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Organic Cation Transporter Preferentially Expressed in Hematopoietic Cells and Leukemias and Uses Thereof

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(54) **ORGANIC CATION TRANSPORTER PREFERENTIALLY EXPRESSED IN HEMATOPOIETIC CELLS AND LEUKEMIAS AND USES THEREOF**

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(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

A novel organic cation transporter (OCT) gene, OCT 6, and use thereof is described. The OCT6 gene is preferentially expressed in human hematopoietic tissues, including CD34+ cells and leukemia cells. Its narrow tissue distribution, substrate specificity, and close homology to other cell membrane transporters make OCT6 an attractive target for the treatment of myeloid diseases.

7 Claims, 10 Drawing Sheets

FIG. 1A

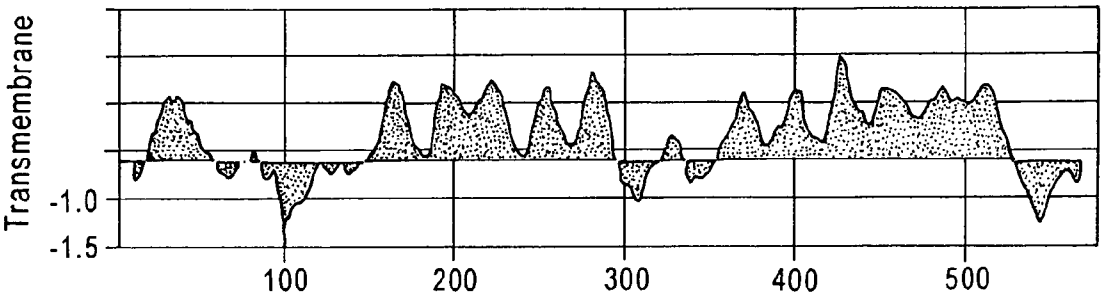
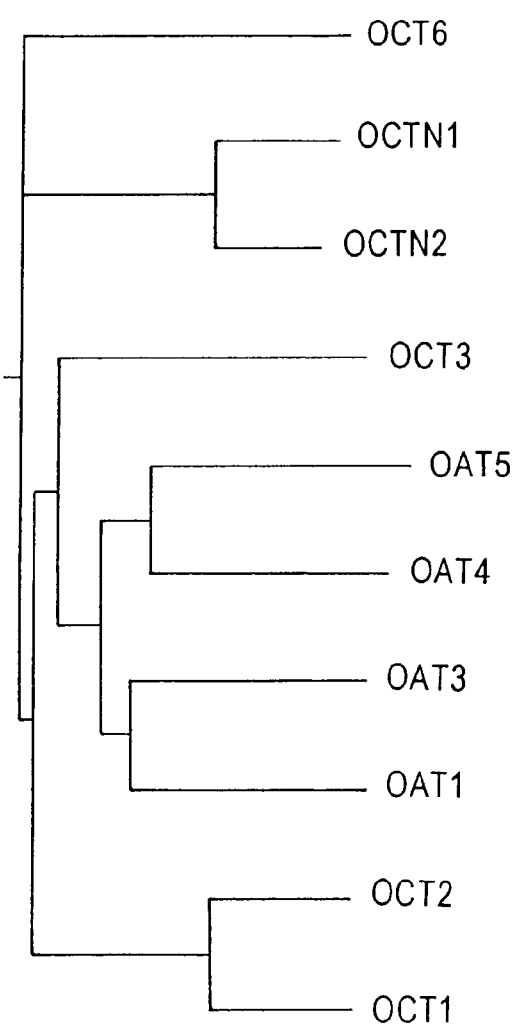

Transmembrane
-1.0
-1.5
100
200
300
400
500

FIG. 1B


OCT6
OCTN1
OCTN2
OCT3
OAT5
OAT4
OAT3
OAT1
OCT2
OCT1

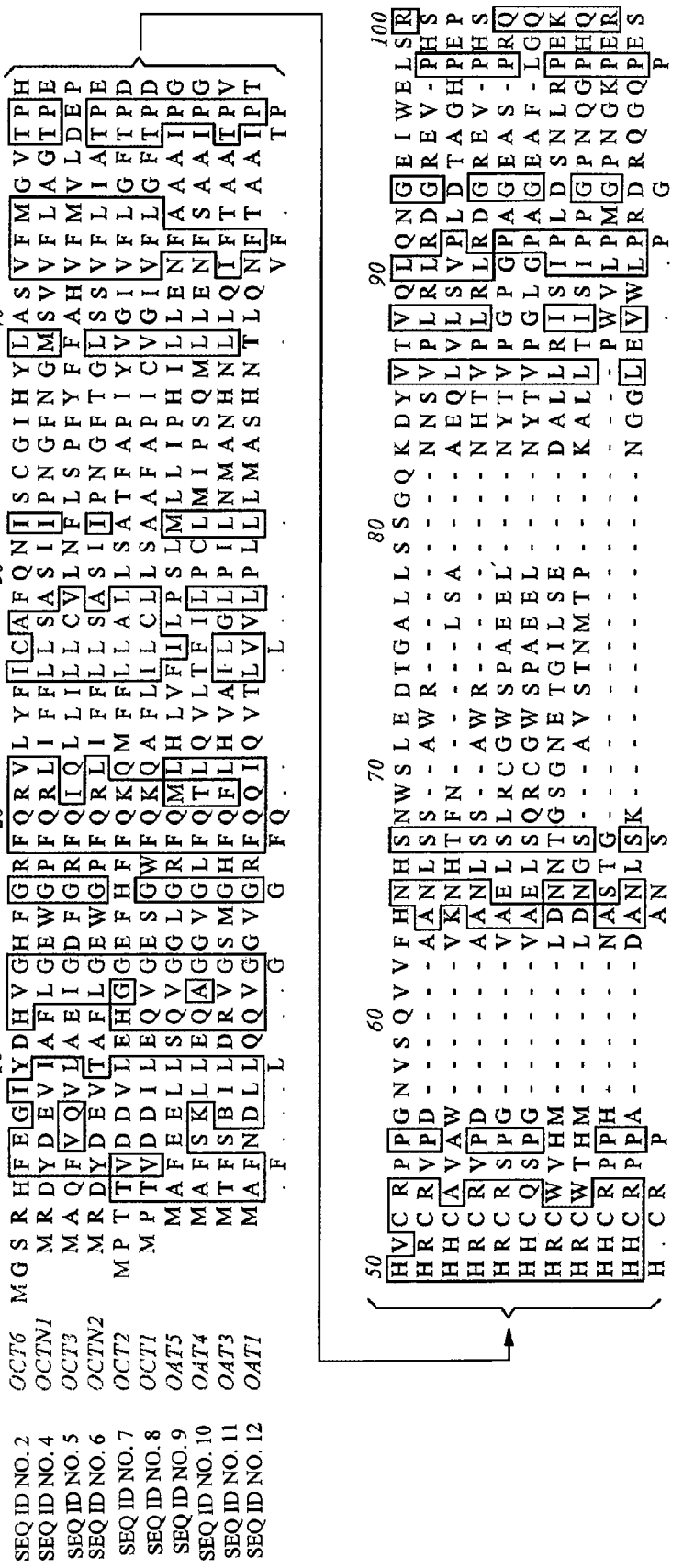
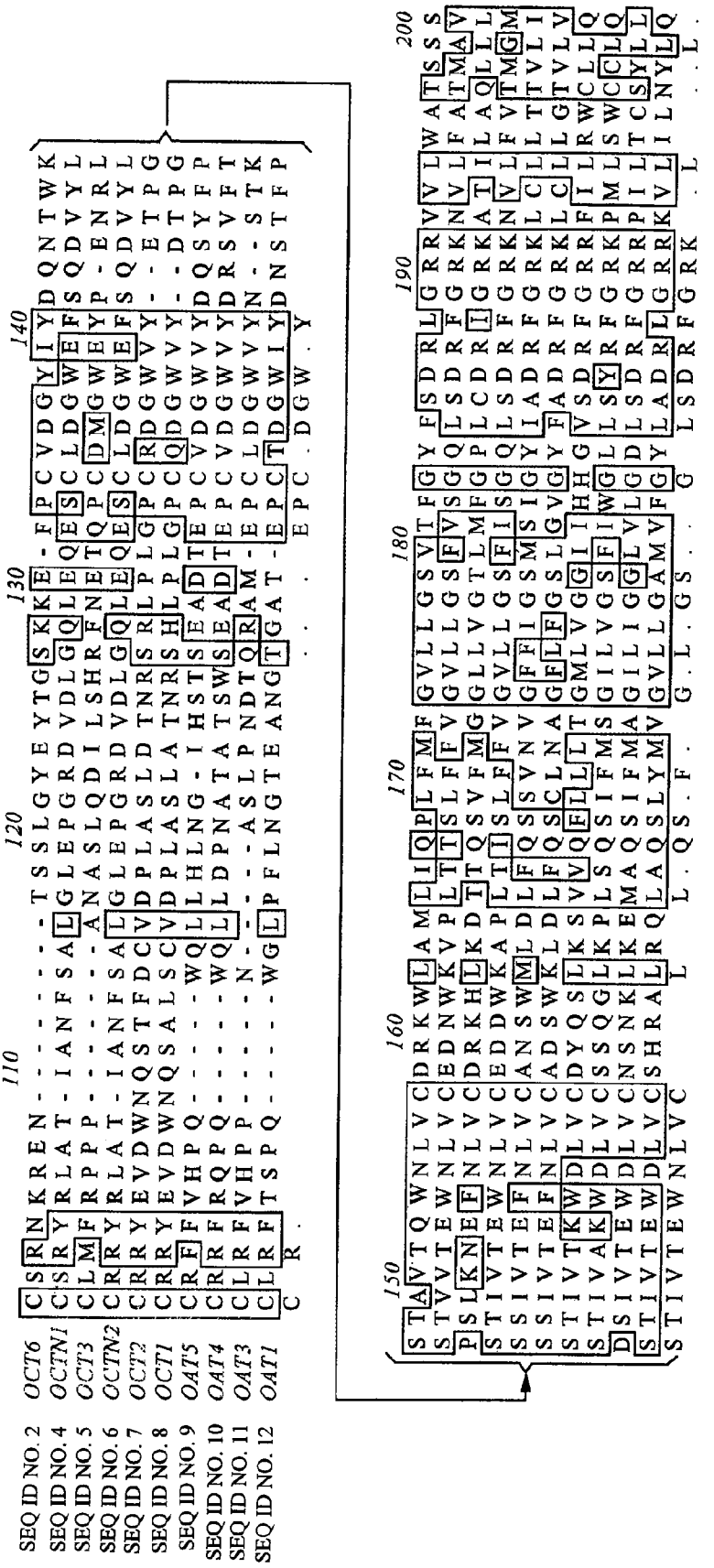

SEQ ID NO. 2 OCT6
SEQ ID NO. 4 OCTN1
SEQ ID NO. 5 OCT3
SEQ ID NO. 6 OCTN2
SEQ ID NO. 7 OCT2
SEQ ID NO. 8 OCT1
SEQ ID NO. 9 OAT5
SEQ ID NO. 10 OAT4
SEQ ID NO. 11 OAT3
SEQ ID NO. 12 OAT1
10
20
30
40
50
60
70
80
90
100

FIG. 2A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SEQ ID NO. 4 OCTN1
SEQ ID NO. 5 OCT3
SEQ ID NO. 6 OCTN2
SEQ ID NO. 7 OCT2
SEQ ID NO. 8 OCT1
SEQ ID NO. 9 OAT5
SEQ ID NO. 10 OAT4
SEQ ID NO. 11 OAT3
SEQ ID NO. 12 OAT1
110
120
130
140
150
160
170
180
190
200

FIG. 2B

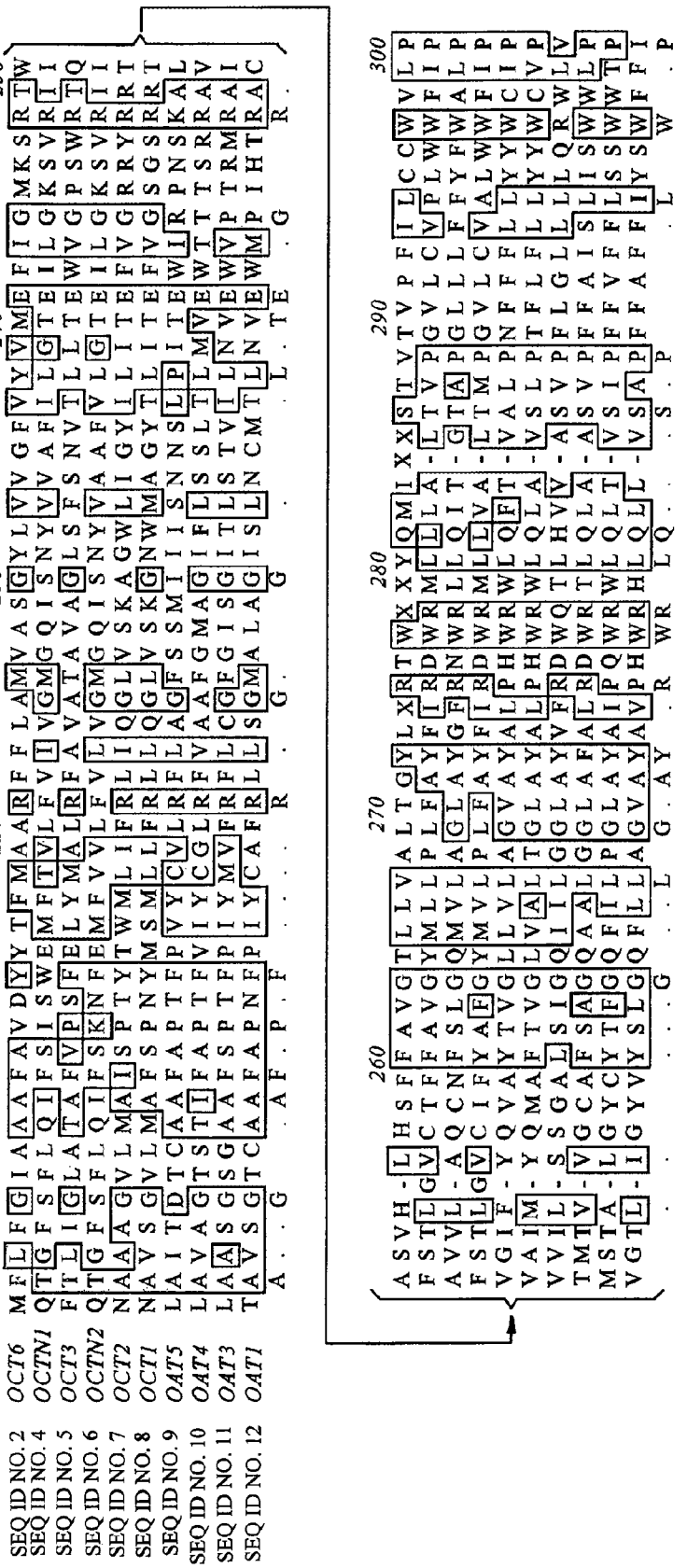
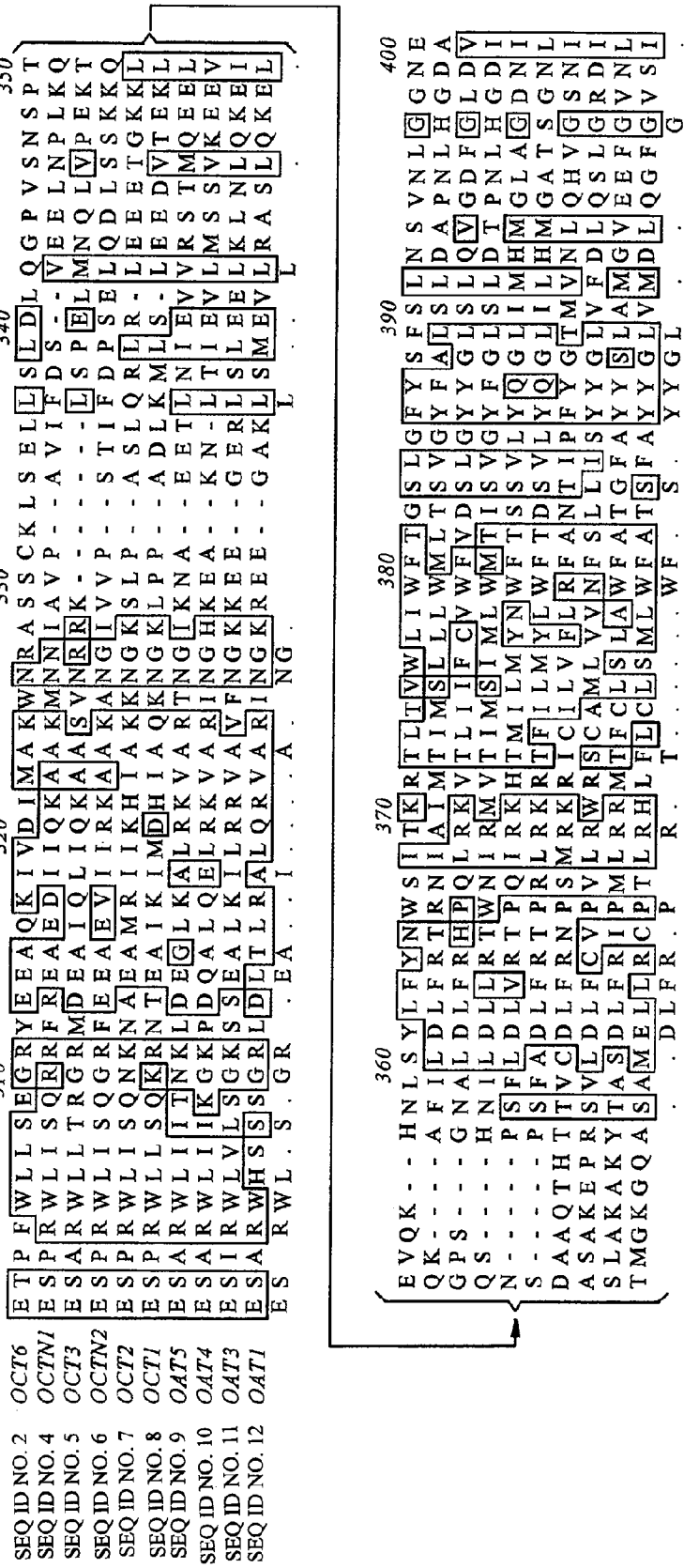

