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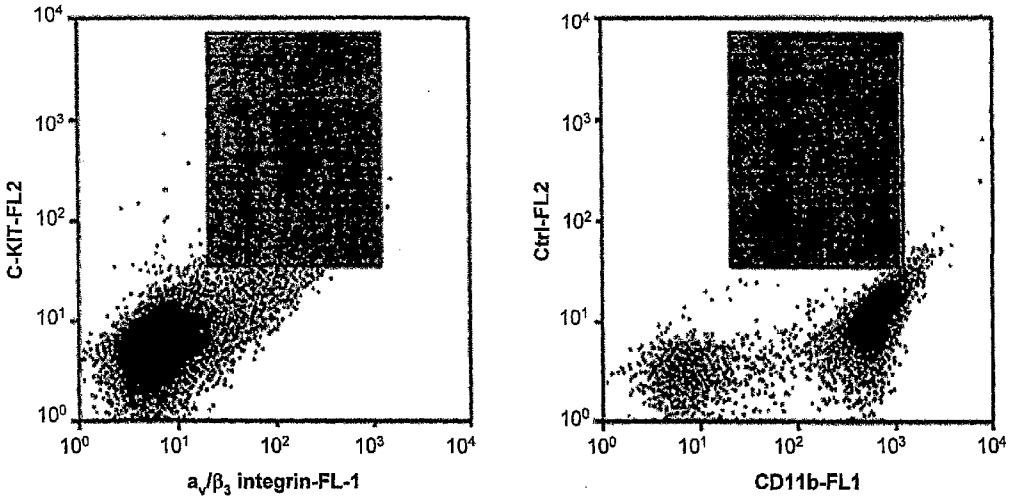
(54) **Title:** EARLY DETECTION OF HEMANGIOSARCOMA AND ANGIOSARCOMA



(57) **Abstract:** A variety of methods, compositions and kits are provided for the early detection, diagnosis and treatment of hemangiosarcoma in dogs and angiosarcomas in humans.

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EARLY DETECTION OF HEMANGIOSARCOMA AND ANGIOSARCOMA

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application is a nonprovisional and claims the benefit of USSN 60/608745, filed September 10, 2004, which is incorporated by reference in its entirety for all purposes.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] This invention was made with Government support under Grant Nos. CA46934 and CA86264 awarded by the National Institutes of Health. The Government has certain rights in this invention.

BACKGROUND

[0003] Canine hemangiosarcoma (HSA) is an incurable tumor of cells that line blood vessels in dogs. Of the approximately 65 million owned dogs in the United States in 2004, between 1.5 and 2.5 million will get this disease and die from it. The disease accounts for about 7% of all canine cancers. Because the disease is extremely indolent, treatment is largely ineffective and microscopic metastases are often present at the time of diagnosis. The tumors at this stage are largely resistant to chemotherapy, and thus standard-of-care (surgery and intensive chemotherapy) provides a median survival of little more than six months (Clifford, C.A., et al. (2000) J. Vet. Intern. Med. 14:479-485; Sorenmo, K., et al. (2000), J. Vet. Intern. Med. 14:395-398; and Sorenmo, K.U., et al. (1993) J. Vet. Intern. Med. 7:370-376). Common primary sites for HSA are spleen and right atrium (visceral), and subcutis. Local infiltration and systemic metastases are the common growth patterns and metastatic sites are wide spread, with lung and liver being the most frequently affected organs (Oksanen, A. (1978) J. Comp. Pathol. 88:585-595; and Brown, N.O., et al., (1985) J. Am. Vet. Med. Assoc. 186:56-58). Morbidity and mortality are usually due to acute internal hemorrhage secondary to tumor rupture. Many dogs die from severe abdominal or thoracic hemorrhage before any treatment can be instituted. Although dogs of any age and breed are susceptible to HSA, it occurs more commonly in dogs beyond middle age, and in breeds such as Golden Retrievers, German Shepherd Dogs, Portuguese Water Dogs, and Skye Terriers, among

others. The estimated lifetime risk of HSA in Golden Retrievers is 1 in 5, illustrating the magnitude of this problem.

[0004] There is presently no effective technology for early diagnosis of HSA. The only means available to diagnose the disease (for cavitary tumors such as those that occur in the spleen or heart) are imaging methods such as ultrasound and radiographs. Ultrasound, however, although moderately specific is not sensitive. Radiographs are neither specific nor sensitive. Careful examination of blood smears may suggest the presence of chronic hemorrhage (anemia and thrombocytopenia) and vascular abnormalities (red blood cell fragmentation) that are consistent with HSA; however, the method is neither sensitive or specific to confirm the diagnosis. A biopsy is required for confirmation of imaging results, and even then, distinction between hemangiosarcoma and benign proliferative lesions (hemangioma, hematoma) can be difficult. Skin biopsies where there is no lesion would be of little use to provide early diagnosis for cutaneous hemangiosarcoma. The same is true for splenic, hepatic (liver), or cardiac (heart) tumors, with the added issue that the risk of these procedures in the absence of a visible tumor (on radiographs or ultrasound) is unacceptable.

[0005] Human angiosarcomas are similar to canine HSA (see, e.g., Fosmire, S.P., et al (2004) Laboratory Investigation 84:562-572). These tumors are uncommon soft tissue sarcomas that can arise in a variety of locations, such as the liver, spleen, skin breast and endocrine organs (see, e.g., Fedok, F.G., et al. (1999) Am J. Otolaryngol. 20:223-231; Hai, S.A., et al., (2000) J. Natl. Med. Assoc. 92:143-146; and Budd, G.T. (2002) Curr. Oncol. Rep. 4:515-519). Like canine HSA, treatment of human angiosarcomas can be challenging and often is not successful.

[0006] Given the severity of canine HSA and human angiosarcomas coupled with the lack of effective treatment options once the tumor has metastasized, it would be useful to have a method for early detection of these two diseases. Early detection would allow for treatment options having a higher chance of successfully treating the tumor.

SUMMARY OF THE CLAIMED INVENTION

[0007] The invention provides methods for early detection of hemangiosarcoma or angiosarcoma in a subject. The method comprises providing a population of cells from the subject and determining the level at which cells within the cell population concurrently express a plurality of cell markers, and the plurality of cell markers comprising at least one primitive hematopoietic cell marker and at least one endothelial cell marker. Such methods

determine whether or not cells within the cell population express at least one leukemia cell marker or leukocyte-specific cell marker. In such methods, at least one primitive hematopoietic cell marker is selected from the group consisting of CD117, CD34, and CD133. At least one endothelial cell marker is selected from the group consisting of CD51/CD61, CD31, CD105, CD106 CD146 and von Willebrand Factor (vWF). At least one leukemia cell marker or leukocyte-specific cell marker is selected from the group consisting of CD18, CD3, CD5, CD21 and CD11b. The level at which cells in the cell population concurrently express the plurality of cell markers is compared with a control level of concurrent expression of the markers. In such methods an increase in the expression level of the plurality of cell markers relative to the control expression level, and the absence of expression of CD18, CD3, CD5, CD21 and/or CD11b collectively are an indication of hemangiosarcoma or angiosarcoma.

[0008] In some methods the determining step comprises incubating the population of cells with labeled antibodies that specifically bind the at least one primitive hematopoietic cell marker, the at least one endothelial cell marker and the at least one one leukemia cell marker or leukocyte-specific cell marker under conditions such that cells expressing the markers become labeled. The antibodies that bind different markers are differentially labeled. Multiparameter flow cytometry is used to detect the labeled cells.

[0009] In some methods the subject is a dog and the method detects hemangiosarcoma. Dog breeds that may be subjects of the invention are selected from the group consisting of a Golden Retriever, a German Shepherd, a Portuguese Water Dog, or a Skye Terrier.

[0010] In some methods the subject is a human and the method detects angiosarcoma.

[0011] Humans screened using themethods of the invention include individuals having a risk factor for angiosarcoma, the risk factor being prior exposure to vinyl chloride, prior exposure to ionizing radiation, mutation in the Von Hippel-Lindau gene or infection with human immunodeficiency virus (HIV).

[0012] Populations of cells used in methods of the invention can be obtained from a blood samples.

[0013] Some methods of the invention comprise determining the level at which cells in the population of cells concurrently express at least one primitive hematopoietic cell marker selected from the group consisting of CD117, CD133 and CD34.

[0014] Some methods of the invention comprise determining the level at which cells in the population concurrently express at least one leukemia cell marker or leukocyte-specific cell marker selected from the group consisting of CD18, CD3, CD5, CD21 and CD11b.

[0015] Some methods of the invention comprise determining the level at which cells in the population concurrently express CD117, CD34, CD51/CD61, and CD18, and/or CD3, CD5, CD21 or CD11b.

[0016] Some methods of the invention further comprise determining the fraction of cells in the cell population that concurrently express the plurality of cell markers. The control is a threshold level representative of the fraction of cells that currently express the plurality of cell markers in a control population. The comparing step comprises comparing the fraction of cells in the cell population that concurrently express the plurality of cell markers with the threshold level.

[0017] In some methods of the invention, the expression level of the plurality of cell markers is determined at the mRNA level or at the protein level.

[0018] Some methods of invention detect hemangiosarcoma in dogs. A population of cells is obtained from a blood sample. The determining step further comprises incubating the population of cells with differentially labeled antibodies that specifically bind to CD117, CD34, CD51/61, and CD 18 and/or CD3, CD5, CD21 or CD11b under conditions such that cells expressing CD117, CD34, CD51/61, and CD 18 and/or CD3, CD5, CD21 or CD11b become labeled. The labeled cells aredetected by multiparameter flow cytometry.

[0019] The invention provides methods for early detection of hemangiosarcoma or angiosarcoma. A population of cells is obtained from the subject and the level at which cells within the cell population concurrently express at least one primitive hematopoietic cell marker, at least one endothelial cell marker and at least one leukemia cell marker or leukocyte-specific cell marker are determined. The at least one primitive hematopoietic cell marker is selected from the group consisting of CD117, CD34 and CD133. The at least one endothelial cell marker is selected from the group consisting of CD51/CD61, CD31, CD105, CD106, CD146 and von Willebrand Factor (vWF). The at least one leukemia cell marker or leukocyte-specific cell marker is selected from the group consisting of CD18, CD3, CD5, CD21 and CD11b. The lower the expression of the at least one leukemia marker or leukocyte-specific cell marker and the greater the concurrent expression of the at least one primitive hematopoietic cell marker and the at least one endothelial cell marker, the greater

the likelihood of hemangiosarcoma or angiosarcoma. Some methods provide early detection of hemangiosarcoma in dogs; other methods provide early detection of angiosarcoma in humans.

[0020] In some methods of the invention, the determining step comprises incubating the population of cells with labeled antibodies that specifically bind the at least one primitive hematopoietic cell marker, the at least one endothelial cell marker and the at least one leukemia cell marker or leukocyte-specific cell marker. The incubations are done under conditions such that cells expressing the markers become labeled. Antibodies that bind different markers are differentially labeled. Labeled cells are detected by multiparameter flow cytometry.

[0021] The invention provides methods for distinguishing between hemangiosarcoma and leukemia. Such methods comprise providing a cell population from a subject suspected of having hemangiosarcoma or leukemia and determining whether cells in the cell population concurrently express a plurality of markers associated with a proliferative primitive hematopoietic cell. The plurality of markers comprise at least one primitive hematopoietic cell marker and at least one endothelial cell marker. Whether the cells in the cell population also express also at least one leukemia marker or leukocyte-specific cell marker is also determined. The at least one primitive hematopoietic cell marker is selected from the group consisting of CD117, CD34 and CD133. The at least one endothelial cell marker is selected from the group consisting of CD51/CD61, CD31, CD105,CD146 and von Willebrand Factor (vWF). The at least one leukemia marker or leukocyte-specific cell marker is selected from the group consisting of CD18, CD3, CD5, CD21 and CD11b. The concurrent expression of the plurality of cell makers and the expression of the at least one leukemia marker or leukocyte-specific cell marker is an indication that the cell sample contains leukemia cells, whereas the concurrent expression of the plurality of cell markers but not expression of the at least one leukemia marker or leukocyte-specific cell marker is an indication that the cell population contains cells from a hemangiosarcoma.

[0022] The invention provides methods of treating a dog having or suspected of having hemangiosarcoma. The method comprises administering an antibody to the dog, wherein the antibody specifically binds CD51/CD61, CD31, or CD105. In some methods, the antibody is linked to a cytotoxic agent.

[0023] Some methods of the invention are directed to treating a dog having or suspected of having hemangiosarcoma, the method comprising administering an antibody to the dog. The antibody is a bispecific antibody that can specifically bind a pair of antigens. The pair of antigens is selected from the group consisting of 1) CD34 AND CD51/CD61, 2) CD117 AND CD51/CD61, 3) CD34 AND CD31, 4) CD117 AND CD31, 5) CD34 AND CD105, and 6) CD117 AND CD105.

[0024] The invention provides methods of collecting cells from a hemangiosarcoma or an angiosarcoma. The methods comprise providing a cell population suspected of containing cells from a hemangiosarcoma or angiosarcoma, and labeling cells in the cell population that concurrently express at least one primitive hematopoietic cell marker and at least one endothelial cell marker. The at least one primitive hematopoietic cell marker is selected from the group consisting of CD117, CD34 and CD133. The at least one endothelial cell marker is selected from the group consisting of CD51/CD61, CD31, CD105, CD106, CD146 and von Willebrand Factor (vWF). The methods further determine whether or not the cells in the cell population express at least one leukemia cell marker or leukocyte-specific cell marker. The at least one leukemia cell marker or leukocyte-specific cell marker is is selected from the group consisting of CD18, CD3, CD5, CD21 and CD11b. The labeled cells are separated from the unlabeled cells if the labeled cells do not express the at least one leukemia cell marker or leukocyte-specific cell marker, thereby collecting cells that are from a hemangiosarcoma or an angiosarcoma.

[0025] The invention provides populations of cells comprising early proliferative endothelial cells that are bound to a plurality of labeled antibodies. The plurality of antibodies comprise an antibody that specifically binds a primitive hematopoietic cell marker, selected from the group consisting of CD117, CD34 and CD133, and an antibody that specifically binds an endothelial cell marker, selected from the group consisting of CD51/CD61, CD31, CD105, CD106 and CD146.

[0026] The invention provides methods to detect residual disease in a subject undergoing treatment for hemangiosarcoma or angiosarcoma. The methods comprise providing a population of cells from the subject, and determining (i) the level at which cells within the cell population concurrently express a plurality of cell markers, the plurality of cell markers comprising at least one primitive hematopoietic cell marker and at least one endothelial cell marker, and (ii) whether cells within the cell population express at least one leukemia cell

marker or leukocyte-specific cell marker. The at least one primitive hematopoietic cell marker is selected from the group consisting of CD117, CD34, CD133. The at least one endothelial cell marker is selected from the group consisting of CD51/CD61, CD31, CD105, CD106 CD146 and von Willebrand Factor (vWF). The at least one leukemia cell marker or leukocyte-specific cell marker is selected from the group consisting of CD18, CD3, CD5, CD21 and CD11b. The methods compare the level at which cells in the cell population concurrently express the plurality of cell markers with the level of concurrent expression of the markers in a control cell population. An increase in the expression level of the plurality of cell markers relative to the expression level of the markers in the control cell population and an absence of expression of CD18, CD3, CD5, CD21 or CD11b are collectively an indication of residual disease in the subject being treated for hemangiosarcoma or angiosarcoma.

[0027] In some methods to detect residual disease in a subject undergoing treatment for hemangiosarcoma or angiosarcoma the subject is a dog and the residual disease is hemangiosarcoma. In other methods, the subject is a human and the residual disease is hemangiosarcoma. Some methods comprise incubating the population of cells with first, second and third antibodies that specifically bind the at least one primitive hematopoietic cell marker, the at least one endothelial cell marker, and the at least one leukemia cell marker or leukocyte-specific cell marker respectively under conditions such that antibodies bind to the markers. The first, second and third antibodies bound to the markers are differentially labeled. Cells bound with labeled antibodies are detected by multiparameter flow cytometry.

[0028] Antibodies used in the methods of the invention can be labeled using a secondary detection scheme to increase sensitivity of the methods.

[0029] The invention provides kits for use in distinguishing between hemangiosarcoma and leukemia. The kits comprise a plurality of antibodies. The antibodies comprise: an antibody that specifically binds a primitive hematopoietic cell marker that is selected from the group consisting of CD117, CD34 and CD133; an antibody that specifically binds an endothelial cell marker that is selected from the group consisting of CD51/CD61, CD31, CD105, CD106, and CD146; and an antibody that specifically binds to a leukemia cell marker or leukocyte-specific cell marker that is selected from the group consisting of CD18, CD3, CD5, CD21 and CD11b.

[0030] In some kits of the invention, the antibodies are labeled such that antibodies that bind different markers bear different labels.

[0031] Some kits of the invention comprise an antibody that specifically binds CD117, an antibody that specifically binds CD34, an antibody that specifically binds CD51/61, and an antibody that specifically binds CD18, and an antibody that specifically binds CD3, CD5, CD21 or CD11b. Other kits of the invention comprise an antibody that specifically binds CD117, an antibody that specifically binds CD34, an antibody that specifically binds CD51/61, an antibody that specifically binds CD18, or an antibody that specifically binds CD3, CD5, CD21 or CD11b.

[0032] Some kits of the invention further comprise instructions on how to use the plurality of antibodies to distinguish between a hemangiosarcoma and leukemia.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] FIGS. 1A-1H illustrate that the light scatter (FIGS. 1A, 1C, 1E and 1G) and fluorescence emission (FIGS. 1B, 1D, 1F and 1H) characteristics of leukocytes and hemangiosarcoma cells are distinct and can be used to distinguish between the two sets of cells. The light scatter plots show forward scatter on the x-axis and side scatter on the y-axis. The fluorescence emission results are for the markers CD51/61 (x-axis) and CD117 (y-axis). FIG. 1A shows the light scatter profile for nucleated cells (white blood cells, tumor cells) in the peripheral blood from a dog with a thoracic hemangiosarcoma. The gate drawn around the cells is used to exclude red blood cells, platelets, and cellular debris, while including all white blood cells (granulocytes, lymphocytes, monocytes) and other nucleated cells that may be present in the circulation (e.g., tumor cells). FIG. 1B depicts the fluorescence emission for the same cells "stained" with isotype control (irrelevant) antibodies conjugated to phycoerythrin (PE control) and fluorescein (FITC control). FIG. 1C also shows the light scatter profile for cells (white blood cells, tumor cells) in the peripheral blood from the same dog. FIG. 1D shows the fluorescence emission for the same cells "stained" with an antibody against CD51/CD61 conjugated to FITC (x-axis) and an antibody against CD117 conjugated to PE (y-axis). FIG. 1E shows the light scatter profile for nucleated cells where a gate is drawn around the area that should contain the leukocytes and FIG. 1F shows the fluorescence emission for this leukocyte population specifically (CD117 vs. CD51/61). FIG. 1G shows the light scatter profile for where a gate is drawn around the area that would contain large

abnormal cells (such as tumor cells) and FIG. 1H depicts the fluorescence emission for this population specifically (CD117 vs. CD51/61).

[0034] FIGS. 2A-2H shows the difference in CD45 expression in conjunction with expression of CD51/CD61 in the same populations (from the same patient) as in FIGS.2A-2H.

[0035] FIGS. 3A and 3B show 2-dimensional flow histograms from a multiparameter flow cytometry assay of anticoagulated peripheral blood from a canine patient using multiple fluorochromes. One fluorochrome is bound to antibodies recognizing c-KIT and α_v/β_3 integrin to detect HSA cells in the sample, (FIG 3A), a second flurochrome is bound to antibodies recognizing CD11b on granulocytes in the sample (FIG. 3B).

[0036] FIGS. 4A-4P show one-dimensional flow cytometry histograms for representative hemangiosarcoma cell lines, DD-1 (FIGS. 4A-4H) and Dal-4(FIGS. 4I-4P), stained using antibodies against irrelevant controls (FIGS 4A and 4I), c-KIT (FIGS. 4B and 4J), CD133 (FIGS. 4C and 4K), CD34 (FIGS 4D and 4L), CD45 (FIGS. 4E and 4M), CD14 (FIGS 4F and 4N), $\alpha_v\beta_3$-integrin (FIGS. 4G and 4O), and CD146 (FIGS. 4H and 4P).

[0037] FIGS 5A-5F show multiparameter flow cytometry data from a dog with splenic hematoma (FIGS. 5A-5C) in comparison with a dog with hemangiosarcoma (FIGS. 5D-5F). Cells positive for CD133 and $\alpha_v\beta_3$ integrin were back-gated to two-dimensional light scatter histograms, and the percentage of positive cells that partitioned to regions encompassing the defined gate for HSA cells was determined.

DETAILED DESCRIPTION

I. Definitions

[0038] As used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the content clearly dictates otherwise.

[0039] Unless defined otherwise, all technical and scientific terms used herein have the meaning commonly understood by a person skilled in the art to which this invention belongs. The following references provide one of skill with a general definition of many of the terms used in this invention: Stedman, T.L., STEDMAN'S MEDICAL DICTIONARY (26th ed., 1995); Singleton *et al.*, DICTIONARY OF MICROBIOLOGY AND MOLECULAR BIOLOGY (2d ed. 1994); THE CAMBRIDGE DICTIONARY OF SCIENCE AND

TECHNOLOGY (Walker ed., 1988); and Hale & Marham, THE HARPER COLLINS DICTIONARY OF BIOLOGY (1991).

[0040] The term "hemangiosarcoma" has its normal meaning in the art and refers generally to malignant neoplasms that are characterized by rapidly proliferating, extensively infiltrating, anaplastic cells derived from blood vessels and lining irregular blood-filled or lumpy spaces. Canine hemangiosarcoma (HSA), for example, arises from transformed vascular endothelial cells, most commonly in the spleen, right atrium or subcutis. Growth patterns are characterized by local infiltration and systemic metastases, with metastatic sites tending to be widespread. The lung and liver are the most frequently affected organs.

[0041] "Angiosarcoma" as used herein has its normal meaning in the art and refers generally to malignant neoplasms occurring most often in the liver, spleen, skin, breast and endocrine organs. These soft tissue sarcomas are believed to originate from the endothelial cells of blood vessels. Microscopically, the tumors are characterized by closely packed round or spindle-shaped cells, some of which line small spaces resembling vascular clefts.

[0042] The term "leukemia" has its normal meaning in the art and generally refers to a disease involving the progressive proliferation of abnormal leukocytes found in hematopoietic tissues, other organs, and usually in the blood in increased numbers. Symptoms of the disease typically include severe anemia, hemorrhages, and enlargement of lymph nodes or the spleen.

[0043] Lymphoma" as used herein refers generally to cancers that develop in the lymphatic system. In humans, one specific type of lymphoma is called Hodgkin's disease, which can be endemic (caused by Epstein Barr virus-dependent transformation of B lymphocytes) or sporadic (not associated with Epstein Barr virus infection), and is characterized by the presence of Reed Sternberg cells. All other lymphomas are grouped together and are called non-Hodgkin's lymphomas.

[0044] A "marker" as used herein refers generally to a protein or its corresponding transcript whose expression, or lack thereof, is characteristic of a particular type of cell or group of cells (e.g., endothelial cells) and/or cellular state (e.g., proliferating or non-proliferating). Some markers are cell-surface proteins whose expression can be detected using antibodies that specifically bind to the cell-surface protein. Specific examples of markers referred to herein include, but are not limited to, CD117, CD34, CD51/61, CD18,

CD45, CD31, CD105, CD106 and CD146. The "markers" referred to herein can include markers from various species (e.g., human and dog).

[0045] An "expression profile," as used herein, refers to a pattern of gene (e.g., marker) expression (e.g., pattern of expression of markers) that is associated with a particular type of cell and/or cellular state. The pattern can include genes (e.g., markers) that are expressed and/or that are not expressed. For instance, an expression profile may include the pattern of genes (e.g., markers) that are expressed and/or not expressed by primitive hematopoietic cells, primitive hematopoietic cells that are malignant (e.g., hemangiosarcoma, angiosarcoma or leukemia), or primitive hematopoietic cells that are malignant, but are distinct from leukemia (e.g., hemangiosarcoma, angiosarcoma). A profile can include the expression of as few as a single gene (marker), but more typically includes the concurrent expression of multiple genes (markers). The expression profile obtained for a particular cell or cellular state can be useful for a variety of applications, including diagnosis of a particular disease or condition and evaluation of various treatment regimes. Expression of genes (markers) that make up the expression profile can be determined at the transcript or protein level.

[0046] "Polypeptide" and "protein" are used interchangeably herein and include a molecular chain of amino acids linked through peptide bonds. The terms do not refer to a specific length of the product. Thus, "peptides," "oligopeptides," and "proteins" are included within the definition of polypeptide. The terms include post-translational modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations and the like.

[0047] As used herein, references to specific polypeptides (e.g., cell markers such as CD117, CD34, CD51/61, CD18, CD45, CD31, CD105 and CD146) refer to a polypeptide having a native amino acid sequence, as well naturally occurring variant forms (e.g., alternatively spliced forms), naturally occurring allelic variants and forms including postranslational modifications. As noted above, the specific protein markers referred to herein include the protein as expressed in various mammals, including humans and dogs.

[0048] "CD117" is the receptor for stem cell factor (SCF) and is thus sometimes referred to as the stem cell factor receptor (SCFR). It is also sometimes referred to in the literature as (c-Kit). An exemplary amino acid sequence from dog is provided in GenBank Accession No. NP_001003181 (SEQ ID NO: 2), which is encoded by the nucleic acid having the sequence of SEQ ID NO:1 (GenBank Accession No. AF044249). An exemplary amino acid sequence from human is provided in GenBank Accession No. AAC50968 (SEQ ID NO:4), which is

encoded by the nucleic acid having the sequence of SEQ ID NO:3 (GenBank Accession No. NM_00022).

[0049] "CD34" is sometimes referred to as the ligand for CD62 or the ligand for L-selectin. CD34 is a protein expressed on early lymphohematopoietic stem and progenitor cells, small-vessel endothelial cells, embryonic fibroblasts, and some cells in fetal and adult nervous tissue. It is also expressed on hematopoietic progenitors derived from fetal yolk sac, embryonic liver, and extra-hepatic embryonic tissues. An exemplary amino acid sequence from dog is provided in GenBank Accession No. AAB41055 (SEQ ID NO:6), which is encoded by the nucleic acid having the sequence of SEQ ID NO:5 (GenBank Accession No. U49457). An exemplary amino acid sequence from human is provided in GenBank Accession No. NP_001764.1 (SEQ ID NO:8), which is encoded by the nucleic acid having the sequence of SEQ ID NO:7 (GenBank Accession No. NM_001773).

[0050] "CD133" is also sometimes referred to in the art as prominin 1, hProminin, and hematopoietic stem cell antigen. CD133 antigen is a 120kDa five transmembrane domain glycoprotein (5-TM) expressed on primitive cell populations, such as CD34 bright hematopoietic stem and progenitor cells, neural and endothelial stem cells, and other primitive cells such as retina and retinoblastoma and developing epithelium. The CD133 gene codes for a pentaspan transmembrane glycoprotein and appears to belong to a molecular family of 5-TM proteins. This "family" includes members from several different species (which may be homologs) including human, mouse, rat, fly, and worm. The 5-transmembrane domain structure includes an extracellular N-terminus, two short intracellular loops, two large extracellular loops and an intracellular C-terminus. CD133 is expressed on primitive hematopoietic stem and progenitor cells and retinoblastoma, as well as on hemangioblasts, neural stem cells, and developing epithelium. Many leukemias express CD133 as well as CD34, but some leukemic blasts are CD133+ and CD34 negative. A predicted partial nucleic acid sequence for dog CD133 corresponds to position 50894 to position 51101 of GenBank Accession No. AAEX01026434.1 (SEQ ID NO:43). An exemplary amino acid sequence from human is provided in GenBank Accession No. NP_006008 (SEQ ID NO:45), which is encoded by the nucleic acid having the sequence of SEQ ID NO:44 (GenBank Accession No.NM_006017).

[0051] "CD51/CD61" is also sometimes referred to in the art as alpha$_v$beta$_3$ ($\alpha_v\beta_3$) integrin, the vitronectin receptor, or glycoprotein IIIa. A predicted partial nucleic acid sequence for

dog CD51 corresponds to position 65528 to position 67792 from GenBank AAEX01022275.1, (SEQ ID NO:9). An exemplary amino acid sequence for dog CD61 is provided in GenBank Accession No. AAD49737.1 (CD61, beta-3, GP IIIa) (SEQ ID NO:13), which is encoded by the nucleic acid having the sequence of SEQ ID NO:12 (GenBank Accession No. AF170525 (beta-3)).

[0052] An exemplary amino acid sequence for human CD51 is provided in GenBank Accession No. NP_002201.1 (alpha-v) (SEQ ID NO:11), which is encoded by the nucleic acid having the sequence of SEQ ID NO:10 (GenBank Accession No. NM_002210). An exemplary amino acid sequence for human CD61 is provided by GenBank Accession No. NP_000203.2 (beta-3) (SEQ ID NO:15), which is encoded by the nucleic having the sequence of SEQ ID NO:14 (GenBank Accession No. NM_000212 (beta-3, GP IIIa)).

[0053] "CD31", also known as glycoprotein IIa (GPIIa), endocam, or platelet endothelial cell adhesion molecule (PECAM-1), refers to a cell adhesion protein that is highly expressed on endothelial cells and often concentrated at the junctions between them. CD31 also is present on virtually all monocytes, platelets, and granulocytes. A predicted partial nucleic acid sequence for dog CD31 corresponds to position 77862 to position 77586 of the minus strand of sequence from chromosome 9 (GenBank AAEX01022173.1) (SEQ ID NO:16). An exemplary amino acid sequence from human is provided in GenBank Accession No. AAH22512 (SEQ ID NO:18), which is encoded by the nucleic acid having the sequence of SEQ ID NO:17 (GenBank Accession No. BC022512).

[0054] "CD105," also sometimes referred to in the art as "endoglin," is a cell-surface glycoprotein that is over-expressed on vascular endothelium, particularly in angiogenic tissues. A predicted partial nucleic acid sequence for dog CD105 corresponds to positions 17214 to position 17370 of GenBank AAEX01025446.1 (SEQ ID NO:19). An exemplary amino acid sequence from human is provided in GenBank Accession No. NP_000109.1 (SEQ ID NO:21), which is encoded by the nucleic acid having the sequence of SEQ ID NO:20 (GenBank Accession No. NM_000118).

[0055] "CD106" is also referred to in the art as VCAM-1 because it is a vascular cell adhesion molecule. It is a member of the immunoglobulin superfamily, C2 subset. This protein is thought to be induced on human endothelial cells by TNF-alpha, IL-1, IFN-gamma or endotoxins. A predicted partial nucleic acid sequence for dog CD106 corresponds to position 134174 to position 135113 of AAEX01044853.1 (SEQ ID NO:22). An exemplary

amino acid sequence from human is provided in GenBank Accession No. NP_001069 (SEQ ID NO:24), which is encoded by the nucleic acid having the sequence of SEQ ID NO:23 (GenBank Accession No. NM_001078).

[0056] "CD146," sometimes also referred to as A32, MCAM, Mel-CAM, MUC18, and S-Endo-1) is a cell-cell adhesion receptor that mediates calcium-independent homotypica endothelial cell adhesion. It is a cell-surface glycoprotein that belongs to the immunoglobulin super-gene family. A predicted partial nucleic acid sequence for dog CD146 corresponds to position 3260 to position 3439 of the sequence from chromosome 5 (GenBank AAEX01009397.1) (SEQ ID NO:25). An exemplary amino acid sequence from human is provided in GenBank Accession No. CAA48332.1 (SEQ ID NO:27), which is encoded by the nucleic acid having the sequence of SEQ ID NO:26 (GenBank Accession No. AF089868).

[0057] "CD3" is a 20 kD non-glycosylated transmembrane protein expressed by T cells.

[0058] "CD5" is a leukocyte-specific cell marker found on B1 and T cells.

[0059] "CD11b" (GenBank Accession No.NM000362) is also referred to as Mac 1α and integrin α_M chain, a . member of the alpha integrin family. Canine CD11b is expressed by granulocytes, monocytes and some macrophages.

[0060] "CD21" is a component of the B-cell Receptor complex. It is a B cell specific marker.

[0061] "CD14" is part of the LPS receptor complex that further comprises TLR4 and MD-2. CD-14 is expressed mainly on monocytes and tissue macrophages in peripheral blood.

[0062] "CD18" is also referred to as ß-2 integrin. CD18 is a cell-surface glycoprotein containing beta-chains that can be non-covalently linked to specific alpha-chains of the CD11 family of leukocyte-adhesion molecules (receptors, leukocyte-adhesion). An exemplary amino acid sequence from dog is provided in GenBank Accession No. AAD56947 (SEQ ID NO:33), which is encoded by the nucleic acid having the sequence of SEQ ID NO:32 (GenBank Accession No. AF181965). An exemplary amino acid sequence from human is provided in GenBank Accession No. AAH05861.1 (SEQ ID NO:35), which is encoded by the nucleic acid having the sequence of SEQ ID NO:34 (GenBank Accession No. BC005861).

[0063] "CD45" is a common leukocyte antigen and is a high-molecular weight glycoprotein expressed on the surface of all leukocytes and their hemopoietic progenitors. The CD45 family consists of multiple members that are all products of a single gene. Predicted partial nucleic acid sequences for dog CD45 are provided in SEQ ID NOS:36-40 (partial sequences from AAEX01013304.1. An exemplary amino acid sequence from human is provided in GenBank Accession No. NP_002829 (SEQ ID NO:42), which is encoded by the nucleic acid having the sequence of SEQ ID NO:41 (GenBank Accession No. Y00638).

[0064] "vWF" is an abbreviation for von Willebrand factor, also called Factor VIII-related antigen (F VIII-ra). vWF is a clotting protein present in the blood that is produced in the cells that line blood vessels and then is released into the blood stream. vWF has two functions: 1) bind and stabilize factor VIII, and 2) bind to platelets and enable them to function normally in making a platelet plug and clot. An exemplary amino acid sequence from dog is provided in GenBank Accession No. AAB93766.2 (SEQ ID NO:29), which is encoded by the nucleic acid having the sequence of SEQ ID NO:28 (GenBank Accession No. U66246). An exemplary amino acid sequence from human is provided in GenBank Accession No. NP_000543 (SEQ ID NO:31), which is encoded by the nucleic acid having the sequence of SEQ ID NO:30 (GenBank Accession No. AH005287).

[0065] The term "antibody" as used herein includes, but is not limited to, antibodies obtained from both polyclonal and monoclonal preparations, as well as the following: (i) chimeric antibody molecules (see, for example, Winter *et al.* (1991) *Nature* 349:293-299; and U.S. Patent No. 4,816,567); (ii) F(ab')2 and F(ab) fragments; (iii) Fv molecules (noncovalent heterodimers, see, for example, Inbar et al. (1972) Proc. Natl. Acad. Sci. USA 69:2659-2662; and Ehrlich et al. (1980) Biochem 19:4091-4096); (iv) single-chain Fv molecules (sFv) (see, for example, Huston et al. (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883); (v) dimeric and trimeric antibody fragment constructs; (vi) humanized antibody molecules (see, for example, Riechmann et al. (1988) Nature 332:323-327; Verhoeyan et al. (1988) Science 239:1534-1536; and U.K. Patent Publication No. GB 2,276,169, published 21 September 1994); (vii) Mini-antibodies or minibodies (i.e., sFv polypeptide chains that include oligomerization domains at their C-termini, separated from the sFv by a hinge region; see, e.g., Pack et al. (1992) Biochem 31:1579-1584; Cumber et al. (1992) J. Immunology 149B:120-126); and, (vii) any functional fragments obtained from such molecules, wherein such fragments retain specific-binding properties of the parent antibody molecule.

[0066] The phrases "specifically binds" when referring to a protein, "specifically immunologically cross reactive with," or simply "specifically immunoreactive with" when referring to an antibody, refers to a binding reaction which is determinative of the presence of the protein in the presence of a heterogeneous population of proteins and other biologics. Thus, under designated conditions, a specified ligand binds preferentially to a particular protein and does not bind in a significant amount to other proteins present in the sample. A molecule or ligand (e.g., an antibody) that specifically binds to a protein has an association constant of at least 10^3 M^{-1} or 10^4 M^{-1}, sometimes 10^5 M^{-1} or 10^6 M^{-1}, in other instances 10^6 M^{-1} or 10^7 M^{-1}, preferably 10^8 M^{-1} to 10^9 M^{-1}, and more preferably, about 10^{10} M^{-1} to 10^{11} M^{-1} or higher. A variety of immunoassay formats can be used to select antibodies specifically immunoreactive with a particular protein. For example, solid-phase ELISA immunoassays are routinely used to select monoclonal antibodies specifically immunoreactive with a protein. *See, e.g.*, Harlow and Lane (1988) *Antibodies, A Laboratory Manual*, Cold Spring Harbor Publications, New York, for a description of immunoassay formats and conditions that can be used to determine specific immunoreactivity.

[0067] The term "label" refers generally to an agent that can be detected by some means (e.g., chemical, physical, electromagnetic or other analytical means). Examples of detectable labels that can be utilized include, but are not limited to, radioisotopes, fluorophores, chromophores, mass labels, electron dense particles, magnetic particles, spin labels, molecules that emit chemiluminescence, electrochemically active molecules, enzymes, cofactors, and enzyme substrates.

[0068] A "subject" can be a mammal, including primates, non-human primates (e.g., monkey, ape, chimpanzee) and mammals other than primates (e.g., cat, dog, rat, mouse). Most typically the subject is a human or a dog.

[0069] A difference is typically considered to be "statistically significant" in general terms if an observed value differs by more than the level of experimental error. A difference, for example, can be "statistically significant" if the probability of the observed difference occurring by chance (the p-value) is less than some predetermined level. As used herein a "statistically significant difference" refers to a p-value that is < 0.05, preferably < 0.01 and most preferably < 0.001.

