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(54) Titre : MARQUEURS DE CELLULES SOUCHES
(54) Title: STEM CELL MARKERS

(57) Abrégé/Abstract:
We disclose gene markers of stem cells, typically prostate stem cells, and in particular cancer stem cells, for example prostate cancer stem cells; therapeutic agents and diagnostic assays based on said stem cell genes; and including screening assays to identify therapeutic agents.

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(54) Title: PROSTATE STEM CELL MARKERS

(57) Abstract: We disclose gene markers of stem cells, typically prostate stem cells, and in particular cancer stem cells, for example prostate cancer stem cells; therapeutic agents and diagnostic assays based on said stem cell genes; and including screening assays to identify therapeutic agents.

Stem Cell Markers

The invention relates to gene markers of stem cells, typically prostate stem cells, and in particular cancer stem cells, for example prostate cancer stem cells; therapeutic agents and diagnostic assays based on said stem cell genes and expression products; and including screening assays to identify therapeutic agents.

BACKGROUND

A problem underlying the effective treatment of cancerous conditions is the identification of a population of cells in a tumour that have the ability of sustaining the growth of a tumour. The evidence suggests that tumours are clonal and are therefore derived from a single cell. However, there are few studies that identify and characterise those cells types that are responsible for maintaining tumour cell growth. Some have searched for these so called "cancer stem cells".

We have identified CD133, which is expressed by primitive haematopoietic stem cells and developing epithelia as a further stem cell marker for prostate epithelia. CD133 cells are restricted to the $\alpha_2\beta_1^{hi}$ population (the receptor for type I collagen) and are located in the basal layer, often at the base of a budding region or branching point (Fig. 1A). $\alpha_2\beta_1^{hi}$ /$CD133^+$ cells exhibit two important attributes of epithelial stem cells: they possess a high *in vitro* proliferative potential (Fig. 1B) and can reconstitute prostatic-like acini in immunocompromised male nude mice Fig. 1C).

In our co-pending application (WO 2005/089043) we describe the isolation of prostate stem cells which have been directly isolated from lymph node and prostate glands from a series of patient samples. These stem cells express markers that characterise the cells with stem cell properties. The following markers are typically expressed as prostate stem cell markers; human epithelial antigen (HEA), CD44, $\alpha_2\beta_1^{hi}$ and CD133. Morphologically the cells range from fibroblastoid (expressing high levels of vimentin which is typical of transformed cells) or epithelial, and are capable of producing progenitors associated with prostate epithelial differentiation. Invasion assays, using Matrigel-coated filters have

determined that these cells have 2-3 fold greater capacity to invade through Matrigel than PC3M (a highly metastatic sub-line of PC3 cells).

DESCRIPTION OF THE DISCLOSURE

We have conducted array analysis of CD133 positive prostate stem cells and compared expression of genes between CD133 positive stem cells and CD133 positive cancer stem cells.

Growth Factors/Receptors

The array analysis has identified a number of genes that encode proteins that are either growth factors/receptors or proteins involved in signal transduction pathways that result in stimulation of cell growth and/or cell proliferation. A group of growth factors, referred to as cytokines, are involved in a number of diverse cellular functions. These include, by example and not by way of limitation, modulation of the immune system, regulation of energy metabolism and control of growth and development. Cytokines mediate their effects via receptors expressed at the cell surface on target cells. Cytokine receptors can be divided into three separate sub groups. Type 1 (e.g. growth hormone (GH) family) receptors are characterised by four conserved cysteine residues in the amino terminal part of their extracellular domain and the presence of a conserved Trp-Ser-Xaa-Trp-Ser motif in the C-terminal part. The repeated Cys motif is also present in Type 2 (interferon family) and Type III (tumour necrosis factor family).

A further group of growth factors are involved in angiogenesis. Angiogenesis is the development of new blood vessels from an existing vascular bed and is a complex multistep process that involves the degradation of components of the extracellular matrix and then the migration, cell-division and differentiation of endothelial cells to form tubules and eventually new vessels. Angiogenesis is involved in pathological conditions such as tumour cell growth. Genes involved in angiogenesis include, by example and not by way of limitation; vascular endothelial growth factor (VEGF, VEGF B, VEGF C, VEGF D); transforming growth factor (TGFb); acidic and basic fibroblast growth factor (aFGF and bFGF); and platelet derived growth factor (PDGF).

Many receptors for growth factors and the like are membrane bound via glycosylphosphatidylinositol (GPI). GPI-anchors are post-translational modifications to proteins that add glycosylphosphatidylinositol which enable these proteins to anchor to the extracellular side of cell membranes. Typically, extracellular proteins which have a GPI anchor do not have transmembrane or cytoplasmic domains. GPI anchor proteins occur in all eukaryotes and form a diverse variety of proteins that includes, for example, membrane associated enzymes and adhesion molecules.

Genes that are involved in signal transduction are often associated with cell membrane localised receptors which upon activation results in a signal transduction cascade leading to activation of transcription and cell proliferation. For example, the PTEN gene product is a multiple-specificity phosphatase that can antagonise phosphoinositide lipid kinases (hereinafter PI3K) by degrading phosphoinositide (PI) (3,4,5) P3 back to PI(4,5)P2 in addition to its ability to dephosphorylate a range of protein targets such as focal adhesion kinase (FAK). Phosphoinositides have been implicated in a variety of cellular processes as diverse as vacuolar protein sorting, cytoskeletal remodelling and mediating intracellular signalling events through which growth factors, hormones and neurotransmitters exert their physiological effects on cellular activity, proliferation and differentiation.

Extracellular Matrix Associated

The array analysis has identified a number of genes that encode proteins that are extracellular matrix proteins. The Extracellular Matrix (ECM) is a complex mixture of non-living material which surrounds cells in multicellular organisms. In vertebrates the ECM comprises a mixture of protein and carbohydrate (and minerals in the example of bone). The protein component comprises proteins and glycoproteins (proteins that are modified by the addition of sugar moieties) such as collagens (collagens I-XII); laminins which are found in the basal lamina a structure to which epithelial cells associate; fibronectin which functions to bind cells to the ECM; and elastins which provide skin with the flexibility. Proteoglycans are also found in the ECM and these glycoproteins comprise more carbohydrate than protein. Several sugars are added to proteoglycans the

most abundant of which is acetylglucosamine. Many proteoglycans are sulphated, for example chondroitin sulphate, heparan sulphate, keratin sulphate and hyaluronic acid.

Most vertebrate cells cannot survive unless associated with the ECM and the loss of anchorage to the ECM is often associated with cell transformation in cancer. Cells attach to the ECM via anchoring molecules expressed by the cell called intergrins which bind the ECM via collagen, laminins and fibronectin. Integrins are cell membrane proteins that bind the extracellular matrix via their extracellular domain which projects from the cell surface. The integrin intracellular domain contacts the actin filaments of the cytoskeleton. In cancer metastasis the primary cancer cell becomes motile and is able to metastase (transfer) to other tissues to form secondary cancers. It is the secondary cancer that eventually kills the subject. In order to metastase the cancer cell has to penetrate the basement membrane of the tissue to gain access to the blood and lymph systems which transports the cancer cell around the body. The degradation of the ECM around a tumour is mainly catalysed by metalloproteases (MMP) which are secreted by stromal cells that surround the tumour. There is increasing evidence that cancer cells stimulate MMP production by fibroblasts by the paracrine secretion of hormones.

MMP's are an expanding group of proteases that can be classified into 3 groups. Group 1 includes collagenases that degrade connective tissue collagen, for example MMP-1, MMP-8 and MMP-13; group 2 includes gelatinases that degrade basement membrane collagens and include MMP-2 and MMP-9; a third group includes the stromelysins that degrade ECM proteoglycans, laminin and fibronectin and include MMP-10 and MMP-11. The activity of MMP's can be enhanced by pro-inflammatory cytokines such as IL-1 and TNFα.

Transcription Factors/Transcription Related

The array analysis has identified a number of genes that encode proteins that are transcription factor proteins or proteins that are related to transcription.

Transcription factors are proteins that bind to DNA enhancer or promoter elements. Often these are near to the start of transcription of a gene. Transcription factors either inhibit or

facilitate RNA polymerase transcription initiation and also the maintenance of an active transcription complex. Transcription factors contain two basic functional domains. A transactivation domain which is a region of the protein which interacts with other parts of the transcription machinery, for example the RNA polymerase or other transcription factors; and a DNA binding domain which comprises amino acids which recognise specific bases within the promoter region of the gene. In some examples enhancer elements can be positioned at a distance from the start of transcription or even within introns, Lewin B, 1994. Genes V, Oxford University Press, Oxford. Frequently DNA binding domains interact with nucleotide sequences or motifs which are sites to which the transcription factor binds to enhance or repress transcription.

An important family of the transcription factors comprises the homeodomain proteins. This family of transcription factors is characterised by the so-called homeodomain region which consists of 16 amino acids arranged in a helix-turn-helix conformation. Some transcription factors have both a homeodomain and a second DNA–binding region. In some examples, the region that comprises the homeodomain and the second DNA–binding region is called the POU domain.

A further example of a family of transcription factors which contain a conserved binding domain is the helix-loop-helix domain. The muscle specific transcription factor MyoD contains this motif, as do several *D. melanogaster* proteins that determine the cell fate in the *D. melanogaster* peripheral nervous system.

A related family of transcription factors are referred to as the basic leucine zipper transcription factor family or bZip. The bZip proteins are dimers, each of whose subunits contain a basic DNA-binding domain at the carboxyl end followed closely by a helix containing several leucine residues. Examples of bZip family members are C/EBP, Ap1, and the yeast transcription factor GCN4

A large group of transcription factors are the nuclear hormone receptors. It is known that steroid hormones increase the transcription of specific groups of genes. Once the hormone has entered the cell, it binds to its specific receptor protein, converting that receptor into a conformation that is able to enter the nucleus and bind specific DNA

sequence motifs. The family of steroid hormone receptors includes proteins that recognise oestrogen, progesterone, testosterone and cortisone as well as non-steroid lipids such as retinoic acid, thyroxine and vitamin D.

It is known that the way in which DNA is packaged as chromatin can influence the expression of genes. There are several levels of structural packaging of DNA leading from a double stranded helix to a mitotic chromosome, after which the DNA is some ~50,000 times shorter than its extended length. Double-stranded helical DNA is wound around the structural unit of a nucleosome, comprising an octamer core composed of 4 types of histones: two each of the H2A, H2B, H3, and H4 proteins. Approximately 166 base pairs are bound to the nucleosome through electrostatic forces between the negatively charged phosphate groups in the DNA backbone and positively charged amino acids (e.g., lysine and arginine) in the histone proteins.

Nucleosomes are organised into the next structural level of the chromatin fibre, also referred to as a solenoid. Chromatin structure is not static and the regulated alteration in structure is termed 'chromatin remodelling'. This process has been defined as any event that alters the nuclease sensitivity of a region of chromatin, and can occur independently or in concert with processes such as transcription.

Reversible acetylation of evolutionary conserved lysine residues in core histone proteins plays a critical role in transcriptional regulation, cell cycle progression, and developmental events. The steady state of histone acetylation is controlled by the enzymatic activities of multiple histone acetyltransferases (HATs) and histone deacetylases (HDACs). Histone hyperacetylation is associated with transcriptional activity while histone hypoacetylation correlates with transcriptional quiescence and so histone deacetylases can be considered as enzymatic transcriptional repressors.

In general, histone deacetylases do not target genes directly through specific DNA-binding sites. Rather, deacetylases are localized to genes targeted for repression as part of a protein complex. Other proteins that are part of this complex, termed co-repressors, are responsible for targeting the genes to be repressed. In humans, four highly homologous class I HDAC enzymes (HDAC1, HDAC2, HDAC3, and HDAC8) have been identified to

date, with HDAC1, HDAC2 and HDAC3 being ubiquitously expressed in many different cell types (Yang *et al.*, 1997 and 2002). HDAC1 and HDAC2 are the human orthologues of the yeast transcriptional regulator RPD3. Analysis of the predicted amino acid sequence of HDAC3 revealed an open reading frame of 428 amino acids with a predicted molecular mass of 49 kDa.

DNA Replication and Repair

The array analysis has identified a number of genes that encode proteins that are involved in DNA replication or repair of DNA. DNA damage can occur through a number of agents. For example, certain wavelengths of radiation, (e.g. gamma rays or X-rays), ultraviolet rays especially UV-C rays that are absorbed strongly by DNA; highly reactive oxygen radicals produced during respiration and other metabolic processes; and chemical mutagens found in the environment which may be man made or naturally occurring.

DNA can be damaged in different ways. For example, the four bases that form DNA can be covalently modified at various positions; deamination of an amino group is a common modification resulting in a mutation of cytosine to uracil. Other modifications include mismatches, for example the conversion of thymidine to uracil, single strand breaks in the phosphate backbone of the DNA molecule and covalent crosslinks between bases which may be intra-strand or inter-strand. Several chemotherapeutic agents used in the treatment of cancer act as crosslinking agents.

The Human Genome Project which has deduced the complete DNA sequence of human DNA has identified around 130 genes thought to be involved in DNA repair and replication. Damaged or inappropriate incorporation of bases can be corrected via several mechanisms. These include direct chemical reversal or excision repair. Excision repair results in removal of the damaged base and replacement with the correct base. There are three mechanisms of excision repair utilised by cells to repair DNA damage.

Base excision repair involves the removal of the damaged base by a DNA glycosylase; removal of its deoxyribose phosphate to produce gapped DNA; replacement of the correct nucleotide by a DNA polymerase β and ligation of the strand break by a DNA ligase.

Nucleotide excision repair involves recognition of the error by one or more protein factors; separating the DNA strands to produce a "bubble" by an enzyme called transcription factor IIH; scission at the 5' and 3' sides of the damaged area; replacement synthesis of the damaged area by DNA polymerases ϵ and σ; and ligation of the strand break by a DNA ligase.

Mismatch repair corrects mismatches in normal bases. The correction of mismatches utilises enzymes involved in base excision repair and proteins that recognise the mismatch for example proteins encoded by MSH2 and scission around the mismatch by MLH 1 and other proteins. A mutation in either of these genes has been associated with an inherited form of colon cancer. The repair of the mismatch is completed by the DNA polymerases ϵ and σ.

In addition the repair of single and double strand breaks in DNA also involves a number of proteins. The repair of single strand breaks utilises many of the proteins involved in base excision repair. A double strand break is repaired either by direct ligation of the free ends of the break or by homologous recombination. Errors in direct ligation are associated with certain cancers, for example Burkitt's lymphoma and B-cell leukaemia. The BRCA-1 and BRCA-2 genes function in homologous recombination and mutations in these genes are associated with breast and ovarian cancer.

We have conducted gene array analysis to identify genes that are characteristic of cancer stem cells which show an up regulation when compared to control stem cell samples from normal or benign stem cell populations. We herein disclose these genes and their use in the identification of therapeutic agents useful in the treatment of cancer, in particular prostate cancer, and in the development of diagnostic assays for the detection of the early on set of tumour cell growth. The present disclosure relates to the identification of cancer stem cell specific genes.

STATEMENTS OF INVENTION

According to a first aspect of the invention there is provided agent that modulates the activity of a cancer stem cell specific nucleic acid molecule, or a polypeptide encoded by a cancer stem nucleic acid molecule, wherein said cancer cell specific nucleic acid molecule is selected from the group consisting of:

i) a nucleic acid molecule consisting of a nucleic acid sequence as represented in SEQ ID NO: 1- 452;

ii) a nucleic acid molecule consisting of a nucleic acid sequence as represented in Table 1 by Genbank accession number;

iii) a nucleic acid molecule that hybridises under stringent hybridisation conditions to the nucleic acid molecule in (i) or (ii) above and which encodes a polypeptide wherein said polypeptide is stem cell specific, characterised in that said agent is for use as a pharmaceutical.

Hybridization of a nucleic acid molecule occurs when two complementary nucleic acid molecules undergo an amount of hydrogen bonding to each other. The stringency of hybridization can vary according to the environmental conditions surrounding the nucleic acids, the nature of the hybridization method, and the composition and length of the nucleic acid molecules used. Calculations regarding hybridization conditions required for attaining particular degrees of stringency are discussed in Sambrook et al., Molecular Cloning: A Laboratory Manual (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 2001); and Tijssen, Laboratory Techniques in Biochemistry and Molecular Biology—Hybridization with Nucleic Acid Probes Part I, Chapter 2 (Elsevier, New York, 1993). The T_m is the temperature at which 50% of a given strand of a nucleic acid molecule is hybridized to its complementary strand. The following is an exemplary set of hybridization conditions and is not limiting:

Very High Stringency (allows sequences that share at least 90% identity to hybridize)

Hybridization:	5x SSC at 65°C for 16 hours
Wash twice:	2x SSC at room temperature (RT) for 15 minutes each
Wash twice:	0.5x SSC at 65°C for 20 minutes each

High Stringency (allows sequences that share at least 80% identity to hybridize)

Hybridization:	5x-6x SSC at 65°C-70°C for 16-20 hours
Wash twice:	2x SSC at RT for 5-20 minutes each
Wash twice:	1x SSC at 55°C-70°C for 30 minutes each

Low Stringency (allows sequences that share at least 50% identity to hybridize)

Hybridization:	6x SSC at RT to 55°C for 16-20 hours
Wash at least twice:	2x-3x SSC at RT to 55°C for 20-30 minutes each.

In a preferred embodiment of the invention said agent is an antagonist. Alternatively, said agent is an agonist.

According to a further aspect of the invention there is provided an agent that modulates the activity of a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule selected from the group consisting of:

i) a nucleic acid molecule as represented in SEQ ID NO: 1- 452,

ii) a nucleic acid molecule that encodes a variant polypeptide wherein said variant polypeptide is modified by addition, deletion or substitution of at least one amino acid residue of the amino acid sequence encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 1-452 wherein said polypeptide is stem cell specific;

iii) a nucleic acid molecule that encodes a polypeptide consisting of an amino acid sequence as represented in Table 1 by Genbank accession number;

characterised in that said agent is for use as a pharmaceutical.

