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(54) **ENDOMETRIAL BIOMARKERS**

ENDOMETRIALE BIOMARKER

BIOMARQUEURS ENDOMÉTRIAUX

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Description

FIELD OF THE INVENTION

[0001] The invention relates to the detection of an endometrial marker, and methods and uses for the detection of an endometrial phase.

BACKGROUND OF THE INVENTION

[0002] Differential tagging with isotopic reagents, such as isotope-coded affinity tags (ICAT) (1) or the more recent variation that uses isobaric tagging reagents, iTRAQ (Applied Biosystems, Foster City, CA), followed by multidimensional liquid chromatography (LC) and tandem mass spectrometry (MS/MS) analysis is a powerful methodology in the search of biomarkers for various disease states.

[0003] Endometrial carcinoma (EmCa), a cancer of the lining of the uterus, is the fourth most common cancer in Canadian women (4). Current methods of diagnosis rely on invasive techniques - biopsy and curettage - and no screening is available. A panel of biomarkers that helps in early diagnosis would, therefore, be useful, especially for highrisks groups, e.g., women who are on Tamoxifen treatment or have hereditary nonpolyposis colorectal cancer syndrome. Although the eventual diagnostic testing for such biomarkers would be most facile from bodily fluids, such as blood or urine, the iTRAQ experiments performed thus far have been on resected EmCa from uterine tissues (hysterectomy specimens) (2, 3). The rationale for this approach is that the concentration of any biomarker is most likely highest in the cancerous tissue itself, and not when diluted in the bodily fluids, thus facilitating discovery. In addition, the use of the cancerous tissue reduces the intrinsic need to demonstrate that any differentially expressed protein detected does indeed originate from the endometrial cancer. By contrast, the origins of differentially expressed protein in the blood could include a variety of potential sites other than the actual tumor. The use of homogenized tissues yields a heterogeneous sample with the proteome being contributed by the stroma, vasculature, blood, and malignant/benign epithelium. This heterogeneity may attenuate, and even mask, the variation in protein expression levels characteristic of cancerous epithelial cells. One remedy for this drawback is the use of laser capture microdissection (LCM) to procure the specific, malignant epithelial cells from the samples (5). This approach, however, is not practical, when 10^3 - 10^4 cells per sample are required for current proteomic techniques, in a global biomarker discovery strategy. Thus far, the types of differentially expressed proteins discovered (2, 3) are primarily medium- to high-abundance proteins, as universal detection methods, including the MS/MS technologies that were employed, are much more efficient in detecting major rather than minor components in a complex mixture.

[0004] A strategy in the search of EmCa markers requires a comparison between the cancerous endometrium and the two major phases, proliferative and secretory, of the normal reproductive-aged endometrium (3, 6). The multiplexing ability afforded by the iTRAQ reagents, which are available in four different tags or flavors, is well suited for such a simultaneous comparison, especially in view of the fact that endometrial carcinoma itself can have two distinct morphologic and physiologic types. Type I cancers are endometrioid in histologic typing, well-differentiated, and estrogen-dependent; and have typically a better prognosis. By contrast, Type II carcinomas are serous and clear cell carcinomas, hormone-independent, and aggressive; and have generally a poorer clinical outcome (7).

[0005] Drapkin, R., et al. (Cancer Res 2005; 65:2162-2169) disclose that WFDC2 is expressed in 93% of serous and 100% of endometrioid epithelial ovarian carcinomas. Galgano, M.T., et al. (Modem Pathology [2006] 19, 847-853) report that expression of WFDC2 was highest in ovarian serous carcinoma, but also moderate to high in adenocarcinomas of the lung, and in occasional breast, transitional cell and pancreatic carcinomas. International patent application WO 2007/081767 A2 discloses a method of assessing whether a patient is afflicted with an endometrial or uterine cancer, in which expression of WFDC2 in a sample obtained from the patient is being assessed. Elevated expression in a patient of HE4, which is also known as WFDC2, was disclosed to be an indication that the patient is afflicted with an endometrial or uterine cancer. The Affymetrix GeneChip Human Genome U133 Array Set HG-U133A (GEO, accession GPL96) discloses the U133 array.

[0006] Ace, C.I, and Okulicz, W.C. (Reproductive Biology and Endocrinology [2004] 2, 54), disclose a high density oligonucleotide microarray screening for mRNA transcript changes from proliferative to adequate secretory endometrium in artificial menstrual cycles in Rhesus monkeys, wherein up- and downregulated genes are disclosed

SUMMARY OF THE INVENTION

[0007] Applicants have identified markers associated with the endometrium, and in particular with proliferative endometrium, secretory endometrium and diseased endometrial tissue. Thus, the invention relates to a novel marker for the endometrium, and in particular a marker of endometrial phase.

[0008] In a first aspect the invention provides a method for detecting at least one endometrial marker associated with

an endometrium phase in a human subject. The at least one endometrial marker comprises WAP four-disulfide core domain 2 polypeptide (WFDC2). The method comprises measuring in a biological sample the amount of the at least one endometrial marker. The biological sample is a sample obtained from the subject. The biological sample is derived from endometrial tissue, such as tumour tissue, or blood. The method also comprises comparing the measured amount with a standard amount, wherein a difference between the measured amount and the standard amount is indicative of the presence of the endometrium phase.

[0009] In a second aspect the invention relates to the use of a diagnostic composition for detecting an endometrium phase in a method for determining endometrial phase in humans. The composition comprises an agent that is capable of binding to at least one endometrial marker listed in Table 1. The at least one marker comprises WFDC2.

[0010] In a third aspect the invention relates to the use of a set of endometrial markers in a method for determining endometrial phase in humans. The set of endometrial markers comprises WAP four-disulfide core domain 2 polypeptide (WFDC2) and at least 1, 2, 3, 4, or 5 of the other markers listed in Table 1.

[0011] In a fourth aspect the invention relates to the use of a kit for conducting the method of the first aspect. The kit comprises at least one binding agent that specifically binds to at least one endometrial marker listed in Table 1, wherein the at least one marker includes WAP four-disulfide core domain 2 polypeptide (WFDC2). The kit also comprises at least one of instructions, compounds, reagents, and containers for using the kit. The binding agent comprises: a detectable substance; a substance that binds directly or indirectly to a detectable substance.

[0012] Disclosed herein are also marker sets that distinguish the endometirum or phases thereof, or endometrial diseases, and uses therefor. A marker set may comprise a plurality of polypeptides and/or polynucleotides encoding such polypeptides comprising or consisting of at least one marker listed in Table 1 and optionally 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 of the markers listed in Table 2. In specific aspects, the markers consist of at least 2, 3,4 or 5 polypeptides listed in Table 1. In an aspect the protein marker sets comprise or consist of protein clusters, or proteins in pathways comprising markers listed in Table 1 and optionally in Table 2.

[0013] The markers identified in Table 1 and optionally Table 2, including but not limited to native-sequence polypeptides, isoforms, chimeric polypeptides, all homologs, fragments, and precursors of the markers, including modified forms of the polypeptides and derivatives are referred to and defined herein as "endometrial marker(s)". Polynucleotides encoding endometrial markers are referred to and defined herein as "endometrial polynucleotide marker(s)", "polynucleotides encoding endometrial markers", or "polynucleotides encoding the marker(s)". The endometrial markers and endometrial polynucleotide markers are sometimes collectively referred to herein as "marker(s)". Markers of endometrial cancer are referred to herein as "endometrial cancer markers", "endometrial cancer polynucleotide markers", and "polynucleotides encoding endometrial cancer markers".

[0014] Endometrial markers listed in Table 1 and optionally Table 2, and polynucleotides encoding the markers, have application in the determination of the status or phase of the endometrium and in the detection of an endometrial disease such as endometrial cancer. Thus, the markers can be used for diagnosis, monitoring (i.e. monitoring progression or therapeutic treatment), prognosis, treatment, or classification of an endometrial disease (e.g. endometrial cancer), or as markers before surgery or after relapse. Contemplated are also methods for assessing the status of an endometrial tissue, and methods for the diagnosis and therapy of an endometrial disease.

[0015] The markers characteristic of different stages or phases of endometrium may be used to identify the physiologic stage or phase of the endometrium within the physiologic cycle. In an aspect, the endometrial markers may be used to assess and manage reproductive disorders and infertility. In particular, endometrial markers associated with the secretory phase or proliferative phase may be used to determine if an endometrium is at the optimum stage or phase for embryo implantation.

[0016] In an embodiment, the endometrial marker is characteristic of the secretory phase, and includes the marker WFDC2 and optionally one or more of glutamate receptor subunit zeta 1 [GenBank Accession NOs. NP_000823, NP_015566, and NP_067544], macrophage migration inhibitory factor [SEQ ID NO. 49], GSK-3 binding protein FRAT1 [GenBank Accession NO. NP_005470], myosin light chain kinase 2 [GenBank Accession No. NP_149109], tropomyosin 1 alpha chain [GeneBank Accession NOs. NP_000357, NP_001018004, NP_001018005, NP_001018006, NP_001018007, NP_001018008, and NP_001018020], and/or polynucleotides encoding the polypeptides.

[0017] In accordance with methods disclosed herein, endometrium can be assessed or characterized, for example, by detecting the presence in the sample of (a) an endometrial marker or fragment thereof; (b) a metabolite which is produced directly or indirectly by an endometrial marker; (c) a transcribed nucleic acid or fragment thereof having at least a portion with which an endometrial polynucleotide marker is substantially identical; and/or (c) a transcribed nucleic acid or fragment thereof, wherein the nucleic acid hybridizes with an endometrial polynucleotide marker.

[0018] The levels of endometrial markers or endometrial polynucleotide markers in a sample may be determined by methods as described herein and generally known in the art. The expression levels may be determined by isolating and determining the level of nucleic acid transcribed from each endometrial polynucleotide. Alternatively or additionally, the levels of endometrial markers translated from mRNA transcribed from an endometrial polynucleotide marker may be determined.

[0019] Disclosed is also a method for characterizing or classifying an endometrial sample comprising detecting a difference in the expression of a first plurality of endometrial markers or endometrial polynucleotide markers relative to a control, the first plurality of markers comprising or consisting of at least 2, 3, 4, or 5 of the markers corresponding to the markers listed in Table 1, and optionally 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 of the markers listed in Table 2. In specific aspects, the plurality of markers consists of at least 3, 4 or 5 of the markers listed in Table 1.

[0020] In an aspect, a method is provided for characterizing an endometrium by detecting endometrial markers or endometrial polynucleotide markers associated with an endometrium stage or phase, or endometrial disease in a subject comprising:

(a) obtaining a sample from a subject;
(b) detecting or identifying in the sample endometrial markers or endometrial polynucleotide markers; and
(c) comparing the detected amount with an amount detected for a standard.

[0021] Furthermore in this disclosure a method is provided for detecting endometrial cancer markers or endometrial cancer polynucleotide markers associated with endometrial cancer in a patient comprising:

(a) obtaining a sample from a patient;
(b) detecting in the sample endometrial cancer markers or endometrial cancer polynucleotide markers; and
(c) comparing the detected amount with an amount detected for a standard.

[0022] The term "detect" or "detecting" includes assaying, imaging or otherwise establishing the presence or absence of the target endometrial markers or polynucleotides encoding the markers, subunits thereof, or combinations of reagent bound targets, and the like, or assaying for, imaging, ascertaining, establishing, or otherwise determining one or more factual characteristics of an endometrium phase or endometrial disease including cancer, metastasis, stage, or similar conditions. The term encompasses diagnostic, prognostic, and monitoring applications for the endometrial markers and polynucleotides encoding the markers.

[0023] Provided is also a method of assessing whether a patient is afflicted with or has a pre-disposition for endometrial disease, in particular endometrial cancer, the method comprising comparing:

(a) levels of endometrial markers or polynucleotides encoding endometrial markers associated with the endometrial disease in a sample from the patient; and
(b) normal levels of endometrial markers or polynucleotides encoding endometrial markers associated with the endometrial disease in samples of the same type obtained from control patients not afflicted with the disease, wherein altered levels of the endometrial markers or the polynucleotides relative to the corresponding normal levels of endometrial markers or polynucleotides is an indication that the patient is afflicted with endometrial disease.

[0024] In an aspect of a method for assessing whether a patient is afflicted with or has a pre-disposition for endometrial cancer, higher levels of endometrial cancer markers (e.g,. WFDC2, clusterin) in a sample relative to the corresponding normal levels is an indication that the patient is afflicted with endometrial cancer.

[0025] In another aspect of a method for assessing whether a patient is afflicted with or has a pre-disposition for endometrial cancer, lower levels of endometrial cancer markers (e.g., mucin 5B) in a sample relative to the corresponding normal levels is an indication that the patient is afflicted with endometrial cancer.

[0026] In a further aspect, a method for screening a subject for endometrial disease is provided comprising (a) obtaining a biological sample from a subject; (b) detecting the amount of endometrial markers associated with the disease in said sample; and (c) comparing said amount of endometrial markers detected to a predetermined standard, where detection of a level of endometrial markers that differs significantly from the standard indicates endometrial disease.

[0027] In an embodiment, a significant difference between the levels of endometrial marker levels in a patient and normal levels is an indication that the patient is afflicted with or has a predisposition to endometrial disease.

[0028] In a particular embodiment the amount of endometrial marker(s) (e.g., WFDC2, clusterin, Cap-G) detected is greater than that of a standard and is indicative of endometrial disease, in particular endometrial cancer. In another particular embodiment the amount of endometrial marker(s) (e.g., mucin 5B) detected is lower than that of a standard and is indicative of endometrial disease, in particular endometrial cancer.

[0029] In aspects of the methods of the invention, the methods are non-invasive for detecting endometrium phase or endometrial disease which in turn allow for diagnosis of a variety of conditions or diseases associated with the endometrium.

[0030] In particular, provided is a non-invasive non-surgical method for detection, diagnosis or prediction of endometrial disease in a subject comprising: obtaining a sample of blood, plasma, serum, urine or saliva or a tissue sample from the subject; subjecting the sample to a procedure to detect endometrial markers or endometrial polynucleotide markers

in the blood, plasma, serum, urine, saliva or tissue; detecting, diagnosing, and predicting endometrial disease by comparing the levels of endometrial markers or endometrial polynucleotide markers to the levels of marker(s) or polynucleotide(s) obtained from a control subject with no endometrial disease.

[0031] In an embodiment, endometrial disease is detected, diagnosed, or predicted by determination of increased levels of markers (e.g one or more Table 1 upregulated markers, and optionally one or more Table 2 up-regulated markers) when compared to such levels obtained from the control.

[0032] In another embodiment, endometrial disease is detected, diagnosed, or predicted by determination of decreased levels of markers (e.g. mucin 5B and optionally one or more Table 2 down-regulated markers) when compared to such levels obtained from the control.

[0033] Provided is also a method for assessing the aggressiveness or indolence of an endometrial disease in particular cancer (e.g. staging), the method comprising comparing:

(a) levels of endometrial markers or polynucleotides encoding endometrial markers associated with the endometrial disease in a patient sample; and
(b) normal levels of the endometrial markers or the polynucleotides in a control sample.

[0034] In an embodiment, a significant difference between the levels in the sample and the normal levels is an indication that the endometrial disease, in particular cancer, is aggressive or indolent. In a particular embodiment, the levels of endometrial markers are higher than normal levels. In another particular embodiment, the levels of endometrial markers are lower than normal levels.

[0035] In an embodiment, a method is provided for diagnosing and/or monitoring Type II endometrial cancer comprising comparing:

(a) levels of Cap-G or polynucleotides encoding Cap-G in a sample from the patient; and

(b) normal levels of Cap-G or polynucleotides encoding same in samples of the same type obtained from control patients not afflicted with endometrial cancer or having a different stage of endometrial cancer, wherein altered levels of Cap-G or polynucleotides encoding same compared with the corresponding normal levels is an indication that the patient is afflicted with Type II endometrial cancer.

[0036] In an embodiment, a method is provided for diagnosing and/or monitoring Type I endometrial cancer comprising comparing

(a) levels of WFDC2 or polynucleotides encoding WFDC2 in a sample from the patient; and
(b) normal levels of WFDC2 or polynucleotides encoding same in samples of the same type obtained from control patients not afflicted with endometrial cancer or having a different stage of endometrial cancer, wherein altered levels of WFDC2 or polynucleotides encoding same compared with the corresponding normal levels is an indication that the patient is afflicted with Type I endometrial cancer.

[0037] In an aspect, a method is provided for determining whether a cancer has metastasized or is likely to metastasize in the future, the method comprising comparing:

(a) levels of endometrial cancer markers or polynucleotides encoding endometrial cancer markers in a patient sample; and
(b) normal levels (or non-metastatic levels) of the endometrial cancer markers or polynucleotides in a control sample.

[0038] In an embodiment, a significant difference between the levels in the patient sample and the normal levels is an indication that the cancer has metastasized or is likely to metastasize in the future.

[0039] In another aspect, provided is a method for monitoring the progression of endometrial disease, in particular endometrial cancer in a patient the method comprising:

(a) detecting endometrial markers or polynucleotides encoding the markers associated with the disease in a sample from the patient at a first time point;
(b) repeating step (a) at a subsequent point in time; and
(c) comparing the levels detected in (a) and (b), and therefrom monitoring the progression of the endometrial disease.

[0040] Contemplated is furthermore a method for determining the effect of an environmental factor on the endometrium or phase thereof, or endometrial disease comprising comparing endometrial polynucleotide markers or endometrial

markers in the presence and absence of the environmental factor.

[0041] Provided is also a method for assessing the potential efficacy of a test agent for inhibiting endometrial disease, and a method of selecting an agent for inhibiting endometrial disease.

[0042] Contemplated is also a method of assessing the potential of a test compound to contribute to an endometrial disease comprising:

(a) maintaining separate aliquots of endometrial diseased cells in the presence and absence of the test compound; and

(b) comparing the levels of endometrial markers or polynucleotides encoding the markers associated with the disease in each of the aliquots.

[0043] A significant difference between the levels of endometrial markers or polynucleotides encoding the markers in an aliquot maintained in the presence of (or exposed to) the test compound relative to the aliquot maintained in the absence of the test compound, indicates that the test compound potentially contributes to endometrial disease.

[0044] Disclosed is furthermore a method of assessing the efficacy of a therapy for inhibiting endometrial disease in a patient. A method comprises comparing: (a) levels of endometrial markers or polynucleotides encoding the markers associated with disease in a first sample from the patient obtained from the patient prior to providing at least a portion of the therapy to the patient; and (b) levels of endometrial markers or polynucleotides encoding the markers associated with disease in a second sample obtained from the patient following therapy.

[0045] In an embodiment, a significant difference between the levels of endometrial markers or polynucleotides encoding the markers in the second sample relative to the first sample is an indication that the therapy is efficacious for inhibiting endometrial disease.

[0046] In a particular embodiment, the method is used to assess the efficacy of a therapy for inhibiting endometrial disease (e.g. endometrial cancer), where lower levels of endometrial markers or polynucleotides encoding same in the second sample relative to the first sample, is an indication that the therapy is efficacious for inhibiting the disease.

[0047] The "therapy" may be any therapy for treating endometrial disease, in particular endometrial cancer, including but not limited to therapeutics, radiation, immunotherapy, gene therapy, and surgical removal of tissue. Therefore, the method can be used to evaluate a patient before, during, and after therapy.

[0048] Certain methods disclosed employ binding agents (e.g. antibodies) that specifically recognize endometrial markers.

[0049] In an embodiment, provided are methods for determining the presence or absence of endometrial disease, in particular endometrial cancer, in a patient, comprising the steps of (a) contacting a biological sample obtained from a patient with one or more binding agent that specifically binds to one or more endometrial markers associated with the disease; and (b) detecting in the sample an amount of marker that binds to the binding agent, relative to a predetermined standard or cut-off value, and therefrom determining the presence or absence of endometrial disease in the patient.

[0050] In another embodiment, disclosed is a method for diagnosing and monitoring an endometrial disease, in particular endometrial cancer, in a subject by quantitating one or more endometrial markers associated with the disease in a biological sample from the subject comprising (a) reacting the biological sample with one or more binding agent specific for the endometrial markers (e.g. an antibody) that are directly or indirectly labelled with a detectable substance; and (b) detecting the detectable substance.

[0051] In another aspect disclosed is a method of using an antibody to detect expression of one or more endometrial marker in a sample, the method comprising: (a) combining antibodies specific for one or more endometrial marker with a sample under conditions which allow the formation of antibody:marker complexes; and (b) detecting complex formation, wherein complex formation indicates expression of the marker in the sample. Expression may be compared with standards and is diagnostic of an endometrial disease, in particular endometrial cancer.

[0052] Embodiments of the methods of the invention involve (a) reacting a biological sample from a subject with antibodies specific for one or more endometrial markers which are directly or indirectly labelled with an enzyme; (b) adding a substrate for the enzyme wherein the substrate is selected so that the substrate, or a reaction product of the enzyme and substrate forms fluorescent complexes; (c) quantitating one or more endometrial markers in the sample by measuring fluorescence of the fluorescent complexes; and (d) comparing the quantitated levels to levels obtained for other samples from the subject patient, or control subjects.

[0053] In another embodiment the quantitated levels are compared to levels quantitated for control subjects (e.g. normal or benign) without an endometrial disease (e.g. cancer) wherein an increase in endometrial marker levels compared with the control subjects is indicative of endometrial disease.

[0054] In a further embodiment the quantitated levels are compared to levels quantitated for control subjects (e.g. normal or benign) without an endometrial disease (e.g. cancer) wherein a decrease in endometrial marker levels compared with the control subjects is indicative of endometrial disease.

[0055] A particular embodiment comprises the following steps

(a) incubating a biological sample with first antibodies specific for one or more endometrial cancer markers which are directly or indirectly labeled with a detectable substance, and second antibodies specific for one or more endometrial cancer markers which are immobilized;
(b) detecting the detectable substance thereby quantitating endometrial cancer markers in the biological sample; and
(c) comparing the quantitated endometrial cancer markers with levels for a predetermined standard.

[0056] The standard may correspond to levels quantitated for samples from control subjects without endometrial cancer (normal or benign), with a different disease stage, or from other samples of the subject. In an embodiment, increased levels of endometrial cancer markers as compared to the standard may be indicative of endometrial cancer. In another embodiment, lower levels of endometrial cancer markers as compared to a standard may be indicative of endometrial cancer.

[0057] Endometrial marker levels can be determined by constructing an antibody microarray in which binding sites comprise immobilized, preferably monoclonal, antibodies specific to a substantial fraction of marker-derived endometrial marker proteins of interest.

[0058] Other methods disclosed herein employ one or more polynucleotides capable of hybridizing to one or more polynucleotides encoding endometrial markers. Thus, methods can be used to monitor an endometrial disease (e.g. cancer) by detecting endometrial polynucleotide markers associated with the disease.

[0059] Thus, there is disclosed a method for diagnosing and monitoring an endometrial disease (e.g. endometrial cancer) in a sample from a subject comprising isolating nucleic acids, preferably mRNA, from the sample; and detecting endometrial marker polynucleotides associated with the disease in the sample. The presence of different levels of endometrial marker polynucleotides in the sample compared to a standard or control may be indicative of endometrium phase, disease, disease stage, and/or a negative or positive prognosis (e.g., longer progression-free and overall survival).

[0060] In embodiments, endometrial cancer marker polynucleotide positive tumors (e.g. higher levels of the polynucleotides compared to a control normal or benign sample) are a negative diagnostic indicator. Positive tumors can be indicative of endometrial cancer, advanced stage disease, lower progression-free survival, and/or overall survival.

[0061] In other embodiments, endometrial cancer marker polynucleotide negative tumors (e.g. lower levels of the polynucleotides compared to a control normal or benign tissue) are a negative diagnostic indicator. Negative tumors can be indicative of endometrial cancer, advanced stage disease, lower progression-free survival, and/or overall survival.