SEQ ID NO. 2 OCT6
SEQ ID NO. 4 OCTN1
SEQ ID NO. 5 OCT3
SEQ ID NO. 6 OCTN2
SEQ ID NO. 7 OCT2
SEQ ID NO. 8 OCT1
SEQ ID NO. 9 OAT5
SEQ ID NO. 10 OAT4
SEQ ID NO. 11 OAT3
SEQ ID NO. 12 OAT1
210
220
230
240
250
260
270
280
290
300

FIG. 2C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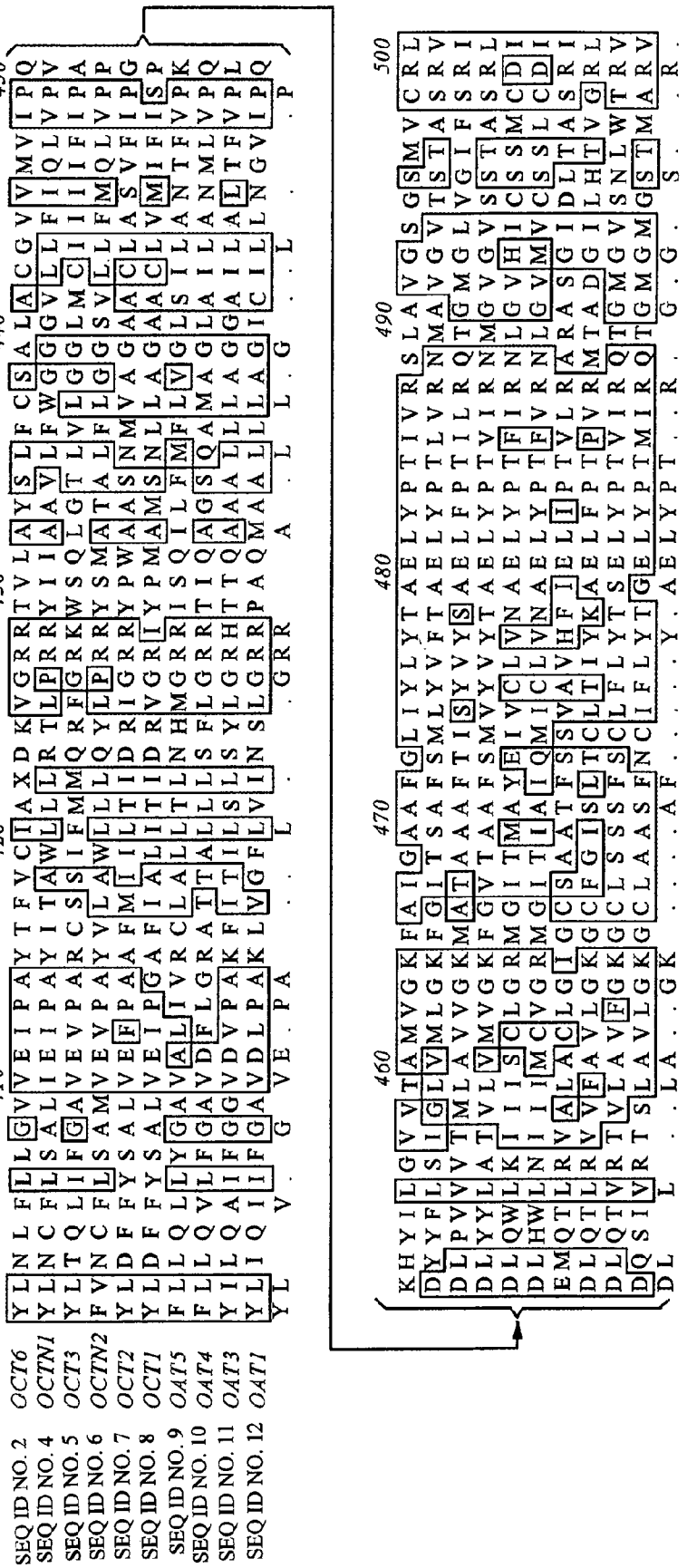
SEQ ID NO. 4 OCTN1
SEQ ID NO. 5 OCT3
SEQ ID NO. 6 OCTN2
SEQ ID NO. 7 OCT2
SEQ ID NO. 8 OCT1
SEQ ID NO. 9 OAT5
SEQ ID NO. 10 OAT4
SEQ ID NO. 11 OAT3
SEQ ID NO. 12 OAT1
310
320
330
340
350
360
370
380
390
400

FIG. 2D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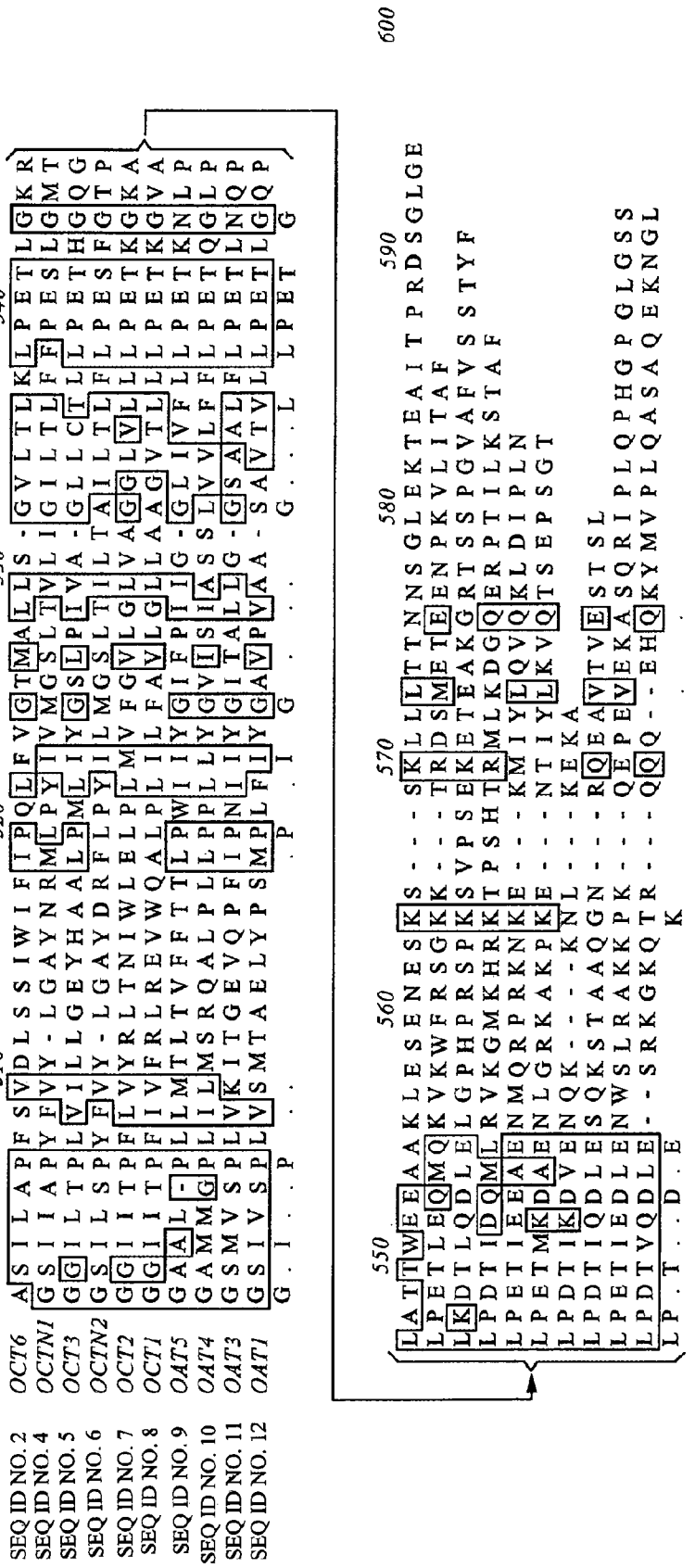
SEQ ID NO. 4 OCTN1
SEQ ID NO. 5 OCT3
SEQ ID NO. 6 OCTN2
SEQ ID NO. 7 OCT2
SEQ ID NO. 8 OCT1
SEQ ID NO. 9 OAT5
SEQ ID NO. 10 OAT4
SEQ ID NO. 11 OAT3
SEQ ID NO. 12 OAT1
410
420
430
440
450
460
470
480
490
500

FIG. 2E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SEQ ID NO. 5 OCT3
SEQ ID NO. 6 OCTN2
SEQ ID NO. 7 OCT2
SEQ ID NO. 8 OCT1
SEQ ID NO. 9 OAT5
SEQ ID NO. 10 OAT4
SEQ ID NO. 11 OAT3
SEQ ID NO. 12 OAT1
510
520
530
540
550
560
570
580
590
600