A variant polypeptide may differ in amino acid sequence by one or more substitutions, additions, deletions, truncations which may be present in any combination. Among preferred variants are those that vary from a reference polypeptide by conservative amino acid substitutions. Such substitutions are those that substitute a given amino acid by another amino acid of like characteristics. The following non-limiting list of amino acids are considered conservative replacements (similar): a) alanine, serine, and threonine; b) glutamic acid and asparatic acid; c) asparagine and glutamine d) arginine and lysine; e) isoleucine, leucine, methionine and valine and f) phenylalanine, tyrosine and tryptophan.

In addition, the invention features polypeptide sequences having at least 75% identity with the polypeptide sequences as hereindisclosed, or fragments and functionally equivalent polypeptides thereof. In one embodiment, the polypeptides have at least 85% identity, more preferably at least 90% identity, even more preferably at least 95% identity, still more preferably at least 97% identity, and most preferably at least 99% identity with the amino acid sequence illustrated herein.

In a preferred embodiment of the invention said agent is a polypeptide. Preferably said polypeptide is an antibody or an active binding part of an antibody.

In a preferred embodiment of the invention said antibody is a monoclonal antibody or active binding part thereof.

In a preferred embodiment of the invention said antibody is a chimeric antibody or a humanised antibody produced by recombinant methods to contain the variable region of said antibody with an invariant or constant region of a human antibody.

Chimeric antibodies are recombinant antibodies in which all of the V-regions of a mouse or rat antibody are combined with human antibody C-regions. Humanised antibodies are recombinant hybrid antibodies which fuse the complimentarity determining regions from a rodent antibody V-region with the framework regions from the human antibody V-regions. The complimentarity determining regions (CDRs) are the regions within the N-terminal domain of both the heavy and light chain of the antibody to where the majority of the variation of the V-region is restricted. These regions form loops at the surface of the antibody molecule. These loops provide the binding surface between the antibody and antigen. Antibodies from non-human animals provoke an immune response to the foreign antibody and its removal from the circulation. Both chimeric and humanised antibodies have reduced antigenicity when injected to a human subject because there is a reduced amount of rodent (i.e. foreign) antibody within the recombinant hybrid antibody, while the human antibody regions do not illicit an immune response. This results in a weaker immune response and a decrease in the clearance of the antibody. This is clearly desirable when using therapeutic antibodies in the treatment of human diseases. Humanised

antibodies are designed to have less "foreign" antibody regions and are therefore thought to be less immunogenic than chimeric antibodies.

In a preferred embodiment of the invention said agent is an antibody fragment.

Various fragments of immunoglobulin or antibodies are known in the art, i.e., Fab, Fab_2, $F(ab')_2$, Fv, Fc, Fd, scFvs, etc. A Fab fragment is a multimeric protein consisting of the immunologically active portions of an immunoglobulin heavy chain variable region and an immunoglobulin light chain variable region, covalently coupled together and capable of specifically binding to an antigen. Fab fragments are generated via proteolytic cleavage (with, for example, papain) of an intact immunoglobulin molecule. A Fab_2 fragment comprises two joined Fab fragments. When these two fragments are joined by the immunoglobulin hinge region, a $F(ab')_2$ fragment results. An Fv fragment is multimeric protein consisting of the immunologically active portions of an immunoglobulin heavy chain variable region and an immunoglobulin light chain variable region covalently coupled together and capable of specifically binding to an antigen. A fragment could also be a single chain polypeptide containing only one light chain variable region, or a fragment thereof that contains the three CDRs of the light chain variable region, without an associated heavy chain variable region, or a fragment thereof containing the three CDRs of the heavy chain variable region, without an associated light chain moiety; and multi specific antibodies formed from antibody fragments, this has for example been described in US patent No 6,248,516. Fv fragments or single region (domain) fragments are typically generated by expression in host cell lines of the relevant identified regions. These and other immunoglobulin or antibody fragments are within the scope of the invention and are described in standard immunology textbooks such as Paul, *Fundamental Immunology* or Janeway et al. *Immunobiology* (cited above). Molecular biology now allows direct synthesis (via expression in cells or chemically) of these fragments, as well as synthesis of combinations thereof.

It is possible to create single variable regions, so called single chain antibody variable region fragments (scFv's). If a hybridoma exists for a specific monoclonal antibody it is well within the knowledge of the skilled person to isolate scFv's from mRNA extracted from said hybridoma via RT PCR. Alternatively, phage display screening can be

undertaken to identify clones expressing scFv's. Alternatively said fragments are "domain antibody fragments". Domain antibodies are the smallest binding part of an antibody (approximately 13kDa). Examples of this technology is disclosed in US6, 248, 516, US6, 291, 158, US6,127, 197 and EP0368684 which are all incorporated by reference in their entirety.

In a preferred method of the invention said antibody fragment is a single chain antibody variable region fragment.

A fragment of an antibody or immunoglobulin can also have bispecific function binding two different epitopes of two different antigens.

Preferably said chimeric/humanised monoclonal antibody to said polypeptide is produced as a fusion polypeptide in an expression vector suitably adapted for transfection or transformation of prokaryotic or eukaryotic cells.

In a further preferred embodiment of the invention said antibodies are opsonic antibodies.

Phagocytosis is mediated by macrophages and polymorphic leukocytes and involves the ingestion and digestion of micro-organisms, damaged or dead cells, cell debris, insoluble particles and activated clotting factors. Opsonins are agents which facilitate the phagocytosis of the above foreign bodies. Opsonic antibodies are therefore antibodies which provide the same function. Examples of opsonins are the Fc portion of an antibody or compliment C3.

Preferably, said antibody is provided with a marker including a conventional label or tag, for example a radioactive and/or fluorescent and/or epitope label or tag.

In an alternative preferred embodiment of the invention said antibody, or antibody fragment had associated therewith or crosslinked thereto a therapeutic agent. Preferably said therapeutic agent is a chemotherapeutic agent.

Preferably said agent is selected from the group consisting of: cisplatin; carboplatin;

cyclosphosphamide; melphalan; carmusline; methotrexate; 5-fluorouracil; cytarabine; mercaptopurine; daunorubicin; doxorubicin; epirubicin; vinblastine; vincristine; dactinomycin; mitomycin C; taxol; L-asparaginase; G-CSF; etoposide; colchicine; derferoxamine mesylate; and camptothecin.

In an alternative preferred embodiment of the invention said agent is a nucleic acid molecule. For example, an antisense nucleic acid; an aptamer; or a small interfering RNA.

In a preferred embodiment of the invention said nucleic acid molecule is a small interfering RNA.

A technique to specifically ablate gene function is through the introduction of double stranded RNA, also referred to as small inhibitory or interfering RNA (siRNA), into a cell which results in the destruction of mRNA complementary to the sequence included in the siRNA molecule. The siRNA molecule comprises two complementary strands of RNA (a sense strand and an antisense strand) annealed to each other to form a double stranded RNA molecule. The siRNA molecule is typically derived from exons of the gene which is to be ablated.

The mechanism of RNA interference is being elucidated. Many organisms respond to the presence of double stranded RNA by activating a cascade that leads to the formation of siRNA. The presence of double stranded RNA activates a protein complex comprising RNase III which processes the double stranded RNA into smaller fragments (siRNAs, approximately 21-29 nucleotides in length) which become part of a ribonucleoprotein complex. The siRNA acts as a guide for the RNase complex to cleave mRNA complementary to the antisense strand of the siRNA thereby resulting in destruction of the mRNA.

According to a further aspect of the invention there is provided a pharmaceutical composition comprising an agent according to the invention.

According to a further aspect of the invention there is provided a composition comprising a nucleic acid molecule selected from the group consisting of:

i) a nucleic acid molecule consisting of a nucleic acid sequence as represented in SEQ ID NO: 1- 452;

ii) a nucleic acid molecule consisting of a nucleic acid sequence as represented in Table 1 by Genbank accession number;

iii) a nucleic acid molecule that hybridises under stringent hybridisation conditions to the nucleic acid molecule in (i) or (ii) above and which encodes a polypeptide wherein said polypeptide is stem cell specific.

According to a further aspect of the invention there is provided a composition comprising a polypeptide comprising an amino acid sequence selected from the group consisting of:

i) a polypeptide comprising an amino acid sequence as represented in Table 1 by Genbank accession number, or a variant polypeptide wherein said variant is modified by addition, deletion or substitution of at least one amino acid residue of the amino acid sequence presented in Table 1 by Genbank accession number;

ii) a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in SEQ ID NO 1- 452;

iii) a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule that hybridises under stringent hybridisation conditions to the nucleic acid molecule in (ii) above and which encodes a polypeptide wherein said polypeptide is stem cell specific wherein said composition is for use as a vaccine.

In a preferred embodiment of the invention said composition includes an adjuvant and/or a carrier.

An adjuvant is a substance or procedure that augments specific immune responses to antigens by modulating the activity of immune cells. Examples of adjuvants include, by example only, Freunds adjuvant, muramyl dipeptides, liposomes. A carrier is an immunogenic molecule which, when bound to a second molecule, augments immune responses to the latter. Some antigens are not intrinsically immunogenic yet may be capable of generating antibody responses when associated with a foreign protein molecule

such as keyhole-limpet haemocyanin or tetanus toxoid. Such antigens contain B-cell epitopes but no T cell epitopes. The protein moiety of such a conjugate (the "carrier" protein) provides T-cell epitopes which stimulate helper T-cells that in turn stimulate antigen-specific B-cells to differentiate into plasma cells and produce antibody against the antigen. Helper T-cells can also stimulate other immune cells such as cytotoxic T-cells, and a carrier can fulfil an analogous role in generating cell-mediated immunity as well as antibodies.

When administered, the therapeutic compositions of the present invention are administered in pharmaceutically acceptable preparations. Such preparations may routinely contain pharmaceutically acceptable concentrations of salt, buffering agents, preservatives, compatible carriers, supplementary immune potentiating agents such as adjuvants and cytokines and optionally other therapeutic agents (for example, cisplatin; carboplatin; cyclosphosphamide; melphalan; carmusline; methotrexate; 5-fluorouracil; cytarabine; mercaptopurine; daunorubicin; doxorubicin; epirubicin; vinblastine; vincristine; dactinomycin; mitomycin C; taxol; L-asparaginase; G-CSF; etoposide; colchicine; derferoxamine mesylate; and camptothecin.

The therapeutics of the invention can be administered by any conventional route, including injection or by gradual infusion over time. The administration may, for example, be oral, intravenous, intraperitoneal, intramuscular, intracavity, subcutaneous, or transdermal. When antibodies are used therapeutically, a preferred route of administration is by pulmonary aerosol. Techniques for preparing aerosol delivery systems containing antibodies are well known to those of skill in the art. Generally, such systems should utilize components which will not significantly impair the biological properties of the antibodies, such as the paratope binding capacity (see, for example, Sciarra and Cutie, "Aerosols," in Remington's Pharmaceutical Sciences, 18th edition, 1990, pp 1694-1712; incorporated by reference). Those of skill in the art can readily determine the various parameters and conditions for producing antibody aerosols without resort to undue experimentation.

The compositions of the invention are administered in effective amounts. An "effective amount" is that amount of a composition that alone, or together with further doses,

produces the desired response. In the case of treating a particular disease, such as cancer, the desired response is inhibiting the progression of the disease. This may involve only slowing the progression of the disease temporarily, although more preferably, it involves halting the progression of the disease permanently. This can be monitored by routine methods or can be monitored according to diagnostic methods of the invention discussed herein.

Such amounts will depend, of course, on the particular condition being treated, the severity of the condition, the individual patient parameters including age, physical condition, size and weight, the duration of the treatment, the nature of concurrent therapy (if any), the specific route of administration and like factors within the knowledge and expertise of the health practitioner. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. It is generally preferred that a maximum dose of the individual components or combinations thereof be used, that is, the highest safe dose according to sound medical judgment. It will be understood by those of ordinary skill in the art, however, that a patient may insist upon a lower dose or tolerable dose for medical reasons, psychological reasons or for virtually any other reasons.

The pharmaceutical compositions used in the foregoing methods preferably are sterile and contain an effective amount of antibody or nucleic acid for producing the desired response in a unit of weight or volume suitable for administration to a patient. The response can, for example, be measured by determining the signal transduction enhanced or inhibited by the composition via a reporter system, by measuring downstream effects such as gene expression, or by measuring the physiological effects of the composition. Likewise, the effects of antisense/siRNA molecules can be readily determined by measuring expression of the individual genes in cells to which an antisense/siRNA composition is added. Other assays will be known to one of ordinary skill in the art and can be employed for measuring the level of the response.

The doses of antibody or nucleic acid administered to a subject can be chosen in accordance with different parameters, in particular in accordance with the mode of administration used and the state of the subject. Other factors include the desired period

of treatment. In the event that a response in a subject is insufficient at the initial doses applied, higher doses (or effectively higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits.

In general, doses of antibody are formulated and administered in doses between 1 ng and 1 mg, and preferably between 10 ng and 100 μg, according to any standard procedure in the art. Where nucleic acids or variants thereof are employed, doses of between 1 ng and 0.1 mg generally will be formulated and administered according to standard procedures. Other protocols for the administration of the compositions will be known to one of ordinary skill in the art, in which the dose amount, schedule of injections, sites of injections, mode of administration (e.g., intra-bone) and the like vary from the foregoing. Administration of the compositions to mammals other than humans, (e.g. for testing purposes or veterinary therapeutic purposes), is carried out under substantially the same conditions as described above. A subject, as used herein, is a mammal, preferably a human, and including a non-human primate, cow, horse, pig, sheep, goat, dog, cat or rodent.

When administered, the pharmaceutical preparations of the invention are applied in pharmaceutically-acceptable amounts and in pharmaceutically-acceptable compositions. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredients. Such preparations may routinely contain salts, buffering agents, preservatives, compatible carriers, and optionally other therapeutic agents. When used in medicine, the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare pharmaceutically-acceptable salts thereof and are not excluded from the scope of the invention. Such pharmacologically and pharmaceutically-acceptable salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, maleic, acetic, salicylic, citric, formic, malonic, succinic, and the like. Also, pharmaceutically-acceptable salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts.

Pharmaceutical compositions may be combined, if desired, with a pharmaceutically-

acceptable carrier. The term "pharmaceutically-acceptable carrier" as used herein means one or more compatible solid or liquid fillers, diluents or encapsulating substances which are suitable for administration into a human. The term "carrier" denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The components of the pharmaceutical compositions also are capable of being co-mingled with the molecules of the present invention, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficacy.

The pharmaceutical compositions may contain suitable buffering agents, including: acetic acid in a salt; citric acid in a salt; boric acid in a salt; and phosphoric acid in a salt.

The pharmaceutical compositions also may contain, optionally, suitable preservatives, such as: benzalkonium chloride; chlorobutanol; parabens and thimerosal.

The pharmaceutical compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well-known in the art of pharmacy. All methods include the step of bringing the active agent into association with a carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing the active compound into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product.

Compositions suitable for oral administration may be presented as discrete units, such as capsules, tablets, lozenges, each containing a predetermined amount of the active compound. Other compositions include suspensions in aqueous liquids or non-aqueous liquids such as syrup, elixir or an emulsion.

Compositions suitable for parenteral administration conveniently comprise a sterile aqueous or non-aqueous preparation of antibody or nucleic acids, which is preferably isotonic with the blood of the recipient. This preparation may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation also may be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-

butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono-or di-glycerides. In addition, fatty acids such as oleic acid may be used in the preparation of injectables. Carrier formulation suitable for oral, subcutaneous, intravenous, intramuscular, etc. administrations can be found in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA.

According to a further aspect of the invention there is provided a vector which is adapted for the expression of the humanised or chimeric antibodies according to the invention.

According to an aspect of the invention there is provided a cell which has been transformed or transfected with the vector encoding the humanised or chimeric antibody according to the invention

According to a further aspect of the invention there is provided a method for the production of the humanised or chimeric antibody according to the invention comprising:

(i) providing a cell transformed or transfected with a vector which comprises a nucleic acid molecule encoding the humanised or chimeric antibody according to the invention;

(ii) growing said cell in conditions conducive to the manufacture of said antibody; and

(iii) purifying said antibody from said cell, or its growth environment.

In a yet further aspect of the invention there is provided a hybridoma cell line which produces a monoclonal antibody as hereinbefore described.

In a further aspect of the invention there is provided a method of producing monoclonal antibodies according to the invention using hybridoma cell lines according to the invention.

In a further aspect of the invention there is provided a method for preparing a hybridoma cell-line producing monoclonal antibodies according to the invention comprising the steps of:

i) immunising an immunocompetent mammal with an immunogen comprising at least one polypeptide having the amino acid sequence as represented in Table 1 by Genbank accession number, or fragments thereof or at least one polypeptide encoded by a nucleic acid molecule as represented in SEQ ID NO 1- 452;

ii) fusing lymphocytes of the immunised immunocompetent mammal with myeloma cells to form hybridoma cells;

iii) screening monoclonal antibodies produced by the hybridoma cells of step (ii) for binding activity to the polypeptide of (i);

iv) culturing the hybridoma cells to proliferate and/or to secrete said monoclonal antibody; and

v) recovering the monoclonal antibody from the culture supernatant.

Preferably, the said immunocompetent mammal is a mouse. Alternatively, said immunocompetent mammal is a rat.

The production of monoclonal antibodies using hybridoma cells is well-known in the art. The methods used to produce monoclonal antibodies are disclosed by Kohler and Milstein in Nature 256, 495-497 (1975) and also by Donillard and Hoffman, "Basic Facts about Hybridomas" in Compendium of Immunology V.II ed. by Schwartz, 1981, which are incorporated by reference.