[0070] A "control value" or simply "control" generally refers to a value (or range of values), such as expression levels, against which an experimental or determined value is

compared. As used herein, the term typically refers to a measure of expression of one or more markers in a sample from a particular individual or population of individuals. For instance, the term can refer to the concentration of cells expressing one or more markers (e.g., the concentration of cells having a particular expression profile) in a sample. In the case of methods in which the risk of hemangiosarcoma or angiosarcoma is being evaluated, the control is typically the concentration or frequency of cells from the same tissue or body fluid as those under test having a particular expression profile as determined for an individual or population of individuals at low-risk for the disease and/or that has no discernible evidence of the disease (e.g., no detectable clinical manifestations). The control can also be the test sample analyzed with an irrelevant antibody or probe or primer instead of an antibody, probe or primer to a desired marker. If the signal from the antibody, probe or primer to the desired marker is not higher than that of the irrelevant control (and a margin of experimental error) expression is considered to be absent. Conversely, if the signal from the antibody, primer or probe to the desired marker is higher than that from an irrelevant control and an appropriate margin of experimental error, the marker is expressed. For comparison of leukemia cell marker levels, test samples can be compared with samples from the same tissue or body source either with individuals at low risk of disease (hemangiosarcoma or leukemia) or individuals known to have leukemia. Examples of suitable controls for dogs include those at low risk for hemangiosarcoma, i.e., dogs other than those at high risk (e.g., dogs beyond middle age, Golden Retrievers, German Shepherd Dog, Portuguese Water Dogs, Skye Terriers, or mixed breed dogs containing predominant derivation from such breeds). Absence of clinical manifestation of hemangiosarcoma or angiosarcoma can be evaluated by imaging techniques such as ultrasound, radiographs and/or magnetic imaging techniques (e.g., MRI), for instance. The control can be based upon a single individual, but more typically is a statistical value (e.g., an average or mean) determined from a population. The control can be determined contemporaneously with the test or experimental value or can be performed prior to the test assay. Thus, the control can be based upon contemporaneous or historical data.

[0071] In some methods, the control is a "threshold level." A "threshold level" as used herein generally refers to a threshold value for the expression level of one or more markers that are associated with hemangiosarcoma and/or angiosarcoma. In some instances, the threshold level is expressed as the concentration of cells that concurrently express the one or more markers of interest. If a measured value for the expression level of the markers in a test sample is above the threshold level, this is a statistically significant indication that the test

sample is from a subject that has hemangiosarcoma or angiosarcoma. If, however, the measured value of the test sample is below the threshold level, this is a statistically significant indication that the test sample is from a subject that does not have hemangiosarcoma or angiosarcoma. As with control values, a threshold level can be based upon a single individual, but more commonly represents a value determined from a population of samples to provide the desired level of statistical certainty. Thus, the threshold value is often a statistical value (e.g., an average or mean) established for a population of individuals.

[0072] The terms "nucleic acid," "polynucleotide," and "oligonucleotide" are used herein to include a polymeric form of nucleotides of any length, including, but not limited to, ribonucleotides or deoxyribonucleotides. There is no intended distinction in length between these terms. Further, these terms refer only to the primary structure of the molecule. Thus, in certain embodiments these terms can include triple-, double- and single-stranded DNA, as well as triple-, double- and single-stranded RNA. They also include modifications, such as by methylation and/or by capping, and unmodified forms of the polynucleotide. More particularly, these terms include polymers containing nonnucleotidic backbones, for example, polyamide (*e.g.*, peptide nucleic acids (PNAs)) and polymorpholino polymers, and other synthetic sequence-specific nucleic acid polymers, providing that the polymers contain nucleobases in a configuration which allows for base pairing and base stacking, such as is found in DNA and RNA.

[0073] The term "expression" or "express" refers to the conversion of sequence information, contained in a gene, into a gene product. The gene product can be the direct transcriptional product of a gene (e.g., a mRNA) or a protein produced by translation of a mRNA. Gene products also include RNAs that are modified, by processes such as capping, polyadenylation, methylation, and editing, and proteins modified by, for example, methylation, acetylation, phosphorylation, ubiquitination, ADP-ribosylation, and glycosylation.

[0074] A "probe" is an nucleic acid capable of binding to a target nucleic acid of complementary sequence through one or more types of chemical bonds, usually through complementary base pairing, usually through hydrogen bond formation, thus forming a duplex structure. The probe binds or hybridizes to a "probe binding site." The probe can be labeled with a detectable label to permit facile detection of the probe, particularly once the probe has hybridized to its complementary target. The label attached to the probe can include

any of a variety of different labels known in the art that can be detected by chemical or physical means, for example. Suitable labels that can be attached to probes include, but are not limited to, radioisotopes, fluorophores, chromophores, mass labels, electron dense particles, magnetic particles, spin labels, molecules that emit chemiluminescence, electrochemically active molecules, enzymes, cofactors, and enzyme substrates. Probes can vary significantly in size. Some probes are relatively short. Generally, probes are at least 7 to 15 nucleotides in length. Other probes are at least 20, 30 or 40 nucleotides long. Still other probes are somewhat longer, being at least 50, 60, 70, 80, 90 nucleotides long. Yet other probes are longer still, and are at least 100, 150, 200 or more nucleotides long. Probes can be of any specific length that falls within the foregoing ranges as well.

[0075] A "primer" is a single-stranded polynucleotide capable of acting as a point of initiation of template-directed DNA synthesis under appropriate conditions (*i.e.*, in the presence of four different nucleoside triphosphates and an agent for polymerization, such as, DNA or RNA polymerase or reverse transcriptase) in an appropriate buffer and at a suitable temperature. The appropriate length of a primer depends on the intended use of the primer but typically is at least 7 nucleotides long and, more typically range from 10 to 30 nucleotides in length. Other primers can be somewhat longer such as 30 to 50 nucleotides long. Short primer molecules generally require cooler temperatures to form sufficiently stable hybrid complexes with the template. A primer need not reflect the exact sequence of the template but must be sufficiently complementary to hybridize with a template. The term "primer site" or "primer binding site" refers to the segment of the target DNA to which a primer hybridizes. The term "primer pair" means a set of primers including a 5' "upstream primer" that hybridizes with the complement of the 5' end of the DNA sequence to be amplified and a 3' "downstream primer" that hybridizes with the 3' end of the sequence to be amplified.

[0076] The term "target nucleic acid" refers to a nucleic acid (often derived from a biological sample), to which the probe is designed to specifically hybridize. It is either the presence or absence of the target nucleic acid that is to be detected, or the amount of the target nucleic acid that is to be quantified. The target nucleic acid has a sequence that is complementary to the nucleic acid sequence of the corresponding probe directed to the target. The term target nucleic acid can refer to the specific subsequence of a larger nucleic acid to which the probe is directed or to the overall sequence (*e.g.*, gene or mRNA) whose expression level it is desired to detect.

[0077] The term "complementary" means that one nucleic acid is identical to, or hybridizes selectively to, another nucleic acid molecule. Selectivity of hybridization exists when hybridization occurs that is more selective than total lack of specificity. Typically, selective hybridization will occur when there is at least about 55% identity over a stretch of at least 14-25 nucleotides, preferably at least 65%, more preferably at least 75%, and most preferably at least 90%. Preferably, one nucleic acid hybridizes specifically to the other nucleic acid. See M. Kanehisa, *Nucleic Acids Res.* 12:203 (1984).

[0078] The term "substantially complementary" means that a primer or probe need not be exactly complementary to its target sequence; instead, the primer or probe need be only sufficiently complementary to selectively hybridize to its respective strand at the desired annealing site. A non-complementary base or multiple bases can be included within the primer or probe, so long as the primer or probe retains sufficient complementarity with its polynucleotide binding site to form a stable duplex therewith.

[0079] A "perfectly matched probe " has a sequence perfectly complementary to a particular target sequence. The probe is typically perfectly complementary to a portion (subsequence) of a target sequence. The term "mismatch probe" refer to probes whose sequence is deliberately selected not to be perfectly complementary to a particular target sequence.

II. Overview

[0080] A variety of methods and kits are provided for detecting the presence of primitive proliferative endothelial cells. This detection capability allows the methods and kits to be used to diagnose and detect the early formation of hemangiosarcoma in dogs or angiosarcoma in humans since these malignant tumors arise from primitive proliferating endothelial cells. The methods can be used to detect or diagnose hemangiosarcoma or angiosarcoma asymptomatic subjects that do not present with typical symptoms associated with the diseases. The methods and kits are based, in part, on the finding that certain primitive proliferating endothelial proteins associated with hemangiosarcomas and angiosarcomas express characteristic markers, including characteristic cell-surface proteins. Cells expressing these characteristic proteins can be distinguished from hematopoietic cells associated with leukemias and lymphomas, which can express some of the same proteins, because hematopoietic cells associated with leukemias and lymphomas express other

characteristic proteins that are not expressed by endothelial cells arising from hemangiosarcomas or angiosarcomas.

[0081] The methods and kits that are provided can be used to detect the existence of hemangiosarcomas and angiosarcomas at earlier stages than existing methods and can be conducted using non-invasive methods. This simplifies detection and means that therapies can be initiated sooner, thereby improving the chances for successfully treating the tumors. The ability to distinguish between hemangiosarcomas/angiosarcomas and leukemia/lymphomas also means that treatments can be tailored to the particular disease, thereby improving the efficacy of treatment. The methods and kits provided can also be used to monitor minimal residual disease in an individual undergoing treatment.

[0082] Antibodies that can be used to treat hemangiosarcoma in dogs and angiosarcomas in humans are also disclosed. Some of the antibodies are conjugated antibodies, which include (1) an antibody that specifically recognizes one or more of the characteristic proteins (i.e., antigens) expressed by the proliferating primitive endothelial cells, and (2) a cytotoxic agent (e.g., a chemotherapeutic) linked to the antibody. These antibodies can optionally be formulated as pharmaceutical compositions for use in the treatment of hemangiosarcoma and angiosarcomas.

III. Methods of Analyzing Primitive Endothelial Cells

A. Detecting Presence of Proliferative Primitive Endothelial Cell

[0083] It has been found that hemangiosarcoma is a tumor of "primitive" endothelial cells, i.e., cells that have not differentiated, that are committed to the endothelial lineage, and whose progeny carry characteristic defects that will similarly prevent or arrest their differentiation. These primitive (undifferentiated) endothelial cells can be distinguished from "benign" differentiated endothelial cells because the primitive endothelial cells express the markers CD117, CD133, and/or CD34. Primitive endothelial cells may also express other antigens, such as a Sca-1 homolog (as is seen in the mouse). Differentiated, normal or benign endothelial cells, in contrast, do not express CD117, CD34 or CD133 (or Sca-1 homolog). Primitive endothelial cells lack expression of proteins normally found in hematopoietic cells committed to leukocyte lineages, including CD18, CD11b, CD3, and CD21. Thus, certain methods that are provided herein involve detecting the presence or absence of primitive endothelial cells by detecting the presence or absence of expression of one or more cell markers that define primitive hematopoietic cells such as CD117, CD34, CD133 and/or a

Sca-1 homolog that distinguish a primitive endothelial cell from a differentiated endothelial cell and/or cells committed to leukocyte lineages. Although detection of primitive hematopoietic cell markers provides some indication of risk of hemangiosarcoma or angiosarcoma, detection of these markers is typically coupled with the detection of expression of other characteristic markers to distinguish primitive endothelial cells per se from other hematopoietic stem cells and to further classify and/or confirm the type of cell as described in the following sections.

[0084] Variable expression of some cell markers, including CD14 and CD45, indicate HSA cells can attain different stages of differentiation. The difference in differentiation can affect response to therapy. Expression of these markers can be determined to identify prognosis or optimal treatment methods for an individual affected with HSA.

B. Assessment of Elevated Risk for Hemangiosarcoma or Angiosarcoma

[0085] Because the cells from a hemangiosarcoma or angiosarcoma are primitive endothelial cells, some methods are designed to detect the concurrent expression of (1) one or more primitive hematopoietic cell markers such as described supra, and (2) one or more endothelial cell markers in a population of cells from a test sample taken from a patient. These methods can be utilized as a diagnostic for hemangiosarcoma or angiosarcoma and/or to evaluate the efficacy of a treatment regime.

[0086] Examples of primitive hematopoietic cell markers include, but are not limited to, CD117, CD34, CD133 and/or a Sca-1 homolog. Examples of suitable endothelial cell markers that can be detected include, but are not limited to, CD51/CD61, CD31, CD105, CD106, CD146 and/or von Willebrand Factor (vWF). The endothelial cell marker can be a marker that is expressed by endothelial cells generally (e.g., CD31, CD105, CD106, CD146), and/or a proliferative endothelial cell marker that is associated with proliferative endothelial cells (e.g., CD51/CD61). Detection of concurrent expression of one or more primitive hematopoietic cell markers in combination with one or more endothelial cell markers thus provides strong evidence for hematopoietic ontogeny with endothelial commitment.

[0087] Some methods can be conducted such that one, some or all of the foregoing primitive hematopoietic cell markers are detected. Likewise, certain methods can be conducted such that one, some or all of the foregoing endothelial cell markers are detected (e.g., 1, 2, 3, 4, 5 or all 6 of the foregoing markers). Thus, the methods can detect any combination of one or more primitive hematopoietic cell markers and one or more

endothelial (committed) cell markers, provided at least one each of a primitive hematopoietic cell marker and an endothelial cell marker are detected. The particular grouping of markers that are detected can be considered an expression profile that is characteristic of a primitive endothelial cell. Thus, the methods can be considered to involve detecting an expression profile that is characteristic of a primitive endothelial cell.

[0088] As one specific example, some methods that are provided involve detecting the concurrent expression of the primitive hematopoietic cell markers CD117 and CD34. These two primitive hematopoietic cell markers are detected in this particular method rather than just one to provide increased confidence that the cell is in fact a primitive hematopoietic cell. These methods also detect one, some or all of the endothelial cell markers listed above. But in certain methods, the cells are also examined for concurrent expression of CD51/61 in combination with CD117 and CD34. It can be useful to detect CD51/61 because its expression indicates not only that the cell is an endothelial cell, but more specifically that the cell is a proliferative endothelial cell. This is helpful because tumor cells from tumors such as hemangiosarcoma and angiosarcomas are proliferative.

[0089] Because bone marrow (hematopoietic) stem cells and precursor endothelial cells are also present in the circulation and concurrently express primitive hematopoietic and endothelial cell markers such as those just described, methods for evaluating the risk of hemangiosarcoma or angiosarcoma also typically involves comparing the concentration, frequency or fraction of cells concurrently expressing the markers in the test sample with respect to a control. This can involve determining, for instance, if there is a statistically significant difference between the frequency or concentration in the test sample as compared to the control. In some instances, this involves determining whether the concentration of cells concurrently expressing the markers in the test sample is above or below a threshold level. If the concentration is above the threshold level, then there is a statistical basis for concluding that the subject from which the test sample was obtained has hemangiosarcoma or angiosarcoma. If, on the other hand, the concentration is below the threshold level, there is a statistical basis for concluding that the subject from which the sample was obtained does not have hemangiosarcoma or angiosarcoma.

[0090] The concentration of cells that concurrently express the primitive hematopoietic cell and the endothelial cell markers is increased if a hemangiosarcoma or angiosarcoma is present because hemangiosarcomas and angiosarcomas by definition are in constant contact

with the blood and thus shed cells into the circulation. This mechanism is also responsible, at least in part, for the high metastatic potential and hematogenous (through the blood) spread of these tumors. Thus, normal circulating precursor endothelial cells and malignant hemangiosarcoma or angiosarcoma cells can be distinguished based upon the quantity of cells that are concurrently expressing the primitive hematopoietic cell markers and the endothelial cell markers. The continuous release of HSA tumor cells into the circulation provides the opportunity to detect these cells in routine blood samples.

[0091] Some diagnostic methods and methods for assessing whether a subject is at elevated risk of hemangiosarcoma or angiosarcoma also involve distinguishing among the primitive hematopoietic cells to determine whether those cells that express the primitive hematopoietic cell marker(s) also express marker(s) that are characteristic of endothelial cells or marker(s) that are characteristic of leukemia or lymphoma. This determination can be done qualitatively or quantitatively. As described in greater detail below, the presence of the leukemia marker, in combination with the primitive hematopoietic cell markers, but not the endothelial cell markers, is an indication that the cells are associated with leukemia or lymphoma. The absence of expression of the leukemia marker, concurrent with the presence of an endothelial marker in contrast, is an indication that cells expressing the primitive hematopoietic cell markers are from a hemangiosarcoma or angiosarcoma rather than being leukemia cells.

C. Methods for Distinguishing Between Hemangiosarcoma or Angiosarcoma and Leukemia

[0092] Hemangiosarcoma/angiosarcoma, leukemia, and lymphoma are all diseases that involve excessive proliferation of cells that originate from bone marrow (hematopoietic) precursors. Thus, the characteristic markers for hemangiosarcoma and angiosarcoma that have been identified can be utilized in combination with specific markers for hematopoietic progenitors committed to leukocyte, erythroid, or thrombopoietic lineages that give rise to leukemias and lymphomas to distinguish between hemangiosarcoma (or angiosarcoma) and leukemia or lymphoma. As indicated above (see also Table 1), the cells from hemangiosarcomas or angiosarcomas, as well as leukemia or lymphoma cells, all can express certain common markers (e.g., primitive hematopoietic cell markers such as CD117, CD34 and CD133). Hemangiosarcoma/angiosarcoma also express markers that identify them as

committed to the endothelial lineage, such as CD51/61, CD31, CD105, CD106, CD146 and vWF.

[0093] In contrast, leukemia and lymphoma cells express markers that are unique to cells committed to traditional blood cell forming lineages (leukocytes, red blood cells, platelets) that include, but are not limited to, CD18 and CD45, which are referred to herein as "leukemia markers." Other leukocyte-specific markers, including CD3, CD21, CD5, and CD11b, are also not expressed by hemangiosarcoma cells. The differential expression of one or more of these leukemia-specific or leukocyte-specific markers can be used to distinguish hemangiosarcoma or angiosarcoma from leukemia or lymphoma. Specifically, detection of expression of leukemia or leukocyte-specific cell markers CD18, CD45, CD3, CD21, CD5 or CD11b in a cell population is an indication of leukemia or lymphoma. Conversely, elevated levels of cells expressing a primitive hematopoietic cell marker such as CD117, CD34 and/or CD133, in combination with an endothelial cell marker such as CD51/61, CD31, CD105, CD106, and/or CD146, in combination with a lack of expression of leukemia or leukocyte-specific cell markers, such as CD18, CD45, CD3, CD21, CD5 and/or CD11b are collectively indicative of hemangiosarcoma or angiosarcoma in a cell population.

[0094] The unique properties of laser light scatter, can also be used independently or in combination with detection of the leukemia markers or leukocyte-specific cell markers to make this distinction. Canine hemangiosarcoma cells are large (they segregate to higher channels than leukocytes based on forward angle (or 0°) light scatter) and they are granular or have complex cytoplasm, resulting in right angle (or 90°) side scatter that is comparable to or higher than granulocytes (neutrophils, eosinophils, basophils). The clear differences between the light scatter patterns of canine hemangiosarcoma cells and canine leukocytes can be seen in FIGS. 1A-1H and FIGS. 2A-2H. Further details regarding differences in the patterns are described in the example below.

[0095] Accordingly, certain cell classification and cell diagnostic methods involve determining whether cells in a test sample from a subject concurrently express at least one primitive hematopoietic cell marker, at least one endothelial cell marker, and at least one leukemia cell marker or leukocyte-specific cell marker. As described above, the primitive hematopoietic cell marker(s) and the endothelial cell marker(s) that are analyzed can include one, some or all of those listed supra. Likewise, the expression of one or multiple leukemia cell or leukocyte-specific cell markers can be analyzed. The markers from these three classes

can be combined in any combination, so long as expression of at least one marker from each class is analyzed.

[0096] Thus, the most thorough assessment or diagnosis of a subject thought to be at increased risk for hemangiosarcoma or angiosarcoma involves (1) assessing whether the subject is at elevated risk for hemangiosarcoma or angiosarcoma as described above by determining if cells in the test sample obtained from the subject concurrently express at least one primitive hematopoietic cell marker and at least one endothelial cell marker at levels that are above that of a control (e.g., a threshold level), and (2) determining if the same cells also concurrently express one or more leukemia or leukocyte-specific cell markers. The expression of the one or more leukemia or leukocyte-specific cell markers can be done qualitatively (e.g., determining whether the marker is expressed by the cells or not) or quantitatively (e.g., with respect to a control such as a threshold level). In some methods, expression of the primitive hematopoietic cell marker(s), the endothelial cell marker(s) and the leukemia or leukocyte-specific cell marker(s) are conducted contemporaneously. As described in greater detail below, this may be accomplished, for example, by incubating cells from a test sample with differentially labeled antibodies that specifically bind markers from the three different classes and then detecting cells that are labeled with the antibodies using multiparameter flow cytometry. Alternatively, concurrent expression of the three classes of markers can be detected at the transcript level using probes that specifically hybridize to a segment of each of the marker transcripts in a hybridization assay and/or primers that specifically amplify the marker transcripts.

[0097] As a specific example of this general approach, some methods for diagnosing hemangiosarcoma in a dog involve testing a population of cells from a dog at risk for hemangiosarcoma for concurrent expression of CD117 and CD34 (examples of primitive hematopoietic cell markers) and CD51/CD61 (an example of a endothelial cell marker), and lack of expression of CD18 (an example of a committed leukocyte cell marker). If the cell population concurrently expresses CD117, CD34 and CD51/61 but not CD18 (i.e., the cells are $CD117^+$, $CD34^+$, $CD51/61^+$, $CD18^-$), then the differential diagnosis is that the dog has a hemangiosarcoma. If, however, the cell population concurrently expresses CD117, CD34, and CD18 (i.e., the cells are $CD117^+$, $CD34^+$, $CD18^+$), then the differential diagnosis is that the dog has leukemia or lymphoma. Absence of expression of these markers (e.g., expression below a threshold level), indicates that the dog is unlikely to be at immediate risk to develop, or to have hemangiosarcoma, leukemia or a lymphoma.

[0098] The same type of analysis would apply to humans, except that $CD117^+$, $CD34^+$, $CD51/61^+$, $CD18^-$ cells indicate that the human has angiosarcoma (rather than hemangiosarcoma which is specific to dogs rather than humans).

[0099] Although the foregoing methods have emphasized the ability to detect or diagnose hemangiosarcoma in dogs or angiosarcoma in humans, it should be clear that the capacity of the methods to distinguish between hemangiosarcoma/angiosarcoma from leukemia/lymphoma means that the methods can be used equally well to detect or diagnose leukemia or lymphoma in dogs or humans. The main difference between methods for diagnosing angiosarcoma and methods for diagnosing leukemia being that in methods for diagnosing angiosarcoma one looks for presence of expression of endothelial cell marker(s) and absence of expression of the leukemia cell marker(s) which rules out leukemia and lymphoma, whereas in methods for diagnosing leukemia one instead looks for presence of expression of the leukemia cell marker(s) and absence of expression of the endothelial cell marker(s). If the leukemia cell marker(s) are found to be expressed concurrently with at least one primitive hematopoietic cell marker and at least one endothelial cell marker, then this indicates that cells are from a subject with leukemia or lymphoma.

[0100] The following table summarizes which markers are associated with hemangiosarcomas, angiosarcomas, leukocyte-specific cells, leukemia and lymphoma, and thus indicates which combination of markers can be used to detect these diseases and distinguish between them.

Table I

Markers	Primitive Endothelial Cells (Hemangiosarcoma and Angiosarcoma)	Benign Endothelial Cells	Leukemia and Lymphoma
Primitive Hematopoietic Cell Markers			
CD117	Yes	No	Variable
CD34	Yes (low to intermediate)	No	Variable
CD133	Yes	No	Variable
Endothelial Cell Markers			
CD51/CD61	Yes	Variable	No

CD31	Yes	Yes	No
CD105	Yes	Yes	No
CD106	Yes	Yes	No
CD146	Yes	Yes	No
Markers to Exclude HSA Cells			
CD18, CD11b, CD3, CD5, and CD21	No	No	Yes
Leukemia Cell Markers			
CD18	No	No	Yes
CD45	Variable (when yes, low to intermediate)	Variable (usually No)	Yes (intermediate to high, except for B cell-chronic lymphocytic leukemia (CLL), which is No)
CD14	Variable (when yes, low to intermediate)	Variable (usually No)	Yes (absent to high, depending on the type of leukemia; highest in monoblastic and monocytic leukemias, low to intermediate in other myeloid leukemias and some B cell leukemias)

IV. Options for Detecting Markers

[0101] Expression of the various markers described above can be detected at the protein level by detecting the expressed proteins themselves, or at the transcript (i.e., mRNA) level by detecting transcript that encodes the corresponding proteins of interest. Conversely, proteins not expressed cannot be detected at the protein level or transcript level by the assays described below. Additional details regarding these various detection options follows.

A. Detecting Expressed Proteins

1. Multiparameter Flow Cytometry

[0102] Flow cytometry is one detection method that can be used to determine the level at which cells in a sample concurrently express the primitive hematopoietic cell markers,

endothelial cell markers and/or leukemia or leukocyte specific cell markers (markers), in addition to the peculiar light scatter patterns, which are different between leukocytes (associated with leukemia and lymphoma) and primitive endothelial cells (associated with hemangiosarcoma and angiosarcoma). These differences are described in greater detail in the example below. Flow cytometry involves the quantitative multiparameter measurement of chemical or physical characteristics of cells in suspension. A flow cytometer can measure, for instance, the cell's light scatter and the electronic cell volume as a cell passes through detectors in the device. The flow cytometer can also measure a cell's axial (at a right angle) light loss and morphological information (derived from the cell shape or time duration of light scatter signals) as it passes through a fluorescent excitation beam. Thus, a flow cytometer can categorize cells on the basis of size, granularity, and fluorophore intensity.

[0103] The methods provided herein that use flow cytometry to detect the level of expression of the markers usually involve a process referred to in the art as "immunophenotyping." In this process, antigens expressed by a cell (e.g., the markers disclosed herein) can be identified by incubating cells with labeled antibodies that recognize different antigens/markers on the cell. The antibodies are generally differentially labeled such that different antigens/markers on the cell surface become labeled with antibodies bearing different labels. After a suitable incubation period, any unbound antibodies are subsequently removed by washing. The resulting labeled cells are then introduced into a flow cytometer where the fluorescent labels can be excited by the excitation beam and the resulting fluorescence emissions detected. Since different antigens/markers are associated with different fluorescent labels, each having a characteristic emission spectrum, the identity of the antigens/markers on the cell can be determined from the fluorescence signals that are detected. In some methods, the cells can also be incubated with a fluorescent dye which intercalates into the DNA, thereby allowing the DNA composition (ploidy) to be determined.

[0104] Additional details regarding the use of flow cytometry to detect cells that concurrently express the different markers disclosed herein are provided in the examples below. Further discussion on flow cytometry sufficient to guide the skilled practitioner is provided by De Rosa, S.C., et al. (2003) Nature Medicine 9:112-117, and Baumgarth, N. and Roederer, M. (2000) J. Immunological Methods 243:77-97.

2. Other Immunological Techniques

[0105] A variety of other immunological techniques can also be used to determine whether cells concurrently express the primitive hematopoietic cell markers, endothelial cell markers and/or leukemia or leukocyte-specific cell markers described herein. Antibodies that specifically bind these markers, for instance, can be used to detect such these markers in various diagnostic assays, including but not limited to, competitive binding assays, direct or indirect sandwich assays, enzyme-linked immunospecific assays (ELISA), and immunoprecipitation assays (see, *e.g., Monoclonal Antibodies: A Manual of Techniques*, CRC Press, Inc. (1987) pp. 147-158). Further guidance regarding the methodology and steps of a variety of antibody assays is provided, for example, in U.S. Patent No. 4,376,110 to Greene; "Immunometric Assays Using Monoclonal Antibodies," in *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, Chap. 14 (1988); Bolton and Hunter, "Radioimmunoassay and Related Methods," in *Handbook of Experimental Immunology* (D.M. Weir, ed.), Vol. 1, chap. 26, Blackwell Scientific Publications, 1986; Nakamura, et al., "Enzyme Immunoassays: Heterogeneous and Homogenous Systems," in *Handbook of Experimental Immunology* (D.M. Weir, ed.), Vol. 1, chap. 27, Blackwell Scientific Publications, 1986; and Current Protocols in Immunology, (John E. Coligan, et al., eds), chap. 2, section I, (1991).

3. Antibodies for Use in Flow Cytometry and Other Immunological Methods

[0106] Antibodies that recognize a number of the foregoing markers as expressed in canines are commercially available, including:

(1) canine CD117 (clone ACK45, BD Biosciences, pycoerythrin (PE) conjugate);

(2) canine CD34 (clone 2E9, BD Biosciences, biotin conjugate);

(3) canine CD51/CD61 (mAb 1976, Chemicon, APC or FITC conjugate);

(4) canine CD18 (clone YKlX490.6.4, Serotec, fluorescein isothiocyanate (FITC) conjugate and clone YFCI18.3, Serotec, FITC or biotin conjugate);

(5) canine CD45 (clone YKlX716.13, Serotec, PE conjugate);

(6) canine CD105 (cross reactive) (clone 8E11, Southern Biotechnology Associates, Birmingham, AL, FITC conjugate);

(7) canine CD133 (clone 13A4, BD Biosciences);

(8)) canine CD11b antibody (clone CA16.3E10, Serotec);

9) canine anti-CD146 (MUC18, S-endo, clone P1H12 conjugated to biotin, catalog #MAB16985B, Chemicon Intl., Temecula, CA);

(10) canine CD CD3 (clone CA17.2A12, Serotec, Inc., FITC conjugate);

(11) canine CD5 antibody (clone YKIX322.3, Serotec, Inc.); and

(12) canine anti-B cell (CD21) antibody (clone Ca2.1D6, Serotec, Inc.).

Antibodies that recognize a number of the foregoing markers as expressed in humans are also commercially available, including:

(1) human CD117 (clone YB5.B8, BD Biosciences, pycoerythrin (PE), or APC, or PE-Cy5 conjugate);

(2) human CD34 (clone 581, BD Biosciences, allophycocyanin (APC) or PE conjugate);

(3) human CD51/CD61 (mAb 1976, Chemicon, biotin or FITC or PE conjugate);

(4) human CD18 (clone 6.7, BD Biosciences, FITC or PE, or APC, or PE-Cy5, or APC conjugate and clone L130, BD Biosciences, FITC conjugate);

(5) human CD45 (clone 2D1, BD Biosciences, APC, FITC, APC-Cy7, PerCP, PerCp-Cy5.5 conjugate and clone H130, BD Biosciences, FITC, PE, APC, biotin, PE-Cy7, PE-Cy5 conjugate);

(6) human CD105 (clone 8E11, Southern Biotechnology Associates, Birmingham, AL, conjugated to FITC);

(7) human anti-CD146 (MUC18, S-endo, clone P1H12 conjugated to biotin, catalog #MAB16985B, Chemicon Intl., Temecula, CA);

(8) human CD106 (clone 1.G11b1, Southern Biotechnology Associates, Birmingham, AL, conjugated to biotin, FITC, or PE);

(9) human CD133 (prominin, human promin-1, antibody AC133 PE, APC, biotin conjugate and antibody 293C3 PE, APC, biotin conjugate, Miltenyi Biotech, Auburn, CA); and

(10) murine CD133 (clone 13A4, eBioscience, San Diego, CA).

[0107] Additional antibodies to any of the markers described herein can be prepared according to routine methods that are known in the art (see, e.g., discussion below in the section on antibodies). Each antibody can also be obtained in purified form without a fluorochrome or biotin label, and labeled to any available fluorochrome in vitro using the AlexaFluor Zenon antibody labeling technology from Invitrogen/Molecular Probes, Eugene, OR (emitting at 16 different wavelengths between 350 and 750 nm) or other equivalent technologies (e.g., Zymed and others). The resulting antibodies can be conjugated to any of a number of different labels, including for example, radioisotopes (*e.g.*, ^{3}H, ^{14}C, ^{32}P, ^{35}S, ^{125}I), fluorophores (*e.g.*, pycoerythrin, fluorescein and rhodamine dyes and derivatives thereof), chromophores, chemiluminescent molecules, and enzyme substrates (e.g., the enzymes luciferase, alkaline phosphatase, beta-galactosidase and horse radish peroxidase).

[0108] Secondary detection systems employing an unlabelled antibody to bind to a cell marker and another labeled antibody to bind to the Fc region of the first antibody can be used in the immunoassays of the invention to increase the sensitivity of the assays.

Other markers that can optionally be detected in combination with those above include vascular endothelial growth factor (VEGF), which is constitutively elevated in HSA tumors, and is found at increased levels in blood samples from affected dogs. c-KIT, and vascular endothelial growth factor receptor-2 (VEGFR-2) are expressed by canine HSA cells in culture. These markers can be monitored in detection and diagnosis of HSA. The VEGF-2 tumor suppressor genes, include PTEN and VHL, are sometimes inactivated in canine HSA as well, providing cells a growth advantage within their microenvironment. Lack of PTEN, and VHL is therefore also an indicator of HSA.

[0109] A series of iterative steps can be used to identify circulating endothelial precursor cells (EPC) or HSA cells in peripheral blood. First, single color staining can be used to define background levels for each antibody and to verify that the relative number of leukocytes ($CD21^{+}$B cells, $CD3^{+}$ and $CD5^{+}$ T cells, $CD14^{+}$ monocytes, and $CD11b^{+}$ granulocytes) in samples are within previously reported reference ranges. Next, antibody combinations can be used for two-color staining. Color compensation can be adjusted using, *e.g.*, BD Biosciences CompBeads. Populations staining positively for one or more of three markers associated with bone marrow progenitor cells (c-KIT, CD34, CD133) and for a marker associated with *proliferating* endothelial cells ($\alpha_v\beta_3$-integrin) can be "back-gated" to

two-dimensional light scatter histograms to define the flow cytometric light scatter parameters of HSA cells versus normal leukocytes. Some protocols can be modified to exclude leukocytes using antibodies against CD5, CD11b, and CD21 labeled with FITC (and/or Alexa Fluor-488) to establish a "dump gate", and EPC can be detected in the remaining cell population by dual staining with antibodies against c-KIT, CD34, or CD133 (conjugated to PE) along with antibodies against $\alpha_v\beta_3$-integrin or CD146 (labeled with Alexa Fluor-647). Preferably at least 100,000 cells can be analyzed for each antibody pair to ensure statistical validity for rare-event determination.

B. Detecting Transcript that Encodes Markers

1. General Considerations

[0110] The level of gene expression and expression of the primitive hematopoietic cell markers, endothelial cell markers and leukemia or leukocyte-specific cell markers can also be detected qualitatively or quantitatively using a number of established techniques including, but not limited to, multiplex PCR, nucleic acid probe arrays, dot blot assays, in-situ hybridization, Northern-blots, and RNase protection assays (RPA). These are described further in the sections that follow.

[0111] Primers and/or probes having sequences that are appropriate for use in such detection schemes can be designed based upon the sequences for the different markers that are provided herein (e.g., SEQ ID NOS:1-45). See, e.g., Mitsuhashi, M. (1996) J. Clin. Lab. Anal. 10:285-93, which is incorporated herein by reference in its entirety for all purposes.

[0112] For the following methods that utilize probes to detect marker expression, the hybridization probes utilized in these methods are of sufficient length to specifically hybridize to a particular marker nucleic acid. Hybridization probes are typically at least 15 nucleotides in length, in some instances 20 to 30 nucleotides in length, in other instances 30 to 50 nucleotides in length, and in still other instances up to the full length of a marker nucleic acid. The probes are labeled with a detectable label, such as a radiolabel, fluorophore, chromophore or enzyme to facilitate detection. Methods for synthesizing the necessary probes include the phosphotriester method described by Narang et al. (1979) Methods of Enzymology 68:90, and the phosphodiester method disclosed by Brown et al. (1979) Methods of Enzymology 68:109.

2. Multiplex PCR

[0113] Various types of multiplex PCR can be utilized to detect expression of the cell markers described herein. Multiplex PCR in general refers to PCR methods in which more than one pair of primers is used, thus allowing the amplification of multiple DNA targets in a single run. If this approach is utilized, typically the methods are conducted as quantitative multiplex PCR so the level of expression can be more readily determined.

[0114] The quantitative multiplex PCR assays that are utilized with the current methods can be conventional quantitative PCR or "real time PCR" methods. Real-time PCR usually monitors the fluorescence emitted during an amplification reaction as an indicator of amplicon production during each PCR cycle (i.e., in real time) as opposed to the endpoint detection by conventional quantitative PCR methods. By recording the amount of fluorescence emission at each cycle, it is possible to monitor the PCR reaction during exponential phase where the first significant increase in the amount of PCR product correlates to the initial amount of target template.

[0115] There are several real-time strategies that can be used to detect the expression of the marker transcripts disclosed herein (i.e., the targets). A requirement that is common to each strategy is a probe bearing fluorescent moieties that is complementary to a section in the amplified target. One example of real-time analysis method that can be utilized with the current methods is the "Taqman" PCR approach. Reagents and equipment for performing such analyses are marketed by Applied Biosystems, Foster City, CA. In this method, the probe used in such assays is typically a short (ca. 20-25 bases) polynucleotide that is labeled with two different fluorescent dyes. The 5' terminus of the probe is typically attached to a reporter dye and the 3' terminus is attached to a quenching dye, although the dyes can be attached at other locations on the probe as well. For each marker transcript, a probe is designed to have at least substantial sequence complementarity with a probe binding site on the marker transcript. Upstream and downstream PCR primers that bind to regions that flank the region encoding each marker are also added to the reaction mixture for use in amplifying the markers of interest.

[0116] When the probe is intact, energy transfer between the two fluorophors occurs and the quencher quenches emission from the reporter. During the extension phase of PCR, the probe is cleaved by the 5' nuclease activity of a nucleic acid polymerase such as Taq polymerase, thereby releasing the reporter dye from the polynucleotide-quencher complex

and resulting in an increase of reporter emission intensity that can be measured by an appropriate detection system.

[0117] One detector which is specifically adapted for measuring fluorescence emissions during quantitative PCR reactions is the ABI 7700 manufactured by Applied Biosystems, Inc. in Foster City, CA. Computer software provided with the instrument is capable of recording the fluorescence intensity of reporter and quencher over the course of the amplification. These recorded values can then be used to calculate the increase in normalized reporter emission intensity on a continuous basis and ultimately quantify the amount of the mRNA being amplified.

