999]. We monitored lactate content in culture supernatants following transfection of various retroviral envelopes and RBD. Lactate accumulation was consistently 3-fold lower in H₁₈₃FEnv- and HTLV RBD-transfected cells than in control- or MLV Env-transfected cells (fig 1b). This decrease in extracellular lactate accumulation after HTLV RBD transfection was DNA dose-dependent. Moreover, we found that the decrease in lactate accumulation following transfection of HTLV RBD was apparent as early as 4 hours after the addition of fresh media (fig 1c).

15

Receptor binding and lactate metabolism

To examine whether a direct relationship exists between binding of the HTLV envelope receptor and diminished extracellular acidification and lactate accumulation, we attempted to generate HTLV-1 RBD (H1_{RBD}) mutants with impaired receptor binding capacities. To this end, mutations resulting in single alanine substitutions were introduced at two different positions in H1_{RBD}, D106 and Y114 which are highly conserved among primate T-lymphotropic viruses. Although both D106A and Y114A RBD mutants were expressed and secreted as efficiently as the wild-type H1_{RBD} (fig 2a), they exhibited significantly reduced (D106A) or non detectable (Y114A) binding to the HTLV receptor as detected by FACS analysis (fig 2b). Moreover, perturbations in lactate metabolism correlated with binding to the HTLV receptor: lactate accumulation was not reduced in cells expressing the non-binding Y114A RBD mutant and was minimally reduced in cells harboring the D106 RBD (fig 2c). Similar results were obtained with H2_{RBD} harboring the same allelic mutations. These data favor a direct association between lactate-related metabolic alterations and HTLV Env receptor binding.

Extracellular lactate accumulates in cell cultures following its transport across cellular membranes by the MCT1 monocarboxylate transporter[Garcia, 1994]. Because HTLV and MLV share a common organization of the extracellular envelope [Kim, 2000] and the receptors for MLV Env are multispanning metabolite transporters [Overbaugh, 2001], we

assessed whether the HTLV RBD bound to MCT1. Moreover, similar to our previous data concerning expression of the HTLV receptor on T cells [Manel, 2003], expression of MCT1 chaperone CD147 [Kirk, 2000] increases during T cell activation [Kasinrerk, 1992]. However, separate and combined overexpression of MCT1 and CD147 did not result in increased H1_{RBD} binding, arguing against a role for these molecules as receptors for HTLV Env.

HTLV receptor and glucose metabolism

In addition to a decrease in extracellular lactate accumulation, expression of the HTLV RBD also led to decreased intracellular lactate content, indicative of metabolic alterations upstream of lactate transport. In cell cultures, lactate accumulation results from the degradation of glucose during anaerobic glycolysis. Therefore, we assessed whether the decreased accumulation of lactate observed upon expression of HTLV RBD was linked to glucose metabolism. We measured glucose consumption as normalized to cellular protein content. Glucose consumption of cells expressing an HTLV RBD within the context of the H₁₈₃FEnv entire envelope or the H1_{RBD} was significantly decreased as compared to control cells (fig 3a) and this defect was detectable as early as 8 hours post transfection. To determine if this decrease in glucose consumption corresponded to a decrease in glucose transport across cellular membrane, we measured 2-deoxyglucose and fructose uptake in control cells and cells expressing HTLV RBD (fig 3b). We observed that expression of either HTLV-1 or HTLV-2 RBD induced an approximatively 4-fold decrease in 2-deoxyglucose uptake, while A-MLV RBD had only a minor effect. Inhibitors of glucose uptake, cytochalasin B and phloretin, also inhibited glucose uptake. Theses results were also true for 3-O-methylglucose transport. Fructose uptake in the same cells was not altered by the presence of HTLV-1 nor HTLV-2 RBD however A-MLV RBD induced a slight decreased. We next evaluated the effect of glucose deprivation on the availability of the HTLV receptor in both adherent human 293T cells and suspension Jurkat T cells. After overnight culture of cells in the absence of glucose, binding of H1_{RBD} was consistently increased by 2-fold in both cell types (fig 3c). This effect of glucose deprivation was specific to HTLV as amphotropic MLV RBD (A_{RBD}) binding was only marginally affected (fig 3c). This phenomenon is reminiscent of a general metabolite transport feedback loop, whereby transporter availability at the cell surface increases upon substrate starvation [Martineau, 1972].

HTLV envelopes bind glucose transporter-1

A simple model whereby the HTLV envelope inhibits glucose consumption via direct binding to a glucose transporter can explain the metabolic effects described above. Upon evaluation of the different glucose transporter candidates, GLUT-1 appears to be the only one 5 encompassing all the known properties of the HTLV receptor. Indeed, GLUT-1 expression is increased upon glucose deprivation and is transports glucose in all vertebrate cells [Mueckler, 1985], while fructose is transported by GLUT-5. Furthermore, GLUT-1 is not expressed on resting primary T cells and its expression is induced upon T cell activation [Rathmell, 2000; Chakrabarti, 1994] with kinetics that are strikingly similar to what we have reported for the 10 HTLV receptor [Manel, 2003]. Since human but not murine erythrocytes have been described to be the cells exhibiting the highest concentration of GLUT-1 [Mueckler, 1994], we evaluated HTLV receptor availability on freshly isolated red blood cells. Binding of H1_{RBD} on human erythrocytes was strikingly efficient, reaching levels higher than those observed on any other tested cell type, whereas A_{RBD} binding to erythrocytes was minimal (fig 4a). On 15 murine erythrocytes however, no significant H1_{RBD} binding could be detected, despite a similar A_{RBD} binding on murine and human erythrocytes. Furthermore, primary human hepatocytes do not express GLUT-1. Accordingly, we were unable to detect H1_{RBD} binding to human primary hepatocytes, while A_{RBD} binding could be readily detected.

In order to directly test the ability of HTLV envelopes to bind GLUT-1, we derived a 20 tagged GLUT-1 expression vector and overexpressed this protein in HeLa cells. Both H1_{RBD} and H2_{RBD} binding was dramatically increased upon GLUT-1 overexpression (fig 4b). This interaction was specific as the HTLV-2 binding-defective mutant, D102A, as well as its 25 HTLV-1 counterpart, D106A, did not bind GLUT-1 (fig 4b). Furthermore, H1_{RBD} and H2_{RBD} binding remained at background levels upon overexpression of the amphotropic MLV envelope receptor, the inorganic phosphate transporter PiT2 [Miller, 1994]. Conversely, 30 binding of A_{RBD} was not increased after GLUT-1 overexpression but as expected, this interaction was increased upon transfection of PiT2 (fig 4b). GLUT-3 is the closest isoform to GLUT-1, and transports glucose with kinetics similar to that of GLUT-1. Thus, we derived a tagged GLUT-3 expression vector. Albeit similar overexpression levels of GLUT-1 and GLUT-3 in 293T cells, GLUT-3 did not induce any increase in H1_{RBD} binding (fig 4c), suggesting that increase H1_{RBD} binding in cells overexpressing GLUT-1 is not an indirect consequence of increased glucose uptake. To determine if GLUT-1 transfected cells were directly responsible for the observed increased in H1_{RBD} binding, we derived fluorescent tagged GLUT-1 and GLUT-3 to uniquely identify GLUT-overexpressing cells in the

course of our FACS analysis. In this context, only cells overexpressing GLUT-1-DsRed2 displayed an significant increase in H1_{RBD} binding, while overexpressing GLUT-3-DsRed2 had no effect on H1_{RBD} binding (fig4d). Consequently, we tested if HTLV glycoproteins directly interacts with GLUT-1 proteins. To this end, we evaluated the ability of H1_{RBD} to 5 immunoprecipitate GLUT-1. As shown on fig 4e, GLUT-1 could be readily detected upon immunoprecipitation with anti-rabbit-Fc-beads when it was co-expressed with H1_{RBD}, but could not be detected when expressed alone or with the H1_{RBD} Y114A mutant. Moreover, a GFP-tagged HTLV-2 RBD colocalized with GLUT-1 but not with Pit2 as assessed by fluorescence microscopy. Therefore, the GLUT-1 glucose transporter is an essential 10 component of the HTLV envelope receptor.

Interaction of GLUT-1 with its ligand cytochalasin B inhibits glucose transport [Kasahara, 1977]. Since we showed that binding of HTLV envelopes to GLUT-1 inhibits glucose consumption and uptake, we tested whether cytochalasin B would abrogate HTLV RBD binding. Indeed, cytochalasin B treatment of Jurkat T cells dramatically inhibited 15 binding of H1_{RBD}, whereas binding of A_{RBD} was not affected (fig 5a). Thus, GLUT-1 directed glucose transport as well as binding of HTLV envelopes to GLUT-1 are similarly inhibited by the cytochalasin B ligand. Altogether, these data demonstrate that GLUT-1 is a receptor for HTLV envelopes.

Viral receptor permits entry and thus infection. No cellular system currently exists that 20 lacks GLUT-1 expression. Thus, we developed a system in which HTLV infection is specifically inhibited at the level of envelope-receptor interaction. In this system, over-expression of HTLV-2 RBD interferes with infecting incoming HTLV particles and specifically decreases HTLV titers by at least 2 logs, while no effect is detected on control A-MLV titers. To determine if GLUT-1 is an entry receptor for HTLV, we overexpressed 25 GLUT-1, GLUT-3 or Pit2 in addition to the interfering H2_{RBD}. While Pit2 and GLUT-3 had no effect on HTLV titers, GLUT-1 completely alleviated the interference to infection induced by H2_{RBD} (fig 5b). Interestingly, both GLUT-1 and GLUT-3, but not Pit2, alleviated the alteration of glucose metabolism induced by the HTLV RBD. Thus, GLUT-1 is an entry receptor for HTLV.

30

Discussion

Here we show that HTLV-1 and -2 envelopes interact with GLUT-1 through their receptor binding domains. This interaction strongly inhibits glucose consumption and glucose uptake, leading to decreased lactate production and a block in extracellular milieu

acidification. Mutations that specifically altered receptor binding of both HTLV-1 and 2 envelopes released the block in glucose consumption, indicative of a direct correlation between receptor binding determinants in the HTLV envelopes and glucose transport. Glucose starvation was rapidly followed by increased binding of HTLV envelopes, 5 highlighting a nutrient-sensing negative feedback loop between glucose availability and cell surface HTLV receptor expression. Further evidence converged to identify GLUT-1 as the receptor, including increased binding of HTLV RBD upon overexpression of GLUT-1 but not GLUT-3, immunoprecipitation of GLUT-1 by H1_{RBD} but not the receptor-binding mutant H1_{RBD} Y114A, uppermost binding of HTLV RBD on human erythrocytes, where GLUT-1 is 10 the major glucose transporter isoform, and no binding of HTLV RBD on human primary hepatocytes and murine erythrocytes, where GLUT-1 is minimally expressed. Finally, GLUT-1 could specifically alleviate interference to infection induced by HTLV RBD. GLUT-1 fits all other known properties of the HTLV receptor. Indeed, as previously demonstrated for the HTLV receptor [Manel, 2003], GLUT-1, but not the GLUT 2-4 isoforms, is not expressed on 15 resting T lymphocytes [Chakrabarti, 1994; Korgun, 2002] and is induced upon immunological [Frauwirth, 2002; Yu, 2003] or pharmacological [Chakrabarti, 1994] activation. Moreover, GLUT-1 orthologues are highly conserved among vertebrates, but are highly divergent between vertebrates and insects [Escher, 1999].