According to a further aspect of the invention there is provided a diagnostic assay for the determination of cancer in a subject comprising the steps of:

i) providing an isolated cell sample;

ii) contacting the sample in (i) with a binding agent(s) that bind to a nucleic acid molecule as represented by the nucleic acid sequence in SEQ ID NO 1- 452;

iii) determining the expression of said nucleic acid molecule in said sample when compared to a normal matched control sample.

In a preferred embodiment of the invention said binding agent(s) is an oligonucleotide primer. Preferably said assay is a polymerase chain reaction.

In an alternative preferred embodiment of the invention said binding agent is an antibody that specifically binds a polypeptide encoded by a nucleic acid molecule as represented in SEQ ID NO 1- 452, or a polypeptide variant comprising an amino acid sequence that varies from a reference amino acid sequence by addition, deletion or substitution of at least one amino acid residue.

In a preferred embodiment of the invention said cancer is prostate cancer.

According to a further aspect of the invention there is provided a kit comprising a binding agent specifically reactive with a nucleic acid molecule as represented by the nucleic acid sequence in SEQ ID NO 1- 452, or an agent specifically reactive with a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in SEQ ID NO 1- 452.

In a preferred embodiment of the invention said kit further comprises an oligonucleotide or antibody specifically reactive with said nucleic acid molecule or said polypeptide.

Preferably said kit comprises a thermostable DNA polymerase and components required for conducting the amplification of nucleic acid. Preferably said kit includes a set of instructions for conducting said polymerase chain reaction and control nucleic acid.

In an alternative preferred embodiment of the invention said kit comprises an antibody specifically reactive with a polypeptide comprising an amino acid sequence encoded by a nucleic acid sequence as represented in SEQ ID NO 1- 452.

Preferably said kit comprises components required for conducting an immunoassay including, for example, a secondary antibody specifically reactive with a primary antibody

that specifically binds said polypeptide(s) and enzyme reagents required to detect the binding of said secondary antibody with said primary antibody.

According to a further aspect of the invention there is provided a method to screen for an agent that modulates the activity of a polypeptide encoded by a nucleic acid molecule selected from the group consisting of:

a) a nucleic acid molecule comprising a nucleic acid sequence as represented in SEQ ID NO 1- 452;

a) a nucleic acid molecule consisting of a nucleic acid sequence as represented in Table 1 by Genbank accession number;

b) a nucleic acid molecule that hybridises under stringent hybridisation conditions to the nucleic acid molecule in (i) or (ii) above and which encodes a polypeptide wherein said polypeptide is stem cell specific;

i) forming a preparation comprising a polypeptide, or sequence variant thereof, and at least one agent to be tested;

ii) determining the activity of said agent with respect to the activity of said polypeptide.

In a preferred method of the invention said agent is an antagonist. In an alternative preferred method of the invention said agent is an agonist.

Agents identified by the screening method of the invention include, antibodies, siRNA, aptamers, small organic molecules, (for example peptides, cyclic peptides), dominant negative variants of the polypeptides herein disclosed.

As mentioned above, the invention also provides, in certain embodiments, "dominant negative" polypeptides derived from the polypeptides hereindisclosed. A dominant negative polypeptide is an inactive variant of a protein, which, by interacting with the cellular machinery, displaces an active protein from its interaction with the cellular machinery or competes with the active protein, thereby reducing the effect of the active protein. For example, a dominant negative receptor which binds a ligand but does not transmit a signal in response to binding of the ligand can reduce the biological effect of expression of the ligand. Likewise, a dominant negative catalytically-inactive kinase

which interacts normally with target proteins but does not phosphorylate the target proteins can reduce phosphorylation of the target proteins in response to a cellular signal. Similarly, a dominant negative transcription factor which binds to another transcription factor or to a promoter site in the control region of a gene but does not increase gene transcription can reduce the effect of a normal transcription factor by occupying promoter binding sites without increasing transcription.

It will be apparent to one skilled in the art that modification to the amino acid sequence of peptides agents could enhance the binding and/or stability of the peptide with respect to its target sequence. In addition, modification of the peptide may also increase the *in vivo* stability of the peptide thereby reducing the effective amount of peptide necessary to inhibit the activity of the polypeptides herein disclosed. This would advantageously reduce undesirable side effects which may result in vivo. Modifications include, by example and not by way of limitation, acetylation and amidation. Alternatively or preferably, said modification includes the use of modified amino acids in the production of recombinant or synthetic forms of peptides. It will be apparent to one skilled in the art that modified amino acids include, for example, 4-hydroxyproline, 5-hydroxylysine, N^6-acetyllysine, N^6-methyllysine, N^6,N^6-dimethyllysine, N^6,N^6,N^6-trimethyllysine, cyclohexyalanine, D-amino acids, ornithine. Other modifications include amino acids with a C_2, C_3 or C_4 alkyl R group optionally substituted by 1, 2 or 3 substituents selected from halo (eg F, Br, I), hydroxy or C_1-C_4 alkoxy. It will also be apparent to one skilled in the art that peptides which retain p53 binding activity could be modified by cyclisation. Cyclisation is known in the art, (see Scott *et al* Chem Biol (2001), 8:801-815; Gellerman et al J. Peptide Res (2001), 57: 277-291; Dutta *et al* J. Peptide Res (2000), 8: 398-412; Ngoka and Gross J Amer Soc Mass Spec (1999), 10:360-363.

According to a further aspect of the invention there is provided a method to treat a subject for a cancer comprising administering an effective amount of an agent according to the invention.

In a preferred method of the invention said subject is human.

In a preferred method of the invention said cancer is prostate cancer.

According to a further aspect of the invention there is provided a method to immunise an animal against a cancerous condition comprising administering an effective amount of a nucleic acid or polypeptide encoded by a nucleic acid molecule selected from the group consisting of according to the invention.

In a preferred method of the invention said animal is a human.

In a further preferred embodiment of the invention said cancer is prostate cancer.

As used herein, the term "cancer"refers to cells having the capacity for autonomous growth, i.e., an abnormal state or condition characterized by rapidly proliferating cell growth. The term is meant to include all types of cancerous growths or oncogenic processes, metastatic tissues or malignantly transformed cells, tissues, or organs, irrespective of histopathologic type or stage of invasiveness. The term "cancer" includes malignancies of the various organ systems, such as those affecting, for example, lung, breast, thyroid, lymphoid, gastrointestinal, and genito-urinary tract, as well as adenocarcinomas which include malignancies such as most colon cancers, renal-cell carcinoma, prostate cancer and/or testicular tumours, non-small cell carcinoma of the lung, cancer of the small intestine and cancer of the esophagus. The term "carcinoma" is art recognized and refers to malignancies of epithelial or endocrine tissues including respiratory system carcinomas, gastrointestinal system carcinomas, genitourinary system carcinomas, testicular carcinomas, breast carcinomas, prostatic carcinomas, endocrine system carcinomas, and melanomas. Exemplary carcinomas include those forming from tissue of the cervix, lung, prostate, breast, head and neck, colon and ovary. The term "carcinoma" also includes carcinosarcomas, e.g., which include malignant tumours composed of carcinomatous and sarcomatous tissues. An "adenocarcinoma" refers to a carcinoma derived from glandular tissue or in which the tumor cells form recognizable glandular structures. The term "sarcoma" is art recognized and refers to malignant tumors of mesenchymal derivation.

Throughout the description and claims of this specification, the words "comprise" and "contain" and variations of the words, for example "comprising" and "comprises", means

"including but not limited to", and is not intended to (and does not) exclude other moieties, additives, components, integers or steps.

Throughout the description and claims of this specification, the singular encompasses the plural unless the context otherwise requires. In particular, where the indefinite article is used, the specification is to be understood as contemplating plurality as well as singularity, unless the context requires otherwise.

Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein unless incompatible therewith.

An embodiment of the invention will now be described by example only and with reference to the following Figures and Materials and Methods;

Figure 1: Verification of CD133 as a stem cell marker of prostatic epithelia: **1A**: A paraffin section of prostatic acini labelled with the nuclear stain DAPI (Blue) and anti-CD133 directly conjugated to PE (Red). **1B**: Basal cells with the phenotype $\alpha_2\beta_1^{hi}$ /$CD133^+$ have a higher colony forming efficiency (CFE) than $\alpha_2\beta_1^{low}$/$CD133^-$. (CFE) was calculated as the number of colonies formed per number of selected cells x100%. CFEs are expressed as the ratio of the control CFE. Results show means ± s.e.m of four experiments. **1C**. Xenografts of prostate acini formed by transplantation of $\alpha_2\beta_1^{hi}$ /$CD133^+$ basal cells stained with (A) Haematoxylin and Eosin, (B) 34βE12, (C) anti-K18, (D) anti-PAP (E) Anti-androgen receptor. Bar 40 μm;

Figure 2: Characterisation of tumour 'stem' cells from a lymph node metastasis of the prostate (LNMP). **2A.** Tumour cells selected on the basis of □$_2$□$_1$/CD133 differentiate in culture. **2B.** Invasion assay activity of LNMP in comparison to PC3M and an immortalised prostate epithelial cell line, PNT1a;

Figure 3a represents NFkB Expression from α_2^{hi}/CD133$^+$ cells (PE434 cells; Gleason 9); Figure 3b represents a FACS dot plot of NFkB and CD133+ expression; 84% of cells are positive for NFkB alone and 0.21% are positive for NFkB and CD133.

Table 1 summarises array analysis of prostate stem cells and prostates cancer stem cells. Genes/nucleic acid and amino acid sequences are identified by Genbank accession number which can be accessed at http://www.ncbi.nlm.nih.gov. Genes are also identified by common name. The content of each accession entry is incorporated by reference and including the amino acid sequences of individual genes.

Materials and Methods

Genotype of isolated tumour stem cells

Using a combination of microsatellite markers associated with sporadic prostate cancer (8p 10q 16p) we can determine whether the isolated HEA$^+$/CD44$^+$/$\alpha_2\beta_1^{hi}$ /CD133$^+$ cells display loss of heterozygosity patterns characteristic of prostate tumours in comparison to blood lymphocyte DNA from the same patient. The analysis is carried out on a microsampling of cultures with 3MM paper and fluorescently labelled PCR primers (MacIntosh et al., 1998). This will enable us to discriminate between normal and cancer cells and determine whether stem cells are indeed targets for transforming events.

Proliferative, differentiative and malignant potential of putative cancer stem cells

Distinct populations of tumour cells are isolated and their proliferative, differentiative and malignant potential determined in vitro and in vivo. The following populations (HEA$^+$/CD44$^-$ (luminal cells), HEA$^+$/CD44$^+$ (basal cells), HEA$^+$/CD44$^+$/$\alpha_2\beta_1^{low}$/CD133$^-$ (transit cells), HEA$^+$/CD44$^+$/$\alpha_2\beta_1^{hi}$/CD133$^+$ (stem cells) are isolated and compared with the unsorted tumour population.

Colony forming efficiency (CFE): anchorage independent and anchorage-dependent growth

The transforming potential of distinct populations (as above) of cancer cells (anchorage independence) is measured by their ability to form colonies in soft agar. Individual colonies are counted after 21 days using an inverted microscope. Comparisons are made of CFE and colony size.

Morphogenesis in gels of reconstituted basement membrane matrix

We have determined the potential of tumour stem cells and their progenitors to undergo glandular morphogenesis in reconstituted basement membrane (e.g. Matrigel). We have demonstrated that normal basal cells can undergo glandular morphogenesis when grown in a collagen based matrix, (e.g. Matrigel) with stroma, in the presence of androgens. Spheroids are generated which are architecturally and phenotypically similar to in vivo acini and are often branched alveolar-and duct like (Lang et al., 2001). In contrast, cancer cells often form large aggregates of spindle-shaped cells with no obvious organisation. Nonetheless, the structures will often contain cells that show some degree of differentiation and can be compared to the original tumour.

Invasion assays

The ability of these stem cells to migrate across Matrigel is determined by the modified Boyden-chamber method (Albini et al., 1987). Migration rates will be evaluated using time-lapse confocal microscopy, using cells labelled with EGFP. We have generated prostate epithelium expressing low levels of EGFP. Recombinant retrovirus based on pLNCX-EGFP(2) generated will be used to infect the cell populations and G418 resistant colonies will be used in motility assays. The low levels of GFP expression will be used to track invasion and motility in real time.

In vivo tumourigenesis

Tumour stem cells must possess key criteria that define normal stem cells: after transplantation they must proliferate, differentiate and self-renew. To determine the

ability of distinct tumour phenotypes, to colonise in vivo, grafts of stem cells, transit cells, basal cells, luminal cells and unsorted cells are introduced into the prostates of 6 to 8 week old male, immuno-compromised mice. The mice are treated hormonally at the time of grafting by subcutaneous implantation of sustained release testosterone pellets. The number of cells from each population that successfully engraft and initiate tumour proliferation is determined by varying the number of cells implanted. The self-renewal capacity of the distinct populations is determined by transplanting serially into secondary recipients.

Array Sample and Data Processing

Total RNA extraction

α_2^{high}/CD133$^+$ cells

Total RNA is extracted from up to 1×10^4 selected cells using QIAgen RNeasy micro columns. Cells are lysed in 100µl RLT buffer + 1% β-mercaptoethanol and the manufactures protocol for "total RNA isolation from animal cells" is followed (RNeasy_Micro0403.pdf, pages 39-44, which is incorporated by reference).

α_2^{low} cells

Total RNA is extracted from between 1×10^5 and 1×10^6 selected cells using QIAgen RNeasy mini columns. Cells are lysed in 350µl RLT buffer + 1% β-mercaptoethanol and the manufactures protocol for "isolation of total RNA from animal cells" cells is followed (RNeasy_Mini0601.pdf, pages 31-35, which is incorporated by reference).

RNA yields are determined spectrophotometrically at 260nm and RNA integrity checked by capillary electrophoresis using an Agilent 2100 bioanalyzer.

Production of fragmented labelled cRNA

Total RNA is amplified using two rounds of cDNA synthesis and IVT (in vitro transcription) and biotin labelled by following the Affymetrix small scale labelling

protocol vII (smallv2_technote.pdf which is incorporated by reference) with the following modifications:

1. 10-50ng of total RNA is used per sample (step 1).
2. T4 DNA polymerase steps in the two second strand cDNA synthesis reactions are omitted (steps 2 & 7).
3. Second cycle, IVT for cRNA amplification and labelling (step 9) uses the Affymetrix GeneChip IVT labelling kit instead of the ENZO BioArray HighYield RNA transcript labelling kit and the Affymetrix eukaryotic sample and array processing standard protocol (expression_s2_manual_0604.pdf, section 2.1.34-2.1.35 which is incorporated by reference) is followed for this stage.

The quality of first and second round cRNA products and fragmented cRNA are checked by capillary electrophoresis using an Agilent 2100 bioanalyzer.

Array Hybridisation

Labelled fragmented cRNA (15µg) is hybridised to oligonucleotide probes on an Affymetrix HG-U133plus2 GeneChip. For hybridisation, washing, staining and scanning the Affymetrix eukaryotic sample and array processing standard protocol (expression_s2_manual_0604.pdf, section 2.2.3-2.3.17 which is incorporated by reference) is followed.

1. Hybridisation is conducted using an Affymetrix Hybridisation Oven 640.
2. Washing and staining stages are conducted using an Affymetrix Fluidics Station 450 using the EukGE-WS2v5 protocol.
3. Scanning of arrays is done with an Affymetrix Gene Scanner 3000.

Data Processing

Scanned GeneChip images are processed using Affymetrix GCOS software to derive an intensity value and flag (present, absent or marginal) for each probe. Probe intensities are derived using the MAS5 algorithm.

Comparisons between different sample datasets are conducted using Agilent GeneSpring GX software. Datasets to be compared are first normalised using three steps (consecutively applied in the order given):

1. Transform values <0.01 to 0.01
2. Normalise each chip to the 50 percentile of the measurements taken for that chip.
3. Normalise each probe to the median of the measurements for that probe.

For the purpose of analysing the data the following parameters are applied:

1. All cells derived from prostate cancer specimens are classed malignant, all cells derived from BPH specimens are classed benign ("tumour type" parameter)
2. All cells obtained by selection for high integrin $\alpha_2\beta_1$ expression and CD133 are classed stem cells, all cells selected for low integrin $\alpha_2\beta_1$ expression are classed committed basal cells ("cell type" parameter).
3. Further interpretations of the data allow for the combining of the above parameters to derive the conditions: malignant stem cells, malignant committed basal cells, benign stem cells and benign committed basal cells.

Low quality and uninformative data is removed using three selections (consecutively applied in the order given):

1. Remove probes flagged "absent" in all samples.
2. Remove probes with standard deviation within a parameter class of >1 in at least 3 of the 4 conditions.
3. Remove probes with less than a 2-fold overall change in normalised expression value between all four of the conditions.

Claims

1. An agent that modulates the activity of a cancer stem cell specific nucleic acid molecule, or a polypeptide encoded by a cancer stem nucleic acid molecule, wherein said cancer cell specific nucleic acid molecule is selected from the group consisting of:

i) a nucleic acid molecule consisting of a nucleic acid sequence as represented in SEQ ID NO: 1- 452;

ii) a nucleic acid molecule that hybridises under stringent hybridisation conditions to the nucleic acid molecule in (i) above and which encodes a polypeptide wherein said polypeptide is stem cell specific for use as a pharmaceutical.

2. An agent according to Claim 1 wherein said agent is an antagonist.

3. An agent according to Claim 1 wherein said agent is an agonist.

4. An agent that modulates the activity of a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule selected from the group consisting of:

i) a polypeptide encoded by a nucleic acid molecule as represented by the nucleic acid sequence in SEQ ID NO 1- 452;

ii) a polypeptide encoded by a nucleic acid molecule that encodes a variant polypeptide wherein said variant polypeptide is modified by addition, deletion or substitution of at least one amino acid residue of the amino acid sequence encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO 1-452 wherein said polypeptide is stem cell specific characterised in that said agent is for use as a pharmaceutical.