FIG. 2F

FIG. 3A

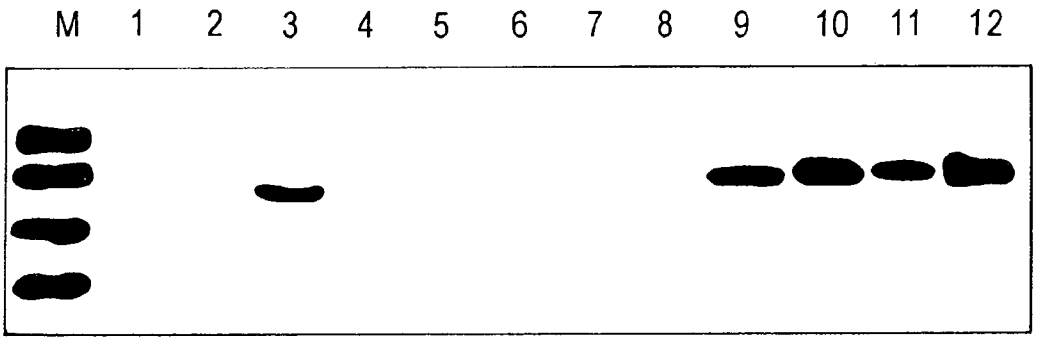


FIG. 3B

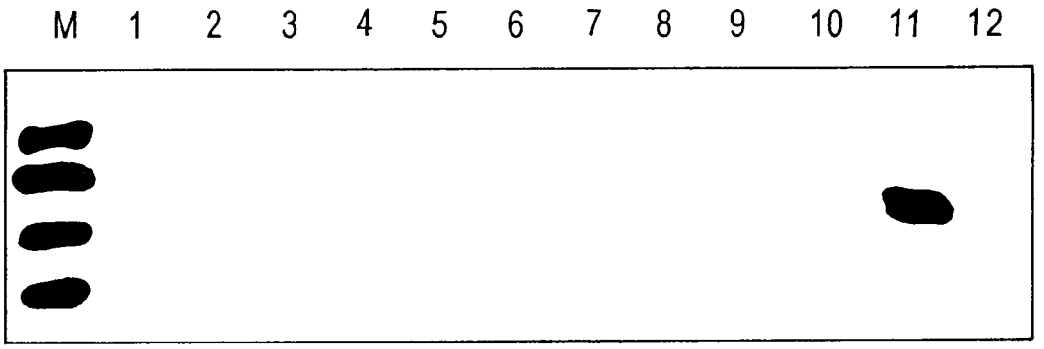
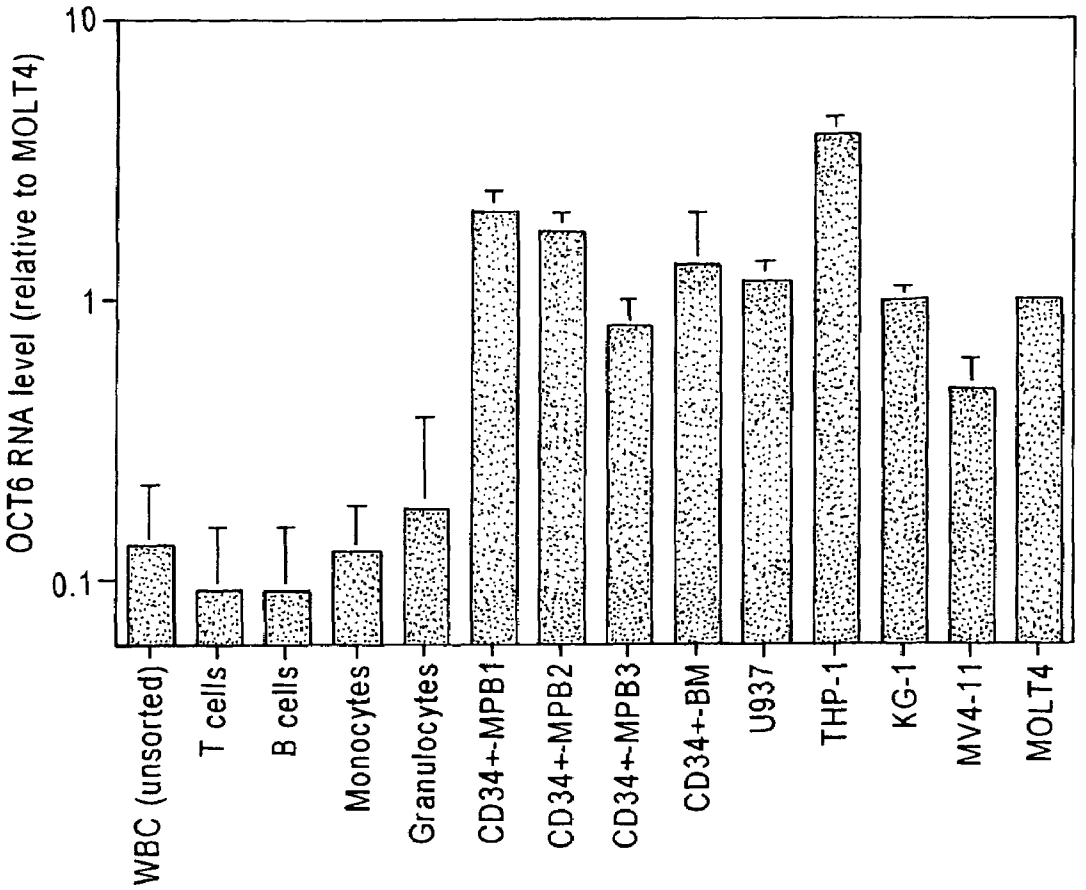
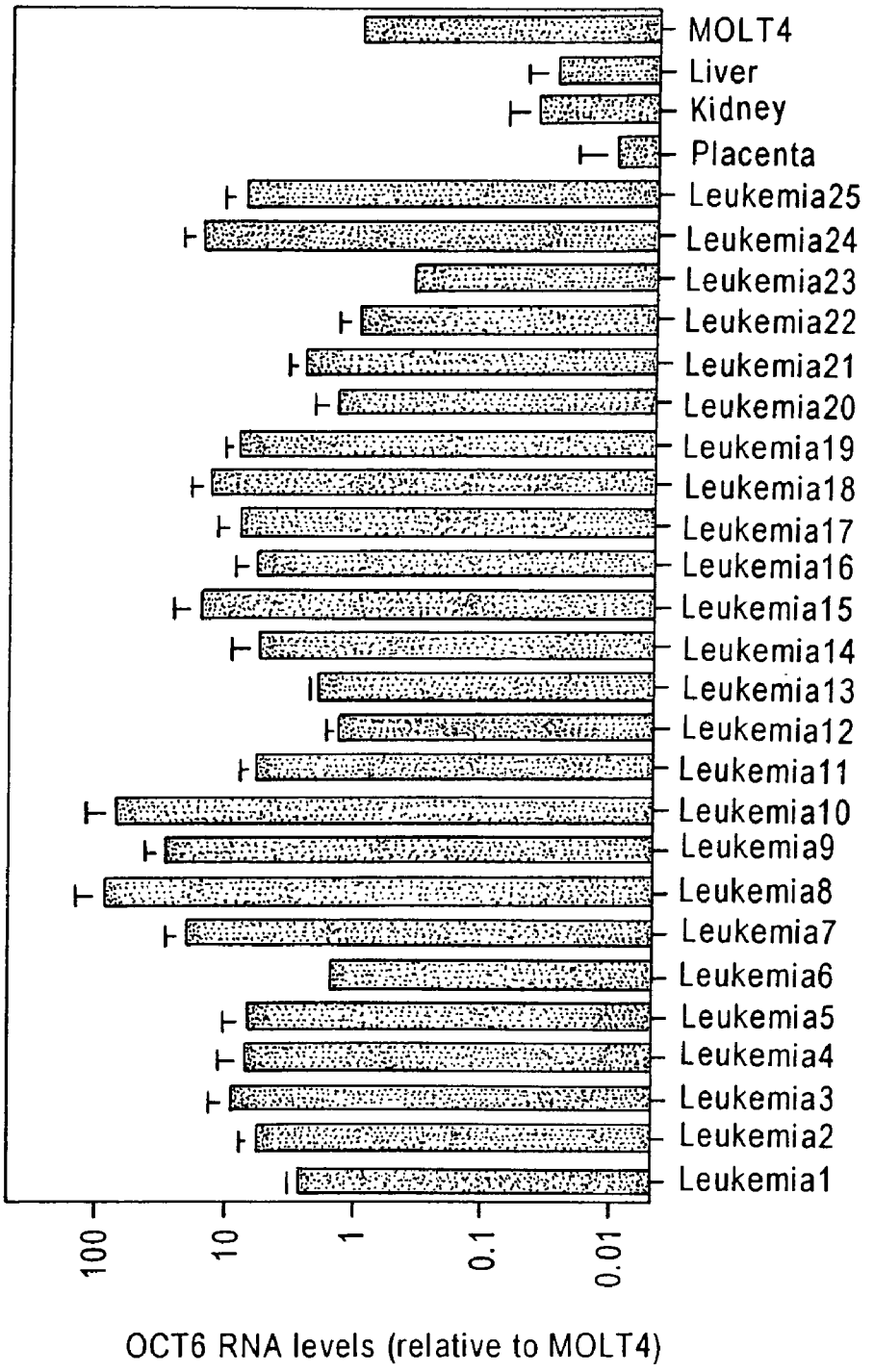


FIG. 4


OCT6 RNA level (relative to MOLT4)
10
1
0.1
WBC (unsorted)
T cells
B cells
Monocytes
Granulocytes
CD34+-MPB1
CD34+-MPB2
CD34+-MPB3
CD34+-BM
U937
THP-1
KG-1
MV4-11
MOLT4


MOLT4
Liver
Kidney
Placenta
Leukemia25
Leukemia24
Leukemia23
Leukemia22
Leukemia21
Leukemia20
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Leukemia18
Leukemia17
Leukemia16
Leukemia15
Leukemia14
Leukemia13
Leukemia12
Leukemia11
Leukemia10
Leukemia9
Leukemia8
Leukemia7
Leukemia6
Leukemia5
Leukemia4
Leukemia3
Leukemia2
Leukemia1
100
10
1
0.1
0.01
OCT6 RNA levels (relative to MOLT4)

FIG. 5

ORGANIC CATION TRANSPORTER PREFERENTIALLY EXPRESSED IN HEMATOPOIETIC CELLS AND LEUKEMIAS AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a divisional application of and claims the benefit of application Ser. No. 10/849,551, filed May 20, 2004 now abandoned, which claims the benefit of U.S. Provisional Application No. 60/471,709, filed May 20, 2003.

FIELD OF THE INVENTION

The invention relates to a gene encoding an organic cation transporter, OCT6, and its use as a target for the treatment of hematological malignancies, and in particular, leukemia. The invention further relates to screening methods for identifying agonists and antagonists/binding partners of OCT6 transport activity.

BACKGROUND OF THE INVENTION

The lipid bilayer of the cellular membrane insulates the intracellular milieu from exposure to hydrophilic compounds. Unlike lipophilic compounds that can diffuse through cellular membranes, water-soluble compounds usually require specific transport mechanisms to gain access to the intracellular space. The regulation of the traffic of polar compounds in both directions across the cellular membrane is a complex process involving several large families of transport proteins.

Most often in cancer research, drug transport is thought of as a mechanism of cellular drug resistance, as drug efflux pumps such as the products of the MDR1 and MRP genes have been shown to be mechanisms of resistance to lipid-soluble anticancer drugs. However, drug transport is a two-way street, and mechanisms also exist for pumping drugs into cells. For polar, water-soluble anticancer agents, drug uptake, and not drug efflux, is the critical determinant of cellular drug accumulation.

Most cancer chemotherapy employs drugs that are lipid-soluble that can easily penetrate the cell membrane of cancer cells. One advantage of using lipid-soluble drugs is that they easily gain intracellular access to different types of cancer cells, so many cancer cells appear to be initially sensitive to these drugs. The disadvantage is that cancer cells learn to increase the activity of drug efflux pumps in the cell membrane to pump lipid-soluble drugs out of the cell, resulting in drug resistance.

In contrast, potential water-soluble anticancer drugs may not survive the preclinical screening process since there is a great deal of variability in the expression of drug transport genes in different types of cancer cells. Variability in transport gene expression may result in variability in accumulation of polar, water-soluble drugs. One approach to more effectively utilize water-soluble anticancer drugs is to identify which of the dozens of transport genes are actually expressed in tumors.

The importance of carrier-mediated anticancer drug uptake is exemplified in reduced folate carrier (RFC) mediated uptake of methotrexate (MTX). Methotrexate (MTX), a reduced folate analogue, is scavenged and retained in cells by mechanisms designed to secure folates from the environment. The major mechanism of MTX uptake at pharmacologic concentrations is the reduced folate carrier (RFC), an OAT transporter with a Km for MTX between approximately 0.8-26 μM. Decreased RFC activity has been observed in several in vitro models of transport-mediated MTX resistance (Biochem. Pharmacol. 11: 1233-1234, 1960). Once rodent and human genes encoding proteins with RFC activity were isolated, the molecular explanations for decreased RFC activity emerged. RFC1 transfection into the transport-deficient MTX^R ZR75 cell line resulted in a 20-fold increase in 6-hour MTX uptake and a concomitant 250-fold increase in sensitivity to MTX relative to control cell clones, showing that the RFC1 gene reconstitutes RFC activity and has a significant impact on MTX cytotoxicity (Moscow, et al., Cancer Res. 55: 3790-3794, 1995).

In different cell lines, MTX transport deficiency has been ascribed either to mutations in the RFC gene or in decreased expression of the RFC gene product. Several studies have demonstrated that RFC1 gene expression is an important determinant of sensitivity to MTX. In in vitro studies, we have found that RFC1 RNA levels correlate with MTX sensitivity in a panel of non-selected cell lines, including breast cancer cell lines (Moscow et al., Int J Cancer. 72: 184-190, 1997).

A plethora of genes with the ability to transport MTX out of the cell have been reported, including MRP1, MRP2, MRP3, MRP4, the organic anion transporters hOAT2 and hOAT3, and the mitoxantrone-resistance protein (BCRP/MXR). However, despite the multitude of MTX export genes, clinical studies have shown a relationship between the expression of RFC1, the mechanism of MTX uptake, and prognosis in Acute Lymphoid Leukemia (ALL) and osteosarcoma. As a result, RFC1 expression and MTX uptake are now implicated as determinants of clinical sensitivity in several types of tumors. Thus, the role of RFC1 in mediating sensitivity of its cytotoxic drug substrates has become a prototype that illustrates the potential role of transporters, like OAT and OCT genes, in determination of anticancer drug selectivity and toxicity.

However, there is a need to identify additional channels, or transporters, that are found in specific cancers, to enable the targeting of different cancers with anticancer agents that are substrates for those transporters.

SUMMARY OF THE INVENTION

The present invention is directed towards a membrane protein that functions to transport hydrophilic substances across cellular membranes. The protein, OCT6, is a new member of the organic cation transporter (OCT) family (SLC22 gene family). Tissue distribution of this protein is distinct from other OCT protein family members; being detected in leukemia, leukemia blast cells and CD34+ cells.

In one aspect, the present invention provides a novel target for hematological malignancies such as leukemia, an OCT6 transporter.

In another aspect of the present invention there is a method for screening potential substrates that selectively bind the OCT6 transporter. The method involves contacting a cell which overexpresses an OCT6 transporter gene with a test compound and determining whether the test compound is a substrate for the OCT6 transporter.

In another aspect, there is a method for screening potential anti-cancer agents in a cell overexpressing an OCT6 transporter gene. The method comprises determining viability of a cell which expresses OCT6 transporter gene incubated in the presence and absence of a test compound and identifying the test compound as a potential anti-cancer agent if there is cellular influx of the test compound and cell death.

In another aspect of the invention, a test kit is provided for screening candidate drugs for hematologic malignancies comprising a mammalian cell line or cells which overexpress OCT6, a control substrate and a detectable substance.

In still another aspect of the invention, there are immunogenic compositions for treating hematological malignancies. In a preferred embodiment, immunogenic compositions for treating leukemia comprise a substrate that binds selectively to a leukemia cell expressing the OCT6 transporter gene. In another preferred embodiment of the invention, the substrate comprises an antibody that selectively binds to the OCT6 transporter protein. Preferably, the OCT6 transporter protein allows cellular uptake of the substrate which then causes cell death. In one embodiment the substrate is cytotoxic and in another preferred embodiment the substrate is coupled with a cytotoxic agent.

In still another aspect, the present invention provides a method for impairing a leukemia cell comprising contacting the cell with a cytotoxic OCT6 transporter protein. In one embodiment the substrate is a cytotoxin and in another embodiment the substrate is coupled to a cytotoxic agent.

In yet another aspect, the present invention provides a method for treating hematological malignancies comprising administering to a subject in need thereof an immunogenic composition comprising a substrate that binds selectively to a cell expressing the OCT6 transporter gene. In a preferred embodiment the OCT6 transporter protein allows cellular uptake of the substrate which then causes cell death. In another preferred embodiment the substrate is cytotoxic. In another preferred embodiment, the substrate is coupled with a cytotoxic agent.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**. A. shows the predicted hydropathy profile of OCT6.

FIG. **1**. B. is a dendrogram showing phylogenic relationship between OCT6 (SEQ ID NO:2) and other OCT and OAT proteins, including, OCTN1 (SEQ ID NO:4), OCT3 (SEQ ID NO:5), OCTN2 (SEQ ID NO:6), OCT2 (SEQ ID NO:7), OCT1 (SEQ ID NO:8), OAT5 (SEQ ID NO:9), OAT4 (SEQ ID NO:10), OAT3 (SEQ ID NO:11), and OAT1 (SEQ ID NO:12).

FIG. **2**A-F. is the CLUSTLAW alignment of OCT6 and other OCT and OAT proteins. The bottom row represents areas of consensus.

FIG. **3**. shows the normal tissue distribution of OCT6 RNA determined by RT-PCR using a cDNA panel. Only 1000× (highest) cDNA concentration is shown. Panel A. 1, salivary gland; 2, thyroid; 3, adrenal; 4, pancreas; 5, ovary; 6, uterus; 7, prostate; 8, skins; 9, peripheral blood leukocytes; 10, bone marrow; 11, fetal brain; 12, fetal liver. Panel B. 1, brain; 2, heart; 3, kidney; 4, spleen; 5, liver; 6, colon; 7, lung; 8, small intestine; 9, muscle; 10, stomach, 11, testis; 12, placenta.

FIG. **4**. shows quantitative RT-PCR for the transporter gene OCT6 performed with RNA extracted from peripheral blood leukocytes, CD34+ cells and additional hematopoietic cell lines. Fresh discarded buffy coats that were twice sorted by FACS using CD14 (monocytes), CD15 (granulocytes), CD3 (T-cells) and CD20 (B-cells). Purities of 99% or better were obtained. For peripheral WBC and sorted subsets, the average±SD represent pooled results from samples from 2 individuals performed in triplicate or quadruplicate. For CD34-selected mobilized peripheral blood (MPB), the results from each of 3 individuals are shown. For CD34-selected bone marrow (CD34+-BM), the results are from one individual. OCT6 levels were normalized to the expression of actin RNA, as a control for equivalence of mRNA template. The units, in log scale, are arbitrary and based on a standard curve of OCT6 RT-PCR in serially diluted HL60 RNA. Unity is defined as the level of OCT6 RNA found in MOLT4 cells.

FIG. **5**. shows quantitative RT-PCR for the gene OCT6 using RNA extracted from leukemic blasts obtained from patients at the time of initial diagnosis. OCT6 levels were normalized to the expression of actin RNA, as a control for equivalence of mRNA template. The OCT6 RNA levels in placenta, liver, kidney and MOLT-4 cell line were determined concurrently and shown for comparison. The units, in log scale, are arbitrary and based on a standard curve of OCT6 RT-PCR in serially diluted HL60 RNA. Unity is defined as the level of OCT6 RNA found in MOLT4 cells.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is based on the discovery and isolation of a new member of the SLC22 gene family (the OCT family of proteins) that is unusual for its distinct pattern of tissue distribution. Rather than the typical high levels of expression in liver, kidney or placenta, high levels of RNA for this transporter were found in some leukemia cell lines, in CD34+ cells, and in circulating leukemia blast cells.