[0062] Provided are methods for determining the presence or absence of an endometrial disease in a subject comprising detecting in the sample levels of nucleic acids that hybridize to one or more polynucleotides encoding endometrial markers associated with the disease, comparing the levels with a predetermined standard or cut-off value, and therefrom determinin the presence or absence of endometrial disease in the subject. In an embodiment, provided are methods for determining the presence or absence of endometrial cancer in a subject comprising (a) contacting a sample obtained from the subject with oligonucleotides that hybridize to one or more polynucleotides encoding endometrial cancer markers; and (b) detecting in the sample a level of nucleic acids that hybridize to the polynucleotides relative to a predetermined cut-off value, and therefrom determining the presence or absence of endometrial cancer in the subject.

[0063] Within certain embodiments, the amount of polynucleotides that are mRNA are detected via polymerase chain reaction using, for example, oligonucleotide primers that hybridize to one or more polynucleotides encoding endometrial markers, or complements of such polynucleotides. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing oligonucleotide probes that hybridize to one or more polynucleotides encoding endometrial markers, or complements thereof.

[0064] When using mRNA detection, the method may be carried out by combining isolated mRNA with reagents to convert to cDNA according to standard methods; treating the converted cDNA with amplification reaction reagents (such as cDNA PCR reaction reagents) in a container along with an appropriate mixture of nucleic acid primers; reacting the contents of the container to produce amplification products; and analyzing the amplification products to detect the presence of one or more endometrial polynucleotide markers in the sample. For mRNA the analyzing step may be accomplished using Northern Blot analysis to detect the presence of endometrial polynucleotide markers. The analysis step may be further accomplished by quantitatively detecting the presence of endometrial polynucleotide markers in the amplification product, and comparing the quantity of marker detected against a panel of expected values for the known presence or absence of the markers in normal and malignant tissue derived using similar primers.

[0065] Therefore, provided is also a method wherein mRNA is detected by (a) isolating mRNA from a sample and combining the mRNA with reagents to convert it to cDNA; (b) treating the converted cDNA with amplification reaction reagents and nucleic acid primers that hybridize to one or more endometrial polynucleotide markers to produce amplification products; (d) analyzing the amplification products to detect an amount of mRNA encoding the endometrial markers; and (e) comparing the amount of mRNA to an amount detected against a panel of expected values for normal and diseased tissue (e.g. malignant tissue) derived using similar nucleic acid primers.

[0066] In particular embodiments, the methods described herein utilize the endometrial polynucleotide markers placed on a microarray so that the expression status of each of the markers is assessed simultaneously.

[0067] In a particular aspect, provided is an endometrial microarray comprising a defined set of genes (i.e., at least 2, 3 4, or 5 genes listed in Table 1 and optionally at least 5 to 10 genes listed in Table 2) whose expression is significantly altered by endometrium phase or endometrial disease. Disclosed is furthermore the use of the microarray as a prognostic tool to predict endometrium phase or endometrial disease. In an embodiment, the endometrial microarray discriminates between endometrial disease resulting from different etiologies.

[0068] In an embodiment, provided are oligonucleotide arrays comprising marker sets described herein. The microarrays provided may comprise probes to markers able to distinguish endometrium phase or disease. In particular, provided are oligonucleotide arrays comprising probes to a subset or subsets of at least 5 to 10 gene markers up to a full set of markers which distinguish endometrium phase or endometrial disease.

[0069] Contemplated is also a method comprising administering to cells or tissues imaging agents that carry labels for imaging and bind to endometrial markers and optionally other markers of an endometrial disease, and then imaging the cells or tissues.

[0070] In an aspect provided is an *in vivo* method comprising administering to a subject an agent that has been constructed to target one or more endometrial markers.

[0071] In a particular embodiment, contemplated is an *in vivo* method comprising administering to a mammal one or more agent that carries a label for imaging and binds to one or more endometrial marker, and then imaging the mammal.

[0072] According to a particular aspect, an *in vivo* method for imaging endometrial cancer is provided comprising:

(a) injecting a patient with an agent that binds to one or more endometrial cancer marker, the agent carrying a label for imaging the endometrial cancer;
(b) allowing the agent to incubate *in vivo* and bind to one or more endometrial cancer marker associated with the endometrial cancer; and
(c) detecting the presence of the label localized to the endometrial cancer.

[0073] In an embodiment the agent is an antibody which recognizes an endometrial cancer marker. In another embodiment the agent is a chemical entity which recognizes an endometrial cancer marker.

[0074] An agent carries a label to image an endometrial marker and optionally other markers. Examples of labels useful for imaging are radiolabels, fluorescent labels (e.g fluorescein and rhodamine), nuclear magnetic resonance active labels, positron emitting isotopes detectable by a positron emission tomography ("PET") scanner, chemiluminescers such as luciferin, and enzymatic markers such as peroxidase or phosphatase. Short-range radiation emitters, such as isotopes detectable by short-range detector probes can also be employed.

[0075] Contemplated are also the localization or imaging methods described herein using multiple markers for an endometrial disease (e.g. endometrial cancer).

[0076] Disclosed are also kits for carrying out the methods disclosed herein. In an embodiment, a kit is for assessing whether a patient is afflicted with an endometrial disease (e.g. endometrial cancer) and it comprises reagents for assessing one or more endometrial markers or polynucleotides encoding the markers.

[0077] Disclosed are further kits comprising marker sets described herein. In an aspect the kit contains a microarray ready for hybridization to target endometrial oligonucleotide markers, plus software for the data analyses.

[0078] Disclosed is also a diagnostic composition comprising an endometrial marker or a polynucleotide encoding the marker. A composition is also disclosed comprising a probe that specifically hybridizes to endometrial polynucleotide markers, or a fragment thereof, or an antibody specific for endometrial markers or a fragment thereof. In another aspect, a composition is disclosed comprising one or more endometrial polynucleotide marker specific primer pairs capable of amplifying the polynucleotides using polymerase chain reaction methodologies. The probes, primers or antibodies can be labeled with a detectable substance.

[0079] Still further the disclosure relates to therapeutic applications for endometrial diseases, in particular endometrial cancer, employing endometrial markers and polynucleotides encoding the markers, and/or binding agents for the markers.

[0080] In an aspect, disclosed are compositions comprising markers or parts thereof associated with an endometrial disease, or antibodies specific for endometrial markers associated with an endometrial disease, and a pharmaceutically acceptable carrier, excipient, or diluent. A method for treating or preventing an endometrial disease, in particular endometrial cancer, in a patient is also disclosed comprising administering to a patient in need thereof, markers or parts thereof associated with an endometrial disease, antibodies specific for endometrial markers associated with an endometrial disease, or a composition disclosed herein. In an aspect disclosed is a method of treating a patient afflicted with or at risk of developing an endometrial disease (e.g. endometrial cancer) comprising inhibiting expression of endometrial markers.

[0081] In an aspect, disclosed are antibodies specific for endometrial markers associated with a disease (e.g. endometrial cancer) that can be used therapeutically to destroy or inhibit the disease (e.g. the growth of endometrial cancer marker expressing cancer cells), or to block endometrial marker activity associated with a disease. In an aspect, endometrial cancer markers may be used in various immunotherapeutic methods to promote immune-mediated destruction

or growth inhibition of tumors expressing endometrial cancer markers.

[0082] Contemplated is also the use of endometrial markers or parts thereof, or antibodies specific for endometrial markers in the preparation or manufacture of a medicament for the prevention or treatment of an endometrial disease e.g. endometrial cancer.

[0083] Another aspect of the disclosure is the use of endometrial markers, peptides derived therefrom, or chemically produced (synthetic) peptides, or any combination of these molecules, for use in the preparation of vaccines to prevent an endometrial disease and/or to treat an endometrial disease.

[0084] Contemplated are vaccines for stimulating or enhancing in a subject to whom the vaccine is administered production of antibodies directed against one or more endometrial markers.

[0085] Disclosed is also a method for stimulating or enhancing in a subject production of antibodies directed against one or more endometrial marker. The method comprises administering to the subject a vaccine of the invention in a dose effective for stimulating or enhancing production of the antibodies.

[0086] Disclosed is further a method for treating, preventing, or delaying recurrence of an endometrial disease (e.g. endometrial cancer). The method comprises administering to the subject a vaccine of the invention in a dose effective for treating, preventing, or delaying recurrence of an endometrial disease (e.g. endometrial cancer).

[0087] Contemplated are the methods, compositions, and kits described herein using additional markers associated with an endometrial disease (e.g. endometrial cancer). The methods described herein may be modified by including reagents to detect the additional markers, or polynucleotides for the markers.

[0088] In particular, contemplated are the methods described herein using multiple markers for an endometrial cancer. Therefore, contemplated is a method for anaylzing a biological sample for the presence of endometrial cancer markers and polynucleotides encoding the markers, and other markers that are specific indicators of cancer, in particular endometrial cancer. The methods described herein may be modified by including reagents to detect the additional markers, or nucleic acids for the additional markers.

[0089] In embodiments of the methods, compositions and kits one or more of the markers listed in Table 1 is used, in particular WFDC2, clusterin and mucin 5B, and optionally one or more listed in Table 2. In another embodiment, the method uses a panel of markers selected from the markers listed in Table 1, and optionally one or more listed in Table 2 in particular a panel comprising two, three or four or more of the markers in Table 1.

DESCRIPTION OF THE TABLES AND DRAWINGS

[0090] The disclosed methods and uses will now be described in relation to the Tables and drawings:

Table Legends

[0091]

Table 1: Differentially expressed proteins in endometrial malignancies/cancer.

Table 2: Differentially expressed proteins in endometrial malignancies/cancer.

Table 3: Average iTRAQ ratios for normal proliferative, normal secretory, Type I and Type II EmCa samples. Ratios in the first panel are from the comparison between the normal proliferative samples. In any given row of this panel, the ratios were normalized to the average normal proliferative ratio. The only exception to this was Cpn 10, which was not observed in the second set of normal proliferative sample comparisons. In this case the ratios reported are relative to the first normal proliferative sample in the set i.e. P1 and P7. The ratios for the rest of the panels (i.e. secretory, Type I and Type II) were relative to the average normal proliferative level. In instances where the average normal proliferative level could not be calculated across all ten normal proliferative samples, the values reported were relative to the corresponding normal proliferative sample in the individual set. (ND: not detected; NQ: not quantified). Ratios deemed to signify differential expression are bolded and shown in a larger font.

Table 4: Individual ratios from each of the three runs on the RP column used to calculate the average ratios for PK reported in Table 3: P. proliferative; S, secretory; I, Type I EmCa; and II, Type II EmCa.

Table 5: Cross-validation of biomarker panel using a two-thirds / one-thirds split. The panel of three potential markers, PK, Cpn10, and AAT, were tested using 10 random splits on which the logistic regression predictor was trained and tested. The high number of true

positives (pos) and negatives (negs), and low number of false positives and negatives for each test set when compared with the training set validates the biomarker panel.

Figure Legends

[0092]

Figure 1: Receiver operating characteristic curve resulting from a logistic regressional analysis using a panel of 3 potential biomarkers: PK, Cpn 10, and AAT.

Figure 2: (a) Dot Blot analysis of β-actin and PIGR. The panel in the middle shows the average of the iTRAQ ratios obtained for PIGR in the twelve pairs of samples in the dot blots. The ratios shown are not normalized to the average normal proliferative sample level in order to show the correlation between the iTRAQ and dot blot results. β-Actin blots performed in duplicate for the same set of samples is shown above and below the Type I and normal proliferative samples respectively. The sample numbers between the actin and PIGR blots correspond to the iTRAQ sample set numbers. The iTRAQ ratios reported in the middle panel for I6b and I10b are relative to the P6 and P10 samples respectively. Despite higher loading in general in the normal proliferative samples as is evident from the β-action blots, the PIGR levels were higher in most Type I samples and correlate well with the iTRAQ result in the center panel.

Figure 3. Immunohistochemical validation of iTRAQ-discovered potential cancer markers using antibodies targeted to PK, Cpn10, and PIGR. Positive staining is brown and is most intense in EmCa samples.

DETAILED DESCRIPTION OF THE INVENTION

[0093] Methods are provided for characterizing the stage or phase of endometrium, detecting the presence of an endometrial disease (e.g. endometrial cancer) in a sample, the absence of a disease (e.g. endometrial cancer) in a sample, the stage or grade of the disease, and other characteristics of endometrial diseases that are relevant to prevention, diagnosis, characterization, and therapy of endometrial diseases such as cancer in a patient, for example, the benign or malignant nature of an endometrial cancer, the metastatic potential of an endometrial cancer, assessing the histological type of neoplasm associated with an endometrial cancer, the indolence or aggressiveness of an endometrial cancer, and other characteristics of endometrial diseases that are relevant to prevention, diagnosis, characterization, and therapy of endometrial diseases such as cancer in a patient. Methods are also provided for assessing the efficacy of one or more test agents for inhibiting an endometrial disease, assessing the efficacy of a therapy for an endometrial disease, monitoring the progression of an endometrial disease, selecting an agent or therapy for inhibiting an endometrial disease, treating a patient afflicted with an endometrial disease, inhibiting an endometrial disease in a patient, and assessing the disease (e.g. carcinogenic) potential of a test compound.

Glossary

[0094] For convenience, certain terms employed in the specification, examples, and appended claims are collected here.

[0095] The recitation of numerical ranges by endpoints herein includes all numbers and fractions subsumed within that range (e.g. 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.90, 4, and 5). It is also to be understood that all numbers and fractions thereof are presumed to be modified by the term "about." Further, it is to be understood that "a," "an," and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to a composition or method comprising "an endometrial marker" includes two or more endometrial markers. The term "about" means plus or minus 0.1 to 50%, 5-50%, or 10-40%, preferably 10-20%, more preferably 10% or 15%, of the number to which reference is being made.

[0096] "Endometrial disease" refers to any disorder, disease, condition, syndrome or combination of manifestations or symptoms recognized or diagnosed as a disorder of the endometrium, including but not limited to hyperplasia and cancer precursors, endometrial cancer or carcinoma, endometriosis, reproductive disorders, and infertility.

[0097] "Endometrial cancer" or "endometrial carcinoma" includes malignant endometrial disease including but not limited to endometrioid, mucinous, and serous adenocarcinomas, adenosquamous carcinomas, clear cell carcinomas, uterine sarcomas including stromal sarcomas, malignant mixed Mullerian tumors (carcinosarcomas), and leiomyosarcomas.

[0098] The terms "sample", "biological sample", and the like mean a material known or suspected of expressing or containing one or more endometrial polynucleotide markers or one or more endometrial markers. A test sample can be used directly as obtained from the source or following a pretreatment to modify the character of the sample. The sample can be derived from any biological source, such as tissues, extracts, or cell cultures, including cells (e.g. tumor cells), cell lysates, and physiological fluids, such as, for example, whole blood, plasma, serum, saliva, ocular lens fluid, cerebral spinal fluid, sweat, urine, milk, ascites fluid, synovial fluid, peritoneal fluid, lavage fluid, and the like. The sample can be obtained from animals, preferably mammals, most preferably humans. The sample can be treated prior to use, such as preparing plasma from blood, diluting viscous fluids, and the like. Methods of treatment can involve filtration, distillation,

extraction, concentration, inactivation of interfering components, the addition of reagents, and the like.

[0099] In embodiments disclosed the sample is a mammalian tissue sample. In a particular embodiment, the tissue is endometrial tissue.

[0100] In another embodiment the sample is a human physiological fluid. In a particular embodiment, the sample is human serum.

[0101] The samples that may be analyzed in accordance with the invention include polynucleotides from clinically relevant sources, preferably expressed RNA or a nucleic acid derived therefrom (cDNA or amplified RNA derived from cDNA that incorporates an RNA polymerase promoter). The target polynucleotides can comprise RNA, including, without limitation total cellular RNA, poly(A)$^+$ messenger RNA (mRNA) or fraction thereof, cytoplasmic mRNA, or RNA transcribed from cDNA (i.e., mRNA; see, for example., Linsley & Schelter, U.S. patent application Ser. No. 09/411,074, or U.S. Pat. Nos. 5,545,522, 5,891,636, or 5,716,785). Methods for preparing total and poly(A)$^+$ RNA are well known in the art, and are described generally, for example, in Sambrook et al., (1989, Molecular Cloning - A Laboratory Manual (2nd Ed.), Vols. 1-3, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.) and Ausubel et al, eds. (1994, Current Protocols in Moelcular Biology, vol. 2, Current Protocols Publishing, New York). RNA may be isolated from eukaryotic cells by procedures involving lysis of the cells and denaturation of the proteins contained in the cells. Additional steps may be utilized to remove DNA. Cell lysis may be achieved with a nonionic detergent, followed by microcentrifugation to remove the nuclei and hence the bulk of the cellular DNA. (See Chirgwin et al., 1979, Biochemistry 18:5294-5299). Poly(A)+RNA can be selected using oligo-dT cellulose (see Sambrook et al., 1989, Molecular Cloning-A Laboratory Manual (2nd Ed.), Vols. 1-3, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.). In the alternative, RNA can be separated from DNA by organic extraction, for example, with hot phenol or phenol/chloroform/isoamyl alcohol.

[0102] It may be desirable to enrich mRNA with respect to other cellular RNAs, such as transfer RNA (tRNA) and ribosomal RNA (rRNA). Most mRNAs contain a poly(A) tail at their 3' end allowing them to be enriched by affinity chromatography, for example, using oligo(dT) or poly(U) coupled to a solid support, such as cellulose or Sephadex™ (see Ausubel et al., eds., 1994, Current Protocols in Molecular Biology, vol. 2, Current Protocols Publishing, New York). Bound poly(A)+mRNA is eluted from the affinity column using 2 mM EDTA/0.1% SDS.

[0103] A sample of RNA can comprise a plurality of different mRNA molecules each with a different nucleotide sequence. In an aspect of the invention, the mRNA molecules in the RNA sample comprise at least 100 different nucleotide sequences.

[0104] Target polynucleotides can be detectably labeled at one or more nucleotides using methods known in the art. The label is preferably uniformly incorporated along the length of the RNA, and more preferably, is carried out at a high degree of efficiency. The detectable label can be a luminescent label, fluorescent label, bio-luminescent label, chemiluminescent label, radiolabel, and colorimetric label. In a particular embodiment, the label is a fluorescent label, such as a fluorescein, a phosphor, a rhodamine, or a polymethine dye derivative. Commercially available fluorescent labels include, for example, fluorescent phosphoramidites such as FluorePrime (Amersham Pharmacia, Piscataway, N.J.), Fluoredite (Millipore, Bedford, Mass.), FAM (ABI, Foster City, Calif.), and Cy3 or Cy5 (Amersham Pharmacia, Piscataway, N.J.).

[0105] Target polynucleotides from a patient sample can be labeled differentially from polynucleotides of a standard. The standard can comprise target polynucleotides from normal individuals (i.e., those not afflicted with or pre-disposed to endometrial disease), in particular pooled from samples from normal individuals. The target polynucleotides can be derived from the same individual, but taken at different time points, and thus indicate the efficacy of a treatment by a change in expression of the markers, or lack thereof, during and after the course of treatment.

[0106] The terms "subject", "individual" and "patient" refer to a warm-blooded animal such as a mammal. In particular, the terms refer to a human. A subject, individual or patient may be afflicted with or suspected of having or being predisposed to endometrial disease or a condition as described herein. The terms also includes domestic animals bred for food or as pets, including horses, cows, sheep, poultry, fish, pigs, cats, dogs, and zoo animals.

[0107] Methods herein for administering an agent or composition to subjects/individuals/patients contemplate treatment as well as prophylactic use. Typical subjects for treatment include persons susceptible to, suffering from or that have suffered a condition or disease described herein. In particular, suitable subjects for treatment in accordance with the invention are persons that are susceptible to, suffering from or that have suffered endometrial cancer.

[0108] The term "endometrial marker" refers to a marker associated with normal or diseased endometrial tissue and comprises or consists of one or more of the polypeptides listed in Table 1, in particular WFDC2, clusterin, and/or mucin 5B, and optionally one or more of the polypeptides listed in Table 2. The term includes native-sequence polypeptides, isoforms, chimeric polypeptides, complexes, all homologs, fragments, precursors, and modified forms and derivatives of the markers.

[0109] An endometrial marker may be associated with a stage or phase of endometrial tissue such as the secretory or proliferative phase. Examples of endometrial markers associated with the secretory phase are WFDC2, and optionally one or more of glutamate receptor subunit zeta 1 [GenBank Accession NOs. NP_000823, NP_015566, and NP_067544], macrophage migration inhibitory factor [SEQ ID NO. 49], GSK-3 binding protein FRAT1 [GenBank Accession NO.

NP_005470], myosin light chain kinase 2 [GenBank Accession No. NP_149109], and tropomyosin 1 alpha chain [GeneBank Accession NOs. NP_000357, NP_001018004, NP_001018005, NP_001018006, NP_001018007, NP_001018008, and NP_001018020].

[0110] An endometrial marker may be associated with an endometrial disease, in particular it may be an endometrial cancer marker. The term "endometrial cancer marker" includes a marker associated with endometrial cancer, in particular a marker listed in Table 1, and optionally a marker listed in Table 2.

[0111] According to the invention, an endometrial cancer marker is WAP four-disulfide core domain 2 (WFDC2). The terms "WAP four-disulfide core domain 2", "WFDC2" "WFDC2 polypeptide" and "WFDC2 protein" include human WAP four-disulfide core domain 2, in particular the native-sequence polypeptide, isoforms, chimeric polypeptides, all homologs, fragments, precursors, complexes, and modified forms and derivatives of human WAP four-disulfide core domain 2. The amino acid sequence for native human WAP four-disulfide core domain 2 includes the amino acid sequences referenced in NCBI Gene ID: 10406, including GenBank Accession Nos. CAG33258, NP_006094, NP_542772, NP_542773, and NP_542774, and the exemplary sequences shown in SEQ ID NOs. 1 to 4.

[0112] In an aspect disclosed, an endometrial cancer marker is clusterin. The terms "clusterin", "clusterin polypeptide" and "clusterin protein" include human clusterin, in particular the native-sequence polypeptide, isoforms, chimeric polypeptides, all homologs, fragments, precursors, complexes, and modified forms and derivatives of human clusterin. The amino acid sequence for native human clusterin includes the amino acid sequences referenced in NCBI Gene ID: 1191, including GenBank Accession Nos. NP_001822, and NP 976084, and the exemplary sequences shown in SEQ ID NOs. 10 and 11.

[0113] In an aspect disclosed herein, an endometrial cancer marker is mucin 5B. The terms "mucin 5B", "mucin 5B polypeptide" and "mucin 5B protein" include human mucin 5B, in particular the native-sequence polypeptide, isoforms, chimeric polypeptides, all homologs, fragments, precursors, complexes, and modified forms and derivatives of human mucin 5B. The amino acid sequence for native human mucin 5B includes the amino acid sequences referenced in NCBI Gene ID: 4587, including GenBank Accession Nos. AAG33673, AAG33673.1, CAA06167.1, AAC51344.1, CAA70926.1, CAA96577.1, AAC67545.1, AAF64523.1, AAB35930.1, AAB61398.1, AAC51343.1, AAB65151.1, CAA52408.1, CAA52910.1, Q14879,Q93043, Q9HC84, Q9NYE4, and the exemplary sequence shown in SEQ ID NO. 14.

[0114] In an aspect disclosed herein, an endometrial cancer marker is leucine aminopeptidase 3 or LAP3. The terms "leucine aminopeptidase 3", "LAP3", "LAP3 polypeptide" and "LAP3 protein" include human LAP3, in particular the native-sequence polypeptide, isoforms, chimeric polypeptides, all homologs, fragments, precursors, complexes, and modified forms and derivatives of human LAP3. The amino acid sequence for native human LAP3 includes the amino acid sequences referenced in NCBI Gene ID: 51056, including GenBank Accession No. NP_056991 and the exemplary sequence shown in SEQ ID NO. 15.