GLUT-1 is thus a new member of the multimembrane spanning metabolite transporters 20 that serve as receptors for retroviral envelopes. Interestingly, until now, all envelopes that recognize these receptors have been encoded by retroviruses that have a so-called simple genetic organization, such as MLV, feline leukemia viruses, porcine endogenous retrovirus and the gibbon ape leukemia virus [Overbaugh, 2001], whereas HTLV belongs to the so-called complex retroviruses which code for several additional regulatory proteins. However, 25 we have shown that in contrast to the wide phylogenetic divergence of their genomic RNA, the envelopes of HTLV and MLV share a similar modular organization with some highly conserved amino acid motifs in their respective receptor binding domains [Kim, 2000].

Cell-to-cell contact appears to be required for HTLV transmission, and the cytoskeleton 30 appears to play a major role in this process [Igakura, 2003]. Indeed, we observed that the HTLV receptor, despite pancellular expression, is specifically concentrated to mobile membrane regions and cell-to-cell contact areas. It should therefore be expected that the HTLV envelope receptor is associated to the cytoskeleton. Importantly, a cytoplasmic-binding partner of GLUT-1, GLUT1CBP, which encodes a PDZ domain, has been reported to link GLUT-1 to the cytoskeleton [Bunn, 1999]. It will therefore be interesting to evaluate the

respective roles of the HTLV envelope, its cytoskeleton-associated cellular partners, such as GLUT-1, GLUT1CBP and their immediate interacting cell components.

Because expression of the HTLV receptor is induced upon glucose starvation, transmission of HTLV may be more efficient in cells that are locally starved for glucose, such 5 as lymphocytes in lymph nodes [Yu, 2003]. Furthermore, the ability of circulating erythrocytes to dock HTLV, as shown here, might provide a means to distribute HTLV to such tissues.

The identification of GLUT-1 as a receptor for HTLV envelopes provides additional 10 clues as to the ubiquitous in vitro expression of the receptor on cell lines and the paradoxical restriction of HTLV tropism to T lymphocytes in vivo. Rapid and dramatic metabolic alterations associated with the blockade of glucose consumption are likely to take place upon expression of the HTLV envelope in vivo, early after infection. Therefore, we propose that in vivo, HTLV infection initially spreads with a large tropism, however early after infection the vast majority of cells that are highly dependent on GLUT-1 activity are rapidly eliminated. In 15 contrast, resting T lymphocytes that have an extremely low metabolic rate and as such are much less dependent on glucose uptake, can tolerate this effect and are therefore maintained in vivo. Furthermore, local imbalances in the access to glucose following HTLV infection may lead to specific physiological alterations [Akaoka, 2001]. In this regard, it will be of interest to study the potential relationship between HTLV-associated neuropathologies and 20 the specific dependence of neurons on GLUT-1 mediated glucose consumption [Siegel, 1998].

Methods.

Cell culture. 293T human embryonic kidney and HeLa cervical carcinoma cells were 25 grown in Dulbecco's modified Eagle medium (DMEM) with high glucose (4.5 g/l) and Jurkat T-cells were grown in RPMI supplemented with 10% fetal bovine serum (FBS) at 37°C in a 5% CO₂-95% air atmosphere. For glucose starvation experiments, cells were grown in either glucose-free DMEM (Life Technologies) or glucose-free RPMI - (Dutscher) with 10% dialyzed FBS (Life Technologies) and glucose (1g/l) was supplemented when indicated.

Expression vectors. Full length envelope expression vectors for HTLV-1 (pCEL/2[Denesvre, 1995]) and Friend ecotropic MLV (pCEL/F [Denesvre, 1995]), have been 30 previously described. For the HTLV-2 envelope, a fragment from pHTE2 [Rosenberg, 1998] encompassing the *tax*, *rex* and *env* genes and the 3' LTR was inserted in the pCSI [Battini, 1999] vector (pCSIX.H2). Full length envelope expression vectors for amphotropic MLV

(pCSI.A), or devoid of its R peptide (pCSI.AΔR), and H₁₈₃FEnv that contains the N-terminal 183 amino acids of the HTLV-1 receptor-binding domain in the F-MLV envelope background, as well as truncated envelope expression vectors, derived from pCSI and encoding either of the first 215 residues of HTLV-1 SU (H1_{RBD}), the first 178 residues of 5 HTLV2-SU (H2_{RBD}) or the first 397 residues of the amphotropic murine leukemia virus (MLV) SU (A_{RBD}), fused to a C-terminal rabbit IgG Fc tag (rFc) or to EGFP (H2_{RBD}-GFP). All point mutations introduced in HTLV-1 and -2 RBD constructs were generated using the quickchange site-directed mutagenesis method and mutations were verified by sequencing. Human *Glut-1* and *Glut-3* cDNA were amplified by PCR from the pLib HeLa cDNA library 10 (Clontech), and inserted into pCHIX, a modified version of the pCSI vector that contains a cassette comprising a factor Xa cleavage site, two copies of the hemagglutinin (HA) tag, and a histidine tag. The resulting construct (pCHIX.hGLUT1) encodes a GLUT-1 protein with a HA-His tag at the C-terminal end. GLUT-1 and GLUT-3 were also inserted in a modified 15 pCSI vector containing a DsRed2 C-terminal tag. Similarly, human CD147 was amplified from 293T total RNA by RT-PCR and inserted into the pCHIX backbone in frame with the HA-His tag (pCHIX.hCD147).

Envelope expression and metabolic measurements. 293T cells were transfected with the various envelope expression vectors using a modified version of the calcium phosphate method. After an overnight transfection, cells were washed in phosphate-buffered saline 20 (PBS) and fresh medium was added. Media were harvested at the indicated time points, filtered through a 0.45-μm pore-size filter, and lactate and glucose were measured with enzymatic diagnostic kits (Sigma). Values were normalized to cellular protein content using the Bradford assay (Sigma) after solubilization of cells in lysis buffer (50 mM Tris-HCl pH 8.0, 150 mM NaCl, 0.1% sodium dodecyl sulfate, 1.0% Nonidet P-40, 0.5% deoxycholate) 25 and clarification by centrifugation.

Assay of hexose uptake. 2-deoxy-D[1-³H]glucose, D[U-¹⁴C]fructose and 3-O-[¹⁴C]methyl-D-glucose were obtained from Amersham. Hexose uptake assay were adapted from Harrison et al (REF HARRISON 1991). After transfection, approximatively 250,000 30 were seeded/well in 24-well plates. The next day, cells were washed two times in PBS, incubated in serum-free DMEM, washed one time in serum-free glucose-free DMEM, and incubated for 20' in 500 μl serum-free glucose-free DMEM modulo inhibitors (20 μM cytochalasin B, 300 μM phloretin; SIGMA). Uptake was initiated by adding labeled hexoses to a final concentration of 0,1 mM (2 μCi/ml for 2-2-deoxy-D[1-³H]glucose and 0,2 μCi/ml for D[U-¹⁴C]fructose and 3-O-[¹⁴C]methyl-D-glucose) and cells were incubated for 5'

additional minutes. Cells were then resuspended in 500 μ l cold serum-free glucose-free DMEM, wash one time in serum-free glucose-free DMEM, and solubilized in 400 μ l of 0,1% SDS. 3 μ l was used for Bradford normalization, while the rest was used for detection of either 3 H or 14 C by liquid scintillation in a Beckman counter.

5 **Western blots.** Culture media (10 μ l) from 293T cells expressing wild type or mutant HTLV-1 RBDs, and/or GLUT-1 or GLUT-3 expression vecotor. were subjected to electrophoresis on SDS-15% acrylamide gels, transferred onto nitrocellulose (Protran; Schleicher & Schuell), blocked in PBS containing 5% powdered milk and 0.5% Tween 20, probed with either a 1:5000 dilution of horseradish peroxidase-conjugated anti-rabbit 10 immunoglobulin or 1:2000 dilution of anti-HA 12CA5 (Roche) monoclonal antibody followed by a 1:5000 dilution of horseradish peroxidase-conjugated anti-mouse immunoglobulin, and visualized using an enhanced chemiluminescence kit (Amersham).

15 **Binding assays.** Binding assays were carried out as previously described [Manel, 2003]. Briefly, 5×10^5 cells (293T, HeLa, Jurkat or freshly isolated human erythrocytes) were incubated with 500 μ l of H1_{RBD}, H2_{RBD} or A_{RBD} supernatants for 30 min at 37°C, washed with PBA (1% BSA, 0.1% sodium azide in PBS), and incubated with a sheep anti-rabbit IgG antibody conjugated to fluorescein isothiocyanate (Sigma). When indicated, cytochalasin B (20 μ M; Sigma) was added to cells for 1 hour prior to binding analyses. Binding was analyzed on a FACSCalibur (Becton Dickinson) and data analysis was performed using CellQuest 20 (Becton Dickinson) and WinMDI (Scripps) softwares.

25 **Infections.** 293T cells were transfected in 6-wells plate, and one day after transfection, medium was replaced by high glucose DMEM supplemented with fructose (5 g/l) and non-essential amino acids. The next day, infection was initiated by adding supernatants containing MLV particles pseuodtyped with either HTLV-2 or A-MLV envelopes. The following day, fresh medim was added, and 24 hours later cells were fixed and stained for alkaline phosphatase activity and dark focus of infection were counted. Viral particles were obtained by transfecting 293T cells with pLAPSN, pGagPoule and either pCSIX.H2 or pCSI.A, and harvesting the 0.45 μ m-filtered supernatants 24 hours latter.

FIGURE LEGENDS

Figure 1 Expression of the HTLV receptor-binding domain alters cellular metabolism.

a, Medium acidification and syncytia formation in 293T cells one day post-transfection with control DNA or Env expression vectors, including syncytial wild-type HTLV-1 Env and HTLV-2 Env, a non-syncytial chimeric H₁₈₃FEnv, and syncytial A-MLV ΔR Env. b, Extracellular lactate and glucose in the culture medium of 293T cells were measured two days following transfection with an irrelevant DNA (control), F-MLV Env, H₁₈₃FEnv, HTLV-1 RBD (H₁RBD) or amphotropic MLV RBD (A_{RBD}) expression vectors. Lactate and glucose concentrations were normalized to cellular protein content. c, 2-deoxyglucose and fructose uptake following transfection of 293T with an irrelevant DNA (control), H₁RBD, H₂RBD or A_{RBD} expression vectors. Control cells were also incubated with glucose transporter inhibitors cytochalasin and phloretin. Data are the means of triplicate measures and are representative of two to three independent experiments. d, Expression of the HTLV and amphotropic-MLV receptors on 293T (1) and Jurkat T (2) cells cultured overnight in the presence or absence of glucose was monitored by binding of H₁RBD and A_{RBD}, respectively.

Figure 2 HTLV receptor properties correlates with GLUT1 properties. a, Expression

of the HTLV and amphotropic-MLV receptors at the surface of human and murine 20 erythrocytes, as well as human primary hepatocytes. b, H₁RBD and A_{RBD} binding to Jurkat cells in the absence or presence of the Glut-1 inhibitor cytochalasin B.

Figure 3 HTLV receptor-binding correlates with altered lactate metabolism. a,

Expression of H₁RBD and the derived mutants D106A and Y114A was monitored by Western 25 blot analysis of the supernatants of 293T cells following transfection with the various expression plasmids. b, Binding of H₁RBD and the D106A and Y114A mutants to the HTLV receptor on HeLa cells. c, Extracellular lactate in the medium of 293T cells one day post transfection with an irrelevant DNA (control), H₁RBD or the H₁RBD D106A and Y114A mutants. Data are representative of three independent experiments.