All patents, patent applications and literature cited in this description are incorporated herein by reference in their entirety. In the case of inconsistencies, the present disclosure, including definitions, will prevail.

OCT Family

Two families of proteins involved in maintaining homeostasis of charged organic compounds are the organic anion transporters (OATs) which carry the SLC21 designation and the organic cation transporters (OCTs), which carry the SLC22 designation (See Table 1). OATs and OCTs each have characteristic patterns of tissue expression, with predominant expression in a tissue involved in the transport of xeriobiotics, i.e., liver, kidney or placenta.

TABLE 1

Organic anion and cation transported genes

Gene Family	Gene Name	Locus Link	Alternative Names
SLC21	SLC21A1	6577	
	SLC21A2	6578	PGT
	SLC21A3	6579	OATP, OATP1, OATP1b, OATP-A
	SLC21A4	28237	OAT-K1, OAT-K2
	SLC21A5	28236	OATP2, OATP-2
	SLC21A6	10599	LST-1, OATP-C
	SLC21A7	28235	OATP3, OATP-3
	SLC21A8	28234	LST2, OATP8, SLC21A8, OATP-8
	SLC21A9	11309	OATP-B
	SLC21A10	28233	OATP4
	SLC21A11	28232	OATP-D
	SLC21A12	28231	LOC51737, OATP-E, POAT
	SLC21A13	28230	OATP5, OATP-5
	SLC21A14	53919	OATP-F
SLC22	SLC22A1	6580	OCT1
	SLC22A2	6582	OCT2
	SLC22A3	6581	OCT3
	SLC22A4	6583	OCTN1
	SLC22A5	6584	OCTN2, CDSP, SCD
	SLC22A6	9356	NKT, OAT1, OAT-1
	SLC22A7	10864	NLT, OAT2, OAT-2
	SLC22A8	9376	OAT3, OAT-3
	SLC22A9		OAT4, OAT-4

The OAT and OCT carriers result in increased cellular accumulation of their respective substrates, despite the fact

that they are carriers that mediate facilitative diffusion. For carriers, the degree of intracellular accumulation may not exceed the extracellular concentration. However, the presence of the carrier allows uptake in comparison to no uptake in the absence of the carrier, and drugs that bind an intracellular target or which are chemically modified in the cells, e.g., by phosphorylation or polyglutamylation, may be eliminated from the substrate pool and not available for transport back across the cellular membrane.

The first five members of the SLC22 family of transporters, OCT1, OCT2, OCT3, OCTN1, and OCTN2, have been characterized as organic cation transporters. The uptake of many cations, such as tetraethylammonium (TEA), N-1-methylnicotineamide (NMN), choline, procainamide, amantadine and morphine are mediated by these polyspecific transporters. In general, these transporters are potential-dependent, but independent of sodium and proton gradients. These genes are all characterized by the presence of 11 or 12 transmembrane domains, as predicted by hydrophobicity analysis, and all have a large hydrophilic loop between transmembrane domain (TMD) 1 and TMD2.

OCT substrates are shown below in Table 2. Tetraethyl ammonium (TEA) is the classic substrate for OCT transporters. In addition, OCT1, OCT2 and OCT3 transport 1-methyl-4-phenylpyridinium (MPP). Compared to OCT2, OCT1 has a higher affinity for some cations (for example mepiperphenidol and procainamide), a similar affinity for others (for example, decynium 22 and quinidine), and a lower affinity for corticosterone (See Koepsell et al., Ann. Rev. Physiol. 60: 243-266, 1998.). OCT3 is an electrogenic transporter for TEA and guanidine. Other physiologic substrates for OCT transporters include dopamine, histamine, epinephrine and norepinephrine, acetylcholine and 5-hydroxytryptamine (Burckhardt, et al., Am J Physiol Renal Physiol. 278: F853-66., 2000.), suggesting an important role for these transporters in the central nervous system, in addition to their role in hepatic and renal clearance. Interestingly, despite its cationic nature, recent studies have identified cimetidine as a selective inhibitor, but not a substrate for several organic cation transporters, including rOCT1, rOCT2, rOCT3, hOCTN1, and hOCTN2.

TABLE 2

OCT Substrates

Common Name	Gene Name	Cell Type	Substrate	KT (uM)
OCT1	SLC22A1	HeLa	TEA	229
OCT1	SLC22A1	Xenopus	MPP	14.6
OCT2	SLC22A2	Xenopus	Norepinephrine	1900
OCT2	SLC22A2	Xenopus	Histamine	1300
OCT2	SLC22A2	Xenopus	Dopamine	390
OCT2	SLC22A2	Xenopus	Serotonin	80
OCT2	SLC22A2	HEK293	MPP	16
OCT2	SLC22A2	HEK293	Dopamine	330
OCT2	SLC22A2	Xenopus	Amantadine	27
OCT2	SLC22A2	Xenopus	Memantine	34
OCT3	SLC22A3	HeLa	TEA	2500
OCT3	SLC22A3	HRPE	MPP	47
OCTN1	SLC22A4	Fibroblasts	L-Carnitine	6.6
OCTN2	SLC22A5	HEK293	L-Carnitine	4.34
OCTN2	SLC22A5	HEK293	L-Carnitine	4.3
OCTN2	SLC22A5	HEK293	D-Carnitine	10.9
OCTN2	SLC22A5	HEK293	Acetyl-L-carnitine	8.5
OCTN2	SLC22A5	Xenopus	L-Carnitine	4.8
OCTN2	SLC22A5	Xenopus	D-Carnitine	98
OCTN2	SLC22A5	JAR	L-Carnitine	3.5

OCT1 and OCT2 are predominantly expressed in the kidney and liver. These transporters are located on the basolateral surface of renal tubules and, therefore, play a role in the removal of organic cations from the blood. OCT3 is most abundantly expressed in placenta. In addition, other tissue-specific roles have been implicated for these transporters. As noted above, OCTs may play a role in transport of endogenous neuroleptic substrates, and OCT3 has been implicated in the disposition of cationic neurotoxins and neurotransmitters in the brain (Wu, et al., J Biol Chem. 273: 32776-86, 1998). Dhillon et al. (Clin Pharmacol Ther. 65: 205, 19996) used RT-PCR followed by functional transport studies (TEA) to identify OCT1 expression in a human mammary epithelial cell line (MCF12A). Further, the OCT1 gene has been shown to be up regulated in lactating mammary epithelial cells.

The OCTN1 gene, cloned from a cDNA, shows sequence similarity to organic cation transporter genes, which is highly expressed in kidney as well as trachea, bone marrow and fetal liver. Recombinant OCTN1 expressed in mammalian cells exhibited saturable uptake of TEA that was pH sensitive. Several others suggest that OCTN1 is a renal proton/organic cation antiporter functioning at the epithelial apical membrane. The uptake of pyrilamine, quinidine, verapamil and L-carnitine were increased by expression of OCTN1 in *Xenopus* oocytes.

Another OCT protein family member, OCTN2, cloned from a human placental trophoblast cell line, is expressed widely in human tissues including kidney, placenta and heart. OCTN2 is more closely related to OCTN1 than to OCT1, OCT2 and OCT3 (Biochem Biophys Res Commun. 246: 589-95, 1998). Transfection of OCTN2 has demonstrated its role in the transport of TEA and carnitine. OCTN2-mediated transport of TEA is sodium independent, whereas transport of carnitine is sodium-dependent. The role of sodium in OCTN2-mediated carnitine transport not only involves the electrogenic gradient, but the presence of sodium also alters the affinity of OCTN2 for carnitine. Germline mutations of OCTN2 result in primary carnitine deficiency, a syndrome of progressive cardiomyopathy and skeletal myopathy. The symptoms associated with this syndrome are thought to result not only from generalized carnitine deficiency from decreased renal carnitine reabsorbtion, but also from inability of cardiac and skeletal myocytes, which ordinarily express OCTN2, to accumulate carnitine. This syndrome demonstrates that tissue-specific OCT-mediated transport is essential for accumulation of required cations in specific tissues.

The present invention identifies a new transport protein in the OCT family, OCT6, preferentially expressed in leukemia cell lines, leukemia blast cells and CD34+ cells. The cell surface localization and the transporter function of the OCT6 gene product suggest its usefulness as a target in the diagnosis and treatment of hematologic malignancies.

As used herein, the term "antibody" refers to an immunoglobulin molecule with a specific amino acid sequence evoked in by an antigen, and characterized by reacting specifically with the antigen in some demonstrable way.

As used herein, the term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the compositions of the present invention are administered.

As used herein, "compound" refers to any agent, chemical, substance, or substrate, whether organic or inorganic, or any protein including antibodies, peptides, polypeptides, peptoids, and the like.

As used herein, the term cytotoxin" or cytoxic agent includes any specific substance, which may or may not be antibody, that inhibits or prevents the functions of cells, causes destruction of cells, or both.

As used herein, the term "derivative" refers to something produced by modification of something pre-existing; for example, a substance or chemical compound that may be produced from another substance or compound of similar structure in one or more steps.

As used herein, the term "fragment" refers to a part of a larger entity, said larger entity comprising by non-limiting example, an antibody, compound or substance.

As used herein, the term "leukemia blast" or "leukemic blast" refers to lymphoblasts, the abnormal immature white blood cells associated with leukemia.

As used herein, the term "monoclonal antibody" is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

As used herein, the term "pharmaceutically acceptable carrier" refers to a carrier that may be administered to a subject, together with one or more liver protecting agents and one or more mushroom powder or extract of the present invention, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the compound.

As used herein, the term "substrate" refers to a substance, compound, agent, antibody or derivatives and/or fragment thereof, acted upon by the OCT6 transporter protein (e.g., a substance that is taken across the cellular membrane by action of the OCT6 transporter protein).

OCT6 (SEQ ID NO:1) was first identified as a potential OCT gene by assembling and sequencing ESTs as described in Example 1 (amino acid sequence of OCT6 is SEQ ID NO:2). The gene sequence proved to be identical to the recently submitted cDNA OKB1 (GenBank AF268892) submitted by M. Okabe and T. Abe, incorporated herein in its entirety. It is also contained within the submitted BAC clone CTA-331P3 (SEQ ID NO: 3) (GenBank AC002464) located at chromosome 6q21, incorporated herein in its entirety. The gene has a predicted protein structure typical of transport proteins with two groups of six transmembrane domains separated by a hydrophilic region (FIG. **1**A). CLUSTALW alignment produced a dendrogram showing the phylogenic relationship between OCT6 and other OAT and OCT proteins (FIG. **1**B). This dendrogram suggests that the distinction between OAT and OCT genes, based on functional studies, obscures the common origin of both families of transporters. The actual CLUSTALW alignment of these genes is shown in FIG. **2** and demonstrates multiple regions of conservation among all of these genes.

Next, according to the methods described in Example 3, quantitative RT PCR analysis of the expression of OCT6 was performed, along with the expression of other OCT genes, in 50 cell lines. The results are shown in Table 3. The two highest expressing cell lines for OCT6 in this panel were two leukemia cell lines, HL60, a human promyelocytic leukemia cell line, and MOLT4, a human acute lymphoblastic leukemia (T-cell) cell line. There was only a low level of expression detected in most of the other cell lines.

TABLE 3

OCT expression in 50 cell lines of the NCI Drug Screen

No.	Cell Line	source	OCT1	OCT2	OCT3	OCTN 2	OCT6
1	CCRF-CEM	Leukemia	0.7	0.7	0.2	0.1	5.7
2	HL-60	Leukemia	0.5	1.3	0.0	0.4	716
3	K-562	Leukemia	1.4	1.2	0.2	1.4	5.2
4	MOLT-4	Leukemia	0.1	1.1	0.5	0.6	46.8
5	RPMI-8226	Leukemia	2.8	2.0	0.1	3.7	6.02
6	SR	Leukemia	1.9	1.1	0.0	0.3	2.6
7	A549/ATCC	Lung cancer	1.7	1.2	161	4.3	1.2
8	HOP-62	Lung cancer	0.8	4.8	0.6	2.4	4.1
9	NCI-H226	Lung cancer	4.8	0.5	0.1	21.1	4.8
10	NCI-H23	Lung cancer	0.5	0.7	0.0	0.3	5.2
11	NCI-H460	Lung cancer	0.7	1.0	0.0	1.7	1.8
12	COLO205	Colon Ca.	4.9	5.3	30.9	2.2	3.6
13	HCC-2998	Colon Ca.	1.5	1.0	0.0	2.6	5.4
14	HCT-116	Colon Ca.	1.7	2.1	0.1	2.8	9.7
15	HCT-15	Colon Ca.	0.9	1.7	0.1	3.5	4.2
16	HT-29	Colon Ca.	1.9	1.2	18.1	1.5	1.5
17	KM-12	Colon Ca.	0.6	1.0	12.2	0.7	2.1
18	SW-620	Colon Ca.	1.0	2.6	40.4	1.9	3.7
19	SF-268	CNS Tumor	0.4	0.8	0.0	0.9	2
20	SF-295	CNS Tumor	0.5	1.2	0.2	1.1	2.5
21	SF-539	CNS Tumor	0.5	0.6	2.3	0.2	5.3
22	SNB-75	CNS Tumor	0.8	1.8	0.0	0.6	2.3
23	U251	CNS Tumor	0.8	0.9	0.0	0.6	7.4
24	LOCIMVI	Melanoma	2.9	2.1	0.1	0.4	3.6
25	MALME-3M	Melanoma	1.5	1.5	0.0	2.3	3
26	M14	Melanoma	1.9	1.4	0.0	1.9	4.7
27	SK-MEL-2	Melanoma	2.1	1.9	0.0	2.2	3.9
28	SK-MEL-5	Melanoma	2.6	1.5	0.0	1.9	2.7
29	UACC-257	Melanoma	3.2	3.6	0.0	1.1	5.4
30	IGROV1	Ovarian Ca.	4.9	5015	17.9	1.8	2.5
31	OVCAR-3	Ovarian Ca.	1.4	0.1	0.0	2.2	14
32	OVCAR-4	Ovarian Ca.	2.6	1.4	0.0	8.9	3.4
33	OVCAR-5	Ovarian Ca.	3.5	2.7	105	10.0	4.8
34	OVCAR-8	Ovarian Ca.	1.1	1.0	0.0	0.8	1.6
35	SK-OV-3	Ovarian Ca.	3.9	1995	9.2	8.5	9.8
36	A498	Renal Ca.	2.2	13.4	180	4.7	1.3
37	ACHN	Renal Ca.	1.1	1.1	0.7	1.2	1.1
38	CAKI_1	Renal Ca.	3.5	2.5	4.8	1.8	2.8

TABLE 3-continued

OCT expression in 50 cell lines of the NCI Drug Screen

No.	Cell Line	source	OCT1	OCT2	OCT3	OCTN 2	OCT6
39	RXF-393	Renal Ca.	1.7	1.2	3.0	0.6	1.2
40	TK-10	Renal Ca.	3.6	5.0	16.8	2.5	8
41	UO-31	Renal Ca.	4.4	1.6	31.2	1.2	2.3
42	PC-3	Prostate Ca.	2.1	0.8	9.6	3.3	4.7
43	DU-145	Prostate Ca.	1.1	1.1	3.4	1.6	3
44	MCF-7	Breast Ca.	0.8	1.8	0.0	10.4	3.5
45	NCI/ADR-RES	Breast Ca.	1.4	1.3	1.1	2.0	2.1
46	MDA-MB-231	Breast Ca.	1.2	0.4	3.9	4.8	1.8
47	HS578T	Breast Ca.	1.0	1.5	0.0	1.2	8.3
48	MDA-MB-435	Breast Ca.	1.9	0.6	0.1	0.7	2.7
49	BT-549	Breast Ca.	1.2	0.8	0.1	0.3	2.6
50	T-47D	Breast Ca.	0.7	1.1	0.1	4.2	8.7

OCT6 is unique among the known members of OCT and OAT genes because of its pattern of tissue distribution. The pattern of expression of the OCT6 gene in the 50 cell lines suggested that its expression might be restricted to hematopoietic tissues. The restricted pattern of expression observed for OCT6 also suggests that therapies using OCT6-specific substrates are unlikely to have widespread toxicity to normal tissues. Therefore, we examined OCT6 expression in a cDNA panel representing a wide cross-section of normal tissues according to the methods of Example 4 (FIG. **3**). This study revealed that OCT6 RNA levels are highest in testis and fetal liver, with lower but detectable levels in peripheral blood leukocytes and bone marrow. Since fetal hematopoiesis occurs in the liver, it is possible that the fetal liver sample may have included both hepatocytes and hematopoietic cells. OCT6 RNA levels were also barely detectable in pancreatic and adrenal tissue. Unlike other OCT genes, expression was not detectable in liver, kidney or placenta.