[0115] In an aspect disclosed herein, an endometrial cancer marker is macrophage capping protein or CAP-G. The terms "macrophage capping protein", "CAP-G", "CAP-G polypeptide" and "CAP-G protein" include human CAP-G, in particular the native-sequence polypeptide, isoforms, chimeric polypeptides, all homologs, fragments, precursors, complexes, and modified forms and derivatives of human CAP-G. The amino acid sequence for native human CAP-G includes the amino acid sequences referenced in NCBI Gene ID: 822, including GenBank Accession Nos. NP_001738 and the exemplary sequence shown in SEQ ID NO. 17.

[0116] In an aspect disclosed herein, an endometrial cancer marker is progestagen-associated endometrial protein (PAEP). The terms "progestagen-associated endometrial protein", "PAEP", "PAEP polypeptide" and "PAEP protein" include human PAEP, in particular the native-sequence polypeptide, isoforms, chimeric polypeptides, all homologs, fragments, precursors, complexes, and modified forms and derivatives of human PAEP. The amino acid sequence for native human PAEP includes the amino acid sequences referenced in NCBI Gene ID: 5047 including GenBank Accession Nos. NP_002562 and NP_001018059, and the exemplary sequence shown in SEQ ID NO. 19.

[0117] A "native-sequence polypeptide" comprises a polypeptide having the same amino acid sequence of a polypeptide derived from nature. Such native-sequence polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term specifically encompasses naturally occurring truncated or secreted forms of a polypeptide, polypeptide variants including naturally occurring variant forms (e.g. alternatively spliced forms or splice variants), and naturally occurring allelic variants.

[0118] The term "polypeptide variant" means a polypeptide having at least about 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, or 99% amino acid sequence identity, particularly at least about 70-80%, more particularly at least about 85%, still more particularly at least about 90%, most particularly at least about 95% amino acid sequence identity with a native-sequence polypeptide. Particular polypeptide variants have at least 70-80%, 85%, 90%, 95% amino acid sequence identity to the sequences identified in Table 1 or 2. Such variants include, for instance, polypeptides wherein one or more amino acid residues are added to, or deleted from, the N- or C-terminus of the full-length or mature sequences of the polypeptide, including variants from other species, but excludes a native-sequence polypeptide. In aspects variants retain the immunogenic activity of the corresponding native-sequence polypeptide.

[0119] Percent identity of two amino acid sequences, or of two nucleic acid sequences is defined as the percentage

of amino acid residues or nucleotides in a candidate sequence that are identical with the amino acid residues in a polypeptide or nucleic acid sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid or nucleic acid sequence identity can be achieved in various conventional ways, for instance, using publicly available computer software including the GCG program package (Devereux J. et al., Nucleic Acids Research 12(1): 387, 1984); BLASTP, BLASTN, and FASTA (Atschul, S.F. etal. J. Molec. Biol. 215: 403-410,1990). The BLAST X program is publicly available from NCBI and other sources (BLAST Manual, Altschul, S. et al. NCBI NLM NIH Bethesda, Md. 20894; Altschul, S. et al. J. Mol. Biol. 215: 403-410, 1990). Skilled artisans can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. Methods to determine identity and similarity are codified in publicly available computer programs.

[0120] An allelic variant may also be created by introducing substitutions, additions, or deletions into a polynucleotide encoding a native polypeptide sequence such that one or more amino acid substitutions, additions, or deletions are introduced into the encoded protein. Mutations may be introduced by standard methods, such as site-directed mutagenesis and PCR-mediated mutagenesis. In an embodiment, conservative substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which an amino acid residue is replaced with an amino acid residue with a similar side chain. Amino acids with similar side chains are known in the art and include amino acids with basic side chains (e.g. Lys, Arg, His), acidic side chains (e.g. Asp, Glu), uncharged polar side chains (e.g. Gly, Asp, Glu, Ser, Thr, Tyr and Cys), nonpolar side chains (e.g. Ala, Val, Leu, Iso, Pro, Trp), beta-branched side chains (e.g. Thr, Val, Iso), and aromatic side chains (e.g. Tyr, Phe, Trp, His). Mutations can also be introduced randomly along part or all of the native sequence, for example, by saturation mutagenesis. Following mutagenesis the variant polypeptide can be recombinantly expressed and the activity of the polypeptide may be determined.

[0121] Polypeptide variants include polypeptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of a native polypeptide which include fewer amino acids than the full length polypeptides. A portion of apolypeptide can be a polypeptide which is for example, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100 or more amino acids in length. Portions in which regions of a polypeptide are deleted can be prepared by recombinant techniques and can be evaluated for one or more functional activities such as the ability to form antibodies specific for a polypeptide.

[0122] A naturally occurring allelic variant may contain conservative amino acid substitutions from the native polypeptide sequence or it may contain a substitution of an amino acid from a corresponding position in a polypeptide homolog, for example, a murine polypeptide.

[0123] An endometrial marker may be part of a chimeric or fusion protein. A "chimeric protein" or "fusion protein" comprises all or part (preferably biologically active) of an endometrial marker operably linked to a heterologous polypeptide (i.e., a polypeptide other than an endometrial marker). Within the fusion protein, the term "operably linked" is intended to indicate that an endometrial marker and the heterologous polypeptide are fused in-frame to each other. The heterologous polypeptide can be fused to the N-terminus or C-terminus of an endometrial marker. A useful fusion protein is a GST fusion protein in which an endometrial marker is fused to the C-terminus of GST sequences. Another example of a fusion protein is an immunoglobulin fusion protein in which all or part of an endometrial marker is fused to sequences derived from a member of the immunoglobulin protein family. Chimeric and fusion proteins can be produced by standard recombinant DNA techniques.

[0124] A modified form of a polypeptide referenced herein includes modified forms of the polypeptides and derivatives of the polypeptides, including post-translationally modified forms such as glycosylated, phosphorylated, acetylated, methylated or lapidated forms of the polypeptides. For example, an N-terminal methionine may be cleaved from a polypeptide, and a new N-terminal residue may or may not be acetylated. In particular, for chaperonin 10 the first residue, methionine, can be cleaved and the second first residue, alanine can be N-acetylated.

[0125] Endometrial markers may be prepared by recombinant or synthetic methods, or isolated from a variety of sources, or by any combination of these and similar techniques.

[0126] "Endometrial polynucleotide marker(s)", polynucleotides encoding the marker(s)", and "polynucleotides encoding endometrial markers" refer to polynucleotides that encode endometrial markers including native-sequence polypeptides, polypeptide variants including a portion of a polypeptide, an isoform, precursor, complex, a chimeric polypeptide, or modified forms and derivatives of the polypeptides. An endometrial polynucleotide marker comprises or consists of one or more of the polynucleotides encoding the polypeptides listed in Table 1 and optionally one or more of the polynucleotides encoding the polypeptides listed in Table 2. In particular, endometrial polynucleotide markers comprise or consist essentially of the polynucleotides encoding WFDC2, clusterin, mucin 5B, leucine aminopeptidase 3 (LAP3), macrophage capping protein (CAP-G), and/or progestagen-associated endometrial protein (PAEP).

[0127] In an aspect, a polynucleotide encodes WFDC2, more particularly a polynucleotide sequence referenced in NCBI Gene ID. 10406, more particularly GenBank Accession Nos. NM_006103, NM_080734, NM_080735, or NM_080736 [and see for example SEQ ID NOs. 5, 6, 7, 8 or 9], or a fragment thereof.

[0128] In an aspect, a polynucleotide encodes clusterin more particularly a polynucleotide sequence referenced in NCBI Gene ID. 1191, more particularly GenBank Accession Nos. NMR_001831 or NM_203339 [and see for example SEQ ID NOs.12 or 13], or fragment thereof.

[0129] In an aspect, a polynucleotide encodes mucin 5B more particularly a polynucleotide sequence referenced in NCBI Gene ID. 4587, more particularly GenBank Accession Nos. AJ004862.1, U78554.1, Y09788.2, Z72496.1, AF086604.1, AF253321.1, S80993.1, U63836.1, U78551.1, U95031.1, X74370.1, or X74955.1, or a fragment thereof.

[0130] In an aspect, a polynucleotide encodes LAP3 more particularly a polynucleotide sequence referenced in NCBI Gene ID. 5106; more particularly GenBank Accession No. NP_015907 [and see for example SEQ ID NO. 16], or a fragment thereof.

[0131] In an aspect, a polynucleotide encodes CAP-G more particularly a polynucleotide sequence referenced in NCBI Gene ID. 822, more particularly GenBank Accession No. NP_001747 [and see for example SEQ ID NO.18], or a fragment thereof.

[0132] In an aspect, a polynucleotide encodes PAEP more particularly a polynucleotide sequence referenced in NCBI Gene ID. 5047, more particularly GenBank Accession Nos. NMR_001018049 or NM_00257 [and see for example SEQ ID NO.20 or 21], or a fragment thereof.

[0133] Endometrial polynucleotide markers include complementary nucleic acid sequences, and nucleic acids that are substantially identical to these sequences (e.g. having at least about 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, or 99% sequence identity).

[0134] Endometrial polynucleotide markers also include sequences that differ from a native sequence due to degeneracy in the genetic code. As one example, DNA sequence polymorphisms within the nucleotide sequence of an endometrial marker may result in silent mutations that do not affect the amino acid sequence. Variations in one or more nucleotides may exist among individuals within a population due to natural allelic variation. DNA sequence polymorphisms may also occur which lead to changes in the amino acid sequence of a polypeptide.

[0135] Endometrial polynucleotide markers also include nucleic acids that hybridize under stringent conditions, preferably high stringency conditions to an endometrial polynucleotide marker, in particular an endometrial cancer polynucleotide marker. Appropriate stringency conditions which promote DNA hybridization are known to those skilled in the art, or can be found in Current Protocols in Molecular Biology, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. For example, 6.0 x sodium chloride/sodium citrate (SSC) at about 45°C, followed by a wash of 2.0 x SSC at 50°C may be employed. The stringency may be selected based on the conditions used in the wash step. By way of example, the salt concentration in the wash step can be selected from a high stringency of about 0.2 x SSC at 50°C. In addition, the temperature in the wash step can be at high stringency conditions, at about 65°C.

[0136] Endometrial polynucleotide markers also include truncated nucleic acids or nucleic acid fragments and variant forms of the nucleic acids that arise by alternative splicing of an mRNA corresponding to a DNA.

[0137] The endometrial polynucleotide markers are intended to include DNA and RNA (e.g. mRNA) and can be either double stranded or single stranded. A polynucleotide may, but need not, include additional coding or non-coding sequences, or it may, but need hot, be linked to other molecules and/or carrier or support materials. The polynucleotides for use in the methods disclosed herein may be of any length suitable for a particular method. In certain applications the term refers to antisense polynucleotides (e.g. mRNA or DNA strand in the reverse orientation to sense cancer polynucleotide markers).

[0138] "Statistically different levels", "significantly altered levels", or "significant difference" in levels of markers in a patient sample compared to a control or standard (e.g. normal levels or levels in other samples from a patient) may represent levels that are higher or lower than the standard error of the detection assay. In particular embodiments, the levels may be 1.5,2, 3, 4, 5, or 6 times higher or lower than the control or standard.

[0139] "Microarray" and "array," refer to nucleic acid or nucleotide arrays or protein or peptide arrays that can be used to detect biomolecules associated with endometrium or a phase thereof or endometrial disease, for instance to measure gene expression. A variety of arrays are made in research and manufacturing facilities worldwide, some of which are available commercially. By way of example, spotted arrays and *in situ* synthesized arrays are two kinds of nucleic acid arrays that differ in the manner in which the nucleic acid materials are placed onto the array substrate. A widely used in situ synthesized oligonucleotide array is GeneChip™ made by Affymetrix, Inc. Oligonucleotide probes that are 20- or 25-base long can be synthesized in silico on the array substrate. These arrays can achieve high densities (e.g., more than 40,000 genes per cm^2). Generally spotted arrays have lower densities, but the probes, typically partial cDNA molecules, are much longer than 20- or 25-mers. Examples of spotted cDNA arrays include LifeArray made by Incyte Genomics and DermArray made by IntegriDerm (or Invitrogen). Pre-synthesized and amplified cDNA sequences are attached to the substrate of spotted arrays. Protein and peptide arrays also are known (see for example, Zhu et al., Science 293:2101 (2001).

[0140] "Binding agent" refers to a substance such as a polypeptide or antibody that specifically binds to one or more endometrial markers. A substance "specifically binds" to one or more endometrial markers if is reacts at a detectable level with one or more endometrial markers, and does not react detectably with peptides containing an unrelated or

different sequence. Binding properties may be assessed using an ELISA, which may be readily performed by those skilled in the art (see for example, Newton et al, Develop. Dynamics 197: 1-13, 1993).

[0141] A binding agent may be a ribosome, with or without a peptide component, an aptamer, an RNA molecule, or a polypeptide. A binding agent may be a polypeptide that comprises one or more endometrial marker sequence, a peptide variant thereof, or a non-peptide mimetic of such a sequence. By way of example, a WFDC2 sequence may be a peptide portion of a WFDC2 that is capable of modulating a function mediated by WFDC2.

[0142] An aptamer includes a DNA or RNA molecule that binds to nucleic acids and proteins. An aptamer that binds to a protein (or binding domain) of an endometrial marker or an endometrial polynucleotide marker can be produced using conventional techniques, without undue experimentation. (For example, see the following publications describing *in vitro* selection of aptamers: Klug et al., Mol. Biol. Reports 20:97-107 (1994); Wallis et al., Chem. Biol. 2:543-552 (1995); Ellington, Curr. Biol. 4:427-429 (1994); Lato et al., Chem. Biol. 2:291-303 (1995); Conrad et al., Mol. Div. 1:69-78 (1995); and Uphoff et al., Curr. Opin. Struct. Biol. 6:281-287 (1996)).

[0143] Antibodies for use in the present invention include but are hot limited to monoclonal or polyclonal antibodies, immunologically active fragments (e.g. a Fab or $(Fab)_2$ fragments), antibody heavy chains, humanized antibodies, antibody light chains, genetically engineered single chain F_v molecules (Ladner et al, U.S. Pat. No. 4,946,778), chimeric antibodies, for example, antibodies which contain the binding specificity of murine antibodies, but in which the remaining portions are of human origin, or derivatives, such as enzyme conjugates or labeled derivatives.

[0144] Antibodies including monoclonal and polyclonal antibodies, fragments and chimeras, may be prepared using methods known to those skilled in the art. Isolated native or recombinant endometrial markers may be utilized to prepare antibodies. (See, for example, Kohler et al. (1975) Nature 256:495-497; Kozbor et al. (1985) J. Immunol Methods 81:31-42; Cote et al. (1983) Proc Natl Acad Sci 80:2026-2030; and Cole et al. (1984) Mol Cell Biol 62:109-120 for the preparation of monoclonal antibodies; Huse et al. (1989) Science 246:1275-1281 for the preparation of monoclonal Fab fragments; and, Pound (1998) Immunochemical Protocols, Humana Press, Totowa, N.J for the preparation of phagemid or B-lymphocyte immunoglobulin libraries to identify antibodies). Antibodies specific for an endometrial marker may also be obtained from scientific or commercial sources.

[0145] In an embodiment of the invention, antibodies are reactive against an endometrial marker if they bind with a K_a of greater than or equal to 10^{-7} M.

Markers

[0146] Disclosed herein is a set of markers correlated with endometrium or phase thereof, or endometrial disease. In an aspect, disclosed is a set of markers identified as useful for detection, diagnosis, prevention and therapy of endometrial disease comprising or consisting of one or more of the markers listed in Table 1. In one aspect, the invention provides the endometrial marker WFDC2 and optionally markers in Table 2 for detection and diagnosis of an endometrium phase. Disclosed is also a method of using endometrial markers listed in Table 1, and optionally in Table 2, to distinguish an endometrium phase or to distinguish endometrial disease.

[0147] In an embodiment, the markers comprise or consist of WAP four-disulfide core domain 2 (WFDC2), mucin 5B, and/or clusterin.

[0148] In an embodiment, the markers comprise or consist of WAP four-disulfide core domain 2 (WFDC2), mucin 5B, and clusterin.

[0149] In an embodiment, the markers comprise or consist of mucin 5B and/or clusterin

[0150] In an embodiment, the markers comprise or consist of WAP four-disulfide core domain 2 (WFDC2), mucin 5B, clusterin, and/or progestagen-associated endometrial protein (PAEP or PP14).

[0151] In an embodiment, the markers comprise or consist of WAP four-disulfide core domain 2 (WFDC2), mucin 5B, clusterin, and progestagen-associated endometrial protein (PAEP or PP14).

[0152] In an embodiment, the markers comprise or consist of mucin 5B, clusterin, and progestagen-associated endometrial protein (PAEP or PP14).

[0153] In an embodiment, the markers comprise or consist of WAP four-disulfide core domain 2 (WFDC2), mucin 5B, clusterin, LAP3 and CAP-G.

[0154] In an embodiment, the markers comprise or consist of mucin 5B, clusterin, LAP3 and CAP-G.

[0155] In an embodiment, the markers comprise or consist of LAP3 and CAP-G.

[0156] In an embodiment, the markers comprise or consist of WFDC2, clusterin, mucin 5B, pyruvate kinase M1/M2 (PK), chaperonin 10 (Cpn10) and α-1-antitrypsin (ATT) and optionally 2,3,4 or more other markers listed in Table 1 and Table 2.

[0157] In an embodiment, the markers comprise or consist of clusterin, mucin 5B, pyruvate kinase M1/M2 (PK), chaperonin 10 (Cpn10) and α-1-antitrypsin (ATT) and optionally 2, 3, 4 or more other markers listed in Table 1 and Table 2.

[0158] In an embodiment, the markers comprise or consist of WFDC2, clusterin, mucin 5B, pyruvate kinase M1/M2 (PK), chaperonin 10 (Cpn10), α-1-antitrypsin, polymeric-immunoglobulin receptor (PIGR), macrophage migration inhib-

itory factor (MIF), creatine kinase B chain (CKB), and/or progestagen-associated endometrial protein (PAEP or PP14).

[0159] In an embodiment, the markers comprise or consist of clusterin, mucin 5B, pyruvate kinase M1/M2 (PK), chaperonin 10 (Cpn10), α-1-antitrypsin, polymeric-immunoglobulin receptor (PIGR), macrophage migration inhibitory factor (MIF), creatine kinase (CKB), and/or progestagen-associated endometrial protein (PAEP or PP 14).

[0160] In embodiments disclosed, a marker is provided which is selected from the group consisting of the polypeptides set forth in Table 1 which polypeptides are up-regulated biomarkers in endometrial cancer and optionally at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 polypeptides set forth in Table 2 which polypeptides are up-regulated biomarkers in endometrial cancer.

[0161] In embodiments disclosed, a marker is provided which is selected from the group consisting of mucin 5B in Table 1 and at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 polypeptides set forth in Table 2 which polypeptides are down-regulated biomarkers in endometrial cancer.

[0162] Disclosed are marker sets that distinguish endometrium phase or endometrial disease and uses therefor. In an aspect, disclosed is a method for classifying an endometrium phase or endometrial disease comprising detecting a difference in the expression of a first plurality of endometrial markers or endometrial polynucleotide markers relative to a control, the first plurality of endometrial markers or endometrial polynucleotide markers comprising or consisting of at least 2, 3, 4, or 5 of the markers listed in Table 1. In specific aspects, the plurality of markers consists of WFDC2, clusterin, and mucin 5B and at least 5 to 10 of the markers listed in Table 2. In specific aspects, a control comprises markers derived from a pool of samples from individual patients with no endometrial disease, or individuals with a known endometrium phase.

[0163] Any of the markers provided herein may be used alone or with other markers of endometrium phase or endometrial disease, or with markers for other phenotypes or conditions.

Detection Methods

[0164] A variety of methods can be employed for the diagnostic and prognostic evaluation of endometrial disease or endometrial status involving one or more endometrial markers and polynucleotides encoding the markers, and the identification of subjects with a predisposition to endometrial diseases or that are receptive to *in vitro* fertilization and embryo transfer procedures. Such methods may, for example, utilize endometrial polynucleotide markers, and fragments thereof, and binding agents (e.g. antibodies) against one or more endometrial markers, including peptide fragments. In particular, the polynucleotides and antibodies may be used, for example, for (1) the detection of the presence of endometrial polynucleotide marker mutations, or the detection of either over- or under-expression of endometrial marker mRNA relative to a non-disorder state or different endometrium phase, or the qualitative or quantitative detection of alternatively spliced forms of endometrial polynucleotide marker transcripts which may correlate with certain conditions or susceptibility toward such conditions; and (2) the detection of either an over- or an under-abundance of one or more endometrial markers relative to a non- disorder state or a different endometrium phase or the presence of a modified (e.g., less than full length) endometrial marker which correlates with a disorder state or a progression toward a disorder state, or a particular endometrium phase.

[0165] Contemplated is also a method for detecting the phase of an endometrial tissue, in particular a secretory endometrial tissue, comprising producing a profile of levels of one or more endometrial marker associated with a known endometrium phase and/or polynucleotides encoding the markers, and optionally other markers associated with the endometrium phase in cells from a patient, and comparing the profile with a reference to identify a profile for the test cells indicative of the endometrium phase. In an aspect, the endometrial markers comprise WFDC2, and optionally one or more of glutamate receptor subunit zeta 1, macrophage migration inhibitory factor, FRAT1, myosin light chain kinase 2, tropomyosin 1 alpha chain, or fragment thereof.

[0166] Contemplated is also a method for detecting an endometrial disease, in particular an endometrial cancer, comprising producing a profile of levels of one or more endometrial marker associated with an endometrial disease and/or polynucleotides encoding the markers, and other markers associated with endometrial disease in cells from a patient, and comparing the profile with a reference to identify a profile for the test cells indicative of disease. In an aspect, the eridometrial markers are one or more of WFDC2, clusterin, and/or mucin 5B and optionally one or more of LAP3, CAP-G, PAEP,chaperonin 10, calgranulin A, calgranulin B, polymeric-immunoglobulin receptor (precursor), phosphatidylethanolamine-binding protein, acidic leucine-rich nuclear phosphoprotein 32 family member A, heat shock 70 kDa protein 6, macrophage migration inhibitory factor, calgizzarin (S100C protein), triosephosphate isomerase, alpha-1-antitrypsin precursor, creatine kinase B chain, (B-CK), pyruvate, M1 or M2 isozyme, transgelin (smooth muscle protein 22-alpha), and heterologous nuclear ribonucleoprotein D0.

[0167] The methods described herein may be used to evaluate the probability of the presence of malignant or pre-malignant cells, for example, in a group of cells freshly removed from a host. Such methods can be used to detect tumors, quantitate their growth, and help in the diagnosis and prognosis of endometrial disease. The methods can be used to detect the presence of cancer metastasis, as well as confirm the absence or removal of all tumor tissue following

surgery, cancer chemotherapy, and/or radiation therapy. They can further be used to monitor cancer chemotherapy and tumor reappearance.

[0168] The methods described herein can be adapted for diagnosing and monitoring endometrial tissue status or an endometrial disease by detecting one or more endometrial markers or polynucleotides encoding the markers in biological samples from a subject. These applications require that the amount of markers or polynucleotides quantitated in a sample from a subject being tested be compared to a predetermined standard or cut-off value. The standard may correspond to levels quantitated for another sample or an earlier sample from the subject, or levels quantitated for a control sample. Levels for control samples from healthy subjects, different endometrial tissue phases, or subjects with an endometrial disease may be established by prospective and/or retrospective statistical studies. Healthy subjects who have no clinically evident disease or abnormalities may be selected for statistical studies. Diagnosis may be made by a finding of statistically different levels of detected endometrial markers associated with disease or polynucleotides encoding same, compared to a control sample or previous levels quantitated for the same subject.

[0169] The methods described herein may also use multiple markers for an endometrial disease, in particular endometrial cancer. Therefore, contemplated is a method for anaylzing a biological sample for the presence of one or more endometrial markers and polynucleotides encoding the markers, and other markers that are specific indicators of an endometrial disease. The methods described herein may be modified by including reagents to detect the additional markers, or polynucleotides for the markers.