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Figure 4 GLUT-1 is a receptor for HTLV envelopes. a, Binding of H₁RBD, H₂RBD,

H₂RBD D102A mutant, and A_{RBD} to control 293T cells or 293T cells overexpressing either GLUT-1 or PiT2. b, Binding of H₂RBD-EGFP to cells overexpressing GLUT-1-HA or GLUT-

3-HA, and corresponding immuoblots using an anti-HA antibody. **c**, Immunoprecipitation of GLUT-1-HA from 293T cells transfected with either an irrelevant construct, GLUT-1 alone, H1RBD alone, H1RBD Y114A alone, GLUT-1 with H1_{RBD} or GLUT-1 with H1_{RBD} Y114A expression vectors. Immunoprecipitation was performed using anti-rabbit-Fc beads and probed with an anti-HA antibody. Total cell extracts were blotted using an anti-rabbit Fc or an anti-HA antibody.

Figure 5 GLUT-1 is an entry receptor for HTLV. Infection titer of MLV particles pseudotypes with HTLV-2 or A-MLV envelopes on 293T cells following transfection of an irrelevant or interfering H2_{RBD} expression vectors alone or in addition to GLUT-1, GLUT-3 or Pit2 expression vectors.

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CLAIMS

1. Use of polypeptides corresponding to the envelope proteins of PTLV, or fragments or
5 sequences derived thereof, said polypeptides being selected for their ability to bind specifically to the ubiquitous vertebrate glucose transporter GLUT1 represented by SEQ ID NO : 2, or of nucleotide sequences encoding said polypeptides, for the preparation of drugs for the prevention or the treatment of pathologies linked to an overexpression of GLUT1 on cell surfaces, and the *in vitro* diagnosis of said pathologies.

10

2. Use according to claim 1, of polypeptides able to bind to at least one of the following fragments of GLUT1 :

- SEQ ID NO : 25 :	NAPQKVIEEFY
- SEQ ID NO : 26 :	NQTWVHRYGESILPTTLTTLWS
- SEQ ID NO : 27 :	KSFEMILILGR
- SEQ ID NO : 28 :	DSIMGNKDL
- SEQ ID NO : 29 :	YSTSIFEKAGVQQP
- SEQ ID NO : 30 :	EQLPWMSYLS
- SEQ ID NO : 31 :	QYVEQLC
20 - SEQ ID NO : 32 :	IVGMCFQYVEQLC

3. Use according to claim 1 or 2, of polypeptides able to bind to at least the following fragment of GLUT1 :

- SEQ ID NO : 32 : IVGMCFQYVEQLC

25

4. Use according to any of claims 1 to 3, of GLUT1 binding polypeptides chosen among the followings :

- the envelope protein of HTLV-1 corresponding to SEQ ID NO : 4, or of HTLV-2 corresponding to SEQ ID NO : 6, or of STLV-1 corresponding to SEQ ID NO : 8, or of
30 STLV-2 corresponding to SEQ ID NO : 10, or of STLV-3 corresponding to SEQ ID NO : 12,
- fragments of the envelope proteins of PTLV, said fragments corresponding to polypeptides delimited in their N-terminal extremity by the amino acid located in position 1 to 90, or in position 75 to 90, and in their C-terminal extremity by the amino acid located in

position 135 to 245, or in position 135 to 150, of said envelope proteins of PTLV, such as SEQ ID NO : 4, 6, 8, 10, 12,

- fragments of the envelope proteins of PTLV, said fragments corresponding to the following polypeptides :

5 * the polypeptide delimited in its N-terminal extremity by the amino acid located in position 83 to 89, and in its C-terminal extremity by the amino acid located in position 139 to 145, of the envelope protein of the strain MT-2 of HTLV-1 corresponding to SEQ ID NO : 4,

10 * the polypeptide delimited in its N-terminal extremity by the amino acid located in position 79 to 85, and in its C-terminal extremity by the amino acid located in position 135 to 141, of the envelope protein of the strain NRA of HTLV-2 corresponding to SEQ ID NO : 6,

* the polypeptide delimited in its N-terminal extremity by the amino acid located in position 83 to 89, and in its C-terminal extremity by the amino acid located in position 139 to 145, of the envelope protein of STLV-1 corresponding to SEQ ID NO : 8,

15 * the polypeptide delimited in its N-terminal extremity by the amino acid located in position 79 to 85, and in its C-terminal extremity by the amino acid located in position 135 to 141, of the envelope protein of STLV-2 corresponding to SEQ ID NO : 10,

* the polypeptide delimited in its N-terminal extremity by the amino acid located in position 82 to 88, and in its C-terminal extremity by the amino acid located in position 138 to 144, of the envelope protein of STLV-3 corresponding to SEQ ID NO : 12,

20 * the polypeptide corresponding to the envelope protein of a variant of HTLV-1, said polypeptide having the following sequence SEQ ID NO : 14,

I	K	K	P	N	P	N	G	G	G	Y	Y	L	A	S	Y	S	D
P	C	S	L	K	C	P	Y	L	G	C	Q	S	W	T	C	P	Y
T	G	A	V	S	S	P	Y	W	K	F	Q	Q	D	V			

25 * the polypeptide corresponding to the envelope protein of a variant of HTLV-1, said polypeptide having the following sequence SEQ ID NO : 16,

V	K	K	P	N	R	N	G	G	G	Y	Y	L	A	S	Y	S	D
P	C	S	L	K	C	P	Y	L	G	C	Q	S	W	T	C	P	Y
T	G	A	V	S	S	P	Y	W	K	F	Q	Q	D	V			

30 * the polypeptide corresponding to the envelope protein of a variant of HTLV-1, said polypeptide having the following sequence SEQ ID NO : 18,

I	K	K	P	N	R	N	G	G	G	Y	Y	L	A	S	Y	S	D
P	C	S	L	K	C	P	Y	L	G	C	Q	S	W	T	C	P	Y
T	G	A	V	S	S	P	Y	W	K	F	Q	Q	D	V			

* the polypeptide corresponding to the envelope protein of a variant of HTLV-1, said polypeptide having the following sequence SEQ ID NO : 20,

5 I K K P N R N G G Y Y L A S Y S D
 P C S L K C P Y L G C Q S W T C P Y
 T G P V S S P Y W K F Q Q D V

* the polypeptide corresponding to the envelope protein of a variant of HTLV-1, said polypeptide having the following sequence SEQ ID NO : 22,

10 I K K P N R N G G Y H S A S Y S D
 C S L K C P Y L G C Q S W T C P Y A
 A V S S P Y W K F Q Q D V N F T Q E

* the polypeptide corresponding to the envelope protein of a variant of HTLV-2, said polypeptide having the following sequence SEQ ID NO : 24,

15 I R K P N R Q G L G Y Y S P S Y N D
 P C S L Q C P Y L G S Q S W T C P Y
 T A P V S T P S W N F H S D V

5. Use of GLUT1 binding polypeptides according to any of claims 1 to 4, characterized in that the pathologies are the followings :

20 - solid tumors, such as brain tumors, squamous cell carcinoma, hypopharyngeal carcinoma, breast cancer, cervical carcinoma, ovarian carcinoma, pancreatic cancer, insulinoma,

25 - inflammatory conditions, such as multiple sclerosis, rheumatoid arthritis,
 - immune or auto-immune diseases, such as autoimmune myocarditis, or in the frame of CD28 T-cell activation, or in the frame of immunomodulation, or systemic lupus erythematosus,

- disorders of the central nervous system, such as facilitated glucose transporter protein type 1 (GLUT1) deficiency syndrome.

6. Use according to any of claims 1 to 5, of GLUT1 binding polypeptides for the *in vitro* detection of GLUT1 on cell surfaces in the frame of processes for the *in vitro* diagnosis of pathologies linked to an overexpression of GLUT1 on cell surfaces, such as pathologies defined in claim 5, said processes comprising the following steps :

30 - contacting a biological sample from an individual with a GLUT1 binding polypeptide, said GLUT1 binding polypeptide being optionally labeled, or susceptible to be recognized by a labeled molecule,

- determining the level of said GLUT1 binding polypeptide bound to the cells contained in the biological sample and comparison with the level of binding of said GLUT1 binding polypeptide to cells contained in the biological sample from an healthy individual.

5 7. Use according to any of claims 1 to 5, of GLUT1 binding polypeptides, or of nucleotide sequences encoding said polypeptides, for the preparation of drug vectors containing at their surface said polypeptides, said vectors being useful for targeting GLUT1 overexpressing cells for the prevention or the treatment of pathologies linked to an overexpression of GLUT1 on cell surfaces, said vectors containing molecules active against
10. said pathologies, or containing genes in the frame of gene therapy of these pathologies.

15 8. Use according to claim 7, for the preparation of drug vectors containing at their surface GLUT1 binding polypeptides, said vectors being useful for targeting GLUT1 overexpressing tumor cells, or cells involved in the inflammatory mechanism, or activated cells of the immune system, or cells of the central nervous system, for the prevention or the treatment of pathologies defined in claim 5.

20 9. Use according to claim 7 or 8, wherein the molecules active against the pathologies are antitumor molecules, or molecules against inflammatory conditions, immune or autoimmune diseases, or disorders of the central nervous system.

25 10. Therapeutic vectors useful for targeting GLUT1 overexpressing cells in pathologies linked to an overexpression of GLUT1 on cell surfaces, such as pathologies defined in claim 5, said vectors containing at their surface GLUT1 binding polypeptides chosen among those defined in claims 1 to 4, and containing molecules active against said pathologies, as defined in claim 9, or containing genes in the frame of gene therapy.

30 11. Pharmaceutical compositions containing therapeutic vectors according to claim 10, in association with a pharmaceutically acceptable carrier.

12. Method for the screening of compounds useful for the prevention or the treatment of pathologies linked to an overexpression of GLUT1 on cell surfaces, and the *in vitro* diagnosis of said pathologies, comprising :

- the contacting of GLUT1 represented by SEQ ID NO : 2, or of fragments as defined in claim 2, or sequences derived thereof, said fragments or derived sequences being able to bind to the envelope proteins of the primate T-cell leukemia viruses (PTLV), or of cells expressing GLUT1, with compounds to be tested,

5 - the selection of compounds able to bind specifically to GLUT1, or fragments or sequences derived thereof.

13. Method for the *in vitro* diagnosis of pathologies linked to an overexpression of GLUT1 on cell surfaces, characterized in that it comprises :

10 - contacting a biological sample from an individual with polypeptides selected for their ability to bind specifically to GLUT1 as defined in claims 1 to 4, said polypeptides being optionally labeled, or susceptible to be recognized by a labeled molecule,

15 - determining the level of said polypeptides bound to the cells contained in the biological sample and comparison with the level of binding of said polypeptides to cells contained in the biological sample from an healthy individual.

14. Method according to claim 13 for the *in vitro* diagnosis of pathologies defined in claim 5.

20 **15.** Kit for the *in vitro* diagnosis of pathologies linked to an overexpression of GLUT1 on cell surfaces according to the method of claim 13 or 14, comprising GLUT1 binding polypeptides as defined in claims 1 to 4, said polypeptides being optionally labeled, and, if necessary reagents for the detection of the binding of said polypeptides to GLUT1 initially present on cell surfaces in the biological sample.