[0118] Information specific to the "TaqMan" type assays are is described, for example, in U.S. Pat Nos. 5,210,015 to Gelfand, 5,538,848 to Livak, et al., and 5,863,736 to Haaland, as well as Heid, C.A., et al., Genome Research, 6:986-994 (1996); Gibson, U.E.M, et al., Genome Research 6:995-1001 (1996); Holland, P. M., et al., Proc. Natl. Acad. Sci. USA 88:7276-7280, (1991); and Livak, K.J., et al., PCR Methods and Applications 357-362 (1995), each of which is incorporated by reference in its entirety for all purposes.

[0119] Another real-time strategy that can be used to detect expression of the markers provided herein utilizes labeled probes called "Molecular Beacons," which are marketed by various entities including Proligo LLC, Boulder, CO. and Synthegen LLC, Houston, TX, under a license from Public Health Research Institute. In methods using this approach, the fluorophore and the quencher, attached to opposite ends of the probe, are held together by a base paired stem that becomes disrupted on hybridization of the loop to a target nucleic acid. Further details regarding the use of molecular beacons are provided by Tyagi, S., and F. R. Kramer (1996) Nature Biotechnology 14: 303-8; and Tyagi S., et al. (2000) Nature Biotechnology 18: 1191-96, each of which is incorporated by reference in its entirety for all purposes.

[0120] Additional details regarding the theory and operation of multiplex PCR assays are described, for example, by Wittwer, C.T., et al. (2001) Methods 25:430-42; Markoulatos, P., et al. (2002) J. Clin. Lab. Anal. 16:47-51; Elnifro, E.M., et al. (2000) J. Clin. Microbiol. Rev. 13:559-570; and Edwards, M.C. and Gibbs, R.A. (1994) PCR Methods Appl. 3:S65-75, each of which is incorporated herein by reference in its entirety for all purposes.

3. Nucleic Acid Probe Arrays

[0121] Marker transcripts can also be detected using a variety of hybridization methods. One example, is the use of nucleic acid probe arrays to detect and quantitate marker transcript. A variety of different types of arrays can be used to detect expression of the markers of interest depending upon the nature of the probes on the arrays. The array probes, can include, for example, synthesized probes of relatively short length (e.g., a 20-mer or a 25-mer), cDNA (full length or fragments of gene), amplified DNA, fragments of DNA (generated by restriction enzymes, for example) and reverse transcribed DNA (see, e.g., Southern et al. (1999) Nature Genetics Supplement 21:5-9 (1999).

[0122] Both custom and generic arrays can be utilized in detecting marker expression levels. Custom arrays can be prepared using probes that hybridize to particular preselected subsequences of mRNA gene sequences of the markers or amplification products prepared from them. Generic arrays are not specially prepared to bind to the marker sequences, but instead are designed to analyze mRNAs irrespective of sequence. Nonetheless, such arrays can still be utilized because marker transcripts only hybridize to those locations that include complementary probes. Thus, the different marker transcript levels can still be determined based upon the extent of binding at those locations bearing probes of complementary sequence.

[0123] In probe array methods, once nucleic acids have been obtained from a test sample, they typically are reversed transcribed into labeled cDNA, although labeled mRNA can be used directly. By differentially labeling the mRNA or cDNA, the expression levels of multiple markers can be determined simultaneously. The test sample containing the labeled nucleic acids is then contacted with the probes of the array. After allowing a period sufficient for any labeled marker nucleic acids present in the sample to hybridize to the probes, the array is typically subjected to one or more high stringency washes to remove unbound nucleic acids and to minimize nonspecific binding to the nucleic acid probes of the arrays. Binding of labeled nucleic acids corresponding to the markers is detected using any of a variety of commercially available scanners and accompanying software programs.

[0124] For example, if the nucleic acids from the sample are labeled with fluorescent labels, hybridization intensity can be determined by, for example, a scanning confocal microscope in photon counting mode. Appropriate scanning devices are described by *e.g.*,

U.S. 5,578,832 to Trulson *et al.*, and U.S. 5,631,734 to Stern *et al.* and are available from Affymetrix, Inc., under the GeneChip™ label.

[0125] Those locations on the probe array that are hybridized to labeled nucleic acid are detected using a reader, such as described by U.S. Patent No. 5,143,854, WO 90/15070, and U.S. 5,578,832. For customized arrays, the hybridization pattern can then be analyzed to determine the presence and/or relative amounts or absolute amounts of known mRNA species in samples being analyzed as described in *e.g.*, WO 97/10365.

[0126] Further guidance regarding the use of probe arrays sufficient to guide one of skill in the art is provided in WO 97/10365, PCT/US/96/143839 and WO 97/27317.

4. Dot Blots and In-situ Hybridization

[0127] Dot blots are another example of a hybridization assay approach that can be utilized to determine the amount of each of the marker transcripts that are present in a sample obtained from a subject being tested. In some assays, for instance, a sample from a subject being tested is spotted on a support (e.g., a filter) and then probed with labeled nucleic acid probes that specifically hybridize with the marker transcript sequences of interest. After the probes have been allowed to hybridize to the immobilized nucleic acids on the filter, unbound nucleic acids are rinsed away and the presence of hybridization complexes detected and quantitated on the basis of the amount of labeled probe bound to the filter. By using differentially labeled probes, transcripts from multiple markers can be detected at the same time.

[0128] In-situ hybridization methods are hybridization methods in which the cells are not lysed prior to hybridization. Because the method is performed in situ, it has the advantage that it is not necessary to prepare RNA from the cells. The method usually involves initially fixing test cells to a support (e.g., the walls of a microtiter well) and then permeabilizing the cells with an appropriate permeabilizing solution. A solution containing labeled probes for the markers of interest is then contacted with the cells and the probes allowed to hybridize with the labeled nucleic acids. Excess probe is digested, washed away and the amount of hybridized probe measured. This approach is described in greater detail by Harris, D. W. (1996) Anal. Biochem. 243:249-256; Singer, et al. (1986) Biotechniques 4:230-250; Haase et al. (1984) Methods in Virology, vol. VII, pp. 189-226; and Nucleic Acid Hybridization: A Practical Approach (Hames, et al., eds., 1987).

5. Northern Blots

[0129] Northern blots can also be used to detect and quantitate marker transcript. Such methods typically involve initially isolating total cellular or poly(A) RNA and separating the RNA on an agarose gel by electrophoresis. The gel is then overlaid with a sheet of nitrocellulose, activated cellulose, or glass or nylon membranes and the separated RNA transferred to the sheet or membrane by passing buffer through the gel and onto the sheet or membrane. The presence and amount of marker transcript present on the sheet or membrane can then be determined by probing with a labeled probe complementary to the marker transcripts to form labeled hybridization complexes that can be detected and optionally quantitated (see, e.g., . Sambrook, et al. (1989) Molecular Cloning – A Laboratory Manual (2nd ed) Vols. 1-3, Cold Spring Harbor Laboratory, Cold Spring Harbor Press, NY).

6. RNAase Protection Assays

[0130] Ribonuclease protection assays (RPA) involve preparing a labeled antisense RNA probe for each of the markers of interest. These probes are subsequently allowed to hybridize in solution with marker transcript contained in a biological sample to form RNA:RNA hybrids. Unhybridized RNA is then removed by digestion with an RNAase, while the RNA:RNA hybrid is protected from degradation. The labeled RNA:RNA hybrid is separated by gel electrophoresis and the band corresponding to the markers detected and quantitated. Usually the labeled RNA probe is radiolabeled and the bands corresponding to the different markers detected and quantitated by autoradiography. RPA is discussed further by (Lynn et al. (1983) Proc. Natl. Acad. Sci. 80:2656; Zinn, et al. (1983) Cell 34:865; and Sambrook, et al. (1989) Molecular Cloning – A Laboratory Manual (2nd ed) Vols. 1-3, Cold Spring Harbor Laboratory, Cold Spring Harbor Press, NY).

V. Samples

A. General Considerations

[0131] Although the methods that are provided can generally be used to detect early formation of hemangiosarcoma in any breed of dog (or mix of breeds), the methods are often used in the early diagnosis of hemangiosarcoma in dogs that are at increased risk for hemangiosarcoma. As indicated in the background section, some dogs are inherently at higher risk than other dogs. These dogs include those of any breed that are beyond middle age and purebred dogs where the prevalence of hemangiosarcoma is high including, but not

limited to, Golden Retrievers, German Shephards, Portugese Water Dogs, or Skye Terriers. Mix breed dogs are also at higher risk if their predominant derivation is from one of the foregoing breeds.

[0132] In the case of angiosarcoma, the methods can also be performed, for example, with samples from any human deemed to potentially have an angiosarcoma. The methods, however, have particular utility with the humans that are at increased risk for angiosarcoma because they have a risk factor that is correlated with angiosarcoma. Examples of such risk factors include, but are not limited to, occupational exposure to vinyl chloride for hepatic angiosarcoma, radiation therapy for mammary angiosarcoma, HIV-1 infection for Kaposi sarcoma, and heritable defects in the Von Hippel-Lindau gene in human infantile angiosarcomas.

B. Samples for Flow Cytometry

[0133] Blood samples are the type of sample most typically utilized in flow cytometry analyses. A typical sample size for flow cytometry is about 10 µl to about 1.0 ml, which includes about 100,000 (10^5) to 2,500,000 (2.5×10^6) cells. One useful sample collection method is to collect blood by venipuncture into evacuated tubes containing an appropriate anticoagulant. The blood is then mixed well with the anticoagulant in the tube to prevent clotting. Various anticoagulants can be used. If the specimens will be processed within thirty hours of collection, then examples of suitable anticoagulants include potassium EDTA, acid citrate dextrose (ACD), or heparin. If, however, the samples will not be processed within 30 hours, of these three anticoagulants, either ACD or heparin should be used.

[0134] Typically, specimens for flow cytometry are maintained and transported (if necessary) under refrigerated temperatures (2-8°C). This maintains the viability of the cells and their expression of antigens. Tubes are usually incubated in the dark to maximize fluorescence capability.

[0135] Once the sample has been combined with the labeled antibodies that specifically bind the markers of interest, the samples are typically vortexed to mix up the antibodies with the cells and break up cell aggregates. A source of protein may be included in the wash buffer to reduce cell clumps and autofluorescence. Before analysis, samples are generally fixed with a fixation solution (e.g., 1-2% buffered paraformaldehyde or formaldehyde).

[0136] Flow cytometry can include processes to distinguish primitive cells from normal cells. Normal leukocytes in a sample can be labeled using antibodies with one fluorochrome (in one color, e.g. FITC). A dump gate can be established to ignore the FITC color associated with the normal leukocytes, and to focus only on cells labeled with fluorochromes of other colors, such as red (PE) and blue (APC). Markers that can be used for the "dump gate" include CD3, CD5, CD11c, CD21, and optionally, CD18. CD45 and/or CD14 are not suitable as "dumpgate" markers, because hemangiosarcoma cells may express these markers at some stage differentiation. CD45 and/or CD14 can be used to distinguish monocytes and monocyte precursor cells from hemangiosarcoma cells based upon expression level, because these markers are expressed at higher levels in monocytes than in hemangiosarcoma cells.

[0137] Samples for analysis can be enriched for hemangiosarcoma cells by separation from erythrocytes and granulocytes by lysis or discontinuous gradients using conventional separation agents such as Ficoll-Hypaque.

[0138] As cultured cells can lose markers of interest after several passages (4-6 weeks), early passage cultured cells or other suitable cells, such as cells stably transfected to express desired markers, are optimal controls.

C. Samples for Transcript Detection

[0139] If marker expression is determined by measuring transcript levels, blood samples are typically used because they can be obtained in a relatively non-invasive manner. The methods can also be conducted with tissue biopsies from the tumor if available, but this is not typical because the methods are usually conducted to detect early onset of disease and because obtaining biopsies is more invasive. Many of the methods involving transcript detection are very sensitive and can be conducted with minimal sample volume (e.g., fractions of a milliliter of a blood sample). A variety of different sample types can be utilized in methods that involve detecting transcript levels including, but not limited to, blood and various samples taken from the tumor such as different types of effusion fluids (e.g., thoracic effusion, peritoneal effusion, pericardial effusion, or cystic fluid within a mass). Effusion fluids are collected from the site of the tumor. Effusion samples are usually treated with anticoagulants as described above for blood samples.

[0140] To measure the transcription level (and thereby the expression level) of the markers, a nucleic acid sample comprising mRNA transcripts of the markers, fragments, or nucleic

acids derived from the mRNA transcripts is obtained. A nucleic acid derived from an mRNA transcript refers to a nucleic acid for whose synthesis the mRNA transcript or a subsequence thereof has ultimately served as a template. Thus, a cDNA reverse transcribed from an mRNA, an RNA transcribed from that cDNA, a DNA amplified from the cDNA, an RNA transcribed from the amplified DNA, are all derived from the mRNA transcript and detection of such derived products is indicative of the presence and/or abundance of the original transcript in a sample. Thus, suitable samples include, but are not limited to, mRNA transcripts of the markers, cDNA reverse transcribed from the mRNA, cRNA transcribed from the cDNA, DNA amplified from the genes, and RNA transcribed from amplified DNA.

[0141] In some methods, a nucleic acid sample is the total mRNA isolated from a biological sample; in other instances, the nucleic acid sample is the total RNA from a biological sample. Any RNA isolation technique that does not select against the isolation of mRNA can be utilized for the purification of such RNA samples. For example, methods of isolation and purification of nucleic acids are described in detail in WO 97/10365, WO 97/27317, Chapter 3 of Laboratory Techniques in *Biochemistry and Molecular Biology: Hybridization With Nucleic Acid Probes,* Part I. *Theory and Nucleic Acid Preparation*, (P. Tijssen, ed.) Elsevier, N.Y. (1993); Chapter 3 of Laboratory Techniques in *Biochemistry and Molecular Biology: Hybridization With Nucleic Acid Probes*, Part 1. Theory and Nucleic Acid Preparation, (P. Tijssen, ed.) Elsevier, N.Y. (1993); and Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press, N.Y., (1989); *Current Protocols in Molecular Biology*, (Ausubel, F.M. *et al.*, eds.) John Wiley & Sons, Inc., New York (1987-1993).

VI. Antibodies

A. General Considerations

[0142] Antibodies that specifically bind to the markers expressed by cells from hemangiosarcomas, angiosarcomas and/or leukemia cells are also provided. These antibodies can be of a variety of different types including, but not limited to, (i) monoclonal antibodies, (ii) chimeric antibody molecules; (iii) F(ab')2 and F(ab) fragments; (iv) Fv molecules; (v) single-chain Fv molecules (sFv); (vi) dimeric and trimeric antibody fragment constructs (e.g., diabodies and triabodies); (vii) humanized antibody molecules or canonized antibody molecules; (viii) Mini-antibodies or minibodies (i.e., sFv polypeptide chains that include oligomerization domains at their C-termini, separated from the sFv by a hinge region; and,

(ix) any functional fragments obtained from such molecules, wherein such fragments retain specific-binding properties of the parent antibody molecule. The antibodies may be of any isotype, e.g., IgM, IgD, IgG, IgA, and IgE, with IgG, IgA and IgM often preferred. Humanized and caninized antibodies (see infra) may comprise sequences from more than one class or isotype.

[0143] The antibodies can be used with or without modification. Frequently, the antibodies are labeled by conjugating, either covalently or non-covalently, a detectable label. As labeled binding entities, the antibodies are particularly useful in diagnostic applications. The label can be any molecule capable of producing, either directly or indirectly, a detectable signal. Suitable labels include, but are not limited to, radioisotopes (*e.g.*, ^{3}H, ^{14}C, ^{32}P, ^{35}S, ^{125}I), fluorophores (*e.g.*, fluorescein and rhodamine dyes and derivatives thereof), chromophores, chemiluminescent molecules, an enzyme substrate (including the enzymes luciferase, alkaline phosphatase, beta-galactosidase and horseradish peroxidase, for example).

[0144] The antibodies can be prepared, for example, using intact polypeptide or fragments containing antigenic determinants from proteins encoded by the markers that are disclosed herein. The polypeptide used to immunize an animal can be from natural sources, derived from translated cDNA, or prepared by chemical synthesis and can be conjugated with a carrier protein. Commonly used carriers include keyhole limpet hemocyanin (KLH), thyroglobulin, bovine serum albumin (BSA), and tetanus toxoid. The coupled peptide is then used to immunize the animal (*e.g.*, a mouse, a rat, or a rabbit). Various adjuvants can be utilized to increase the immunological response, depending on the host species and include, but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface actives substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, dinitrophenol and carrier proteins, as well as human adjuvants such as BCG (bacille Calmette-Guerin) and *Corynebacterium parvum*.

[0145] Cultured hemangiosarcoma cell lines that express the markers can be prepared as described by Fosmire, S. P. et al. (2004) Laboratory Investigation 84:562-572, which is incorporated herein by reference in its entirety for all purposes.

B. Monoclonal Antibodies

[0146] Monoclonal antibodies that specifically recognize the markers described herein can be made from antigen-containing fragments of the protein marker by the hybridoma

technique, for example, of Kohler and Milstein (Nature, 256:495-497, (1975); and U.S. Pat. No. 4,376,110). See also, Harlow & Lane, *Antibodies, A Laboratory Manual* (C.S.H.P., NY, 1988); and Goding et al., Monoclonal Antibodies: Principles and Practice (2d ed.) Acad. Press, N.Y. Human monoclonal antibodies that recognize the markers can be generated using, for example, the human B-cell hybridoma technique (Kosbor *et al.*, *Immunology Today* 4:72 (1983); for a review, *see also*, Larrick *et al.*, U.S. Pat. No. 5,001,065). The EBV-hybridoma technique is another approach to prepare monoclonal antibodies to the markers (see, e.g., Monoclonal Antibodies and Cancer Therapy, (1985) Alan R. Liss Inc., New York, N.Y., pp. 77-96).

C. Human Antibodies

[0147] Human monoclonal antibodies against a known antigen such as the markers disclosed herein can also be made using transgenic animals having elements of a human immune system (see, e.g., U.S. Pat. Nos. 5,569,825 and 5,545,806) or using human peripheral blood cells (Casali et al., 1986, Science 234:476). Human antibodies to the protein markers can be produced by screening a DNA library from human B cells according to the general protocol outlined by Huse et al., 1989, Science 246:1275. Antibodies binding to the protein markers are selected. Sequences encoding such antibodies (or binding fragments) are then cloned and amplified. The protocol described by Huse is often used with phage-display technology (see infra).

D. Humanized/Caninized and Chimeric Antibodies

[0148] Humanized or chimeric antibodies designed to reduce their potential antigenicity, without reducing their affinity for their target, are also provided. Preparation of chimeric, human-like and humanized antibodies have been described in the art (see, e.g., U.S. Pat. Nos. 5,585,089 and 5,530,101; Queen, et al., 1989, Proc. Nat'l Acad. Sci. USA 86:10029; and Verhoeyan et al., 1988, Science 239:1534). Humanized immunoglobulins have variable framework regions substantially from a human immunoglobulin (termed an acceptor immunoglobulin) and complementarity determining regions substantially from a non-human (e.g., mouse) immunoglobulin (referred to as the donor immunoglobulin). The constant region(s), if present, are also substantially from a human immunoglobulin.

[0149] The same approach taken in preparing humanized antibodies can also be used to incorporate the canine framework or constant region from dog immunoglobulins with the

complementarity determining or variable region from another animal such as mouse, rat, rabbit or hamster, for instance.

E. Antibodies Prepared by Phage Display

[0150] Antibodies produced by the phage display methods that have specific binding affinity for the markers described herein are also included. Antibodies of this type can be produced using established methods (see, e.g., Dower et al., WO 91/17271, WO 92/01047; and Vaughan et al., 1996, Nature Biotechnology, 14: 309). In these methods, libraries of phage are produced in which members display different antibodies on their outer surfaces. Antibodies are usually displayed as Fv or Fab fragments. Phage displaying antibodies with a desired specificity are selected by affinity enrichment to a desired marker.

F. Bispecific and Hybrid Antibodies

[0151] Hybrid antibodies that can bind to a plurality of the markers disclosed herein are also provided. In such hybrid antibodies, one heavy and light chain pair is usually from an antibody against one marker and the other pair from an antibody raised against another marker. This results in the property of multi-functional valency, i.e., the ability to bind at least two different epitopes simultaneously, where at least one epitope is the epitope to which the anti-complex antibody binds. Such hybrids can be formed by fusion of hybridomas producing the respective component antibodies, or by recombinant techniques.

[0152] A hybrid antibody can bind any combination of two or more markers described herein (e.g., any two markers selected from the group consisting of CD117, CD34, CD133, CD51/61, CD31, CD105, CD106, CD146, vWF, CD18 and CD45). Examples of particular pairs that can be recognized by the hybrid antibody include, but are not limited to: 1) CD34 and CD51/61; 2) CD117 and CD51/61; 3) CD34 and CD31; 4) CD117 and CD31; and 5) CD34 and CD105; and 6) CD117 and CD105.

G. Antibodies Conjugated to a Cytotoxic Agent

[0153] The various antibodies that are provided can be used in the preparation of immunotoxins designed to kill cells that express one or more markers disclosed herein that are associated with a hemangiosarcoma or angiosarcoma (e.g., cells from hemangiosarcomas, angiosarcomas and/or or leukocyte or leukemia or lymphoma cells). These immunotoxins typically include two components and can be used to kill selected cells expressing the desired

marker(s) in vitro or in vivo. One component is the "delivery vehicle," which is capable of delivering the toxic agent to a particular cell type, such as cells expressing the desired marker(s). The delivery vehicle in this instance is an antibody that specifically recognizes one or more of the markers described herein. To improve the selectivity in delivery, the antibody can be a hybrid antibody that binds at least two of the markers. The second component is a cytotoxic agent that usually is fatal to a cell when attached or adsorbed to the cell. The two components are chemically bonded to one another by any of a variety of well-known chemical procedures. For example, when the cytotoxic agent is a protein and the second component is an intact immunoglobulin, the linkage may be by way of heterobifunctional cross-linkers, e.g., SPDP, carbodiimide, glutaraldehyde, or the like. Further guidance regarding the production of various immunotoxins can be found, for example, in "Monoclonal Antibody-Toxin Conjugates: Aiming the Magic Bullet," Thorpe et al., Monoclonal Antibodies in Clinical Medicine, Academic Press, pp. 168-190 (1982), which is incorporated herein by reference in its entirety for all purposes. The components may also be linked genetically (see Chaudhary et al., Nature 339:394 (1989), incorporated herein by reference in its entirety for all purposes).

[0154] A variety of cytotoxic agents are suitable for use in immunotoxins. Cytotoxic agents can include radionuclides, such as Iodine-131 or other isotopes of iodine, Yttrium-90, Rhenium-188, and Bismuth-212 or other alpha emitters; a number of chemotherapeutic drugs, such as vindesine, methotrexate, adriamycin, and cisplatin; and cytotoxic proteins such as ribosomal inhibiting proteins like pokeweed antiviral protein, Pseudomonas exotoxin A, ricin, diphtheria toxin, ricin A chain, or an agent active at the cell surface, such as the phospholipase enzymes (e.g., phospholipase C).

VII. Pharmaceutical Compositions

[0155] The antibodies that are described herein, either in unconjugated form or conjugated to a cytotoxic agent, can serve as the active ingredient in pharmaceutical compositions formulated for use in the various applications disclosed herein. These pharmaceutical compositions may comprise a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are determined in part by the particular composition being administered, as well as by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of pharmaceutical compositions of the present invention (see, e.g., Remington's Pharmaceutical Sciences, 17th ed. 1985)).

[0156] Formulations suitable for administration include aqueous and non-aqueous solutions, isotonic sterile solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. In the practice of this invention, compositions can be administered, for example, orally, topically, intravenously, intraperitoneally, subcutaneously, intrathecally (for intracranial angiosarcoma, *e.g.*) or intratumorally when the tumor is in the subcutaneous space. The formulations of compounds can be presented in unit-dose or multi-dose sealed containers, such as ampoules and vials. Solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

[0157] The composition can be administered by means of an infusion pump, for example, of the type used for delivering chemotherapy to specific organs or tumors. Compositions of the inventions can be injected using a syringe or catheter directly into a tumor or at the site of a primary tumor prior to or after excision; or systemically following excision of the primary tumor. The compositions of the invention can be administered topically or locally as needed. For prolonged local administration, the enzymes may be administered in a controlled release implant injected at the site of a tumor. For topical treatment of a skin condition, the formulation may be administered to the skin in an ointment or gel.

[0158] The antibodies and pharmaceutical compositions thereof are particularly useful for parenteral administration, *i.e.*, subcutaneously, intramuscularly or intravenously. The compositions for parenteral administration will commonly comprise a solution of the antibody or antibody conjugate or a cocktail thereof dissolved in an acceptable carrier, preferably an aqueous carrier. A variety of aqueous carriers can be used, *e.g.*, water, buffered water, phosphate buffered saline (PBS), 0.4% saline, 0.3% glycine, human albumin solution and the like. These solutions are sterile and generally free of particulate matter. These compositions may be sterilized by conventional, well-known sterilization techniques. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, toxicity adjusting agents and the like, for example sodium acetate, sodium chloride, potassium chloride, calcium chloride and sodium lactate. The concentration of antibody in these formulations can vary widely, *i.e.*, from less than about 0.005%, usually at least about 1% to as much as 15 or 20% by weight and will be selected primarily based on fluid volumes, viscosities, etc., in accordance with the particular mode of administration selected.

[0159] The dose administered to a subject should be sufficient to effect a beneficial response in the subject over time (e.g., to reduce tumor size or tumor load). Early detection may allow for prolonged remission/survival since the tumor would not yet be clinically evident and would be more amenable to control or elimination using the aforementioned treatments. The optimal dose level for any patient will depend on a variety of factors including the efficacy of the specific modulator employed, the age, body weight, physical activity, and diet of the patient, and on the severity of a particular disease. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects that accompany the administration of a particular compound or vector in a particular subject.

VIII. Treatment Methods

[0160] Once a subject has been diagnosed using the methods provided herein as having an elevated risk of hemangiosarcoma or angiosarcoma, various treatment options can be implemented. One option is to conduct surgery to try to excise the tumor (if a tumor mass is grossly detectable) using standard surgical procedures in the art. Another option is to begin chemotherapy to try to eradicate the tumor. Of course combined treatment regimes using both surgery and chemotherapy can be implemented.

[0161] The antibodies and methods disclosed herein can in a sense be used "prophylactically" in that they can be used to detect "tumor cells" before the tumor is clinically detectable using existing state-of-the-art techniques. This means that treatment (e.g., administration of antibodies such as described herein) need not be administered blindly simply to ward off the disease. Rather treatments can be tailored to the subject's particular needs when the disease is still at a microscopic stage, thereby increasing the ability to prevent the tumor from progressing to clinically evident disease. Antibodies of the invention can be combined with antibodies against other molecules expressed in hemangiosarcomas. These include VEGF, c-KIT, and VEGFR-2.

[0162] In therapeutic applications, compositions (e.g., the antibodies and pharmaceutical compositions provided herein or to other molecules present on hemangiosarcomas as described above) are administered to a subject that already has been diagnosed as having a hemangiosarcoma or an angiosarcoma (e.g., using the methods provided herein). The composition is administered in an amount sufficient to cure or at least partially arrest the disease and its complications (e.g., to reduce the tumor size or arrest its spread). An amount adequate to accomplish this is defined as a "therapeutically effective dose." Amounts

effective for this use will depend upon the severity of the disease, the extent to which the tumor has metastasized, the age and weight of the subject, and other factors known to those of skill in the art, but generally range from about 1 to about 200 mg of antibody per dose, with dosages of from 5 to 70 mg per patient being more commonly used. Dosing schedules will vary with the disease state and status of the patient, and will typically range from a single bolus dosage or continuous infusion to multiple administrations per day (e.g., every 4-6 hours), or as indicated by the treating physician and the patient's condition.

[0163] It must be kept in mind that the materials of this invention may generally be employed in serious disease states, that is life-threatening or potentially life-threatening situations. In such cases, in view of the minimization of extraneous substances and the lower probability of "foreign substance" rejections which are achieved using certain antibodies described herein (e.g., chimeric or humanized antibodies),it is possible, and may be felt desirable by the treating clinician, to administer substantial excesses of these antibodies

IX. Other Applications

A. Monitoring High Risk Individuals for Disease

[0164] The methods that are provided can be used as part of a monitoring program for dogs at high risk for hemangiosarcomas and for humans at high risk for angiosarcomas (see supra). In such a program, the methods as described above are repeated at intervals determined by the responsible clinician to monitor whether there is any change in the status of the subject. In such methods, the expression data can be compared against a variety of different values. The data may be compared, for example, with a control that establishes a threshold level that provides a statistical basis for concluding whether the subject has hemangiosarcoma or angiosarcoma. Alternatively, the expression data may be compared with the expression level from the prior measurement. Depending upon the trend that is observed, the clinician may opt to simply further monitor the subject or initiate treatment.

B. Detection of residual disease in individuals undergoing treatment.

[0165] The markers used initially to detect and diagnose HSA can also be used to monitor disease progression, in individuals being treated for the disease. Such techniques allow

caregivers to monitor efficacy of treatment regimens and allow modification of those regimens based on an individual's response.

C. Identification of Cells Expressing Desired Markers

[0166] The methods that are provided herein can also be utilized to select and collect cells that express the desired markers. For example, cells that express markers characteristic of hemangiosarcoma or angiosarcoma (e.g., cells expressing a primitive hematopoietic cell marker, an endothelial cell marker but not a leukemia or leukocyte-specific cell marker) can be identified using the antibody tagging methods described above. These cells can be selected and collected using any of a variety of cell sorters that are known in the art.

[0167] Once collected, the cells may be cultured in suitable media at 37 °C for a period of time (e.g., 2 hr) to promote internalization of surface antigens with bound antibodies. The antibodies once taken up can be broken down by lysosomal or proteosomal degradation, with new synthesis or recycling to the surface of the characteristic antigens.

[0168] The collected cells can be used in a variety of other applications including, for example, to (1) identify early genetic lesions to define events in molecular progression; (2) identify genes or proteins that interact with environmental factors (e.g., cigarette smoke, other environmental carcinogens) to promote cancer; (3) derive novel diagnostic tests (e.g., new, improved antibodies); and (4) derive xenotransplant tumor models in mice (putting the human or dog tumor in an immunodeficient mouse (see, e.g., Akhtar et al, (2004) Neoplasia, 6:106-116) to test specific therapies in vivo.

X. Kits

[0169] Kits that can be used in the methods described herein are also provided. The kits in general include one or more species that can be used to detect the expression of one or more primitive hematopoietic cell markers, one or more endothelial cell markers and/or one or more leukemia or leukocyte-specific cell markers. The kits can thus be used, for example, to diagnose the presence of hemangiosarcomas in dogs and angiosarcomas in humans.

[0170] The species included in the kits that are used to detect the presence of the maker(s) can be an antibody that specifically binds to a marker, a probe that specifically hybridizes to a target sequence of a marker that encodes the marker, and/or a primer that can be utilized to specifically amplify a target sequence (e.g., a sequence that encodes a marker). The

antibodies, probes and/or primers are typically stored in suitable storage containers. The antibodies, probes and/or primers that are included in a kit may be labeled. If so, they are typically differentially labeled so antibodies, probes or primers specific for different markers have different labels. If the antibodies, probes or primers are not labeled, the kits can include suitable labels such as described herein. Kits may also include instructions that provide directions on how to use the antibodies, probes and/or primers to detect expression of the markers.

[0171] One example of a kit that can be used to distinguish between a hemangiosarcoma or angiosarcoma and leukemia contains a plurality of antibodies, including: (1) at least one antibody that specifically binds to a primitive hematopoietic cell marker, (2) at least one antibody that specifically binds to an endothelial cell marker, and (3) at least one antibody that specifically binds to a leukemia marker.

[0172] A specific example of such an antibody kit is one that contains an antibody that specifically binds CD117, an antibody that specifically binds CD34, an antibody that specifically binds CD51/61 and an antibody that binds CD18, CD45, CD3, CD21, CD5 or CD11b. Other kits include the same antibodies but include an antibody that can bind more than one leukemia or leukocyte-specific cell marker selected from the group consisting of CD18, CD45, CD3, CD21, CD5 and CD11b.

[0173] Other related kits, rather than including antibodies, include probes that specifically hybridize with nucleic acids encoding these particular markers and/or primers that specifically amplify nucleic acids encoding these particular markers.

[0174] The following examples are provided to illustrate certain aspects of the methods and compositions that are provided. As such, they should not be construed to limit the scope of the claimed invention.

EXAMPLE 1

Detection of Hemangiosarcomas in Dogs

I. Materials and Methods

A. Flow Cytometer

[0175] Beckman Coulter Epics XL flow cytometer, catalog #6605464 (Beckman Coulter, Inc., Hialeah, FL) running the Expo 32 software package, catalog #6605433 (Beckman

Coulter, Inc.), or BD FACSCalibur™ flow cytometer, catalog #343020 (Becton Dickinson Immunocytometry Systems, Mountain View, CA) running the BD CellQuest™ software package, catalog #342182 (BD Biosciences Immunocytometry Systems).

B. Antibodies

[0176] The testing described in this example was conducted with the antibodies listed below. However, these antibodies are available in different conjugate forms to provide flexibility for multiparameter flow cytometry, and all can be conjugated to a variety of fluorochromes using the AlexaFluor technology (Molecular Probes-Invitrogen, Eugene, OR, see http://www.probes.com/handbook/sections/0103.html). In addition, Serotec, Inc. and BD Biosciences offer a range of canine leukocyte typing reagents that can be incorporated into the assay (for example, see http://www.bdbiosciences.com/pdfs/brochures/03-7900030-3-A1.pdf).

[0177] a. Control antibody-1: Mouse IgG2a conjugated to phycoerythrin (PE), clone G155-178, catalog #559319, BD Pharmingen™ (San Diego, CA)

[0178] b. Control antibody-2: Mouse IgG1, k conjugated to fluorescein isothiocyanate (FITC), clone MOPC-2, catalog #1554679, BD Pharmingen™ (San Diego, CA)

[0179] c. Control antibody-3 and second-step reagent: Goat Anti-Mouse IgG & IgM (human adsorbed) conjugated to FITC, catalog #555988, BD Pharmingen™ (San Diego, CA)

[0180] d. Control antibody-4 and second-step reagent: Sheep Anti-Mouse IgG (whole molecule) F(ab')2 fragment, affinity isolated, conjugated to PE, catalog#P8547, Sigma-Aldrich (St. Louis, MO)

[0181] e. Anti-CD117 (c-Kit): clone ACK45 (Rat IgG2b, κ) conjugated to PE, catalog #553869, BD Pharmingen™ (San Diego, CA)

[0182] f. Anti-CD34: clone 2E9 (Ms IgG1, κ) conjugated to biotin, catalog #550427, BD Pharmingen™ (San Diego, CA)

[0183] g. Anti-CD51/61($\alpha_v\beta_3$ integrin): clone LM606 (Ms IgG1) conjugated to FITC, catalog #MAB1976F, Chemicon Intl., (Temecula, CA)

[0184] h. Anti-CD146 (MUC18, S-endo): clone P1H12 conjugated to biotin, catalog #MAB16985B, Chemicon Intl., (Temecula, CA)

[0185] i. Anti-CD105 (endoglin): clone 8E11 (Ms IgM, κ) conjugated to FITC, catalog #9810-02, Southern Biotechnology Associates (Birmingham, AL)

[0186] j. Anti-CD3: clone CA17.2A12 (Ms IgG1) conjugated to FITC, catalog #MCA1774F, Serotec, Inc. (Raleigh, NC)

[0187] k. Anti-canine B-cells (probably CD21): clone CA2.1D6 (Ms IgG1) conjugated to PE, catalog #MCA1781PE, Serotec, Inc. (Raleigh, NC)

[0188] l. Anti- CD5: clone YKIX322.3 (Rat IgG2a) conjugated to FITC, catalog #MCA1037F, Serotec, Inc. (Raleigh, NC)

[0189] m. Anti-LFA-1 (CD11a and/or CD18):

- Anti-CD11/18 (LFA-1): clone YKIX490.6.4 (Rat IgG2c) conjugated to FITC, catalog #MCA1040F, Serotec, Inc. (Raleigh, NC)
- Anti-CD18 (integrin ß2 chain): clone CA1.4E9 (Ms IgG1) unconjugated, catalog #MCA1780, Serotec, Inc. (Raleigh, NC)
- Anti-CD11a (integrin αL): clone HI111 (Ms IgG1, κ) conjugated to PE-Cy5 (BD Cy-Chrome™), catalog #551131, BD Pharmingen™ (San Diego, CA)

[0190] n. Anti-CD45: clone YKIX716.13 (Rat IgG2b) conjugated to PE, catalog #MCA1042PE, Serotec, Inc. (Raleigh, NC)

[0191] o. Anti-CD90 (Thy-1): clone YKIX337.217 (Rat IgG2b) unconjugated, catalog #MCA1036G, Serotec, Inc. (Raleigh, NC)

[0192] p. Anti-CD8: clone YCATE55.9 (Rat IgG1) conjugated to PE, catalog #MCA1039PE, Serotec, Inc. (Raleigh, NC)

[0193] q. Anti-CD4: clone YKIX302.9 (Rat IgG2a) conjugated to FITC, catalog #MCA1038F, Serotec, Inc. (Raleigh, NC)

[0194] r. Anti-CD14: clone M5E2 (Ms IgG2a, κ) conjugated to PE, catalog #555398, BD Pharmingen™ (San Diego, CA)

[0195] s. Anti-CD133 clone 13A4 (Rat IgG1, κ)conjugated to PE, catalog #12-1331-82, eBioscience (San Diego, CA)

[0196] t. Labeled streptavidin secondary reagents and labeling kits:

- Streptavidin-FITC (ZyMAX grade), catalog #43-8311, Zymed Laboratories (South San Francisco, CA)
- Streptavidin-PE, catalog #15-4301, Zymed Laboratories (South San Francisco, CA)
- Streptavidin-APC, catalog #SA1005, Caltag Laboratories (Burlingame, CA)
- Alexa Fluor® 647 Monoclonal Antibody Labeling Kit, catalog # A-20186, Invitrogen (Carlsbad, CA)
- Alexa Fluor® 488 Monoclonal Antibody Labeling Kit, catalog # A30006, Invitrogen (Carlsbad, CA)

C. Solutions

[0197] a. RBC lysis buffer: 8.3g/L of ammonium chloride (NH_4Cl) in 10 mM Tris, pH 7.2, catalog #R7757, Sigma-Aldrich (St. Louis, MO).