Nucleic Acid Methods/Assays

[0170] As noted herein an endometrial disease or phase may be detected based on the level of endometrial polynucleotide markers in a sample. Techniques for detecting polynucleotides such as polymerase chain reaction (PCR) and hybridization assays are well known in the art.

[0171] Probes may be used in hybridization techniques to detect endometrial polynucleotide markers. The technique generally involves contacting and incubating nucleic acids (e.g. recombinant DNA molecules, cloned genes) obtained from a sample from a patient or other cellular source with a probe under conditions favorable for the specific annealing of the probes to complementary sequences in the nucleic acids. After incubation, the non-annealed nucleic acids are removed, and the presence of nucleic acids that have hybridized to the probe if any are detected.

[0172] Nucleotide probes for use in the detection of nucleic acid sequences in samples may be constructed using conventional methods known in the art. Suitable probes may be based on nucleic acid sequences encoding at least 5 sequential amino acids from regions of an endometrial polynucleotide marker, preferably they comprise 10-200, more particularly 10-30, 10-40, 20-50, 40-80, 50-150, 80-120 nucleotides in length.

[0173] The probes may comprise DNA or DNA mimics (e.g., derivatives and analogues) corresponding to a portion of an organism's genome, or complementary RNA or RNA mimics. Mimics are polymers comprising subunits capable of specific, Watson-Crick-like hybridization with DNA, or of specific hybridization with RNA. The nucleic acids can be modified at the base moiety, at the sugar moiety, or at the phosphate backbone.

[0174] DNA can be obtained using standard methods such as polymerase chain reaction (PCR) amplification of genomic DNA or cloned sequences. (See, for example, in Innis et al., eds., 1990, PCR Protocols: A Guide to Methods and Applications, Academic Press Inc., San Diego, Calif.). Computer programs known in the art can be used to design primers with the required specificity and optimal amplification properties, such as Oligo version 5.0 (National Biosciences). Controlled robotic systems may be useful for isolating and amplifying nucleic acids.

[0175] A nucleotide probe may be labeled with a detectable substance such as a radioactive label that provides for an adequate signal and has sufficient half-life such as ^{32}P, ^{3}H, ^{14}C or the like. Other detectable substances that may be used include antigens that are recognized by a specific labeled antibody, fluorescent compounds, enzymes, antibodies specific for a labeled antigen, and luminescent compounds. An appropriate label may be selected having regard to the rate of hybridization and binding of the probe to the nucleotide to be detected and the amount of nucleotide available for hybridization. Labeled probes may be hybridized to nucleic acids on solid supports such as nitrocellulose filters or nylon membranes as generally described in Sambrook et al, 1989, Molecular Cloning, A Laboratory Manual (2nd ed.). The nucleic acid probes may be used to detect endometrial polynucleotide markers, preferably in human cells. The nucleotide probes may also be useful in the diagnosis of an endometrial disease involving one or more endometrial polynucleotide markers, in monitoring the progression of such disorder, or monitoring a therapeutic treatment.

[0176] The detection of endometrial polynucleotide markers may involve the amplification of specific gene sequences using an amplification method such as polymerase chain reaction (PCR), followed by the analysis of the amplified molecules using techniques known to those skilled in the art. Suitable primers can be routinely designed by one of skill in the art.

[0177] By way of example, at least two oligonucleotide primers may be employed in a PCR based assay to amplify a portion of a polynucleotide encoding one or more endometrial marker derived from a sample, wherein at least one of the oligonucleotide primers is specific for (i.e. hybridizes to) a polynucleotide encoding the endometrial marker. The

amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis.

[0178] In order to maximize hybridization under assay conditions, primers and probes employed in the methods disclosed herein generally have at least about 60%, preferably at least about 75%, and more preferably at least about 90% identity to a portion of a polynucleotide encoding an endometrial marker; that is, they are at least 10 nucleotides, and preferably at least 20 nucleotides in length. In an embodiment the primers and probes are at least about 10-40 nucleotides in length.

[0179] Hybridization and amplification techniques described herein may be used to assay qualitative and quantitative aspects of endometrial polynucleotide marker expression. For example, RNA may be isolated from a cell type or tissue known to express an endometrial polynucleotide marker and tested utilizing the hybridization (e.g. standard Northern analyses) or PCR techniques referred to herein.

[0180] The primers and probes may be used in the above-described methods *in situ* i.e directly on tissue sections (fixed and/or frozen) of patient tissue obtained from biopsies or resections.

[0181] In an aspect of this disclosure, a method is provided employing reverse transcriptase-polymerase chain reaction (RT-PCR), in which PCR is applied in combination with reverse transcription. Generally, RNA is extracted from a sample tissue using standard techinques (for example, guanidine isothiocyanate extraction as described by Chomcynski and Sacchi, Anal. Biochem. 162:156-159,1987) and is reverse transcribed to produce cDNA. The cDNA is used as a template for a polymerase chain reaction. The cDNA is hybridized to a set of primers, at least one of which is specifically designed against an endometrial marker sequence. Once the pimer and template have annealed a DNA polymerase is employed to extend from the primer, to synthesize a copy of the template. The DNA strands are denatured, and the procedure is repeated many times until sufficient DNA is generated to allow visualization by ethidium bromide staining and agarose gel electrophoresis.

[0182] Amplification may be performed on samples obtained from a subject with a suspected endometrial disease and an individual who is not afflicted with an endometrial disease. The reaction may be performed on several dilutions of cDNA spanning at least two orders of magnitude. A statistically significant difference in expression in several dilutions of the subject sample as compared to the same dilutions of the non-disease sample may be considered positive for the presence of an endometrial disease.

[0183] In an embodiment, disclosed are methods for determining the presence or absence of an endometrial disease in a subject comprising (a) contacting a sample obtained from the subject with oligonucleotides that hybridize to endometrial polynucleotide markers; and (b) detecting in the sample a level of nucleic acids that hybridize to the polynucleotides relative to a predetermined cut-off value, and therefrom determining the presence or absence of an endometrial disease in the subject. In an aspect, the endometrial disease is cancer and the endometrial markers are one or more of WFDC2, clusterin, and mucin 5B and optionally one or more of LAP3, CAP-G, PAEP, chaperonin 10, calgranulin A, calgranulin B, polymeric-immunoglobulin receptor (precursor), phosphatidylethanolamine-binding protein, acidic leucine-rich nuclear phosphoprotein 32 family member A, heat shock 70 kDa protein 6, macrophage migration inhibitory factor, calgizzarin (S100C protein), triosephosphate isomerase, alpha-1-antitrypsin precursor, creatine kinase B chain, (B-CK), pyruvate, M1 or M2 isozyme, transgelin (smooth muscle protein 22-alpha), and heterologous nuclear ribonucleoprotein D0. In an embodiment, the endometrial disease is cancer and the endometrial markers are one or more of WFDC2, clusterin, and mucin 5B and optionally one or more of chaperonin 10, polymeric-immunoglobulin receptor (precursor), macrophage migration inhibitory factor, alpha-1-antitrypsin, creatine kinase B chain, (B-CK), and pyruvate kinase M1 or M2 isozyme. In another embodiment, the endometrial disease is cancer and the endometrial markers are one or more of WFDC2, clusterin, mucin 5B, LAP3 and/or CAP-G, PAEP, and optionally one or more of chaperonin 10, polymeric-immunoglobulin receptor (precursor), macrophage migration inhibitory factor, alpha-1-antitrypsin, creatine kinase B chain, (B-CK), and pyruvate kinase M1 or M2 isozyme. In another embodiment, the endometrial disease is cancer and the endometrial markers are WFDC2, clusterin, and mucin 5B, and optionally one or more of chaperonin 10, polymeric-immunoglobulin receptor (precursor), macrophage migration inhibitory factor, alpha-1-antitrypsin, creatine kinase B chain, (B-CK), and pyruvate kinase M1 or M2 isozyme. In another embodiment, the endometrial disease is cancer and the endometrial markers are WFDC2, clusterin, mucin 5B, chaperonin 10, alpha-1-antitrypsin, and pyruvate kinase M1 or M2 isozyme.

[0184] In another embodiment, disclosed are methods for determining uterine receptivity of a subject to *in vitro* fertilization comprising (a) contacting a sample obtained from the subject with oligonucleotides that hybridize to endometrial polynucleotide markers associated with an endometrial tissue phase (e.g. secretory phase); and (b) detecting in the sample a level of nucleic acids that hybridize to the polynucleotides relative to a predetermined cut-off value, wherein the presence or absence of the endometrial marker polynucleotides as compared to non-receptive controls indicates uterine receptivity. In an aspect, the endometrial markers are WFDC2 and optionally one or more of glutamate receptor subunit zeta 1, macrophage migration inhibitory factor, FRAT1, myosin light chain kinase 2, tropomyosin 1 alpha chain, or fragments thereof

[0185] Disclosed herein is a method wherein an endometrial marker mRNA is detected by (a) isolating mRNA from a sample and combining the mRNA with reagents to convert it to cDNA; (b) treating the converted cDNA with amplification

reaction reagents and nucleic acid primers that hybridize to one or more endometrial marker polynucleotides, to produce amplification products; (d) analyzing the amplification products to detect amounts of mRNA encoding endometrial polynucleotide markers; and (e) comparing the amount of mRNA to an amount detected against a panel of expected values for normal and malignant tissue derived using similar nucleic acid primers.

[0186] Endometrial cancer marker-positive samples or alternatively higher levels in patients compared to a control (e.g. non-cancerous tissue) may be indicative of late stage disease, and/or that the patient is not responsive to chemotherapy. Alternatively, negative samples or lower levels compared to a control (e.g. non-cancerous tissue or negative samples) may be indicative of progressive disease and shorter overall survival.

[0187] In another embodiment, there are disclosed methods for determining the presence or absence of endometrial cancer in a subject comprising (a) contacting a sample obtained from the subject with oligonucleotides that hybridize to one or more endometrial cancer polynucleotide markers; and (b) detecting in the sample levels of nucleic acids that hybridize to the polynucleotides relative to a predetermined cut-off value, and therefrom determining the presence or absence of endometrial cancer in the subject. In an embodiment, the endometrial cancer polynucleotide markers encode one or more polypeptides listed in Table 1. In particular, the endometrial markers are one or more of WFDC2, clusterin, mucin 5B, LAP3, CAP-G, and/or PAEP, and optionally one or more of chaperonin 10, calgranulin A, calgranulin B, polymeric-immunoglobulin receptor (precursor), phosphatidylethanolamine-binding protein, acidic leucine-rich nuclear phosphoprotein 32 family member A, heat shock 70 kDa protein 6, macrophage migration inhibitory factor, calgizzarin (S100C protein), triosephosphate isomerase, alpha-1-antitrypsin precursor, creatine kinase B chain, (B-CK), pyruvate, M1 or M2 isozyme, transgelin (smooth muscle protein 22-alpha), and heterologous nuclear ribonucleoprotein D0, or fragments thereof.

[0188] In particular, disclosed is a method wherein WFDC2, clusterin, and/or mucin 5B mRNA is detected by (a) isolating mRNA from a sample and combining the mRNA with reagents to convert it to cDNA; (b) treating the converted cDNA with amplification reaction reagents and nucleic acid primers that hybridize to a polynucleotide encoding WFDC2, clusterin, and/or mucin 5B, to produce amplification products; (d) analyzing the amplification products to detect an amount of mRNA encoding WFDC2, clusterin, and/or mucin 5B; and (e) comparing the amount of mRNA to an amount detected against a panel of expected values for normal and malignant tissue derived using similar nucleic acid primers.

[0189] Endometrial cancer marker-positive samples or alternatively higher levels, in particular significantly higher levels of WFDC2 and/or clusterin polynucleotides in patients compared to a control (e.g. normal or benign) are indicative of endometrial cancer. Negative samples or lower levels (e.g., of mucin 5B polynucleotides) compared to a control (e.g. normal or benign) may also be indicative of progressive disease and poor overall survival.

[0190] Oligonucleotides or longer fragments derived from an endometrial cancer polynucleotide marker may be used as targets in a microarray. The microarray can be used to simultaneously monitor the expression levels of large numbers of genes and to identify genetic variants, mutations, and polymorphisms. The information from the microarray may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, and to develop and monitor the activities of therapeutic agents.

[0191] The preparation, use, and analysis of microarrays are well known to a person skilled in the art. (See, for example, Brennan, T. M. et al. (1995) U.S. Pat. No. 5,474,796; Schema, et al. (1996) Proc. Natl. Acad. Sci. 93:10614-10619; Baldeschweiler et al. (1995), PCT Application WO95/251116; Shalon, D. et al. (I 995) PCT application WO95/35505; Heller, R. A. et al. (1997) Proc. Natl. Acad. Sci. 94:2150-2155; and Heller, M. J. et al. (1997) U.S. Pat. No. 5,605,662.)

[0192] Thus, the disclosure also includes an array comprising one or more endometrial polynucleotide markers (in particular the markers listed in Table 1) and optionally other markers (e.g. markers listed in Table 2). The array can be used to assay expression of endometrial polynucleotide markers in the array. The array allows the quantitation of expression of one or more endometrial polynucleotide markers.

[0193] Microarrays typically contain at separate sites nanomolar quantities of individual genes, cDNAs, or ESTs on a substrate (e.g.nitrocellulose or silicon plate), or photolithographically prepared glass substrate. The arrays are hybridized to cDNA probes using conventional techniques with gene-specific primer mixes. The target polynucleotides to be analyzed are isolated, amplified and labeled, typically with fluorescent labels, radiolabels or phosphorous label probes. After hybridization is completed, the array is inserted into the scanner, where patterns of hybridization are detected. Data are collected as light emitted from the labels incorporated into the target, which becomes bound to the probe array. Probes that completely match the target generally produce stronger signals than those that have mismatches. The sequence and position of each probe on the array are known, and thus by complementarity, the identity of the target nucleic acid applied to the probe array can be determined.

[0194] Microarrays are prepared by selecting polynucleotide probes and immobilizing them to a solid support or surface. The probes may comprise DNA sequences, RNA sequences, copolymer sequences of DNA and RNA, DNA and/or RNA analogues, or combinations thereof. The probe sequences may be full or partial fragments of genomic DNA, or they may be synthetic oligonucleotide sequences synthesized either enzymatically *in vivo*, enzymatically *in vitro* (e.g., by PCR), or non-enzymatically *in vitro.*

[0195] The probe or probes used in the methods can be immobilized to a solid support or surface which may be either

porous or non-porous. For example, the probes can be attached to a nitrocellulose or nylon membrane or filter covalently at either the 3' or the 5' end of the polynucleotide probe. The solid support may be a glass or plastic surface. In an aspect, hybridization levels are measured to microarrays of probes consisting of a solid support on the surface of which are immobilized a population of polynucleotides, such as a population of DNA or DNA mimics, or, alternatively, a population of RNA or RNA mimics. A solid support may be a nonporous or, optionally, a porous material such as a gel.

[0196] In accordance with embodiments of the disclosure, a microarray is provided comprising a support or surface with an ordered array of hybridization sites or "probes" each representing one of the markers described herein. The microarrays can be addressable arrays, and in particular positionally addressable arrays. Each probe of the array is typically located at a known, predetermined position on the solid support such that the identity of each probe can be determined from its position in the array. In preferred embodiments, each probe is covalently attached to the solid support at a single site.

[0197] Microarrays used are preferably (a) reproducible, allowing multiple copies of a given array to be produced and easily compared with each other; (b) made from materials that are stable under hybridization conditions; (c) small, (e.g., between 1 cm^2 and 25 cm^2, between 12 cm^2 and 13 cm^2, or 3 cm^2; and (d) comprise a unique set of binding sites that will specifically hybridize to the product of a single gene in a cell (e.g., to a specific mRNA, or to a specific cDNA derived therefrom). However, it will be appreciated that larger arrays may be used particularly in screening arrays, and other related or similar sequences will cross hybridize to a given binding site.

[0198] In accordance with an aspect of the disclosure, the microarray is an array in which each position represents one of the markers described herein (e.g. the markers listed in Table 1 and optionally Table 2). Each position of the array can comprise a DNA or DNA analogue based on genomic DNA to which a particular RNA or cDNA transcribed from a genetic marker can specifically hybridize. A DNA or DNA analogue can be a synthetic oligomer or a gene fragment. In an embodiment, probes representing each of the endometrial markers and endometrial polynucleotide markers is present on the array. In a preferred embodiment, the array comprises at least 5 of the endometrial polynucleotide markers.

[0199] Probes for the microarray can be synthesized using N-phosphonate or phosphoramidite chemistries (Froehler et al., 1986, Nucleic Acid Res. 14:5399-5407; McBride et al., 1983, Tetrahedron Lett. 24:246-248). Synthetic sequences are typically between about 10 and about 500 bases, 20-100 bases, or 40-70 bases in length. Synthetic nucleic acid probes can include non-natural bases, such as, without limitation, inosine. Nucleic acid analogues such as peptide nucleic acid may be used as binding sites for hybridization. (see, e.g., Egholm et al., 1993, Nature 363:566-568; U.S. Pat. No. 5,539,083).

[0200] Probes can be selected using an algorithm that takes into account binding energies, base composition, sequence complexity, cross-hybridization binding energies, and secondary structure (see Friend et al., International Patent Publication WO 01/05935, published Jan. 25, 2001).

[0201] Positive control probes, (e.g., probes known to be complementary and hybridize to sequences in the target polynucleotides), and negative control probes, (e.g., probes known to not be complementary and hybridize to sequences in the target polynucleotides) are typically included on the array. Positive controls can be synthesized along the perimeter of the array or synthesized in diagonal stripes across the array. A reverse complement for each probe can be next to the position of the probe to serve as a negative control.

[0202] The probes can be attached to a solid support or surface, which may be made from glass, plastic (e.g., polypropylene, nylon), polyacrylamide, nitrocellulose, gel, or other porous or nonporous material. The probes can be printed on surfaces such as glass plates (see Schena et al., 1995, Science 270:467-470). This method may be particularly useful for preparing microarrays of cDNA (See also, DeRisi et al., 1996, Nature Genetics 14:457-460; Shalon et al., 1996, Genome Res. 6:639-645; and Schena et al., 1995, Proc. Natl. Acad. Sci. U.S.A. 93:10539-11286).

[0203] High-density oligonucleotide arrays containing thousands of oligonucleotides complementary to defined sequences, at defined locations on a surface can be produced using photolithographic techniques for synthesis in situ (see, Fodor et al., 1991, Science 251:767-773; Pease et al., 1994, Proc. Natl. Acad. Sci. U.S.A. 91:5022-5026; Lockhart et al., 1996, Nature Biotechnology 14:1675; U.S. Pat. Nos. 5,578,832; 5,556,752; and 5,510,270) or other methods for rapid synthesis and deposition of defined oligonucleotides (Blanchard et al., Biosensors & Bioelectronics 11:687-690). Using these methods oligonucleotides (e.g., 60-mers) of known sequence are synthesized directly on a surface such as a derivatized glass slide. The array produced may be redundant, with several oligonucleotide molecules per RNA.

[0204] Microarrays can be made by other methods including masking (Maskos and Southern, 1992, Nuc. Acids. Res. 20:1679-1684). In an embodiment, microarrays are produced by synthesizing polynucleotide probes on a support wherein the nucleotide probes are attached to the support covalently at either the 3' or the 5' end of the polynucleotide.

[0205] Disclosed are microarrays comprising a disclosed marker set. In one embodiment, disclosed is a microarray for distinguishing endometrial disease samples comprising a positionally-addressable array of polynucleotide probes bound to a support, the polynucleotide probes comprising a plurality of polynucleotide probes of different nucleotide sequences, each of the different nucleotide sequences comprising a sequence complementary and hybridizable to a plurality of genes, the plurality consisting of at least 2, 3, 4, 5, or 6 of the genes corresponding to the markers listed in Table 1 and optionally at least 2 to 18, 5 to 16, or 10 to 15 of the genes corresponding to the markers listed in Table 2.

An aspect provides microarrays comprising at least 4, 5, or 6 of the polynucleotides encoding the markers listed in Table 1.

[0206] Disclosed are gene marker sets that distinguish endometrium phase or endometrial disease and uses therefor. In an aspect, the disclosure provides a method for classifying an endometrium phase or disease comprising detecting a difference in the expression of a first plurality of genes relative to a control, the first plurality of genes consisting of at least 3, 4, 5, or 6 of the genes encoding the markers listed in Table 1. In specific aspects, the plurality of genes consists of at least 4 or 5 of the genes encoding the markers listed in Table 1 amd optionally at least 2 to 18, 5 to 16, or 10 to 15 of the genes corresponding to the markers listed in Table 2. In another specific aspect, the control comprises nucleic acids derived from a pool of samples from individual control patients.

[0207] Disclosed is a method for classifying an endometrium phase or endometrial disease by calculating the similarity between the expression of at least 3, 4, 5, or 6 polynucleotides encoding markers listed in Table 1 in a sample to the expression of the same markers in a control pool, comprising the steps of:

(a) labeling nucleic acids derived from a sample, with a first fluorophore to obtain a first pool of fluorophore-labeled nucleic acids;

(b) labeling with a second fluorophore a first pool of nucleic acids derived from two or more endometrial disease samples, and a second pool of nucleic acids derived from two or more control samples;

(c) contacting the first fluorophore-labeled nucleic acid and the first pool of second fluorophore-labeled nucleic acid with a first microarray under conditions such that hybridization can occur, and contacting the first fluorophore-labeled nucleic acid and the second pool of second fluorophore-labeled nucleic acid with a second microarray under conditions such that hybridization can occur, detecting at each of a plurality of discrete loci on the first microarray a first flourescent emission signal from the first fluorophore-labeled nucleic acid and a second fluorescent emission signal from the first pool of second fluorophore-labeled genetic matter that is bound to the first microarray and detecting at each of the marker loci on the second microarray the first fluorescent emission signal from the first fluorophore-labeled nucleic acid and a third fluorescent emission signal from the second pool of second fluorophore-labeled nucleic acid;

(d) determining the similarity of the sample to patient and contol pools by comparing the first fluorescence emission signals and the second fluorescence emission signals, and the first emission signals and the third fluorescence emission signals; and

(e) classifying the sample as endometrial disease where the first fluorescence emission signals are more similar to the second fluorescence emission signals than to the third fluorescent emission signals, and classifying the sample as non-endometrial disease where the first fluorescence emission signals are more similar to the third fluorescence emission signals than to the second fluorescent emission signals, wherein the first microarray and the second microarray are similar to each other, exact replicas of each other, or are identical, and wherein the similarity is defined by a statistical method such that the cell sample and control are similar where the p value of the similarity is less than 0.01.

[0208] In aspects, the array can be used to monitor the time course of expression of one or more endometrial polynucleotide markers in the array. This can occur in various biological contexts such as tumor progression.

[0209] The array is also useful for ascertaining differential expression patterns of endometrial polynucleotide markers, and optionally other markers, in normal and abnormal cells. This may provide a battery of nucleic acids that could serve as molecular targets for diagnosis or therapeutic intervention.

Protein Methods

[0210] Binding agents may be used for a variety of diagnostic and assay applications. There are a variety of assay formats known to the skilled artisan for using a binding agent to detect a target molecule in a sample. (For example, see Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988). In general, the presence or absence of an endometrial disease (e.g. cancer) or an endometrium phase in a subject may be determined by (a) contacting a sample from the subject with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined standard or cut-off value.

[0211] In particular embodiments of the invention, the binding agent is an antibody. Antibodies specifically reactive with one or more endometrial marker, or derivatives, such as enzyme conjugates or labeled derivatives, may be used to detect one or more endometrial marker in various samples (e.g. biological materials). They may be used as diagnostic or prognostic reagents and they may be used to detect abnormalities in the level of expression of one or more endometrial marker, or abnormalities in the structure, and/or temporal, tissue, cellular, or subcellular location of one or more endometrial marker. Antibodies may also be used to screen potentially therapeutic compounds *in vitro* to determine their effects on disorders (e.g. endometrial cancer) involving one or more endometrial markers, and other conditions. *In vitro* immunoassays may also be used to assess or monitor the efficacy of particular therapies.