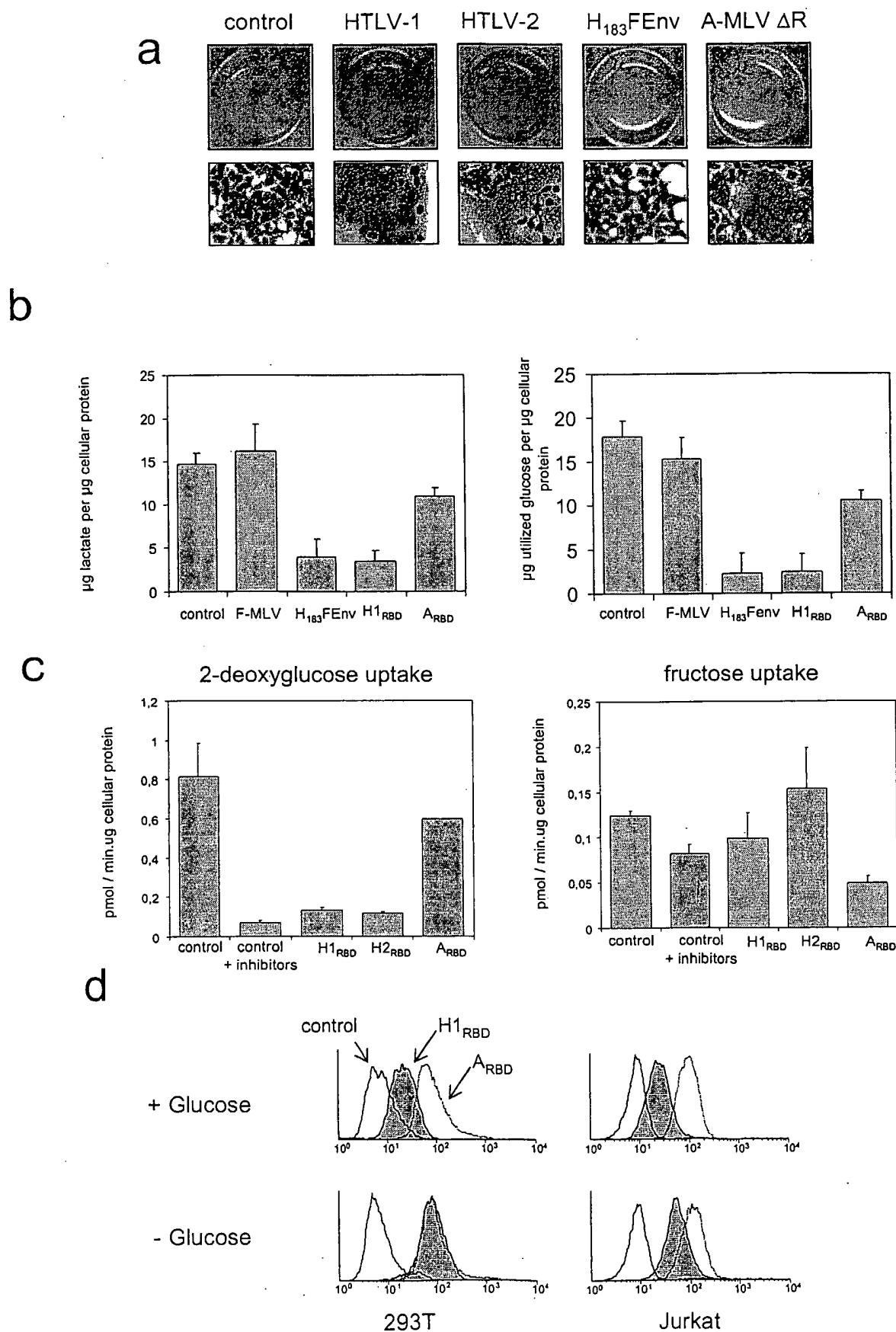


Figure 1

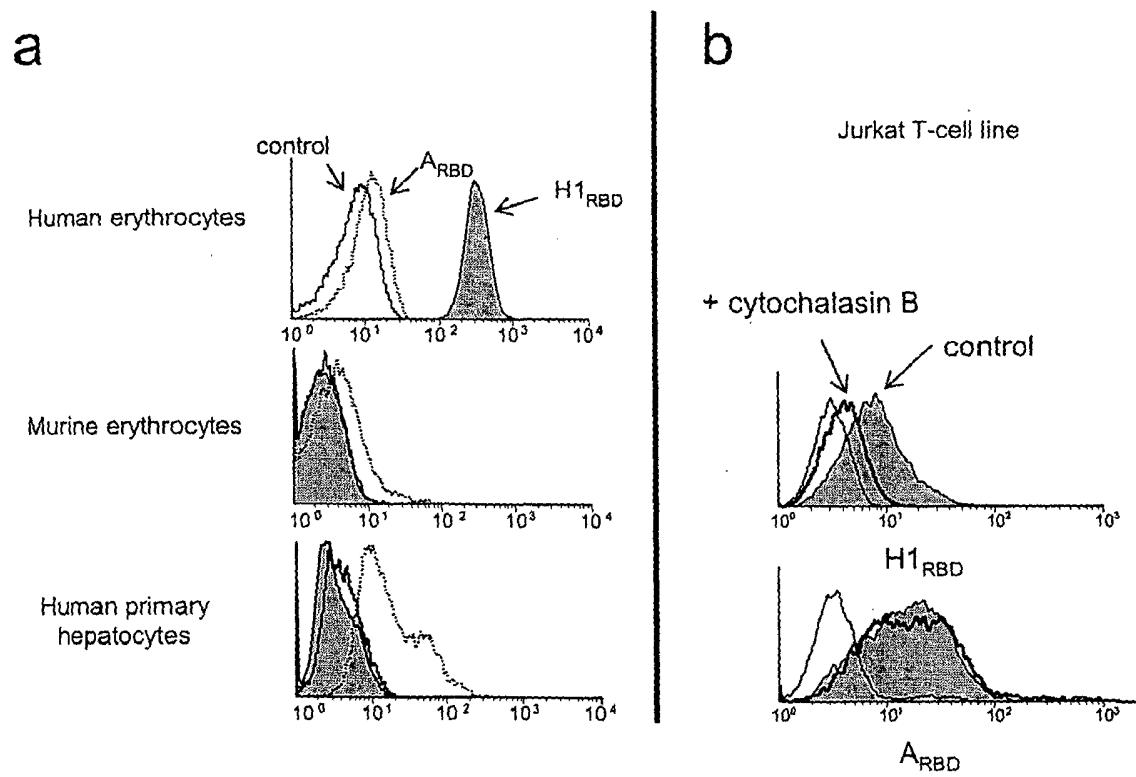


Figure 2

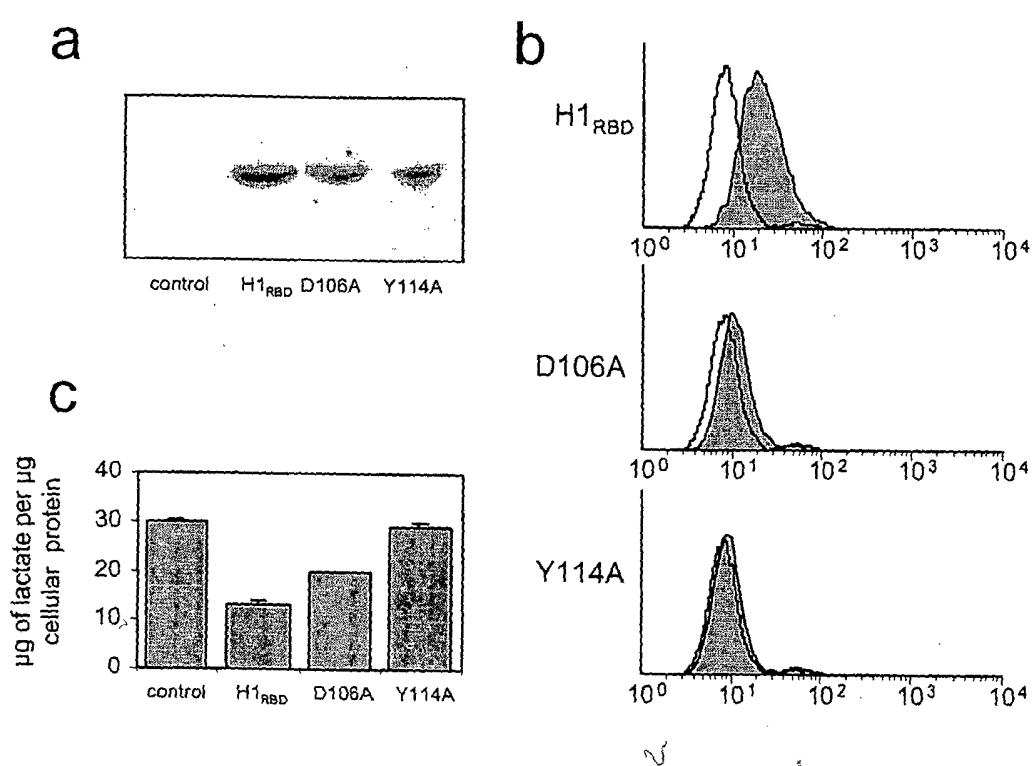


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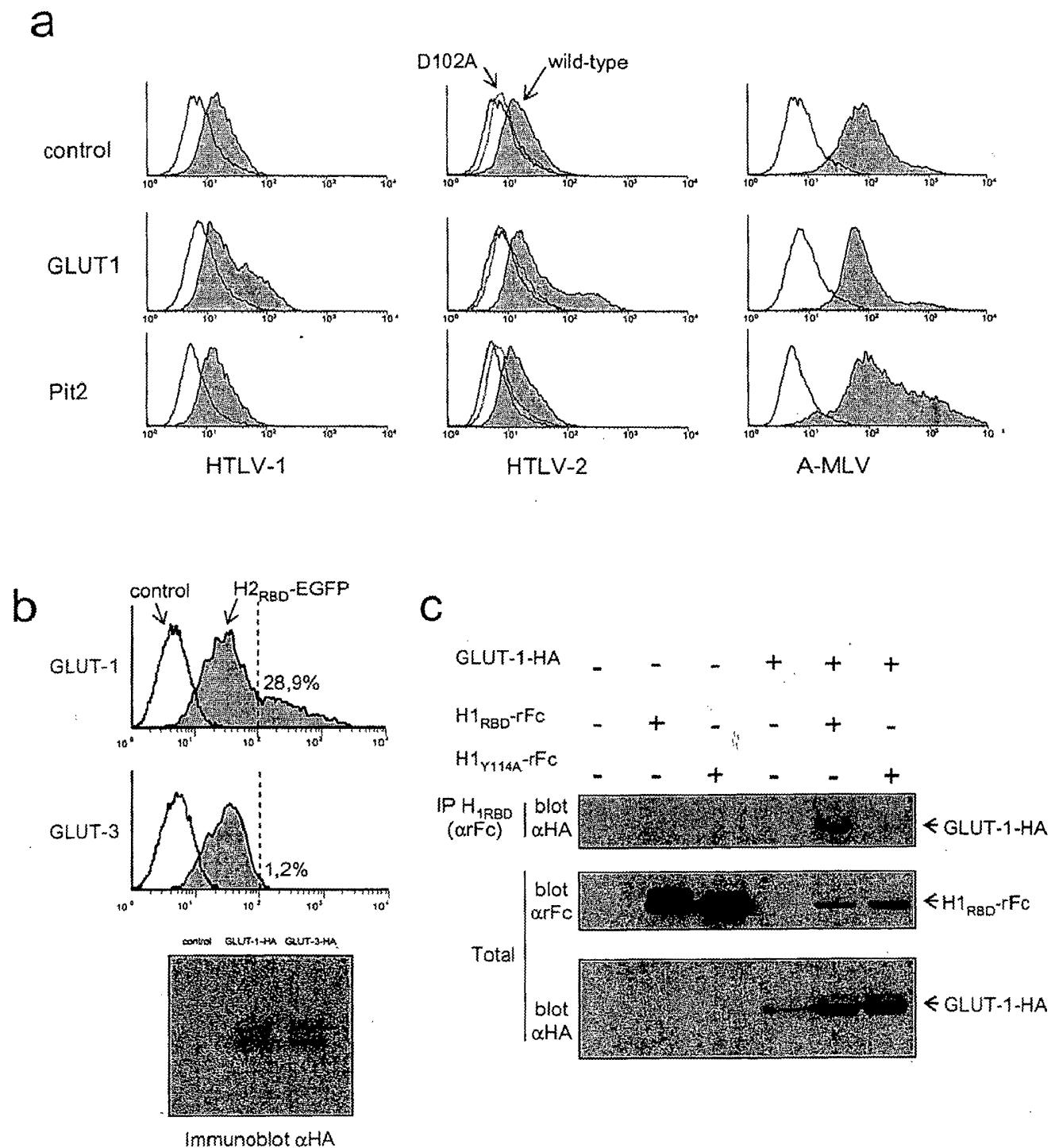