To determine whether OCT6 RNA expression in hematopoietic cells was lineage-specific, leukocytes were sorted from discarded buffy coat specimens by flow cytometry, and purified subpopulations were examined for OCT6 RNA expression according to the methods described in Example 5. OCT6 expression was also examined in a population of CD34+ cells. As can be seen in FIG. **4**, the expression of OCT6 was highly enriched in CD34+ cells in comparison to the other cell populations. Also, significant levels of OCT6 expression (relative to MOLT4) were found in other hematopoietic cell lines: U937, a human histiocytic lymphoma cell line; THP-1, a human acute monocytic leukemia cell line; KG-1, a human erythroleukemia cell line; and MV-4-11, a human biphenotypic (B-cell and myelomonocytic) leukemia cell line.

The high levels of OCT6 RNA in some leukemia cell lines and CD34+ cells also raised the question as to whether this gene was highly expressed in actual leukemias. To address this issue, the RNA levels of OCT6 in 25 samples of peripheral leukemic cells were measured according to the methods set out in Example 6. The FAB classification of these samples are shown in Table 4. These results are shown in FIG. **5**, and demonstrate that the majority of specimens contained RNA levels for OCT6 that exceeded the level found in MOLT4 cell line, the second highest expressing cell line among those examined, and exceed by orders of magnitude the levels found in placenta, kidney and liver.

TABLE 4

Phenotypes of leukemia specimens

Sample Number	Description
1	CML, blast crisis
2	CML, blast crisis
3	CML, stable phase
4	CML, probably stable phase
5	CML, accelerated phase
6	ALL
7	ALL
8	AML
9	ALL
10	ALL
11	ALL
12	AML
13	AML
14	AML
15	AML
16	ALL, biphenotypic
17	ALL, biphenotypic
18	AML
19	AML, M2
20	AML, M2
21	AML, M4
22	AML, M4
23	AML, M1
24	AML
25	AML, M4

Due to the OCT6 protein's location on the cellular membrane and its function as an intracellular transporter, the OCT6 transporter protein has been identified as a therapeutic target. Basic principles of cellular pharmacology suggest that increase in intracellular accumulation will lead to increased intracellular effect. For anticancer drugs, this principle has been studied extensively in the context of lipophilic drugs, which require no specific mechanism for cellular uptake, and export pumps such as the product of the multidrug resistance gene, MDR1, whose overexpression of MDR1 leads to increased cellular resistance by decreasing intracellular concentrations of drug (Moscow, J. A., Schneider, E. S., Ivy, S. P., and Cowan, K. H. Multidrug resistance. In: H. M. Pinedo, D. L. Longo, and B. A. Chabner (eds.), Cancer chemotherapy and biological response modifiers. Annual 17. New York: Elsevier, 1997). The same principle applies to charged, hydrophilic drugs of the present invention, except that the determinants of sensitivity depend on uptake as opposed to efflux. As such, cells overexpressing an OCT6 transporter are likely to be highly sensitive to cytotoxic OCT6 substrates.

Drug Screening

Accordingly, the present invention provides methods for screening potential substrates of, and potential therapeutic agents against hematological malignancies like leukemia that overexpress, the OCT6 transporter. In particular, potential therapeutic agents are screened for the ability to be a substrate recognized by an OCT6 transporter protein. Preferably, potential substrates are screened for the ability to confer cytotoxic effects on a cell overexpressing OCT6 transporter protein. More preferably, agents are screened for the ability to preferentially cause cellular uptake into, and cell death of, cells overexpressing the OCT6 transporter. Most preferably, the agents are screened for the ability to cause cell death of cancer cells such as leukemia overexpressing the OCT6 transporter as compared to normal cells.

A method for screening potential substrates of the OCT6 transporter protein comprises providing a cell or cell line which expresses OCT6 and a test compound, incubating the test compound and cell line and analyzing the cell or cell line to determine if there was a cellular influx of the test compound. Analysis of the cell line to determine whether cellular uptake of the test compound occurred can be accomplished by any means known in the art. For example, a test compound can be tagged with a detectable label prior to contact with a cell and then observed under microscopy or by other means for its location. Non-limiting examples of labels include green fluorescent protein, alkaline phosphatase, horseradish peroxidase, rease, f3-galactosidase, CAT, luciferase, an immunogenic tag peptide sequence, an extrinsically activatable enzyme, an extrinsically activatable toxin, an extrinsically activatable fluor, an extrinsically activatable quenching agent, a radioactive element or an antibody.

A method for screening candidate anti-cancer agents comprises determining the viability of a mammalian cell which expresses OCT6 incubated in the presence and absence of a test compound and identifying the test compound as a potential anti-leukemia agent if there is a cellular uptake of the test compound and cell death. Analysis of cell viability can be accomplished by any means known in the art.

It is well known in the art that viability of a cell can be determined by contacting the cell with a dye and viewing it under a microscope. Viable cells can be observed to have an intact membrane and do not stain, whereas dying or dead cells having "leaky" membranes do stain. Incorporation of the dye by the cell indicates the death of the cell. The most common dye used in the art for determining viability is trypan blue. Viability of cells can also be determined by detecting DNA synthesis. Cells can be cultured in cell medium with labeled nucleotides (e.g., ^{3}H thymidine). The uptake or incorporation of the labeled nucleotides indicates DNA synthesis and cell viability. In addition, colonies formed by cells cultured in medium indicate cell growth and is another means to test viability of the cells.

Identification and/or observation of cells undergoing apoptosis can be another method of determining cell viability. Apoptosis is a specific mode of cell death recognized by a characteristic pattern of morphological, biochemical, and molecular changes. Cells going through apoptosis appear shrunken, and rounded; they also can be observed to become detached from culture dish. Thermophological changes involve a characteristic pattern of condensation of chromatin and cytoplasm which can be readily identified by microscopy. When stained with a DNA-binding dye, such as H33258, apoptotic cells display classic condensed and punctate nuclei instead of homogeneous and round nuclei.

The hallmark of apoptosis is the endonucleolysis, a molecular change in which nuclear DNA is initially degraded at the linker sections of nucleosomes to give rise to fragments equivalent to single and multiple nucleosomes. When these DNA fragments are subjected to gel electrophoresis, they reveal a series of DNA bands which are positioned approximately equally distant from each other on the gel. The size difference between the two bands next to each other is about the length of one nucleosome (i.e., 20 base pairs). This characteristic display of the DNA bands is called a DNA ladder and it indicates apoptosis of the cell. Apoptotic cells can be identified by flow cytometric methods based on measurement of cellular DNA content, increased sensitivity of DNA to denaturation, or altered light scattering properties. These methods are well known in the art and are within the contemplation of the invention.

Abnormal DNA breaks are also characteristic of apoptosis and can be detected by any means known in the art. In one embodiment, DNA breaks are labeled with biotinylated dUTP (b-dUTP). Cells are fixed and incubated in the presence of biotinylated dUTP with either exogenous terminal transferase (terminal DNA transferase assay; TdT assay) or DNA polymerase (nick translation assay; NT assay). The biotinylated dUTP is incorporated into the chromosome at the places where abnormal DNA breaks are repaired, and are detected with fluorescein conjugated to avidin under fluorescence microscopy.

Kits

The present invention provides kits that can be used in the above screening methods. In one embodiment, a kit comprises a substantially isolated polypeptide comprising an OCT6 epitope which is specifically immunoreactive with only test compound(s) that are substrates of the OCT6 transporter protein. Binding of a test compound to the OCT6 epitope is indicative that the test compound is a OCT6 substrate. In another embodiment, a kit comprises a cell line that overexpresses an OCT6 transporter protein. Binding and/or cellular uptake of a test compound via the OCT6 protein is indicative that the test compound is a OCT6 substrate. Preferably, the kits of the present invention further comprise a control compound or antibody which does not react with the OCT6 transporter protein. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of a test compound to an OCT6 epitope and/or cellular uptake of a test compound. For example, the test compound may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate.

The detectable substance may be coupled or conjugated either directly to the test compound (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Pat. No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Further non-limiting examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, nonradioactive paramagnetic metal ions, immunogenic tag peptide sequences, extrinsically activatable toxins, extrinsically activatable quenching agents, or antibodies. Non-limiting examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/bi-

otin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{111}In or ^{99}Tc.

Immunogenic Compositions

The present invention also provides immunogenic compositions for the treatment of hematological malignancies. Non-limiting exemplary hematological malignancies include, but are not limited to, Hodgkin's disease, leukemia such as, acute lymphoid (lymphocytic or lymphoblastic) leukemia (ALL), acute myeloid (myelogenous or myeloblastic) leukemia (AML), acute lymphoid leukemia, biphenotypic (ALL, biphentoypic), acute undifferentiated leukemia (AUL), chronic myeloid (myelogenous or granulocytic) leukemia (CML), erythroleukemia, granuloxytic leukemia, lymphoma, monocytic leukemia, myleoma, myelomonocytic leukemia, myelodysplastic syndromes, non-Hodgkin lymphoma, progranulocytic leukemia.

According to the invention immunogenic compositions for the treatment of hematological malignancies comprise a substrate recognized by an OCT6 transporter protein. Preferably, the substrate is a compound that binds selectively or specifically to a OCT6 transporter protein. In a preferred embodiment, the compound binds selectively to the OCT6 transporter protein encoded by a nucleotide sequence of SEQ ID NO:1. The compound may be a cytotoxin or coupled or conjugated with a cytoxic agent. Preferably the cytoxin or cytotoxic agent is a chemotherapeutic agent.

The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a pharmaceutically acceptable carrier.

Cell surface proteins like the OCT6 transporter can be utilized in antibody-based targeting strategies. In still another aspect of the invention, antibodies can be developed by known methods in the art against the external epitope of OCT6 transporter protein. In a preferred embodiment, antibodies are substrates of the OCT6 protein. The antibodies may be polyclonal antibodies or monoclonal antibodies.

Polyclonal antibodies to an antigen-of-interest can be produced by various procedures well known in the art. For example, a polypeptide of the invention can be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to induce the production of sera containing polyclonal antibodies specific for the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and *corynebacterium parvum*. Such adjuvants are also well known in the art.

Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: Monoclonal Antibodies and T-Cell Hybridomas 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties).

The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate, such as, for example, a linker known in the art, using techniques known in the art. (See, for example, U.S. Pat. No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention.) Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{111}In or ^{99}Tc.

Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ^{213}Bi. Non-limiting examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

The conjugates of the invention can be used for modifying a given biological response such as inducing cell death for the treatment and prevention of hematological malignancies like leukemia. The therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity for inducing cell death. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, a-interferon, .beta.-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g.,

TNF-alpha, TNF-beta, AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi et al., Int. Immunol., 6:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a thrombotic agent or an anti-angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Therapeutic Treatment

The present invention is further directed to methods for preventing and treating hematological malignancies such as leukemia. According to the invention, hematological malignancies comprise without limitation, Hodgkin's disease, leukemia such as, acute lymphoid (lymphocytic or lymphoblastic) leukemia (ALL), acute myeloid (myelogenous or myeloblastic) leukemia (AML), acute lymphoid leukemia, biphenotypic (ALL, biphentoypic), acute undifferentiated leukemia (AUL), chronic myeloid (myelogenous or granulocytic) leukemia (CML), erythroleukemia, granuloxytic leukemia, lymphoma, monocytic leukemia, myleoma, myelomonocytic leukemia, myelodysplastic syndromes, non-Hodgkin lymphoma, progranulocytic leukemia.

Methods of treatment of the present invention comprise administering to a subject in need thereof an immunogenic composition of the present invention. The compositions may be administered with a pharmaceutically acceptable carrier.

Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate. etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The amount of the compound of the invention which will be effective in the treatment, inhibition and prevention of hematological malignancies can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

Various other delivery systems are known and can be used to administer a composition of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (See, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

In another embodiment, the compound or composition can be delivered in a vesicle, in particular a liposome (See Langer, Science 249:1527-1533 (1990); Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); Lopez-Berestein, ibid., pp. 317-327; see generally ibid.)

In yet another embodiment, the compound or composition can be delivered in a controlled release system. In one

embodiment, a pump may be used (see Langer, supra; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321: 574 (1989)). In another embodiment, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Fla. (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); see also Levy et al., Science 228: 190 (1985); During et al., Ann. Neurol. 25:351 (1989); Howard et al., J. Neurosurg. 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138 (1984)).

In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered in vivo to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Pat. No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (see e.g., Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

EXAMPLES

The following examples are presented for the illustrative purposes and it is to be understood that the present invention is not limited to those precise embodiments, and that various changes and modifications can be effected therein by one skilled in the art without departing from the scope and spirit of the invention as defined by the appended claims.

Example 1

OCT6 Nucleotide Sequence Identification and Analysis

OCT6 was first identified as a potential OCT gene by assembling and sequencing ESTs. BLAST searches of human ESTs in GenBank data base identified AI040384 (654 bp), AA033971 (714 bp) and H70190 (474 bp) sequences from three fetal liver IMAGE clones, 1656502, 429904 and 212935 respectively. IMAGE clone 1656502 (3', insert 1337 bp) ended the predicted 3' stop codon, whereas IMAGE clone 429904 (5', insert 996 bp) and IMAGE clone 212935 (5', insert 966 bp) aligned with the 5'-coding region. All clones were obtained from the IMAGE Consortium through the American Type Culture Collection (Manassas, Va.). Each clone was sequenced in both directions. The sequences were determined using ABI Prism™ 377 DNA sequencer (Perkin-Elmer). Our assemblage proved to be identical to the recently submitted cDNA OKB1 (AF268892) submitted by M. Okabe and T. Abe. We have dubbed this gene OCT6 as OCTN1 and OCTN2 may be considered as OCT4 and OCT5 respectively.

The OCT6 gene (SEQ ID NO:1) is also contained within BAC clone CTA-331P3 (SEQ ID NO:3) (GenBank AC002464) located at chromosome 6q21. It is divided into 6 exons that span 42 kb on the human genome, from nucleotide 79,570 to nucleotide 120490 on CTA-331P3.

The gene has a predicted protein structure typical of transport proteins with 2 groups of 6 transmembrane domains separated by a hydrophilic region (FIG. **1**A). The large hydrophilic region between TMD1 and TMD2 is typical of OCT and OAT genes and is presumed to be located on the outside surface of the cell membrane. The OCT6 protein contains potential sites for N-glycosylation and phosphorylation, which will be described below in Methods. Of interest, the protein sequence also contains a 22 amino acid leucine zipper motif, starting at amino acid 146, suggesting that there may be a physical interaction between OCT6 and ion channels or other membrane-associated proteins.

CLUSTALW alignment produced a dendrogram showing the phylogenic relationship between OCT6 and other OAT and OCT proteins (FIG. **1**B). This dendrogram suggests that the distinction between OAT and OCT genes, based on functional studies, obscures the common origin of both families of transporters. The actual CLUSTALW alignment of these genes is shown in FIG. **2** and demonstrates multiple regions of conservation among all of these genes.