[0212] In an aspect, there is disclosed a method for monitoring or diagnosing an endometrial disease (e.g. cancer) in a subject by quantitating one or more endometrial markers in a biological sample from the subject comprising reacting the sample with antibodies specific for one or more endometrial markers, which are directly or indirectly labeled with detectable substances and detecting the detectable substances. In a particular embodiment of the invention, endometrial markers are quantitated or measured.

[0213] In an aspect of the disclosure, a method for detecting an endometrial disease (e.g. cancer) is provided comprising:

(a) obtaining a sample suspected of containing one or more endometrial markers associated with an endometrial disease;
(b) contacting said sample with antibodies that specifically bind to the endometrial markers under conditions effective to bind the antibodies and form complexes;
(c) measuring the amount of endometrial markers present in the sample by quantitating the amount of the complexes; and
(d) comparing the amount of endometrial markers present in the samples with the amount of endometrial markers in a control, wherein a change or significant difference in the amount of endometrial markers in the sample compared with the amount in the control is indicative of an endometrial disease.

[0214] In an embodiment, contemplated is a method for monitoring the progression of an endometrial disease (e.g. cancer) in an individual, comprising:

(a) contacting antibodies which bind to one or more endometrial markers with a sample from the individual so as to form complexes comprising the antibodies and one or more endometrial markers in the sample;
(b) determining or detecting the presence or amount of complex formation in the sample;
(c) repeating steps (a) and (b) at a point later in time; and
(d) comparing the result of step (b) with the result of step (c), wherein a difference in the amount of complex formation is indicative of disease, disease stage, and/or progression of the disease in said individual.

[0215] The amount of complexes may also be compared to a value representative of the amount of the complexes from an individual not at risk of, or afflicted with, an endometrial disease at different stages. A significant difference in complex formation may be indicative of advanced disease e.g. advanced endometrial cancer, or an unfavourable prognosis.

[0216] In aspects of diagnosis and monitoring of endometrial cancer, the endometrial markers are one or more of WFDC2, clusterin, mucin 5B, LAP3, CAP-G, and PAEP, more particularly WFDC2, clusterin, and/or mucin 5B, and optionally one or more of chaperonin 10, calgranulin A, calgranulin B, polymeric-immunoglobulin receptor (precursor), phosphatidylethanolamine-binding protein, acidic leucine-rich nuclear phosphoprotein 32 family member A, heat shock 70 kDa protein 6, macrophage migration inhibitory factor, calgizzarin (S100C protein), triosephosphate isomerase, alpha-1-antitrypsin precursor, creatine kinase B chain, (B-CK), pyruvate kinase M1 or M2 isozyme, transgelin (smooth muscle protein 22-alpha), and heterologous nuclear ribonucleoprotein D0, more particularly chaperonin 10, alpha-1-antitrypsin precursor and pyruvate kinase M1 or M2 isozyme, or fragments thereof.

[0217] In embodiments of the methods of the invention, WFDC2 and/or clusterin is detected in samples and higher levels, in particular significantly higher levels compared to a control (normal or benign) is indicative of endometrial cancer.

[0218] In aspects of the invention for characterizing endometrium phase the endometrial markers comprise WFDC2 and one or more of glutamate receptor subunit zeta 1, macrophage migration inhibitory factor, FRAT1, myosin light chain kinase 2, tropomyosin 1 alpha chain, and fragments thereof.

[0219] In another embodiment, disclosed are methods for determining uterine receptivity of a subject to *in vitro* fertilization comprising (a) contacting a sample obtained from the subject with antibodies that bind to one or more endometrial marker associated with a certain endometrium phase (e.g. secretory phase); and (b) detecting in the sample a level of endometrial marker relative to a predetermined cut-off value, wherein the presence or absence of the endometrial marker as compared to non-receptive controls indicates uterine receptivity. In a particular embodiment, the markers comprise WFDC2, clusterin, and/or mucin 5B and optionally one or more of glutamate receptor subunit zeta 1, macrophage migration inhibitory factor, FRAT1, myosin light chain kinase 2, tropomyosin 1 alpha chain, and fragments thereof, more particularly WFDC2, glutamate receptor subunit zeta 1 or a fragment thereof, and/or macrophage migration inhibitory factor.

[0220] Antibodies may be used in any known immunoassays that rely on the binding interaction between antigenic determinants of one or more endometrial marker and the antibodies. Immunoassay procedures for *in vitro* detection of antigens in fluid samples are also well known in the art. [See for example, Paterson et al., Int. J. Can. 37:659 (1986) and Burchell et al., Int. J. Can. 34:763 (1984) for a general description of immunoassay procedures]. Qualitative and/or

quantitative determinations of one or more endometrial marker in a sample may be accomplished by competitive or non-competitive immunoassay procedures in either a direct or indirect format. Detection of one or more endometrial marker using antibodies can be done utilizing immunoassays which are run in either the forward, reverse or simultaneous modes. Examples of immunoassays are radioimmunoassays (RIA), enzyme immunoassays (e.g. ELISA), immunofluorescence, immunoprecipitation, latex agglutination, hemagglutination, histochemical tests, and sandwich (immunometric) assays. These terms are well understood by those skilled in the art. A person skilled in the art will know, or can readily discern, other immunoassay formats without undue experimentation.

[0221] According to an embodiment of the invention, an immunoassay for detecting one or more endometrial markers in a biological sample comprises contacting binding agents that specifically bind to endometrial markers in the sample under conditions that allow the formation of first complexes comprising a binding agent and endometrial markers and determining the presence or amount of the complexes as a measure of the amount of endometrial markers contained in the sample. In a particular embodiment, the binding agents are labeled differently or are capable of binding to different labels.

[0222] Antibodies may be used to detect and quantify one or more endometrial markers in a sample in order to diagnose and treat pathological states. In particular, the antibodies may be used in immunohistochemical analyses, for example, at the cellular and sub-subcellular level, to detect one or more endometrial markers, to localize them to particular endometrial cells and tissues (e.g. tumor cells and tissues), and to specific subcellular locations, and to quantitate the level of expression.

[0223] Immunohistochemical methods for the detection of antigens in tissue samples are well known in the art. For example, immunohistochemical methods are described in Taylor, Arch. Pathol. Lab. Med. 102:112 (1978). Briefly, in the context of the present methods, a tissue sample obtained from a subject suspected of having an endometrial-related problem is contacted with antibodies, preferably monoclonal antibodies recognizing one or more endometrial markers. The site at which the antibodies are bound is determined by selective staining of the sample by standard immunohistochemical procedures. The same procedure may be repeated on the same sample using other antibodies that recognize one or more endometrial markers. Alternatively, a sample may be contacted with antibodies against one or more endometrial markers simultaneously, provided that the antibodies are labeled differently or are able to bind to a different label. The tissue sample may be normal endometrial tissue, a cancer tissue or a benign tissue.

[0224] An antibody microarray in which binding sites comprise immobilized, preferably monoclonal, antibodies specific to a substantial fraction of marker-derived endometrial markers of interest can be utilized in the present invention. Antibody arrays can be prepared using methods known in the art [(see for example, Zhu et al., Science 293:2101 (2001) and reference 20].

[0225] Antibodies specific for one or more endometrial marker may be labelled with a detectable substance and localised in biological samples based upon the presence of the detectable substance. Examples of detectable substances include, but are not limited to, the following: radioisotopes (e.g., ^{3}H, ^{14}C, ^{35}S, ^{125}I, ^{131}I), fluorescent labels (e.g., FITC, rhodamine, lanthanide phosphors), luminescent labels such as luminol; enzymatic labels (e.g., horseradish peroxidase, beta-galactosidase, luciferase, alkaline phosphatase, acetylcholinesterase), biotinyl groups (which can be detected by marked avidin e.g., streptavidin containing a fluorescent marker or enzymatic activity that can be detected by optical or colorimetric methods), predetermined polypeptide epitopes recognized by a secondary reporter (e.g., leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). In some embodiments, labels are attached via spacer arms of various lengths to reduce potential steric hindrance. Antibodies may also be coupled to electron dense substances, such as ferritin or colloidal gold, which are readily visualised by electron microscopy.

[0226] One of the ways an antibody can be detectably labeled is to link it directly to an enzyme. The enzyme when later exposed to its substrate will produce a product that can be detected. Examples of detectable substances that are enzymes are horseradish peroxidase, beta-galactosidase, luciferase, alkaline phosphatase, acetylcholinesterase, malate dehydrogenase, ribonuclease, urease, catalase, glucose-6-phosphate, staphylococcal nuclease, delta-5-steriod isomerase, yeast alcohol dehydrogenase, alpha-glycerophosphate, triose phosphate isomerase, asparaginase, glucose oxidase, and acetylcholine esterase.

[0227] For increased sensitivity in an immunoassay system a fluorescence-emitting metal atom such as Eu (europium) and other lanthanides can be used. These can be attached to the desired molecule by means of metal-chelating groups such as DTPA or EDTA.

[0228] A bioluminescent compound may also be used as a detectable substance. Bioluminescence is a type of chemiluminescence found in biological systems where a catalytic protein increases the efficiency of the chemiluminescent reaction. The presence of a bioluminescent molecule is determined by detecting the presence of luminescence. Examples of bioluminescent detectable substances are luciferin, luciferase and aequorin.

[0229] Indirect methods may also be employed in which the primary antigen-aritibody reaction is amplified by the introduction of a second antibody, having specificity for the antibody reactive against one or more endometrial markers. By way of example, if the antibody having specificity against one or more endometrial marker is a rabbit IgG antibody, the second antibody may be goat anti-rabbit gamma-globulin labelled with a detectable substance as described herein.

[0230] Methods for conjugating or labelling the antibodies discussed above may be readily accomplished by one of ordinary skill in the art. (See for example Inman, Methods In Enzymology, Vol. 34, Affinity Techniques, Enzyme Purification: Part B, Jakoby and Wichek (eds.), Academic Press, New York, p. 30,1974; and Wilchek and Bayer, "The Avidin-Biotin Complex in Bioanalytical Applications,"Anal. Biochem. 171:1-32, 1988 re methods for conjugating or labelling the antibodies with enzyme or ligand binding partner).

[0231] Cytochemical techniques known in the art for localizing antigens using light and electron microscopy may be used to detect one or more endometrial markers. Generally, antibodies may be labeled with detectable substances and one or more endometrial markers may be localised in tissues and cells based upon the presence of the detectable substances.

[0232] In the context of the methods of the invention, the sample, binding agents (e.g. antibodies specific for one or more endometrial markers), or one or more endometrial markers may be immobilized on a carrier or support. Examples of suitable carriers or supports are agarose, cellulose, nitrocellulose, dextran, Sephadex, Sepharose, liposomes, carboxymethyl cellulose, polyacrylamides, polystyrene, gabbros, filter paper, magnetite, ion-exchange resin, plastic film, plastic tube, glass, polyamine-methyl vinyl-ether-maleic acid copolymer, amino acid copolymer, ethylene-maleic acid copolymer, nylon, silk, etc. The support material may have any possible configuration including spherical (e.g. bead), cylindrical (e.g. inside surface of a test tube or well, or the external surface of a rod), or flat (e.g. sheet, test strip). Thus, the carrier may be in the shape of, for example, a tube, test plate, well, beads, disc, sphere, etc. The immobilized antibody may be prepared by reacting the material with a suitable insoluble carrier using known chemical or physical methods, for example, cyanogen bromide coupling. An antibody may be indirectly immobilized using a second antibody specific for the antibody. For example, mouse antibody specific for an endometrial marker may be immobilized using sheep anti-mouse IgG Fc fragment specific antibody coated on the carrier or support.

[0233] Where a radioactive label is used as a detectable substance, one or more endometrial marker may be localized by radioautography. The results of radioautography may be quantitated by determining the density of particles in the radioautographs by various optical methods, or by counting the grains.

[0234] Time-resolved fluorometry may be used to detect a signal. For example, the method described in Christopoulos TK and Diamandis EP Anal Chem 1992:64:342-346 may be used with a conventional time-resolved fluorometer.

[0235] In accordance with an embodiment of the invention, a method is provided wherein one or more endometrial marker antibodies are directly or indirectly labelled with enzymes, substrates for the enzymes are added wherein the substrates are selected so that the substrates, or a reaction product of an enzyme and substrate, form fluorescent complexes with a lanthanide metal (e.g. europium, terbium, samarium, and dysprosium, preferably europium and terbium). A lanthanide metal is added and one or more endometrial cancer markers are quantitated in the sample by measuring fluorescence of the fluorescent complexes. Enzymes are selected based on the ability of a substrate of the enzyme, or a reaction product of the enzyme and substrate, to complex with lanthanide metals such as europium and terbium. Suitable enzymes and substrates that provide fluorescent complexes are described in U.S. Patent No. 5,3112,922 to Diamandis. Examples of suitable enzymes include alkaline phosphatase and β-galactosidase. Preferably, the enzyme is alkaline phosphatase.

[0236] Examples of enzymes and substrates for enzymes that provide such fluorescent complexes are described in U.S. Patent No. 5,312,922 to Diamandis. By way of example, when the antibody is directly or indirectly labelled with alkaline phosphatase the substrate employed in the method may be 4-methylumbelliferyl phosphate, 5-fluorosalicyl phosphate, or diflunisal phosphate. The fluorescence intensity of the complexes is typically measured using a time-resolved fluorometer e.g. a CyberFluor 615 Imunoanalyzer (Nordion International, Kanata, Ontario).

[0237] One or more endometrial marker antibodies may also be indirectly labelled with an enzyme. For example, the antibodies may be conjugated to one partner of a ligand binding pair, and the enzyme may be coupled to the other partner of the ligand binding pair. Representative examples include avidin-biotin, and riboflavin-riboflavin binding protein. In an embodiment, the antibodies are biotinylated, and the enzyme is coupled to streptavidin. In another embodiment, an antibody specific for endometrial marker antibody is labeled with an enzyme.

[0238] In accordance with an embodiment, the present invention provides means for determining one or more endometrial markers in a sample by measuring one or more endometrial markers by immunoassay. It will be evident to a skilled artisan that a variety of immunoassay methods can be used to measure one or more-endometrial markers. In general, an immunoassay method may be competitive or noncompetitive. Competitive methods typically employ an immobilized or immobilizable antibody to one or more endometrial marker and a labeled form of one or more endometrial marker. Sample endometrial markers and labeled endometrial markers compete for binding to antibodies to endometrial markers. After separation of the resulting labeled endometrial markers that have become bound to antibodies (bound fraction) from that which has remained unbound (unbound fraction), the amount of the label in either bound or unbound fraction is measured and may be correlated with the amount of endometrial markers in the test sample in any conventional manner, e.g., by comparison to a standard curve.

[0239] In an aspect, a non-competitive method is used for the determination of one or more endometrial markers, with the most common method being the "sandwich" method. In this assay, two antibodies to endometrial markers are

employed. One of the antibodies to endometrial markers is directly or indirectly labeled (sometimes referred to as the "detection antibody") and the other is immobilized or immobilizable (sometimes referred to as the "capture antibody"). The capture and detection antibodies can be contacted simultaneously or sequentially with the test sample. Sequential methods can be accomplished by incubating the capture antibody with the sample, and adding the detection antibody at a predetermined time thereafter (sometimes referred to as the "forward" method); or the detection antibody can be incubated with the sample first and then the capture antibody added (sometimes referred to as the "reverse" method). After the necessary incubation(s) have occurred, to complete the assay, the capture antibody is separated from the liquid test mixture, and the label is measured in at least a portion of the separated capture antibody phase or the remainder of the liquid test mixture. Generally it is measured in the capture antibody phase since it comprises endometrial cancer markers bound by ("sandwiched" between) the capture and detection antibodies. In an embodiment, the label may be measured without separating the capture antibodies and liquid test mixture.

[0240] In a typical two-site immunometric assay for endometrial markers, one or both of the capture and detection antibodies are polyclonal antibodies or one or both of the capture and detection antibodies are monoclonal antibodies (i.e. polyclonal/polyclonal, monoclonal/monoclonal, or monoclonal/polyclonal). The label used in the detection antibody can be selected from any of those known conventionally in the art. The label may be an enzyme or a chemiluminescent moiety, but it can also be a radioactive isotope, a fluorophor, a detectable ligand (e.g., detectable by a secondary binding by a labeled binding partner for the ligand), and the like. In a particular aspect, the antibody is labelled with an enzyme which is detected by adding a substrate that is selected so that a reaction product of the enzyme and substrate forms fluorescent complexes. The capture antibody may be selected so that it provides a means for being separated from the remainder of the test mixture. Accordingly, the capture antibody can be introduced to the assay in an already immobilized or insoluble form, or can be in an immobilizable form, that is, a form which enables immobilization to be accomplished subsequent to introduction of the capture antibody to the assay. An immobilized capture antibody may comprise an antibody covalently or noncovalently attached to a solid phase such as a magnetic particle, a latex particle, a microtiter plate well, a bead, a cuvette, or other reaction vessel. An example of an immobilizable capture antibody is antibody which has been chemically modified with a ligand moiety, e.g., a hapten, biotin, or the like, and which can be subsequently immobilized by contact with an immobilized form of a binding partner for the ligand, e.g., an antibody, avidin, or the like. In an embodiment, the capture antibody may be immobilized using a species specific antibody for the capture antibody that is bound to the solid phase.

[0241] The above-described immunoassay methods and formats are intended to be exemplary and are not limiting.

Computer Systems

[0242] Analytic methods contemplated herein can be implemented by use of computer systems and methods described below and known in the art. Thus, the disclosure provides computer readable media comprising one or more endometrial markers, and/or polynucleotides encoding one or more endometrial markers, and optionally other markers (e.g. markers of endometrial cancer). "Computer readable media" refers to any medium that can be read and accessed directly by a computer, including but not limited to magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage media such as CD-ROM; electrical storage media such as RAM and ROM; and hybrids of these categories such as magnetic/optical storage media. Thus, contemplated are computer readable medium having recorded thereon markers identified for patients and controls.

[0243] "Recorded" refers to a process for storing information on computer readable medium. The skilled artisan can readily adopt any of the presently known methods for recording information on computer readable medium to generate manufactures comprising information on one or more endometrial markers, and optionally other markers.

[0244] A variety of data processor programs and formats can be used to store information on one or more endometrial markers, and/or polynucleotides encoding one or more endometrial markers, and other markers on computer readable medium. For example, the information can be represented in a word processing text file, formatted in commercially-available software such as WordPerfect and MicroSoft Word, or represented in the form of an ASCII file; stored in a database application, such as DB2, Sybase, Oracle, or the like. Any number of dataprocessor structuring formats (e.g., text file or database) may be adapted in order to obtain computer readable medium having recorded thereon the marker information.

[0245] By providing the marker information in computer readable form, one can routinely access the information for a variety of purposes. For example, one skilled in the art can use the information in computer readable form to compare marker information obtained during or following therapy with the information stored within the data storage means.

[0246] Disclosed is a medium for holding instructions for performing a method for determining uterine endometrial receptivity of a patient, or whether a patient has an endometrial disease (e.g. endometrial cancer) or a pre-disposition to an endometrial disease (e.g. cancer), comprising determining the presence or absence of one or more endometrial markers, and/or polynucleotides encoding one or more endometrial markers, and optionally other markers, and based on the presence or absence of the one or more endometrial markers, and/or polynucleotides encoding one or more

endometrial markers, arid optionally other markers, determining uterine endometrial receptivity, endometrial disease (e.g. cancer) or a pre-disposition to an endometrial disease (e.g. cancer), and optionally recommending a procedure pr treatment.

[0247] Disclosed is also in an electronic system and/or in a network, a method for determining uterine endometrial receptivity of a patient, whether a subject has an endometrial disease (e.g. cancer) or a pre-disposition to an endometrial disease (e.g. cancer), comprising determining the presence or absence of one or more endometrial markers, and/or polynucleotides encoding one or more endometrial markers, and optionally other markers (e.g. cancer markers), and based on the presence or absence of the one or more endometrial markers, and/or polynucleotides encoding one or more endometrial markers, and optionally other markers, determining the uterine endometrial receptivity of the patient, whether the subject has an endometrial disease (e.g. cancer) or a pre-disposition to an endometrial disease (e.g. cancer), and optionally recommending a procedure or treatment.

[0248] Disclosed is further in a network, a method for determining whether a subject is receptive to *in vitro* fertilization, has an endometrial disease (e.g. cancer) or a pre-disposition to an endometrial disease (e.g. cancer) comprising: (a) receiving phenotypic information on the subject and information on one or more endometrial markers, and/or polynucleotides encoding one or more endometrial markers, and optionally other markers associated with samples from the subject; (b) acquiring information from the network corresponding to the one or more endometrial markers, and/or polynucleotides encoding one or more endometrial markers, and optionally other markers; and (c) based on the phenotypic information and information on the one or more endometrial markers, and/or polynucleotides encoding one or more endometrial markers, and optionally other markers, determining whether the subject is receptive to *in vitro* fertilization, has an endometrial disease (e.g. cancer) or a pre-disposition to an endometrial disease (e.g. cancer); and (d) optionally recommending procedure or treatment.

[0249] Disclosed is still further a system for identifying selected records that identify a diseased endometrial cell or tissue (e.g. cancer cell or tissue) or an endometrium phase. A system generally comprises a digital computer; a database server coupled to the computer; a database coupled to the database server having data stored therein, the data comprising records of data comprising one or more endometrial markers, and/or polynucleotides encoding one or more endometrial markers, and optionally other endometrial markers, and a code mechanism for applying queries based upon a desired selection criteria to the data file in the database to produce reports of records which match the desired selection criteria.

[0250] In an aspect, a method is provided for detecting endometrial cancer tissue or cells using a computer having a processor, memory, display, and input/output devices, the method comprising the steps of:

(a) creating records of one or more endometrial cancer markers, and/or polynucleotides encoding one or more endometrial cancer markers, and optionally other markers of cancer identified in a sample suspected of containing endometrial cancer cells or tissue;
(b) providing a database comprising records of data comprising one or more endometrial cancer markers, and/or polynucleotides encoding one or more endometrial cancer markers, and optionally other markers of cancer; and
(c) using a code mechanism for applying queries based upon a desired selection criteria to the data file in the database to produce reports of records of step (a) which provide a match of the desired selection criteria of the database of step (b) the presence of a match being a positive indication that the markers of step (a) have been isolated from cells or tissue that are endometrial cancer cells or tissue.

[0251] Contemplated is a business method for determining whether a subject is receptive to *in vitro* fertilization, has an endometrial disease (e.g. cancer) or a pre-disposition to endometrial cancer comprising: (a) receiving phenotypic information on the subject and information on one or more endometrial markers, and/or polynucleotides encoding the markers, and optionally other markers, associated with samples from the subject; (b) acquiring information from a network corresponding to one or more endometrial markers, and/or polynucleotides encoding the markers, and optionally other markers; and (c) based on the phenotypic information, information on one or more endometrial markers, and/or polynucleotides encoding the markers, and optionally other markers, and acquired information, determining whether the subject is receptive to *in vitro* fertilization, has an endometrial disease (e.g. cancer) or a pre-disposition to an endometrial disease (e.g. cancer); and (d) optionally recommending procedure or treatment.

[0252] In an aspect of the disclosure, the computer systems, components, and methods described herein are used to monitor disease or determine the stage of disease, or determine uterine endometrial receptivity.

Imaging Methods

[0253] Binding agents, in particular antibodies, specific for one or more endometrial markers may also be used in imaging methodologies in the management of an endometrial disease or determining uterine endometrial receptivity.

[0254] In an aspect, disclosed is a method for imaging tumors associated with one or more endometrial cancer markers.

[0255] Contemplated are also imaging methods described herein using multiple markers for an endometrial disease

or endometrium phase. Preferably each agent is labeled so that it can be distinguished during the imaging.