Figure 4

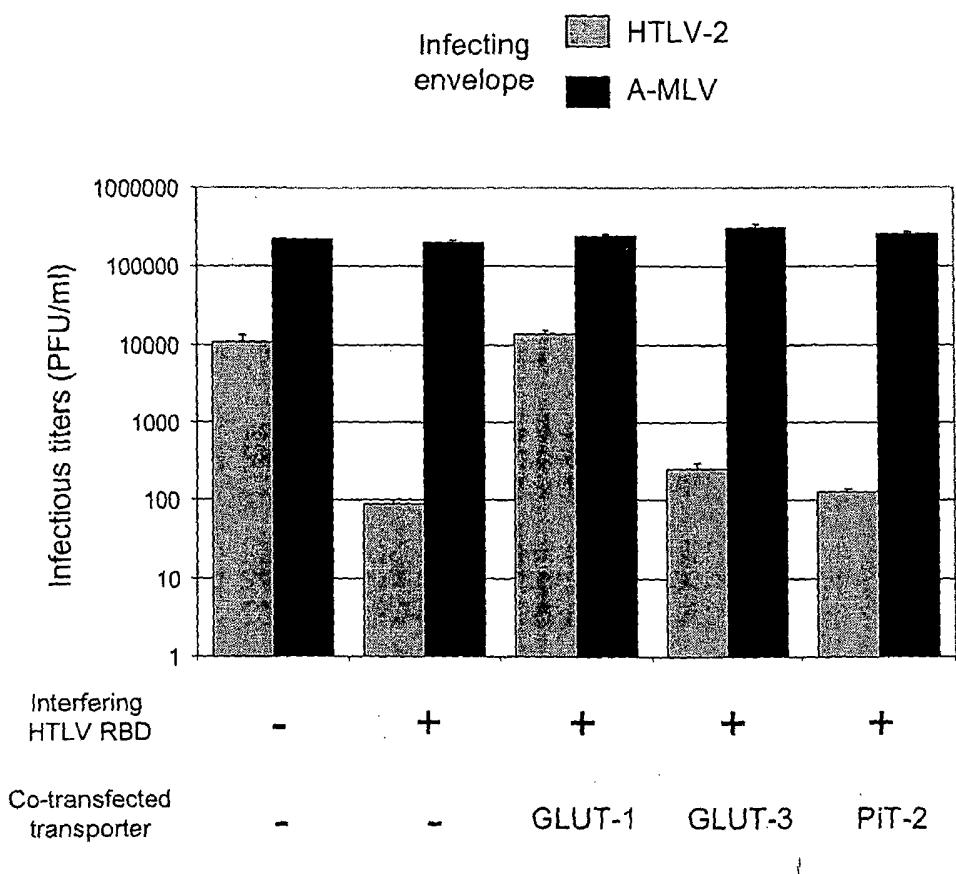


Figure 5

SEQUENCE LISTING

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Trp Ser Leu Ser Val Ala Ile Phe Ser Val Gly Gly Met Ile Gly Ser	
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Phe Ser Val Gly Leu Phe Val Asn Arg Phe Gly Arg Arg Asn Ser Met	
85 90 95	

Leu Met Met Asn Leu Leu Ala Phe Val Ser Ala Val Leu Met Gly Phe
100 105 110

Ser Lys Leu Gly Lys Ser Phe Glu Met Leu Ile Leu Gly Arg Phe Ile
115 120 125

Ile Gly Val Tyr Cys Gly Leu Thr Thr Gly Phe Val Pro Met Tyr Val
130 135 140

Gly Glu Val Ser Pro Thr Ala Phe Arg Gly Ala Leu Gly Thr Leu His
145 150 155 160

Gln Leu Gly Ile Val Val Gly Ile Leu Ile Ala Gln Val Phe Gly Leu
165 170 175

Asp Ser Ile Met Gly Asn Lys Asp Leu Trp Pro Leu Leu Leu Ser Ile
180 185 190

Ile Phe Ile Pro Ala Leu Leu Gln Cys Ile Val Leu Pro Phe Cys Pro
195 200 205

Glu Ser Pro Arg Phe Leu Leu Ile Asn Arg Asn Glu Glu Asn Arg Ala
210 215 220

Lys Ser Val Leu Lys Lys Leu Arg Gly Thr Ala Asp Val Thr His Asp
225 230 235 240

Leu Gln Glu Met Lys Glu Glu Ser Arg Gln Met Met Arg Glu Lys Lys
245 250 255

Val Thr Ile Leu Glu Leu Phe Arg Ser Pro Ala Tyr Arg Gln Pro Ile
260 265 270

Leu Ile Ala Val Val Leu Gln Leu Ser Gln Gln Leu Ser Gly Ile Asn
275 280 285

Ala Val Phe Tyr Tyr Ser Thr Ser Ile Phe Glu Lys Ala Gly Val Gln
290 295 300

Gln Pro Val Tyr Ala Thr Ile Gly Ser Gly Ile Val Asn Thr Ala Phe
305 310 315 320

Thr Val Val Ser Leu Phe Val Val Glu Arg Ala Gly Arg Arg Thr Leu
325 330 335

His Leu Ile Gly Leu Ala Gly Met Ala Gly Cys Ala Ile Leu Met Thr
340 345 350

Ile Ala Leu Ala Leu Leu Glu Gln Leu Pro Trp Met Ser Tyr Leu Ser
355 360 365

Ile Val Ala Ile Phe Gly Phe Val Ala Phe Phe Glu Val Gly Pro Gly
370 375 380

Pro Ile Pro Trp Phe Ile Val Ala Glu Leu Phe Ser Gln Gly Pro Arg
385 390 395 400

Pro Ala Ala Ile Ala Val Ala Gly Phe Ser Asn Trp Thr Ser Asn Phe
405 410 415

Ile Val Gly Met Cys Phe Gln Tyr Val Glu Gln Leu Cys Gly Pro Tyr
420 425 430

Val Phe Ile Ile Phe Thr Val Leu Leu Val Leu Phe Phe Ile Phe Thr
435 440 445

Tyr Phe Lys Val Pro Glu Thr Lys Gly Arg Thr Phe Asp Glu Ile Ala
450 455 460

Ser Gly Phe Arg Gln Gly Gly Ala Ser Gln Ser Asp Lys Thr Pro Glu
465 470 475 480

Glu Leu Phe His Pro Leu Gly Ala Asp Ser Gln Val
485 490

<210> 3
<211> 924
<212> DNA
<213> Human T-cell lymphotropic virus type 1

<220>
<221> CDS
<222> (1)..(924)
<223>

<400> 3
atg ggt aag ttt ctc gcc act ttg att tta ttc ttc cag ttc tgc ccc 48
Met Gly Lys Phe Leu Ala Thr Leu Ile Leu Phe Phe Gln Phe Cys Pro
1 5 10 15

ctc atc ctc ggt gat tac agc ccc agc tgc tgt act ctc aca att gga 96
Leu Ile Leu Gly Asp Tyr Ser Pro Ser Cys Cys Thr Leu Thr Ile Gly
20 25 30

gtc tcc tca tac cac tct aaa ccc tgc aat cct gcc cag cca gtt tgt	144
Val Ser Ser Tyr His Ser Lys Pro Cys Asn Pro Ala Gln Pro Val Cys	
35 40 45	
tcg tgg acc ctc gac ctg ctg gcc ctt tca gcg gat cag gcc cta cag	192
Ser Trp Thr Leu Asp Leu Leu Ala Ser Ala Asp Gln Ala Leu Gln	
50 55 60	
ccc ccc tgc cct aat cta gta agt tac tcc agc tac cat gcc acc tat	240
Pro Pro Cys Pro Asn Leu Val Ser Tyr Ser Tyr His Ala Thr Tyr	
65 70 75 80	
tcc cta tat cta ttc cct cat tgg att aaa aag cca aac cga aat ggc	288
Ser Leu Tyr Leu Phe Pro His Trp Ile Lys Lys Pro Asn Arg Asn Gly	
85 90 95	
gga ggc tat tat tca gcc tct tat tca gac cct tgt tcc tta aag tgc	336
Gly Gly Tyr Tyr Ser Ala Ser Tyr Ser Asp Pro Cys Ser Leu Lys Cys	
100 105 110	
cca tac ctg ggg tgc caa tca tgg acc tgc ccc tat aca gga gcc gtc	384
Pro Tyr Leu Gly Cys Gln Ser Trp Thr Cys Pro Tyr Thr Gly Ala Val	
115 120 125	
tcc agc ccc tac tgg aag ttt cag caa gat gtc aat ttt act caa gaa	432
Ser Ser Pro Tyr Trp Lys Phe Gln Gln Asp Val Asn Phe Thr Gln Glu	
130 135 140	
gtt tca cgc ctc aat att aat ctc cat ttt tca aaa tgc ggt ttt ccc	480
Val Ser Arg Leu Asn Ile Asn Leu His Phe Ser Lys Cys Gly Phe Pro	
145 150 155 160	
ttc tcc ctt cta gtc gac gct cca gga tat gac ccc atc tgg ttc ctt	528
Phe Ser Leu Leu Val Asp Ala Pro Gly Tyr Asp Pro Ile Trp Phe Leu	
165 170 175	
aat acc gaa ccc agc caa ctg cct ccc acc gcc cct cct cta ctc ccc	576
Asn Thr Glu Pro Ser Gln Leu Pro Pro Thr Ala Pro Pro Leu Leu Pro	
180 185 190	
cac tct aac cta gac cac atc ctc gag ccc tct ata cca tgg aaa tca	624
His Ser Asn Leu Asp His Ile Leu Glu Pro Ser Ile Pro Trp Lys Ser	
195 200 205	
aaa ctc ctg acc ctt gtc cag tta acc cta caa agc act aat tat act	672
Lys Leu Leu Thr Leu Val Gln Leu Thr Leu Gln Ser Thr Asn Tyr Thr	
210 215 220	
tgc att gtc tgt atc gat cgt gcc agc cta tcc act tgg cac gtc cta	720
Cys Ile Val Cys Ile Asp Arg Ala Ser Leu Ser Thr Trp His Val Leu	
225 230 235 240	
tac tct ccc aac gtc tct gtt cca tcc tct tct acc ccc ctc ctt	768
Tyr Ser Pro Asn Val Ser Val Pro Ser Ser Ser Thr Pro Leu Leu	
245 250 255	
tac cca tcg tta gcg ctt cca gcc ccc cac ctg acg tta cca ttt aac	816
Tyr Pro Ser Leu Ala Leu Pro Ala Pro His Leu Thr Leu Pro Phe Asn	
260 265 270	