5. An agent according to Claim 4 wherein said agent is a polypeptide.

6. An agent according to Claim 5 wherein said polypeptide is an antibody or an active binding part of an antibody.

7. An agent according to Claim 6 wherein said antibody is a monoclonal antibody or active binding part thereof.

8. An agent according to Claim 6 or 7 wherein said antibody is a chimeric antibody or a humanised antibody.

9. An agent according to any of Claims 6-8 wherein said agent is an antibody fragment.

10. An agent according to Claim 9 wherein said fragment is selected from the group consisting of; Fab; Fab_2; $F(ab')_2$; Fv; Fc; Fd; or scFvs.

11. An agent according to Claim 10 wherein said antibody fragment is a single chain antibody variable region fragment.

12. An agent according to Claim 10 or 11 wherein said antibody is bispecific binding two different epitopes of two different antigens.

13. An agent according to any of Claims 6-12 wherein said antibody is an opsonic antibody.

14. An agent according to any of Claims 6-13 wherein said antibody is provided with a marker or tag.

15. An agent according to any of Claims 6-14 wherein said antibody, or antibody fragment, has associated therewith or crosslinked thereto a therapeutic agent.

16. An agent according to Claim 15 wherein said therapeutic agent is a chemotherapeutic agent.

17. An agent according to Claim 15 or 16 wherein said agent is selected from the group consisting of: cisplatin; carboplatin; cyclosphosphamide; melphalan; carmusline; methotrexate; 5-fluorouracil; cytarabine; mercaptopurine; daunorubicin; doxorubicin; epirubicin; vinblastine; vincristine; dactinomycin; mitomycin C; taxol; L-asparaginase; G-CSF; etoposide; colchicine; derferoxamine mesylate; and camptothecin.

18. An agent according to any of Claims 1-3 wherein said agent is a nucleic acid molecule.

19. An agent according to Claim 18 wherein said nucleic acid molecule is selected from the group consisting of: an antisense nucleic acid, an aptamer or a small interfering RNA.

20. An agent according to Claim 19 wherein said nucleic acid molecule is a small interfering RNA.

21. An agent according to Claim 19 or 20 wherein said small interfering RNA is 21-29 nucleotides in length.

22. A pharmaceutical composition comprising an agent according to any of Claims 1-21.

23. A composition comprising a nucleic acid molecule selected from the group consisting of:

i) a nucleic acid molecule consisting of a nucleic acid sequence as represented in SEQ ID NO: 1- 452;

ii) a nucleic acid molecule that hybridises under stringent hybridisation conditions to the nucleic acid molecule in (i) above and which encodes a polypeptide wherein said polypeptide is stem cell specific, for use as a vaccine.

24. A composition comprising a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule as represented in SEQ ID NO 1- 452, or a variant polypeptide wherein said variant is modified by addition, deletion or substitution of at least one amino acid residue of the amino acid sequence encoded by a nucleic acid molecule as represented in SEQ ID NO 1- 452 for use as a vaccine.

25. A composition according to Claim 23 or 24 wherein said composition includes an adjuvant and/or a carrier.

26. A vector which is adapted for the expression of a humanised or chimeric antibody or an antibody fragment according to any of Claims 8-14.

27. A cell which has been transformed or transfected with the vector according to Claim 26 encoding the humanised or chimeric antibody or an antibody fragment.

28. A method for the production of a humanised or chimeric antibody or an antibody fragment comprising:

i) providing a cell transformed or transfected with a vector which comprises a nucleic acid molecule encoding the humanised or chimeric antibody or antibody fragment according to any of Claims 8-14;

ii) growing said cell in conditions conducive to the manufacture of said antibody or fragment; and

iii) purifying said antibody or fragment from said cell, or its growth environment.

29. A hybridoma cell line which produces a monoclonal antibody according to Claim 7.

30. A method of producing monoclonal antibodies according to Claim 7 comprising using a hybridoma cell line according to Claim 29.

31. A method for preparing a hybridoma cell-line producing a monoclonal antibody comprising the steps of:

i) immunising an immunocompetent mammal with an immunogen comprising at least one polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in SEQ ID NO 1- 452, or fragments thereof;

ii) fusing lymphocytes of the immunised immunocompetent mammal with myeloma cells to form hybridoma cells;

iii) screening monoclonal antibodies produced by the hybridoma cells of step (ii) for binding activity to the polypeptide of (i);

iv) culturing the hybridoma cells to proliferate and/or to secrete said monoclonal antibody; and

v) recovering the monoclonal antibody from the culture supernatant.

32. A diagnostic assay for the determination of cancer in a subject comprising the steps of:

i) providing an isolated cell sample;

ii) contacting the sample in (i) with a binding agent(s) that binds to a nucleic acid molecule as represented by the nucleic acid sequence in SEQ ID NO 1- 452, or a nucleic acid molecule that hybridises to said nucleic acid molecule under stringent hybridisation conditions and encodes a variant polypeptide; and

iv) determining the expression of said nucleic acid molecule in said sample when compared to a normal matched control sample.

33. An assay according to Claim 32 wherein said binding agent(s) is an oligonucleotide primer.

34. An assay according to Claim 33 wherein said assay is a polymerase chain reaction.

35. An assay according to Claim 32 wherein said binding agent is an antibody that specifically binds said polypeptide encoded by a nucleic acid molecule as represented by the nucleic acid sequence in SEQ ID NO 1- 452, or a polypeptide variant comprising an amino acid sequence that varies from a reference amino acid sequence by addition, deletion or substitution of at least one amino acid residue.

36. An assay according to any of Claims 32-35 wherein said cancer is prostate cancer.

37. A kit comprising a binding agent specifically reactive with a nucleic acid molecule as represented in SEQ ID NO 1- 452, or an agent specifically reactive with a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in SEQ ID NO 1- 452.

38. A kit according to Claim 37 wherein said kit further comprises an oligonucleotide or antibody specifically reactive with said nucleic acid molecule or said polypeptide.

39. A kit according to Claim 37 or 38 wherein said kit comprises a thermostable DNA polymerase and components required for conducting the amplification of nucleic acid.

40. A kit according to any of Claims 37-39 wherein said kit includes a set of instructions for conducting said polymerase chain reaction and control nucleic acid.

41. A kit according to any of Claims 37-40 wherein said kit comprises an antibody specifically reactive with said polypeptide.

42. A kit according to Claim 41 wherein said kit comprises components required for conducting an immunoassay including, for example, a secondary antibody specifically reactive with a primary antibody that specifically binds said polypeptide(s) and enzyme reagents required to detect the binding of said secondary antibody with said primary antibody.

43. A method to screen for an agent that modulates the activity of a polypeptide encoded by a nucleic acid molecule selected from the group consisting of:

a) a nucleic acid molecule consisting of a nucleic acid sequence as represented in SEQ ID NO 1- 452;

b) a nucleic acid molecule that hybridises under stringent hybridisation conditions to the nucleic acid molecule in (i) above and which encodes a polypeptide wherein said polypeptide is stem cell specific;

i) forming a preparation comprising a polypeptide, or sequence variant thereof, and at least one agent to be tested;

ii) determining the activity of said agent with respect to the activity of said polypeptide.

44. A method according to Claim 43 wherein said agent is an antagonist.

45. A method according to Claim 43 wherein said agent is an agonist.

46. A method to treat a subject for a cancer comprising administering an effective amount of an agent according any of Claims 1-21.

47. A method according to Claim 46 wherein said subject is human.

48. A method according to Claim 46 or 47 wherein the cancer is prostate cancer.

49. A method to immunise an animal against a cancerous condition comprising administering an effective amount of a nucleic acid or polypeptide encoded by a nucleic acid molecule selected from the group consisting of:

i) a nucleic acid molecule consisting of a nucleic acid sequence as represented in SEQ ID NO 1- 452;

ii) a nucleic acid molecule that hybridises under stringent hybridisation conditions to the nucleic acid molecule in (i) above and which encodes a polypeptide wherein said polypeptide is stem cell specific.

50. A method according to Claim 49 wherein said animal is a human.

51. A method according to Claim 50 wherein said cancer is prostate cancer.

Fig 1A

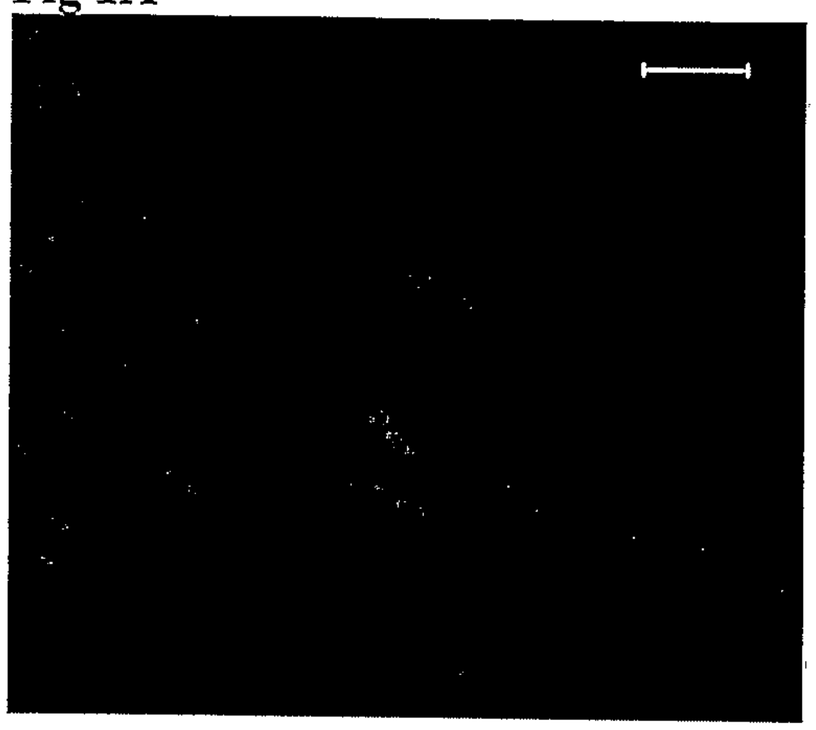


Fig 1B

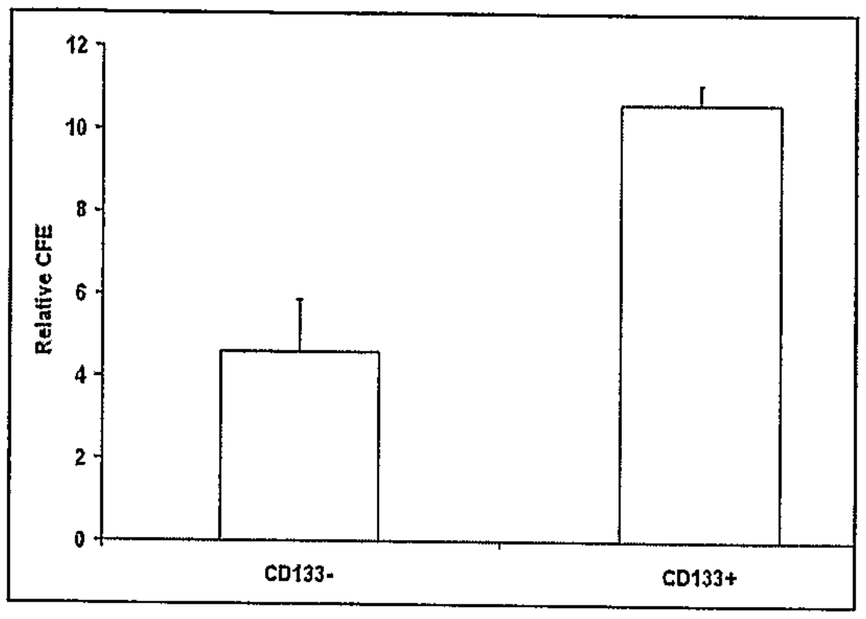


Fig 1C

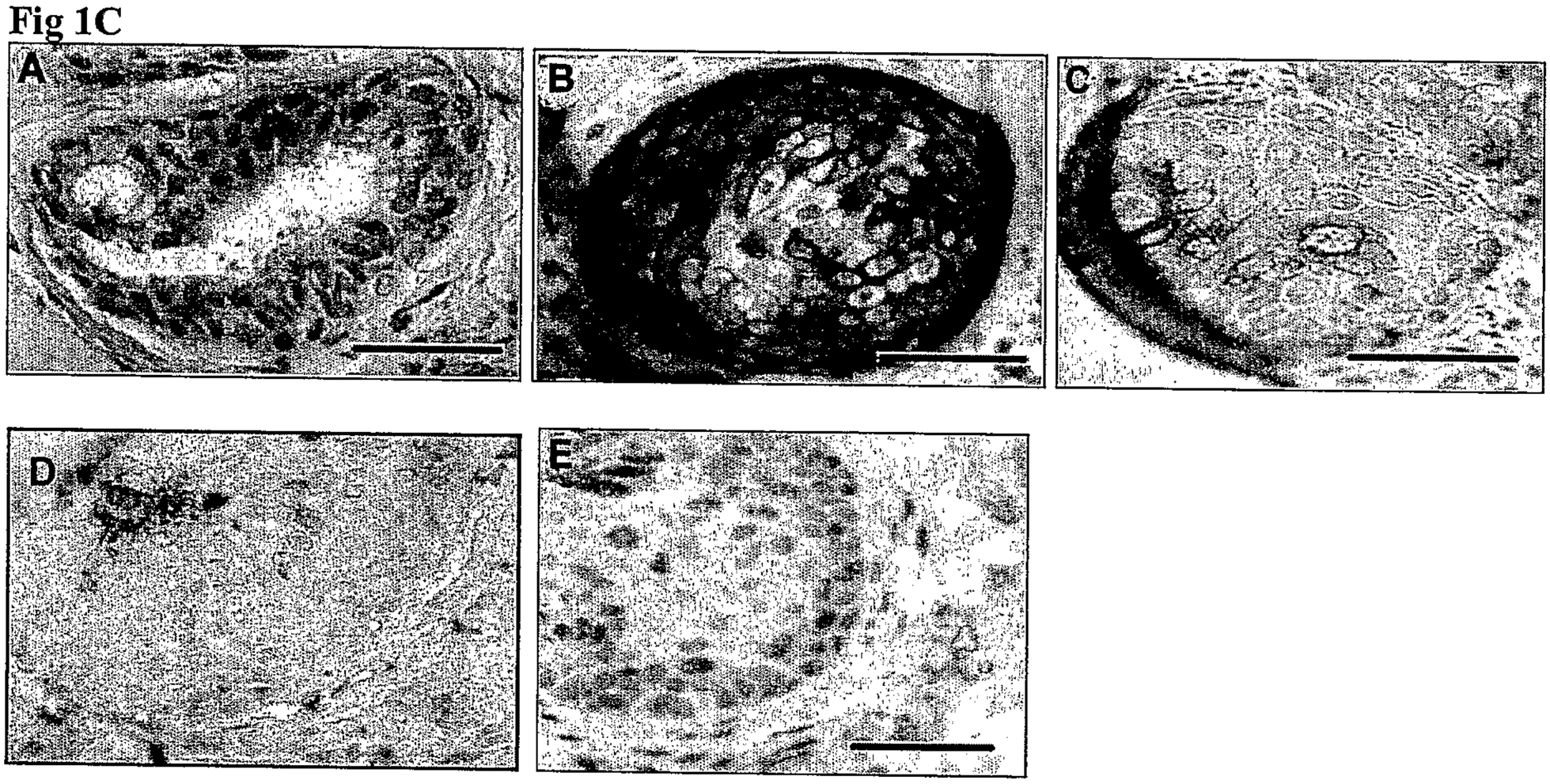
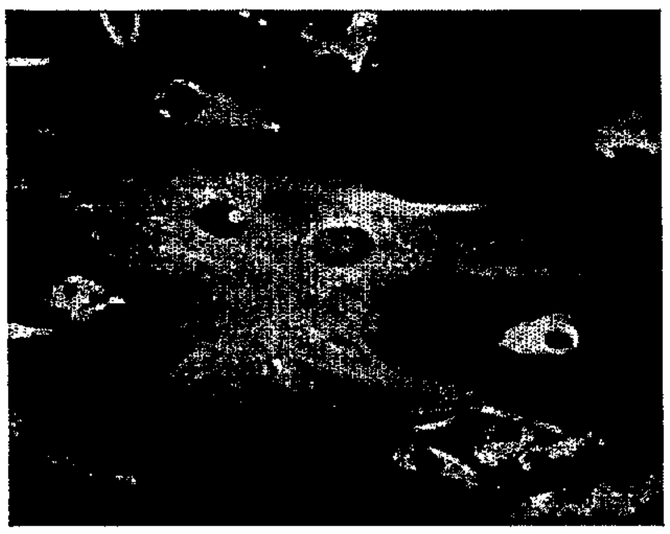
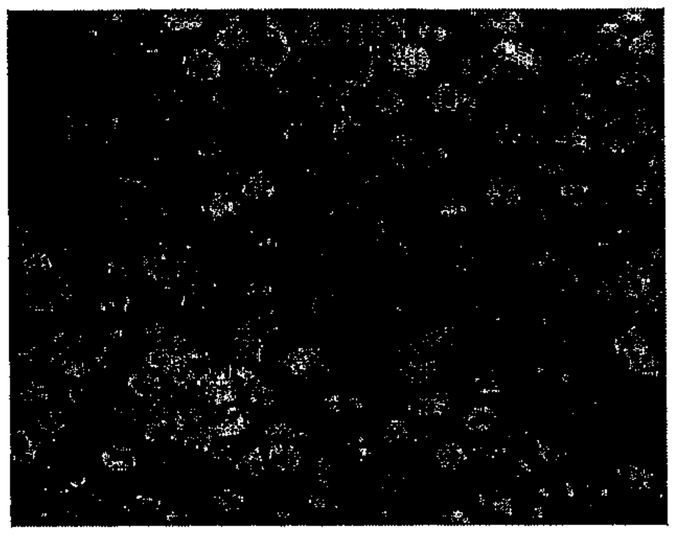