[0256] In an embodiment the method is an *in vivo* method and a subject or patient is administered one or more agents that carry an imaging label and that are capable of targeting or binding to one or more endometrial markers. The agent is allowed to incubate *in vivo* and bind to the endometrial markers associated with endometrial cells or tissues of a particular phase or associated with diseased cells or tissues, (e.g. an endometrial tumor). The presence of the label is localized to the endometrial cells or tissues, and the localized label is detected using imaging devices known to those skilled in the art.

[0257] The agent may be an antibody or chemical entity that recognizes the endometrial markers. In an aspect of the disclosure, the agent is a polyclonal antibody or monoclonal antibody, or fragments thereof, or constructs thereof including but not limited to, single chain antibodies, bifunctional antibodies, molecular recognition units, and peptides or entities that mimic peptides. The antibodies specific for the endometrial markers used in the methods of the invention may be obtained from scientific or commercial sources, or isolated native endometrial markers or recombinant endometrial markers may be utilized to prepare antibodies etc. as described herein.

[0258] An agent may be a peptide that mimics the epitope for an antibody specific for an endometrial marker and binds to the marker. The peptide may be produced on a commercial synthesizer using conventional solid phase chemistry. By way of example, a peptide may be prepared that includes either tyrosine, lysine, or phenylalanine to which N_2S_2 chelate is complexed (See U.S. Patent No. 4,897,255). An anti-endocrine marker peptide conjugate is then combined with a radiolabel (e.g. sodium ^{99m}Tc pertechnetate or sodium ^{188}Reperrhenate) and it may be used to locate an endometrial marker producing cell or tissue (e.g. tumor).

[0259] The agent carries a label to image the endometrial markers. The agent may be labelled for use in radionuclide imaging. In particular, the agent may be directly or indirectly labelled with a radioisotope. Examples of radioisotopes that may be used in the present invention are the following: ^{277}Ac, ^{211}At, ^{128}Ba, ^{131}Ba, ^{7}Be, ^{204}Bi, ^{205}Bi, ^{206}Bi, ^{76}Br, ^{77}Br, ^{82}Br, ^{109}Cd, ^{47}Ca, ^{11}C, ^{14}C, ^{36}Cl, ^{48}Cr, ^{51}Cr, ^{62}Cu, ^{64}Cu, ^{67}Cu, ^{165}Dy, ^{155}Eu, ^{18}F, ^{153}Gd, ^{66}Ga, ^{67}Ga, ^{68}Ga, ^{72}Ga, ^{198}Au, ^{3}H, ^{166}Ho, ^{111}In, ^{113m}In, ^{115m}In, ^{123}I, ^{125}I, ^{131}I, ^{189}Ir, ^{191m}Ir, ^{192}Ir, ^{194}Ir, ^{52}Fe, ^{55}Fe, ^{59}Fe, ^{177}Lu, ^{15}O, $^{191m-191}$Os, ^{109}Pd, ^{32}P, ^{33}P, ^{42}K, ^{226}Ra, ^{186}Re, ^{188}Re, ^{82m}Rb, ^{153}Sm, ^{46}Sc, ^{47}Sc, ^{72}Se, ^{75}Se, ^{105}Ag, ^{22}Na, ^{24}Na, ^{89}Sr, ^{35}S, ^{38}S, ^{177}Ta, ^{96}Tc, ^{99m}Tc, ^{201}Tl, ^{202}Tl, ^{113}Sn, ^{117m}Sn, ^{121}Sn, ^{166}Yb, ^{169}Yb, ^{175}Yb, ^{88}Y, ^{90}Y, ^{62}Zn and ^{65}Zn. Preferably the radioisotope is ^{131}I, ^{125}I, ^{123}I, ^{111}I, ^{99m}Tc, ^{90}Y, ^{186}Re, ^{188}Re, ^{32}P, ^{153}Sm, ^{67}Ga, ^{201}Tl ^{77}Br, or ^{18}F, and is imaged with a photoscanning device.

[0260] Procedures for labeling biological agents with the radioactive isotopes are generally known in the art. U.S. Pat. No. 4,302,438 describes tritium labeling procedures. Procedures for iodinating, tritium labeling, and ^{35}S labeling especially adapted for murine monoclonal antibodies are described by Goding, J. W. (supra, pp 124-126) and the references cited therein. Other procedures for iodinating biological agents, such as antibodies, binding portions thereof, probes, or ligands, are described in the scientific literature [see Hunter and Greenwood, Nature 144:945 (1962), David et al., Biochemistry 13:1014-1021 (1974), and U.S. Pat. Nos. 3,867,517 and 4,376,110]. Iodinating procedures for agents are described by Greenwood, F. et al., Biochem. J. 89:114-123 (1963); Marchalonis, J., Biochem. J. 113:299-305 (1969); and Morrison, M. et al., Immunochemistry, 289-297 (1971). ^{99m} Tc-labeling procedures are described by Rhodes, B. et al. in Burchiel, S. et al. (eds.), Tumor Imaging: The Radioimmunochemical Detection of Cancer, New York: Masson 111-123 (1982) and the references cited therein. Labelling of antibodies or fragments with technetium-99m are also described for example in U.S. Pat. No. 5,317,091, U.S. Pat. No. 4,478,815, U.S. Pat. No. 4,478,818, U.S. Pat. No. 4,472,371, U.S. Pat. No. Re 32,417, and U.S. Pat. No. 4,311,688. Procedures suitable for ^{111} In-labeling biological agents are described by Hnatowich, D. J. et al., J. Immul. Methods, 65:147-157 (1983), Hnatowich, D. et al., J. Applied Radiation, 35:554-557 (1984), and Buckley, R. G. et al., F.E.B.S. 166:202-204 (1984).

[0261] An agent may also be labeled with a paramagnetic isotope for purposes of an *in vivo* method. Examples of elements that are useful in magnetic resonance imaging include gadolinium, terbium, tin, iron, or isotopes thereof. (See, for example, Schaefer et al., (1989) JACC 14,472-480; Shreve et al., (1986) Magn. Reson. Med. 3,336-340; Wolf, G L., (1984) Physiol. Chem. Phys. Med. NMR 16, 93-95; Wesbey et al., (1984) Physiol. Chem. Phys. Med. NMR 16, 145-155; Runge et al., (1984) Invest. Radiol. 19, 408-415 for discussions on *in vivo* nuclear magnetic resonance imaging.)

[0262] In the case of a radiolabeled agent, the agent may be administered to the patient, it is localized to the cell or tissue (e.g. tumor) having an endometrial marker with which the agent binds, and is detected or "imaged" *in vivo* using known techniques such as radionuclear scanning using e.g., a gamma camera or emission tomography. [See for example, A. R. Bradwell et al., "Developments in Antibody Imaging", Monoclonal Antibodies for Cancer Detection and Therapy, R. W. Baldwin et al., (eds.), pp. 65-85 (Academic Press 1985)]. A positron emission transaxial tomography scanner, such as designated Pet VI located at Brookhaven National Laboratory, can also be used where the radiolabel emits positrons (e.g., ^{11}C, ^{18}F, ^{15}O, and ^{13}N).

[0263] Whole body imaging techniques using radioisotope labeled agents can be used for locating diseased cells and tissues (e.g. primary tumors and tumors which have metastasized). Antibodies specific for endometrial markers, or fragments thereof having the same epitope specificity, are bound to a suitable radioisotope, or a combination thereof, and administered parenterally. For endometrial cancer, administration preferably is intravenous. The biodistribution of

the label can be monitored by scintigraphy, and accumulations of the label are related to the presence of endometrial cancer cells. Whole body imaging techniques are described in U.S. Pat. Nos. 4,036,945 and 4,311,688. Other examples of agents useful for diagnosis and therapeutic use that can be coupled to antibodies and antibody fragments include metallothionein and fragments (see, U.S. Pat. No. 4,732,864). These agents are useful in diagnosis staging and visualization of cancer, in particular endometrial cancer, so that surgical and/or radiation treatment protocols can be used more efficiently.

[0264] An imaging agent may carry a bioluminescent or chemiluminescent label. Such labels include polypeptides known to be fluorescent, bioluminescent or chemiluminescent, or, that act as enzymes on a specific substrate (reagent), or can generate a fluorescent, bioluminescent or chemiluminescent molecule. Examples of bioluminescent or chemiluminescent labels include luciferases, aequorin, obelin, mnemiopsin, berovin, a phenanthridinium ester, and variations thereof and combinations thereof. A substrate for the bioluminescent or chemiluminescent polypeptide may also be utilized in a method of the invention. For example, the chemiluminescent polypeptide can be luciferase and the reagent luciferin. A substrate for a bioluminescent or chemiluminescent label can be administered before, at the same time (e.g., in the same formulation), or after administration of the agent.

[0265] An imaging agent may comprise a paramagnetic compound, such as a polypeptide chelated to a metal, e.g., a metalloporphyrin. The paramagnetic compound may also comprise a monocrystalline nanoparticle, e.g., a nanoparticle comprising a lanthanide (e.g., Gd) or iron oxide; or, a metal ion comprising a lanthanide. "Lanthanides" refers to elements of atomic numbers 58 to 70, a transition metal of atomic numbers 21 to 29,42 or 44, a Gd(III), a Mn(II), or an element comprising a Fe element. Paramagnetic compounds can also comprise a neodymium iron oxide ($NdFeO_3$) or a dysprosium iron oxide ($DyFeO_3$). Examples of elements that are useful in magnetic resonance imaging include gadolinium, terbium, tin, iron, or isotopes thereof. (See, for example, Schaefer et al., (1989) JACC 14, 472-480; Shreve et al., (1986) Magn. Reson. Med. 3, 336-340; Wolf, G L., (1984) Physiol. Chem. Phys. Med. NMR 16, 93-95; Wesbey et al., (1984) Physiol. Chem. Phys. Med. NMR 16,145-155; Runge et al., (1984) Invest. Radiol. 19, 408-415 for discussions on *in vivo* nuclear magnetic resonance imaging.)

[0266] An image can be generated in a method disclosed herein by computer assisted tomography (CAT), magnetic resonance spectroscopy (MRS) image, magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), or bioluminescence imaging (BLI) or equivalent.

[0267] Computer assisted tomography (CAT) and computerized axial tomography (CAT) systems and devices well known in the art can be utilized. (See, for example, U.S. Patent Nos. 6,151,377; 5,946,371; 5,446,799; 5,406,479; 5,208,581; 5,109,397). The invention may also utilize animal imaging modalities, such as MicroCAT.TM. (ImTek, Inc.).

[0268] Magnetic resonance imaging (MRI) systems and devices well known in the art can be utilized. For a description of MRI methods and devices see, for example, U.S. Patent Nos. 6,151,377; 6,144,202; 6,128,522; 6,127,825; 6,121,775; 6,119,032; 6,115,446; 6,111,410; 602,891; 5,555,251; 5,455,512; 5,450,010; 5,378,987; 5,214,382; 5,031,624; 5,207,222; 4,985,678; 4,906,931; 4,558,279. MRI and supporting devices are commercially available for example, from Bruker Medical GMBH; Caprius; Esaote Biomedica; Fonar; GE Medical Systems (GEMS); Hitachi Medical Systems America; Intermagnetics General Corporation; Lunar Corp.; MagneVu; Marconi Medicals; Philips Medical Systems; Shimadzu; Siemens; Toshiba America Medical Systems; including imaging systems, by, e.g., Silicon Graphics. Animal imaging modalities such as micro-MRIs may also be utilized.

[0269] Positron emission tomography imaging (PET) systems and devices well known in the art can be utilized. For example, a method may use the system designated Pet VI located at Brookhaven National Laboratory. For descriptions of PET systems and devices see, for example, U.S. Pat. Nos. 6,151,377; 6,072,177; 5,900,636; 5,608,221; 5,532,489; 5,272,343; 5,103,098. Animal imaging modalities such as micro-PETs (Corcorde Microsystems, Inc.) can also be used.

[0270] Single-photon emission computed tomography (SPECT) systems and devices well known in the art can be utilized. (See, for example, U.S. Patents. Nos. 6,115,446; 6,072,177; 5,608,221; 5,600,145; 5,210,421; 5,103,098.) The methods may also utilize animal imaging modalities, such as micro-SPECTs.

[0271] Bioluminescence imaging includes bioluminescence, fluorescence or chemiluminescence or other photon detection systems and devices that are capable of detecting bioluminescence, fluorescence or chemiluminescence. Sensitive photon detection systems can be used to detect bioluminescent and fluorescent proteins externally; see, for example, Contag (2000) Neoplasia 2:41-52; Zhang (1994) Clin. Exp. Metastasis 12:87-92. The methods of the invention can be practiced using any such photon detection device, or variation or equivalent thereof, or in conjunction with any known photon detection methodology, including visual imaging. By way of example, an intensified charge-coupled device (ICCD) camera coupled to an image processor may be used in the present invention. (See, e.g., U.S. Pat. No. 5,650,135). Photon detection devices are also commercially available from Xenogen, Hamamatsue.

Screening Methods

[0272] Contemplated are also methods for evaluating test agents or compounds for their ability to inhibit an endometrial disease (e.g. cancer), potentially contribute to an endometrial disease (e.g. cancer), or inhibit or enhance an endometrium

phase. Test agents and compounds include but are not limited to peptides such as soluble peptides including Ig-tailed fusion peptides, members of random peptide libraries and combinatorial chemistry-derived molecular libraries made of D- and/or L-configuration amino acids, phosphopeptides (including members of random or partially degenerate, directed phosphopeptide libraries), antibodies [e.g. polyclonal, monoclonal, humanized, anti-idiotypic, chimeric, single chain antibodies, fragments, (e.g. Fab, $F(ab)_2$, and Fab expression library fragments, and epitope-binding fragments thereof)], and small organic or inorganic molecules. The agents or compounds may be endogenous physiological compounds or natural or synthetic compounds.

[0273] The disclosure provides a method for assessing the potential efficacy of a test agent for inhibiting an endometrial disease (e.g. cancer) in a patient, the method comprising comparing:

(a) levels of one or more endometrial markers, and/or polynucleotides encoding endometrial markers, and optionally other markers in a first sample obtained from a patient and exposed to the test agent; and
(b) levels of one or more endometrial markers and/or polynucleotides encoding endometrial markers, and optionally other markers, in a second sample obtained from the patient, wherein the sample is not exposed to the test agent, wherein a significant difference in the levels of expression of one or more endometrial markers, and/or polynucleotides encoding one or more endometrial markers, and optionally the other markers, in the first sample, relative to the second sample, is an indication that the test agent is potentially efficacious for inhibiting an endometrial disease (e.g. cancer) in the patient.

[0274] The first and second samples may be portions of a single sample obtained from a patient or portions of pooled samples obtained from a patient.

[0275] In an aspect, disclosed is a method of selecting an agent for inhibiting an endometrial disease (e.g. cancer) in a patient comprising:

(a) obtaining a sample from the patient;
(b) separately maintaining aliquots of the sample in the presence of a plurality of test agents;
(c) comparing one or more endometrial markers, and/or polynucleotides encoding endometrial markers, and optionally other markers, in each of the aliquots; and
(d) selecting one of the test agents which alters the levels of one or more endometrial markers, and/or polynucleotides encoding endometrial markers, and optionally other markers in the aliquot containing that test agent, relative to other test agents.

[0276] In a further aspect, disclosed is a method of selecting an agent for inhibiting or enhancing an endometrium phase in a patient comprising:

(a) obtaining a sample of endometrium in a selected phase (e.g. secretory or proliferative phase);
(b) separately maintaining aliquots of the sample in the presence of a plurality of test agents;
(c) comparing one or more endometrial markers, and/or polynucleotides encoding endometrial markers, and optionally other markers, in each of the aliquots; and
(d) selecting one of the test agents which alters the levels of one or more endometrial markers, and/or polynucleotides encoding endometrial markers, and optionally other markers in the aliquot containing that test agent, relative to other test agents.

[0277] Still another aspect of the present disclosure provides a method of conducting a drug discovery business comprising:

(a) providing one or more methods or assay systems for identifying agents that inhibit an endometrial disease (e.g. endometrial cancer) or affect an endometrium phase in a patient;
(b) conducting therapeutic profiling of agents identified in step (a), or further analogs thereof, for efficacy and toxicity in animals; and
(c) formulating a pharmaceutical preparation including one or more agents identified in step (b) as having an acceptable therapeutic profile.

[0278] In certain embodiments, the subject method can also include a step of establishing a distribution system for distributing the pharmaceutical preparation for sale, and may optionally include establishing a sales group for marketing the pharmaceutical preparation.

[0279] Contemplated is a method of assessing the potential of a test compound to contribute to an endometrial disease (e.g. endometrial cancer) comprising:

(a) maintaining separate aliquots of cells or tissues from a patient with an endometrial disease (e.g. cancer) in the presence and absence of the test compound; and
(b) comparing one or more endometrial markers, and/or polynucleotides encoding endometrial markers, and optionally other markers in each of the aliquots.

[0280] A significant difference between the levels of the markers in the aliquot maintained in the presence of (or exposed to) the test compound relative to the aliquot maintained in the absence of the test compound, indicates that the test compound possesses the potential to contribute to an endometrial disease (e.g. endometrial cancer).

Kits

[0281] The invention also contemplates the use of kits for carrying out the methods of the invention. Kits may typically comprise two or more components required for performing a diagnostic assay. Components include but are not limited to compounds, reagents, containers, and/or equipment.

[0282] The methods described herein may be performed by utilizing pre-packaged diagnostic kits comprising one or more specific endometrial marker polynucleotide or antibody described herein, which may be conveniently used, e.g., in clinical settings to screen and diagnose patients and to screen and identify those individuals exhibiting a predisposition to developing an endometrial disease.

[0283] In an embodiment, a container with a kit comprises a binding agent as described herein. By way of example, the kit may contain antibodies or antibody fragments which bind specifically to epitopes of one or more endometrial markers and optionally other markers, antibodies against the antibodies labelled with an enzyme; and a substrate for the enzyme. The kit may also contain microtiter plate wells, standards, assay diluent, wash buffer, adhesive plate covers, and/or instructions for carrying out a method of the invention using the kit.

[0284] In an aspect of the invention, the kit includes antibodies or fragments of antibodies which bind specifically to an epitope of one or more polypeptide listed in Table 1 and optionally one or more polypeptide listed in Table 2 and means for detecting binding of the antibodies to their epitope associated with tumor cells, either as concentrates (including lyophilized compositions), which may be further diluted prior to use or at the concentration of use, where the vials may include one or more dosages. Where the kits are intended for *in vivo* use, single dosages may be provided in sterilized containers, having the desired amount and concentration of agents. Containers that provide a formulation for direct use, usually do not require other reagents, as for example, where the kit contains a radiolabelled antibody preparation for *in vivo* imaging.

[0285] A kit may be designed to detect the level of polynucleotides encoding one or more endometrial polynucleotide markers in a sample. In an embodiment, the polynucleotides encode one or more polynucleotides encoding a polypeptide listed in Table 1 and optionally one or more polynucleotides listed in Table 2. Such kits generally comprise at least one oligonucleotide probe or primer, as described herein, that hybridizes to a polynucleotide encoding one or more endometrial cancer markers. Such an oligonucleotide may be used, for example, within a PCR or hybridization procedure. Additional components that may be present within the kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate detection of a polynucleotide encoding one or more endometrial cancer markers.

[0286] Disclosed is furthermore a kit containing a micoarray described herein ready for hybridization to target endometrial polynucleotide markers, plus software for the data analysis of the results. The software to be included with the kit comprises data analysis methods, in particular mathematical routines for marker discovery, including the calculation of correlation coefficients between clinical categories and marker expression. The software may also include mathematical routines for calculating the correlation between sample marker expression and control marker expression, using array-generated fluorescence data, to determine the clinical classification of the sample.

[0287] The reagents suitable for applying the screening methods of the invention to evaluate compounds may be packaged into convenient kits described herein providing the necessary materials packaged into suitable containers.

[0288] Contemplated is a kit for assessing the presence of endometrial cells, wherein the kit comprises antibodies specific for one or more endometrial markers, or primers or probes for polynucleotides encoding same, and optionally probes, primers or antibodies specific for other markers associated with an endometrial disease (e.g. cancer).

[0289] Disclosed is furthermore a kit for assessing the suitability of each of a plurality of test compounds for inhibiting an endometrial disease (e.g. endometrial cancer) in a patient. The kit comprises reagents for assessing one or more endometrial markers or polynucleotides encoding same, and optionally a plurality of test agents or compounds.

[0290] Additionally disclosed is a kit for assessing the potential of a test compound to contribute to an endometrial disease (e.g. cancer). The kit comprises endometrial diseased cells (e.g. cancer cells) and reagents for assessing one or more endometrial markers, polynucleotides encoding same, and optionally other markers associated with an endometrial disease.

Therapeutic Applications

[0291] One or more endometrial markers may be targets for immunotherapy. Immunotherapeutic methods include the use of antibody therapy, *in vivo* vaccines, and *ex vivo* immunotherapy approaches.

[0292] In one aspect, disclosed are one or more endometrial marker antibodies that may be used systemically to treat an endometrial disease associated with the marker. In particular, the endometrial disease is endometrial cancer and one or more endometrial marker antibodies may be used systemically to treat endometrial cancer. Preferably antibodies are used that target the tumor cells but not the surrounding non-tumor cells and tissue.

[0293] Thus, there is disclosed a method of treating a patient susceptible to, or having a disease (e.g. cancer) that expresses one or more endometrial marker (in particular a marker up-regulated in endometrial cancer, for example, an up-regulated marker in Table 1 and optionally an up-regulated marker in Table 2), comprising administering to the patient an effective amount of an antibody that binds specifically to one or more endometrial marker.

[0294] In another aspect, disclosed is a method of inhibiting the growth of tumor cells expressing one or more endometrial cancer markers, comprising administering to a patient an antibody which binds specifically to one or more endometrial cancer markers in an amount effective to inhibit growth of the tumor cells.

[0295] One or more endometrial marker antibodies may also be used in a method for selectively inhibiting the growth of, or killing a cell expressing one or more endometrial marker (e.g. tumor cell expressing one or more endometrial cancer marker) comprising reacting one or more endometrial marker antibody immunoconjugate or immunotoxin with the cell in an amount sufficient to inhibit the growth of, or kill the cell.

[0296] By way of example, unconjugated antibodies to endometrial cancer markers may be introduced into a patient such that the antibodies bind to endometrial cancer marker expressing cancer cells and mediate growth inhibition of such cells (including the destruction thereof), and the tumor, by mechanisms which may include complement-mediated cytolysis, antibody-dependent cellular cytotoxicity, altering the physiologic function of one or more endometrial cancer markers, and/or the inhibition of ligand binding or signal transduction pathways. In addition to unconjugated antibodies to endometrial cancer markers, one or more endometrial cancer marker antibodies conjugated to therapeutic agents (e.g. immunoconjugates) may also be used therapeutically to deliver the agent directly to one or more endometrial cancer marker expressing tumor cells and thereby destroy the tumor. Examples of such agents include abrin, ricin A, *Pseudomonas* exotoxin, or diphtheria toxin; proteins such as tumor necrosis factor, alpha-interferon, beta-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; and biological response modifiers such as lymphokines, interleukin-1, interleukin-2, interleukin-6, granulocyte macrophage colony stimulating factor, granulocyte colony stimulating factor, or other growth factors.

[0297] Cancer immunotherapy using one or more endometrial cancer marker antibodies may utilize the various approaches that have been successfully employed for cancers, including but not limited to colon cancer (Arlen et al., 1998, Crit Rev Immunol 18: 133-138), multiple myeloma (Ozaki et al., 1997, Blood 90: 3179-3186; Tsunenati et al., 1997, Blood 90: 2437-2444), gastric cancer (Kasprzyk et al., 1992, Cancer Res 52: 2771-2776), B-cell lymphoma (Funakoshi et al., 1996, J Immunther Emphasis Tumor Immunol 19: 93-101), leukemia (Zhong et al., 1996, Leuk Res 20: 581-589), colorectal cancer (Moun et al., 1994, Cancer Res 54: 6160-6166); Velders et al., 1995, Cancer Res 55: 4398-4403), and breast cancer (Shepard et al., 1991, J Clin Immunol 11: 117-127).