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tgg acc cac tgc ttt gac ccc cag att caa gct ata gtc tcc tcc ccc 864
Trp Thr His Cys Phe Asp Pro Gln Ile Gln Ala Ile Val Ser Ser Pro
275 280 285

tgt cat aac tcc ctc atc ctg ccc ccc ttt tcc ttg tca cct gtt ccc 912
Cys His Asn Ser Leu Ile Leu Pro Pro Phe Ser Leu Ser Pro Val Pro
290 295 300

acc cta gga tcc 924
Thr Leu Gly Ser
305

<210> 4

<211> 308

<212> PRT

<213> Human T-cell lymphotropic virus type 1

<400> 4

Met Gly Lys Phe Leu Ala Thr Leu Ile Leu Phe Phe Gln Phe Cys Pro 1
1 5 10 15

Leu Ile Leu Gly Asp Tyr Ser Pro Ser Cys Cys Thr Leu Thr Ile Gly 20
25 30

Val Ser Ser Tyr His Ser Lys Pro Cys Asn Pro Ala Gln Pro Val Cys 35
35 40 45

Ser Trp Thr Leu Asp Leu Leu Ala Leu Ser Ala Asp Gln Ala Leu Gln 50
50 55 60

Pro Pro Cys Pro Asn Leu Val Ser Tyr Ser Ser Tyr His Ala Thr Tyr 65
65 70 75 80

Ser Leu Tyr Leu Phe Pro His Trp Ile Lys Lys Pro Asn Arg Asn Gly 85
85 90 95

Gly Gly Tyr Tyr Ser Ala Ser Tyr Ser Asp Pro Cys Ser Leu Lys Cys 100
100 105 110

Pro Tyr Leu Gly Cys Gln Ser Trp Thr Cys Pro Tyr Thr Gly Ala Val 115
115 120 125

Ser Ser Pro Tyr Trp Lys Phe Gln Gln Asp Val Asn Phe Thr Gln Glu 130
130 135 140

Val Ser Arg Leu Asn Ile Asn Leu His Phe Ser Lys Cys Gly Phe Pro 145
145 150 155 160

Phe Ser Leu Leu Val Asp Ala Pro Gly Tyr Asp Pro Ile Trp Phe Leu
165 170 175

Asn Thr Glu Pro Ser Gln Leu Pro Pro Thr Ala Pro Pro Leu Leu Pro
180 185 190

His Ser Asn Leu Asp His Ile Leu Glu Pro Ser Ile Pro Trp Lys Ser
195 200 205

Lys Leu Leu Thr Leu Val Gln Leu Thr Leu Gln Ser Thr Asn Tyr Thr
210 215 220

Cys Ile Val Cys Ile Asp Arg Ala Ser Leu Ser Thr Trp His Val Leu
225 230 235 240

Tyr Ser Pro Asn Val Ser Val Pro Ser Ser Ser Ser Thr Pro Leu Leu
245 250 255

Tyr Pro Ser Leu Ala Leu Pro Ala Pro His Leu Thr Leu Pro Phe Asn
260 265 270

Trp Thr His Cys Phe Asp Pro Gln Ile Gln Ala Ile Val Ser Ser Pro
275 280 285

Cys His Asn Ser Leu Ile Leu Pro Pro Phe Ser Leu Ser Pro Val Pro
290 295 300

Thr Leu Gly Ser
305

<210> 5
<211> 912
<212> DNA
<213> Human T-cell lymphotropic virus type 2

<220>
<221> CDS
<222> (1)..(912)
<223>

<400> 5
atg ggt aac gtt ttc ttc cta ctt tta ttc agt ctc aca cac ttc cca 48
Met Gly Asn Val Phe Phe Leu Leu Leu Phe Ser Leu Thr His Phe Pro
1 5 10 15

cca gtc cag cag agc cga tgc aca ctc acg gtt ggt att tcc tcc tac 96
Pro Val Gln Gln Ser Arg Cys Thr Leu Thr Val Gly Ile Ser Ser Tyr
20 25 30

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cac tcc agc ccc tgt agc cca acc caa ccc gtc tgc acg tgg aac ctc	144
His Ser Ser Pro Cys Ser Pro Thr Gln Pro Val Cys Thr Trp Asn Leu	
35 40 45	
gac ctt aat tcc cta acg acg gac cag cga cta cat ccc ccc tgc cct	192
Asp Leu Asn Ser Leu Thr Thr Asp Gln Arg Leu His Pro Pro Cys Pro	
50 55 60	
aac cta att act tac tct ggc ttc cac aaa act tat tcc tta tac tta	240
Asn Leu Ile Thr Tyr Ser Gly Phe His Lys Thr Tyr Ser Leu Tyr Leu	
65 70 75 80	
ttc cca cat tgg ata aag aag cca aat aga cag ggc cta gga tac tac	288
Phe Pro His Trp Ile Lys Lys Pro Asn Arg Gln Gly Leu Gly Tyr Tyr	
85 90 95	
tcg ccc tcc tat aat gac cct tgc tcg cta caa tgc ccc tac tta ggc	336
Ser Pro Ser Tyr Asn Asp Pro Cys Ser Leu Gln Cys Pro Tyr Leu Gly	
100 105 110	
tgc caa tca tgg aca tgc cca tac acg ggc ccc gtc tcc agt cca tcc	384
Cys Gln Ser Trp Thr Cys Pro Tyr Thr Gly Pro Val Ser Ser Pro Ser	
115 120 125	
tgg aag ttt cac tca gat gta aat ttc acc caa gaa gtc agc caa gtg	432
Trp Lys Phe His Ser Asp Val Asn Phe Thr Gln Glu Val Ser Gln Val	
130 135 140	
tcc ctt cga cta cac ttc tct aag tgc ggc tcc tcc atg acc ctt cta	480
Ser Leu Arg Leu His Phe Ser Lys Cys Gly Ser Ser Met Thr Leu Leu	
145 150 155 160	
gta gat gcc cct gga tat gat cct tta tgg ttc atc acc tca gaa ccc	528
Val Asp Ala Pro Gly Tyr Asp Pro Leu Trp Phe Ile Thr Ser Glu Pro	
165 170 175	
act cag cct ccc cca act cct ccc cca ctg gtc cat gac tcc gac ctt	576
Thr Gln Pro Pro Pro Thr Pro Pro Leu Val His Asp Ser Asp Leu	
180 185 190	
gaa cac gtc cta acc ccc tcc acg tct tgg aca acc aaa atg ctc aag	624
Glu His Val Leu Thr Pro Ser Thr Ser Trp Thr Thr Lys Met Leu Lys	
195 200 205	
ttt atc cag ctg acc ttg cag agc acc aat tac tcc tgc atg gtt tgc	672
Phe Ile Gln Leu Thr Leu Gln Ser Thr Asn Tyr Ser Cys Met Val Cys	
210 215 220	
gtg gat aga tcc agc ctc tca tcc tgg cat gtg ctc tac acc ccc aac	720
Val Asp Arg Ser Ser Leu Ser Ser Trp His Val Leu Tyr Thr Pro Asn	
225 230 235 240	
atc tcc att ccc caa caa acc tcc tcc cga acc atc ctc ttt cct tct	768
Ile Ser Ile Pro Gln Gln Thr Ser Ser Arg Thr Ile Leu Phe Pro Ser	
245 250 255	
ctt gcc ctg ccc gct cct cca ttc caa ccc ttc cct tgg acc cat tgc	816
Leu Ala Leu Pro Ala Pro Pro Phe Gln Pro Phe Pro Trp Thr His Cys	
260 265 270	

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tac caa cct cgc cta cag gca ata acg aca gat gac tgc aac aac tcc 864
Tyr Gln Pro Arg Leu Gln Ala Ile Thr Thr Asp Asp Cys Asn Asn Ser
275 280 285

att atc ctc ccc cct ttt tcc ctc gcc ccc gta cct cct ccg gcg aca 912
Ile Ile Leu Pro Pro Phe Ser Leu Ala Pro Val Pro Pro Pro Ala Thr
290 295 300

<210> 6
<211> 304
<212> PRT
<213> Human T-cell lymphotropic virus type 2

<400> 6

Met Gly Asn Val Phe Phe Leu Leu Phe Ser Leu Thr His Phe Pro
1 5 10 15

Pro Val Gln Gln Ser Arg Cys Thr Leu Thr Val Gly Ile Ser Ser Tyr
20 25 30

His Ser Ser Pro Cys Ser Pro Thr Gln Pro Val Cys Thr Trp Asn Leu
35 40 45

Asp Leu Asn Ser Leu Thr Thr Asp Gln Arg Leu His Pro Pro Cys Pro
50 55 60

Asn Leu Ile Thr Tyr Ser Gly Phe His Lys Thr Tyr Ser Leu Tyr Leu
65 70 75 80

Phe Pro His Trp Ile Lys Lys Pro Asn Arg Gln Gly Leu Gly Tyr Tyr
85 90 95

Ser Pro Ser Tyr Asn Asp Pro Cys Ser Leu Gln Cys Pro Tyr Leu Gly
100 105 110

Cys Gln Ser Trp Thr Cys Pro Tyr Thr Gly Pro Val Ser Ser Pro Ser
115 120 125

Trp Lys Phe His Ser Asp Val Asn Phe Thr Gln Glu Val Ser Gln Val
130 135 140

Ser Leu Arg Leu His Phe Ser Lys Cys Gly Ser Ser Met Thr Leu Leu
145 150 155 160

Val Asp Ala Pro Gly Tyr Asp Pro Leu Trp Phe Ile Thr Ser Glu Pro
165 170 175

Thr Gln Pro Pro Pro Thr Pro Pro Pro Leu Val His Asp Ser Asp Leu
 180 185 190

Glu His Val Leu Thr Pro Ser Thr Ser Trp Thr Thr Lys Met Leu Lys
 195 200 205

Phe Ile Gln Leu Thr Leu Gln Ser Thr Asn Tyr Ser Cys Met Val Cys
 210 215 220

Val Asp Arg Ser Ser Leu Ser Ser Trp His Val Leu Tyr Thr Pro Asn
 225 230 235 240

Ile Ser Ile Pro Gln Gln Thr Ser Ser Arg Thr Ile Leu Phe Pro Ser
 245 250 255

Leu Ala Leu Pro Ala Pro Pro Phe Gln Pro Phe Pro Trp Thr His Cys
 260 265 270

Tyr Gln Pro Arg Leu Gln Ala Ile Thr Thr Asp Asp Cys Asn Asn Ser
 275 280 285

Ile Ile Leu Pro Pro Phe Ser Leu Ala Pro Val Pro Pro Pro Ala Thr
 290 295 300

<210> 7
 <211> 1467
 <212> DNA
 <213> Simian T-cell lymphotropic virus type 1

<220>
 <221> CDS
 <222> (1)..(1467)
 <223>

<400> 7
 atg ggt aag ttt ctc gcc act ttg att tta ttc ttc cag ttc tgc ccc 48
 Met Gly Lys Phe Leu Ala Thr Leu Ile Leu Phe Phe Gln Phe Cys Pro
 1 5 10 15

ctc att ctc ggt gat tac agc ccc agc tgc tgt act ctc aca att gga 96
 Leu Ile Leu Gly Asp Tyr Ser Pro Ser Cys Cys Thr Leu Thr Ile Gly
 20 25 30

gtc tcc tca tac ctc tct aaa ccc tgc aat cct gcc cag cca gtt tgt 144
 Val Ser Ser Tyr Leu Ser Lys Pro Cys Asn Pro Ala Gln Pro Val Cys
 35 40 45

tca tgg acc ctc gac cta ctg gcc ctt tca gca gac caa gcc cta cag 192
 Ser Trp Thr Leu Asp Leu Leu Ala Leu Ser Ala Asp Gln Ala Leu Gln
 50 55 60