[0198] b. Phosphate buffered saline (PBS): 8g/L of sodium chloride (NaCl), 0.2g/L of potassium chloride (KCl), 1.44g/L of sodium phosphate (Na_2PO_4), 0.24g/L of potassium dihydrogen phosphate (KH_2PO_4).

[0199] c. Staining buffer: PBS with 0.1% (0.1 g/100 mL) of bovine serum albumin (BSA) and 0.1% sodium azide (NaN_3). Can substitute 0.1% fetal bovine serum (FBS) or 0.1% horse serum for BSA.

D. Dogs

[0200] Blood samples from health dogs and from dogs with biopsy-confirmed HSA, leukemia, or other splenic abnormalities (nodular hyperplasia, splenic hematoma) were obtained from a protocol reviewed and approved by the Institutional Animal Care and Use Committee and the Institutional Review Board of AMC Cancer Center. Dog owners were required to sign Informed Consent donating blood and tumor samples to Dr. Jaime Modiano at AMC Cancer Center/ University of Colorado Health Science Center. Whole blood samples were submitted from veterinary clinics throughout the United States and shipped at 4°C in EDTA using a priority overnight courier.

[0201] a. The Dal-4 cell line was derived from a male Dalmatian (see Fosmire, S. P., et al. (2004) Laboratory Investigation 84:562-572).

[0202] b. The DD-1 cell line was derived from a male Golden Retriever/Great Pyrenees mix (see Fosmire et al, Lab Invest, 2004).

[0203] c. Normal blood samples (unaffected dog controls) were obtained from seven dogs.

[0204] d. Samples were obtained from three dogs with leukemia (chronic lymphocytic leukemia or acute lymphoblastic leukemia).

[0205] e. Samples from affected dogs (biopsy-confirmed hemangiosarcoma) were obtained from 10 dogs.

II. Methods

A. Sample Acquisition

[0206] Cell lines were maintained as described by Fosmire, S. P., et al. (2004) Laboratory Investigation 84:562-572. Briefly, cells were fed three times weekly and passaged when they reached approximately 80% confluence in F12K media (ATCC, Manassas, VA) supplemented with 10% fetal bovine serum (Hyclone, Logan, UT), endothelial growth supplements (BD Biosciences, San Jose, CA), and 100,000 IU/ml of high molecular weight heparin (Sigma-Aldrich, St. Louis, MO).

[0207] Sterile venous blood samples from normal or affected dogs were obtained at the attending veterinarians' offices with Informed Consent of the owners by jugular venipuncture using 22 gauge needles and collected into 6-ml syringes using standard procedures of veterinary care. Blood was immediately transferred into evacuated 3-ml collection tubes containing EDTA.

[0208] Sterile thoracic, pericardial, or peritoneal effusions from affected dogs with thoracic, atrial, or splenic/hepatic hemangiosarcoma were collected by thoracocentesis, pericardiocentesis, or pleurocentesis using standard procedures of veterinary care. The effusions were immediately transferred into evacuated 3-ml collection tubes containing EDTA

B. Sample Preparation

[0209] Cell lines were detached using 0.1 mM EDTA and sterile cell scrapers to maintain the integrity of extracellular antigens, washed in PBS, and resuspended in staining buffer at the indicated concentrations for staining. In some procedures, cells were separated using a discontinuous Ficoll-hypaque gradient. HSA cells from four cell lines (DD-1, Dal-4, CHAD-G4.1, and CHAD-B7.4) were shown to float on the Ficoll-hypaque gradient with a similar buoyant density as other blood mononuclear cells.

[0210] Blood samples were subjected to red blood cell lysis using the following procedure. Blood was transferred to 15 ml conical tubes and centrifuged at 2,000 RPM (1,600 x *g*) for 15 min in a Sorvall RT-6000 centrifuge. Plasma was aspirated under vacuum and cells were washed in 10 volumes of PBS. Cell suspension was again centrifuged at the same speed for 15 minutes and supernatant was aspirated under vacuum. Cells were gently resuspended in 3 volumes of RBC lysis buffer and incubated at 37 °C. After 10 minutes, five volumes of PBS were added to the sample and the cells were centrifuged as above. The procedure was repeated twice. The remaining white blood cells (nucleated blood cells) were counted using an automated particle analyzer (Cell-Dyn 1200, Abbott Diagnostics, Santa Clara, CA), resuspended in staining buffer and divided into 3 x 10^5 to 1 x 10^6 per condition for staining.

C. Cell Labeling/Immunophenotyping

[0211] All procedures were at 4 °C (except where noted). Plates, cells and antibodies were kept on ice and centrifuged at 4 °C.

[0212] Preparation of Antibodies: Total staining volume was 25 µl/sample. Directly conjugated antibodies were used at 5 µl/sample (as recommended by the manufacturers for "1 test"); negative control antibodies were used at 2 µl/sample.

- Negative controls for Streptavidin-APC, Control antibody-FITC, Control antibody-PE were prepared individually, in pairs (APC-FITC, APC-PE, FITC-PE), and for three-color staining (APC-FITC-PE)
- Experimental conditions included anti-CD117-PE, anti-CD34-biotin, anti-CD51/CD61-FITC, and anti-CD45-PE prepared individually, in pairs, or for three-color staining (anti-CD117, anti-CD34, anti-CD51/CD61)

[0213] Red blood cells were lysed as described above. Cells were divided into aliquots of 5x10^5 cells in 100 µl of staining buffer into individual wells of a 96 well, round-bottom plate and centrifuged 2 min at 1,200 RPM using a plate adaptor in the RT-6000 centrifuge. Supernatant was discarded by inverting the plate and shaking vigorously without dislodging the pellets.

[0214] The blocking step included adding 10 µg/ml of non-specific antibody (e.g., goat IgG) in 5 µl for 10 min. Primary antibodies (negative controls or test antibodies) were then added as indicated above in a total volume of 25 µl and incubated at 4 °C for 30 min.

[0215] One hundred µl of staining buffer were then added to each well with gentle agitation and the plates were centrifuged as described above. The cell pellets were washed once more in 100 µl of staining buffer.

[0216] Samples that did not require a second step reagent (directly conjugated antibodies) were resuspended in 100 µl of staining buffer and transferred to 12 x 75 polystyrene tubes. Each sample was fixed in 2% neutral buffered formalin (by adding an additional 350 µl of staining buffer and 150 µl of 10% formalin). Samples were kept protected from light at 4 °C until analysis (<48 hr).

[0217] Samples that required a second step reagent (e.g., streptavidin-APC or anti-mouse FITC) were kept in the 96 well plates. Streptavidin-APC was used at a concentration of 2 µg/ml in 50 µl. Anti-mouse-FITC was used at 1 µg/ml in 50 µl. Samples were incubated for 20 min at 4 °C. At the end of the incubation period, 100 µl of staining buffer were added to each well with gentle agitation and the plates were centrifuged as described above. The cell pellets were washed once more in 100 µl of staining buffer.

[0218] Samples were resuspended in 100 µl of staining buffer and transferred to 12 x 75 polystyrene tubes. Each sample was fixed in 2% neutral buffered formalin (by adding an additional 350 µl of staining buffer and 150 µl of 10% formalin). Samples were kept protected from light at 4 °C until analysis (<48 hr).

D. Flow Cytometry

[0219] The instrument was calibrated daily as per the manufacturers' directions.

[0220] Cells were calibrated by running a positive control sample and a negative control sample to determine the extent of adjustment needed, if any, for the detectors and for color compensation.

[0221] Gates were set based on the negative control samples for cell populations based on light scatter and fluorescence emission.

[0222] Each sample was run on the "high" setting (>300 events/second) and 5000 to 20,000, or preferably, >100,000 events, were acquired in the light scatter gates.

[0223] Samples were analyzed by assessment of fluorescence for each antigen based on the whole population and based on gating of discrete subpopulations identified based on light scatter properties.

Blood from dogs with HSA, leukemia, and nodular hyperplasia was used to optimize flow cytometry conditions. Blood from fourteen dogs (seven with HSA, six normal, and one splenic

E. Threshold Level

[0224] The threshold for the analysis to date was based on negative controls.

[0225] A reference range can be established based on the numbers of detectable cells that have the test markers in a suitable population of disease-free, low risk dogs.

F. Controls

[0226] The controls included non-specific antibodies (to determine background staining that is not antigen-specific), blood from normal healthy dogs (to determine the extent of circulating cells that express the markers in these samples), leukemia cells (to distinguish between leukemia and hemangiosarcoma), and separation of normal cell populations and hemangiosarcoma cell populations in patient samples (see below).

III. Results

[0227] Results obtained from samples from the dogs listed above show that:

[0228] a. Canine hemangiosarcoma cells express approximately equivalent levels of CD34 and CD117;

[0229] b. Canine hemangiosarcoma cells express CD105, CD146, and CD51/CD61;

[0230] c. Canine hemangiosarcoma cells express variable levels of CD45 and CD14, which are generally distinguishable from the levels of CD45 and CD14 seen in canine leukocytes;

[0231] d. Circulating canine hemangiosarcoma cells express equivalent levels of CD34 to those seen in cultured canine hemangiosarcoma cells;

[0232] e. Canine hemangiosarcoma cells have unique light scatter patterns that are distinguishable from the light scatter seen in canine leukocytes (FIGS. 1A-1H and FIGS. 2A-2H). Canine hemangiosarcoma cells are large (they segregate to higher channels than leukocytes based on forward angle (or 0°) light scatter) and they are granular or have complex cytoplasm, resulting in right angle (or 90°) side scatter that is comparable to or higher than granulocytes (neutrophils, eosinophils, basophils).

[0233] Hemangiosarcoma cells and leukocytes or leukemia cells will be generally distinguishable based on light scatter by using a laser power setting that localizes the mean forward light scatter for the lymphoid cells to approximately channel 250 (of 1024) and the mean right angle light scatter for the lymphoid cells to approximately channel 25 (of 1024). Under these conditions, monocytes will usually localize at or near channel 400 for the mean forward light scatter and at or near channel 50 for the mean right angle light scatter; granulocytes will usually localize at or near channel 400 for the mean forward light scatter and at or near channel 300 for the mean right angle light scatter. Leukemia cells will usually localize between channels approximately 300 and approximately 1,000 for the mean forward light scatter and between channels approximately 25 and approximately 300 for the mean right angle light scatter. In contrast, hemangiosarcoma cells will usually localize between channels approximately 400 and approximately 1,000 for the mean forward light scatter and between channels approximately 300 and approximately 1,000 for the mean right angle light scatter. Certain types of leukemia cells and hemangiosarcoma cells may show overlapping light scatter properties. These include chronic granulocytic leukemia and possibly some types of myeloid leukemias such as megakaryocytic leukemia. In the subclinical stage where such circulating cells may not manifest as clinical disease, these diseases (leukemia and hemangiosarcoma) can be distinguished based on the expression of cell markers as described herein.

[0234] f. Normal canine leukocytes (FIGS. 1E and 1F) and canine leukemia cells (not shown) do not express CD51/CD61;

[0235] g. The patterns of expression of CD117/CD51/CD61 (FIGS. 1E-1H) and of CD45/CD51/CD61 (FIGS. 2E-2H) are distinct between canine leukocytes and canine hemangiosarcoma cells;

[0236] h. Blood from unaffected healthy dogs will be used to establish precise reference ranges for expression of CD34+, CD117+, CD51/CD61+, CD45, CD18+ in these cells, individually and in groups;

[0237] i. Blood from unaffected healthy dogs to which known concentrations of hemangiosarcoma cells are added will be used to define the sensitivity of the assay; and

[0238] j. Blinded samples similar to those used to define the sensitivity in (g) can be used to define the specificity of the assay.

IV. Conclusions

[0239] The results obtained herein demonstrate that multiparameter flow cytometry can be used to identify canine hemangiosarcoma cells in the circulation of dogs with this disease and to distinguish these malignant cells from normal canine leukocytes.

[0240] The same approach described in this example can be used to detect and diagnose angiosarcoma in human subjects. As described supra, antibodies specific for the markers that are analyzed in the analysis are commercially available.

EXAMPLE 2

Hemangiosarcoma Detection in Dogs by Determining HSA cell levels

[0241] The light scatter parameters of HSA cells as defined in Example 1 were used to define the flow cytometric light scatter parameters of HSA cells versus normal leukocytes to determine HSA levels in patient samples.

[0242] The percentage of cells co-expressing one or more markers of immature bone marrow precursor cells (c-KIT, CD34, CD133) and $\alpha_v\beta_3$-integrin ranged between 0.5% and 2.0% for dogs with HSA, and was generally less than 0.1% for unaffected dogs (0.03% in a dog with splenic hematoma, see FIGS. 5A-5C, except for two highly conditioned, healthy dogs that had 0.2-0.3% EPCin the circulation. The mean, median, standard deviation, and standard error of the mean for each group were 0.90, 0.93, 0.26, and 0.10 for dogs with HSA, and 0.10, 0.04, 0.13 and 0.05 for unaffected dogs. Non-parametric analyses (analysis of variance, Wilcoxon rank test, Wilcoxon two-sample test, and Kruskal-Wallis test) all indicate the two groups were significantly different from each other ($p<0.01$); working on the assumption that EPC in the circulation are rare events that follow a Poisson distribution, the results show a trend for increased frequency ($t=2.22$) of EPC in the blood from dogs with biopsy confirmed HSA.

[0243] When the same criteria were applied using antibodies against peripheral blood leukocytes (CD3, CD21, CD11b), the frequency of gated cells was also $<<0.1\%$, whether applied to normal or leukemic white blood cells.

[0244] Analyses was done of samples in which leukocytes were excluded by using a "dump gate" for T cells (CD5), B cells (CD21), and granulocytes (CD11b) labeled with FITC. Two dogs were unaffected, while another had HSA of the right atrium. The frequency of cells

obtained using this method was similar to that obtained without using the "dump gate" both for the unaffected dogs (0%, 0.01%) and for the affected dog (0.5%), although interpretation was much simpler due to the reduced background noise.

EXAMPLE 3

Expression of HSA Markers in Established Cell Lines

[0245] Four established canine cell lines of HSA origin were monitored for expression of bone marrow precursor cell markers (*e.g.*, c-KIT, CD34, CD133), using flow cytometry and/or immunofluorescence techniques described in Example 1. Differences in expression from other cell lineages of hematopoietic differentiation, as well as from mature, fully differentiated, leukocytes and vascular endothelial cells and proteins that define lineage commitment to T-lymphocytes (CD3), B-lymphocytes (CD21), granulocytes (CD11b), and vascular endothelial cells (CD105, CD146, $\alpha_v\beta_3$-integrin) are shown in Table 2.

Table 2

Surface Markers	**Cell Lines**			
	DD-1	Dal-4	CHAD G4.1	CHAD B7.4
CD3	-	-	-	-
CD11b	-	-	-	-
CD14	+[1]	-	-	-
CD21	-	-	-	-
CD34	+	+	+	-
CD45	+	+[2]	+[1]	+[1]
$\alpha_v\beta_3$-integrin (CD51/CD61)	+	+	+	+
CD105	+	+	+	+
CD133	+	+	+	+
c-KIT (CD117)	+	+	+	+
CD146	+	+	+	+

[1] Expression was only upregulated in the presence of endothelial growth factors

[2] A subpopulation of approximately 5% of the cells was positive

[0246] Each of the cell lines is positive for c-KIT, CD133, $\alpha_v\beta_3$-integrin, CD105 and CD146; none express prototypical leukocyte markers CD3, CD21 or CD11b, and the expression of CD34, CD45 and CD14 is variable (See, *e.g.*, FIGS. 4A-4P). These cell lines all express CD105, CD146 and $\alpha_v\beta_3$-integrin. While other hematopoietic tumors (leukemias, mast cells tumors and multiple myeloma) can express one or more of these markers, the pattern of co-expression where cells have c-KIT/CD34/CD133 and $\alpha_v\beta_3$-integrin, but no detectable leukocyte markers (CD3, CD21, or CD11b), seems to be uniquely associated with HSA.

[0247] It is noteworthy that under conditions of logarithmic growth certain subpopulations in the cultures lacked expression of CD133, CD105, and CD146, and the density of receptor expression was also variable. HSA cell lines have also been shown to express VEGFR2. The levels of expression for CD45, CD34 and CD105 increase in DD-1 and CHAD-B7.4 cells when they are cultured in the presence of endothelial growth factors as compared to basal media (F12K media supplemented with 10% fetal bovine serum). In addition, when the lines are maintained in culture for extended periods of time (*e.g.*, more than 10-15 passages), there is a tendency by the cells to down regulate expression of CD133, c-KIT, CD34, and CD105. For example, CD34, which was positive in Dal-4 cells and in early passage DD-1 cells, was lost in DD-1 cells after several passages (see FIGS. 4D and 4L). Various non-mutually exclusive possibilities can account for these changes: (1) expression of these proteins is unnecessary in the artificial environment of tissue culture, (2) the cell lines are genetically unstable and "drift", or (3) "stem cells" in the populations are lost at the expense of differentiated progeny.

*****

[0248] All publications, patents and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual publication, patent or patent application were specifically and individually.

WHAT IS CLAIMED IS:

1. A method for early detection of hemangiosarcoma or angiosarcoma in a subject, the method comprising:

(a) providing a population of cells from the subject;

(b) determining (i) the level at which cells within the cell population concurrently express a plurality of cell markers, the plurality of cell markers comprising at least one primitive hematopoietic cell marker and at least one endothelial cell marker, and (ii) whether or not cells within the cell population express at least one leukemia cell marker or leukocyte-specific cell marker, wherein

the at least one primitive hematopoietic cell marker is selected from the group consisting of CD117, CD34, and CD133;

the at least one endothelial cell marker is selected from the group consisting of CD51/CD61, CD31, CD105, CD106 CD146 and von Willebrand Factor (vWF); and

the at least one leukemia cell marker or leukocyte-specific cell marker is selected from the group consisting of CD18, CD3, CD5, CD21 and CD11b; and

(c) comparing the level at which cells in the cell population concurrently express the plurality of cell markers with a control level of concurrent expression of the markers, wherein (1) an increase in the expression level of the plurality of cell markers relative to the control expression level, and (2) the absence of expression of CD18, CD3, CD5, CD21 and/or CD11b collectively are an indication of hemangiosarcoma or angiosarcoma.

2. The method of claim 1, wherein the determining comprises

incubating the population of cells with labeled antibodies that specifically bind the at least one primitive hematopoietic cell marker, the at least one endothelial cell marker and the at least one one leukemia cell marker or leukocyte-specific cell marker under conditions such that cells expressing the markers become labeled, and wherein antibodies that bind different markers are differentially labeled; and

detecting labeled cells by multiparameter flow cytometry.

3. The method of claim 1, wherein the subject is a dog and the method detects hemangiosarcoma.

4. The method of claim 3, wherein the dog is a purebred dog from a breed where the prevalence of hemangiosarcoma is high, or a mix breed dog containing predominant derivation from a breed where the prevalence of hemangiosarcoma is high.

5. The method of claim 4, wherein the breed is selected from the group consisting of a Golden Retriever, a German Shepherd, a Portuguese Water Dog, or a Skye Terrier.

6. The method of claim 1, wherein the subject is a human and the method detects angiosarcoma.

7. The method of claim 6, wherein the human has a risk factor for angiosarcoma, the risk factor being prior exposure to vinyl chloride, prior exposure to ionizing radiation, mutation in the Von Hippel-Lindau gene or infection with human immunodeficiency virus (HIV).

8. The method of claim 1, wherein the population of cells is obtained from a blood sample.

9. The method of claim 1, wherein the determining comprises determining the level at which cells in the population of cells concurrently express at least one primitive hematopoietic cell marker selected from the group consisting of CD117, CD133 and CD34.

10. The method of claim 1, wherein the determining comprises determining the level at which cells in the population of cells concurrently express at least one leukemia cell marker or leukocyte-specific cell marker selected from the group consisting of CD18, CD3, CD5, CD21 and CD11b.

11. The method of claim 1, wherein the determining comprises determining the level at which cells in the population of cells concurrently express CD117, CD34, CD51/CD61, and CD18, and/or CD3, CD5, CD21 or CD11b.

12. The method of claim 1, wherein

the determining step further comprises determining the fraction of cells in the cell population that concurrently express the plurality of cell markers;

the control is a threshold level representative of the fraction of cells that currently express the plurality of cell markers in a control population; and

the comparing step comprises comparing the fraction of cells in the cell population that concurrently express the plurality of cell markers with the threshold level.

13. The method of claim 1, wherein the expression level of the plurality of cell markers is determined at the mRNA level.

14. The method of claim 1, wherein the expression level of the plurality of cell markers is determined at the protein level.

15. The method of claim 12, wherein

the subject is a dog and the method detects hemangiosarcoma;

the population of cells is obtained from a blood sample; and

the determining step further comprises (i) incubating the population of cells with differentially labeled antibodies that specifically bind to CD117, CD34, CD51/61, and CD 18 and/or CD3, CD5, CD21 or CD11b under conditions such that cells expressing CD117, CD34, CD51/61, and CD 18 and/or CD3, CD5, CD21 or CD11b become labeled; and (ii) detecting labeled cells by multiparameter flow cytometry.

16. A method for early detection of hemangiosarcoma or angiosarcoma, the method comprising:

(a) obtaining a population of cells from the subject; and

(b) determining the level at which cells within the cell population concurrently express at least one primitive hematopoietic cell marker, at least one endothelial cell marker and at least one leukemia cell marker or leukocyte-specific cell marker, wherein

the at least one primitive hematopoietic cell marker is selected from the group consisting of CD117, CD34 and CD133;

the at least one endothelial cell marker is selected from the group consisting of CD51/CD61, CD31, CD105, CD106, CD146 and von Willebrand Factor (vWF);

the at least one leukemia cell marker or leukocyte-specific cell marker is selected from the group consisting of CD18, CD3, CD5, CD21 and CD11b; and wherein

the lower the expression of the at least one leukemia marker or leukocyte-specific cell marker and the greater the concurrent expression of the at least one

primitive hematopoietic cell marker and the at least one endothelial cell marker, the greater the likelihood of hemangiosarcoma or angiosarcoma.

17. The method of claim 16, wherein the subject is a dog and the method detects hemangiosarcoma.

18. The method of claim 16, wherein the subject is a human and the method detects angiosarcoma.

19. The method of claim 16, wherein the population of cells is obtained from a blood sample.

20. The method of claim 16, wherein the determining step comprises

incubating the population of cells with labeled antibodies that specifically bind the at least one primitive hematopoietic cell marker, the at least one endothelial cell marker and the at least one leukemia cell marker or leukocyte-specific cell marker under conditions such that cells expressing the markers become labeled, and wherein antibodies that bind different markers are differentially labeled; and

detecting labeled cells by multiparameter flow cytometry.

21. A method for distinguishing between hemangiosarcoma and leukemia, the method comprising:

(a) providing a cell population from a subject suspected of having hemangiosarcoma or leukemia; and

(b) determining (i) whether cells in the cell population concurrently express a plurality of markers associated with a proliferative primitive hematopoietic cell, wherein the plurality of markers comprise at least one primitive hematopoietic cell marker and at least one endothelial cell marker, and (ii) whether the cells in the cell population express at least one leukemia marker or leukocyte-specific cell marker, wherein

the at least one primitive hematopoietic cell marker is selected from the group consisting of CD117, CD34 and CD133;

the at least one endothelial cell marker is selected from the group consisting of CD51/CD61, CD31, CD105,CD146 and von Willebrand Factor (vWF); and

the at least one leukemia marker or leukocyte-specific cell marker is selected from the group consisting of CD18, CD3, CD5, CD21 and CD11b;

and wherein

the concurrent expression of the plurality of cell makers and the expression of the at least one leukemia marker or leukocyte-specific cell marker is an indication that the cell sample contains leukemia cells, whereas

the concurrent expression of the plurality of cell markers but not expression of the at least one leukemia marker or leukocyte-specific cell marker is an indication that the cell population contains cells from a hemangiosarcoma.

22. A kit for use in distinguishing between hemangiosarcoma and leukemia, the kit comprising a plurality of antibodies that comprise:

(a) an antibody that specifically binds a primitive hematopoietic cell marker that is selected from the group consisting of CD117, CD34 and CD133;

(b) an antibody that specifically binds an endothelial cell marker that is selected from the group consisting of CD51/CD61, CD31, CD105, CD106, and CD146; and

(c) an antibody that specifically binds to a leukemia cell marker or leukocyte-specific cell marker that is selected from the group consisting of CD18, CD3, CD5, CD21 and CD11b.

23. The kit of claim 22, wherein the antibodies are labeled such that antibodies that bind different markers bear different labels.

24. The kit of claim 23, where the plurality of antibodies comprise an antibody that specifically binds CD117, an antibody that specifically binds CD34, an antibody that specifically binds CD51/61, and an antibody that specifically binds CD18, and an antibody that specifically binds CD3, CD5, CD21 or CD11b.

25. The kit of claim 23, where the plurality of antibodies comprise an antibody that specifically binds CD117, an antibody that specifically binds CD34, an antibody that specifically binds CD51/61, an antibody that specifically binds CD18, or an antibody that specifically binds CD3, CD5, CD21 or CD11b.

26. The kit of claim 22, further comprising instructions on how to use the plurality of antibodies to distinguish between a hemangiosarcoma and leukemia.

27. A method of treating a dog having or suspected of having hemangiosarcoma, the method comprising administering an antibody to the dog, wherein the antibody specifically binds CD51/CD61, CD31, or CD105.

28. The method of claim 27, wherein the antibody is linked to a cytotoxic agent.

29. A method of treating a dog having or suspected of having hemangiosarcoma, the method comprising administering an antibody to the dog, wherein the antibody is a bispecific antibody that can specifically bind a pair of antigens, wherein the pair is selected from the group consisting of 1) CD34 AND CD51/CD61, 2) CD117 AND CD51/CD61, 3) CD34 AND CD31, 4) CD117 AND CD31, 5) CD34 AND CD105, and 6) CD117 AND CD105.

30. The method of claim 29, wherein the bispecific antibody is linked to a cytotoxic agent.

31. A method of collecting cells from a hemangiosarcoma or an angiosarcoma, the method comprising:

(a) providing a cell population suspected of containing cells from a hemangiosarcoma or angiosarcoma;

(b) labeling cells in the cell population that concurrently express at least one primitive hematopoietic cell marker and at least one endothelial cell marker, wherein

the at least one primitive hematopoietic cell marker is selected from the group consisting of CD117, CD34 and CD133;

the at least one endothelial cell marker is selected from the group consisting of CD51/CD61, CD31, CD105, CD106, CD146 and von Willebrand Factor (vWF); and

(c) determining whether or not the cells in the cell population express at least one leukemia cell marker or leukocyte-specific cell marker, wherein the at least one leukemia cell marker or leukocyte-specific cell marker is is selected from the group consisting of CD18, CD3, CD5, CD21 and CD11b; and

(d) separating the labeled cells from the unlabeled cells if the labeled cells do not express the least one leukemia cell marker or leukocyte-specific cell marker, thereby collecting cells that are from a hemangiosarcoma or an angiosarcoma.

32. A population of cells comprising early proliferative endothelial cells that are bound to a plurality of labeled antibodies, the plurality of antibodies comprising:

(a) an antibody that specifically binds a primitive hematopoietic cell marker that is selected from the group consisting of CD117, CD34 and CD133; and

(b) an antibody that specifically binds an endothelial cell marker that is selected from the group consisting of CD51/CD61, CD31, CD105, CD106 and CD146.

33. A method for detecting residual disease in a subject undergoing . treatment for hemangiosarcoma or angiosarcoma, the method comprising:

(a) providing a population of cells from the subject;

(b) determining (i) the level at which cells within the cell population concurrently express a plurality of cell markers, the plurality of cell markers comprising at least one primitive hematopoietic cell marker and at least one endothelial cell marker, and (ii) whether cells within the cell population express at least one leukemia cell marker or leukocyte-specific cell marker, wherein

the at least one primitive hematopoietic cell marker is selected from the group consisting of CD117, CD34, CD133;

the at least one endothelial cell marker is selected from the group consisting of CD51/CD61, CD31, CD105, CD106 CD146 and von Willebrand Factor (vWF); and

the at least one leukemia cell marker or leukocyte-specific cell marker is selected from the group consisting of CD18, CD3, CD5, CD21 and CD11b; and

(c) comparing the level at which cells in the cell population concurrently express the plurality of cell markers with the level of concurrent expression of the markers in a control cell population, wherein (1) an increase in the expression level of the plurality of cell markers relative to the expression level of the markers in the control cell population, (2) an absence of expression of CD18, CD3, CD5, CD21 or CD11b are collectively an indication of residual disease in the subject being treated for hemangiosarcoma or angiosarcoma.

34. The method of claim 33, wherein the subject is a dog and the residual disease is hemangiosarcoma.

35. The method of claim 33, wherein the subject is a human and the residual disease is hemangiosarcoma.

36. The method of claim 33, wherein determining comprises

incubating the population of cells with first, second and third antibodies that specifically bind the at least one primitive hematopoietic cell marker, the at least one endothelial cell marker, and the at least one leukemia cell marker or leukocyte-specific cell marker respectively under conditions such that antibodies bind to the markers,

wherein the first, second and third antibodies bound to the markers are differentially labeled;

and detecting cells to which are bound labeled antibodies by multiparameter flow cytometry.

37. The method of any of claims 2, 20 or 36, wherein one or more of the antibodies is labeled using a secondary detection scheme to increase sensitivity of the method.