[0298] In the practice of such a method, endometrial cancer marker antibodies capable of inhibiting the growth of cancer cells expressing endometrial cancer markers are administered in a therapeutically effective amount to cancer patients whose tumors express or overexpress one or more endometrial cancer markers. The method may provide a specific, effective and long-needed treatment for endometrial cancer. The antibody therapy methods may be combined with other therapies including chemotherapy and radiation.

[0299] Patients may be evaluated for the presence and level of expression or overexpression of one or more endometrial markers in diseased cells and tissues (e.g. tumors), in particular using immunohistochemical assessments of tissue, quantitative imaging as described herein, or other techniques capable of reliably indicating the presence and degree of expression of one or more endometrial markers. Immunohistochemical analysis of tumor biopsies or surgical specimens may be employed for this purpose.

[0300] Endometrial marker antibodies useful in treating disease (e.g. cancer) include those that are capable of initiating a potent immune response against the disease (e.g. tumor) and those that are capable of direct cytotoxicity. In this regard, endometrial marker antibodies may elicit cell lysis by either complement-mediated or antibody-dependent cell cytotoxicity (ADCC) mechanisms, both of which require an intact Fc portion of the immunoglobulin molecule for interaction with effector cell Fc receptor sites or complement proteins.

[0301] Endometrial marker antibodies that exert a direct biological effect on tumor growth may also be useful. Such antibodies may not require the complete immunoglobulin to exert the effect. Potential mechanisms by which such directly cytotoxic antibodies may act include inhibition of cell growth, modulation of cellular differentiation, modulation of tumor angiogenesis factor profiles, and the induction of apoptosis. The mechanism by which a particular antibody exerts an anti-tumor effect may be evaluated using any number of *in vitro* assays designed to determine ADCC, antibody-dependent

macrophage-mediated cytotoxicity (ADMMC), complement-mediated cell lysis, and others known in the art.

[0302] The anti-tumor activity of a particular endometrial cancer marker antibody, or combination of endometrial cancer marker antibodies, may be evaluated *in vivo* using a suitable animal model. Xenogenic cancer models, where human cancer explants or passaged xenograft tissues are introduced into immune compromised animals, such as nude or SCID mice, may be employed.

[0303] Contemplated is the administration of single endometrial marker antibodies as well as combinations, or "cocktails", of different individual antibodies such as those recognizing different epitopes of other markers. Such cocktails may have certain advantages inasmuch as they contain antibodies that bind to different epitopes of endometrial markers and/or exploit different effector mechanisms or combine directly cytotoxic antibodies with antibodies that rely on immune effector functionality. Such antibodies in combination may exhibit synergistic therapeutic effects. In addition, the administration of one or more endometrial marker specific antibodies may be combined with other therapeutic agents, including but not limited to chemotherapeutic agents, androgen-blockers, and immune modulators (e.g., IL2, GM-CSF). The endometrial marker specific antibodies may be administered in their "naked" or unconjugated form, or may have therapeutic agents conjugated to them.

[0304] The endometrial marker specific antibodies used may be formulated into pharmaceutical compositions comprising a carrier suitable for the desired delivery method. Suitable carriers include any material which when combined with the antibodies retains the function of the antibody and is non-reactive with the subject's immune systems. Examples include any of a number of standard pharmaceutical carriers such as sterile phosphate buffered saline solutions, bacteriostatic water, and the like (see, generally, Remington's Pharmaceutical Sciences 16.sup.th Edition, A. Osal., Ed., 1980).

[0305] One or more endometrial marker specific antibody formulations may be administered via any route capable of delivering the antibodies to the a disease (e.g. tumor) site. Routes of administration include, but are not limited to, intravenous, intraperitoneal, intramuscular, intratumor, intradermal, and the like. Preferably, the route of administration is by intravenous injection. Antibody preparations may be lyophilized and stored as a sterile powder, preferably under vacuum, and then reconstituted in bacteriostatic water containing, for example, benzyl alcohol preservative, or in sterile water prior to injection.

[0306] Treatment will generally involve the repeated administration of the antibody preparation via an acceptable route of administration such as intravenous injection (IV), at an effective dose. Dosages will depend upon various factors generally appreciated by those of skill in the art, including the type of disease and the severity, grade, or stage of the disease, the binding affinity and half life of the antibodies used, the degree of endometrial marker expression in the patient, the extent of circulating endometrial markers, the desired steady-state antibody concentration level, frequency of treatment, and the influence of any chemotherapeutic agents used in combination with the treatment method. Daily doses may range from about 0.1 to 100 mg/kg. Doses in the range of 10-500 mg antibodies per week may be effective and well tolerated, although even higher weekly doses may be appropriate and/or well tolerated. A determining factor in defining the appropriate dose is the amount of a particular antibody necessary to be therapeutically effective in a particular context. Repeated administrations may be required to achieve disease inhibition or regression. Direct administration of one or more endometrial marker antibodies is also possible and may have advantages in certain situations.

[0307] Patients may be evaluated for serum cancer markers in order to assist in the determination of the most effective dosing regimen and related factors. The endometrial cancer assay methods described herein, or similar assays, may be used for quantitating circulating endometrial marker levels in patients prior to treatment. Such assays may also be used for monitoring throughout therapy, and may be useful to gauge therapeutic success in combination with evaluating other parameters such as serum levels of endometrial markers.

[0308] Disclosed are further vaccines formulated to contain one or more endometrial marker or fragment thereof.

[0309] In an embodiment, the disclosure provides a method of vaccinating an individual against one or more endometrial marker listed in Table 1 and optionally one or more maker listed in Table 2, comprising the step of inoculating the individual with the marker or fragment thereof that lacks activity, wherein the inoculation elicits an immune response in the individual thereby vaccinating the individual against the marker.

[0310] The use in anti-cancer therapy of a tumor antigen in a vaccine for generating humoral and cell-mediated immunity is well known and, for example, has been employed in prostate cancer using human PSMA and rodent PAP immunogens (Hodge et al., 1995, Int. J. Cancer 63: 231-237; Fong et al., 1997, J. Immunol. 159: 3113-3117). These and similar methods can be practiced by employing one or more endometrial markers, or fragment thereof, or endometrial polynucleotide markers and recombinant vectors capable of expressing and appropriately presenting endometrial marker immunogens.

[0311] By way of example, viral gene delivery systems may be used to deliver one or more endometrial polynucleotide markers. Various viral gene delivery systems which can be used in the practice of this aspect include, but are not limited to, vaccinia, fowlpox, canarypox, adenovirus, influenza, poliovirus, adeno-associated virus, lentivirus, and sindbus virus (Restifo, 1996, Curr. Opin. Immunol. 8: 658-663). Non-viral delivery systems may also be employed by using naked DNA encoding one or more endometrial cancer marker or fragment thereof introduced into the patient (e.g., intramus-

cularly) to induce an anti-tumor response.

[0312] Various *ex vivo* strategies may also be employed. One approach involves the use of cells to present one or more endometrial marker to a patient's immune system. For example, autologous dendritic cells which express MHC class I and II, may be pulsed with one or more endometrial marker or peptides thereof that are capable of binding to MHC molecules, to thereby stimulate the patients' immune systems (See, for example, Tjoa et al., 1996, Prostate 28: 65-69; Murphy et al., 1996, Prostate 29: 371-380).

[0313] Anti -idiotypic endometrial marker specific antibodies can also be used in therapy as a vaccine for inducing an immune response to cells expressing one or more endometrial marker. The generation of anti-idiotypic antibodies is well known in the art and can readily be adapted to generate anti-idiotypic endometrial cancer marker specific antibodies that mimic an epitope on one or more endometrial cancer markers (see, for example, Wagner et. al., 1997, Hybridoma 16: 33-40; Foon et al., 1995, J Clin Invest 96: 334-342; Herlyn et al., 1996, Cancer Immunol Immunother 43: 65-76). Such an antibody can be used in anti-idiotypic therapy as presently practiced with other anti-idiotypic antibodies directed against antigens associated with disease (e.g. tumor antigens).

[0314] Genetic immunization methods may be utilized to generate prophylactic or therapeutic humoral and cellular immune responses directed against cells expressing one or more endometrial cancer marker. One or more DNA molecules encoding endometrial markers, constructs comprising DNA encoding one or more endometrial markers/immunogens and appropriate regulatory sequences may be injected directly into muscle or skin of an individual, such that the cells of the muscle or skin take-up the construct and express the encoded endometrial markers/immunogens. The endometrial markers/immunogens may be expressed as cell surface proteins or be secreted. Expression of one or more endometrial markers results in the generation of prophylactic or therapeutic humoral and cellular immunity against the disease (e.g. cancer). Various prophylactic and therapeutic genetic immunization techniques known in the art may be used.

[0315] Disclosed are further methods for inhibiting cellular activity (e.g., cell proliferation, activation, or propagation) of a cell expressing one or more endometrial marker. This method comprises reacting immunoconjugates described herein (e.g., a heterogeneous or homogenous mixture) with the cell so that endometrial markers form complexes with the immunoconjugates. A subject with a neoplastic or preneoplastic condition can be treated when the inhibition of cellular activity results in cell death.

[0316] In another aspect, methods are disclosed for selectively inhibiting a cell expressing one or more endometrial marker by reacting any one or a combination of the immunoconjugates of the invention with the cell in an amount sufficient to inhibit the cell. Amounts include those that are sufficient to kill the cell or sufficient to inhibit cell growth or proliferation.

[0317] Vectors derived from retroviruses, adenovirus, herpes or vaccinia viruses, or from various bacterial plasmids, may be used to deliver polynucleotides encoding endometrial cancer markers to a targeted organ, tissue, or cell population. Methods well known to those skilled in the art may be used to construct recombinant vectors that will express antisense polynucleotides for endometrial markers. (See, for example, the techniques described in Sambrook et al (supra) and Ausubel et al (supra)).

[0318] Methods for introducing vectors into cells or tissues include those methods discussed herein and which are suitable for *in* vivo, *in vitro* and ex *vivo* therapy. For *ex vivo* therapy, vectors may be introduced into stem cells obtained from a patient and clonally propagated for autologous transplant into the same patient (See U.S. Pat. Nos. 5,399,493 and 5,437,994). Delivery by transfection and by liposome are well known in the art.

[0319] Genes encoding endometrial markers can be turned off by transfecting a cell or tissue with vectors that express high levels of a desired endometrial marker-encoding fragment. Such constructs can inundate cells with untranslatable sense or antisense sequences. Even in the absence of integration into the DNA, such vectors may continue to transcribe RNA molecules until all copies are disabled by endogenous nucleases.

[0320] Modifications of gene expression can be obtained by designing antisense molecules, DNA, RNA or PNA, to the regulatory regions of a gene encoding an endometrial marker, i.e., the promoters, enhances, and introns. Preferably, oligonucleotides are derived from the transcription initiation site, e.g. between -10 and +10 regions of the leader sequence. The antisense molecules may also be designed so that they block translation of mRNA by preventing the transcript from binding to ribosomes. Inhibition may also be achieved using "triple helix" base-pairing methodology. Triple helix pairing compromises the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Therapeutic advances using triplex DNA were reviewed by Gee J E et al (In: Huber B E and B I Carr (1994) Molecular and Immunologic Approaches, Futura Publishing Co, Mt Kisco N.Y.).

[0321] Ribozymes are enzymatic RNA molecules that catalyze the specific cleavage of RNA. Ribozymes act by sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. It is therefore contemplated to use engineered hammerhead motif ribozyme molecules that can specifically and efficiently catalyze endonucleolytic cleavage of sequences encoding an endometrial marker.

[0322] Specific ribozyme cleavage sites within any potential RNA target may initially be identified by scanning the target molecule for ribozyme cleavage sites which include the following sequences, GUA, GUU and GUC. Once the sites are identified, short RNA sequences of between 15 and 20 ribonucleotides corresponding to the region of the target

gene containing the cleavage site may be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be determined by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

[0323] One or more endometrial markers and polynucleotides encoding the markers, and fragments thereof, may be used in the treatment of an endometrial disease (e.g. endometrial cancer) in a subject. In an aspect the endometrial markers and polynucleotides encoding the markers are endometrial cancer markers that are down-regulated in endometrial cancer, for example, mucin 5B and one or more of the down-regulated markers listed in Table 2. The markers or polynucleotides may be formulated into compositions for administration to subjects suffering from an endometrial disease. Disclosed is thus also a composition comprising one or more endometrial markers or polynucleotides encoding the markers, or a fragment thereof, and a pharmaceutically acceptable carrier, excipient or diluent. A method for treating or preventing an endometrial disease in a subject is also provided comprising administering to a patient in need thereof, one or more endometrial markers or polynucleotides encoding the markers, or a composition described herein.

[0324] Disclosed is further a method of inhibiting an endometrial disease (e.g. endometrial cancer) in a patient comprising:

(a) obtaining a sample comprising diseased cells from the patient;
(b) separately maintaining aliquots of the sample in the presence of a plurality of test agents;
(c) comparing levels of one or more endometrial markers, and/or polynucleotides encoding one or more endometrial markers in each aliquot;
(d) administering to the patient at least one of the test agents which alters the levels of the endometrial markers, and/or polynucleotides encoding one or more endometrial markers in the aliquot containing that test agent, relative to the other test agents.

[0325] Endometrial markers in uterine biopsy tissue or fluid and sera may vary between known fertile and infertile women during the window of implantation, deviate in women undergoing ovarian hyperstimulation/ovulation induction, and correlate, with successful initiation of pregnancy. Therefore, endometrial markers disclosed herein may serve as minimally or noninvasive markers of uterine receptivity for implantation.

[0326] Disclosed is further a method of determining uterine endometrial receptivity by first obtaining a serum, uterine fluid or endometrial biopsy sample from a patient and detecting the presence of an endometrial marker associated with a certain endometrium phase, wherein the presence or absence of an endometrial marker as compared to controls indicates uterine receptivity. In an embodiment, the endometrium phase is the secretory phase. Where necessary for the evaluation, repetitive samples may be collected throughout the menstrual cycle. Non-receptive controls are both women who are in the non-fertile stage of the menstrual cycle and women with known uterine dysfunction where an endometrial marker is not present or present on the endometrium throughout the menstrual cycle or certain endometrium phases.

[0327] Disclosed is further a method of monitoring the effects of ovarian hyperstimulation and/or ovulation induction protocols on uterine receptivity either for individual women receiving the treatment or for the evaluation of new protocols. In an embodiment, the method comprises: (a) obtaining a serum, uterine or fluid or endometrial biopsy sample from a patient receiving the treatments; and (b) detecting the presence of an endometrial marker described herein present in the endometrium at the time of fertilization, early embryogenesis, and implantation; wherein presence or absence of an endometrial marker indicates receptivity. A disruption of the normal cyclic presence of an endometrial marker indicates that the treatment may adversely affect uterine receptivity. This disruption may include non-cyclic presence of an endometrial marker or an aberrant presence of an endometrial marker as compared to controls.

[0328] In an aspect disclosed is a method of determining a probability of successful implantation with an ovarian stimulation *in vitro* fertilization and embryo transfer procedure, comprising:

(a) determining a level of an endometrial marker in a sample obtained from a patient who has undergone an ovarian stimulation *in vitro* fertilization and embryo transfer procedure; and
(b) determining a probability of successful implantation based on the patient's determined endometrial marker level;

wherein a significantly different endometrial marker level relative to a standard level is associated with a decreased or increased probability of successful implantation.

[0329] Disclosed is also a method of contraception by interrupting the cyclic presence of an endometrial marker. The interruption can be to reduce or eliminate a marker present during the uterine receptivity window for implantation of the menstrual cycle and to thereby alter the cyclic presence/pattern of a marker. The interruption can utilize an antagonist of a marker. The term antagonist or antagonizing is used in its broadest sense. Antagonism can include any mechanism or treatment that results in inhibition, inactivation, blocking or reduction or alteration of cyclic presence of an endometrial marker.

[0330] An active therapeutic substance described herein may be administered in a convenient manner such as by injection (subcutaneous, intravenous, etc.), oral administration, inhalation, transdermal application, or rectal administration. Depending on the route of administration, the active substance may be coated in a material to protect the substance from the action of enzymes, acids and other natural conditions that may inactivate the substance. Solutions of an active compound as a free base or pharmaceutically acceptable salt can be prepared in an appropriate solvent with a suitable surfactant. Dispersions may be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof, or in oils.

[0331] The compositions described herein can be prepared by per se known methods for the preparation of pharmaceutically acceptable compositions which can be administered to subjects, such that an effective quantity of the active substance is combined in a mixture with a pharmaceutically acceptable vehicle. Suitable vehicles are described, for example, in Remington's Pharmaceutical Sciences (Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., USA 1985). On this basis, the compositions include, albeit not exclusively, the active substances in association with one or more pharmaceutically acceptable vehicles or diluents, and contained in buffered solutions with a suitable pH and isoosmotic with the physiological fluids.

[0332] The compositions are indicated as therapeutic agents either alone or in conjunction with other therapeutic agents or other forms of treatment. The compositions may be administered concurrently, separately, or sequentially with other therapeutic agents or therapies.

[0333] The therapeutic activity of compositions and agents/compounds identified using a method described herein and may be evaluated *in vivo* using a suitable animal model.

[0334] The following non-limiting example is illustrative of the present invention:

Example 1

Experimental Procedures

Samples and reagents

[0335] Endometrial tissues were retrieved from an in-house, dedicated, research endometrialtissue bank. With patient consent, samples from hysterectomy specimens had been flashfrozen in liquid nitrogen within 20 minutes of devitalizing. The patient consent forms and tissue-banking procedures were approved by the Research Ethics Boards of York University, Mount Sinai Hospital, University Health Network, and North York General Hospital. These frozen samples were sectioned and stored at -80 °C. The histologic diagnosis for each sample was confirmed using microscopic examination of a hematoxylin and eosin-stained frozen section of each research tissue block. The tissue from the mirror face of the histologic section was then washed three times in approximately 1 mL of phosphate-buffered saline (PBS) with a cocktail of protease inhibitors as described previously (1mM AEBSF, 10 μM leupeptin, 1 μg/mL aprotinin, and 1 μM pepstatin) (3). The washed tissue was then homogenized in 0.5 mL PBS with protease inhibitors, using a handheld homogenizer. These homogenates were then flash frozen in liquid nitrogen and stored at -80 °C until use. Samples were thawed and clarified by centrifugation and the protein concentration determined by a Bradford-type assay using BioRad's protein quantification reagent (Bio-Rad, Mississauga, ON, Canada). Two hundred micrograms of each of the forty samples was then labeled individually with an iTRAQ tag. As double the manufacturer's suggested amounts (Applied Biosystems) were used two individual vials of each tag for labeling each sample were also used. Trypsin digestion and labeling were performed as per the manufacturer's protocol. Normal proliferative, normal secretory, Type I cancer, and Type II cancer samples, were labeled with the 114, 115, 116 and 117 tags, respectively. The trypsin digested and labeled samples were then mixed in sets of four with each set containing one of each type of labels, thus resulting in ten sets in total.

Strong cation exchange (*SCX*) *separation conditions*

[0336] Each set of labeled samples was then separated by SCX fractionation using an HP1050 high-performance liquid chromatography (HPLC) instrument (Agilent, Palo Alto, CA, USA) with a 2.1-mm internal diameter (ID) x 100 mm length PolyLC Polysulfoethyl A column packed with 5 μm beads with 300 A pores (The Nest Group, Southborough, MA, USA). A 2.1-mm ID x 10-mm length guard column of the same material was fitted immediately upstream of the analytical column. Separation was performed as previously described (3). Briefly, each pooled sample set was diluted with the loading buffer (15 mM KH_2PO_4 in 25% acetonitrile, pH 3.0) to a total volume of 2 mL and the pH adjusted to 3.0 with phosphoric acid. Samples were then filtered using a 0.45-μm syringe filter (Millipore, Cambridge, ON, Canada) before loading onto the column. Separation was performed using a linear binary gradient over 1 hour. Buffer A was identical in composition to the loading buffer, while Buffer B was Buffer A containing 350 mM KCl. Fractions were collected every two minutes using an SF-2120 Super Fraction Collector (Advantec MFS, Dublin, CA, USA), after an initial wait of 2 minutes to accommodate the void volume. This resulted in a total of 30 SCX fractions per sample set: These fractions were dried by speed vacuuming (Thermo Savant SC110 A, Holbrook, NY, USA) and resuspended in 30 μL of 0.1%

formic acid each.

LC-MS/MS Run conditions

[0337] The fractions from 6 to 25 were then analyzed by nano LC-MS/MS using the LC Packings Ultimate instrument (Amsterdam, The Netherlands) fitted with a 1-μL sample loop. Samples were loaded onto a 5-mm reverse phase (RP) C18 precolumn (LC Packings) at 50 μL per minute and washed for 4 minutes before switching the precolumn in-line with the separation column. The separation column used was either a 75-μm ID x 150-mm length Pepmap RP column from LC Packings packed with 3- μm C18 beads with 100 A pores, or an in-house equivalent packed with similar beads from Kromasil (The Nest Group). The flow rate used for separation on the RP column was 200 nL/min while the gradient was as shown in the table below.

Time (min)	0	10	15	125	145	150	160	162	188
% B	5	5	15	35	60	80	80	5	Stop

[0338] Samples were analyzed on a Q-STAR Pulsar i mass spectrometer (Applied Biosystems /MDS SCIEX, Foster City, CA) in Information-Dependent Acquisition (IDA) mode with the scan cycles set up to perform a 1-s MS Scan followed by 5 MS/MS scans of the 5 most abundant peaks for 2 s each. For the first set of runs, the acquisition method was set up to allow one repetition of any m/z followed by a dynamic exclusion for a period of 60 s. The method was also set up to select the smallest peaks in the MS scan that are nearest to a threshold of 10 counts on every fourth scan. The last set of runs were performed using the same method but without any repetitions and with a dynamic exclusion of 30 s. Each sample was run a minimum of 2 times and a maximum of 3 times. The last run for each sample was performed using an inclusion list populated by m/z values that corresponded to peptides that appear to be proteotypic (8, 9) for proteins that were deemed to be of interest after devaluating the results of the first set of runs. Relative protein abundances were determined using the MS/MS scans of iTRAQ-labeled peptides (3). The iTRAQ-labeled peptides fragmented under collision-induced dissociation (CID) conditions to give reporter ions at 114.1, 115.1, 116.1, and 117.1 Th. Larger, sequence-information-rich fragment, ions were also produced under these conditions and gave the identity of the protein from which the peptide was analyzed. The ratios of peak areas of the iTRAQ reporter ions reflect the relative abundances of the peptides and the proteins in the samples.

Data Analysis

[0339] The software used (Applied Biosystems / MDS SCIEX) for data acquisition for the first set of runs was Analyst 1.0 SP8, while the software for the second run onwards was Analyst 1.1. Data were analyzed using ProQUANT 1.0 or 1.1, respectively, and the database searched was the Celera human database (human KBMS 20041109) provided by Applied Biosystems. Tolerance for the searches was set for 0.4 Da for the MS and 0.2 Da for the MS/MS spectra. The two parameters used to evaluate the quality of the peptide matches were the *score* and the *confidence* and are described in detail in the literature accompanying the software. Briefly, the score is a ProQUANT-generated value based on the number of ions that matches the theoretical list of fragments of the peptide in question, while the confidence, also a ProQUANT-generated value, is calculated from empirical data. The algorithm used to calculate the confidence incorporates the *distance score* calculated for the peptide, as well as factors such as the total number of results returned in the search. The distance score itself is calculated by determining the difference between the particular peptide's score and that of the 7th highest scoring peptide for that particular MS/MS spectrum, and is a measure of the confidence of the match. Only those peptides scoring higher than a score of 20 and a confidence of 75 were retained in the ProQUANT search. The ProQUANT results were then grouped using ProGroup viewer, which reports the lowest number of non-redundant protein identities that would account for the peptides identified along with the ratios for the relative abundance of these proteins after normalizing. Normalizing was performed by first calculating the median ratio of all proteins reported. Peptides that contribute to the protein identification but with ratios of the iTRAQ signature peaks smaller than 40 counts between the pair of labeled peaks in question were excluded from this calculation. The resulting median ratio was the normalizing factor used and was termed the *applied bias.* This normalizing factor is based on the assumption that most of the protein levels in the test samples should be similar to those in the control, with the exception of those that are specific to the condition of the test sample itself (i.e., malignant or benign), thus minimizing any systematic error. When the ratio for a protein from a set of constituent peptides is calculated, peptide ratios with smaller errors are weighted more heavily by the program. All peptides used for this calculation were unique to the given protein; peptides that were common to other isoforms or proteins of the same family were ignored. ProGroup also assesses the confidence of the protein identities reported. The ProGroup confidence score cut-off used was 1.3, which corresponds to a confidence limit of 95%. On occasion, the ratios of some proteins that were not automatically given by the ProGroup software were

also reported, using the ratios returned by the ProQUANT searches. These were typically instances in which the confidence in the sequence of the identifying peptides were lower than the specified cut-off for reporting by ProGroup, but for which there were more confident results for the same peptides from a different sample run. Identities of these peptides were manually verified prior to inclusion. Lastly, the ratios for each of the potential markers were averaged across all the runs in which they were identified.