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ccc ccc tgc cct aat cta gta agt tac tcc agc tac cat gcc acc tat	70	75	80	240
Pro Pro Cys Pro Asn Leu Val Ser Tyr Ser Ser Tyr His Ala Thr Tyr				
65				
tcc cta tat cta ttc cct cat tgg att aaa aag cca aac cga aat ggc	85	90	95	288
Ser Leu Tyr Leu Phe Pro His Trp Ile Lys Lys Pro Asn Arg Asn Gly				
gga ggc tat tat tcg gcc tct tat tca gac cca tgt tct tta aag tgc	100	105	110	336
Gly Gly Tyr Tyr Ser Ala Ser Tyr Ser Asp Pro Cys Ser Leu Lys Cys				
cca tac tta ggg tgc caa tca tgg acc tgc ccc tat aca gga gtc gtc	115	120	125	384
Pro Tyr Leu Gly Cys Gln Ser Trp Thr Cys Pro Tyr Thr Gly Val Val				
tcc agc ccc tat tgg aaa ttt cag caa gat gtc aat ttt act caa gaa	130	135	140	432
Ser Ser Pro Tyr Trp Lys Phe Gln Gln Asp Val Asn Phe Thr Gln Glu				
gtt tca cac ctc aat att aat ctc cat ttc tca aaa tgc ggt ttt ccc	145	150	155	480
Val Ser His Leu Asn Ile Asn Leu His Phe Ser Lys Cys Gly Phe Pro				
ttc tcc ctt cta atc gac gct cca gga tat gac ccc atc tgg ttc ctt	165	170	175	528
Phe Ser Leu Leu Ile Asp Ala Pro Gly Tyr Asp Pro Ile Trp Phe Leu				
aat acc gaa ccc agc caa ctg cct ccc acc gcc cct cct cta ctc ccc	180	185	190	576
Asn Thr Glu Pro Ser Gln Leu Pro Pro Thr Ala Pro Pro Leu Leu Pro				
cac tct aac ctg gac cac atc ctc gag ccc tct ata cca tgg aaa tca	195	200	205	624
His Ser Asn Leu Asp His Ile Leu Glu Pro Ser Ile Pro Trp Lys Ser				
aaa ctt ctg act ctt gtc cag cta acc cta caa agc act aat tac act	210	215	220	672
Lys Leu Leu Thr Leu Val Gln Leu Thr Leu Gln Ser Thr Asn Tyr Thr				
tgc atc gtc tgt ata gac cgt gcc agc ctc tct act tgg cat gtc ctg	225	230	235	720
Cys Ile Val Cys Ile Asp Arg Ala Ser Leu Ser Thr Trp His Val Leu				
tac tct ccc aac gtc tct gtt ccg tcc tct tct tct acc ccc ctc ctt	245	250	255	768
Tyr Ser Pro Asn Val Ser Val Pro Ser Ser Ser Thr Pro Leu Leu				
tac ccg tcg tta gcg ctt cca gct ccc cac ctg acg cta cca ttt aac	260	265	270	816
Tyr Pro Ser Leu Ala Leu Pro Ala Pro His Leu Thr Leu Pro Phe Asn				
tgg acc cac tgc ttt gac ccc cag att caa gct ata gtc tcc tcc ccc	275	280	285	864
Trp Thr His Cys Phe Asp Pro Gln Ile Gln Ala Ile Val Ser Ser Pro				
tgt cat aac tcc ctc atc ctg ccc ccc ttt tcc ttg tca cct gtt ccc	290	295	300	912
Cys His Asn Ser Leu Ile Leu Pro Pro Phe Ser Leu Ser Pro Val Pro				

acc cta gga tcc cgc tcc cgc cga gcg gta ccg gtg gcg gtc tgg ctt	960
Thr Leu Gly Ser Arg Ser Arg Arg Ala Val Pro Val Ala Val Trp Leu	
305 310 315 320	
gtc tcc gcc ctg gcc atg gga gca ggc att gct ggc ggg att acc ggc	1008
Val Ser Ala Leu Ala Met Gly Ala Gly Ile Ala Gly Gly Ile Thr Gly	
325 330 335	
tcc atg tcc ctc gcc tca gga aag agc ctc cta cat gag gtg gac aaa	1056
Ser Met Ser Leu Ala Ser Gly Lys Ser Leu Leu His Glu Val Asp Lys	
340 345 350	
gat att tcc caa tta act caa gca ata gtc aaa aac cac aaa aat cta	1104
Asp Ile Ser Gln Leu Thr Gln Ala Ile Val Lys Asn His Lys Asn Leu	
355 360 365	
ctc aaa att gca cag tat gct gcc cag aac agg cga ggc ctt gat ctc	1152
Leu Lys Ile Ala Gln Tyr Ala Ala Gln Asn Arg Arg Gly Leu Asp Leu	
370 375 380	
ctg ttc tgg gag caa gga gga tta tgc aaa gca tta caa gaa cag tgc	1200
Leu Phe Trp Glu Gln Gly Gly Leu Cys Lys Ala Leu Gln Glu Gln Cys	
385 390 395 400	
tgt ttt cta aat att acc aat tcc cat gtc tca ata cta caa gaa aga	1248
Cys Phe Leu Asn Ile Thr Asn Ser His Val Ser Ile Leu Gln Glu Arg	
405 410 415	
ccc ccc ctt gag aat cga gtc ctc act ggc tgg ggc ctt aac tgg gac	1296
Pro Pro Leu Glu Asn Arg Val Leu Thr Gly Trp Gly Leu Asn Trp Asp	
420 425 430	
ctt ggc ctc tca cag tgg gct cga gag gcc tta caa act ggg atc acc	1344
Leu Gly Leu Ser Gln Trp Ala Arg Glu Ala Leu Gln Thr Gly Ile Thr	
435 440 445	
ctt gtt gca cta ctc ctt ctc gtt atc ctt gca gga cca tgc atc ctc	1392
Leu Val Ala Leu Leu Leu Val Ile Leu Ala Gly Pro Cys Ile Leu	
450 455 460	
cgt cag ctg cga cac ctc ccc tcg cgc gtc aga tac ccc cat tat tct	1440
Arg Gln Leu Arg His Leu Pro Ser Arg Val Arg Tyr Pro His Tyr Ser	
465 470 475 480	
ctt ata aac cct gag tca tcc ctg taa	1467
Leu Ile Asn Pro Glu Ser Ser Leu	
485	

<210> 8
 <211> 488
 <212> PRT
 <213> Simian T-cell lymphotropic virus type 1
 <400> 8

Met Gly Lys Phe Leu Ala Thr Leu Ile Leu Phe Phe Gln Phe Cys Pro
 1 5 10 15

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Leu Ile Leu Gly Asp Tyr Ser Pro Ser Cys Cys Thr Leu Thr Ile Gly
20 25 30

Val Ser Ser Tyr Leu Ser Lys Pro Cys Asn Pro Ala Gln Pro Val Cys
35 40 45

Ser Trp Thr Leu Asp Leu Leu Ala Leu Ser Ala Asp Gln Ala Leu Gln
50 55 60

Pro Pro Cys Pro Asn Leu Val Ser Tyr Ser Ser Tyr His Ala Thr Tyr
65 70 75 80

Ser Leu Tyr Leu Phe Pro His Trp Ile Lys Lys Pro Asn Arg Asn Gly
85 90 95

Gly Gly Tyr Tyr Ser Ala Ser Tyr Ser Asp Pro Cys Ser Leu Lys Cys
100 105 110

Pro Tyr Leu Gly Cys Gln Ser Trp Thr Cys Pro Tyr Thr Gly Val Val
115 120 125

Ser Ser Pro Tyr Trp Lys Phe Gln Gln Asp Val Asn Phe Thr Gln Glu
130 135 140

Val Ser His Leu Asn Ile Asn Leu His Phe Ser Lys Cys Gly Phe Pro
145 150 155 160

Phe Ser Leu Leu Ile Asp Ala Pro Gly Tyr Asp Pro Ile Trp Phe Leu
165 170 175

Asn Thr Glu Pro Ser Gln Leu Pro Pro Thr Ala Pro Pro Leu Leu Pro
180 185 190

His Ser Asn Leu Asp His Ile Leu Glu Pro Ser Ile Pro Trp Lys Ser
195 200 205

Lys Leu Leu Thr Leu Val Gln Leu Thr Leu Gln Ser Thr Asn Tyr Thr
210 215 220

Cys Ile Val Cys Ile Asp Arg Ala Ser Leu Ser Thr Trp His Val Leu
225 230 235 240

Tyr Ser Pro Asn Val Ser Val Pro Ser Ser Ser Ser Thr Pro Leu Leu
245 250 255

Tyr Pro Ser Leu Ala Leu Pro Ala Pro His Leu Thr Leu Pro Phe Asn
260 265 270

Trp Thr His Cys Phe Asp Pro Gln Ile Gln Ala Ile Val Ser Ser Pro
275 280 285

Cys His Asn Ser Leu Ile Leu Pro Pro Phe Ser Leu Ser Pro Val Pro
290 295 300

Thr Leu Gly Ser Arg Ser Arg Arg Ala Val Pro Val Ala Val Trp Leu
305 310 315 320

Val Ser Ala Leu Ala Met Gly Ala Gly Ile Ala Gly Gly Ile Thr Gly
325 330 335

Ser Met Ser Leu Ala Ser Gly Lys Ser Leu Leu His Glu Val Asp Lys
340 345 350

Asp Ile Ser Gln Leu Thr Gln Ala Ile Val Lys Asn His Lys Asn Leu
355 360 365

Leu Lys Ile Ala Gln Tyr Ala Ala Gln Asn Arg Arg Gly Leu Asp Leu
370 375 380

Leu Phe Trp Glu Gln Gly Gly Leu Cys Lys Ala Leu Gln Glu Gln Cys
385 390 395 400

Cys Phe Leu Asn Ile Thr Asn Ser His Val Ser Ile Leu Gln Glu Arg
405 410 415

Pro Pro Leu Glu Asn Arg Val Leu Thr Gly Trp Gly Leu Asn Trp Asp
420 425 430

Leu Gly Leu Ser Gln Trp Ala Arg Glu Ala Leu Gln Thr Gly Ile Thr
435 440 445

Leu Val Ala Leu Leu Leu Val Ile Leu Ala Gly Pro Cys Ile Leu
450 455 460

Arg Gln Leu Arg His Leu Pro Ser Arg Val Arg Tyr Pro His Tyr Ser
465 470 475 480

Leu Ile Asn Pro Glu Ser Ser Leu
485

<210> 9
 <211> 1461
 <212> DNA
 <213> Simian T-cell lymphotropic virus type 2

<220>
 <221> CDS
 <222> (1)...(1461)
 <223>

<400> 9 48
 atg ggt aag ata att gct ttc ctt tta ttc cat ctt aca tgt atc aca
 Met Gly Lys Ile Ile Ala Phe Leu Leu Phe His Leu Thr Cys Ile Thr
 1 5 10 . 15