Fig 2A

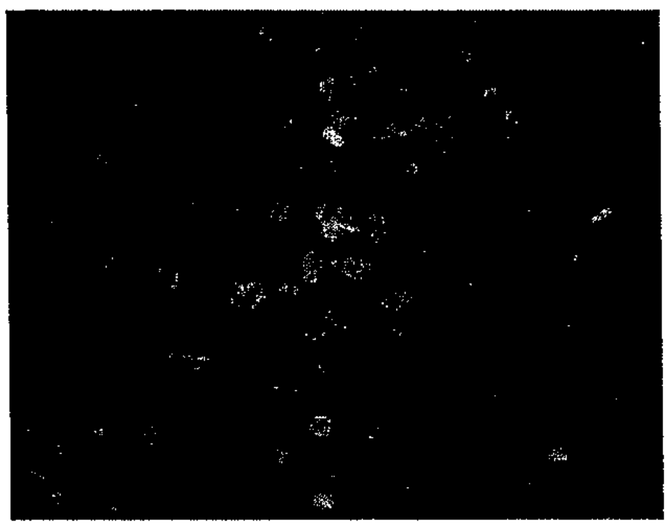
Vimentin



Cytokeratin 18



E-Cadherin



PSA



Fig 2B

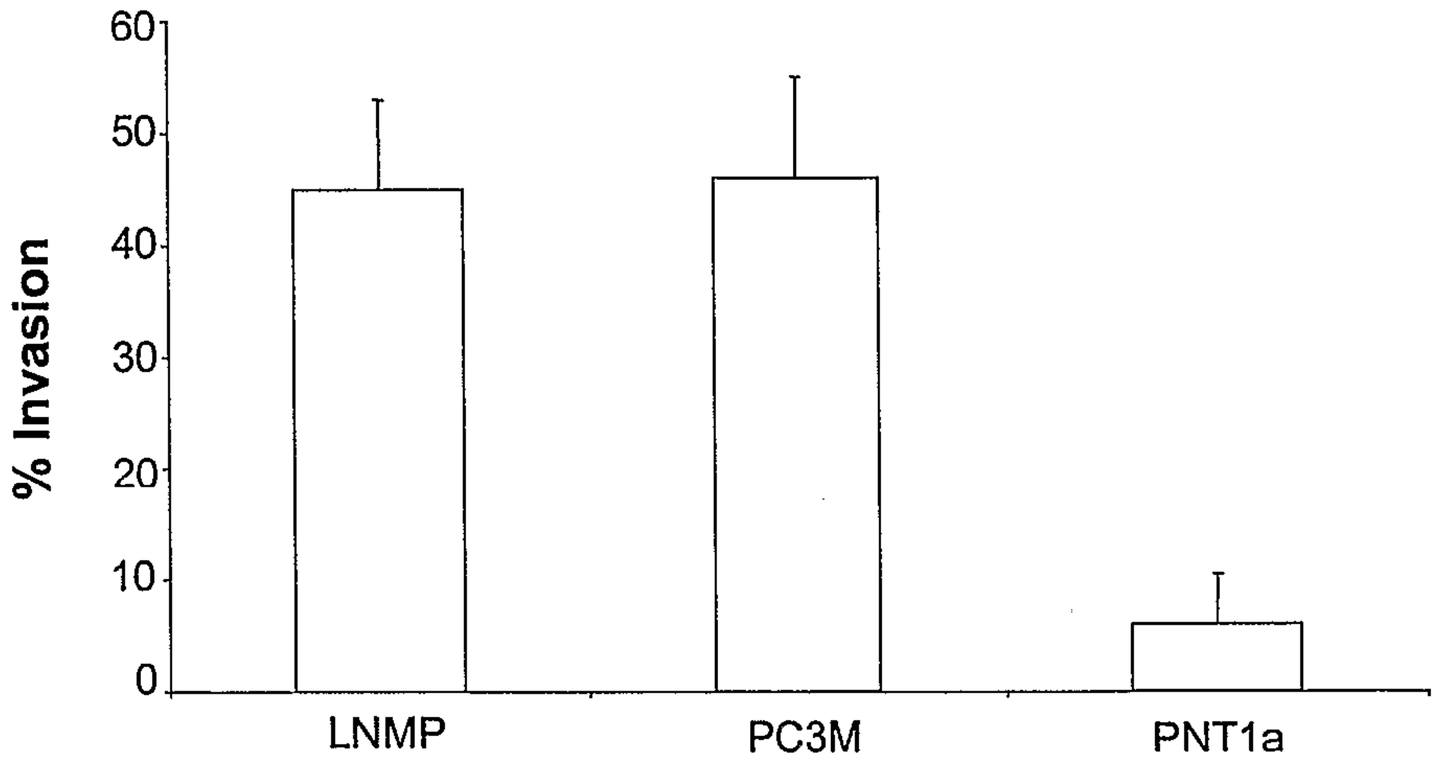


Figure 3a

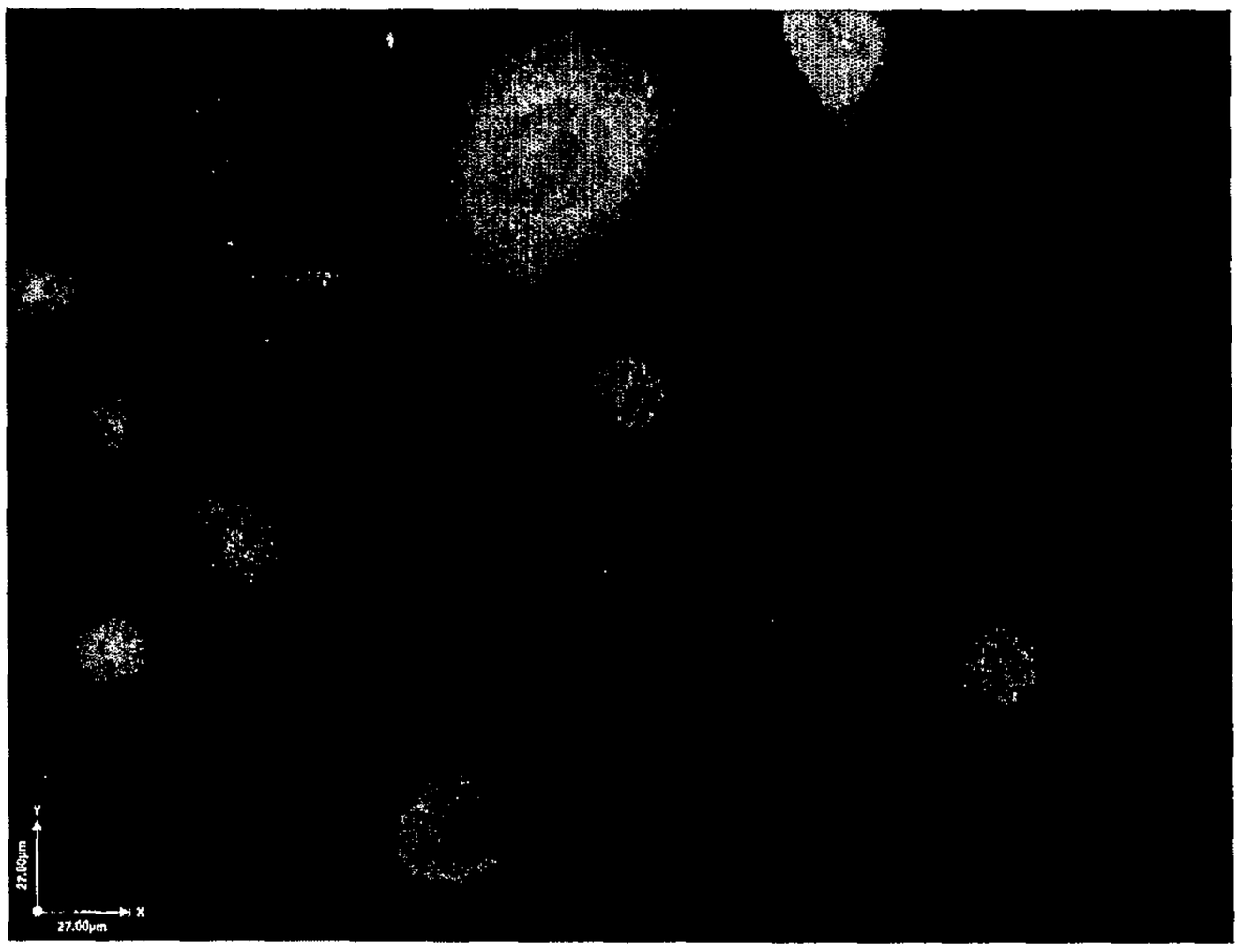
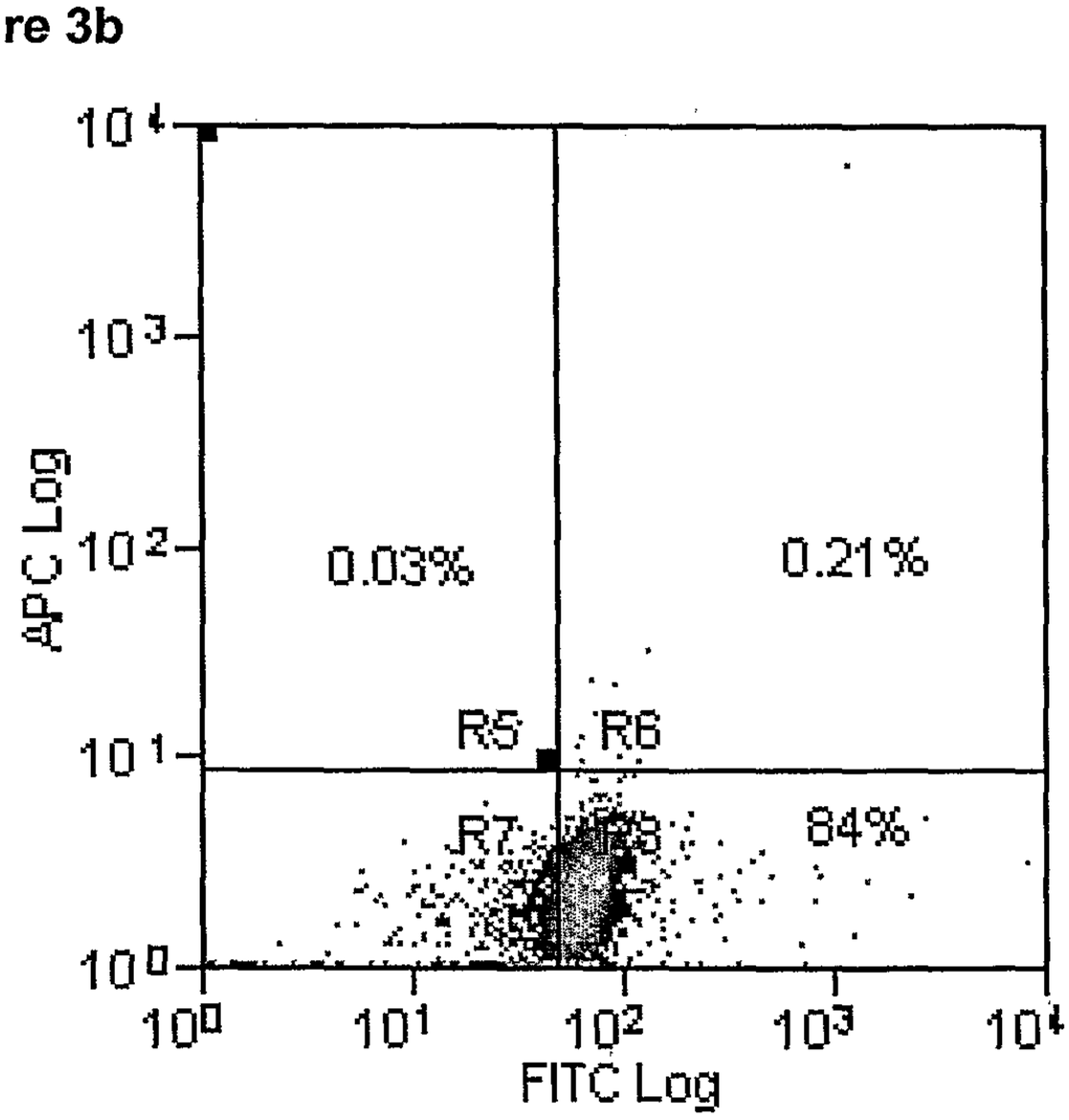


Figure 3b



4115

Cell Type
Tumour Type Malignant

Probe	Gene Name	Mean Expression	Min Fold Up	Rank	GeneBank	Gene Title	Doc No
224940_s_at	PAPPA	211.9	4.31	1	BF107618	pregnancy-associated plasma protein A, pappalysin 1	1
239876_at	NFKB1	186.2	2.77	2	R37337	Nuclear factor of kappa light polypeptide gene enhancer in B-cells 1 (p105)	2
232017_at	TJP2	205.0	2.20	3	AK025185	tight junction protein 2 (zona occludens 2)	3
238563_at	ABI1	148.8	2.09	4	AV762916	Abl-interactor 1	4
243509_at	BTG1	142.9	2.02	5	AI475680	B-cell translocation gene 1, anti-proliferative	5
205207_at	IL6	1179.8	1.98	6	NM_000600	interleukin 6 (interferon, beta 2)	6
239629_at	CFLAR	209.8	1.93	7	AI634046	CASP8 and FADD-like apoptosis regulator	7
228180_at	SMU1	162.7	1.89	8	AA805653	Smu-1 suppressor of mec-8 and unc-52 homolog (C. elegans)	8
206027_at	S100A3	289.4	1.85	9	NM_002960	S100 calcium binding protein A3	9
230000_at	C17orf27	195.6	1.85	10	AI523817	chromosome 17 open reading frame 27	10
1553185_at	RASEF	810.6	1.83	11	NM_152573	RAS and EF-hand domain containing	11
236251_at	ITGAV	287.3	1.83	12	AA228366	Integrin, alpha V (vitronectin receptor, alpha polypeptide, antigen CD51)	12
242903_at	IFNGR1	137.4	1.78	13	AI458949	Interferon gamma receptor 1	13
1557578_at	PHLDB2	135.2	1.74	14	BQ722176	Pleckstrin homology-like domain, family B, member 2	14
224822_at	DLC1	122.1	1.74	15	AA524250	deleted in liver cancer 1	15
213742_at	SFRS11	195.0	1.74	16	AW241752	splicing factor, arginine/serine-rich 11	16
235060_at	DKFZp547E087	163.5	1.72	17	AL047052	hypothetical gene LOC283846	17
236475_at	MICAL2	164.7	1.72	18	W86183	Microtubule associated monoxygenase, calponin and LIM domain containing 2	18
226661_at	CDCA2	134.5	1.72	19	T90295	cell division cycle associated 2	19
237183_at	AI023433	292.5	1.69	20	AI023433	---	20
220322_at	IL1F9	452.7	1.67	21	NM_019618	interleukin 1 family, member 9	22
230494_at	AI671885	222.6	1.63	22	AI671885	---	23
1556211_a_at	N62827	295.9	1.63	23	N62827	CDNA FLJ38810 fis, clone LIVER2006251	24
1557996_at	AK091784	103.3	1.62	24	AK091784	---	25
232330_at	FLJ10803	115.1	1.57	25	AK024861	Hypothetical protein FLJ10803	26
232865_at	AFF4	116.4	1.57	26	N59653	AF4/FMR2 family, member 4	27
229467_at	PCBP2	134.7	1.57	27	AA504356	Poly(rC) binding protein 2	28
219380_x_at	POLH	123.2	1.53	28	NM_006502	polymerase (DNA directed), eta	29
242558_at	AW362945	142.3	1.53	29	AW362945	CDNA FLJ45490 fis, clone BRTHA2005831	30
228990_at	C1orf79	221.2	1.53	30	AI339426	chromosome 1 open reading frame 79	31
228335_at	CLDN11	223.5	1.52	31	AW264204	claudin 11 (oligodendrocyte transmembrane protein)	32
234326_at	AK024901	46.1	2.88	32	AK024901	CDNA: FLJ21248 fis, clone COL01235	229
244612_at	AW117181	39.2	2.77	33	AW117181	---	230
238884_at	CTNND1	50.1	2.72	34	AW195351	Catenin (cadherin-associated protein), delta 1	231
242875_at	PSEN1	53.2	2.69	35	AI659439	Presenilin 1 (Alzheimer disease 3)	232
230456_at	OAF	91.6	2.68	36	BE501559	OAF homolog (Drosophila)	233
235652_at	TRIM45	82.4	2.46	37	AI431345	Tripartite motif-containing 45	234
229272_at	FNBP4	60.2	2.37	38	AI083506	Formin binding protein 4	236
240314_at	NCOR1	50.0	2.32	39	AI018235	Nuclear receptor co-repressor 1	237
240458_at	ITPR2	39.8	2.22	40	AI242023	Family with sequence similarity 20, member C	238
242389_at	BE887449	94.2	2.21	41	BE887449	CDNA FLJ33355 fis, clone BRACE2005151	239