The hydropathy profile analysis, multiple sequence alignments of amino acid sequences using CLUSTALW and the phylogenetic tree were all produced with MacVector software.

Example 2

Molecular Cloning of OCT6

BLAST searches of human ESTs in GenBank data base identified AI040384 (654 bp), AA033971 (714 bp) and H70190 (474 bp) sequences from three fetal liver IMAGE clones, 1656502, 429904 and 212935 respectively. IMAGE clone 1656502 (3', insert 1337 bp) ended the predicted 3' stop codon, whereas IMAGE clone 429904 (5', insert 996 bp) and IMAGE clone 212935 (5', insert 966 bp) aligned with the 5'-coding region. All clones were obtained from the IMAGE Consortium through the American Type Culture Collection (Manassas, Va.). Each clone was sequenced in both directions. The sequences were determined using ABI Prism™ 377 DNA sequencer (Perkin-Elmer).

Example 3

Quantitative RT-PCR of OCT6 RNA Levels in Cancer Cell Lines

Total RNA isolated from 50 cell lines used in the NCI drug screen program was provided by the Developmental Therapeutics Program, NCI. Quantitative RT-PCR for detecting OAT-X transporter gene expression was performed by using a Roche LightCycler, which uses real time fluorescence detection for quantitative measurement of PCR products. A gene-specific primer pair was designed with Oligo 4.0 software and purchased from Integrated DNA Technologies, Inc. (Coralville, Iowa) (F: 5'-GGCACATTTATTCACCAAGACCAG-3') (SEQ ID NO: 13) and (F: 5'-TGTGGACCTCAGCAG-CATTTGGAT-3') (SEQ ID NO:14). The specificity of the PCR reaction was confirmed by directly determining the DNA sequence of the PCR product. First, cDNA was synthesized from total RNA using SuperScript First-Strand Synthesis System (GIBCO/BRL) in a 20 μl volume following the instructions supplied by the manufacturer. The cDNA treated with RNAse H for 20 minutes at 37° C. and stored at −20° C. Then, 2 ul of cDNA reaction was amplified in a standard PCR reaction condition, using 0.3 μM primer concentration, with the addition of SYBR Green I Dye. After 30 seconds denature at 95° C., the amplification reaction proceeded through 45-50 cycles of 95° C. denature for 0 second, 62-65° C. annealing

for 10 seconds and a 72° C. extension for 40 seconds, with slopes of 20° C./s, 20° C./s and 2° C./s, respectively.

Fluorescence was acquired during each cycle after heating to a temperature just below the product melting temperature. Quantification was performed using the LightCycler analysis software. The log-linear portion of the standard amplification curve was identified, and the 'crossing point', a threshold of relative fluorescence, was determined as the best fit through the log-linear region above the background fluorescence (noise) band. The quantification of PCR product then was derived by plotting fluorescence data in the log linear region of each sample to determine a calculated number of cycles needed to reach the fluorescence crossing point. The calculated number of cycles required to reach the crossing point is proportional to the amount of target RNA in the sample. The relative amount of product was described in arbitrary units by interpolation of the data using a standard curve of a series of dilutions of a standard cell line RNA. The quantitative measurement of each gene in each cell line was normalized to the relative amount of actin RNA in each cell line, as a control for equivalent cDNA loading in each sample. The results represent the average of 3 independent determinations performed in duplicate.

A melting curve analysis was performed with positive control RNA prior analysis of the cell lines to enhance sensitivity and the specificity of the data. Amplified products usually melt quickly at a temperature characteristic for the products. The fluorescence signal was acquired at a temperature just below the Tm of the specific PCR product and above the Tm of the primer dimers. All specific PCR products displayed a single, sharply melting curve with a narrow peak. In addition, PCR products were confirmed for specificity and correct size by visualization of the LightCycler products on a 1% agarose gel.

Example 4

Tissue Distribution

First strand cDNAs derived from 24 adult and fetal tissues (RAPID-SCAN gene expression panel, OriGene Technologies, Rockville, Md.). The PCR primers used in this study were the same as used in the quantitative RT-PCR studies. The PCR reaction samples were denatured at 94° C. for 30 seconds, annealed and extended at 64° C. for 30 sec for 35 cycles. The PCR products were then visualized on 1% agarose gels.

Example 5

Cell Sorting

All human specimens were obtained in accordance with institutional IRB guidelines. Leukocytes from fresh discarded buffy coats were isolated after RBC lysis with ammonium chloride and labeled with lineage specific antibodies (CD14, monocytes; CD15, granulocytes; CD3, T-cells; and CD20, B-cells), and isolated using a FACSVantage flow cytometer. Each population was sorted twice to ensure purities of at least 99%. CD34 cells were obtained from discarded aliquots of G-CSF-mobilized peripheral blood stem cell collections from cancer patients. For each sample, the PCR results represent the pooled average of cells from 2 individuals performed in triplicate or quadruplicate.

Example 6

OCT6 RNA Levels in Leukemic Blasts

Total RNA was extracted from leukemia specimens using QIAGEN RNeasy midi kit. 150 ng of total RNA were used as a template for the first strand cDNA synthesis with the Oligo (dT) primer using the super script system (GIBCO BRL) according to the manufacturer's protocol. Quantitative real-time RT-PCR was performed using an iCycler thermal cycler with methods similar to those described above for the Roche LightCycler. The results represent the average of 3 independent determination performed in duplicate.

Although illustrative embodiments of the present invention have been described in detail, it is to be understood that the present invention is not limited to those precise embodiments, and that various changes and modifications can be effected therein by one skilled in the art without departing from the scope and spirit of the invention as defined by the appended claims.

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Met Ala Val Gln Thr Gly Phe Ser Phe Leu Gln Ile Phe Ser Ile Ser
            180                 185                 190

Trp Glu Met Phe Thr Val Leu Phe Val Ile Val Gly Met Gly Gln Ile
        195                 200                 205

Ser Asn Tyr Val Val Ala Phe Ile Leu Gly Thr Glu Ile Leu Gly Lys
    210                 215                 220

Ser Val Arg Ile Ile Phe Ser Thr Leu Gly Val Cys Thr Phe Phe Ala
225                 230                 235                 240

Val Gly Tyr Met Leu Leu Pro Leu Phe Ala Tyr Phe Ile Arg Asp Trp
                245                 250                 255

Arg Met Leu Leu Leu Ala Leu Thr Val Pro Gly Val Leu Cys Val Pro
            260                 265                 270

Leu Trp Trp Phe Ile Pro Glu Ser Pro Arg Trp Leu Ile Ser Gln Arg
        275                 280                 285

Arg Phe Arg Glu Ala Glu Asp Ile Ile Gln Lys Ala Ala Lys Met Asn
    290                 295                 300

Asn Ile Ala Val Pro Ala Val Ile Phe Asp Ser Val Glu Glu Leu Asn
305                 310                 315                 320

Pro Leu Lys Gln Gln Lys Ala Phe Ile Leu Asp Leu Phe Arg Thr Arg
                325                 330                 335

Asn Ile Ala Ile Met Thr Ile Met Ser Leu Leu Leu Trp Met Leu Thr
            340                 345                 350

Ser Val Gly Tyr Phe Ala Leu Ser Leu Asp Ala Pro Asn Leu His Gly
        355                 360                 365

Asp Ala Tyr Leu Asn Cys Phe Leu Ser Ala Leu Ile Glu Ile Pro Ala
    370                 375                 380

Tyr Ile Thr Ala Trp Leu Leu Leu Arg Thr Leu Pro Arg Arg Tyr Ile
385                 390                 395                 400

Ile Ala Ala Val Leu Phe Trp Gly Gly Gly Val Leu Leu Phe Ile Gln
                405                 410                 415

Leu Val Pro Val Asp Tyr Tyr Phe Leu Ser Ile Gly Leu Val Met Leu
            420                 425                 430

Gly Lys Phe Gly Ile Thr Ser Ala Phe Ser Met Leu Tyr Val Phe Thr
        435                 440                 445

Ala Glu Leu Tyr Pro Thr Leu Val Arg Asn Met Ala Val Gly Val Thr
    450                 455                 460

Ser Thr Ala Ser Arg Val Gly Ser Ile Ile Ala Pro Tyr Phe Val Tyr
465                 470                 475                 480

Leu Gly Ala Tyr Asn Arg Met Leu Pro Tyr Ile Val Met Gly Ser Leu
                485                 490                 495

Thr Val Leu Ile Gly Ile Leu Thr Leu Phe Phe Pro Glu Ser Leu Gly
            500                 505                 510

Met Thr Leu Pro Glu Thr Leu Glu Gln Met Gln Lys Val Lys Trp Phe
        515                 520                 525

Arg Ser Gly Lys Lys Thr Arg Asp Ser Met Glu Thr Glu Glu Asn Pro
    530                 535                 540

Lys Val Leu Ile Thr Ala Phe
545                 550
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<210> SEQ ID NO 5
<211> LENGTH: 551
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 5

Met Ala Gln Phe Val Gln Val Leu Ala Glu Ile Gly Asp Phe Gly Arg
1 5 10 15

Phe Gln Ile Gln Leu Leu Ile Leu Leu Cys Val Leu Asn Phe Leu Ser
20 25 30

Pro Phe Tyr Phe Phe Ala His Val Phe Met Val Leu Asp Glu Pro His
35 40 45

His Cys Ala Val Ala Trp Val Lys Asn His Thr Phe Asn Leu Ser Ala
50 55 60

Ala Glu Gln Leu Val Leu Ser Val Pro Leu Asp Thr Ala Gly His Pro
65 70 75 80

Glu Pro Cys Leu Met Phe Arg Pro Pro Pro Ala Asn Ala Ser Leu Gln
85 90 95

Asp Ile Leu Ser His Arg Phe Asn Glu Thr Gln Pro Cys Asp Met Gly
100 105 110

Trp Glu Tyr Pro Glu Asn Arg Leu Pro Ser Leu Lys Asn Glu Phe Asn
115 120 125

Leu Val Cys Asp Arg Lys His Leu Lys Asp Thr Thr Gln Ser Val Phe
130 135 140

Met Gly Gly Leu Leu Val Gly Thr Leu Met Phe Gly Pro Leu Cys Asp
145 150 155 160

Arg Ile Gly Arg Lys Ala Thr Ile Leu Ala Gln Leu Leu Leu Phe Thr
165 170 175

Leu Ile Gly Leu Ala Thr Ala Phe Val Pro Ser Phe Glu Leu Tyr Met
180 185 190

Ala Leu Arg Phe Ala Val Ala Thr Ala Val Ala Gly Leu Ser Phe Ser
195 200 205

Asn Val Thr Leu Leu Thr Glu Trp Val Gly Pro Ser Trp Arg Thr Gln
210 215 220

Ala Val Val Leu Ala Gln Cys Asn Phe Ser Leu Gly Gln Met Val Leu
225 230 235 240

Ala Gly Leu Ala Tyr Gly Phe Arg Asn Trp Arg Leu Leu Gln Ile Thr
245 250 255

Gly Thr Ala Pro Gly Leu Leu Leu Phe Phe Tyr Phe Trp Ala Leu Pro
260 265 270

Glu Ser Ala Arg Trp Leu Leu Thr Arg Gly Arg Met Asp Glu Ala Ile
275 280 285

Gln Leu Ile Gln Lys Ala Ala Ser Val Asn Arg Arg Lys Leu Ser Pro
290 295 300

Glu Leu Met Asn Gln Leu Val Pro Glu Lys Thr Gly Pro Ser Gly Asn
305 310 315 320

Ala Leu Asp Leu Phe Arg His Pro Gln Leu Arg Lys Val Thr Leu Ile
325 330 335

Ile Phe Cys Val Trp Phe Val Asp Ser Leu Gly Tyr Tyr Gly Leu Ser
340 345 350

Leu Gln Val Gly Asp Phe Gly Leu Asp Val Tyr Leu Thr Gln Leu Ile
355 360 365

Phe Gly Ala Val Glu Val Pro Ala Arg Cys Ser Ser Ile Phe Met Met

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    370                 375                 380

Gln Arg Phe Gly Arg Lys Trp Ser Gln Leu Gly Thr Leu Val Leu Gly
385                 390                 395                 400

Gly Leu Met Cys Ile Ile Ile Ile Phe Ile Pro Ala Asp Leu Pro Val
                405                 410                 415

Val Val Thr Met Leu Ala Val Val Gly Lys Met Ala Thr Ala Ala Ala
            420                 425                 430

Phe Thr Ile Ser Tyr Val Tyr Ser Ala Glu Leu Phe Pro Thr Ile Leu
        435                 440                 445

Arg Gln Thr Gly Met Gly Leu Val Gly Ile Phe Ser Arg Ile Gly Gly
    450                 455                 460

Ile Leu Thr Pro Leu Val Ile Leu Leu Gly Glu Tyr His Ala Ala Leu
465                 470                 475                 480

Pro Met Leu Ile Tyr Gly Ser Leu Pro Ile Val Ala Gly Leu Leu Cys
                485                 490                 495

Thr Leu Leu Pro Glu Thr His Gly Gln Gly Leu Lys Asp Thr Leu Gln
            500                 505                 510

Asp Leu Glu Leu Gly Pro His Pro Arg Ser Pro Lys Ser Val Pro Ser
        515                 520                 525

Glu Lys Glu Thr Glu Ala Lys Gly Arg Thr Ser Ser Pro Gly Val Ala
    530                 535                 540

Phe Val Ser Ser Thr Tyr Phe
545                 550


<210> SEQ ID NO 6
<211> LENGTH: 557
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

Met Arg Asp Tyr Asp Glu Val Thr Ala Phe Leu Gly Glu Trp Gly Pro
1               5                   10                  15

Phe Gln Arg Leu Ile Phe Phe Leu Leu Ser Ala Ser Ile Ile Pro Asn
            20                  25                  30

Gly Phe Thr Gly Leu Ser Ser Val Phe Leu Ile Ala Thr Pro Glu His
        35                  40                  45

Arg Cys Arg Val Pro Asp Ala Ala Asn Leu Ser Ser Ala Trp Arg Asn
    50                  55                  60

His Thr Val Pro Leu Arg Leu Arg Asp Gly Arg Glu Val Pro His Ser
65                  70                  75                  80

Cys Arg Arg Tyr Arg Leu Ala Thr Ile Ala Asn Phe Ser Ala Leu Gly
                85                  90                  95

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

Cys Leu Asp Gly Trp Glu Phe Ser Gln Asp Val Tyr Leu Ser Thr Ile
        115                 120                 125

Val Thr Glu Trp Asn Leu Val Cys Glu Asp Asp Trp Lys Ala Pro Leu
    130                 135                 140

Thr Ile Ser Leu Phe Phe Val Gly Val Leu Leu Gly Ser Phe Ile Ser
145                 150                 155                 160

Gly Gln Leu Ser Asp Arg Phe Gly Arg Lys Asn Val Leu Phe Val Thr
                165                 170                 175

Met Gly Met Gln Thr Gly Phe Ser Phe Leu Gln Ile Phe Ser Lys Asn
            180                 185                 190
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Phe Glu Met Phe Val Val Leu Phe Val Leu Val Gly Met Gly Gln Ile
        195                 200                 205

Ser Asn Tyr Val Ala Ala Phe Val Leu Gly Thr Glu Ile Leu Gly Lys
    210                 215                 220

Ser Val Arg Ile Ile Phe Ser Thr Leu Gly Val Cys Ile Phe Tyr Ala
225                 230                 235                 240

Phe Gly Tyr Met Val Leu Pro Leu Phe Ala Tyr Phe Ile Arg Asp Trp
                245                 250                 255

Arg Met Leu Leu Val Ala Leu Thr Met Pro Gly Val Leu Cys Val Ala
            260                 265                 270

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

Arg Phe Glu Glu Ala Glu Val Ile Ile Arg Lys Ala Ala Lys Ala Asn
    290                 295                 300