atc act aaa cag agc cgg tgc acg ctt acg gta ggt gtc tcc tcg tat 96
 Ile Thr Lys Gln Ser Arg Cys Thr Leu Thr Val Gly Val Ser Ser Tyr
 20 25 30

cac tct agt ccc tgc agt ctt gcc caa cct atc tgc acc tgg gat ctc 144
 His Ser Ser Pro Cys Ser Leu Ala Gln Pro Ile Cys Thr Trp Asp Leu
 35 40 45

gac ctt cat tcc tta act aca gac caa cgt ctg tac cct cca tgc ccc 192
 Asp Leu His Ser Leu Thr Thr Asp Gln Arg Leu Tyr Pro Pro Cys Pro
 50 55 60

aat cta gtt tct tac tct aac ttc cac aag tcc tac tcc tta tat ttg 240
 Asn Leu Val Ser Tyr Ser Asn Phe His Lys Ser Tyr Ser Leu Tyr Leu
 65 70 75 80

ttc ccg cac tgg gta aaa aag cca aat aga caa ggc ctg gga tac tat 288
 Phe Pro His Trp Val Lys Lys Pro Asn Arg Gln Gly Leu Gly Tyr Tyr
 85 90 95

tct gca tcc tac agc gac ccc tgc tcg ctc cag tgc cct tat tta gga 336
 Ser Ala Ser Tyr Ser Asp Pro Cys Ser Leu Gln Cys Pro Tyr Leu Gly
 100 105 110

agc cag tct tgg aca tgc cct tac acc ggc ccc atc tcc agc ccg tct 384
 Ser Gln Ser Trp Thr Cys Pro Tyr Thr Gly Pro Ile Ser Ser Pro Ser
 115 120 125

tgg agg ttc cac cga gat gtt aac ttc acc caa gag gtc aac cat gta 432
 Trp Arg Phe His Arg Asp Val Asn Phe Thr Gln Glu Val Asn His Val
 130 135 140

acc ctc cgg cta cac ttc tcc cga tgt ggc tct tct atg acc ctc ctc 480
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 145 150 155 160

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 Ile Asp Ala Pro Gly Tyr Asp Pro Leu Trp Phe Ile Ser Ser Glu Pro
 165 170 175

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 Thr Gln Pro Pro Pro Thr Ser Pro Pro Leu Val Arg Asp Ser Asp Leu
 180 185 190

gaa cat atc tta acc ccc tcc tcc tgg gct act agg atg cta acc	624
Glu His Ile Leu Thr Pro Ser Ser Ser Trp Ala Thr Arg Met Leu Thr	
195 200 205	
ctc atc caa cta act cta caa agt acc aat tat tct tgc atg gtt tgt	672
Leu Ile Gln Leu Thr Leu Gln Ser Thr Asn Tyr Ser Cys Met Val Cys	
210 215 220	
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Ile Asp Arg Thr Ser Leu Ser Ser Trp His Val Leu Tyr Thr Pro Asn	
225 230 235 240	
atc tct gcc tca cct ggg ggc gac tcc ttg cct ata ctt tat ccc tcc	768
Ile Ser Ala Ser Pro Gly Gly Asp Ser Leu Pro Ile Leu Tyr Pro Ser	
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Arg Ser Arg Arg Ala Ile Pro Val Ala Val Trp Leu Val Ser Ala Leu	
305 310 315 320	
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325 330 335	
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Ala Ser Ser Arg Ser Leu Leu Phe Glu Val Asp Lys Asp Ile Ser His	
340 345 350	
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Leu Thr Gln Ala Ile Val Lys Asn His Gln Asn Ile Leu Arg Val Ala	
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Gln Tyr Ala Ala Gln Asn Arg Arg Gly Leu Asp Leu Leu Phe Trp Glu	
370 375 380	
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385 390 395 400	
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18/29

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Leu Leu Leu Val Ile Leu Phe Gly Pro Cys Ile Leu Arg Gln Leu Gln
450 455 460

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Ser Leu Pro His Arg Leu Gln Asn Arg His Asn Gln Tyr Ser Leu Ile
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<213> Simian T-cell lymphotropic virus type 2

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Asp Leu His Ser Leu Thr Thr Asp Gln Arg Leu Tyr Pro Pro Cys Pro
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Asn Leu Val Ser Tyr Ser Asn Phe His Lys Ser Tyr Ser Leu Tyr Leu
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Phe Pro His Trp Val Lys Lys Pro Asn Arg Gln Gly Leu Gly Tyr Tyr
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Ser Ala Ser Tyr Ser Asp Pro Cys Ser Leu Gln Cys Pro Tyr Leu Gly
100 105 110

Ser Gln Ser Trp Thr Cys Pro Tyr Thr Gly Pro Ile Ser Ser Pro Ser
115 120 125

Trp Arg Phe His Arg Asp Val Asn Phe Thr Gln Glu Val Asn His Val
130 135 140

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Thr Leu Arg Leu His Phe Ser Arg Cys Gly Ser Ser Met Thr Leu Leu
145 150 155 160

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165 170 175

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180 185 190

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195 200 205

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260 265 270

Tyr Gln Pro His Leu Gln Ala Val Thr Thr Ala Asn Cys Asn Asn Ser
275 280 285

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325 330 335

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370 375 380

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Gln Gly Gly Leu Cys Lys Ala Ile Gln Glu Gln Cys Cys Phe Leu Asn
 385 390 395 400

Ile Ser Asn Thr His Val Ser Val Leu Gln Glu Arg Pro Pro Leu Glu
 405 410 415

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 420 425 430

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cct gcc tcc tct ggc aat ccc agt cgg tgc acc ctg ttc ata ggg gcc 96
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tct tcc tac cac tcc agc cct tgc ggg tcc agc ctc cca cgg tgt acc 144
 Ser Ser Tyr His Ser Ser Pro Cys Gly Ser Ser Leu Pro Arg Cys Thr
 35 40 45

tgg aat ctt gac cta ttc tcc ctc acg aaa gat caa agc cta agc ccc 192
 Trp Asn Leu Asp Leu Phe Ser Leu Thr Lys Asp Gln Ser Leu Ser Pro
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 Pro Cys Pro Asp Leu Ile Thr Tyr Ser Gln Tyr His Lys Pro Tyr Ser
 65 70 75 80

ctg tat gta ttc cct cat tgg ata act aaa cct aac cgc cgg ggc tta	288
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85 90 95	
ggt tac tat tcc gct tcc tac tca gac ccc tgt gcc ata cag tgc cct	336
Gly Tyr Tyr Ser Ala Ser Tyr Ser Asp Pro Cys Ala Ile Gln Cys Pro	
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Tyr Leu Gly Cys Gln Ser Trp Thr Cys Pro Tyr Thr Gly Pro Val Ser	
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165 170 175	
tcc cag gcc aca cag gct cca ccc aca cct gcc cct ctc ata cgg gac	576
Ser Gln Ala Thr Gln Ala Pro Pro Thr Pro Ala Pro Leu Ile Arg Asp	
180 185 190	
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Ser Asp Leu Gln Tyr Ile Leu Glu Pro Pro Ile Pro Trp Ser Ser Lys	
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225 230 235 240	
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245 250 255	
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Leu Arg Pro Ala Leu Ala Ile Pro Ala Ser Asn Ile Thr Pro Pro Phe	
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Pro Trp Thr His Cys Tyr Arg Pro Pro Pro Gln Ala Ile Ser Ser Glu	
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35 40 45

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50 55 60

Pro Cys Pro Asp Leu Ile Thr Tyr Ser Gln Tyr His Lys Pro Tyr Ser
65 70 75 80

Leu Tyr Val Phe Pro His Trp Ile Thr Lys Pro Asn Arg Arg Gly Leu
85 90 95

Gly Tyr Tyr Ser Ala Ser Tyr Ser Asp Pro Cys Ala Ile Gln Cys Pro
100 105 110

Tyr Leu Gly Cys Gln Ser Trp Thr Cys Pro Tyr Thr Gly Pro Val Ser
115 120 125

Ser Pro His Trp Arg Tyr Thr Tyr Asp Leu Asn Phe Thr Gln Glu Val
130 135 140

Ser Ser Val Ser Leu His Leu His Phe Ser Lys Cys Gly Ser Ser Phe
145 150 155 160

Ser Phe Leu Leu Asp Ala Pro Gly Tyr Asp Pro Val Trp Phe Leu Ser
165 170 175

Ser Gln Ala Thr Gln Ala Pro Pro Thr Pro Ala Pro Leu Ile Arg Asp
180 185 190

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195 200 205

Ile Leu Asn Leu Ile Leu Leu Thr Leu Lys Ser Thr Asn Tyr Ser Cys
210 215 220

Met Val Cys Val Asp Arg Ser Ser Leu Ser Ser Trp His Val Leu Tyr
225 230 235 240

Gly Pro Thr Gln Val Pro Ser Pro Pro Asp Pro Gln Ala Arg Ser Ile
245 250 255

Leu Arg Pro Ala Leu Ala Ile Pro Ala Ser Asn Ile Thr Pro Pro Phe
260 265 270

Pro Trp Thr His Cys Tyr Arg Pro Pro Pro Gln Ala Ile Ser Ser Glu
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24/29

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20 25 30

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20 25 30

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Ser Asp Pro Cys Ser Leu Lys Cys Pro Tyr Leu Gly Cys Gln Ser Trp	
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<210> 27
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<400> 31

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/004624A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/15 C07K14/47 A61K38/16 G01N33/574

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K

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

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

EPO-Internal, BIOSIS, MEDLINE, PAJ, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category ^o	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>HARRIS D S ET AL: "POLARIZED DISTRIBUTION OF GLUCOSE TRANSPORTER ISOFORMS IN CACO-2 CELLS" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 89, no. 16, 1992, pages 7556-7560, XP002254293 1992 ISSN: 0027-8424 page 7557, column 1, line 4 - line 11 page 7557, column 2, paragraph 2; figures 1,3A page 7559, column 2, last paragraph</p> <p>-----</p> <p style="text-align: center;">-/--</p>	12

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

19 August 2004

Date of mailing of the international search report

10/09/2004

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European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Pilat, D

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/004624

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MENDEZ LUIS E ET AL: "Expression of glucose transporter-1 in cervical cancer and its precursors." GYNECOLOGIC ONCOLOGY, vol. 86, no. 2, August 2002 (2002-08), pages 138-143, XP002254294 August, 2002 ISSN: 0090-8258 cited in the application page 140, column 2, line 7 - page 141, column 1, line 2; table 3 page 142, column 1, paragraph 1	12
X	WO 96/41193 A (SINAI SCHOOL MEDICINE ;BURSTEIN DAVID E (US); HABER RICHARD S (US)) 19 December 1996 (1996-12-19) claims	12
A	WO 98/03197 A (UNIV ROCKEFELLER) 29 January 1998 (1998-01-29) page 4, line 34 - page 7, line 2; claims	10,11
A	WO 92/13946 A (GENELABS INC) 20 August 1992 (1992-08-20) page 26 - page 28	10,11
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