5/15

236966_at	ARMC8	73.4	2.16	42	BF942281	armadillo repeat containing 8	240
243598_at	GPD2	36.4	2.11	43	AI393727	Glycerol-3-phosphate dehydrogenase 2 (*mitochondrial*)	241
242343_x_at	ZNF518	84.3	2.10	44	H57111	Zinc finger protein 518	242
239203_at	FLJ39575	58.7	2.09	45	AW014728	hypothetical protein FLJ39575	243
244356_at	PTPN12	38.5	2.07	46	AL079909	Protein tyrosine phosphatase, non-receptor type 12	244
1562473_at	PEX5L	43.1	2.07	47	BC037943	Peroxisomal biogenesis factor 5-like	245
235925_at	LOC440282	54.1	2.06	48	AW057520	Hypothetical protein LOC145783	246
244387_at	AW979271	41.3	1.98	49	AW979271	Transcribed locus	247
223781_x_at	ADH4	98.8	1.93	50	M15943	alcohol dehydrogenase 4 (class II), pi polypeptide	248
232930_at	DOCK1	42.4	1.91	51	AK000789	Dedicator of cytokinesis 1	250
236168_at	ACSL3	66.6	1.88	52	BF512846	Acyl-CoA synthetase long-chain family member 3	252
236210_at	DDX31	39.5	1.87	53	AW628575	DEAD (Asp-Glu-Ala-Asp) box polypeptide 31	253
243088_at	C2orf4	60.1	1.82	54	W84667	Chromosome 2 open reading frame 4	254
239017_at	T79422	65.2	1.80	55	T79422	Transcribed locus, moderately similar to XP_497913.1 PREDICTED: similar to RIKEN cDNA E330026B02 [Homo sapiens]	255
1556416_s_at	SEC31L1	91.3	1.80	56	AF086242	SEC31-like 1 (S. cerevisiae)	256
1564378_a_at	EXT1	62.2	1.79	57	AK025101	*Exostoses (multiple) 1*	257
239978_at	PITPNB	48.5	1.79	58	BF109370	Phosphatidylinositol transfer protein, beta	258
234608_at	LAMA3	87.6	1.78	59	AK024889	laminin, alpha 3	259
1560659_at	LOC150759	57.4	1.76	60	AL832439	Hypothetical protein LOC150759	260
242814_at	SERPINB9	66.6	1.76	61	AI986192	serpin peptidase inhibitor, clade B (ovalbumin), member 9	262
233599_at	C9orf3	68.2	1.75	62	AK025151	Chromosome 9 open reading frame 3	263
220090_at	CRNN	97.4	1.73	63	NM_016190	cornulin	264
215296_at	CDC42BPA	36.8	1.72	64	AK027000	*CDC42 binding protein kinase alpha* (DMPK-like)	265
228693_at	C3orf6	88.7	1.71	65	AI681307	chromosome 3 open reading frame 6	266
216112_at	HHLA2	50.9	1.70	66	AU157200	HERV-H LTR-associating 2	267
236755_at	TBC1D23	41.5	1.69	67	AW195589	TBC1 domain family, member 23	268
1566477_at	ARFGAP3	37.8	1.68	68	AL832530	ADP-ribosylation factor GTPase activating protein 3	270
232511_at	AK022838	89.0	1.67	69	AK022838	CDNA clone IMAGE:5310744	271
39966_at	CSPG5	45.1	1.67	70	AF059274	chondroitin sulfate proteoglycan 5 (neuroglycan C)	272
232094_at	C15orf29	60.4	1.66	71	AU144048	chromosome 15 open reading frame 29	273
243664_at	TXNL1	35.4	1.65	72	AA629944	Thioredoxin-like 1	274
1557384_at	ZNF131	48.4	1.65	73	AL832081	Zinc finger protein 131 (clone pHZ-10)	275
230892_at	DERA	52.6	1.65	74	AI912194	2-deoxyribose-5-phosphate aldolase homolog (C. elegans)	276
229765_at	AW511239	57.8	1.65	75	AW511239	Transcribed locus	277
241916_at	PLSCR1	87.0	1.64	76	AI984040	Phospholipid scramblase 1	278
220576_at	PGAP1	72.3	1.64	77	NM_024989	GPI deacylase	279
244015_at	EIF4G3	43.8	1.64	78	AA704163	Eukaryotic translation initiation factor 4 gamma, 3	280
240385_at	GATA6	42.5	1.64	79	BF002339	GATA binding protein 6	281
1556931_at	CDC42	40.8	1.64	80	AF086337	Cell division cycle 42 (GTP binding protein, 25kDa)	283
240656_at	SIPA1L1	63.9	1.63	81	AI798924	Signal-induced proliferation-associated 1 like 1	284
230868_at	HIAT1	71.5	1.63	82	BF433103	Hippocampus abundant transcript 1	285
242853_at	FLJ34208	61.7	1.63	83	C18965	Hypothetical gene supported by AK091527	286
230503_at	AA151917	75.2	1.63	84	AA151917	Transcribed locus	287
206508_at	TNFSF7	41.2	1.62	85	NM_001252	*tumor necrosis factor* (ligand) superfamily, member 7	289
232890_at	AK021423	50.8	1.60	86	AK021423	Transcribed locus, moderately similar to NP_055301.1 neuronal	290

						thread protein AD7c-NTP [Homo sapiens]	
232141_at	U2AF1	72.1	1.59	87	AU144161	U2(RNU2) small nuclear RNA auxiliary factor 1	291
233976_at	AA758732	36.6	1.58	88	AA758732	Transcribed locus	292
236079_at	DKFZp667E0512	61.6	1.57	89	AA649070	hypothetical protein DKFZp667E0512	293
242369_x_at	NCOA2	41.0	1.57	90	AI561070	Nuclear receptor coactivator 2	294
234196_at	TMCC3	75.3	1.57	91	AK025030	Transmembrane and coiled-coil domain family 3	295
206866_at	CDH4	40.0	1.57	92	NM_001794	cadherin 4, type 1, R-cadherin (retinal)	296
236707_at	DAPP1	86.9	1.56	93	AA521016	dual adaptor of phosphotyrosine and 3-phosphoinositides	297
230791_at	AU146924	81.8	1.55	94	AU146924	---	298
242837_at	SFRS4	99.8	1.55	95	AI435248	Splicing factor, arginine/serine-rich 4	299
1559249_at	ATXN1	41.3	1.55	96	BC010948	Ataxin 1	300
236930_at	NUMB	41.4	1.54	97	AW167424	Numb homolog (Drosophila)	301
232431_at	NR3C1	59.7	1.54	98	AI934556	Nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	302
242920_at	KIAA0999	81.3	1.54	99	AW590838	KIAA0999 protein	303
233313_at	AU158316	56.0	1.53	100	AU158316	---	304
205525_at	CALD1	85.0	1.52	101	NM_018495	caldesmon 1	305
238908_at	CALU	77.0	1.52	102	BG392414	Calumenin	306
232238_at	ASPM	44.7	1.52	103	AK001380	asp (abnormal spindle)-like, microcephaly associated (Drosophila)	307
208797_s_at	GOLGA8A /// GOLGA8B	58.0	1.51	104	AI829170	golgi autoantigen, golgin subfamily a, 8A /// golgi autoantigen, golgin subfamily a, 8B	308
1556345_s_at	MCCC2	39.3	1.51	105	AF086534	Methylcrotonoyl-Coenzyme A carboxylase 2 (beta)	309
230119_at	AK025975	35.8	1.51	106	AK025975	CDNA: FLJ22322 fis, clone HRC05532	310
239348_at	USP31	85.5	1.51	107	AI285970	Ubiquitin specific peptidase 31	311
241812_at	DNAPTP6	81.8	1.51	108	AV648669	DNA polymerase-transactivated protein 6	312
230651_at	THOC2	74.1	1.51	109	AI018256	THO complex 2	313
209897_s_at	SLIT2	93.5	1.50	110	AF055585	slit homolog 2 (Drosophila)	314
226179_at	SLC25A37	367.8	1.49	111	N63920	solute carrier family 25, member 37	33
222303_at	AV700891	450.2	1.49	112	AV700891	---	34
1556007_s_at	AI377389	138.0	1.49	113	AI377389	---	35
232527_at	AU146179	109.6	1.48	114	AU146179	---	36
215529_x_at	C21orf106	188.2	1.48	115	AI590053	chromosome 21 open reading frame 106	37
215067_x_at	PRDX2	102.6	1.47	116	AU147942	peroxiredoxin 2	38
1558783_at	WTAP	145.0	1.47	117	AK024805	Wilms tumor 1 associated protein	39
242535_at	AI245300	145.1	1.46	118	AI245300	Transcribed locus	40
229694_at	BRWD2	173.0	1.46	119	BF062828	bromodomain and WD repeat domain containing 2	41
227208_at	DLNB14	380.7	1.46	120	BF446390	similar to DLNB14	42
203184_at	FBN2	1160.0	1.46	121	NM_001999	fibrillin 2 (congenital contractural arachnodactyly)	43
210944_s_at	CAPN3	211.2	1.45	122	BC003169	calpain 3, (p94)	44
236254_at	VPS13B	181.0	1.45	123	BE048857	vacuolar protein sorting 13B (yeast)	45
224288_x_at	AF336882	107.8	1.44	124	AF336882	---	46
241223_x_at	SFXN1	144.9	1.44	125	AI821721	Sideroflexin 1	47
212027_at	RBM25	975.1	1.42	126	AI925305	RNA binding motif protein 25	48
233595_at	USP34	122.0	1.42	127	AK024341	Ubiquitin specific peptidase 34	49
242539_at	AW665509	107.5	1.42	128	AW665509	Transcribed locus	50
243768_at	SENP6	114.8	1.41	129	AA026388	SUMO1/sentrin specific peptidase 6	51
214016_s_at	SFPQ	975.0	1.41	130	AL558875	Splicing factor proline/glutamine-rich (polypyrimidine tract binding protein associated)	52
211040_x_at	GTSE1	201.7	1.41	131	BC006325	G-2 and S-phase expressed 1 /// G-2 and S-phase expressed 1	53
1555136_at	FGD6	125.9	1.40	132	BC013319	FYVE, RhoGEF and PH domain containing 6	55

236715_x_at	UACA	153.0	1.40	133	BF056139	uveal autoantigen with coiled-coil domains and ankyrin repeats	56
234723_x_at	AK024881	168.3	1.38	134	AK024881	---	59
204345_at	COL16A1	501.8	1.38	135	NM_001856	collagen, type XVI, alpha 1	60
229490_s_at	IQGAP3	205.4	1.38	136	AW271106	IQ motif containing GTPase activating protein 3	61
214131_at	CYorf15B	161.6	1.37	137	AL049280	chromosome Y open reading frame 15B	62
206792_x_at	PDE4C	673.5	1.37	138	NM_000923	phosphodiesterase 4C, cAMP-specific (phosphodiesterase E1 dunce homolog, Drosophila)	63
242467_at	CSNK1A1	113.8	1.36	139	BF433200	Casein kinase 1, alpha 1	64
207730_x_at	KIAA1881	378.0	1.35	140	NM_017932	KIAA1881	66
225293_at	COL27A1	660.4	1.35	141	AK021957	collagen, type XXVII, alpha 1	67
238642_at	AW367571	134.5	1.35	142	AW367571	---	68
232597_x_at	SFRS2IP	115.8	1.34	143	AK025132	Splicing factor, arginine/serine-rich 2, interacting protein	69
216187_x_at	KNS2	649.2	1.32	144	AF222691	Kinesin 2	70
235571_at	AW300953	117.9	1.32	145	AW300953	Transcribed locus, moderately similar to NP_060312.1 hypothetical protein FLJ20489 [Homo sapiens]	71
220071_x_at	C15orf25	381.5	1.32	146	NM_018097	chromosome 15 open reading frame 25	72
1562416_at	AI524619	103.2	1.31	147	AI524619	---	73
218308_at	TACC3	171.0	1.31	148	NM_006342	transforming, acidic coiled-coil containing protein 3	74
214715_x_at	ZNF160	560.5	1.31	149	AK024789	zinc finger protein 160	75
212382_at	TCF4	177.1	1.31	150	BF433429	Transcription factor 4	76
228723_at	NPTN	149.2	1.31	151	AL360198	Neuroplastin	77
223679_at	CTNNB1	156.7	1.30	152	AF130085	Catenin (cadherin-associated protein), beta 1, 88kDa	78
221591_s_at	FAM64A	114.3	1.30	153	BC005004	family with sequence similarity 64, member A	79
1556126_s_at	BM668595	138.2	1.29	154	BM668595	---	80
227406_at	GABPB2	120.3	1.29	155	AI286203	GA binding protein transcription factor, beta subunit 2	81
231766_s_at	COL12A1	209.9	1.29	156	U73778	collagen, type XII, alpha 1	82
232674_at	UCN2	140.9	1.29	157	BC002647	urocortin 2	83
234762_x_at	NLN	495.7	1.28	158	AK026655	Neurolysin (metallopeptidase M3 family)	85
236274_at	EIF3S9	117.5	1.28	159	AW129967	eukaryotic translation initiation factor 3, subunit 9 eta, 116kDa	86
223494_at	MGEA5	325.9	1.28	160	AF307332	meningioma expressed antigen 5 (hyaluronidase)	87
221264_s_at	TARDBP	129.2	1.28	161	NM_031214	TAR DNA binding protein /// TAR DNA binding protein	88
230180_at	DDX17	434.1	1.28	162	AA521056	DEAD (Asp-Glu-Ala-Asp) box polypeptide 17	89
1559496_at	AL833123	103.1	1.27	163	AL833123	---	90
212021_s_at	MKI67	185.7	1.27	164	AU132185	antigen identified by monoclonal antibody Ki-67	91
212384_at	BAT1	119.5	1.26	165	AI282485	HLA-B associated transcript 1	93
229811_at	LAMA5	120.3	1.26	166	AI307745	Laminin, alpha 5	101
235714_at	AA203132	127.1	1.26	167	AA203132	---	102
232347_x_at	AK021441	121.6	1.25	168	AK021441	---	103
237768_x_at	TAF15	130.7	1.25	169	AA825925	TAF15 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 68kDa	104
211454_x_at	AF336878	238.2	1.25	170	AF336878	---	105
207828_s_at	CENPF	213.0	1.25	171	NM_005196	centromere protein F, 350/400ka (mitosin)	106
225242_s_at	URB	255.2	1.25	172	AW303375	steroid sensitive gene 1	107
232098_at	DST	110.7	1.24	173	AK025142	dystonin	108
209136_s_at	USP10	154.1	1.24	174	BG390445	ubiquitin specific peptidase 10	109
235508_at	PML	133.5	1.24	175	AW291023	promyelocytic leukemia	110
241347_at	KIAA1618	145.5	1.24	176	AA936632	KIAA1618	111
224254_x_at	AF116695	121.6	1.24	177	AF116695	---	112
217523_at	CD44	363.9	1.24	178	AV700298	CD44 antigen (homing function and Indian blood group system)	113

204863_s_at	IL6ST	114.4	1.24	179	BE856546	interleukin 6 signal transducer (gp130, oncostatin M receptor)	114
217679_x_at	AI683552	345.1	1.24	180	AI683552	Transcribed locus, weakly similar to NP_055301.1 neuronal thread protein AD7c-NTP [Homo sapiens]	115
242608_x_at	ZNF410	222.7	1.24	181	AW517479	Zinc finger protein 410	116
215179_x_at	PGF	566.4	1.24	182	AK023843	Placental growth factor, vascular endothelial growth factor-related protein	117
222774_s_at	NETO2	243.7	1.23	183	AI335263	neuropilin (NRP) and tolloid (TLL)-like 2	118
219442_at	MGC3020	123.7	1.23	184	NM_024048	hypothetical protein MGC3020	119
218662_s_at	HCAP-G	223.9	1.23	185	NM_022346	chromosome condensation protein G	120
228793_at	JMJD1C	110.4	1.23	186	BF002296	jumonji domain containing 1C	121
242509_at	MGC17624	157.9	1.23	187	R71072	MGC17624 protein	122
204538_x_at	NPIP /// LOC339047 /// LOC440341	642.8	1.22	188	NM_006985	nuclear pore complex interacting protein /// hypothetical protein LOC339047 /// similar to hypothetical protein LOC339047	123
214594_x_at	ATP8B1	268.8	1.22	189	BG252666	ATPase, Class I, type 8B, member 1	124
213593_s_at	TRA2A	130.6	1.22	190	AW978896	Transformer-2 alpha	125
224549_x_at	SND1	485.7	1.22	191	AF194537	Staphylococcal nuclease domain containing 1 /// Staphylococcal nuclease domain containing 1	126
213956_at	CAP350	207.1	1.22	192	AW299294	centrosome-associated protein 350	127
237475_x_at	AI151104	382.6	1.22	193	AI151104	CH5400	129
241303_x_at	INPP4B	156.6	1.21	194	AA436194	Inositol polyphosphate-4-phosphatase, type II, 105kDa	130
244197_x_at	CNOT2	252.9	1.21	195	AI859990	CCR4-NOT transcription complex, subunit 2	131
208798_x_at	GOLGA8A	742.9	1.21	196	AF204231	golgi autoantigen, golgin subfamily a, 8A	132
234788_x_at	FLJ13611	139.3	1.21	197	AK024819	Hypothetical protein FLJ13611	133
208707_at	EIF5	173.6	1.21	198	BE552334	eukaryotic translation initiation factor 5	134
224771_at	NAV1	355.5	1.20	199	AI937060	neuron navigator 1	135
208246_x_at	TK2	416.5	1.20	200	NM_017618	Thymidine kinase 2, mitochondrial	136
204294_at	AMT	169.8	1.20	201	NM_000481	aminomethyltransferase (glycine cleavage system protein T)	137
228520_s_at	APLP2	298.8	1.20	202	AA022510	Amyloid beta (A4) precursor-like protein 2	138
202771_at	FAM38A	991.8	1.20	203	NM_014745	family with sequence similarity 38, member A	139
224667_x_at	C10orf104	422.5	1.20	204	AK023981	chromosome 10 open reading frame 104	140
227070_at	GLT8D2	103.1	1.20	205	W63754	glycosyltransferase 8 domain containing 2	141
232471_at	BE143535	127.9	1.20	206	BE143535	---	142
215600_x_at	AK022174	350.0	1.19	207	AK022174	---	143
243683_at	MORF4L2	116.5	1.19	208	H43976	Mortality factor 4 like 2	145
225546_at	EEF2K	327.9	1.19	209	W68180	eukaryotic elongation factor-2 kinase	146
229520_s_at	C14orf118	133.4	1.19	210	BF060678	chromosome 14 open reading frame 118	147
202998_s_at	LOXL2	591.5	1.18	211	NM_002318	lysyl oxidase-like 2	148
201328_at	ETS2	1626.9	1.18	212	AL575509	v-ets erythroblastosis virus E26 oncogene homolog 2 (avian)	149
228559_at	BF111626	158.9	1.17	213	BF111626	CDNA clone IMAGE:6043059	151
211445_x_at	NACAP1 /// LOC389240	962.3	1.17	214	AF315951	nascent-polypeptide-associated complex alpha polypeptide pseudogene 1 /// similar to alpha NAC/1.9.2. protein	152
218980_at	FHOD3	371.0	1.17	215	NM_025135	formin homology 2 domain containing 3	153
228260_at	ELAVL2	284.3	1.16	216	AL161628	ELAV (embryonic lethal, abnormal vision, Drosophila)-like 2 (Hu antigen B)	154
228069_at	FAM54A	144.8	1.16	217	AL138828	family with sequence similarity 54, member A	155
231735_s_at	PRO1073	643.9	1.16	218	NM_014086	PRO1073 protein	156
204472_at	GEM	285.5	1.16	219	NM_005261	GTP binding protein overexpressed	157