Gly Ile Val Val Pro Ser Thr Ile Phe Asp Pro Ser Glu Leu Gln Asp
305                 310                 315                 320

Leu Ser Ser Lys Lys Gln Gln Ser His Asn Ile Leu Asp Leu Leu Arg
                325                 330                 335

Thr Trp Asn Ile Arg Met Val Thr Ile Met Ser Ile Met Leu Trp Met
            340                 345                 350

Thr Ile Ser Val Gly Tyr Phe Gly Leu Ser Leu Asp Thr Pro Asn Leu
        355                 360                 365

His Gly Asp Ile Phe Val Asn Cys Phe Leu Ser Ala Met Val Glu Val
    370                 375                 380

Pro Ala Tyr Val Leu Ala Trp Leu Leu Leu Gln Tyr Leu Pro Arg Arg
385                 390                 395                 400

Tyr Ser Met Ala Thr Ala Leu Phe Leu Gly Gly Ser Val Leu Leu Phe
                405                 410                 415

Met Gln Leu Val Pro Pro Asp Leu Tyr Tyr Leu Ala Thr Val Leu Val
            420                 425                 430

Met Val Gly Lys Phe Gly Val Thr Ala Ala Phe Ser Met Val Tyr Val
        435                 440                 445

Tyr Thr Ala Glu Leu Tyr Pro Thr Val Val Arg Asn Met Gly Val Gly
    450                 455                 460

Val Ser Ser Thr Ala Ser Arg Leu Gly Ser Ile Leu Ser Pro Tyr Phe
465                 470                 475                 480

Val Tyr Leu Gly Ala Tyr Asp Arg Phe Leu Pro Tyr Ile Leu Met Gly
                485                 490                 495

Ser Leu Thr Ile Leu Thr Ala Ile Leu Thr Leu Phe Leu Pro Glu Ser
            500                 505                 510

Phe Gly Thr Pro Leu Pro Asp Thr Ile Asp Gln Met Leu Arg Val Lys
        515                 520                 525

Gly Met Lys His Arg Lys Thr Pro Ser His Thr Arg Met Leu Lys Asp
    530                 535                 540

Gly Gln Glu Arg Pro Thr Ile Leu Lys Ser Thr Ala Phe
545                 550                 555


<210> SEQ ID NO 7
<211> LENGTH: 555
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

Met Pro Thr Thr Val Asp Asp Val Leu Glu His Gly Gly Glu Phe His
1               5                   10                  15
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Phe Phe Gln Lys Gln Met Phe Phe Leu Leu Ala Leu Leu Ser Ala Thr
            20                  25                  30

Phe Ala Pro Ile Tyr Val Gly Ile Val Phe Leu Gly Phe Thr Pro Asp
        35                  40                  45

His Arg Cys Arg Ser Pro Gly Val Ala Glu Leu Ser Leu Arg Cys Gly
    50                  55                  60

Trp Ser Pro Ala Glu Glu Leu Asn Tyr Thr Val Pro Gly Pro Gly Pro
65                  70                  75                  80

Ala Gly Glu Ala Ser Pro Arg Gln Cys Arg Arg Tyr Glu Val Asp Trp
                85                  90                  95

Asn Gln Ser Thr Phe Asp Cys Val Asp Pro Leu Ala Ser Leu Asp Thr
            100                 105                 110

Asn Arg Ser Arg Leu Pro Leu Gly Pro Cys Arg Asp Gly Trp Val Tyr
        115                 120                 125

Glu Thr Pro Gly Ser Ser Ile Val Thr Glu Phe Asn Leu Val Cys Ala
    130                 135                 140

Asn Ser Trp Met Leu Asp Leu Phe Gln Ser Ser Val Asn Val Gly Phe
145                 150                 155                 160

Phe Ile Gly Ser Met Ser Ile Gly Tyr Ile Ala Asp Arg Phe Gly Arg
                165                 170                 175

Lys Leu Cys Leu Leu Thr Thr Val Leu Ile Asn Ala Ala Ala Gly Val
            180                 185                 190

Leu Met Ala Ile Ser Pro Thr Tyr Thr Trp Met Leu Ile Phe Arg Leu
        195                 200                 205

Ile Gln Gly Leu Val Ser Lys Ala Gly Trp Leu Ile Gly Tyr Ile Leu
    210                 215                 220

Ile Thr Glu Phe Val Gly Arg Arg Tyr Arg Arg Thr Val Gly Ile Phe
225                 230                 235                 240

Tyr Gln Val Ala Tyr Thr Val Gly Leu Leu Val Leu Ala Gly Val Ala
                245                 250                 255

Tyr Ala Leu Pro His Trp Arg Trp Leu Gln Phe Thr Val Ala Leu Pro
            260                 265                 270

Asn Phe Phe Phe Leu Leu Tyr Tyr Trp Cys Ile Pro Glu Ser Pro Arg
        275                 280                 285

Trp Leu Ile Ser Gln Asn Lys Asn Ala Glu Ala Met Arg Ile Ile Lys
    290                 295                 300

His Ile Ala Lys Lys Asn Gly Lys Ser Leu Pro Ala Ser Leu Gln Arg
305                 310                 315                 320

Leu Arg Leu Glu Glu Glu Thr Gly Lys Lys Leu Asn Pro Ser Phe Leu
                325                 330                 335

Asp Leu Val Arg Thr Pro Gln Ile Arg Lys His Thr Met Ile Leu Met
            340                 345                 350

Tyr Asn Trp Phe Thr Ser Ser Val Leu Tyr Gln Gly Leu Ile Met His
        355                 360                 365

Met Gly Leu Ala Gly Asp Asn Ile Tyr Leu Asp Phe Phe Tyr Ser Ala
    370                 375                 380

Leu Val Glu Phe Pro Ala Ala Phe Met Ile Ile Leu Thr Ile Asp Arg
385                 390                 395                 400

Ile Gly Arg Arg Tyr Pro Trp Ala Ala Ser Asn Met Val Ala Gly Ala
                405                 410                 415

Ala Cys Leu Ala Ser Val Phe Ile Pro Gly Asp Leu Gln Trp Leu Lys
            420                 425                 430
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Ile Ile Ile Ser Cys Leu Gly Arg Met Gly Ile Thr Met Ala Tyr Glu
        435                 440                 445

Ile Val Cys Leu Val Asn Ala Glu Leu Tyr Pro Thr Phe Ile Arg Asn
    450                 455                 460

Leu Gly Val His Ile Cys Ser Ser Met Cys Asp Ile Gly Gly Ile Ile
465                 470                 475                 480

Thr Pro Phe Leu Val Tyr Arg Leu Thr Asn Ile Trp Leu Glu Leu Pro
                485                 490                 495

Leu Met Val Phe Gly Val Leu Gly Leu Val Ala Gly Gly Leu Val Leu
            500                 505                 510

Leu Leu Pro Glu Thr Lys Gly Lys Ala Leu Pro Glu Thr Ile Glu Glu
        515                 520                 525

Ala Glu Asn Met Gln Arg Pro Arg Lys Asn Lys Glu Lys Met Ile Tyr
    530                 535                 540

Leu Gln Val Gln Lys Leu Asp Ile Pro Leu Asn
545                 550                 555


<210> SEQ ID NO 8
<211> LENGTH: 554
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

Met Pro Thr Val Asp Asp Ile Leu Glu Gln Val Gly Glu Ser Gly Trp
1               5                   10                  15

Phe Gln Lys Gln Ala Phe Leu Ile Leu Cys Leu Leu Ser Ala Ala Phe
            20                  25                  30

Ala Pro Ile Cys Val Gly Ile Val Phe Leu Gly Phe Thr Pro Asp His
        35                  40                  45

His Cys Gln Ser Pro Gly Val Ala Glu Leu Ser Gln Arg Cys Gly Trp
    50                  55                  60

Ser Pro Ala Glu Glu Leu Asn Tyr Thr Val Pro Gly Leu Gly Pro Ala
65                  70                  75                  80

Gly Glu Ala Phe Leu Gly Gln Cys Arg Arg Tyr Glu Val Asp Trp Asn
                85                  90                  95

Gln Ser Ala Leu Ser Cys Val Asp Pro Leu Ala Ser Leu Ala Thr Asn
            100                 105                 110

Arg Ser His Leu Pro Leu Gly Pro Cys Gln Asp Gly Trp Val Tyr Asp
        115                 120                 125

Thr Pro Gly Ser Ser Ile Val Thr Glu Phe Asn Leu Val Cys Ala Asp
    130                 135                 140

Ser Trp Lys Leu Asp Leu Phe Gln Ser Cys Leu Asn Ala Gly Phe Leu
145                 150                 155                 160

Phe Gly Ser Leu Gly Val Gly Tyr Phe Ala Asp Arg Phe Gly Arg Lys
                165                 170                 175

Leu Cys Leu Leu Gly Thr Val Leu Val Asn Ala Val Ser Gly Val Leu
            180                 185                 190

Met Ala Phe Ser Pro Asn Tyr Met Ser Met Leu Leu Phe Arg Leu Leu
        195                 200                 205

Gln Gly Leu Val Ser Lys Gly Asn Trp Met Ala Gly Tyr Thr Leu Ile
    210                 215                 220

Thr Glu Phe Val Gly Ser Gly Ser Arg Arg Thr Val Ala Ile Met Tyr
225                 230                 235                 240

Gln Met Ala Phe Thr Val Gly Leu Val Ala Leu Thr Gly Leu Ala Tyr
                245                 250                 255
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Ala Leu Pro His Trp Arg Trp Leu Gln Leu Ala Val Ser Leu Pro Thr
            260                 265                 270

Phe Leu Phe Leu Leu Tyr Tyr Trp Cys Val Pro Glu Ser Pro Arg Trp
        275                 280                 285

Leu Leu Ser Gln Lys Arg Asn Thr Glu Ala Ile Lys Ile Met Asp His
    290                 295                 300

Ile Ala Gln Lys Asn Gly Lys Leu Pro Pro Ala Asp Leu Lys Met Leu
305                 310                 315                 320

Ser Leu Glu Glu Asp Val Thr Glu Lys Leu Ser Pro Ser Phe Ala Asp
                325                 330                 335

Leu Phe Arg Thr Pro Arg Leu Arg Lys Arg Thr Phe Ile Leu Met Tyr
            340                 345                 350

Leu Trp Phe Thr Asp Ser Val Leu Tyr Gln Gly Leu Ile Leu His Met
        355                 360                 365

Gly Ala Thr Ser Gly Asn Leu Tyr Leu Asp Phe Leu Tyr Ser Ala Leu
    370                 375                 380

Val Glu Ile Pro Gly Ala Phe Ile Ala Leu Ile Thr Ile Asp Arg Val
385                 390                 395                 400

Gly Arg Ile Tyr Pro Met Ala Met Ser Asn Leu Leu Ala Gly Ala Ala
                405                 410                 415

Cys Leu Val Met Ile Phe Ile Ser Pro Asp Leu His Trp Leu Asn Ile
            420                 425                 430

Ile Ile Met Cys Val Gly Arg Met Gly Ile Thr Ile Ala Ile Gln Met
        435                 440                 445

Ile Cys Leu Val Asn Ala Glu Leu Tyr Pro Thr Phe Val Arg Asn Leu
    450                 455                 460

Gly Val Met Val Cys Ser Ser Leu Cys Asp Ile Gly Gly Ile Ile Thr
465                 470                 475                 480

Pro Phe Ile Val Phe Arg Leu Arg Glu Val Trp Gln Ala Leu Pro Leu
                485                 490                 495

Ile Leu Phe Ala Val Leu Gly Leu Leu Ala Ala Gly Val Thr Leu Leu
            500                 505                 510

Leu Pro Glu Thr Lys Gly Val Ala Leu Pro Glu Thr Met Lys Asp Ala
        515                 520                 525

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

Lys Val Gln Thr Ser Glu Pro Ser Gly Thr
545                 550


<210> SEQ ID NO 9
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

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

Gln Met Leu His Leu Val Phe Ile Leu Pro Ser Leu Met Leu Leu Ile
            20                  25                  30

Pro His Ile Leu Leu Glu Asn Phe Ala Ala Ala Ile Pro Gly His Arg
        35                  40                  45

Cys Trp Val His Met Leu Asp Asn Asn Thr Gly Ser Gly Asn Glu Thr
    50                  55                  60

Gly Ile Leu Ser Glu Asp Ala Leu Leu Arg Ile Ser Ile Pro Leu Asp
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65                  70                  75                  80

Ser Asn Leu Arg Pro Glu Lys Cys Arg Phe Phe Val His Pro Gln Trp
                85                  90                  95

Gln Leu Leu His Leu Asn Gly Ile His Ser Thr Ser Glu Ala Asp Thr
            100                 105                 110

Glu Pro Cys Val Asp Gly Trp Val Tyr Asp Gln Ser Tyr Phe Pro Ser
        115                 120                 125

Thr Ile Val Thr Lys Trp Asp Leu Val Cys Asp Tyr Gln Ser Leu Lys
    130                 135                 140

Ser Val Val Gln Phe Leu Leu Leu Thr Gly Met Leu Val Gly Gly Ile
145                 150                 155                 160

Ile His His Gly Val Ser Asp Arg Phe Gly Arg Arg Phe Ile Leu Arg
                165                 170                 175

Trp Cys Leu Leu Gln Leu Ala Ile Thr Asp Thr Cys Ala Ala Phe Ala
            180                 185                 190

Pro Thr Phe Pro Val Tyr Cys Val Leu Arg Phe Leu Ala Gly Phe Ser
        195                 200                 205

Ser Met Ile Ile Ile Ser Asn Asn Ser Leu Pro Ile Thr Glu Trp Ile
    210                 215                 220

Arg Pro Asn Ser Lys Ala Leu Val Val Ile Leu Ser Ser Gly Ala Leu
225                 230                 235                 240

Ser Ile Gly Gln Ile Ile Leu Gly Gly Leu Ala Tyr Val Phe Arg Asp
                245                 250                 255

Trp Gln Thr Leu His Val Val Ala Ser Val Pro Phe Leu Gly Leu Leu
            260                 265                 270

Leu Leu Gln Arg Trp Leu Val Glu Ser Ala Arg Trp Leu Ile Ile Thr
        275                 280                 285

Asn Lys Leu Asp Glu Gly Leu Lys Ala Leu Arg Lys Val Ala Arg Thr
    290                 295                 300

Asn Gly Ile Lys Asn Ala Glu Glu Thr Leu Asn Ile Glu Val Val Arg
305                 310                 315                 320

Ser Thr Met Gln Glu Glu Leu Asp Ala Ala Gln Thr Lys Thr Thr Val
                325                 330                 335

Cys Asp Leu Phe Arg Asn Pro Ser Met Arg Lys Arg Ile Cys Ile Leu
            340                 345                 350

Val Phe Leu Arg Phe Ala Asn Thr Ile Pro Phe Tyr Gly Thr Met Val
        355                 360                 365

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

Gly Ala Val Ala Leu Ile Val Arg Cys Leu Ala Leu Leu Thr Leu Asn
385                 390                 395                 400

His Met Gly Arg Arg Ile Ser Gln Ile Leu Phe Met Phe Leu Val Gly
                405                 410                 415

Leu Ser Ile Leu Ala Asn Thr Phe Val Pro Lys Glu Met Gln Thr Leu
            420                 425                 430

Arg Val Ala Leu Ala Cys Leu Gly Ile Gly Cys Ser Ala Ala Thr Phe
        435                 440                 445

Ser Ser Val Ala Val His Phe Ile Glu Leu Ile Pro Thr Val Leu Arg
    450                 455                 460

Ala Arg Ala Ser Gly Ile Asp Leu Thr Ala Ser Arg Ile Gly Ala Ala
465                 470                 475                 480

Leu Pro Leu Leu Met Thr Leu Thr Val Phe Phe Thr Thr Leu Pro Trp
                485                 490                 495
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Ile Ile Tyr Gly Ile Phe Pro Ile Ile Gly Gly Leu Ile Val Phe Leu
            500                 505                 510