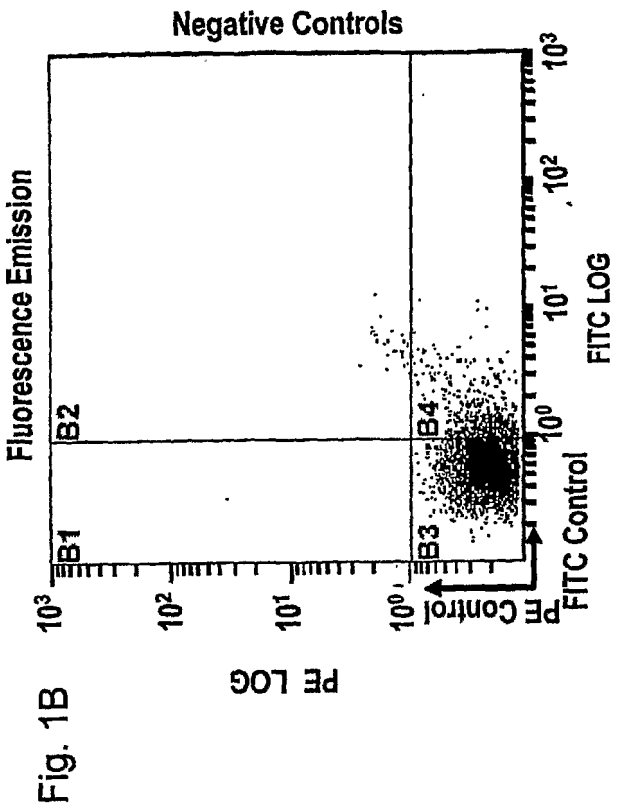


Fig. 1B

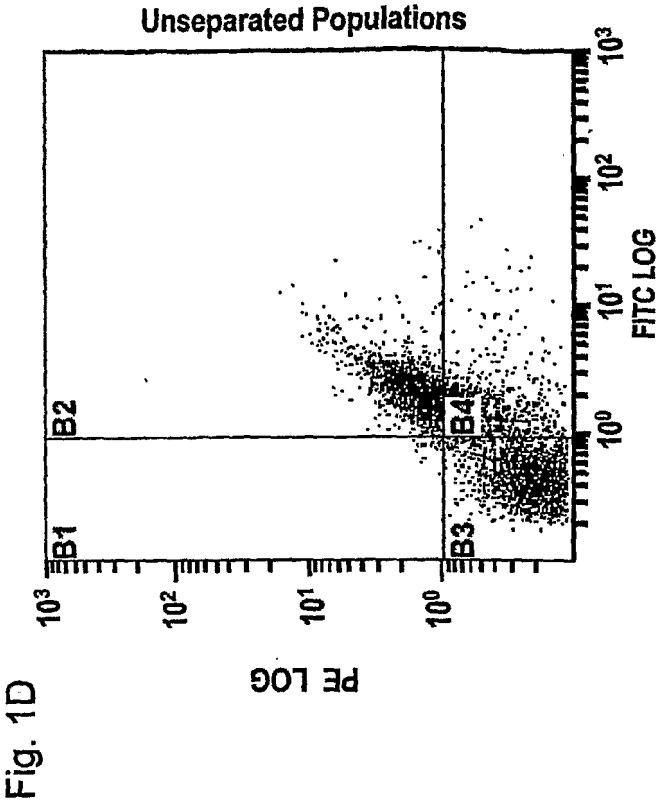


Fig. 1D

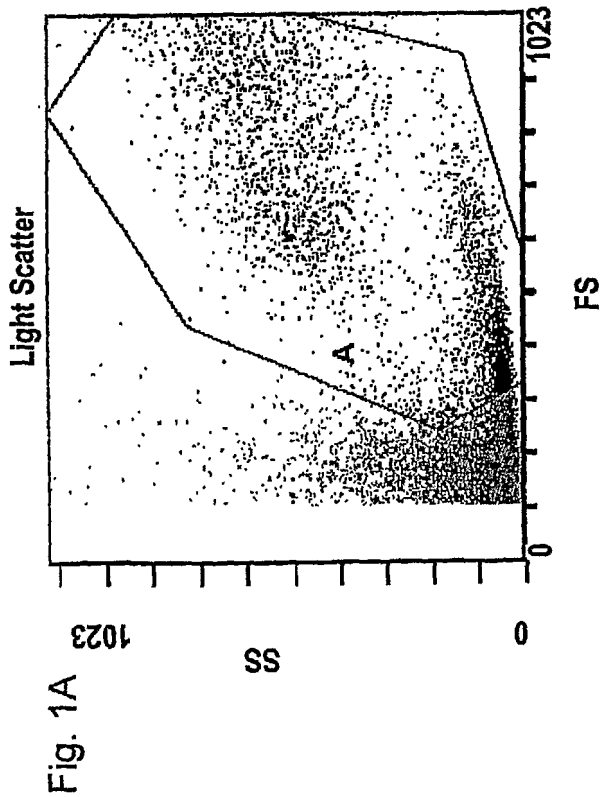


Fig. 1A

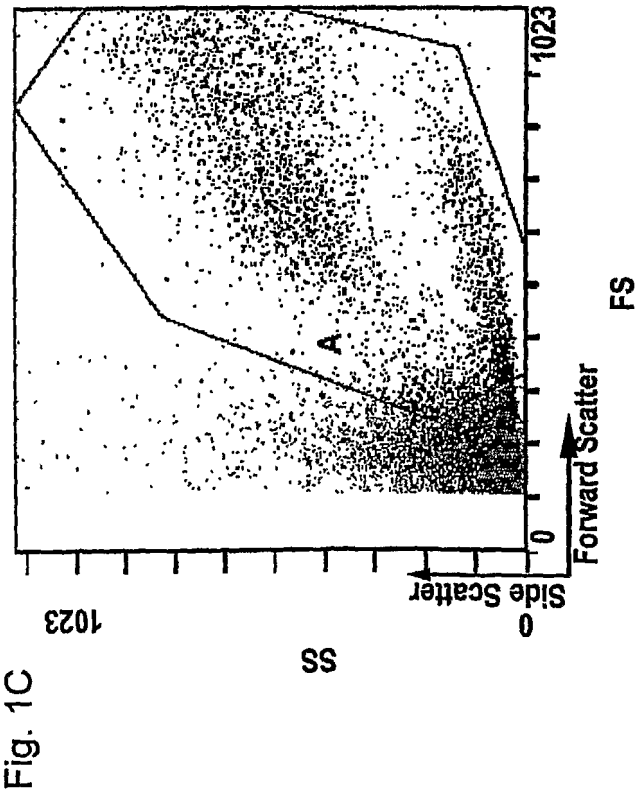


Fig. 1C

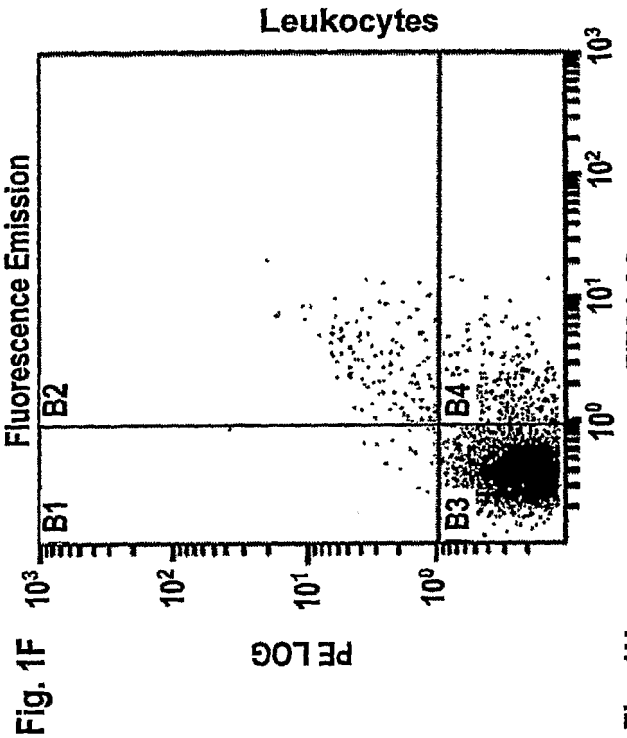


Fig. 1F

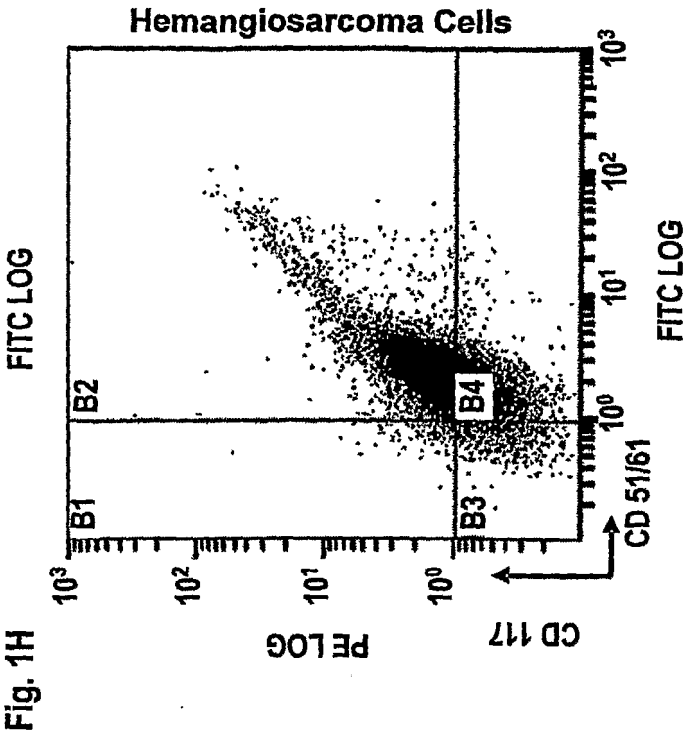


Fig. 1H

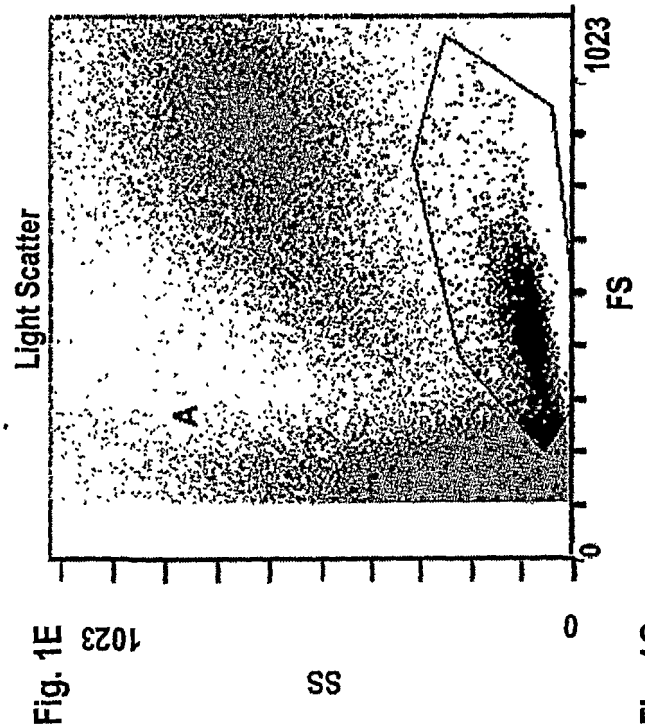


Fig. 1E

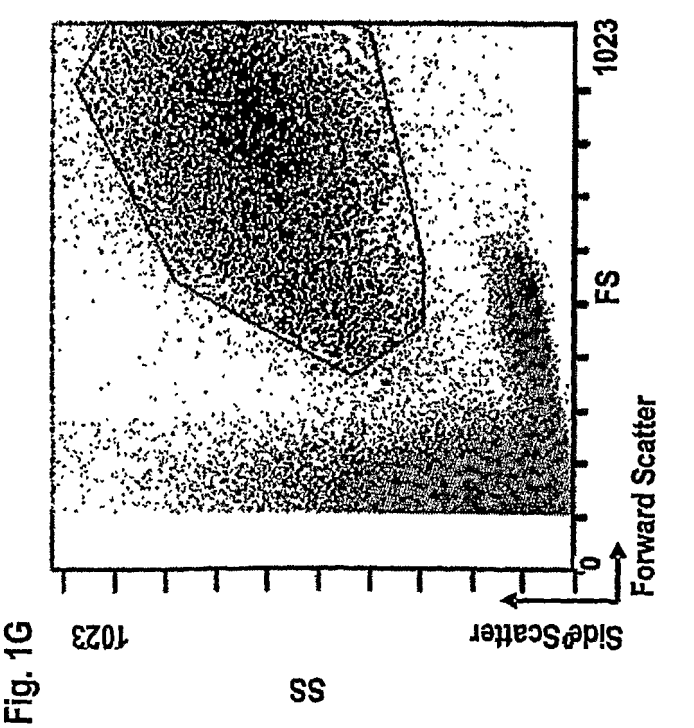


Fig. 1G

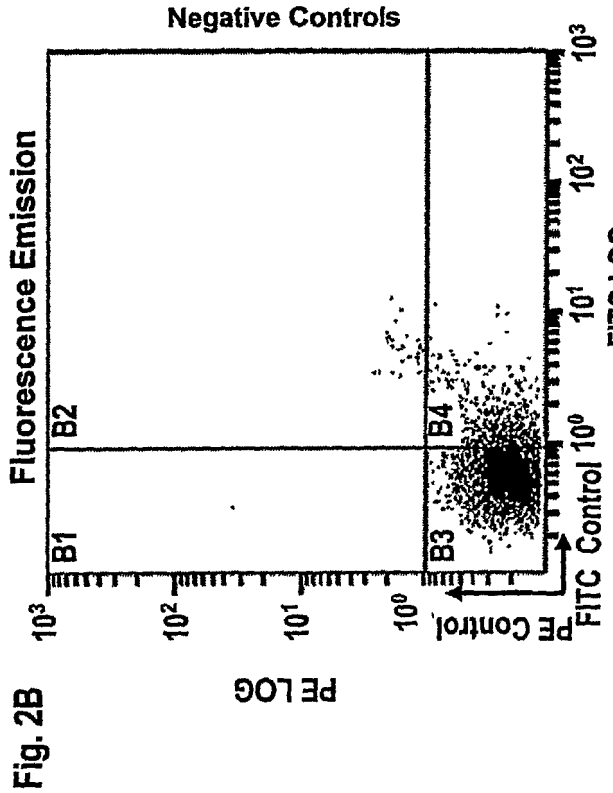


Fig. 2B

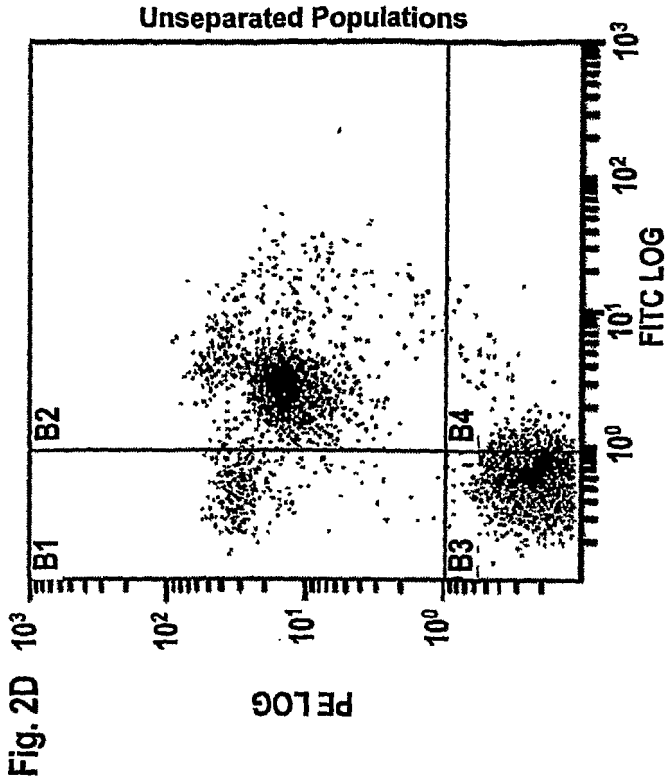


Fig. 2D

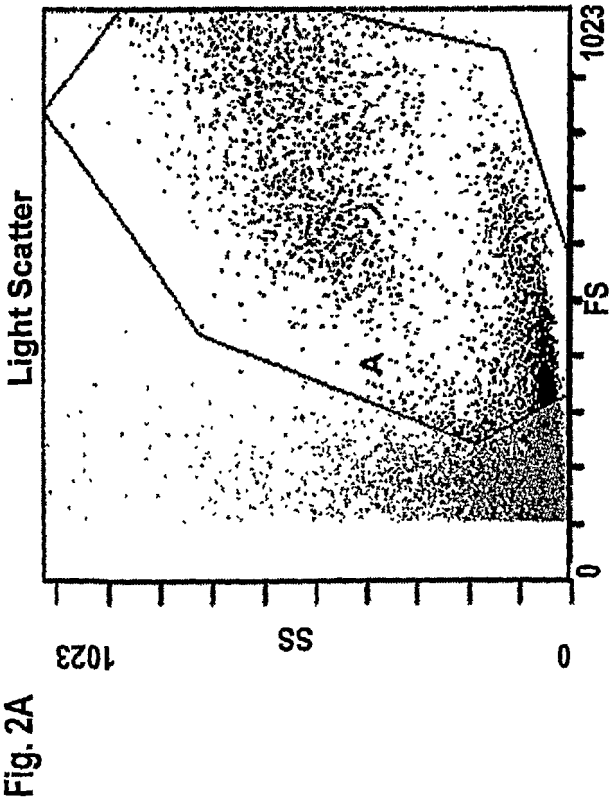


Fig. 2A

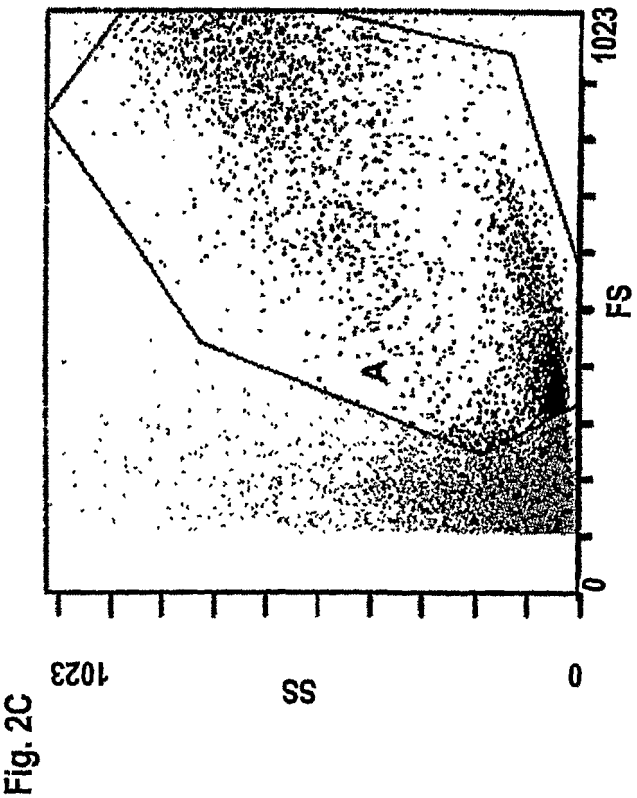


Fig. 2C

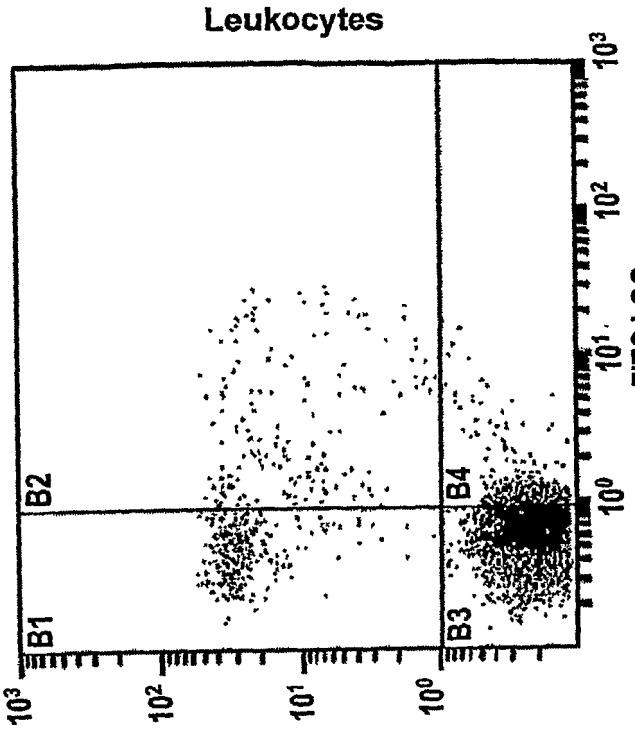


Fig. 2F

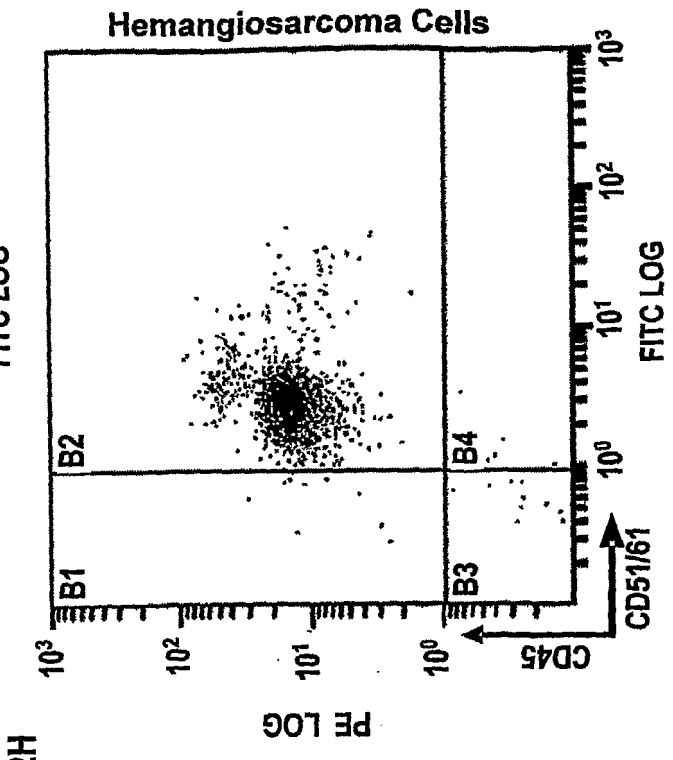


Fig. 2H

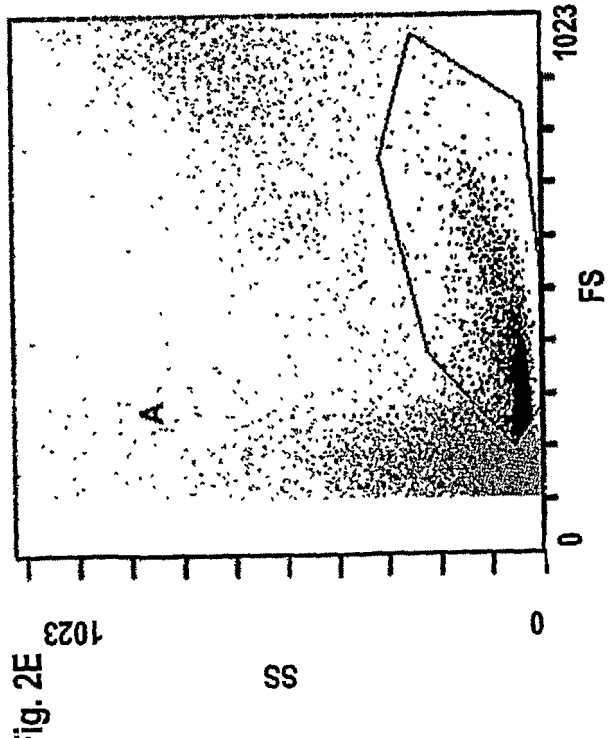


Fig. 2E

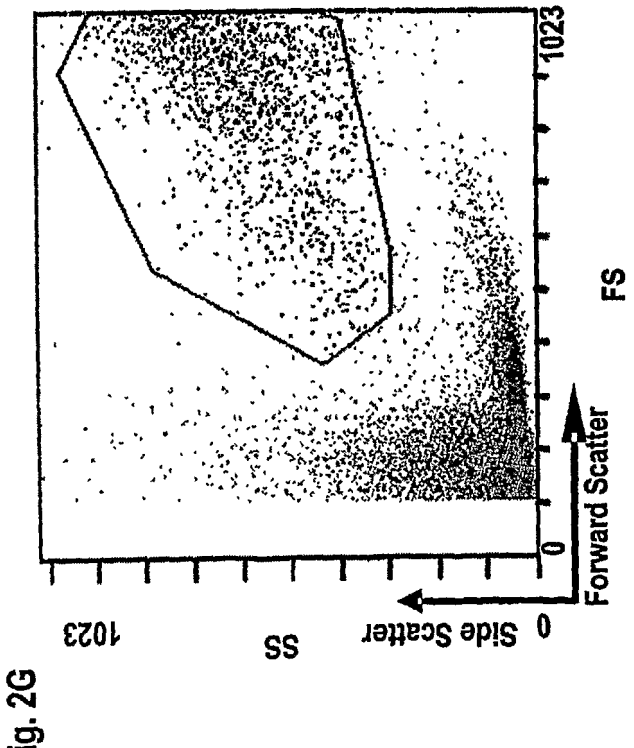
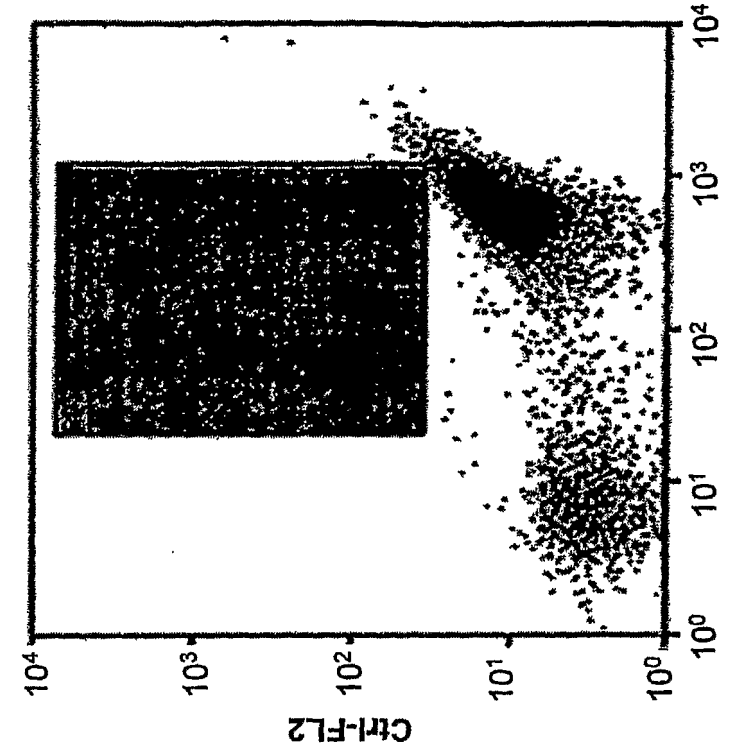


Fig. 2G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10^1
10^2
10^3
10^4

Fig. 3B

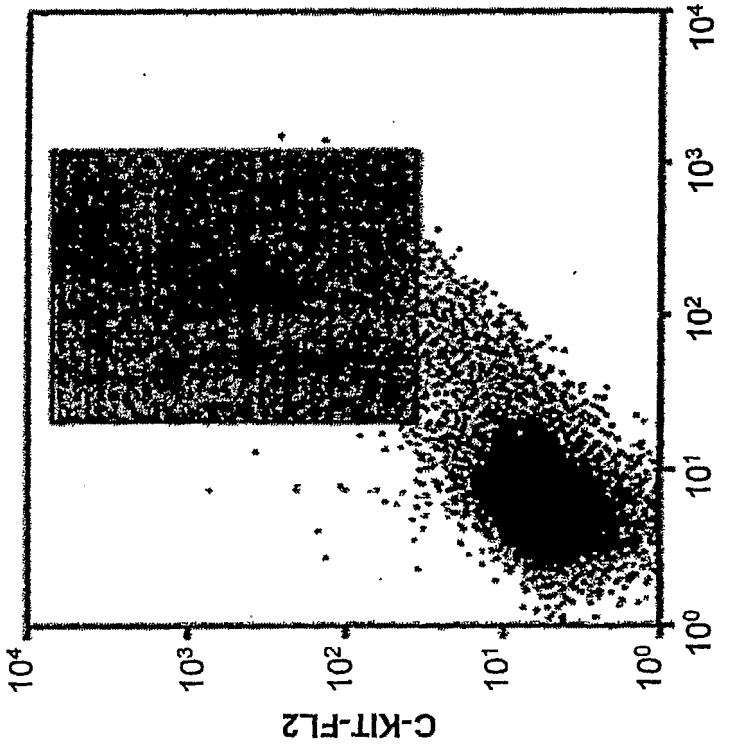

a_v/β_3 integrin-FL-1
C-KIT-FL2
10^0
10^1
10^2
10^3
10^4

Fig. 3A

DD-1

Fig. 4A Control

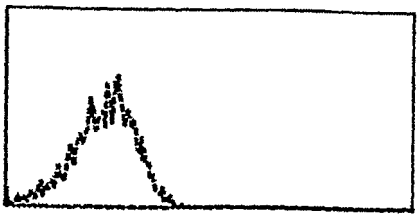


Fig. 4B C-Kit

Fig. 4C CD133

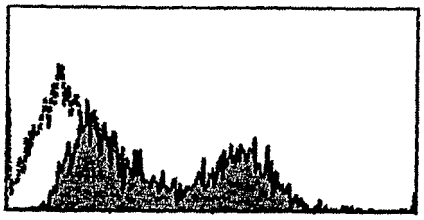


Fig. 4D CD34

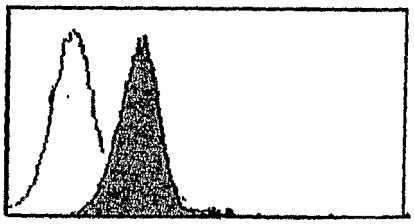


Fig. 4E CD45

Fig. 4F CD14

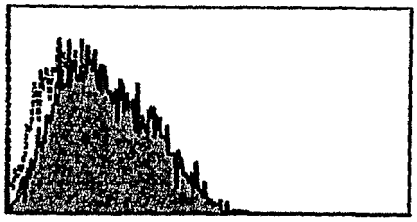


Fig. 4G $\alpha_v\beta_3$-integrin

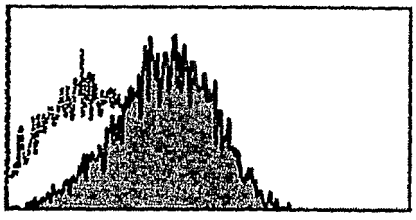
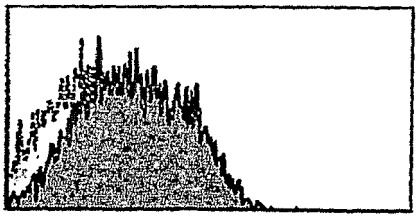


Fig. 4H CD146



Dal-4

Fig. 4I

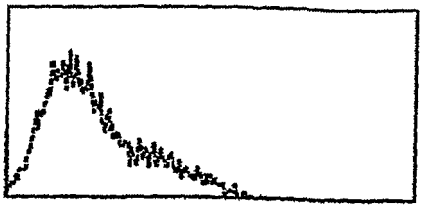


Fig. 4J

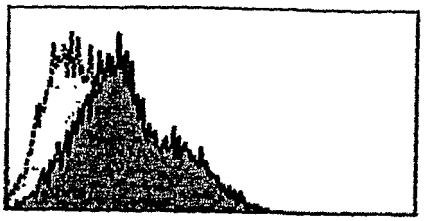


Fig. 4K

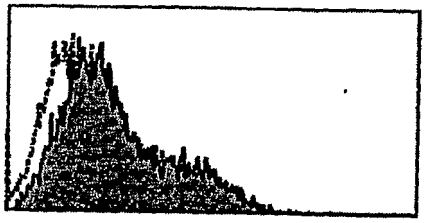
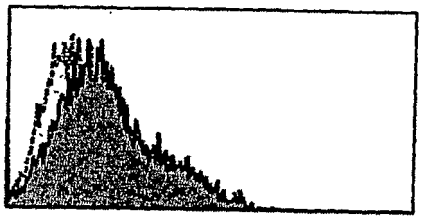


Fig. 4L



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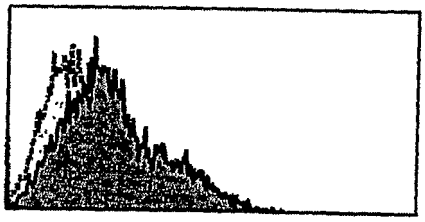


Fig. 4N

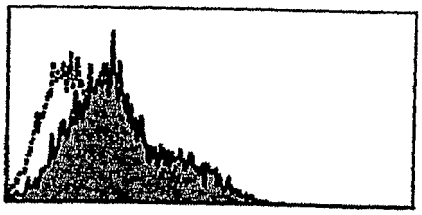


Fig. 4O

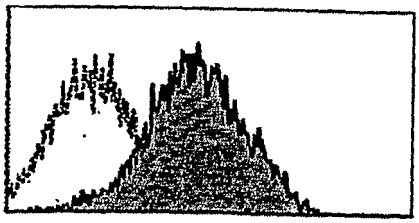


Fig. 4P

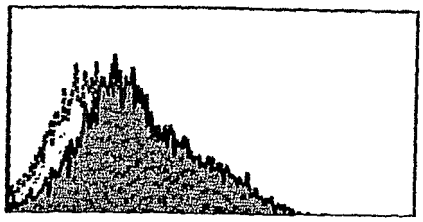


Fig. 5A Splenic Hematoma

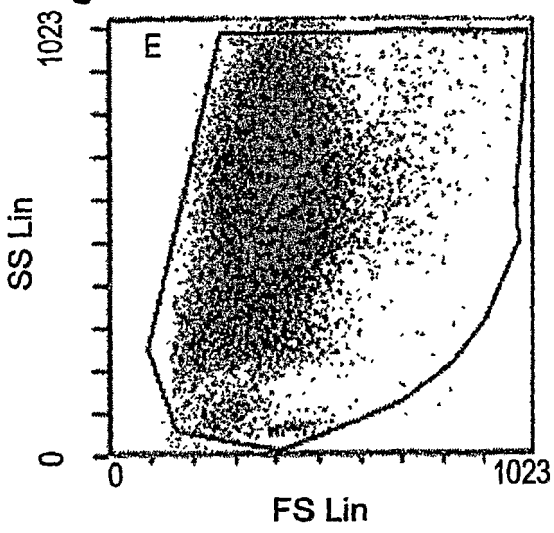


Fig. 5B

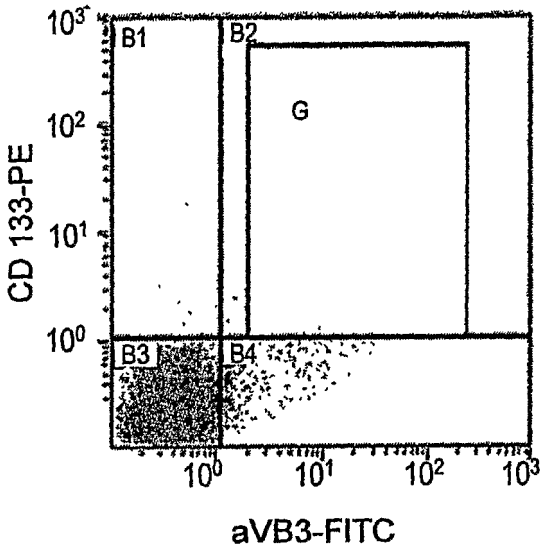


Fig. 5C

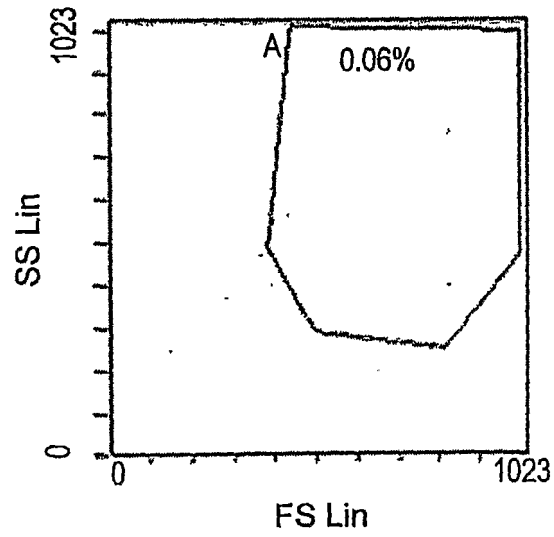


Fig. 5D Hemangiosarcoma

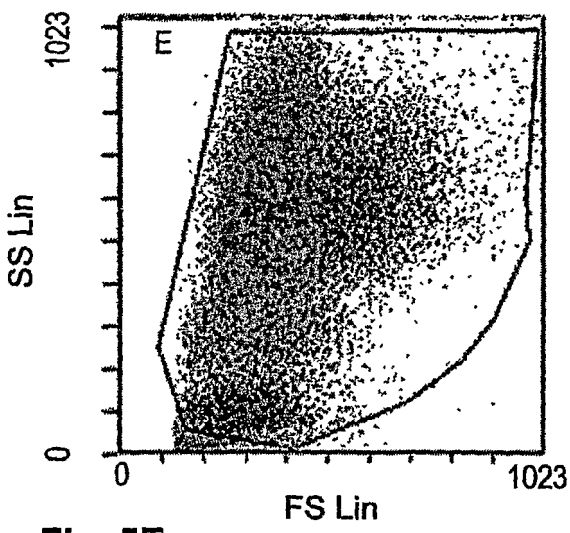


Fig. 5E

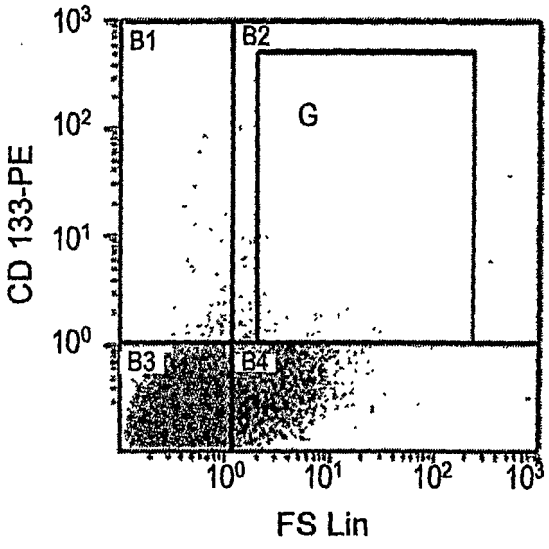
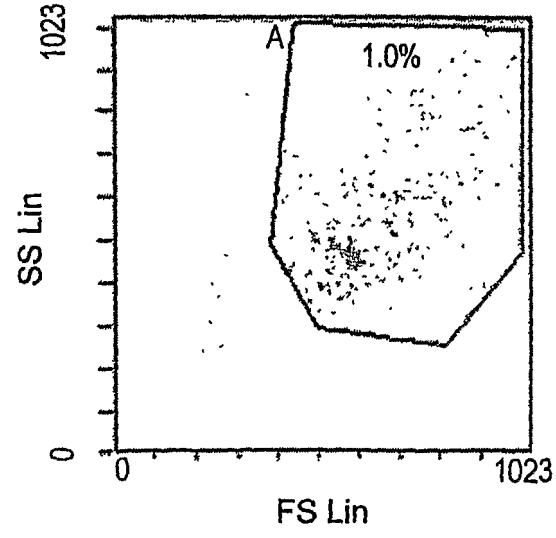


Fig. 5F



SEQUENCE LISTING

(SEQ ID NO:1): Nucleic acid sequence for dog CD117 (AF044249)

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(SEQ ID NO:4): Protein sequence for human CD117 (AAC50968)

>gi|1817733|gb|AAC50968.1| KIT protein [Homo sapiens]

MRGARGAWDFLCVLLLLLRVQTGSSQPSVSPGEPSPPSIHPGKSDLIVRVGDEIRLLCTDPG
FVKWTFEILDETNENKQNEWITEKAEATNTGKYTCTNKHGLSNSIYVFVRDPAKLFLVDRSL
YGKEDNDTLVRCPLTDPEVTNYSLKGCQGKPLPKDLRFIPDPKAGIMIKSVKRAYHRLCLHC
SVDQEGKSVLSEKFILKVRPAFKAVPVVSVSKASYLLREGEEFTVTCTIKDVSSSVYSTWKR
ENSQTKLQEKYNSWHHGDFNYERQATLTISSARVNDSGVFMCYANNTFGSANVTTTLEVVDK
GFINIFPMINTTVFVNDGENVDLIVEYEAFPKPEHQQWIYMNRTFTDKWEDYPKSENESNIR
YVSELHLTRLKGTEGGTYTFLVSNSDVNAAIAFNVYVNTKPEILTYDRLVNGMLQCVAAGFP
EPTIDWYFCPGTEQRCSASVLPVDVQTLNSSGPPFGKLVVQSSIDSSAFKHNGTVECKAYND
VGKTSAYFNFAFKGNNKEQIHPHTLFTPLLIGFVIVAGMMCIIVMILTYKYLQKPMYEVQWK
VVEEINGNNYVYIDPTQLPYDHKWEFPRNRLSFGKTLGAGAFGKVVEATAYGLIKSDAAMTV
AVKMLKPSAHLTEREALMSELKVLSYLGNHMNIVNLLGACTIGGPTLVITEYCCYGDLLNFL
RRKRDSFICSKQEDHAEAALYKNLLHSKESSCSDSTNEYMDMKPGVSYVVPTKADKRRSVRI
GSYIERDVTPAIMEDDELALDLEDLLSFSYQVAKGMAFLASKNCIHRDLAARNILLTHGRIT
KICDFGLARDIKNDSNYVVKGNARLPVKWMAPESIFNCVYTFESDVWSYGIFLWELFSLGSS
PYPGMPVDSKFYKMIKEGFRMLSPEHAPAEMYDIMKTCWDADPLKRPTFKQIVQLIEKQISE
STNHIYSNLANCSPNRQKPVVDHSVRINSVGSTASSSQPLLVHDDV

(SEQ ID NO:5): Nucleic acid sequence for dog CD34 (U49457)

>gi|1224105|gb|U49457.1|CFU49457 Canis familiaris hematopoietic progenitor cell marker CD34 mRNA, complete cds

CCCCCCTCGGCCTCCAGGGCGGCGGCAACCCCGGCCCCCGCTCCCGTCCCCCGCCTGCGGGG
CTGAGCCGAGCGCTCGCGGTGGCGGCGGCCAAGCGGAGGGGCCGGCCTTGCCAGGAACGCGG
AGGGAGGGGTGGGGAGAGACAGCCAGCTCGCCCACCCCGCTCCGGGCGGAGGGCGGAGGGCG
GCGGGCGGCGGGCGGCGGCGCGTCCCGGGGCCGAGCGCGTCTGTCCGGAGCCGAGCGGAGCG
GCGCGGGAAGGATGCTGGCGGGCAGGGGCGCGCGCGCGGGCGGCGGGCTGCCGCGGGGCTGG
ACCGCGCTCTGCCTGCTCAGTCTGCTGCCCTTTGGGTTCACAAACACAGAAACCGTGATTAC
TCCTACCACAGTGCCAACCTCCACAGAAATAATGTCAGCTGTTTCTGAGAATACATCCAAAC
GGGAAGCCATCACACTAACTCCTTCTGGAACTACCACCCTGTACTCTGTCTCTCAAGACAGC
AGTGGGACCACAGCAACCATCTCAGAGACTACAGTCCATGTCACATCTACCTCTGAGATCAC
CCTAACGCCTGGGACCATGAACTCTTCTGTTCAGTCGCAGACCTCTTTAGCTATCACGGTAT
CTTTTACCCCAACCAACTTTTCAACTTCAAGTGTGACCTTGGAGCCCAGCCTGCTACCTGGA
AATGGTTCGGATCCCCCCTACAACAGCACCAGCCTTGTGACATCCCCCACGGAATATTATAC
ATCACTTTCTCCTACCCCAAGTAGAAATGACACCCCAAGTACCATCAAGGGAGAAATCAAAT
GTTCCGGAGTCAAAGAAGTGAAATTGAACCAAGGTATCTGCCTAGAGCTAAATGAGACCTCC
AGCTGTGAGGACTTTAAGAAAGATAACGAAGAAAAACTGACCCAAGTCCTGTGTGAGAAGGA
GCCAGCTGAGGCTGGGGCCGGGGTGTGCTCCCTGCTTCTGGCCCAGTCTGAGGTGAGGCCTC
ACTGCCTGCTGCTGGTCTTGGCCAACAAAACAGAACTTTTCAGTAAACTCCAACTTCTGAGA
AAGCACCAGTCTGACCTGAAAAAGCTGGGGATCCGAGACTTCACTGAACAAGATGTTGGGAG
CCACCAGAGCTATTCCCGCAAGACCCTGATTGCACTGGTCACCTCAGGGATCCTGCTGGCTG
TCTTGGGCACCACTGGTTACTTCCTGATGAACCGCCGCAGTTGGAGCCCTACAGGAGAAAGG
CTGGGCGAAGACCCTTATTACACGGAGAACGGTGGAGGCCAGGGCTATAGCTCAGGCCCTGG
GGTCTCCCCTGAGGCTCAGGGAAAGGCCAGTGTGAACCGTGGGCCTCAGGAGAACGGGACCG
GCCAGGCCACGTCCAGAAACGGCCATTCAGCAAGACAACACATGGTGGCTGATACAGAATTG
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CCACATGCTGCCTCTGTGCTGGAGCTGCCACCACTTACATTCTAGCCTTTCCTGCTGCACAC
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CACCAGCTCACTGTGGATTCAGGCAACCGGCTTCCCTCATGCTCTCCGGGCTCCCTGAGCTC
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CCCCAACCCCCTCACTGTTCTGTACCCCCATATAGTCAGGGCCCCCGACATCTCCAGAGGAC
CTTCATCACAAGCCATCTCCTCTGTAGGTGGCCCAGGTTCTCATTTATTTTTTTAGGTATTT
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AATTAAAGTGATACCGAGACACATCTGTTCTGTGTCGCTGCCCCAGCCAGGTGTGTCTGAAT
GCCACGGCGGTGTCCCTGGTGTCCCGGTCAGACCCGGCCAGACTTCCCAATGATGTGGTAGA

GAGGGGTGACCCTGGAAAGAGGTGGGCCCATCTCGGGGGATACAGGCAAAAGCCAGGGTGCT
GCCCCTTGGCCAAGTGTCCCTATGGGTGGGGGGGGTTGGAGG

(SEQ ID NO:6): Protein sequence for dog CD34 (AAB41055)
>gi|1224106|gb|AAB41055.1| hematopoietic progenitor cell marker CD34