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						in skeletal muscle	
219392_x_at	FLJ11029	621.1	1.16	220	NM_018304	hypothetical protein FLJ11029	158
209408_at	KIF2C	275.1	1.15	221	U63743	kinesin family member 2C	160
213514_s_at	DIAPH1	119.6	1.15	222	AU158818	diaphanous homolog 1 (Drosophila)	161
216858_x_at	AL080112	141.7	1.15	223	AL080112	---	162
219493_at	SHCBP1	136.7	1.15	224	NM_024745	SHC SH2-domain binding protein 1	163
213979_s_at	CTBP1	406.9	1.15	225	BF984434	Hypothetical protein LOC285463	164
235274_at	AA740632	154.2	1.15	226	AA740632	CDNA clone IMAGE:4814008	165
227399_at	VGL-3	121.1	1.15	227	AI754423	vestigial-like 3	166
242233_at	KIAA1219	149.9	1.14	228	AI739332	KIAA1219 protein	167
207165_at	HMMR	408.2	1.14	229	NM_012485	hyaluronan-mediated motility receptor (RHAMM)	168
224093_at	IFNK	663.8	1.14	230	AF315688	interferon, kappa	169
210679_x_at	BC002629	157.4	1.14	231	BC002629	---	170
229483_at	AA760738	109.4	1.13	232	AA760738	---	171
242748_at	SREBF2	101.5	1.13	233	AA112403	Sterol regulatory element binding transcription factor 2	172
203325_s_at	COL5A1	172.7	1.13	234	AI130969	collagen, type V, alpha 1	173
1555967_at	AA362254	116.3	1.13	235	AA362254	CDNA FLJ30424 fis, clone BRACE2008881, weakly similar to ZINC FINGER PROTEIN 195	174
212926_at	SMC5L1	128.5	1.12	236	AW183677	SMC5 structural maintenance of chromosomes 5-like 1 (yeast)	176
218355_at	KIF4A	111.0	1.12	237	NM_012310	kinesin family member 4A	177
204270_at	SKI	119.4	1.12	238	AI568728	v-ski sarcoma viral oncogene homolog (avian)	179
205681_at	BCL2A1	134.5	1.11	239	NM_004049	BCL2-related protein A1	182
231234_at	CTSC	256.2	1.11	240	AV699565	cathepsin C	183
228564_at	LOC375295	124.3	1.11	241	AI569804	hypothetical gene supported by BC013438	184
218039_at	NUSAP1	685.6	1.11	242	NM_016359	nucleolar and spindle associated protein 1	185
243147_x_at	AW118707	103.2	1.10	243	AW118707	---	186
202760_s_at	AKAP2 /// PALM2-AKAP2	1071.0	1.10	244	NM_007203	A kinase (PRKA) anchor protein 2 /// PALM2-AKAP2 protein	187
214902_x_at	FLJ42393	173.1	1.10	245	AL080232	FLJ42393 protein	188
228613_at	BF183535	179.2	1.09	246	BF183535	CDNA FLJ37498 fis, clone BRAWH2016028	190
217853_at	TNS3	521.4	1.09	247	NM_022748	Tensin 3	191
215628_x_at	PPP2CA	158.5	1.09	248	AL049285	Protein phosphatase 2 (formerly 2A), catalytic subunit, alpha isoform	193
215588_x_at	RIOK3	196.3	1.08	249	AK024958	RIO kinase 3 (yeast)	194
219610_at	RGNEF	254.4	1.08	250	NM_022448	Rho-guanine nucleotide exchange factor	195
226237_at	COL8A1	1163.3	1.07	251	AL359062	Collagen, type VIII, alpha 1	196
202368_s_at	TRAM2	143.4	1.07	252	AI986461	translocation associated membrane protein 2	197
227566_at	HNT	441.3	1.07	253	AW085558	neurotrimin	198
230930_at	LOC338620	348.4	1.06	254	AI435839	hypothetical protein LOC338620	199
204682_at	LTBP2	1849.6	1.06	255	NM_000428	latent transforming growth factor beta binding protein 2	200
229200_at	LOC400813	119.9	1.06	256	N40199	Hypothetical LOC400813	201
201292_at	TOP2A	239.1	1.06	257	AL561834	topoisomerase (DNA) II alpha 170kDa	202
209969_s_at	STAT1	540.9	1.06	258	BC002704	signal transducer and activator of transcription 1, 91kDa	203
216384_x_at	LOC440085	796.7	1.06	259	AF257099	similar to prothymosin alpha	204
210230_at	LOC388388	186.1	1.05	260	BC003629	Chromodomain helicase DNA binding protein 3	205
210020_x_at	CALML3	1433.3	1.05	261	M58026	calmodulin-like 3	206
214791_at	LOC93349	174.3	1.05	262	AK023116	hypothetical protein BC004921	207
222039_at	LOC146909	143.8	1.05	263	AA292789	hypothetical protein LOC146909	208
228141_at	NUDT4	225.3	1.05	264	AA173223	Nudix (nucleoside diphosphate linked moiety X)-type motif 4 pseudogene 2	210
201859_at	PRG1	361.4	1.05	265	NM_002727	proteoglycan 1, secretory granule	211
202796_at	SYNPO	306.7	1.05	266	NM_007286	synaptopodin	212
228919_at	AA601031	167.6	1.04	267	AA601031	---	213

218735_s_at	ZNF544	302.5	1.04	268	AA349848	zinc finger protein 544	214
204502_at	SAMHD1	143.8	1.04	269	NM_015474	SAM domain and HD domain 1	215
230629_s_at	EP400	100.8	1.03	270	AI809582	E1A binding protein p400	216
1557987_at	LOC641298	141.2	1.03	271	BC042832	PI-3-kinase-related kinase SMG-1 - like locus	217
208975_s_at	KPNB1	376.5	1.03	272	L38951	karyopherin (importin) beta 1	218
213010_at	PRKCDBP	199.3	1.03	273	AI088622	protein kinase C, delta binding protein	219
235964_x_at	C20orf118	485.8	1.02	274	AA603344	Chromosome 20 open reading frame 118	220
216565_x_at	LOC391020	358.1	1.02	275	AL121994	similar to Interferon-induced transmembrane protein 3 (Interferon-inducible protein 1-8U)	221
229400_at	HOXD10	1097.2	1.02	276	AW299531	homeo box D10	222
232266_x_at	CDC2L5	615.7	1.01	277	AK024379	Cell division cycle 2-like 5 (cholinesterase-related cell division controller)	223
209459_s_at	ABAT	628.6	1.01	278	AF237813	4-aminobutyrate aminotransferase	224
220796_x_at	SLC35E1	511.9	1.01	279	NM_024881	solute carrier family 35, member E1	225
244804_at	SQSTM1	347.4	1.01	280	AW293441	Sequestosome 1	226
208790_s_at	PTRF	124.6	1.01	281	AF312393	polymerase I and transcript release factor	227
215467_x_at	DHX9	72.0	1.50	282	AK001442	DEAH (Asp-Glu-Ala-His) box polypeptide 9	315
239600_at	AA968447	40.6	1.49	283	AA968447	CDNA FLJ26461 fis, clone KDN03867	316
239731_at	AI674685	66.8	1.49	284	AI674685	Transcribed locus	317
241775_at	SCFD1	54.8	1.49	285	AW298119	Sec1 family domain containing 1	318
235662_at	MGC15407	40.6	1.49	286	AI125867	Similar to RIKEN cDNA 4931428D14 gene	319
235518_at	SLC8A1	56.3	1.48	287	AI741439	solute carrier family 8 (sodium/calcium exchanger), member 1	323
240815_at	SEMA3C	63.8	1.48	288	R62588	Sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3C	324
240279_at	WDFY2	51.5	1.47	289	BF056273	WD repeat and FYVE domain containing 2	325
215269_at	TMEM1	43.9	1.47	290	AI922538	transmembrane protein 1	326
233399_x_at	LOC441383	90.0	1.46	291	AU145662	hypothetical gene supported by AF086559; BC065734	327
237006_at	AFF1	52.7	1.46	292	AA703523	DDHD domain containing 2	328
219650_at	FLJ20105	91.4	1.46	293	NM_017669	FLJ20105 protein	329
235023_at	VPS13C	85.0	1.46	294	AA828371	Vacuolar protein sorting 13C (yeast)	330
1556352_at	AI692624	56.8	1.45	295	AI692624	CDNA FLJ30440 fis, clone BRACE2009185	331
242068_at	BIRC6	89.8	1.45	296	AA608834	Splicing factor, arginine/serine-rich 12	333
1552301_a_at	CORO6	56.8	1.45	297	NM_032854	coronin 6	334
243216_x_at	USP40	54.3	1.45	298	T87178	Ubiquitin specific peptidase 40	335
217715_x_at	ZNF354A	99.9	1.44	299	BE045142	Zinc finger protein 354A	336
216026_s_at	POLE	77.7	1.44	300	AL080203	polymerase (DNA directed), epsilon	337
201261_x_at	BGN	43.1	1.44	301	BC002416	biglycan	338
239784_at	AA398740	52.2	1.44	302	AA398740	MRNA, chromosome 1 specific transcript KIAA0504	339
239557_at	LRRFIP2	49.2	1.44	303	AW474960	Leucine rich repeat (in FLII) interacting protein 2	340
217667_at	AV761014	38.6	1.43	304	AV761014	---	341
231696_x_at	TMEM50B	35.2	1.42	305	AV648424	Transmembrane protein 50B	342
238595_at	AV702101	52.3	1.42	306	AV702101	Transcribed locus, moderately similar to XP_508016.1 PREDICTED: similar to oligonucleotide/oligosaccharide-binding fold containing 1 [Pan troglodytes]	343
230024_at	AARSL	91.2	1.42	307	AI183453	Alanyl-tRNA synthetase like	344
216176_at	HCRP1	39.1	1.42	308	AK025343	hepatocellular carcinoma-related HCRP1	345
1556543_at	ZCCHC7	45.6	1.42	309	AF086013	Zinc finger, CCHC domain containing 7	346

214723_x_at	KIAA1641	83.0	1.41	310	AB046861	KIAA1641	347
241391_at	AA654772	44.3	1.41	311	AA654772	Transcribed locus	348
222252_x_at	UBQLN4 /// UBQLN4P	60.1	1.40	312	AK023354	ubiquilin 4 /// ubiquilin 4 pseudogene	349
239516_at	LYPLAL1	40.4	1.40	313	AI806583	Lysophospholipase-like 1	350
1568815_a_at	DDX50	47.1	1.40	314	AA903184	DEAD (Asp-Glu-Ala-Asp) box polypeptide 50	352
217610_at	AL047879	45.1	1.40	315	AL047879	---	353
219906_at	FLJ10213	74.2	1.39	316	NM_018029	hypothetical protein FLJ10213	354
244674_at	RBM6	61.3	1.39	317	AA936428	RNA binding motif protein 6	355
202800_at	SLC1A3	58.8	1.39	318	NM_004172	solute carrier family 1 (glial high affinity glutamate transporter), member 3	356
236294_at	HUWE1	78.1	1.39	319	R37670	HECT, UBA and WWE domain containing 1	357
242485_at	PTK2	64.9	1.39	320	AW178807	PTK2 protein tyrosine kinase 2	358
1564430_at	BAT2D1	49.9	1.39	321	BC007549	BAT2 domain containing 1	359
242743_at	IL4R	78.6	1.38	322	AA767714	Interleukin 4 receptor	360
236277_at	PAK3	66.5	1.38	323	H23551	P21 (CDKN1A)-activated kinase 3	361
228119_at	LRCH3	81.4	1.38	324	AI598213	leucine-rich repeats and calponin homology (CH) domain containing 3	362
239313_at	LOC401320	41.7	1.38	325	AI803568	Hypothetical LOC401320	363
243039_at	AI042377	52.4	1.38	326	AI042377	---	364
239163_at	UBE2B	42.3	1.38	327	AW364833	ubiquitin-conjugating enzyme E2B (RAD6 homolog)	365
239597_at	PAN3	45.6	1.38	328	AA993566	PABP1-dependent poly A-specific ribonuclease subunit PAN3	366
1570351_at	ADAMTS6	79.1	1.38	329	BC020916	ADAM metallopeptidase with thrombospondin type 1 motif, 6	367
236951_at	BE550891	45.7	1.37	330	BE550891	CDNA FLJ46889 fis, clone UTERU3017995, highly similar to Homo sapiens likely ortholog of rat p47 (p47)	369
1562442_a_at	SSBP1	37.2	1.37	331	BC008402	single-stranded DNA binding protein 1	370
242146_at	SNRPA1	52.5	1.37	332	AA872471	Small nuclear ribonucleoprotein polypeptide A'	371
232304_at	PELI1	44.1	1.37	333	AK026714	Pellino homolog 1 (Drosophila)	372
243184_at	TJP1	61.3	1.37	334	AW173166	Tight junction protein 1 (zona occludens 1)	374
1561915_at	BC031319	40.9	1.36	335	BC031319	CDNA clone IMAGE:5278237	375
222368_at	AW972351	56.9	1.36	336	AW972351	---	376
240478_at	AA648983	79.0	1.36	337	AA648983	Transcribed locus	377
239780_at	KIF1B	38.0	1.36	338	AA468422	Kinesin family member 1B	378
228524_at	ADCK5	58.1	1.35	339	BE856488	aarF domain containing kinase 5	379
239596_at	SLC30A7	35.3	1.35	340	AA521381	solute carrier family 30 (zinc transporter), member 7	380
216229_x_at	HCG2P7	72.3	1.35	341	X81001	HLA complex group 2 pseudogene 7	381
243591_at	LAMC1	98.3	1.35	342	AI887749	Laminin, gamma 1 (formerly LAMB2)	382
210229_s_at	CSF2	93.9	1.35	343	M11734	colony stimulating factor 2 (granulocyte-macrophage)	383
228271_at	AW001186	55.1	1.35	344	AW001186	CDNA FLJ41736 fis, clone HLUNG2019058	384
1565786_x_at	BQ953917	38.4	1.35	345	BQ953917	CDNA FLJ35490 fis, clone SMINT2008590	385
243792_x_at	PTPN13	44.6	1.34	346	AI281371	Protein tyrosine phosphatase, non-receptor type 13 (APO-1/CD95 (Fas)-associated phosphatase)	387
222159_at	AK023058	43.5	1.34	347	AK023058	---	388
211106_at	SUPT3H	37.2	1.34	348	AF064804	suppressor of Ty 3 homolog (S. cerevisiae)	389
214153_at	ELOVL5	42.7	1.34	349	BE467941	ELOVL family member 5, elongation of long chain fatty acids (FEN1/Elo2, SUR4/Elo3-like, yeast)	390
1560081_at	LOC90408	45.4	1.33	350	AL702091	hypothetical protein LOC90408	391
1556221_a_at	BM992214	95.4	1.33	351	BM992214	CDNA FLJ35137 fis, clone PLACE6009419	392
242862_x_at	AI804210	76.5	1.33	352	AI804210	Transcribed locus, moderately similar to XP_509882.1 PREDICTED: hypothetical protein	393