Leu Pro Glu Thr Lys Asn Leu Pro Leu Pro Asp Thr Ile Lys Asp Val
        515                 520                 525

Glu Asn Gln Lys Lys Asn Leu Lys Glu Lys Ala
    530                 535


<210> SEQ ID NO 10
<211> LENGTH: 550
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

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

Gln Thr Leu Gln Val Leu Thr Phe Ile Leu Pro Cys Leu Met Ile Pro
            20                  25                  30

Ser Gln Met Leu Leu Glu Asn Phe Ser Ala Ala Ile Pro Gly His Arg
        35                  40                  45

Cys Trp Thr His Met Leu Asp Asn Gly Ser Ala Val Ser Thr Asn Met
    50                  55                  60

Thr Pro Lys Ala Leu Leu Thr Ile Ser Ile Pro Pro Gly Pro Asn Gln
65                  70                  75                  80

Gly Pro His Gln Cys Arg Arg Phe Arg Gln Pro Gln Trp Gln Leu Leu
                85                  90                  95

Asp Pro Asn Ala Thr Ala Thr Ser Trp Ser Glu Ala Asp Thr Glu Pro
            100                 105                 110

Cys Val Asp Gly Trp Val Tyr Asp Arg Ser Val Phe Thr Ser Thr Ile
        115                 120                 125

Val Ala Lys Trp Asp Leu Val Cys Ser Ser Gln Gly Leu Lys Pro Leu
    130                 135                 140

Ser Gln Ser Ile Phe Met Ser Gly Ile Leu Val Gly Ser Phe Ile Trp
145                 150                 155                 160

Gly Leu Leu Ser Tyr Arg Phe Gly Arg Lys Pro Met Leu Ser Trp Cys
                165                 170                 175

Cys Leu Gln Leu Ala Val Ala Gly Thr Ser Thr Ile Phe Ala Pro Thr
            180                 185                 190

Phe Val Ile Tyr Cys Gly Leu Arg Phe Val Ala Ala Phe Gly Met Ala
        195                 200                 205

Gly Ile Phe Leu Ser Ser Leu Thr Leu Met Val Glu Trp Thr Thr Thr
    210                 215                 220

Ser Arg Arg Ala Val Thr Met Thr Val Val Gly Cys Ala Phe Ser Ala
225                 230                 235                 240

Gly Gln Ala Ala Leu Gly Gly Leu Ala Phe Ala Leu Arg Asp Trp Arg
                245                 250                 255

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

Ser Trp Trp Leu Pro Glu Ser Ala Arg Trp Leu Ile Ile Lys Gly Lys
        275                 280                 285

Pro Asp Gln Ala Leu Gln Glu Leu Arg Lys Val Ala Arg Ile Asn Gly
    290                 295                 300

His Lys Glu Ala Lys Asn Leu Thr Ile Glu Val Leu Met Ser Ser Val
305                 310                 315                 320

Lys Glu Glu Val Ala Ser Ala Lys Glu Pro Arg Ser Val Leu Asp Leu
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                325                 330                 335

Phe Cys Val Pro Val Leu Arg Trp Arg Ser Cys Ala Met Leu Val Val
            340                 345                 350

Asn Phe Ser Leu Leu Ile Ser Tyr Tyr Gly Leu Val Phe Asp Leu Gln
        355                 360                 365

Ser Leu Gly Arg Asp Ile Phe Leu Leu Gln Ala Leu Phe Gly Ala Val
    370                 375                 380

Asp Phe Leu Gly Arg Ala Thr Thr Ala Leu Leu Leu Ser Phe Leu Gly
385                 390                 395                 400

Arg Arg Thr Ile Gln Ala Gly Ser Gln Ala Met Ala Gly Leu Ala Ile
                405                 410                 415

Leu Ala Asn Met Leu Val Pro Gln Asp Leu Gln Thr Leu Arg Val Val
            420                 425                 430

Phe Ala Val Leu Gly Lys Gly Cys Phe Gly Ile Ser Leu Thr Cys Leu
        435                 440                 445

Thr Ile Tyr Lys Ala Glu Leu Phe Pro Thr Pro Val Arg Met Thr Ala
    450                 455                 460

Asp Gly Ile Leu His Thr Val Gly Arg Leu Gly Ala Met Met Gly Pro
465                 470                 475                 480

Leu Ile Leu Met Ser Arg Gln Ala Leu Pro Leu Leu Pro Pro Leu Leu
                485                 490                 495

Tyr Gly Val Ile Ser Ile Ala Ser Ser Leu Val Val Leu Phe Phe Leu
            500                 505                 510

Pro Glu Thr Gln Gly Leu Pro Leu Pro Asp Thr Ile Gln Asp Leu Glu
        515                 520                 525

Ser Gln Lys Ser Thr Ala Ala Gln Gly Asn Arg Gln Glu Ala Val Thr
    530                 535                 540

Val Glu Ser Thr Ser Leu
545                 550


<210> SEQ ID NO 11
<211> LENGTH: 542
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

Met Thr Phe Ser Glu Ile Leu Asp Arg Val Gly Ser Met Gly His Phe
1               5                   10                  15

Gln Phe Leu His Val Ala Ile Leu Gly Leu Pro Ile Leu Asn Met Ala
            20                  25                  30

Asn His Asn Leu Leu Gln Ile Phe Thr Ala Ala Thr Pro Val His His
        35                  40                  45

Cys Arg Pro Pro His Asn Ala Ser Thr Gly Pro Trp Val Leu Pro Met
    50                  55                  60

Gly Pro Asn Gly Lys Pro Glu Arg Cys Leu Arg Phe Val His Pro Pro
65                  70                  75                  80

Asn Ala Ser Leu Pro Asn Asp Thr Gln Arg Ala Met Glu Pro Cys Leu
                85                  90                  95

Asp Gly Trp Val Tyr Asn Ser Thr Lys Asp Ser Ile Val Thr Glu Trp
            100                 105                 110

Asp Leu Val Cys Asn Ser Asn Lys Leu Lys Glu Met Ala Gln Ser Ile
        115                 120                 125

Phe Met Ala Gly Ile Leu Ile Gly Gly Leu Val Leu Gly Asp Leu Ser
    130                 135                 140
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Asp Arg Phe Gly Arg Arg Pro Ile Leu Thr Cys Ser Tyr Leu Leu Leu
145                 150                 155                 160

Ala Ala Ser Gly Ser Gly Ala Ala Phe Ser Pro Thr Phe Pro Ile Tyr
                165                 170                 175

Met Val Phe Arg Phe Leu Cys Gly Phe Gly Ile Ser Gly Ile Thr Leu
            180                 185                 190

Ser Thr Val Ile Leu Asn Val Glu Trp Val Pro Thr Arg Met Arg Ala
        195                 200                 205

Ile Met Ser Thr Ala Leu Gly Tyr Cys Tyr Thr Phe Gly Gln Phe Ile
    210                 215                 220

Leu Pro Gly Leu Ala Tyr Ala Ile Pro Gln Trp Arg Trp Leu Gln Leu
225                 230                 235                 240

Thr Val Ser Ile Pro Phe Phe Val Phe Phe Leu Ser Ser Trp Trp Thr
                245                 250                 255

Pro Glu Ser Ile Arg Trp Leu Val Leu Ser Gly Lys Ser Ser Glu Ala
            260                 265                 270

Leu Lys Ile Leu Arg Arg Val Ala Val Phe Asn Gly Lys Lys Glu Glu
        275                 280                 285

Gly Glu Arg Leu Ser Leu Glu Glu Leu Lys Leu Asn Leu Gln Lys Glu
    290                 295                 300

Ile Ser Leu Ala Lys Ala Lys Tyr Thr Ala Ser Asp Leu Phe Arg Ile
305                 310                 315                 320

Pro Met Leu Arg Arg Met Thr Phe Cys Leu Ser Leu Ala Trp Phe Ala
                325                 330                 335

Thr Gly Phe Ala Tyr Tyr Ser Leu Ala Met Gly Val Glu Glu Phe Gly
            340                 345                 350

Val Asn Leu Tyr Ile Leu Gln Ile Ile Phe Gly Gly Val Asp Val Pro
        355                 360                 365

Ala Lys Phe Ile Thr Ile Leu Ser Leu Ser Tyr Leu Gly Arg His Thr
    370                 375                 380

Thr Gln Ala Ala Ala Leu Leu Leu Ala Gly Gly Ala Ile Leu Ala Leu
385                 390                 395                 400

Thr Phe Val Pro Leu Asp Leu Gln Thr Val Arg Thr Val Leu Ala Val
                405                 410                 415

Phe Gly Lys Gly Cys Leu Ser Ser Ser Phe Ser Cys Leu Phe Leu Tyr
            420                 425                 430

Thr Ser Glu Leu Tyr Pro Thr Val Ile Arg Gln Thr Gly Met Gly Val
        435                 440                 445

Ser Asn Leu Trp Thr Arg Val Gly Ser Met Val Ser Pro Leu Val Lys
    450                 455                 460

Ile Thr Gly Glu Val Gln Pro Phe Ile Pro Asn Ile Ile Tyr Gly Ile
465                 470                 475                 480

Thr Ala Leu Leu Gly Gly Ser Ala Ala Leu Phe Leu Pro Glu Thr Leu
                485                 490                 495

Asn Gln Pro Leu Pro Glu Thr Ile Glu Asp Leu Glu Asn Trp Ser Leu
            500                 505                 510

Arg Ala Lys Lys Pro Lys Gln Glu Pro Glu Val Glu Lys Ala Ser Gln
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Arg Ile Pro Leu Gln Pro His Gly Pro Gly Leu Gly Ser Ser
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<210> SEQ ID NO 12
<211> LENGTH: 550
<212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

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Gln Gln Ile Gln Val Thr Leu Val Val Leu Pro Leu Leu Leu Met Ala
            20                  25                  30

Ser His Asn Thr Leu Gln Asn Phe Thr Ala Ala Ile Pro Thr His His
        35                  40                  45

Cys Arg Pro Pro Ala Asp Ala Asn Leu Ser Lys Asn Gly Gly Leu Glu
    50                  55                  60

Val Trp Leu Pro Arg Asp Arg Gln Gly Gln Pro Glu Ser Cys Leu Arg
65                  70                  75                  80

Phe Thr Ser Pro Gln Trp Gly Leu Pro Phe Leu Asn Gly Thr Glu Ala
                85                  90                  95

Asn Gly Thr Gly Ala Thr Glu Pro Cys Thr Asp Gly Trp Ile Tyr Asp
            100                 105                 110

Asn Ser Thr Phe Pro Ser Thr Ile Val Thr Glu Trp Asp Leu Val Cys
        115                 120                 125

Ser His Arg Ala Leu Arg Gln Leu Ala Gln Ser Leu Tyr Met Val Gly
    130                 135                 140

Val Leu Leu Gly Ala Met Val Phe Gly Tyr Leu Ala Asp Arg Leu Gly
145                 150                 155                 160

Arg Arg Lys Val Leu Ile Leu Asn Tyr Leu Gln Thr Ala Val Ser Gly
                165                 170                 175

Thr Cys Ala Ala Phe Ala Pro Asn Phe Pro Ile Tyr Cys Ala Phe Arg
            180                 185                 190

Leu Leu Ser Gly Met Ala Leu Ala Gly Ile Ser Leu Asn Cys Met Thr
        195                 200                 205

Leu Asn Val Glu Trp Met Pro Ile His Thr Arg Ala Cys Val Gly Thr
    210                 215                 220

Leu Ile Gly Tyr Val Tyr Ser Leu Gly Gln Phe Leu Leu Ala Gly Val
225                 230                 235                 240

Ala Tyr Ala Val Pro His Trp Arg His Leu Gln Leu Leu Val Ser Ala
                245                 250                 255

Pro Phe Phe Ala Phe Phe Ile Tyr Ser Trp Phe Phe Ile Glu Ser Ala
            260                 265                 270

Arg Trp His Ser Ser Ser Gly Arg Leu Asp Leu Thr Leu Arg Ala Leu
        275                 280                 285

Gln Arg Val Ala Arg Ile Asn Gly Lys Arg Glu Glu Gly Ala Lys Leu
    290                 295                 300

Ser Met Glu Val Leu Arg Ala Ser Leu Gln Lys Glu Leu Thr Met Gly
305                 310                 315                 320

Lys Gly Gln Ala Ser Ala Met Glu Leu Leu Arg Cys Pro Thr Leu Arg
                325                 330                 335

His Leu Phe Leu Cys Leu Ser Met Leu Trp Phe Ala Thr Ser Phe Ala
            340                 345                 350

Tyr Tyr Gly Leu Val Met Asp Leu Gln Gly Phe Gly Val Ser Ile Tyr
        355                 360                 365

Leu Ile Gln Val Ile Phe Gly Ala Val Asp Leu Pro Ala Lys Leu Val
    370                 375                 380

Gly Phe Leu Val Ile Asn Ser Leu Gly Arg Arg Pro Ala Gln Met Ala
385                 390                 395                 400
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-continued

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Ala Leu Leu Leu Ala Gly Ile Cys Ile Leu Leu Asn Gly Val Ile Pro
                405                 410                 415

Gln Asp Gln Ser Ile Val Arg Thr Ser Leu Ala Val Leu Gly Lys Gly
            420                 425                 430

Cys Leu Ala Ala Ser Phe Asn Cys Ile Phe Leu Tyr Thr Gly Glu Leu
        435                 440                 445

Tyr Pro Thr Met Ile Arg Gln Thr Gly Met Gly Met Gly Ser Thr Met
    450                 455                 460

Ala Arg Val Gly Ser Ile Val Ser Pro Leu Val Ser Met Thr Ala Glu
465                 470                 475                 480

Leu Tyr Pro Ser Met Pro Leu Phe Ile Tyr Gly Ala Val Pro Val Ala
                485                 490                 495

Ala Ser Ala Val Thr Val Leu Leu Pro Glu Thr Leu Gly Gln Pro Leu
            500                 505                 510

Pro Asp Thr Val Gln Asp Leu Glu Ser Arg Lys Gly Lys Gln Thr Arg
        515                 520                 525

Gln Gln Gln Glu His Gln Lys Tyr Met Val Pro Leu Gln Ala Ser Ala
    530                 535                 540

Gln Glu Lys Asn Gly Leu
545                 550


<210> SEQ ID NO 13
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically synthesized

<400> SEQUENCE: 13

ggcacattta ttcaccaaga ccag                                          24


<210> SEQ ID NO 14
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically synthesized

<400> SEQUENCE: 14

tgtggacctc agcagcattt ggat                                          24
```

What is claimed is:

1. A method of screening candidate substrates of the organic cation transporter 6 (OCT6) comprising:

a. providing a test agent;

b. providing mammalian cells or a mammalian cell line which express OCT6;

c. incubating the test agent with the cells or cell line; and

d. determining whether the test agent is a substrate for OCT6,

wherein the mammalian cells or mammalian cell line provided in step b, are leukemia cells or a leukemia cell line, respectively.

2. The method of claim **1** wherein the test agent is coupled to a detectable substance.

3. The method of claim **2** wherein the detectable substance is selected from the group consisting of extrinsically activatable enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, nonradioactive paramagnetic metal ions, immunogenic tag peptide sequences, extrinsically activatable toxins, extrinsically activatable quenching agents, and antibodies.

4. The method of claim **1** wherein the step of determining whether the test agent is a substrate for OCT6 comprises analyzing whether the test agent is located intracellularly.

5. The method of claim **1**, wherein step (d) comprises determining the viability of the cells or cell line.

6. The method of claim **5**, wherein the viability of the cells or cell line is determined by applying a dye to the cells or cell line, wherein incorporation of the dye by the cells is indicative of death of the cells or cell line.

7. The method of claim **6**, wherein the dye is trypan blue.

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