MLAGRGARAGGGLPRGWTALCLLSLLPFGFTNTETVITPTTVPTSTEIMSAVSENTSKREAI
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TNFSTSSVTLEPSLLPGNGSDPPYNSTSLVTSPTEYYTSLSPTPSRNDTPSTIKGEIKCSGV
KEVKLNQGICLELNETSSCEDFKKDNEEKLTQVLCEKEPAEAGAGVCSLLLAQSEVRPHCLL
LVLANKTELFSKLQLLRKHQSDLKKLGIRDFTEQDVGSHQSYSRKTLIALVTSGILLAVLGT
TGYFLMNRRSWSPTGERLGEDPYYTENGGGQGYSSGPGVSPEAQGKASVNRGPQENGTGQAT
SRNGHSARQHMVADTEL

(SEQ ID NO:7): Nucleic acid sequence for human CD34 (NM_001773) >gi|4502660|ref|NM_001773.1| Homo sapiens CD34 antigen (CD34), mRNA

CCCGGGCGGAGGGGGCGGGAAGAGCGCGTCCTGGCCAAGCCGAGTAGTGTCTTCCACTCGGT
GCGTCTCTCTAGGAGCCGCGCGGGAAGGATGCTGGTCCGCAGGGGCGCGCGCGCAGGGCCCA
GGATGCCGCGGGGCTGGACCGCGCTTTGCTTGCTGAGTTTGCTGCCTTCTGGGTTCATGAGT
CTTGACAACAACGGTACTGCTACCCCAGAGTTACCTACCCAGGGAACATTTTCAAATGTTTC
TACAAATGTATCCTACCAAGAAACTACAACACCTAGTACCCTTGGAAGTACCAGCCTGCACC
CTGTGTCTCAACATGGCAATGAGGCCACAACAAACATCACAGAAACGACAGTCAAATTCACA
TCTACCTCTGTGATAACCTCAGTTTATGGAAACACAAACTCTTCTGTCCAGTCACAGACCTC
TGTAATCAGCACAGTGTTCACCACCCCAGCCAACGTTTCAACTCCAGAGACAACCTTGAAGC
CTAGCCTGTCACCTGGAAATGTTTCAGACCTTTCAACCACTAGCACTAGCCTTGCAACATCT
CCCACTAAACCCTATACATCATCTTCTCCTATCCTAAGTGACATCAAGGCAGAAATCAAATG
TTCAGGCATCAGAGAAGTGAAATTGACTCAGGGCATCTGCCTGGAGCAAAATAAGACCTCCA
GCTGTGCGGAGTTTAAGAAGGACAGGGGAGAGGGCCTGGCCCGAGTGCTGTGTGGGGAGGAG
CAGGCTGATGCTGATGCTGGGGCCCAGGTATGCTCCCTGCTCCTTGCCCAGTCTGAGGTGAG
GCCTCAGTGTCTACTGCTGGTCTTGGCCAACAGAACAGAAATTTCCAGCAAACTCCAACTTA
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GCAAGCCACCAGAGCTATTCCCAAAAGACCCTGATTGCACTGGTCACCTCGGGAGCCCTGCT
GGCTGTCTTGGGCATCACTGGCTATTTCCTGATGAATCGCCGCAGCTGGAGCCCCACAGGAG
AAAGGCTGGAGCTGGAACCCTGACCACTCTTCAGGAAGAAAGGAGTCTGCACATGCAGCTGC
ACCCTCCCTCCGATCCTTCCTCCCACCTCCCCCTCCCCCTTCTCCCACCCCTGCCCCCACTT
CCTGTTTGGGCCCTCTCCCATCCAGTGTCTCACAGCCCTGCTTACCAGATAATGCTACTTTA
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GCTCAGGACCTGGGACCTCCCCTGAGGCTCAGGGAAAGGCCAGTGTGAACCGAGGGGCTCAG
GAAAACGGGACCGGCCAGGCCACCTCCAGAAACGGCCATTCAGCAAGACAACACGTGGTGGC
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TCTCTGCATCTGACCACGTGCTACCCCCATGCTGGAGGTGACATCTCTTACGCCCAACCCTT
CCCCACTGCACACACCTCAGAGGCTGTTCTTGGGGCCCTACACCTTGAGGAGGGGCAGGTAA
ACTCCTGTCCTTTACACATTCGCTCCCTGGAGCAGACTCTGGTCTTCTTTGGGTAAACGTGT
GACGGGGGAAAGCCAAGGTCTGGAGAAGCTCCCAGGAACAACTGATGGCCTTGCAGCACTCA
CACAGGACCCCCTTCCCCTACCCCCTCCTCTCTGCCGCAATACAGGAACCCCCAGGGGAAAG
ATGAGCTTTTCTAGGCTACAATTTTCTCCCAGGAAGCTTTGATTTTTACCGTTTCTTCCCTG
TATTTTCTTTCTCTACTTTGAGGAAACCAAAGTAACCTTTTGCACCTGCTCTCTTGTAATGA

TATAGCCAGAAAAACGTGTTGCCTTGAACCACTTCCCTCATCTCTCCTCCAAGACACTGTGG
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CATTTGCAGAGTCCTGCACAGTTTTCTGGCTGGAGCCTAGAACAGGCCTCCCAAGTTTTAGG
ACAAACAGCTCAGTTCTAGTCTCTCTGGGGCCACACAGAAACTCTTTTTGGGCTCTTTTTTC
TCCCTCTGGATCAAAGTAGGCAGGACCATGGGACCAGGTCTTGGAGCTGAGCCTCTCACCTG
TACTCTTCCGAAAAATCCTCTTCCTCTGAGGCTGGATCCTAGCCTTATCCTCTGATCTCCAT
GGCTTCCTCCTCCCTCCTGCCGACTCCTGGGTTGAGCTGTTGCCTCAGTCCCCCAACAGATG
CTTTTCTGTCTCTGCCTCCCTCACCCTGAGCCCCTTCCTTGCTCTGCACCCCCATATGGTCA
TAGCCCAGATCAGCTCCTAACCCTTATCACCAGCTGCCTCTTCTGTGGGTGACCCAGGTCCT
TGTTTGCTGTTGATTTCTTTCCAGAGGGGTTGAACAGGGATCCTGGTTTCAATGACGGTTGG
AAATAGAAATTTCCAGAGAAGAGAGTATTGGGTAGATATTTTTTCTGAATACAAAGTGATGT
GTTTAAATACTGCAATTAAAGTGATACTGAAACACAAAAAAAAAAAAAAAAAA

(SEQ ID NO:8): Protein sequence for human CD34 (NP_001764.1)
>gi|4502661|ref|NP_001764.1| CD34 antigen [Homo sapiens]

MLVRRGARAGPRMPRGWTALCLLSLLPSGFMSLDNNGTATPELPTQGTFSNVSTNVSYQETT
TPSTLGSTSLHPVSQHGNEATTNITETTVKFTSTSVITSVYGNTNSSVQSQTSVISTVFTTP
ANVSTPETTLKPSLSPGNVSDLSTTSTSLATSPTKPYTSSSPILSDIKAEIKCSGIREVKLT
QGICLEQNKTSSCAEFKKDRGEGLARVLCGEEQADADAGAQVCSLLLAQSEVRPQCLLLVLA
NRTEISSKLQLMKKHQSDLKKLGILDFTEQDVASHQSYSQKTLIALVTSGALLAVLGITGYF
LMNRRSWSPTGERLELEP

(SEQ ID NO:9): Predicted Nucleic acid sequence for dog CD51, partial sequence from AAEX01022275.1 position 65528 to position 67792

GATGGGCTTTTTTAAACGTGTCCGGCCACCGCAGGAAGAGCAAGAAAGGGAACAGCTTCAAC
CTCATGAAAATGGCGAAGGAAACTCAGAAACTTAACGGTCATTTTTAAGTCATGCTACGCTC
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CCAAGACTGTACTGCTGATGGTGCCCATTGGTGTTAACCACACAACAAGGGCAATGGGTGTC
AACTTTTTTGTCATTACTAAGTTCAAACGTACGTGTAATACACACCACTGACTTGCGTTTTT
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TCTTTTGTACAGGAGCTTACTGTTAATACACATTACACTACAGTTGAGTTTTTAAGCTACTA
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CAGTTTGTATACGTTTAGGTTCTATTTCAAATCCTTTAAGCCAACCTATACTAAAAATTCTA
TGATCAAAAATGCCTCTTTTGTGTAATAGTTTTAATTTCCGCTACTCATCATCATGCTTAAA
GCCATATGCGTTTGGAAATCATTTCTGAAGTACAGAAATTCCATTGTATTAGTCTGGCTATC
TGCAATACAAAAAAAAAAATATATATATATATATATCATTTAAGTTAAAAGACTGTAGTTCT
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TGCGTGGAATTGAAATTCTTAAAGTAGCTTGCTGGTTTGCTTCCGGCAATAATAGCATGATG
CTCACACGGACATTACCTTAGCTTAGCAAGGGTATCATCTGTAAAACCAGTCTCAGCTACCA
AAATAACGTAGAGTAGTGACTTTTATAAGCAATACAAGTTATTGGGAGCCTTTTAAAACTTT
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CATTGTAATTTTATCTGCCTGGAGGGTGATGATTCTTCTAGAGGAATAATGTGATTTAGTCA
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TTCACCAAACAGTCACTAAGTTGACGACTTTCACTTTATACCTGTTTCCCCACTGAATGGTA
GTCATCCCTGAAAGTAGATGTTGGATAGAAATCCACTCTTCACAAGAAATGTTAGTTTGCTT
TTGCACGGTCTGTTCCTCCTGTGGCCTGTAGCTCAAGGTATAATCATGTGTGGGAGACTGAA
GGATATTGGTGTTGGAAGCATGATGTTTTAAGTTCCCTTTTATGAAATGTAGTTTTGAGCAA
TAGTATTTTCTTTTAAAAAATGAAAACGTGTATCTCTACGGAACTATGGTAGAAGTATGATT
TGGAAGCTTACACTTCGAGGAAAATGTTTGGGA

(SEQ ID NO:10): Nucleic acid sequence for human CD51 (NM_002210) >gi|40217844|ref|NM_002210.2| Homo sapiens integrin, alpha V (vitronectin receptor, alpha polypeptide, antigen CD51) (ITGAV), mRNA

GCTGCGTGGAGCGGCGGAGCCGGAGGGAAGCAAAGGACCGTCTGCGCTGCTGTCCCCGCCCC
GCGCGCTCTGCGCCCCTCGTCCCTGGCGGTCGCTCCGAAGCTCAGCCCTCTTGCCTGCCCCG
GAGCTGTCCCGGGCTAGCCGAGAAGAGAGCGGCCGGCAAGTTTGGGCGCGCGCAGGCGGCGG
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GCACAAGCTATTTTTGATGACAGCTATTTGGGTTATTCTGTGGCTGTCGGAGATTTCAATGG
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AAGAACATGACTATTTCAAGGGGGGGACTGATGCAGTGTGAGGAATTGATAGCGTATCTGCG
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GCATTTTTATTAAAATACTGTGTAGTTCTTTGAGATAGTTGCTTATGCATATAGTAAGTATT
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ACCAATAAATTTAAAATTTTTTAAGAAAAATATTTTTATCCTAGGGCCAAGTGTTGCCTGCC
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ATTTTTTCTGTTTCTCTTTTCTCTTAACGATTATCACTGTAATTCTGAATCTGAAAGGTAAA
ACAATTAGTCAAAATATTATTGCCATCATTCTACCTGTGTTATGAAACTACTTATTCATAGT
TAATTCTCATTAACACTTACATTTCCATAAAGAAAACTCAAGTATTAATAAAAGAGACTTTA
CTGGCTTAAGAGGGCTGTGAAAGATTTTTGATAGTGAATCATGACCCTAAGGGAGAGATTTG
TGTGATAAAAGTATTGTATATAATAGATCAGCGATTTTTGTAAGGCAAACAGAATTTGTAAG
TTGGCAGATCTTCCTAAGTTGCAAAATGTAATGATGAGCTTGGTGGAGAAGAATGAGTCGTT
CTTGGAATACCTATGTGCAGCCACTACCCATCTCAATGTCACCTTGTTTGCATTCTTGGATA
GCTTGTATATGTAGTAGTTTGATGAATAATTTAAAGAAAAACACCTAAAATTTGAAAAATGA
TTGTAGGATCAAAAAAGGCAGATGAAATTACTTAATACTCAGTGTTTTGGAGAGTATTCCTT
TTAGTTTGTTGGTTGGCTGGTTTGAACGATAGAAATATGCAGCATGCAATATATGCTTATAT
TTCATTTTAATTTCTGATATATAATGAACTTCTTGGGAGAGGTACTGAATCTTTGATGTTTT
TTGTCATTGTTCTCAAGTGCAATATAACAATGTAACCAAATCTAGATAATTTCAAAGTTGTC
ATTAATTTAGTAAGCCTAATATAAACAAATATTTGTATTATTTTTGTTAGCAGGAAAGAGTG
ATTAAGTGAGGTTATTTACCCCTAAATGGTCCATTCTGCATTGTATTTCAGGCTGGAAATGA
ATTATTCTTTACCAGTTTTGAAACACTTTGAAATATCCTAAGGTAACTTGGAAGCTGTGTAG
TATATCAAATTAATTTGCTACCTAATAACATAGAAAGTAAATATCTTTGTGGTCACCCACAT
TGGGTGAGACAGAAAATGAATCTGTTCTAAAATTTGTAATTTGCTAACTTGATTTGAGTTAG
TGAAAACTGGTACAGTGTTCTGCTTGATTTACAACATGTAACTTGTGACTGTACAATAAACA
TAAGCATATGGTACCAAAAAAAAAAAAAAA

(SEQ ID NO:11): Protein sequence for human CD51 (NP_002201.1)
>gi|4504763|ref|NP_002201.1| integrin alpha-V precursor; Integrin, alpha-V (vitronectin receptor, alpha polypeptide); antigen identified by monoclonal antibody L230 [Homo sapiens]

MAFPPRRRLRLGPRGLPLLLSGLLLPLCRAFNLDVDSPAEYSGPEGSYFGFAVDFFVPSASS
RMFLLVGAPKANTTQPGIVEGGQVLKCDWSSTRRCQPIEFDATGNRDYAKDDPLEFKSHQWF
GASVRSKQDKILACAPLYHWRTEMKQEREPVGTCFLQDGTKTVEYAPCRSQDIDADGQGFCQ
GGFSIDFTKADRVLLGGPGSFYWQGQLISDQVAEIVSKYDPNVYSIKYNNQLATRTAQAIFD
DSYLGYSVAVGDFNGDGIDDFVSGVPRAARTLGMVYIYDGKNMSSLYNFTGEQMAAYFGFSV
AATDINGDDYADVFIGAPLFMDRGSDGKLQEVGQVSVSLQRASGDFQTTKLNGFEVFARFGS
AIAPLGDLDQDGFNDIAIAAPYGGEDKKGIVYIFNGRSTGLNAVPSQILEGQWAARSMPPSF
GYSMKGATDIDKNGYPDLIVGAFGVDRAILYRARPVITVNAGLEVYPSILNQDNKTCSLPGT
ALKVSCFNVRFCLKADGKGVLPRKLNFQVELLLDKLKQKGAIRRALFLYSRSPSHSKNMTIS
RGGLMQCEELIAYLRDESEFRDKLTPITIFMEYRLDYRTAADTTGLQPILNQFTPANISRQA

HILLDCGEDNVCKPKLEVSVDSDQKKIYIGDDNPLTLIVKAQNQGEGAYEAELIVSIPLQAD
FIGVVRNNEALARLSCAFKTENQTRQVVCDLGNPMKAGTQLLAGLRFSVHQQSEMDTSVKFD
LQIQSSNLFDKVSPVVSHKVDLAVLAAVEIRGVSSPDHIFLPIPNWEHKENPETEEDVGPVV
QHIYELRNNGPSSFSKAMLHLQWPYKYNNNTLLYILHYDIDGPMNCTSDMEINPLRIKISSL
QTTEKNDTVAGQGERDHLITKRDLALSEGDIHTLGCGVAQCLKIVCQVGRLDRGKSAILYVK
SLLWTETFMNKENQNHSYSLKSSASFNVIEFPYKNLPIEDITNSTLVTTNVTWGIQPAPMPV
PVWVIILAVLAGLLLLAVLVFVMYRMGFFKRVRPPQEEQEREQLQPHENGEGNSET

(SEQ ID NO:12): Nucleic acid sequence for dog CD61 (AF170525)

>gi|5733735|gb|AF170525.1|AF170525 Canis familiaris
glycoprotein GPIIIa (GPIIIa) mRNA, complete cds

ATGCGGGCGCGGCCGCTCTGGGCCGCGGTGCTGCTGCTGGGGGCGCTGGCGGGCACCGGCGT
CGGAGTGTCCAACATCTGTACCACACGAGGTGTCCACTCCTGCCAGCAATGTCTAGCTGTGA
GTCCTGTGTGTGCCTGGTGCTCAGATGAGGCCCTGCCTCTGGGCTCTCCCCGCTGTAACCTG
AAGGAAAATCTGCTGAAGGATAACTGTGCCCTGGAATCCATTGAGTTCCCCATCAGTGAGGT
CCGCATCCTGGAGGCCAGGCCCCTTAGCAACAAGGGCTCTGGAGACAGCTCCCAGATTACTC
AAGTCAGCCCTCAGAGGATTGCGCTGCGGCTCCGGCCAGATGATTCAAAGAATTTCTCCATC
CAAGTTCGGCAAGTAGAGGATTACCCTGTGGACATCTACTACTTGATGGACCTGTCTTATTC
CATGAAGGATGATCTGTCGAGCATCCAGAACCTAGGCACCAGGCTGGCCTCCCAGATGCACA
AGCTCACCAGTAACTTGCGGATTGGCTTCGGGGCTTTTGTGGACAAGCCTGTGTCTCCATAC
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GCCTATGTTTGGCTACAAACATGTGCTGACGCTAACTGACCAGGTGACCCGCTTCAATGAGG
AAGTGAAAAAGCAGAGTGTGTCACGGAACCGAGATGCCCCAGAGGGCGGCTTTGATGCTATC
ATGCAGGCTACAGTCTGTGATGAGAAGATTGGCTGGAGGAATGATGCATCCCACTTGCTGGT
ATTTACCACTGATGCCAAGACCCATATAGCGCTGGATGGAAGGCTGGCAGGCATTGTCCAAC
CTAACGATGGGCAGTGTCACATTGGCAGTGACAACCATTATTCTGCCTCCACTACCATGGAT
TATCCCTCTCTGGGACTGATGACAGAGAAGCTCTCCCAGAAAAACATCAATTTGATCTTTGC
AGTAACGGAAAATGTGGTCAATCTCTACCAGAACTACAGTGAGCTCATCCCAGGGACCACAG
TGGGGATTCTGTCTACGGATTCCAGCAATGTCCTTCAGCTCATTGTTGATGCTTATGGAAAA
ATCCGCTCTAAAGTGGAGCTGGAAGTGCGTGACCTCCCTGAGGAGTTGTCTCTATCGTTCAA
CGCCACCTGTCTCAACAATGAGGTCATCCCGGGCCTCAAGTCTTGTGTCGGCCTCAAGATTG
GAGACACGGTGAGCTTCAGCATTGAGGCCAAAGTGCGAGGCTGCCCCCAGGAGAAGGAGAAG
TCCTTCACCATCAAGCCTGTGGGCTTCAAAGACAGCCTCACCATCCAGGTCACCTTTGACTG
TGACTGTGCCTGCCAGGCCCAGGCTGAGCCTTCCAGTCACCGCTGCAACAATGGCAATGGGA
CCTTTGAGTGTGGGGTGTGCCTCTGTGGGCCTGGCTGGCTGGGGTCCCAGTGTGAATGCTCG
GAAGAGGACTATCATCCCTCCCAGCAGGACGAGTGCAGCCCCCGGGAGGGCCAGCCCGCCTG
CAGCCAGCGGGGCGAGTGCCTGTGTGGCCAATGTGTCTGCCATAGCAGTGACTTTGGCAAGA
TCACGGGCAAGTACTGCGAGTGTGATGACTTCTCCTGTGTCCGCTACAAGGGGGAGATGTGC
TCAGGCCATGGCCAGTGCAGCTGTGGGGACTGCCTGTGTGACTCCGACTGGACCGGCTACTA
CTGCAACTGTACCACGCGCACTGACACGTGCATGTCCAGCAACGGGCTGCTGTGCGGCGGTC
GGGGCAAGTGTGAGTGTGGCAGCTGCGTGTGCATCCAACCTGGCTCCTACGGGGACACCTGC
GAGAAGTGCCCCACCTGCCCTGACGCCTGCACCTTTAAGAAGGAGTGTGTGGAGTGTAAGAA
ATTTGACCGAGGAACTCTCCATGATGATAATACCTGCAACCGTTACTGTCGTGATGAGATTG
AGTCTGTGAAGGAGCTTAAGGATACTGGCAAGGATGCAGTGAATTGTACATACAAGAATGAG
GATGACTGTGTTGTCAGATTTCAGTACTATGAAGACTCCAGTGGAAAGTCCATTCTCTATGT
GGTAGAAGAGCCAGAGTGTCCCAAGGGTCCTGACATCCTGGTGGTCCTGCTTTCAGTGATGG

GGGCCATTTTGCTCATTGGCCTTGCTACTCTGCTCATCTGGAAGCTCCTCATCACCATCCAT
GATCGGAAGGAGTTTGCTAAATTTGAGGAAGAGCGAGCCAGAGCAAAATGGGACACAGCCAA
CAACCCACTGTATAAAGAGGCCACATCCACTTTTACCAACATCACCTACCGGGGCACTTAAC
ACCAAGGAGCCATCCTCA

(SEQ ID NO:13): Protein sequence for dog CD61 (AAD49737.1)
>gi|5733736|gb|AAD49737.1|AF170525_1 glycoprotein GPIIIa [Canis familiaris]

MRARPLWAAVLLLGALAGTGVGVSNICTTRGVHSCQQCLAVSPVCAWCSDEALPLGSPRCNL
KENLLKDNCALESIEFPISEVRILEARPLSNKGSGDSSQITQVSPQRIALRLRPDDSKNFSI
QVRQVEDYPVDIYYLMDLSYSMKDDLSSIQNLGTRLASQMHKLTSNLRIGFGAFVDKPVSPY
MYISPPEALKNPCYDMKTTCLPMFGYKHVLTLTDQVTRFNEEVKKQSVSRNRDAPEGGFDAI
MQATVCDEKIGWRNDASHLLVFTTDAKTHIALDGRLAGIVQPNDGQCHIGSDNHYSASTTMD
YPSLGLMTEKLSQKNINLIFAVTENVVNLYQNYSELIPGTTVGILSTDSSNVLQLIVDAYGK
IRSKVELEVRDLPEELSLSFNATCLNNEVIPGLKSCVGLKIGDTVSFSIEAKVRGCPQEKEK
SFTIKPVGFKDSLTIQVTFDCDCACQAQAEPSSHRCNNGNGTFECGVCLCGPGWLGSQCECS
EEDYHPSQQDECSPREGQPACSQRGECLCGQCVCHSSDFGKITGKYCECDDFSCVRYKGEMC
SGHGQCSCGDCLCDSDWTGYYCNCTTRTDTCMSSNGLLCGGRGKCECGSCVCIQPGSYGDTC
EKCPTCPDACTFKKECVECKKFDRGTLHDDNTCNRYCRDEIESVKELKDTGKDAVNCTYKNE
DDCVVRFQYYEDSSGKSILYVVEEPECPKGPDILVVLLSVMGAILLIGLATLLIWKLLITIH
DRKEFAKFEEERARAKWDTANNPLYKEATSTFTNITYRGT

(SEQ ID NO:14): Nucleic acid sequence for human CD61 (NM_000212)
>gi|47078291|ref|NM_000212.2| Homo sapiens integrin, beta 3 (platelet glycoprotein IIIa, antigen CD61) (ITGB3), mRNA

CGCCGCGGGAGGCGGACGAGATGCGAGCGCGGCCGCGGCCCCGGCCGCTCTGGGCGACTGTG
CTGGCGCTGGGGGCGCTGGCGGGCGTTGGCGTAGGAGGGCCCAACATCTGTACCACGCGAGG
TGTGAGCTCCTGCCAGCAGTGCCTGGCTGTGAGCCCCATGTGTGCCTGGTGCTCTGATGAGG
CCCTGCCTCTGGGCTCACCTCGCTGTGACCTGAAGGAGAATCTGCTGAAGGATAACTGTGCC
CCAGAATCCATCGAGTTCCCAGTGAGTGAGGCCCGAGTACTAGAGGACAGGCCCCTCAGCGA
CAAGGGCTCTGGAGACAGCTCCCAGGTCACTCAAGTCAGTCCCCAGAGGATTGCACTCCGGC
TCCGGCCAGATGATTCGAAGAATTTCTCCATCCAAGTGCGGCAGGTGGAGGATTACCCTGTG
GACATCTACTACTTGATGGACCTGTCTTACTCCATGAAGGATGATCTGTGGAGCATCCAGAA
CCTGGGTACCAAGCTGGCCACCCAGATGCGAAAGCTCACCAGTAACCTGCGGATTGGCTTCG
GGGCATTTGTGGACAAGCCTGTGTCACCATACATGTATATCTCCCCACCAGAGGCCCTCGAA
AACCCCTGCTATGATATGAAGACCACCTGCTTGCCCATGTTTGGCTACAAACACGTGCTGAC
GCTAACTGACCAGGTGACCCGCTTCAATGAGGAAGTGAAGAAGCAGAGTGTGTCACGGAACC
GAGATGCCCCAGAGGGTGGCTTTGATGCCATCATGCAGGCTACAGTCTGTGATGAAAAGATT
GGCTGGAGGAATGATGCATCCCACTTGCTGGTGTTTACCACTGATGCCAAGACTCATATAGC
ATTGGACGGAAGGCTGGCAGGCATTGTCCAGCCTAATGACGGGCAGTGTCATGTTGGTAGTG
ACAATCATTACTCTGCCTCCACTACCATGGATTATCCCTCTTTGGGGCTGATGACTGAGAAG
CTATCCCAGAAAAACATCAATTTGATCTTTGCAGTGACTGAAAATGTAGTCAATCTCTATCA
GAACTATAGTGAGCTCATCCCAGGGACCACAGTTGGGGTTCTGTCCATGGATTCCAGCAATG
TCCTCCAGCTCATTGTTGATGCTTATGGGAAAATCCGTTCTAAAGTAGAGCTGGAAGTGCGT
GACCTCCCTGAAGAGTTGTCTCTATCCTTCAATGCCACCTGCCTCAACAATGAGGTCATCCC
TGGCCTCAAGTCTTGTATGGGACTCAAGATTGGAGACACGGTGAGCTTCAGCATTGAGGCCA

AGGTGCGAGGCTGTCCCCAGGAGAAGGAGAAGTCCTTTACCATAAAGCCCGTGGGCTTCAAG
GACAGCCTGATCGTCCAGGTCACCTTTGATTGTGACTGTGCCTGCCAGGCCCAAGCTGAACC
TAATAGCCATCGCTGCAACAATGGCAATGGGACCTTTGAGTGTGGGGTATGCCGTTGTGGGC
CTGGCTGGCTGGGATCCCAGTGTGAGTGCTCAGAGGAGGACTATCGCCCTTCCCAGCAGGAC
GAATGCAGCCCCCGGGAGGGTCAGCCCGTCTGCAGCCAGCGGGGCGAGTGCCTCTGTGGTCA
ATGTGTCTGCCACAGCAGTGACTTTGGCAAGATCACGGGCAAGTACTGCGAGTGTGACGACT
TCTCCTGTGTCCGCTACAAGGGGGAGATGTGCTCAGGCCATGGCCAGTGCAGCTGTGGGGAC
TGCCTGTGTGACTCCGACTGGACCGGCTACTACTGCAACTGTACCACGCGTACTGACACCTG
CATGTCCAGCAATGGGCTGCTGTGCAGCGGCCGCGGCAAGTGTGAATGTGGCAGCTGTGTCT
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ACCTTTAAGAAAGAATGTGTGGAGTGTAAGAAGTTTGACCGGGGAGCCCTACATGACGAAAA
TACCTGCAACCGTTACTGCCGTGACGAGATTGAGTCAGTGAAAGAGCTTAAGGACACTGGCA
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GAAGATTCTAGTGGAAAGTCCATCCTGTATGTGGTAGAAGAGCCAGAGTGTCCCAAGGGCCC
TGACATCCTGGTGGTCCTGCTCTCAGTGATGGGGGCCATTCTGCTCATTGGCCTTGCCGCCC
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GAACGCGCCAGAGCAAAATGGGACACAGCCAACAACCCACTGTATAAAGAGGCCACGTCTAC
CTTCACCAATATCACGTACCGGGGCACTTAATGATAAGCAGTCATCCTCAGATCATTATCAG
CCTGTGCCACGATTGCAGGAGTCCCTGCCATCATGTTTACAGAGGACAGTATTTGTGGGGAG
GGATTTGGGGCTCAGAGTGGGGTAGGTTGGGAGAATGTCAGTATGTGGAAGTGTGGGTCTGT
GTGTGTGTATGTGGGGGTCTGTGTGTTTATGTGTGTGTGTTGTGTGTGGGAGTGTGTAATTT
AAAATTGTGATGTGTCCTGATAAGCTGAGCTCCTTAGCCTTTGTCCCAGAATGCCTCCTGCA
GGGATTCTTCCTGCTTAGCTTGAGGGTGACTATGGAGCTGAGCAGGTGTTCTTCATTACCTC
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TACCTCTGCCTCCTTTCCCCTCCCTCAGGCCGAAGGAGGAGTCAGGGAGAGCTGAACTATTA
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TTGCAAGCTAATTCTTTGACCTGTTGGGAGTGAGGATGTCTGGGCCACTCAGGGGTCATTCA
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TGGCAGCTCTACTCTGGAGGTTTGTTTAGAAGAAGTGTGTCACCCTTAGGCCAGCACCATCT
CTTTACCTCCTAATTCCACACCCTCACTGCTGTAGACATTTGCTATGAGCTGGGGATGTCTC
TCATGACCAAATGCTTTTCCTCAAAGGGAGAGAGTGCTATTGTAGAGCCAGAGGTCTGGCCC
TATGCTTCCGGCCTCCTGTCCCTCATCCATAGCACCTCCACATACCTGGCCCTGTGCCTTGG
TGTGCTGTATCCATCCATGGGGCTGATTGTATTTACCTTCTACCTCTTGGCTGCCTTGTGAA
GGAATTATTCCCATGAGTTGGCTGGGAATAAGTGCCAGGATGGAATGATGGGTCAGTTGTAT
CAGCACGTGTGGCCTGTTCTTCTATGGGTTGGACAACCTCATTTTAACTCAGTCTTTAATCT
GAGAGGCCACAGTGCAATTTTATTTTATTTTTCTCATGATGAGGTTTTCTTAACTTAAAAGA
ACATGTATATAAACATGCTTGCATTATATTTGTAAATTTATGTGATGGCAAAGAAGGAGAGC
ATAGGAAACCACACAGACTTGGGCAGGGTACAGACACTCCCACTTGGCATCATTCACAGCAA
GTCACTGGCCAGTGGCTGGATCTGTGAGGGGCTCTCTCATGATAGAAGGCTATGGGGATAGA
TGTGTGGACACATTGGACCTTTCCTGAGGAAGAGGGACTGTTCTTTTGTCCCAGAAAAGCAG
TGGCTCCATTGGTGTTGACATACATCCAACATTAAAAGCCACCCCCAAATGCCCAAGAAAAA
AAGAAAGACTTATCAACATTTGTTCCATGAGCAGAAAACTGGAGCTCTGGCCTCAGTGTTAC
AGCTAAATAATCTTTAATTAAGGCAAGTCACTTTCTTCTTCTTAAAGCTGTTTTCTAGTTTG
AGAAATGATGGGATTTTAGCAGCCAGTCTTGAAGGTCTCTTTCAGTATCAACATTCTAAGAT
GCTGGGACTTACTGTGTCATCAAATGTGCGGTTAAGATTCTCTGGGATATTGATACTGTTTG
TGTTTTTAGTTGGGAGATCTGAGAGACCTGGCTTTGGCAAGAGCAGATGTCATTCCATATCA
CCTTTCTCAATGAAAGTCTCATTCTATCCTCTCTCCAAACCCGTTTTCCAACATTTGTTAAT
AGTTACGTCTCTCCTGATGTAGCACTTAAGCTTCATTTAGTTATTATTTCTTTCTTCACTTT
GCACACATTTGCATCCACATATTAGGGAAGAGGAATCCATAAGTAGCTGAAATATCTATTCT

GTATTATTGTGTTAACATTGAGAATAAGCCTTGGAATTAGATATGGGGCAATGACTGAGCCC
TGTCTCACCCATGGATTACTCCTTACTGTAGGGAATGGCAGTATGGTAGAGGGATAAATAGG
GGGCGGGGAGGGATAGTCATGGATCCAAGAAGTCCTTAGAAATAGTGGCAGGGAACAGGTGT
GGAAGCTCATGCCTGTAATTATAACCTTCAGCTACTAAGACAGGTGTGGTGGCTCACGCCTG
TGATTATAATCTTCAGTTACTAAGACAGAGTCCATGAGAGTGTTAATGGGACATTTTCTTTA
GATAAGATGTTTTATATGAAGAAACTGTATCAAAGGGGGAAGAAAATGTATTTAACAGGTGA
ATCAAATCAGGAATCTTGTCTGAGCTACTGGAATGAAGTTCACAGGTCTTGAAGACCA

(SEQ ID NO:15): Protein sequence for human CD61 (NP_000203.2)
>gi|47078292|ref|NP_000203.2| integrin beta chain, beta 3 precursor; platelet glycoprotein IIIa precursor [Homo sapiens]

MRARPRPRPLWATVLALGALAGVGVGGPNICTTRGVSSCQQCLAVSPMCAWCSDEALPLGSP
RCDLKENLLKDNCAPESIEFPVSEARVLEDRPLSDKGSGDSSQVTQVSPQRIALRLRPDDSK
NFSIQVRQVEDYPVDIYYLMDLSYSMKDDLWSIQNLGTKLATQMRKLTSNLRIGFGAFVDKP
VSPYMYISPPEALENPCYDMKTTCLPMFGYKHVLTLTDQVTRFNEEVKKQSVSRNRDAPEGG
FDAIMQATVCDEKIGWRNDASHLLVFTTDAKTHIALDGRLAGIVQPNDGQCHVGSDNHYSAS
TTMDYPSLGLMTEKLSQKNINLIFAVTENVVNLYQNYSELIPGTTVGVLSMDSSNVLQLIVD
AYGKIRSKVELEVRDLPEELSLSFNATCLNNEVIPGLKSCMGLKIGDTVSFSIEAKVRGCPQ
EKEKSFTIKPVGFKDSLIVQVTFDCDCACQAQAEPNSHRCNNGNGTFECGVCRCGPGWLGSQ
CECSEEDYRPSQQDECSPREGQPVCSQRGECLCGQCVCHSSDFGKITGKYCECDDFSCVRYK
GEMCSGHGQCSCGDCLCDSDWTGYYCNCTTRTDTCMSSNGLLCSGRGKCECGSCVCIQPGSY
GDTCEKCPTCPDACTFKKECVECKKFDRGALHDENTCNRYCRDEIESVKELKDTGKDAVNCT
YKNEDDCVVRFQYYEDSSGKSILYVVEEPECPKGPDILVVLLSVMGAILLIGLAALLIWKLL
ITIHDRKEFAKFEEERARAKWDTANNPLYKEATSTFTNITYRGT

(SEQ ID NO:16): Predicted Nucleic acid sequence for dog CD31, partial sequence contained within chromosome 9 sequence (AAEX01022173.1) position 77862 to position 77586 on the minus strand

GAATCCTTCTCTAATCCCAAATTCCACGTCAGCCCCGAAGGAGTGATCACAGAAGGAGATCA
GCTCTACATTAGGTGCACCATTCAAGTGACACATCTGGTCCAAGCATTTCCAGAAATCATAA
TCCAGAAGGACAAGGCAATTGTAGCACACAAGAGGCATGGTAACGAAGCCACCTACTCAGTG
ATGGCCATGGCGGAGCACAATGGCAATTACACATGCAAAGTGGAAGCCAGCCGGATATCCAA
GGTCAGCAGCATCGTGGTCAACATAACAG

(SEQ ID NO:17): Nucleic acid sequence for human CD31(BC022512)
>gi|18490918|gb|BC022512.1| Homo sapiens platelet/endothelial cell adhesion molecule (CD31 antigen), mRNA (cDNA clone MGC:26550 IMAGE:4816878), complete cds

TTTCCAGCCATGGCTGCCATTACCTGACCAGCGCCACAGCCGGTCTCTCTGCAGGCGCCGGG
AGAAGTGACCAGAGCAATTTCTGCTTTTCACAGGGCGGGTTTCTCAACGGTGACTTGTGGGC
AGTGCCTTCTGCTGAGCGAGTCATGGCCCGAAGGCAGAACTAACTGTGCCTGCAGTCTTCAC
TCTCAGGATGCAGCCGAGGTGGGCCCAAGGGGCCACGATGTGGCTTGGAGTCCTGCTGACCC
TTCTGCTCTGTTCAAGCCTTGAGGGTCAAGAAAACTCTTTCACAATCAACAGTGTTGACATG
AAGAGCCTGCCGGACTGGACGGTGCAAAATGGGAAGAACCTGACCCTGCAGTGCTTCGCGGA