						XP_509882 [Pan troglodytes]	
240139_at	UBE2D2	41.3	1.33	353	AI949690	Ubiquitin-conjugating enzyme E2D 2 (UBC4/5 homolog, yeast)	394
208268_at	ADAM28	63.4	1.33	354	NM_021777	ADAM metallopeptidase domain 28	395
229398_at	RAB18	40.0	1.33	355	AI769954	RAB18, member RAS oncogene family	396
204153_s_at	MFNG	62.7	1.32	356	NM_002405	manic fringe homolog (Drosophila)	397
242287_at	RSN	69.7	1.32	357	AI090487	Restin (Reed-Steinberg cell-expressed intermediate filament-associated protein)	398
232216_at	YME1L1	97.7	1.31	358	AA828049	YME1-like 1 (S. cerevisiae)	399
242735_x_at	T85294	85.5	1.31	359	T85294	Transcribed locus	400
220764_at	PPP4R2	38.4	1.31	360	NM_019853	protein phosphatase 4, regulatory subunit 2	401
230713_at	ZCCHC11	62.3	1.31	361	BF115786	Zinc finger, CCHC domain containing 11	402
238299_at	LASS5	62.6	1.31	362	AW005866	LAG1 longevity assurance homolog 5 (S. cerevisiae)	403
239234_at	OGDH	62.2	1.31	363	AW452419	Oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide)	404
219142_at	RASL11B	40.4	1.31	364	NM_023940	RAS-like, family 11, member B	405
1569886_a_at	FLJ90231	35.3	1.31	365	BC040605	hypothetical protein FLJ90231	406
1552309_a_at	NEXN	54.3	1.31	366	NM_144573	nexilin (F actin binding protein)	407
1565558_at	LOC400567	94.7	1.30	367	N67305	Hypothetical gene supported by AK093801	410
241613_at	SNTB2	40.6	1.30	368	AW296081	Syntrophin, beta 2 (dystrophin-associated protein A1, 59kDa, basic component 2)	411
239930_at	AA604126	69.4	1.30	369	AA604126	CDNA FLJ40677 fis, clone THYMU2022289	412
225656_at	EFHC1	79.6	1.30	370	AI564473	EF-hand domain (C-terminal) containing 1	413
202384_s_at	TCOF1	61.9	1.29	371	AW167713	Treacher Collins-Franceschetti syndrome 1	414
242492_at	AA412065	63.9	1.29	372	AA412065	---	415
235405_at	GSTA4	77.8	1.29	373	N79662	glutathione S-transferase A4	416
241294_at	AP1G1	35.8	1.29	374	AI939422	Adaptor-related protein complex 1, gamma 1 subunit	417
234753_x_at	AK026434	53.3	1.28	375	AK026434	CDNA: FLJ22781 fis, clone KAIA1958	418
235661_at	T99553	79.2	1.28	376	T99553	Transcribed locus	419
231697_s_at	TMEM49	88.6	1.28	377	AV660825	Transmembrane protein 49	420
236368_at	BF059292	55.5	1.28	378	BF059292	---	421
219985_at	HS3ST3A1	60.5	1.28	379	NM_006042	heparan sulfate (glucosamine) 3-O-sulfotransferase 3A1	423
242554_at	TPCN2	40.7	1.27	380	AA923516	Two pore segment channel 2	425
243912_x_at	APOBEC3F	44.4	1.27	381	BF511268	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3F	426
242890_at	PPP1R13B	80.4	1.26	382	AI650364	Protein phosphatase 1, regulatory (inhibitor) subunit 13B	427
1557170_at	NEK8	52.5	1.26	383	AI073943	NIMA (never in mitosis gene a)-related kinase 8	428
242407_at	RERE	42.9	1.26	384	H71242	Arginine-glutamic acid dipeptide (RE) repeats	429
1562063_x_at	FLJ20719 /// AE2 /// LOC200030 /// AE01 /// AG1	86.7	1.26	385	BM041211	hypothetical protein FLJ20719 /// hypothetical protein AE2 /// hypothetical protein LOC200030 /// AE01 mRNA /// AG1 protein	430
223152_at	PPP1R12C	52.8	1.26	386	AF312028	protein phosphatase 1, regulatory (inhibitor) subunit 12C	431
232615_at	FLJ39739	99.1	1.26	387	AA632758	FLJ39739 protein	432
223797_at	PRO2852	71.1	1.26	388	AF130079	hypothetical protein PRO2852	433
232333_at	AU147805	40.7	1.26	389	AU147805	CDNA FLJ12284 fis, clone MAMMA1001757	434
240410_at	LOC200230	57.3	1.26	390	AI928355	Similar to KIAA0386	435
233017_x_at	AK022388	74.4	1.26	391	AK022388	---	436
232264_at	AK022204	45.6	1.25	392	AK022204	---	437
243305_at	KLHDC5	72.8	1.25	393	AA903710	Kelch domain containing 5	438
217016_x_at	FLJ23172	40.7	1.25	394	AK026825	hypothetical LOC389177	439
242431_at	ARIH1	50.4	1.25	395	AI656728	Ariadne homolog, ubiquitin-conjugating enzyme E2 binding	441

						protein, 1 (Drosophila)	
238130_at	NFATC2IP	91.4	1.25	396	AW469292	nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 2 interacting protein	442
1559038_at	SEPT2	80.8	1.25	397	BC043180	septin 2	443
239448_at	AI475033	67.6	1.25	398	AI475033	---	444
1559716_at	C18orf37	69.0	1.25	399	AK095502	chromosome 18 open reading frame 37	445
234562_x_at	CMTM8	44.9	1.24	400	AK000115	CKLF-like MARVEL transmembrane domain containing 8	447
1557227_s_at	TPR	64.4	1.24	401	AW235355	translocated promoter region (to activated MET oncogene)	449
233914_s_at	SBF2	55.4	1.24	402	AK022478	SET binding factor 2	451
213520_at	RECQL4	47.6	1.24	403	NM_004260	RecQ protein-like 4	453
242324_x_at	CCBE1	81.6	1.24	404	AA740403	collagen and calcium binding EGF domains 1	454
244132_x_at	AI267414	35.9	1.23	405	AI267414	CDNA FLJ37998 fis, clone CTONG2012001	456
230193_at	WDR66	56.7	1.23	406	AI479075	WD repeat domain 66	457
233223_at	NEDD9	59.8	1.23	407	AK000850	Neural precursor cell expressed, developmentally down-regulated 9	458
206104_at	ISL1	84.7	1.23	408	NM_002202	ISL1 transcription factor, LIM/homeodomain, (islet-1)	459
236022_at	MYOHD1	77.9	1.23	409	AI650341	Myosin head domain containing 1	460
228983_at	AI692591	67.1	1.23	410	AI692591	Transcribed locus	461
201710_at	MYBL2	63.7	1.23	411	NM_002466	v-myb myeloblastosis viral oncogene homolog (avian)-like 2	462
232288_at	KIAA0251	36.4	1.23	412	AK026209	KIAA0251 protein	463
1557049_at	LOC149478	63.4	1.23	413	BQ183759	Hypothetical protein LOC149478	464
1569086_at	EML2	41.0	1.22	414	BC000856	Homo sapiens, clone IMAGE:3459231, mRNA /// Echinoderm microtubule associated protein like 2	465
232551_at	BRD4	52.5	1.22	415	AA521443	Bromodomain containing 4	466
212913_at	MSH5	82.1	1.22	416	BE674960	mutS homolog 5 (E. coli)	467
237005_at	LOC442075	35.4	1.21	417	AI923935	weakly similar to serine/threonine protein kinase Kp78	468
238070_at	CHD1L	69.7	1.21	418	AA573217	Chromodomain helicase DNA binding protein 1-like	469
34260_at	KIAA0683	80.5	1.21	419	AB014583	KIAA0683 gene product	470
230590_at	SSH2	36.7	1.21	420	BE675486	Slingshot homolog 2 (Drosophila)	471
238172_at	NDUFA10	41.4	1.21	421	AA192765	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 10, 42kDa	472
242052_at	BICD1	80.9	1.20	422	AW979272	Bicaudal D homolog 1 (Drosophila)	473
235138_at	PUM2	71.1	1.20	423	AA565051	Pumilio homolog 2 (Drosophila)	474
1552621_at	POLR2J2	70.4	1.20	424	BQ613856	DNA directed RNA polymerase II polypeptide J-related gene	475
202957_at	HCLS1	70.1	1.20	425	NM_005335	hematopoietic cell-specific Lyn substrate 1	476
244054_at	SKIL	88.9	1.20	426	AI760298	SKI-like	477
236417_at	MFN1	55.0	1.19	427	BE644770	Mitofusin 1	478
236592_at	AI791859	61.4	1.19	428	AI791859	Transcribed locus	479
216115_at	NF1	42.5	1.19	429	AK024873	Neurofibromin 1 (neurofibromatosis, von Recklinghausen disease, Watson disease)	480
238049_at	NS3TP2	79.8	1.18	430	AW971198	HCV NS3-transactivated protein 2	481
241865_at	GNB1	67.5	1.18	431	AI056689	Guanine nucleotide binding protein (G protein), beta polypeptide 1	484
219702_at	PLAC1	35.6	1.17	432	NM_021796	placenta-specific 1	485
241906_at	ZNF708	62.3	1.17	433	BF001773	Zinc finger protein 708 (KOX8)	486
1558732_at	AK074900	78.5	1.17	434	AK074900	---	487
236869_at	AI857429	44.7	1.17	435	AI857429	Transcribed locus	488
242646_at	SUV420H1	55.6	1.17	436	AA702946	Suppressor of variegation 4-20 homolog 1 (Drosophila)	489
237018_at	AKAP13	47.2	1.17	437	AI051967	A kinase (PRKA) anchor protein 13	490
210282_at	ZNF198	60.2	1.17	438	AL136621	zinc finger protein 198	491
239721_at	UBE2H	69.8	1.16	439	AI280328	Ubiquitin-conjugating enzyme E2H (UBC8 homolog, yeast)	492
232613_at	AA704301	55.1	1.16	440	AA704301	---	493

1556373_a_at	AF086212	51.4	1.15	441	AF086212	CDNA FLJ36277 fis, clone THYMU2003242	494
242673_at	UBE3C	40.7	1.15	442	AA931284	Ubiquitin protein ligase E3C	495
236816_at	FLJ13089	51.8	1.15	443	BF110370	hypothetical protein FLJ13089	496
243404_at	AA553477	50.1	1.15	444	AA553477	Transcribed locus	497
232274_at	CCNL2	81.6	1.15	445	AK000685	cyclin L2	499
239571_at	MEF2A	74.9	1.14	446	AI123399	MADS box transcription enhancer factor 2, polypeptide A (myocyte enhancer factor 2A)	501
237864_at	RAB22A	35.4	1.14	447	AI990122	RAB22A, member RAS oncogene family	502
242932_at	FARP2	72.0	1.14	448	AW292329	FERM, RhoGEF and pleckstrin domain protein 2	503
239347_at	LOC389143	78.2	1.14	449	BF448159	Hypothetical LOC389143	504
241140_at	LMO7	36.9	1.14	450	AA702962	LIM domain 7	505
1559391_s_at	B4GALT5	37.0	1.14	451	AI084451	UDP-Gal:betaGlcNAc beta 1,4-galactosyltransferase, polypeptide 5	506
213906_at	MYBL1	65.6	1.14	452	AW592266	v-myb myeloblastosis viral oncogene homolog (avian)-like 1	507
232530_at	PLD1	54.4	1.14	453	AA132961	phospholipase D1, phophatidylcholine-specific	508
231597_x_at	AI371550	56.8	1.14	454	AI371550	---	509
233867_at	ZSWIM6	56.3	1.14	455	AK000119	Zinc finger, SWIM-type containing 6	510
220232_at	SCD5	94.1	1.13	456	NM_024906	stearoyl-CoA desaturase 5	511
205536_at	VAV2	35.2	1.13	457	NM_003371	vav 2 oncogene	513
213931_at	ID2 /// ID2B	37.3	1.13	458	AI819238	inhibitor of DNA binding 2, dominant negative helix-loop-helix protein /// inhibitor of DNA binding 2B, dominant negative helix-loop-helix protein	514
1555933_at	KIAA2013	41.8	1.12	459	AB095933	KIAA2013	515
211504_x_at	ROCK2	45.0	1.12	460	D87931	Rho-associated, coiled-coil containing protein kinase 2	516
234687_x_at	LIMD1	69.3	1.12	461	M80651	LIM domains containing 1	517
214985_at	AF070571	43.4	1.12	462	AF070571	Clone 24739 mRNA sequence	518
230203_at	LOC440918	41.1	1.12	463	AI866583	LOC440918	520
232528_at	UBE2E3	72.5	1.12	464	AI338705	Ubiquitin-conjugating enzyme E2E 3 (UBC4/5 homolog, yeast)	521
204836_at	GLDC	40.2	1.11	465	NM_000170	glycine dehydrogenase (decarboxylating; glycine decarboxylase, glycine cleavage system protein P)	522
244633_at	PIAS2	39.1	1.11	466	AA404996	Protein inhibitor of activated STAT, 2	524
206382_s_at	BDNF	56.6	1.11	467	NM_001709	brain-derived neurotrophic factor	525
212949_at	BRRN1	66.8	1.10	468	D38553	barren homolog (Drosophila)	526
236007_at	AKAP10	91.0	1.10	469	AU147278	A kinase (PRKA) anchor protein 10	527
236123_at	ST7L	52.6	1.10	470	BE220209	Suppression of tumorigenicity 7 like	528
213605_s_at	MGC22265	75.3	1.10	471	AL049987	(clone CB1) mRNA fragment /// Hypothetical protein MGC22265	529
240180_at	BE219849	50.9	1.10	472	BE219849	MRNA full length insert cDNA clone EUROIMAGE 1090207	531
227896_at	BCCIP	91.2	1.09	473	AI373643	BRCA2 and CDKN1A interacting protein	533
227349_at	AI807356	55.0	1.09	474	AI807356	---	534
228563_at	GJA7	87.8	1.09	475	BE504215	gap junction protein, alpha 7, 45kDa (connexin 45)	535
235952_at	AA521504	38.9	1.09	476	AA521504	Transcribed locus, moderately similar to NP_008471.1 NADH dehydrogenase subunit 1 [Canis familiaris]	536
1556690_s_at	AW341225	58.7	1.09	477	AW341225	---	537
232311_at	AU147899	37.3	1.09	478	AU147899	---	538
238566_at	BF592775	39.0	1.09	479	BF592775	Transcribed locus	540
242918_at	NASP	56.9	1.08	480	AU144734	Nuclear autoantigenic sperm protein (histone-binding)	541
239654_at	CHD9	47.1	1.08	481	T98846	Chromodomain helicase DNA binding protein 9	542
230746_s_at	STC1	99.8	1.08	482	AW003173	Stanniocalcin 1	543
241741_at	C20orf155	47.3	1.08	483	AI339837	chromosome 20 open reading frame 155	544

235417_at	SPOCD1	67.1	1.08	484	BF689253	SPOC domain containing 1	545
238589_s_at	ATXN2	47.6	1.08	485	AW601184	Ataxin 2	546
217482_at	AK021987	56.1	1.08	486	AK021987	---	547
207075_at	CIAS1	62.2	1.08	487	NM_004895	cold autoinflammatory syndrome 1	548
232889_at	LOC153561	80.6	1.07	488	AU147591	hypothetical protein LOC153561	550
242448_at	AI800895	40.1	1.07	489	AI800895	CDNA FLJ33367 fis, clone BRACE2005661	551
244669_at	LOC441164	78.4	1.07	490	T16443	Chromosome 6 open reading frame 160	552
242859_at	TFCP2	51.4	1.07	491	BE156563	Transcription factor CP2	553
238534_at	LRRFIP1	48.0	1.06	492	AA262583	Leucine rich repeat (in FLII) interacting protein 1	555
236462_at	YEATS2	45.0	1.06	493	AA742310	YEATS domain containing 2	556
1560512_at	BQ027635	77.5	1.06	494	BQ027635	CDNA FLJ30409 fis, clone BRACE2008615	557
235773_at	ZIK1	55.6	1.06	495	AW029293	zinc finger protein interacting with K protein 1	558
235613_at	IQWD1	43.2	1.06	496	BF476152	IQ motif and WD repeats 1	559
244579_at	TRPS1	76.7	1.06	497	AI086336	Trichorhinophalangeal syndrome I	560
236379_at	EPB41	69.6	1.05	498	AW771958	Erythrocyte membrane protein band 4.1 (elliptocytosis 1, RH-linked)	561
217497_at	ECGF1	71.8	1.04	499	AW613387	endothelial cell growth factor 1 (platelet-derived)	563
215462_at	PLK3	64.4	1.04	500	AI978990	polo-like kinase 3 (Drosophila)	564
242695_at	USP15	48.0	1.04	501	BF512254	Ubiquitin specific peptidase 15	565
242108_at	TPCN1	96.7	1.04	502	AA001615	Two pore segment channel 1	566
233869_x_at	BDH1	35.7	1.04	503	AL050097	3-hydroxybutyrate dehydrogenase, type 1	567
233984_at	KIAA0831	36.1	1.04	504	AL133091	KIAA0831	568
1564796_at	EMP1	38.7	1.04	505	BC017854	epithelial membrane protein 1	569
242476_at	AI436356	67.2	1.03	506	AI436356	Transcribed locus, strongly similar to NP_777610.1 hypothetical protein FLJ30435 [Homo sapiens]	570
204509_at	CA12	42.9	1.03	507	NM_017689	carbonic anhydrase XII	572
222358_x_at	AI523613	73.3	1.03	508	AI523613	Transcribed locus, weakly similar to XP_517655.1 PREDICTED: similar to KIAA0825 protein [Pan troglodytes]	573
214017_s_at	DHX34	46.4	1.02	509	AA039439	DEAH (Asp-Glu-Ala-His) box polypeptide 34	574
239422_at	GPC2	39.3	1.02	510	AI863264	glypican 2 (cerebroglycan)	575
219400_at	CNTNAP1	41.9	1.02	511	NM_003632	contactin associated protein 1	576
215032_at	RREB1	41.5	1.02	512	AK022442	ras responsive element binding protein 1	579
1556053_at	DNAJC7	66.7	1.02	513	AL556987	DnaJ (Hsp40) homolog, subfamily C, member 7	580
238847_at	AW378585	62.6	1.02	514	AW378585	Transcribed locus	581
228885_at	MAMDC2	46.7	1.01	515	AI862120	MAM domain containing 2	582
210785_s_at	C1orf38	98.2	1.01	516	AB035482	chromosome 1 open reading frame 38	583
240176_at	LOC391426	48.5	1.00	517	AI078180	Similar to ENSANGP00000004103	584
235154_at	TAF3	54.4	1.00	518	BG250498	TAF3 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 140kDa	585
229974_at	EVC2	73.3	1.00	519	AA234305	Ellis van Creveld syndrome 2 (limbin)	586