TGTCAGCACCACCTCTCACGTCAAGCCTCAGCACCAGATGCTGTTCTATAAGGATGACGTGC
TGTTTTACAACATCTCCTCCATGAAGAGCACAGAGAGTTATTTTATTCCTGAAGTCCGGATC
TATGACTCAGGGACATATAAATGTACTGTGATTGTGAACAACAAAGAGAAAACCACTGCAGA
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TCCAAGGTGGGATCGTGAGGGTCAACTGTTCTGTCCCAGAGGAAAAGGCCCCAATACACTTC
ACAATTGAAAAACTTGAACTAAATGAAAAAATGGTCAAGCTGAAAAGAGAGAAGAATTCTCG
AGACCAGAATTTTGTGATACTGGAATTCCCCGTTGAGGAACAGGACCGCGTTTTATCCTTCC
GATGTCAAGCTAGGATCATTTCTGGGATCCATATGCAGACCTCAGAATCTACCAAGAGTGAA
CTGGTCACCGTGACGGAATCCTTCTCTACACCCAAGTTCCACATCAGCCCCACCGGAATGAT
CATGGAAGGAGCTCAGCTCCACATTAAGTGCACCATTCAAGTGACTCACCTGGCCCAGGAGT
TTCCAGAAATCATAATTCAGAAGGACAAGGCGATTGTGGCCCACAACAGACATGGCAACAAG
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CAGCCGCATATCCAAGGTCAGCAGCATCGTGGTCAACATAACAGAACTATTTTCCAAGCCCG
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ATCGATCAGTGGAACTTTGCCTATTTCTTACCAACTTTTAAAAACAAGTAAAGTTTTGGAGA
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TACCAGTGTGTTGCAGATAATTGCCATTCCCACGCCAAAATGTTAAGTGAGGTTCTGAGGGT
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CCATGGAAGAAAGGACTTATTGCAGTGGTTATCATCGGAGTGATCATTGCTCTCTTGATCAT
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ACAAAGATCTAGGAAAGAAGGACACAGAGACAGTGTACAGTGAAGTCCGGAAAGCTGTCCCT
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AGGGGCTGTTGAATTTCCCACATACACTCCTTCCACCAAGTTGGAACATCCTTGGAAATTGG
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CCTTCAAAGGCTTGTAGTTTTGGGTAGTCCTTGTTCTTTGGAAATACACAGTGCTGACCAGA
CAGCCTCCCCCTGTCCCCTCTATGACCTCGCCCTCCACAAATGGGAAAACCAGACTACTTGG
GAGCACCGCCTGTGAAATACCAACCTGAAGACACGGTTCATTCAGGCAACGCACAAAACAGA
AAATGAAGGTGGAACAAGCACAGATGTTCTTCAACTGTTTTTGTCTACACTCTTTCTCTTTT
CCTCTACCATGCTGAAGGCTGAAAGACAGGAAGATGGTGCCATCAGCAAATATTATTCTTAA
TTGAAAACTTGAAAAAAAAAAAAAAAA

(SEQ ID NO:18): Protein sequence for human CD31 (AAH22512)

>gi|18490919|gb|AAH22512.1| Platelet/endothelial cell adhesion molecule (CD31 antigen) [Homo sapiens]

MQPRWAQGATMWLGVLLTLLLCSSLEGQENSFTINSVDMKSLPDWTVQNGKNLTLQCFADVS
TTSHVKPQHQMLFYKDDVLFYNISSMKSTESYFIPEVRIYDSGTYKCTVIVNNKEKTTAEYQ
VLVEGVPSPRVTLDKKEAIQGGIVRVNCSVPEEKAPIHFTIEKLELNEKMVKLKREKNSRDQ
NFVILEFPVEEQDRVLSFRCQARIISGIHMQTSESTKSELVTVTESFSTPKFHISPTGMIME
GAQLHIKCTIQVTHLAQEFPEIIIQKDKAIVAHNRHGNKAVYSVMAMVEHSGNYTCKVESSR
ISKVSSIVVNITELFSKPELESSFTHLDQGERLNLSCSIPGAPPANFTIQKEDTIVSQTQDF
TKIASKSDSGTYICTAGIDKVVKKSNTVQIVVCEMLSQPRISYDAQFEVIKGQTIEVRCESI
SGTLPISYQLLKTSKVLENSTKNSNDPAVFKDNPTEDVEYQCVADNCHSHAKMLSEVLRVKV
IAPVDEVQISILSSKVVESGEDIVLQCAVNEGSGPITYKFYREKEGKPFYQMTSNATQAFWT
KQKANKEQEGEYYCTAFNRANHASSVPRSKILTVRVILAPWKKGLIAVVIIGVIIALLIIAA
KCYFLRKAKAKQMPVEMSRPAVPLLNSNNEKMSDPNMEANSHYGHNDDVGNHAMKPINDNKE
PLNSDVQYTEVQVSSAESHKDLGKKDTETVYSEVRKAVPDAVESRYSRTEGSLDGT

(SEQ ID NO:19): Predicted Nucleic acid sequence for dog CD105, partial sequence from AAEX01025446.1, position 17214 to position 17370

CCTCCAGGGGTGGCTGTGAGGATTCAGAGCTGATAAGGCCACCGACTGCCTAGGGTGGGGCC
TGGGGCACTGGGGTGTTCGGCCCCTGAGGCCGGGTTAACTGTCCCCCAGGGTACAGACCCTG
TTCAGAGGGCCTCGGGGAAACCTCCCAGCCCCC

(SEQ ID NO:20): Nucleic acid sequence for human CD105 (NM_000118)

>gi|4557554|ref|NM_000118.1| Homo sapiens endoglin (Osler-Rendu-Weber syndrome 1) (ENG), mRNA

CCTGGGCCGGCCGGGCTGGATGAGCCGGGAGCTCCCTGCTGCCGGTCATACCACAGCCTTCA
TCTGCGCCCTGGGGCCAGGACTGCTGCTGTCACTGCCATCCATTGGAGCCCAGCACCCCCTC
CCCGCCCATCCTTCGGACAGCAACTCCAGCCCAGCCCCGCGTCCCTGTGTCCACTTCTCCTG
ACCCCTCGGCCGCCACCCCAGAAGGCTGGAGCAGGGACGCCGTCGCTCCGGCCGCCTGCTCC
CCTCGGGTCCCCGTGCGAGCCCACGCCGGCCCCGGTGCCCGCCCGCAGCCCTGCCACTGGAC
ACAGGATAAGGCCCAGCGCACAGGCCCCCACGTGGACAGCATGGACCGCGGCACGCTCCCTC
TGGCTGTTGCCCTGCTGCTGGCCAGCTGCAGCCTCAGCCCCACAAGTCTTGCAGAAACAGTC
CATTGTGACCTTCAGCCTGTGGGCCCCGAGAGGGGCGAGGTGACATATACCACTAGCCAGGT
CTCGAAGGGCTGCGTGGCTCAGGCCCCCAATGCCATCCTTGAAGTCCATGTCCTCTTCCTGG
AGTTCCCAACGGGCCCGTCACAGCTGGAGCTGACTCTCCAGGCATCCAAGCAAAATGGCACC
TGGCCCCGAGAGGTGCTTCTGGTCCTCAGTGTAAACAGCAGTGTCTTCCTGCATCTCCAGGC
CCTGGGAATCCCACTGCACTTGGCCTACAATTCCAGCCTGGTCACCTTCCAAGAGCCCCCGG
GGGTCAACACCACAGAGCTGCCATCCTTCCCCAAGACCCAGATCCTTGAGTGGGCAGCTGAG
AGGGGCCCCATCACCTCTGCTGCTGAGCTGAATGACCCCCAGAGCATCCTCCTCCGACTGGG
CCAAGCCCAGGGGTCACTGTCCTTCTGCATGCTGGAAGCCAGCCAGGACATGGGCCGCACGC
TCGAGTGGCGGCCGCGTACTCCAGCCTTGGTCCGGGGCTGCCACTTGGAAGGCGTGGCCGGC
CACAAGGAGGCGCACATCCTGAGGGTCCTGCCGGGCCACTCGGCCGGGCCCCGGACGGTGAC
GGTGAAGGTGGAACTGAGCTGCGCACCCGGGGATCTCGATGCCGTCCTCATCCTGCAGGGTC
CCCCCTACGTGTCCTGGCTCATCGACGCCAACCACAACATGCAGATCTGGACCACTGGAGAA
TACTCCTTCAAGATCTTTCCAGAGAAAAACATTCGTGGCTTCAAGCTCCCAGACACACCTCA
AGGCCTCCTGGGGGAGGCCCGGATGCTCAATGCCAGCATTGTGGCATCCTTCGTGGAGCTAC
CGCTGGCCAGCATTGTCTCACTTCATGCCTCCAGCTGCGGTGGTAGGCTGCAGACCTCACCC
GCACCGATCCAGACCACTCCTCCCAAGGACACTTGTAGCCCGGAGCTGCTCATGTCCTTGAT
CCAGACAAAGTGTGCCGACGACGCCATGACCCTGGTACTAAAGAAAGAGCTTGTTGCGCATT

TGAAGTGCACCATCACGGGCCTGACCTTCTGGGACCCCAGCTGTGAGGCAGAGGACAGGGGT
GACAAGTTTGTCTTGCGCAGTGCTTACTCCAGCTGTGGCATGCAGGTGTCAGCAAGTATGAT
CAGCAATGAGGCGGTGGTCAATATCCTGTCGAGCTCATCACCACAGCGGAAAAAGGTGCACT
GCCTCAACATGGACAGCCTCTCTTTCCAGCTGGGCCTCTACCTCAGCCCACACTTCCTCCAG
GCCTCCAACACCATCGAGCCGGGGCAGCAGAGCTTTGTGCAGGTCAGAGTGTCCCCATCCGT
CTCCGAGTTCCTGCTCCAGTTAGACAGCTGCCACCTGGACTTGGGGCCTGAGGGAGGCACCG
TGGAACTCATCCAGGGCCGGGCGGCCAAGGGCAACTGTGTGAGCCTGCTGTCCCCAAGCCCC
GAGGGTGACCCGCGCTTCAGCTTCCTCCTCCACTTCTACACAGTACCCATACCCAAAACCGG
CACCCTCAGCTGCACGGTAGCCCTGCGTCCCAAGACCGGGTCTCAAGACCAGGAAGTCCATA
GGACTGTCTTCATGCGCTTGAACATCATCAGCCCTGACCTGTCTGGTTGCACAAGCAAAGGC
CTCGTCCTGCCCGCCGTGCTGGGCATCACCTTTGGTGCCTTCCTCATCGGGGCCCTGCTCAC
TGCTGCACTCTGGTACATCTACTCGCACACGCGTGAGTACCCCAGGCCCCCACAGTGAGCAT
GCCGGGCCCCTCCATCCACCCGGGGGAGCCCAGTGAAGCCTCTGAGGGATTGAGGGGCCCTG
GCAGGACCCTGACCTCCGCCCCTGCCCCCGCTCCCGCTCCCAGGTTCCCCCAGCAAGCGGGA
GCCCGTGGTGGCGGTGGCTGCCCCGGCCTCCTCGGAGAGCAGCAGCACCAACCACAGCATCG
GGAGCACCCAGAGCACCCCCTGCTCCACCAGCAGCATGGCATAGCCCCGGCCCCCCGCGCTC
GCCCAGCAGGAGAGACTGAGCAGCCGCCAGCTGGGAGCACTGGTGTGAACTCACCCTGGGAG
CCAGTCCTCCACTCGACCCAGAATGGAGCCTGCTCTCCGCGCCTACCCTTCCCGCCTCCCTC
TCAGAGGCCTGCTGCCAGTGCAGCCACTGGCTTGGAACACCTTGGGGTCCCTCCACCCCACA
GAACCTTCAACCCAGTGGGTCTGGGATATGGCTGCCCAGGAGACAGACCACTTGCCACGCTG
TTGTAAAAACCCAAGTCCCTGTCATTTGAACCTGGATCCAGCACTGGTGAACTGAGCTGGGC
AGGAAGGGAGAACTTGAAACAGATTCAGGCCAGCCCAGCCAGGCCAACAGCACCTCCCCGCT
GGGAAGAGAAGAGGGCCCAGCCCAGAGCCACCTGGATCTATCCCTGCGGCCTCCACACCTGA
ACTTGCCTAACTAACTGGCAGGGGAGACAGGAGCCTAGCGGAGCCCAGCCTGGGAGCCCAGA
GGGTGGCAAGAACAGTGGGCGTTGGGAGCCTAGCTCCTGCCACATGGAGCCCCCTCTGCCGG
TCGGGCAGCCAGCAGAGGGGGAGTAGCCAAGCTGCTTGTCCTGGGCCTGCCCCTGTGTATTC
ACCACCAATAAATCAGACCATGAAACCTGAAAAAAAAAAAAA

(SEQ ID NO:21): Protein sequence for human CD105 (NP_000109.1)

>gi|4557555|ref|NP_000109.1| endoglin precursor; Endoglin [Homo sapiens]

MDRGTLPLAVALLLASCSLSPTSLAETVHCDLQPVGPERGEVTYTTSQVSKGCVAQAPNAIL
EVHVLFLEFPTGPSQLELTLQASKQNGTWPREVLLVLSVNSSVFLHLQALGIPLHLAYNSSL
VTFQEPPGVNTTELPSFPKTQILEWAAERGPITSAAELNDPQSILLRLGQAQGSLSFCMLEA
SQDMGRTLEWRPRTPALVRGCHLEGVAGHKEAHILRVLPGHSAGPRTVTVKVELSCAPGDLD
AVLILQGPPYVSWLIDANHNMQIWTTGEYSFKIFPEKNIRGFKLPDTPQGLLGEARMLNASI
VASFVELPLASIVSLHASSCGGRLQTSPAPIQTTPPKDTCSPELLMSLIQTKCADDAMTLVL
KKELVAHLKCTITGLTFWDPSCEAEDRGDKFVLRSAYSSCGMQVSASMISNEAVVNILSSSS
PQRKKVHCLNMDSLSFQLGLYLSPHFLQASNTIEPGQQSFVQVRVSPSVSEFLLQLDSCHLD
LGPEGGTVELIQGRAAKGNCVSLLSPSPEGDPRFSFLLHFYTVPIPKTGTLSCTVALRPKTG
SQDQEVHRTVFMRLNIISPDLSGCTSKGLVLPAVLGITFGAFLIGALLTAALWYIYSHTREY
PRPPQ

(SEQ ID NO:22): Predicted Nucleic acid sequence for dog CD106, partial sequence from AAEX01044853.1, position 134174 to position 135113

TTCCAGGAAGAGAAAATAACAAGGACTATTTTTCTCCAGAACTACTCGTGCTTTATTGTGCA
TCTTCCTTGATAATACCAGCCATTGGGATGATCATTTACTTTGCCAGAAGAGCCAACATGAA
GGGGTCATACAGTCTTGTAGAAGCACAGAAATCAAAAGTGTAGCTAATGTTTGCAATGGTCA
ACTAGAGACACTATTTATCAGTCCAAATTCTTAATACTGCTCATCATTCCATGAGGGAAACA
AACTAAGAGTCCAGACTTCCCTGAATGTAGTGAATTCTTGGAAAGAAATGGCTTCCTGTGCC
CCATGCTGTGAGCAAGAGGCTAAAAGAAAACTTTCTGCCTGAAACTGGAGTAGCTCCTTGAT
GTGTATATACAATAACATGATCTGTACATATGTAAAATAAATTTATGCCATAGGAGGATCAC
TTGGAATAACAGCACTCTATAGTTAGATCTTCAAAATATTTAAACAGTGTTGCCTCGGTTGG
TCGTAACGGAATGCATCTTAAGAAAATTTAACATGAATATTGACTGGCAGCTAACCTATGTC
ATCTTCTTAATATTTTGTTTTCTTTAACAAAATTTTATTTTGGTAAAATTTATTTCATTGAC
AATAATTTCATGTTTTATGAAGATACCAAGGTTTATCTTTTTATGGGTAAATGATAAACCAA
CAAGGCACTAGGTTCACCTTCAGGTACTAAATACTTCAACCCATGGTATAATGGTTGACTGG
ATTTCTCTGGATGGTACTTACATGGTACGAAGATGTTTTATGATGTTGTTTATCAGACTTTT
GTGTAACTTTTCCAATGTGGTCTAAAATGCAACTGCTTTTGATTTTCTTTTGTAAATGTTTA
GGGGTTCTTTTTGTATAGTAAAGTGATAATATCCAGAATTAGAA

(SEQ ID NO:23): Nucleic acid sequence for human CD106 (NM_001078)

>gi|18201907|ref|NM_001078.2| Homo sapiens vascular cell adhesion molecule 1 (VCAM1), transcript variant 1, mRNA

CGCGGTATCTGCATCGGGCCTCACTGGCTTCAGGAGCTGAATACCCTCCCAGGCACACACAG
GTGGGACACAAATAAGGGTTTTGGAACCACTATTTTCTCATCACGACAGCAACTTAAAATGC
CTGGGAAGATGGTCGTGATCCTTGGAGCCTCAAATATACTTTGGATAATGTTTGCAGCTTCT
CAAGCTTTTAAAATCGAGACCACCCCAGAATCTAGATATCTTGCTCAGATTGGTGACTCCGT
CTCATTGACTTGCAGCACCACAGGCTGTGAGTCCCCATTTTTCTCTTGGAGAACCCAGATAG
ATAGTCCACTGAATGGGAAGGTGACGAATGAGGGGACCACATCTACGCTGACAATGAATCCT
GTTAGTTTTGGGAACGAACACTCTTACCTGTGCACAGCAACTTGTGAATCTAGGAAATTGGA
AAAAGGAATCCAGGTGGAGATCTACTCTTTTCCTAAGGATCCAGAGATTCATTTGAGTGGCC
CTCTGGAGGCTGGGAAGCCGATCACAGTCAAGTGTTCAGTTGCTGATGTATACCCATTTGAC
AGGCTGGAGATAGACTTACTGAAAGGAGATCATCTCATGAAGAGTCAGGAATTTCTGGAGGA
TGCAGACAGGAAGTCCCTGGAAACCAAGAGTTTGGAAGTAACCTTTACTCCTGTCATTGAGG
ATATTGGAAAAGTTCTTGTTTGCCGAGCTAAATTACACATTGATGAAATGGATTCTGTGCCC
ACAGTAAGGCAGGCTGTAAAAGAATTGCAAGTCTACATATCACCCAAGAATACAGTTATTTC
TGTGAATCCATCCACAAAGCTGCAAGAAGGTGGCTCTGTGACCATGACCTGTTCCAGCGAGG
GTCTACCAGCTCCAGAGATTTTCTGGAGTAAGAAATTAGATAATGGGAATCTACAGCACCTT
TCTGGAAATGCAACTCTCACCTTAATTGCTATGAGGATGGAAGATTCTGGAATTTATGTGTG
TGAAGGAGTTAATTTGATTGGGAAAAACAGAAAAGAGGTGGAATTAATTGTTCAAGAGAAAC
CATTTACTGTTGAGATCTCCCCTGGACCCCGGATTGCTGCTCAGATTGGAGACTCAGTCATG
TTGACATGTAGTGTCATGGGCTGTGAATCCCCATCTTTCTCCTGGAGAACCCAGATAGACAG
CCCTCTGAGCGGGAAGGTGAGGAGTGAGGGGACCAATTCCACGCTGACCCTGAGCCCTGTGA
GTTTTGAGAACGAACACTCTTATCTGTGCACAGTGACTTGTGGACATAAGAAACTGGAAAAG
GGAATCCAGGTGGAGCTCTACTCATTCCCTAGAGATCCAGAAATCGAGATGAGTGGTGGCCT
CGTGAATGGGAGCTCTGTCACTGTAAGCTGCAAGGTTCCTAGCGTGTACCCCCTTGACCGGC
TGGAGATTGAATTACTTAAGGGGGAGACTATTCTGGAGAATATAGAGTTTTTGGAGGATACG
GATATGAAATCTCTAGAGAACAAAAGTTTGGAAATGACCTTCATCCCTACCATTGAAGATAC
TGGAAAAGCTCTTGTTTGTCAGGCTAAGTTACATATTGATGACATGGAATTCGAACCCAAAC
AAAGGCAGAGTACGCAAACACTTTATGTCAATGTTGCCCCCAGAGATACAACCGTCTTGGTC
AGCCCTTCCTCCATCCTGGAGGAAGGCAGTTCTGTGAATATGACATGCTTGAGCCAGGGCTT
TCCTGCTCCGAAAATCCTGTGGAGCAGGCAGCTCCCTAACGGGGAGCTACAGCCTCTTTCTG

AGAATGCAACTCTCACCTTAATTTCTACAAAAATGGAAGATTCTGGGGTTTATTTATGTGAA
GGAATTAACCAGGCTGGAAGAAGCAGAAAGGAAGTGGAATTAATTATCCAAGTTACTCCAAA
AGACATAAAACTTACAGCTTTTCCTTCTGAGAGTGTCAAAGAAGGAGACACTGTCATCATCT
CTTGTACATGTGGAAATGTTCCAGAAACATGGATAATCCTGAAGAAAAAAGCGGAGACAGGA
GACACAGTACTAAAATCTATAGATGGCGCCTATACCATCCGAAAGGCCCAGTTGAAGGATGC
GGGAGTATATGAATGTGAATCTAAAAACAAAGTTGGCTCACAATTAAGAAGTTTAACACTTG
ATGTTCAAGGAAGAGAAAACAACAAAGACTATTTTTCTCCTGAGCTTCTCGTGCTCTATTTT
GCATCCTCCTTAATAATACCTGCCATTGGAATGATAATTTACTTTGCAAGAAAAGCCAACAT
GAAGGGGTCATATAGTCTTGTAGAAGCACAGAAATCAAAAGTGTAGCTAATGCTTGATATGT
TCAACTGGAGACACTATTTATCTGTGCAAATCCTTGATACTGCTCATCATTCCTTGAGAAAA
ACAATGAGCTGAGAGGCAGACTTCCCTGAATGTATTGAACTTGGAAAGAAATGCCCATCTAT
GTCCCTTGCTGTGAGCAAGAAGTCAAAGTAAAACTTGCTGCCTGAAGAACAGTAACTGCCAT
CAAGATGAGAGAACTGGAGGAGTTCCTTGATCTGTATATACAATAACATAATTTGTACATAT
GTAAAATAAAATTATGCCATAGCAAGATTGCTTAAAATAGCAACACTCTATATTTAGATTGT
TAAAATAACTAGTGTTGCTTGGACTATTATAATTTAATGCATGTTAGGAAAATTTCACATTA
ATATTTGCTGACAGCTGACCTTTGTCATCTTTCTTCTATTTTATTCCCTTTCACAAAATTTT
ATTCCTATATAGTTTATTGACAATAATTTCAGGTTTTGTAAAGATGCCGGGTTTTATATTTT
TATAGACAAATAATAAGCAAAGGGAGCACTGGGTTGACTTTCAGGTACTAAATACCTCAACC
TATGGTATAATGGTTGACTGGGTTTCTCTGTATAGTACTGGCATGGTACGGAGATGTTTCAC
GAAGTTTGTTCATCAGACTCCTGTGCAACTTTCCCAATGTGGCCTAAAAATGCAACTTCTTT
TTATTTTCTTTTGTAAATGTTTAGGTTTTTTTGTATAGTAAAGTGATAATTTCTGGAATTAG
AAAAAAAAAAAAAAAAAAA

(SEQ ID NO:24): Protein sequence for human CD106 (NP_001069)
>gi|4507875|ref|NP_001069.1| vascular cell adhesion molecule 1 isoform a precursor; CD106 antigen [Homo sapiens]

MPGKMVVILGASNILWIMFAASQAFKIETTPESRYLAQIGDSVSLTCSTTGCESPFFSWRTQ
IDSPLNGKVTNEGTTSTLTMNPVSFGNEHSYLCTATCESRKLEKGIQVEIYSFPKDPEIHLS
GPLEAGKPITVKCSVADVYPFDRLEIDLLKGDHLMKSQEFLEDADRKSLETKSLEVTFTPVI
EDIGKVLVCRAKLHIDEMDSVPTVRQAVKELQVYISPKNTVISVNPSTKLQEGGSVTMTCSS
EGLPAPEIFWSKKLDNGNLQHLSGNATLTLIAMRMEDSGIYVCEGVNLIGKNRKEVELIVQE
KPFTVEISPGPRIAAQIGDSVMLTCSVMGCESPSFSWRTQIDSPLSGKVRSEGTNSTLTLSP
VSFENEHSYLCTVTCGHKKLEKGIQVELYSFPRDPEIEMSGGLVNGSSVTVSCKVPSVYPLD
RLEIELLKGETILENIEFLEDTDMKSLENKSLEMTFIPTIEDTGKALVCQAKLHIDDMEFEP
KQRQSTQTLYVNVAPRDTTVLVSPSSILEEGSSVNMTCLSQGFPAPKILWSRQLPNGELQPL
SENATLTLISTKMEDSGVYLCEGINQAGRSRKEVELIIQVTPKDIKLTAFPSESVKEGDTVI
ISCTCGNVPETWIILKKKAETGDTVLKSIDGAYTIRKAQLKDAGVYECESKNKVGSQLRSLT
LDVQGRENNKDYFSPELLVLYFASSLIIPAIGMIIYFARKANMKGSYSLVEAQKSKV

(SEQ ID NO:25): Predicted Nucleic acid sequence for dog CD146, partial sequence from chromosome 5 sequence (AAEX01009397.1) position 3260 to position 3439

gggttcacattcagtcgtcccagatcgtggagtccagtggtctgtacaccttggagagcgtt
ctgaaggcccagctggccaaagaggataaagatgcccagttttactgtgagctcaactaccg
gctgcccagcgggaaccacatgaaggagtctcaggaagtcactgtccaggttttct

(SEQ ID NO:26): Nucleic acid sequence for human CD146

(AF089868)

>gi|4336423|gb|AF089868.1|AF089868 Homo sapiens cell surface glycoprotein P1H12 precursor, mRNA, complete cds

GGCACGAGCTCCGGCCGGGAAGCATGGGGCTTCCCAGGCTGGTCTGCGCCTTCTTGCTCGCC
GCCTGCTGCTGCTGTCCTCGCGTCGCGGGTGTGCCCGGAGAGGCTGAGCAGCCTGCGCCTGA
GCTGGTGGAGGTGGAAGTGGGCAGCACAGCCCTTCTGAAGTGCGGCCTCTCCCAGTCCCAAG
GCAACCTCAGCCATGTCGACTGGTTTTCTGTCCACAAGGAGAAGCGGACGCTCATCTTCCGT
GTGCGCCAGGGCCAGGGCCAGAGCGAACCTGGGGAGTACGAGCAGCGGCTCAGCCTCCAGGA
CAGAGGGGCTACTCTGGCCCTGACTCAAGTCACCCCCCAAGACGAGCGCATCTTCTTGTGCC
AGGGCAAGCGCCCTCGGTCCCAGGAGTACCGCATCCAGCTCCGCGTCTACAAAGCTCCGGAG
GAGCCAAACATCCAGGTCAACCCCCTGGGCATCCCTGTGAACAGTAAGGAGCCTGAGGAGGT
CGCTACCTGTGTAGGGAGGAACGGGTACCCCATTCCTCAAGTCATCTGGTACAAGAATGGCC
GGCCTCTGAAGGAGGAGAAGAACCGGGTCCACATTCAGTCGTCCCAGACTGTGGAGTCGAGT
GGTTTGTACACCTTGCAGAGTATTCTGAAGGCACAGCTGGTTAAAGAAGACAAAGATGCCCA
GTTTTACTGTGAGCTCAACTACCGGCTGCCCAGTGGGAACCACATGAAGGAGTCCAGGGAAG
TCACCGTCCCTGTTTTCTACCCGACAGAAAAAGTGTGGCTGGAAGTGGAGCCCGTGGGAATG
CTGAAGGAAGGGGACCGCGTGGAAATCAGGTGTTTGGCTGATGGCAACCCTCCACCACACTT
CAGCATCAGCAAGCAGAACCCCAGCACCAGGGAGGCAGAGGAAGAGACAACCAACGACAACG
GGGTCCTGGTGCTGGAGCCTGCCCGGAAGGAACACAGTGGGCGCTATGAATGTCAGGGCCTG
GACTTGGACACCATGATATCGCTGCTGAGTGAACCACAGGAACTACTGGTGAACTATGTGTC
TGACGTCCGAGTGAGTCCCGCAGCCCCTGAGAGACAGGAAGGCAGCAGCCTCACCCTGACCT
GTGAGGCAGAGAGTAGCCAGGACCTCGAGTTCCAGTGGCTGAGAGAAGAGACAGACCAGGTG
CTGGAAAGGGGGCCTGTGCTTCAGTTGCATGACCTGAAACGGGAGGCAGGAGGCGGCTATCG
CTGCGTGGCGTCTGTGCCCAGCATACCCGGCCTGAACCGCACACAGCTGGTCAACGTGGCCA
TTTTTGGCCCCCCTTGGATGGCATTCAAGGAGAGGAAGGTGTGGGTGAAAGAGAATATGGTG
TTGAATCTGTCTTGTGAAGCGTCAGGGCACCCCCGGCCCACCATCTCCTGGAACGTCAACGG
CACGGCAAGTGAACAAGACCAAGATCCACAGCGAGTCCTGAGCACCCTGAATGTCCTCGTGA
CCCCGGAGCTGTTGGAGACAGGTGTTGAATGCACGGCCTCCAACGACCTGGGCAAAAACACC
AGCATCCTCTTCCTGGAGCTGGTCAATTTAACCACCCTCACACCAGACTCCAACACAACCAC
TGGCCTCAGCACTTCCACTGCCAGTCCTCATACCAGAGCCAACAGCACCTCCACAGAGAGAA
AGCTGCCGGAGCCGGAGAGCCGGGGCGTGGTCATCGTGGCTGTGATTGTGTGCATCCTGGTC
CTGGCGGTGCTGGGCGCTGTCCTCTATTTCCTCTATAAGAAGGGCAAGCTGCCGTGCAGGCG
CTCAGGGAAGCAGGAGATCACGCTGCCCCCGTCTCGTAAGAGCGAACTTGTAGTTGAAGTTA
AGTCAGATAAGCTCCCAGAAGAGATGGGCCTCCTGCAGGGCAGCAGCGGTGACAAGAGGGCT
CCGGGAGACCAGGGAGAGAAATACATCGATCTGAGGCATTAGCCCCGAATCACTTCAGCTCC
CTTCCCTGCCTGGACCATTCCCAGCTCCCTGCTCACTCTTCTCTCAGCCAAAGCCTCCAAAG
GGACTAGAGAGAAGCCTCCTGCTCCCCTCGCCTGCACACCCCCTTTCAAAGGGCCACTGGGT
TAGGACCTGAGGACCTCACTTGGCCCTGCAAGGCCCGCTTTTCAGGGACCAGTCCACCACCA
TCTCCTCCACGTTGAGTGAAGCTCATCCCAAGCAAGGAGCCCCAGTCTCCCGAGCGGGTAGG
AGAGTTTCTTGCAGAACGTGTTTTTTCTTTACACACATTATGGCTGTAAATACCTGGCTCCT
GCCAGCAGCTGAGCTGGGTAGCCTCTCTGAGCTGGTTTCCTGCCCCAAAGGCTGGCTTCCAC
CATCCAGGTGCACCACTGAAGTGAGGACACACCGGAGCCAGGCGCCTGCTCATGTTGAAGTG
CGCTGTTCACACCCGCTCCGGAGAGCACCCCAGCAGCATCCAGAAGCAGCTGCAGTGTTGCT
GCCACCACCCTCCTGTCTGCCTCTTCAAAGTCTCCTGTGACATTTTTTCTTTGGTCAGAAGC
CAGGAACTGGTGTCATTCCTTAAAAGATACGTGCCGGGGCCAGGTGTGGTGGCTCACGCCTG
TAATCCCAGCACTTTGGGAGGCCGAGGCGGGCGGATCACAAAGTCAGGACGAGACCATCCTG
GCTAACACGGTGAAACCCTGTCTCTACTAAAAATACAAAAAAAAATTAGCTAGGCGTAGTGG
TTGGCACCTATAGTCCCAGCTACTCGGAAGGCTGAAGCAGGAGAATGGTATGAATCCAGGAG
GTGGAGCTTGCAGTGAGCCGAGACCGTGCCACTGCACTCCAGCCTGGGCAACACAGCGAGAC
TCCGTCTCGAGGAAAAAAAAAGAAAAGACGCGTGCCTGCGGTGAGGAAGCTGGGCGCTGTTT

TCGAGTTCAGGTGAATTAGCCTCAATCCCCCGTGTTCACTTGGCTCCCATAGCCCTCTTGAT
GGATCACGTAAAACTGAAAGGCAGCGGGGAGCAGACAAAGATGAGGTCTACACTGTCCTTCA
TGGGGATTAAAGCTATGGTTATATTAGCACCAAACTTCTACAAACCAAGCTCAGGGCCCCAA
CCCTAGAAGGGCCCAAATGAGAGAATGGTACTTAGGGATGGAAAACGGGCCTGGCTAGAGCT
ACGGGTGTGTGTGTCTGTCTATGTGTATGCATACATATGTGTGTATATATGGTTTTGTCAGG
TGTGTAAATTTGCAAATTGTTTCCTTTATATATGTATGTATATATATATATGAAAATATATA
TATATATGAAAAATAAAGCTTAATTGTCCCAGAAAAAAAAAAAAAAAAA

(SEQ ID NO:27): Protein sequence for human CD146 (CAA48332.1)
>gi|825693|emb|CAA48332.1| melanoma associated glycoprotein [Homo sapiens]

MGLPRLVCAFLLAACCCCPRVAGVPGEAEQPAPELVEVEVGSTALLKCGLSQSQGNLSHVDW
FSVHKEKRTLIFRVRQGQGQSEPGEYEQRLSLQDRGATLALTQVTPQDERIFLCQGKRPRSQ
EYRIQLRVYKAPEEPNIQVNPLGIPVNSKEPEEVATCVGRNGYPIPQVIWYKNGRPLKEEKN
RVHIQSSQTVESSGLYTLQSILKAQLVKEDKDAQFYCELNYRLPSGNHMKESREVTVPVFYP
TEKVWLEVEPVGMLKEGDRVEIRCLADGNPPPHFSISKQNPSTREAEEETTNDNGVLVLEPA
RKEHSGRYECQAWNLDTMISLLSEPQELLVNYVSDVRVSPAAPERQEGSSLTLTCEAESSQD
LEFQWLREETDQVLERGPVLQLHDLKREAGGGYRCVASVPSIPGLNRTQLVKLAIFGPPWMA
FKERKVWVKENMVLNLSCEASGHPRPTISWNVNGTASEQDQDPQRVLSTLNVLVTPELLETG
VECTASNDLGKNTSILFLELVNLTTLTPDSNTTTGLSTSTASPHTRANSTSTERKLPEPESR
GVVIVAVIVCILVLAVLGAVLYFLYKKGKLPCRRSGKQEITLPPSRKTELVVEVKSDKLPEE
MGLLQGSSGDKRAPGDQGEKYIDLRH

(SEQ ID NO:28): Nucleic acid sequence for dog vWF (U66246)
>gi|40786759|gb|U66246.2|CFU66246 Canis familiaris von Willebrand factor mRNA, complete cds

TCGGCCTCAGCTGCTGGGAGCATGGCCTAGGCCGGTGGCGCTGTCGTGCGGCCACCTTCCCA
ACGGACCTTCGAGATACCTGTTGGCCCCGCTTGCAGGGAAAGATGAGTCCTACCAGACTTGT
GAGGGTGCTGCTGGCTCTGGCCCTCATCTTGCCAGGGAAACTTTGTACAAAAGGGACTGTTG
GAAGGTCATCGATGGCCCGATGTAGCCTCTTCGGAGGTGACTTCATCAACACCTTTGATGAG
AGCATGTACAGCTTTGCGGGAGATTGCAGTTACCTCCTGGCTGGGGACTGCCAGGAACACTC
CGTCTCACTTATCGGGGGTTTCCAAAATGGCAAAAGAGTGAGCCTCTCCGTGTATCTCGGAG
AATTTTTCGACATTCATTTGTTTGTCAATGGTACCATGCTGCAGGGGACCCAAAGCATCTCC
ATGCCCTACGCCTCCAATGGGCTGTATCTAGAGGCCGAGGCTGGCTACTACAAGCTGTCCAG
TGAGGCCTACGGCTTTGTGGCCAGAATTGATGGCAATGGCAACTTTCAAGTCCTGCTGTCAG
ACAGATACTTCAACAAGACCTGTGGGCTGTGTGGCAACTTTAATATCTTTGCTGAGGATGAC
TTCAGGACTCAAGAAGGGACGTTGACTTCGGACCCCTATGACTTTGCCAACTCCTGGGCCCT
GAGCAGTGGGGAACAACGGTGCAAACGGGTGTCCCCTCCCAGCAGCCCATGCAATGTCTCCT
CTGATGAAGTGCAGCAGGTCCTGTGGGAGCAGTGCCAGCTCCTGAAGAGTGCCTCGGTGTTT
GCCCGCTGCCACCCGCTGGTGGACCCTGAGCCTTTTGTCGCCCTGTGTGAAAGGACTCTGTG
CACCTGTGTCCAGGGGATGGAGTGCCCTTGTGGGGTCCTCCTGGAGTACGCCCGGGCCTGTG
CCCAGCAGGGGGTTGTCTTGTACGGCTGGACCGACCACAGCGTCTGCCGACCAGCATGCCCT
GCTGGCATGGAGTACAAGGAGTGCGTGTCCCCTTGCACCAGAACTTGCCAGAGCCTTCATGT
CAAAGAAGTGTGTCAGGAGCAATGTGTAGATGGCTGCAGCTGCCCCGAGGGCCAGCTCCTGG
ATGAAGGCCACTGCGTGGGAAGTGCTGAGTGTTCCTGTGTGCATGCTGGGCAACGGTACCCT
CCGGGCGCCTCCCTCTTACAGGACTGCCACACCTGCATTTGCCGAAATAGCCTGTGGATCTG
CAGCAATGAAGAATGCCCAGGCGAGTGTCTGGTCACAGGACAGTCCCACTTCAAGAGCTTCG

ACAACAGGTACTTCACCTTCAGTGGGATCTGCCAGTACCTGCTGGCCCAGGACTGCCAGGAC
CACACCTTCTCTGTTGTCATAGAGACTGTCCAGTGTGCCGATGACCTGGATGCTGTCTGCAC
CCGCTCGGTCACCGTCCGCCTGCCTGGACATCACAACAGCCTTGTGAAGCTGAAGCATGGGG
GAGGAGTCTCCATGGATGGCCAGGATATCCAGATTCCTCTCCTGCAAGGTGACCTCCGCATC
CAGCACACCGTGATGGCCTCCGTGCGCCTCAGCTACGGGGAGGACCTGCAGATGGATTGGGA
CGGCCGGGGCAGGCTGCTGGTGACGCTGTCCCCGGCCTACGCGGGGAAGACGTGCGGCCTGT
GCGGGAACTACAACGGCAACCGGGGGGACGACTTCGTGACGCCCGCAGGCCTGGCGGAGCCC
CTGGTGGAGGACTTCGGGAACGCCTGGAAGCTGCTCGGGGCCTGCGAGAACCTGCAGAAGCA
GCACCGCGATCCCTGCAGCCTCAACCCGCGCCAGGCCAGGTTTGCGGAGGAGGCGTGCGCGC
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(SEQ ID NO:29): Protein sequence for dog vWF (AAB93766.2)

>gi|40786760|gb|AAB93766.2| von Willebrand factor [Canis familiaris]

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(SEQ ID NO:30): Nucleic acid sequence for human vWF (AH005287) >gi|340355|gb|AH005287.1|SEG_HUMVWFA Human von Willebrand factor gene

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(SEQ ID NO:31): Protein sequence for human vWF (NP_000543)
>gi|4507907|ref|NP_000543.1| von Willebrand factor precursor; Coagulation factor VIII VWF (von Willebrand factor) [Homo sapiens]

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(SEQ ID NO:32): Nucleic acid sequence for dog CD18 (AF181965)
>gi|5932409|gb|AF181965.1|AF181965 Canis familiaris B-2 integrin (ITGB2) mRNA, partial cds

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CCACGTGGACGACAGCCGGGAGTGTGTGGGGGGCCCCCAAATCGCCCCCATCGTGGGCGGCA
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CTGAGTGACCTCCGCGAGTTCAAGCGATTCGAGAAGGAGAAGCTCAGGTCCCAGTGGAACAA
CGACAACCCCCTTTTCAAGAGCGCCACCACCACAGTCATGAACCCCAGGTTTGCTGAGAGTT
AGGGCGCTCGGCGGAGACGGCGCTGGCTGAGC

(SEQ ID NO:33): Protein sequence for dog CD18 (AAD56947)
>gi|5932410|gb|AAD56947.1|AF181965_1 B-2 integrin [Canis familiaris]

LLLTLEGLLFLWAASCQECTKYKVSTCRDCVESGPGCAWCQKLNFTGLGEPDSVRCDTREQL
LLKGCAADDIMDPQSLAEIQEDKKGGRQQLSPQKVTLYLRPGQAAAFNVTFRRAKGYPIDLY
YLMDLSYSMLDDLINVKKLGGDLLRALNEITESGRIGFGSFVDKTVLPFVNTHPEKLKNPCP
NKEKECQAPFAFRHVLKLTNNSNKFQTEVGKQLISGNLDAPEGGLDAMMQVAACPEQIGWRN
VTRLLVFATDDGFHFAGDGKLGAILTPNDGRCHLEDNMYKRSNEFDYPSVGQLAHKLAESNI
QPIFAVTKRMVTTYEKLTEVIPKSAVGELSDDSSNVVQLIKNAYNKLSSRVFLDHSLAPSTL
KVTYDSFCSNGVSQVDQPRGDCDGVQINVPITFQVKVTATECIQEQSFIIRALGFTDTVTVH
VIPQCECQCRDVGQDHGLCSGKGSLECGICRCEAGYIGKNCECLTHGRSSQELEGSCRRDNS
SLICSGLGDCLCGQCVCHRSDVPNKNIFGRYCECDNVNCERYDGQVCGGKVRGSCNCGKCQC
EQNYEGSACQCVKSTQGCLSTEGIECNGRGRCRCNVCECDGGYQPPLCGDCLGCPSPCGRYI
TCAQCLKFKQGPSGRNCSVECGNVGLLSKPPEKGRRCKERDLEGCWITYTLRQRAGWDSYEI
HVDDSRECVGGPQIAPIVGGTVSGVVLIGILLLAIWKALTHLSDLREFKRFEKEKLRSQWNN
DNPLFKSATTTVMNPRFAES

(SEQ ID NO:34) Nucleic acid sequence for human CD18 (BC005861) >gi|38114829|gb|BC005861.2| Homo sapiens integrin, beta 2 (antigen CD18 (p95), lymphocyte function-associated antigen 1; macrophage antigen 1 (mac-1) beta subunit), mRNA (cDNA clone MGC:3628 IMAGE:3532902), complete cds

GTTGGGCCTGAGACCGTCACCAAGACCCCTTCCCTCCACAGGACATGCTGGGCCTGCGCCCC
CCACTTCTCGCCCTGGTGGGGCTGCTCTCCCTCGGGTGCGTCCTCTCTCAGGAGTGCACGAA
GTTCAAGGTCAGCAGCTGCCGGGAATGCATCGAGTCGGGGCCCGGCTGCACCTGGTGCCAGA
AGCTGAACTTCACAGGGCCGGGGGATCCTGACTCCATTCGCTGCGACACCCGGCCACAGCTG
CTCATGAGGGGCTGTGCGGCTGACGACATCATGGACCCCACAAGCCTCGCTGAAACCCAGGA
AGACCACAATGGGGGCCAGAAGCAGCTGTCCCCACAAAAAGTGACGCTTTACCTGCGACCAG
GCCAGGCAGCAGCGTTCAACGTGACCTTCCGGCGGGCCAAGGGCTACCCCATCGACCTGTAC
TATCTGATGGACCTCTCCTACTCCATGCTTGATGACCTCAGGAATGTCAAGAAGCTAGGTGG
CGACCTGCTCCGGGCCCTCAACGAGATCACCGAGTCCGGCCGCATTGGCTTCGGGTCCTTCG
TGGACAAGACCGTGCTGCCGTTCGTGAACACGCACCCTGATAAGCTGCGAAACCCATGCCCC
AACAAGGAGAAAGAGTGCCAGCCCCCGTTTGCCTTCAGGCACGTGCTGAAGCTGACCAACAA
CTCCAACCAGTTTCAGACCGAGGTCGGGAAGCAGCTGATTTCCGGAAACCTGGATGCACCCG
AGGGTGGGCTGGACGCCATGATGCAGGTCGCCGCCTGCCCGGAGGAAATCGGCTGGCGCAAC
GTCACGCGGCTGCTGGTGTTTGCCACTGATGACGGCTTCCATTTCGCGGGCGACGGGAAGCT
GGGCGCCATCCTGACCCCCAACGACGGCCGCTGTCACCTGGAGGACAACTTGTACAAGAGGA
GCAACGAATTCGACTACCCATCGGTGGGCCAGCTGGCGCACAAGCTGGCTGAAAACAACATC
CAGCCCATCTTCGCGGTGACCAGTAGGATGGTGAAGACCTACGAGAAACTCACCGAGATCAT
CCCCAAGTCAGCCGTGGGGGAGCTGTCTGAGGACTCCAGCAATGTGGTCCATCTCATTAAGA
ATGCTTACAATAAACTCTCCTCCAGGGTATTCCTGGATCACAACGCCCTCCCCGACACCCTG
AAAGTCACCTACGACTCCTTCTGCAGCAATGGAGTGACGCACAGGAACCAGCCCAGAGGTGA
CTGTGATGGCGTGCAGATCAATGTCCCGATCACCTTCCAGGTGAAGGTCACGGCCACAGAGT
GCATCCAGGAGCAGTCGTTTGTCATCCGGGCGCTGGGCTTCACGGACATAGTGACCGTGCAG

GTCCTTCCCCAGTGTGAGTGCCGGTGCCGGGACCAGAGCAGAGACCGCAGCCTCTGCCATGG
CAAGGGCTTCTTGGAGTGCGGCATCTGCAGGTGTGACACTGGCTACATTGGGAAAAACTGTG
AGTGCCAGACACAGGGCCGGAGCAGCCAGGAGCTGGAAGGAAGCTGCCGGAAGGACAACAAC
TCCATCATCTGCTCAGGGCTGGGGGACTGTGTCTGCGGGCAGTGCCTGTGCCACACCAGCGA
CGTCCCCGGCAAGCTGATATACGGGCAGTACTGCGAGTGTGACACCATCAACTGTGAGCGCT
ACAACGGCCAGGTCTGCGGCGGCCCGGGGAGGGGGCTCTGCTTCTGCGGGAAGTGCCGCTGC
CACCCGGGCTTTGAGGGCTCAGCGTGCCAGTGCGAGAGGACCACTGAGGGCTGCCTGAACCC
GCGGCGTGTTGAGTGTAGTGGTCGTGGCCGGTGCCGCTGCAACGTATGCGAGTGCCATTCAG
GCTACCAGCTGCCTCTGTGCCAGGAGTGCCCCGGCTGCCCCTCACCCTGTGGCAAGTACATC
TCCTGCGCCGAGTGCCTGAAGTTCGAAAAGGGCCCCTTTGGGAAGAACTGCAGCGCGGCGTG
TCCGGGCCTGCAGCTGTCGAACAACCCCGTGAAGGGCAGGACCTGCAAGGAGAGGGACTCAG
AGGGCTGCTGGGTGGCCTACACGCTGGAGCAGCAGGACGGGATGGACCGCTACCTCATCTAT
GTGGATGAGAGCCGAGAGTGTGTGGCAGGCCCCAACATCGCCGCCATCGTCGGGGGCACCGT
GGCAGGCATCGTGCTGATCGGCATTCTCCTGCTGGTCATCTGGAAGGCTCTGATCCACCTGA
GCGACCTCCGGGAGTACAGGCGCTTTGAGAAGGAGAAGCTCAAGTCCCAGTGGAACAATGAT
AATCCCCTTTTCAAGAGCGCCACCACGACGGTCATGAACCCCAAGTTTGCTGAGAGTTAGGA
GCACTTGGTGAAGACAAGGCCGTCAGGACCCACCATGTCTGCCCCATCACGCGGCCGAGACA
TGGCTTGCCACAGCTCTTGAGGATGTCACCAATTAACCAGAAATCCAGTTATTTTCCACCCT
CAAAATGACAGCCATGGCCGGCCGGGTGCTTCTGGGGGCTCGTCGGGGGGACAGCTCCACTC
TGACTGGCACAGTCTTTGCATGGAGACTTGAGGAGGGAGGGCTTGAGGTTGGTGAGGTTAGG
TGCGTGTTTCCTGTGCAAGTCAGGACATCAGTCTGATTAAAGGTGGTGCCAATTTATTTACA
TTTAAACTTGTCAGGGTATAAAATGACATCCCATTAATTATATTGTTAATCAATCACGTGTA
TAGAAAAAAAATAAAACTTCAATACAGGCTGTCCATGGAAAAAAAAAAAAAAAAAAAAAA

(SEQ ID NO:35): Protein sequence for human CD18 (AAH05861.1)
>gi|13543407|gb|AAH05861.1| ITGB2 protein [Homo sapiens]

MLGLRPPLLALVGLLSLGCVLSQECTKFKVSSCRECIESGPGCTWCQKLNFTGPGDPDSIRC
DTRPQLLMRGCAADDIMDPTSLAETQEDHNGGQKQLSPQKVTLYLRPGQAAAFNVTFRRAKG
YPIDLYYLMDLSYSMLDDLRNVKKLGGDLLRALNEITESGRIGFGSFVDKTVLPFVNTHPDK
LRNPCPNKEKECQPPFAFRHVLKLTNNSNQFQTEVGKQLISGNLDAPEGGLDAMMQVAACPE
EIGWRNVTRLLVFATDDGFHFAGDGKLGAILTPNDGRCHLEDNLYKRSNEFDYPSVGQLAHK
LAENNIQPIFAVTSRMVKTYEKLTEIIPKSAVGELSEDSSNVVHLIKNAYNKLSSRVFLDHN
ALPDTLKVTYDSFCSNGVTHRNQPRGDCDGVQINVPITFQVKVTATECIQEQSFVIRALGFT
DIVTVQVLPQCECRCRDQSRDRSLCHGKGFLECGICRCDTGYIGKNCECQTQGRSSQELEGS
CRKDNNSIICSGLGDCVCGQCLCHTSDVPGKLIYGQYCECDTINCERYNGQVCGGPGRGLCF
CGKCRCHPGFEGSACQCERTTEGCLNPRRVECSGRGRCRCNVCECHSGYQLPLCQECPGCPS
PCGKYISCAECLKFEKGPFGKNCSAACPGLQLSNNPVKGRTCKERDSEGCWVAYTLEQQDGM
DRYLIYVDESRECVAGPNIAAIVGGTVAGIVLIGILLLVIWKALIHLSDLREYRRFEKEKLK
SQWNNDNPLFKSATTTVMNPKFAES

(SEQ ID NO:36): Predicted Nucleic acid sequence for dog CD45 (AAEX01013304.1), partial sequence within chromosome 7 sequence positions 18132 to 17986

tcttttaaagagttactggaaacctgaagtgatgattgctgctcagggacccctaaaagag
accattggtgacttttggcagatgatattccaaagaaaagtcaaagtcattgttatg---

(SEQ ID NO:37): Predicted Nucleic acid sequence for dog CD45 (AAEX01013304.1), partial sequence within chromosome 7 sequence positions 19420 to 19293

atgactttaacagagtgccactaaaacatgaactggagatgagcaaagagagtgagcatgat
tcagatgaatcttctgatgatgacagtgactcagaggaaacaagtagatacatcaatgcgtc
tttt

(SEQ ID NO:38): Predicted Nucleic acid sequence for dog CD45 (AAEX01013304.1), partial sequence within chromosome 7 sequence positions 27292 to 27135

aaaaaagagaaggccaccggaagagaggtgactcacattcagttcaccagctggccagacca
tggggtgcctgaagatcctcacctgcttctgaagctgcggaggagagtgaacgctttcagca
acttcttcagtggccccattgtggtgcactgcag---

(SEQ ID NO:39): Predicted Nucleic acid sequence for dog CD45 (AAEX01013304.1), partial sequence within chromosome 7 sequence positions 26930 to 26791

cagtgctggtgtgggacgcacaggcacctatattggaattgatgccatgctagaaggcctgg
aagcggaaaacaaagtagatgtttatggttatgttgtcaagctaaggcgacagagatgcttg
atggtccaagtggagg---

(SEQ ID NO:40): Predicted Nucleic acid sequence for dog CD45 (AAEX01013304.1), partial sequence within chromosome 7 sequence positions 35370 to 35260

gatgatgaaaaacaactgatgactgtggagccaatccatgcagatattttgttggaaactta
taagaggaagatcgctgatgaaggaagactgtttctggctgaatttcag---

(SEQ ID NO:41): Nucleic acid sequence for human CD45 (Y00638)
>gi|34280|emb|Y00638.1|HSLCAR Human mRNA for leukocyte common antigen (T200)

GGAAATTGTTCCTCGTCTGATAAGACAACAGTGGAGAAAGGACGCATGCTGTTTCTTAGGGA
CACGGCTGGCTTCCAGATATGACCATGTATTTGTGGCTTAAACTCTTGGCATTTGGCTTTGC
CTTTCTGGACACAGAAGTATTTGTGACAGGGCAAAGCCCAACACCTTCCCCCACTGGATTGA
CTACAGCAAAGATGCCCAGTGTTCCACTTTCAAGTGACCCCTTACCTACTCACACCACTGCA
TTCTCACCCGCAAGCACCTTTGAAAGAGAAAATGACTTCTCAGAGACCACAACTTCTCTTAG
TCCAGACAATACTTCCACCCAAGTATCCCCGGACTCTTTGGATAATGCTAGTGCTTTTAATA
CCACAGGTGTTTCATCAGTACAGACGCCTCACCTTCCCACGCACGCAGACTCGCAGACGCCC
TCTGCTGGAACTGACACGCAGACATTCAGCGGCTCCGCCGCCAATGCAAAACTCAACCCTAC
CCCAGGCAGCAATGCTATCTCAGATGTCCCAGGAGAGAGGAGTACAGCCAGCACCTTTCCTA
CAGACCCAGTTTCCCCATTGACAACCACCCTCAGCCTTGCACACCACAGCTCTGCTGCCTTA
CCTGCACGCACCTCCAACACCACCATCACAGCGAACACCTCAGATGCCTACCTTAATGCCTC
TGAAACAACCACTCTGAGCCCTTCTGGAAGCGCTGTCATTTCAACCACAACAATAGCTACTA
CTCCATCTAAGCCAACATGTGATGAAAAATATGCAAACATCACTGTGGATTACTTATATAAC
AAGGAAACTAAATTATTTACAGCAAAGCTAAATGTTAATGAGAATGTGGAATGTGGAAACAA
TACTTGCACAAACAATGAGGTGCATAACCTTACAGAATGTAAAAATGCGTCTGTTTCCATAT
CTCATAATTCATGTACTGCTCCTGATAAGACATTAATATTAGATGTGCCACCAGGGGTTGAA
AAGTTTCAGTTACATGATTGTACACAAGTTGAAAAAGCAGATACTACTATTTGTTTAAAATG
GAAAAATATTGAAACCTTTACTTGTGATACACAGAATATTACCTACAGATTTCAGTGTGGTA
ATATGATATTTGATAATAAAGAAATTAAATTAGAAAACCTTGAACCCGAACATGAGTATAAG
TGTGACTCAGAAATACTCTATAATAACCACAAGTTTACTAACGCAAGTAAAATTATTAAAAC
AGATTTTGGGAGTCCAGGAGAGCCTCAGATTATTTTTTGTAGAAGTGAAGCTGCACATCAAG

GAGTAATTACCTGGAATCCCCCTCAAAGATCATTTCATAATTTTACCCTCTGTTATATAAAA
GAGACAGAAAAAGATTGCCTCAATCTGGATAAAAACCTGATCAAATATGATTTGCAAAATTT
AAAACCTTATACGAAATATGTTTTATCATTACATGCCTACATCATTGCAAAAGTGCAACGTA
ATGGAAGTGCTGCAATGTGTCATTTCACAACTAAAAGTGCTCCTCCAAGCCAGGTCTGGAAC
ATGACTGTCTCCATGACATCAGATAATAGTATGCATGTCAAGTGTAGGCCTCCCAGGGACCG
TAATGGCCCCCATGAACGTTACCATTTGGAAGTTGAAGCTGGAAATACTCTGGTTAGAAATG
AGTCGCATAAGAATTGCGATTTCCGTGTAAAAGATCTTCAATATTCAACAGACTACACTTTT
AAGGCCTATTTTCACAATGGAGACTATCCTGGAGAACCCTTTATTTTACATCATTCAACATC
TTATAATTCTAAGGCACTGATAGCATTTCTGGCATTTCTGATTATTGTGACATCAATAGCCC
TGCTTGTTGTTCTCTACAAAATCTATGATCTACATAAGAAAAGATCCTGCAATTTAGATGAA
CAGCAGGAGCTTGTTGAAAGGGATGATGAAAAACAACTGATGAATGTGGAGCCAATCCATGC
AGATATTTTGTTGGAAACTTATAAGAGGAAGATTGCTGATGAAGGAAGACCTTTTCTGGCTG
AATTTCAGAGCATCCCGCGGGTGTTCAGCAAGTTTCCTATAAAGGAAGCTCGAAAGCCCTTT
AACCAGAATAAAAACCGTTATGTTGACATTCTTCCTTATGATTATAACCGTGTTGAACTCTC
TGAGATAAACGGAGATGCAGGGTCAAACTACATAAATGCCAGCTATATTGATGGTTTCAAAG
AACCCAGGAAATACATTGCTGCACAAGGTCCCAGGGATGAAACTGTTGATGATTTCTGGAGG
ATGATTTGGGAACAGAAAGCCACAGTTATTGTCATGGTCACTCGATGTGAAGAAGGAAACAG
GAACAAGTGTGCAGAATACTGGCCGTCAATGGAAGAGGGCACTCGGGCTTTTGGAGATGTTG
TTGTAAAGATCAACCAGCACAAAAGATGTCCAGATTACATCATTCAGAAATTGAACATTGTA
AATAAAAAAGAAAAAGCAACTGGAAGAGAGGTGACTCACATTCAGTTCACCAGCTGGCCAGA
CCACGGGGTGCCTGAGGATCCTCACTTGCTCCTCAAACTGAGAAGGAGAGTGAATGCCTTCA
GCAATTTCTTCAGTGGTCCCATTGTGGTGCACTGCAGTGCTGGTGTTGGGCGCACAGGAACC
TATATCGGAATTGATGCCATGCTAGAAGGCTTGGAAGCCGAGAACAAAGTGGATGTTTATGG
TTATGTTGTCAAGCTAAGGCGACAGAGATGCCTGATGGTTCAAGTAGAGGCCCAGTACATCT
TGATCCATCAGGCTTTGGTGGAATACAATCAGTTTGGAGAAACAGAAGTGAATTTGTCTGAA
TTACATCCATATCTACATAACATGAAGAAAAGGGATCCACCCAGTGAGCCGTCTCCACTAGA
GGCTGAATTCCAGAGACTTCCTTCATATAGGAGCTGGAGGACACAGCACATTGGAAATCAAG
AAGAAAATAAAAGTAAAAACAGGAATTCTAATGTCATCCCATATGACTATAACAGAGTGCCA
CTTAAACATGAGCTGGAAATGAGTAAAGAGAGTGAGCATGATTCAGATGAATCCTCTGATGA
TGACAGTGATTCAGAGGAACCAAGCAAATACATCAATGCATCTTTTATAATGAGCTACTGGA
AACCTGAAGTGATGATTGCTGCTCAGGGACCACTGAAGGAGACCATTGGTGACTTTTGGCAG
ATGATCTTCCAAAGAAAAGTCAAAGTTATTGTTATGCTGACAGAACTGAAACATGGAGACCA
GGAAATCTGTGCTCAGTACTGGGGAGAAGGAAAGCAAACATATGGAGATATTGAAGTTGACC
TGAAAGACACAGACAAATCTTCAACTTATACCCTTCGTGTCTTTGAACTGAGACATTCCAAG
AGGAAAGACTCTCGAACTGTGTACCAGTACCAATATACAAACTGGAGTGTGGAGCAGCTTCC
TGCAGAACCCAAGGAATTAATCTCTATGATTCAGGTCGTCAAACAAAAACTTCCCCAGAAGA
ATTCCTCTGAAGGGAACAAGCATCACAAGAGTACACCTCTACTCATTCACTGCAGGGATGGA
TCTCAGCAAACGGGAATATTTTGTGCTTTGTTAAATCTCTTAGAAAGTGCGGAAACAGAAGA
GGTAGTGGATATTTTTCAAGTGGTAAAAGCTCTACGCAAAGCTAGGCTAGGCATGGTTTCCA
CATTCGAGCAATATCAATTCCTATATGACGTCATTGCCAGCACCTACCCTGCTCAGAATGGA
CAAGTAAAGAAAAACAACCATCAAGAAGATAAAATTGAATTTGATAATGAAGTGGACAAAGT
AAAGCAGGATGCTAATTGTGTTAATCCACTTGGTGCCCCAGAAAAGCTCCCTGAAGCAAAGG
AACAGGCTGAAGGTTCTGAACCCACGAGTGGCACTGAGGGGCCAGAACATTCTGTCAATGGT
CCTGCAAGTCCAGCTTTAAATCAAGGTTCATAGGAAAAGACATAAATGAGGAAACTCCAAAC
CTCCTGTTAGCTGTTATTTCTATTTTTGTAGAAGTAGGAAGTGAAAATAGGTATACAGTGGA
TTAATTAAATGCAGCGAACCAATATTTGTAGAAGGGTTATATTTTACTACTGTGGAAAAATA
TTTAAGATAGTTTTGCCAGAACAGTTTGTACAGACGTATGCTTATTTTAAAATTTTATCTCT
TATTCAGTAAAAAACAACTTCTTTGTAATCGTTATGAGTGTATATGTATGTGTGTATGGGTG
TGTGTTTGTGTGAGAGACAGAGAAAGAGAGAGAATTC

(SEQ ID NO:42): Protein sequence for human CD45 (NP_002829)

>gi|18641347|ref|NP_002829.2| protein tyrosine phosphatase, receptor type, C isoform 1 precursor; protein tyrosine phosphatase, receptor type, c polypeptide; leukocyte-common antigen; T200 glycoprotein; SCID due to PTPRC deficiency; CD45 antigen; human homolog of severe combined immunodeficiency due to PTPRC deficiency [Homo sapiens]

MYLWLKLLAFGFAFLDTEVFVTGQSPTPSPTGLTTAKMPSVPLSSDPLPTHTTAFSPASTFE
RENDFSETTTSLSPDNTSTQVSPDSLDNASAFNTTGVSSVQTPHLPTHADSQTPSAGTDTQT
FSGSAANAKLNPTPGSNAISDVPGERSTASTFPTDPVSPLTTTLSLAHHSSAALPARTSNTT
ITANTSDAYLNASETTTLSPSGSAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLFTA
KLNVNENVECGNNTCTNNEVHNLTECKNASVSISHNSCTAPDKTLILDVPPGVEKFQLHDCT
QVEKADTTICLKWKNIETFTCDTQNITYRFQCGNMIFDNKEIKLENLEPEHEYKCDSEILYN
NHKFTNASKIIKTDFGSPGEPQIIFCRSEAAHQGVITWNPPQRSFHNFTLCYIKETEKDCLN
LDKNLIKYDLQNLKPYTKYVLSLHAYIIAKVQRNGSAAMCHFTTKSAPPSQVWNMTVSMTSD
NSMHVKCRPPRDRNGPHERYHLEVEAGNTLVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGD
YPGEPFILHHSTSYNSKALIAFLAFLIIVTSIALLVVLYKIYDLHKKRSCNLDEQQELVERD
DEKQLMNVEPIHADILLETYKRKIADEGRLFLAEFQSIPRVFSKFPIKEARKPFNQNKNRYV
DILPYDYNRVELSEINGDAGSNYINASYIDGFKEPRKYIAAQGPRDETVDDFWRMIWEQKAT
VIVMVTRCEEGNRNKCAEYWPSMEEGTRAFGDVVVKINQHKRCPDYIIQKLNIVNKKEKATG
REVTHIQFTSWPDHGVPEDPHLLLKLRRRVNAFSNFFSGPIVVHCSAGVGRTGTYIGIDAML
EGLEAENKVDVYGYVVKLRRQRCLMVQVEAQYILIHQALVEYNQFGETEVNLSELHPYLHNM
KKRDPPSEPSPLEAEFQRLPSYRSWRTQHIGNQEENKSKNRNSNVIPYDYNRVPLKHELEMS
KESEHDSDESSDDDSDSEEPSKYINASFIMSYWKPEVMIAAQGPLKETIGDFWQMIFQRKVK
VIVMLTELKHGDQEICAQYWGEGKQTYGDIEVDLKDTDKSSTYTLRVFELRHSKRKDSRTVY
QYQYTNWSVEQLPAEPKELISMIQVVKQKLPQKNSSEGNKHHKSTPLLIHCRDGSQQTGIFC
ALLNLLESAETEEVVDIFQVVKALRKARPGMVSTFEQYQFLYDVIASTYPAQNGQVKKNNHQ
EDKIEFDNEVDKVKQDANCVNPLGAPEKLPEAKEQAEGSEPTSGTEGPEHSVNGPASPALNQ
GS

(SEQ ID NO:43): Predicted Nucleic acid sequence for dog CD133, partial sequence within (AAEX01026434.1) position 50894 to position 51101

agattatctactatgaaatcgggattattatttgtgctgtcctggggctgctctttgtgatt
ctgatgccgctggtgggattttgctttggtctgtgtcgttgctgtaacaaatgtggtggaga
aatgcatcagcgacagaagaaaaatggggccttcctgaggaaatactttacagtctccctcc
tggtgatttgtatattcataag

(SEQ ID NO:44) Nucleic acid sequence for human CD133 (NM_006017)

>gi|5174386|ref|NM_006017.1| Homo sapiens prominin 1 (PROM1), mRNA

CCAAGTTCTACCTCATGTTTGGAGGATCTTGCTAGCTATGGCCCTCGTACTCGGCTCCCTGT
TGCTGCTGGGGCTGTGCGGGAACTCCTTTTCAGGAGGGCAGCCTTCATCCACAGATGCTCCT
AAGGCTTGGAATTATGAATTGCCTGCAACAAATTATGAGACCCAAGACTCCCATAAAGCTGG

ACCCATTGGCATTCTCTTTGAACTAGTGCATATCTTTCTCTATGTGGTACAGCCGCGTGATT
TCCCAGAAGATACTTTGAGAAAATTCTTACAGAAGGCATATGAATCCAAAATTGATTATGAC
AAGCCAGAAACTGTAATCTTAGGTCTAAAGATTGTCTACTATGAAGCAGGGATTATTCTATG
CTGTGTCCTGGGGCTGCTGTTTATTATTCTGATGCCTCTGGTGGGGTATTTCTTTTGTATGT
GTCGTTGCTGTAACAAATGTGGTGGAGAAATGCACCAGCGACAGAAGGAAAATGGGCCCTTC
CTGAGGAAATGCTTTGCAATCTCCCTGTTGGTGATTTGTATAATAATAAGCATTGGCATCTT
CTATGGTTTTGTGGCAAATCACCAGGTAAGAACCCGGATCAAAAGGAGTCGGAAACTGGCAG
ATAGCAATTTCAAGGACTTGCGAACTCTCTTGAATGAAACTCCAGAGCAAATCAAATATATA
TTGGCCCAGTACAACACTACCAAGGACAAGGCGTTCACAGATCTGAACAGTATCAATTCAGT
GCTAGGAGGCGGAATTCTTGACCGACTGAGACCCAACATCATCCCTGTTCTTGATGAGATTA
AGTCCATGGCAACAGCGATCAAGGAGACCAAAGAGGCGTTGGAGAACATGAACAGCACCTTG
AAGAGCTTGCACCAACAAAGTACACAGCTTAGCAGCAGTCTGACCAGCGTGAAAACTAGCCT
GCGGTCATCTCTCAATGACCCTCTGTGCTTGGTGCATCCATCAAGTGAAACCTGCAACAGCA
TCAGATTGTCTCTAAGCCAGCTGAATAGCAACCCTGAACTGAGGCAGCTTCCACCCGTGGAT
GCAGAACTTGACAACGTTAATAACGTTCTTAGGACAGATTTGGATGGCCTGGTCCAACAGGG
CTATCAATCCCTTAATGATATACCTGACAGAGTACAACGCCAAACCACGACTGTCGTAGCAG
GTATCAAAAGGGTCTTGAATTCCATTGGTTCAGATATCGACAATGTAACTCAGCGTCTTCCT
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AAATTTACCTACATTGGAAGAGTATGATTCATACTGGTGGCTGGGTGGCCTGGTCATCTGCT
CTCTGCTGACCCTCATCGTGATTTTTTACTACCTGGGCTTACTGTGTGGCGTGTGCGGCTAT
GACAGGCATGCCACCCCGACCACCCGAGGCTGTGTCTCCAACACCGGAGGCGTCTTCCTCAT
GGTTGGAGTTGGATTAAGTTTCCTCTTTTGCTGGATATTGATGATCATTGTGGTTCTTACCT
TTGTCTTTGGTGCAAATGTGGAAAAACTGATCTGTGAACCTTACACGAGCAAGGAATTATTC
CGGGTTTTGGATACACCCTACTTACTAAATGAAGACTGGGAATACTATCTCTCTGGGAAGCT
ATTTAATAAATCAAAAATGAAGCTCACTTTTGAACAAGTTTACAGTGACTGCAAAAAAAATA
GAGGCACTTACGGCACTCTTCACCTGCAGAACAGCTTCAATATCAGTGAACATCTCAACATT
AATGAGCATACTGGAAGCATAAGCAGTGAATTGGAAAGTCTGAAGGTAAATCTTAATATCTT
TCTGTTGGGTGCAGCAGGAAGAAAAAACCTTCAGGATTTTGCTGCTTGTGGAATAGACAGAA
TGAATTATGACAGCTACTTGGCTCAGACTGGTAAATCCCCCGCAGGAGTGAATCTTTTATCA
TTTGCATATGATCTAGAAGCAAAAGCAAACAGTTTGCCCCCAGGAAATTTGAGGAACTCCCT
GAAAAGAGATGCACAAACTATTAAAACAATTCACCAGCAACGAGTCCTTCCTATAGAACAAT
CACTGAGCACTCTATACCAAAGCGTCAAGATACTTCAACGCACAGGGAATGGATTGTTGGAG
AGAGTAACTAGGATTCTAGCTTCTCTGGATTTTGCTCAGAACTTCATCACAAACAATACTTC
CTCTGTTATTATTGAGGAAACTAAGAAGTATGGGAGAACAATAATAGGATATTTTGAACATT
ATCTGCAGTGGATCGAGTTCTCTATCAGTGAGAAAGTGGCATCGTGCAAACCTGTGGCCACC
GCTCTAGATACTGCTGTTGATGTCTTTCTGTGTAGCTACATTATCGACCCCTTGAATTTGTT
TTGGTTTGGCATAGGAAAAGCTACTGTATTTTTACTTCCGGCTCTAATTTTTGCGGTAAAAC
TGGCTAAGTACTATCGTCGAATGGATTCGGAGGACGTGTACGATGATGTTGAAACTATACCC
ATGAAAAATATGGAAAATGGTAATAATGGTTATCATAAAGATCATGTATATGGTATTCACAA
TCCTGTTATGACAAGCCCATCACAACATTGATAGCTGATGTTGAAACTGCTTGAGCATCAGG
ATACTCAAAGTGGAAAGGATCACAGATTTTTGGTAGTTTCTGGGTCTACAAGGACTTTCCAA
ATCCAGGAGCAACGCCAGTGGCAACGTAGTGACTCAGGCGGGCACCAAGGCAACGGCACCAT
TGGTCTCTGGGTAGTGCTTTAAGAATGAACACAATCACGTTATAGTCCATGGTCCATCACTA
TTCAAGGATGACTCCCTCCCTTCCTGTCTATTTTTGTTTTTTACTTTTTTACACTGAGTTTC
TATTTAGACACTACAACATATGGGGTGTTTGTTCCCATTGGATGCATTTCTATCAAAACTCT
ATCAAATGTGATGGCTAGATTCTAACATATTGCCATGTGTGGAGTGTGCTGAACACACACCA
GTTTACAGGAAAGATGCATTTTGTGTACAGTAAACGGTGTATATACCTTTTGTTACCACAGA
GTTTTTTAAACAAATGAGTATTATAGGACTTTCTTCTAAATGAGCTAAATAAGTCACCATTG
ACTTCTTGGTGCTGTTGAAAATAATCCATTTTCACTAAAAGTGTGTGAAACCTACAGCATAT
TCTTCACGCAGAGATTTTCATCTATTATACTTTATCAAAGATTGGCCATGTTCCACTTGGAA
ATGGCATGCAAAAGCCATCATAGAGAAACCTGCGTAACTCCATCTGACAAATTCAAAAGAGA

GAGAGAGATCTTGAGAGAGAAATGCTGTTCGTTCAAAAGTGGAGTTGTTTTAACAGATGCCA
ATTACGGTGTACAGTTTAACAGAGTTTTCTGTTGCATTAGGATAAACATTAATTGGAGTGCA
GCTAACATGAGTATCATCAGACTAGTATCAAGTGTTCTAAAATGAAATATGAGAAGATCCTG
TCACAATTCTTAGATCTGGTGTCCAGCATGGATGAAACCTTTGAGTTTGGTCCCTAAATTTG
CATGAAAGCACAAGGTAAATATTCATTTGCTTCAGGAGTTTCATGTTGGATCTGTCATTATC
AAAAGTGATCAGCAATGAAGAACTGGTCGGACAAAATTTAACGTTGATGTAATGGAATTCCA
GATGTAGGCATTCCCCCCAGGTCTTTTCATGTGCAGATTGCAGTTCTGATTCATTTGAATAA
AAAGGAACTTGG

(SEQ ID NO:45): Protein sequence for human CD133 (NP_006008)

>gi|5174387|ref|NP_006008.1| prominin 1; hProminin; prominin (mouse)-like 1; prominin-like 1 (mouse); hematopoietic stem cell antigen [Homo sapiens]

MALVLGSLLLLGLCGNSFSGGQPSSTDAPKAWNYELPATNYETQDSHKAGPIGILFELVHIF
LYVVQPRDFPEDTLRKFLQKAYESKIDYDKPETVILGLKIVYYEAGIILCCVLGLLFIILMP
LVGYFFCMCRCCNKCGGEMHQRQKENGPFLRKCFAISLLVICIIISIGIFYGFVANHQVRTR
IKRSRKLADSNFKDLRTLLNETPEQIKYILAQYNTTKDKAFTDLNSINSVLGGGILDRLRPN
IIPVLDEIKSMATAIKETKEALENMNSTLKSLHQQSTQLSSSLTSVKTSLRSSLNDPLCLVH
PSSETCNSIRLSLSQLNSNPELRQLPPVDAELDNVNNVLRTDLDGLVQQGYQSLNDIPDRVQ
RQTTTVVAGIKRVLNSIGSDIDNVTQRLPIQDILSAFSVYVNNTESYIHRNLPTLEEYDSYW
WLGGLVICSLLTLIVIFYYLGLLCGVCGYDRHATPTTRGCVSNTGGVFLMVGVGLSFLFCWI
LMIIVVLTFVFGANVEKLICEPYTSKELFRVLDTPYLLNEDWEYYLSGKLFNKSKMKLTFEQ
VYSDCKKNRGTYGTLHLQNSFNISEHLNINEHTGSISSELESLKVNLNIFLLGAAGRKNLQD
FAACGIDRMNYDSYLAQTGKSPAGVNLLSFAYDLEAKANSLPPGNLRNSLKRDAQTIKTIHQ
QRVLPIEQSLSTLYQSVKILQRTGNGLLERVTRILASLDFAQNFITNNTSSVIIEETKKYGR
TIIGYFEHYLQWIEFSISEKVASCKPVATALDTAVDVFLCSYIIDPLNLFWFGIGKATVFLL
PALIFAVKLAKYYRRMDSEDVYDDVETIPMKNMENGNNGYHKDHVYGIHNPVMTSPSQH

专利名称(译)	早期发现血管肉瘤和血管肉瘤		
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摘要(译)

提供了多种方法，组合物和试剂盒，用于早期检测，诊断和治疗人和狗的血管肉瘤中的血管肉瘤。