[0340] As mentioned previously, the ten normal proliferative samples were also compared against each other in a separate series of experiments. Samples for this second series of experiments were grouped in three sets. The first of these sets contained the proliferative samples used in the first four sets of samples in the experiments comparing the cancerous samples, i.e., P1 - P4, the second set comprised proliferative samples P4 -P7, and the third set P7 - P10. In cases where the particular protein of interest was identified in all the three sample sets in these proliferative sample comparisons, the expression ratios were all recalculated relative to one proliferative sample, typically P1. These adjusted ratios were then used to calculate the average normal proliferative ratio, which was in turn used to normalize all the individual normal proliferative ratios themselves. This calculation was also performed on the individual expression ratios for the EmCa sample comparisons, thus permitting them to first be expressed relative to P1 and then relative to the average normal proliferative level.

Dot-Blot and Immunohistochemical verification

[0341] Verification of the differential expression levels of potential markers discovered using iTRAQ analysis was provided by dot-blot analyses and/or immunohistochemical analyses using antibodies specific to the protein of interest. Dot-blot analysis was performed by spotting 2 μg of each homogenate on a nitrocellulose filter (BioRad); after blocking with 5% (w/v) skimmed milk in Tris-buffered saline (TBS, 20 mM Tris pH 7.5, 150 mM NaCl), each filter was probed by incubating it with a primary antibody in 5% bovine serum albumin in TBS with 0.1% Tween 20 overnight with shaking. An additional blot was probed with antibody specific for β-actin. Additionally, selected proteins identified in the iTRAQ study were verified and localized using immunohistochemistry of proliferative, secretory, and EmCa tissues fixed in 10% buffered formalin and embedded in paraffin blocks. The antibodies were applied in an appropriate dilution determined through a pilot study and immunohistochemically visualized using a diaminobenzidine chromogen. Interpretations of the immunohistochemically stained sections were conducted using a standardized microscopic review to assess positive staining (brown) for the targeted proteins in four tissue components: epithelium/carcinoma, endometrial stroma, any white blood cells, and glandular secretions. Antibodies used for these verifications were purchased from various commercial sources: β-actin, Cell Signaling Technologies (Pickering, ON, Canada); polymeric immunoglobulin receptor (PIGR), Cedarlane Laboratories (Hornby, ON, Canada); pyruvate kinase (PK) M2, ScheBo Biotech AG (Glessen, Germany); and chaperonin 10 (Cpn 10), Stressgen (Victoria, BC, Canada).

Statistical analysis

[0342] Evaluation of differential expression in the iTRAQ analyses was performed using two statistical approaches. A preliminary evaluation of the data was carried out using a power analysis. For this, the ratios of areas of the iTRAQ reporter ions beyond which differential expression is considered significant, are given by $2 \times SD^2 \times (Z\alpha + Z\beta)^2 / N^{0.5}$, where SD is the standard deviation, $(Z\alpha + Z\beta)^2$ is the power index, and N is the number of sample sets (10). The standard deviations of the cytoplasmic structural proteins, actin and β-5-tubulin, were used to estimate the variation of protein concentrations between individual patients and sets. These averaged to be ~0.3 over many iTRAQ analyses (see, e.g., Table 3). A power index of 10.5 was used for confidence limits of 95% for Type I and 90% for Type II errors (10). Thus for N = 2, the ratios must be <0.51 or >1.97 to indicate differential expression; for N = 10, the criteria relax to <0.70 or >1.43. The three most significant and consistent biomarkers were then chosen as explanatory input variables in a logistic regression model as a discriminator between malignant and normal samples. If p denotes the predicted probability that a case i whose observed marker values are given by the vector x(i) = (x(i, marker 1), x(i, marker 2), x(i, marker 3)) is malignant. Then the logistic regression discriminator has the form

$$p(\text{case i is malignant} \mid x(i)) = \exp(\alpha + \Sigma \beta j x(i,j)) / [1 + \exp(\alpha + \Sigma \beta j x(i,j))]$$

where the index 'i' denotes the individual sample and 'j' is a summation index that runs over the markers. Analogously, logistic regression discriminators were defined for each of the three markers individually. For a training set S of marker values x(i) (i=1,...,n) the model parameters α and βj were determined by maximizing the multiplicative likelihood over S, using R Statistics (version 2.0.1). The discriminators were trained using the average observed iTRAQ ratios as marker

observations in the malignant and benign cases. Here, the malignant cases comprise a total of 20 Type I and Type II cancer cases, while the benign cases comprise ten normal proliferative and ten normal secretory cases. Receiver Operating Characteristic (ROC) curves were calculated from the predictive scores of the parametrized logistic regression model by varying thresholds for "positive" calls between 0 and 1. Sensitivities, specificities, predictive values (PV), and positive predictive values (PPV) were calculated using a cutoff value of 0.5 on the logistic regression predictor. For any given ROC curve, the area-under-the-curve (AUC) value was determined using the Mann-Whitney statistics (11, 12).

Results

[0343] Of all the proteins identified in the across the sample sets analyzed, only a few displayed distinct trends in their levels of differential expression across any of the three categories relative to the proliferative phase. These proteins, all confidently identified with more than two peptide matches in each case, are given in Table 3, along with two structural proteins: actin and β-5-tubulin as controls. Two samples initially classified as Type II cancers (II6 and II10) were subsequently reclassified as predominantly Type I (after histological re-examination) and are shown in Table 3 as I6b and I10b. The expression ratios shown are the averages of the replicate analyses. For pyruvate kinase M1/M2, polymeric immunoglobulin receptor precursor, macrophage migration inhibitory factor (MIF), α-1-antitrypsin (AAT), creatine kinase chain B (CKB), transgelin, actin, and β-5-tubulin, the ratios are those relative to the averages of the proliferative phase samples. Observations of the other listed proteins were incomplete in the proliferative phase comparisons; for these proteins, the ratios are relative to the specific proliferative phase samples used in the pairing. Table 4 shows the details of PK results as an illustration of the typical analytical precision achievable. Due to the scope of this study, the various runs for each sample set were often temporally separated by as much as six months. The ratios determined, however, varied typically by no more than ±20%. PCMs such as PK, PIGR, Cpn 10, MIF, AAT, CKB and transgelin were verified in this extensive study. Two proteins reported earlier (3), phosphatidylethanolamine binding protein (PEBP) and heterogenous nuclear ribonucleoprotein D0 (hnRNP D0) do not show consistent differential expression in this expanded study. Three new proteins showing differential expression in the 10 sets examined are WAP four-disulfide core domain protein 2 (WFDC2), clusterin, and mucin 5B. In addition, progestagen-associated endometrial protein, also known as PP 14 and known to be selectively overexpressed in the secretory phase (13, 14), is evident.

[0344] In Table 3, ratios that are bolded were determined to indicate differential expression via a power analysis. Differential expression is not observed in every sample set. For example, eight out of 12 Type I cancer samples, six out of eight Type II cancer samples, and zero out of 10 secretory phase samples overexpress PK. Similarly, seven out of 12 Type I cancer samples, four out of eight Type II cancer samples, and two out of 10 secretory phase samples underexpress AAT; six out of 10 Type I cancer samples, four out of eight Type II cancer samples, and two out of 10 secretory phase samples overexpress PIGR. Performances of the other proteins (except the two structural proteins) are comparable. By contrast, for actin and β-5-tubulin, virtually all sample sets showed no significant differential expression.

[0345] The comparisons of the ten proliferative samples afford an estimate on the variation of the abundances of proteins across samples or individual patients. An analysis of the following nine consistently observed proteins, PIGR, PK, Cpn 10, MIF, AAT, CKB, transgelin, actin, and β-5-tubulin, in the proliferative and secretory phases (thus giving 18 cases) shows that 13 out of 18 cases have relative standard deviations (RSDs) ≤ 30%, three out of 18 cases have RSDs 31-40%, and two out of 18 cases have RSDs > 40%. The two structural proteins, actin and β-5-tubulin, exhibit RSDs of 25-32% in the Type I and Type II EmCa samples. However, of the 14 remaining cases in the malignant samples, five out of 14 cases have RSDs ≤ 30%, three out of 14 cases have RSDs 31-40%, and six out of 14 cases have RSDs > 40%. Thus there are typically much larger patient-to-patient variations across the malignant samples.

[0346] In a second statistical analysis strategy, all listed proteins in Table 3 were screened for their individual association with malignant or benign status using the two sample *t*-test. Four proteins were deemed to provide the maximal allowable number of individual components in a panel that constitute robust and reproducible results, i.e., without losing validity due to overfitting. At a *t*-test, significance threshold of $p = 0.005$, the following four proteins were found to be differentially expressed between cancer and normal cases: PK ($p = 1.24 \times 10^{-7}$), Cpn 10 ($p = 2.2 \times 10^{-3}$), AAT ($p = 8.97 \times 10^{-4}$), and CKB ($p = 2.06 \times 10^{-4}$). AAT is more uniformly expressed than CKB within the combined proliferative and secretory samples, and was included in a candidate panel marker together with PK and Cpn10. The performance is shown in Figure 1. Evidently the use of the panel of three potential markers permits discrimination between cancer and normal samples, achieving an AUC of 0.96, and a sensitivity, selectivity, PV and PPV of 0.95 each. This was an improvement over the result when using the single best marker (PK), which achieved an AUC of 0.95, a sensitivity of 0.85, selectivity of 0.90, PV of 0.875 and PPV of 0.895. To assess whether the panel would be reproducible and valid in its predictive performance on independent data, two thirds / one third cross-validation were used. The set of 40 samples was split 10 times randomly into training and test sets of, respectively, 26 and 14 samples; the data from the 26 samples were used as input variables to train the logistic regression predictor. To maintain proportions and make the performance of the predictor over the random splits more comparable, the random selection was programmed such that identical absolute numbers of benign and malignant cases were assigned to training and test sets in each of the 10 data splits (i.e., 13

benign/13 malignant in each training set; 7 benign/7 malignant in each test set). Once the logistic regression discriminator was parametrically specified on a training set, it was used as a predictor to make calls for each of the 14 "independent" test cases, by using a cut-off value of 0.5. The accuracy of these calls, compared to the actual disease status of the test cases, was evaluated in terms of fractions of true positives (sensitivity) and false positives (1-specificity), for each of the ten test sets (Table 5). The similarity in performances between the training and test sets validates the predictability and ruggedness of the panel of biomarkers.

[0347] Support for the iTRAQ results was provided by dot-blot analyses of the same 40 samples. Figure 2 shows the results of the PIGR and β-actin blots; the latter was used for normalizing the protein loading. It is evident that the relative intensities of the dots do qualitatively correlate with the ratios across the sample sets as reported in the iTRAQ analyses. Additionally, immunohistochemistry validated the overexpression of PK, PIGR, and Cpn 10 in the malignant epithelium of EmCa tissues (Figure 3). Intense positive staining (brown) is evident in the epithelial cells of the glands in the cancer samples for PK, Cpn 10 and PIGR. By contrast, the glands of normal proliferative and secretory endometrium show absence of, or only weak, staining. For PIGR, intense staining is also evident within the lumen of the glands of one of the two Type I EmCa tissues, consistent with the expectation that this protein is cell-surface bound or secreted (15).

Discussion

[0348] Pyruvate kinase M1/M2 was demonstrated as being overexpressed in EmCa samples by both cICAT and iTRAQ methods (3). This result has been verified in this study, where PK appears to be an effective marker for differentiating between both Types I and II EmCa and normal endometrial tissues. Pyruvate kinase's significance as a cancer biomarker has increasingly been recognized. A number of studies have suggested that PK M2, in particular, is present primarily in a dimeric form in tumors and that it is useful as a biomarker in the early detection of tumors (16, 17). In fact the M2 isoform, after initial expression at the fetal stage, was reported to be prevalent only in proliferating cells and tumors (17). PK overexpression in tumor cells is understandable and can be explained on the basis of the key role that it plays in the generation of ATP in the glycolytic pathway. Under the hypoxic conditions that are typical for tumors, this pathway is a critical route by which tumors satisfy the higher energy requirements needed for proliferation (reviewed in ref. 18). Another study demonstrated that PK M2, in combination with any of three tumor markers (CEA, CA72-4, CA19-9) for gastrointestinal cancer, results in improved sensitivity for detection of colorectal, gastric and esophageal cancers (19).

[0349] Polymeric immunoglobulin receptor precursor was previously observed to be overexpressed in EmCa and has been verified in this study (3). PIGR is part of the immune response system and is typically expressed by epithelial cells. Its primary role is the transport of dimeric IgA from the basolateral surface of the epithelium to the apical surface where they are released into exocrine secretions (20,21). It is, therefore, plausible that the overexpression is part of the host's response to the presence of the cancerous cells themselves or to the carcinogenic stimulus. This would also suggest possible mechanistic explanations for the less aggressive nature of the Type I cancer. These possible explanations stem from the fact that the cleaved form of PIGR, known as the secretory component (SC), is a known inhibitor of the proinflammatory cytokine IL-8 and acts by forming an inactive complex with this chemokine, thereby preventing chemotaxis of polymorphonuclear neutrophils (PMN) (22). While it is generally accepted that PMNs play an anti-tumorigenic role (23), there are instances where this might not hold true. A recent study showed that melanoma cell extravasation is facilitated by PMNs and that blocking either the IL-8 receptors on PMN or neutralizing the soluble IL-8 in cell suspensions reduced extravasation of these melanoma cells (24). Thus the inhibiton of PMN accumulation might reduce the potential for metastases to occur. PMNs might also facilitate tumor progression through the release of enzymes that are responsible for activation of matrix metalloproteinase-2 (MMP-2) from its inactive proMMP-2 form (25). In turn, MMP-2 is known to be involved with angiogenesis and tumor invasion (25). Consequently, the increased level of PIGR in the Type I cancer might result in the effective inhibition of angiogenesis and prevention of tumor invasion. Such a contradictory role for cells that are part of the immune response is well documented. A similar role for macrophages was recently described in a review, which demonstrated that macrophages facilitate tumor progression by enabling angiogenesis and tumor cell motility as a result of increased intravasation (26). Thus the inhibition of PMN migration by PIGR overexpression might result in the inhibition of angiogenesis, tumor invasion, and metastases thereby accounting for the less aggressive nature of the Type I cancer.

[0350] A closer examination of the factors that affect the expression levels of the potential markers is also enlightening. The factors influencing the expression levels of PIGR include induction by cytokines such as IL-4, TNFα, IFN-γ (21, 27, 28). Signaling pathways that are involved with the response to induction by such ligands include the STAT, NFκB and p38-MAPK pathways (21, 22, 27, 28). In addition, there are cofactors that are also known to be involved with upregulation of PIGR expression. One such cofactor is *all-trans* retinoic acid (RA), which is a metabolite of vitamin A (29). RA enhances the upregulation of PIGR expression in response to IL-4 and IFN-γ stimulations. RA and NFκB also regulate the expression levels of some of the other potential markers discovered in this study and are discussed below. It is also noteworthy that NFκB has been specifically linked with endometrial cancer by various other studies (30, 31).

[0351] WAP 4-disulfide core domain protein 2, which is also known as HE4, belongs to a family of proteins that are

known to be proteinase inhibitors. WFDC2 is known to be overexpressed in a range of different cell lines including ovarian, renal, lung, colon, and breast lines. In a recent study, WFDC2 showed upregulation in mRNA levels during the secretory phase in rhesus monkeys (32). This result is consistent with the iTRAQ results that were observed in the secretory-phase samples (Table 3). The bulk of the initial studies on WFDC2 were focused on using it as a biomarker for ovarian carcinoma (34). However, an investigation on the expression levels of this protein in various human tissues using DNA microarrays, followed by validation with immunohistochemistry, has confirmed that overexpression is also observed in 90% of endometrial adenocarcinomas (34). It is noteworthy that a recent review has suggested that the overexpression of WFDC2 is a good, early marker for ovarian cancer, even better than CA125 for that purpose. However, WFDC2 did not show as high an overexpression in clear cell as opposed to epithelial ovarian carcinomas and might not prove useful for diagnosis of the former (35). This last aspect appears to mirror the results with Type II EmCa in which overexpression levels, on average, were also not as high as those in Type I EmCa - Type II endometrial cancers are serous and/or clear cell cancers (36).

[0352] Another noteworthy point is that NFκB might also play a role in regulating the expression levels of WFDC2, through a binding site identified in the promoter region of WFDC2, as well as other proteins belonging to this family (35). This link with NFκB appears to be in common between WFDC2 and PIGR above, thus suggesting a possible common means for the overexpression of both proteins.

[0353] Mucin 5B is a new potential EmCa marker found in this study. This protein has not been previously reported to be a marker for or associated with endometrial cancer. Mucins in general, however, have been associated with various cancers and have been proposed to promote tumor cell invasion and metastases (37). In the case of lung cancer, tumors of patients who were smokers showed a higher level of Mucin 5B, and these patients tended to show higher degrees of post-operative relapse (37). Furthermore, it has been demonstrated that Mucin 5B mRNA expression is enhanced by RA, a factor in common with PIGR above (38). The 5' flanking region of Mucin 5B has two NFκB binding sites, suggesting another element in common with PIGR and WFDC2 (38).

[0354] Alpha-1-antitrypsin is a secreted glycoprotein, which like WFDC2 is a protease inhibitor. In this study, the expression levels are down-regulated relative to the normal proliferative samples. AAT is known to inhibit angiogenesis and tumor growth, thus underexpression would have forseeable implications for cancer (39). The precedence for such downregulation of expression levels for AAT in cancers has been discussed previously (3).

[0355] Clusterin is another new potential biomarker for EmCa found in this study. It is an anti-apoptotic glycoprotein that has been implicated in resistance to various cell-death triggers (40). Independent validation for the findings is provided by the TMA results available from the Human Protein Atlas (41). Their results show rare, moderately stained cells in the stroma, and no staining in the glandular cells or the myometrium in the normal endometrial samples: By contrast, five out of 12 endometrial cancer samples show moderate cytoplasmic staining in the epithelial cells and another four show weak staining. Overexpression of clusterin has previously been reported for various cancers, including hepatocellular, breast, prostate and urothelial bladder carcinoma (42-45). Of particular interest is a study that showed inhibition of clusterin expression aided in sensitivity to chemotherapy, thus making clusterin a useful therapeutic target (43). Moreover, another study demonstrated that Tamoxifen, a drug used to treat breast cancer, enhanced clusterin expression levels, which in turn was linked to an increased potential for metastases of breast cancer cells. This, in their view, suggests a possible mechanism for the increase of endometrial cancer in postmenopausal women undergoing Tamoxifen treatment for breast cancer (46).

[0356] The small increase observed in the levels of creatine kinase B (CKB) in the secretory phase in this study was consistent with the findings of another study that had demonstrated a similar increase in the secretory phase over the proliferative phase, using 2D gels followed by tryptic digestion and partial N-terminus sequencing (47). Additionally, other independent enzyme-activity studies showed a greater than 3-fold increase in the activity for creatine kinase B in the secretory phase over the proliferative phase (48). CKB is underexpressed in EmCa; the extent is apparently larger in Type II than Type I samples. This downregulation has also been observed in various other cancers including colon and lung adenocarcinomas as well as squamous cell carcinomas (49).

[0357] Cpn 10, calgizzarin, transgelin and MIF are all proteins previously detected as being differentially expressed in EmCa samples; these have all also been implicated in various other forms of cancer (3, 50). Macrophage capping protein (Cap-G) and leucine aminopeptidase 3 (LAP 3) were identified in a sufficient number of EmCa samples to justify inclusion in the list of differentially expression proteins in this study. They showed apparent trends in expression levels in Type II EmCa, suggesting that they might prove useful as subjects of a targeted investigation. Cap-G belongs to the gelsolin family of proteins, which upon activation by Ca2+, is responsible for capping barbed ends of actin filaments (51). Thus Cap-G affects the actin filament structure within a cell, and as non-muscle cells require to rapidly reorganize the actin filament network in order to change shape during movement, it is conceivable that Cap-G is one of the proteins involved in the mechanism by which a tumor cell metastasizes. This could be the reason that it appears to be overexpressed to a larger extent in the more aggressive Type II than in Type I EmCa. Currently, not much detail is known about the function and the distribution of expression for LAP3. Interestingly, placental leucine aminopeptidase (P-LAP) has been linked specifically with EmCa and an increased expression level of P-LAP is associated with a poor prognosis (52).

However, a BLAST search between the LAP3 and P-LAP amino acid sequence returned no significant homology, thus making LAP3 a potentially novel marker for endometrial cancer.

[0358] Some commonalities appear among the various PCMs discussed above. One of these is the possible implication of PMNs. As noted individually above, PMNs and PIGR expression levels are closely linked. In fact, not only can the PIGR expression level affect PMN chemotaxis, but also PMN-expressed enzymes, such as NE and PR3, known to cleave PIGR to form SC (22). Furthermore, under specific conditions, supernatants from activated PMNs have been shown to induce PIGR expression through the NFκB pathway (22). Thus PMNs might conceivably be the potential common element that was alluded to earlier, which could elicit a response through NFκB sites in WFDC2 and PIGR as well as Mucin 5B. Another possible association between PMNs and WFDC2 is the fact that in some cell types, other proteins belonging to the WFDC family, namely, SLPI and elafin, are known to inhibit NE (22). Anti-proteinase activity by WFDC2 has not yet been demonstrated but inferred on the basis of its similarity to SLPI and elafin (35); it is, therefore, possible that WFDC2 may play a role in inhibiting PMN-expressed enzymes in the endometrium, akin to that of SLPI and elafin in the other cell types. Another antiproteinase that might have some irifluence on the possible role of PMNs in this context is AAT, a known inhibitor of the PMN-released enzyme NE. Lastly, it has also been proposed that one of the mechanisms by which PMNs cause the overexpression of PIGR is through the release of IL-1β. (22). IL-1 is also known to cause an increase in the clusterin expression level, thus representing another link between clusterin and the aforementioned biomarkers (53).

[0359] In the study, the ten sample sets were correlated by comparing the ten proliferative samples among themselves. An alternative strategy is to pool the ten proliferative samples and compare every other sample to the proliferative pool. As shown previously, the relative expression level (ratio) for any given PCM across the ten-sample sets appears to vary with a relative standard deviation typically $\leq$ 30%. Some of this variation may reflect genuine person-to-person differences; however, a significant contribution to this observed variation must also stem from differing proportions of cancerous glands within the samples that were homogenized, or differing stages and extents of the EmCa. It may be useful to record the proportion of cancerous tissue present in each sample. Accounting for such a factor might help to reduce the range of differential expression observed within each PCM. A perhaps conceptually simplest means in addressing this issue would be to analyze laser capture microdissected (LCM-ed) cancerous glands or epithelial cells. Relative expression of PCMs would then be evaluated against similarly procured epithelial cells from normal endometrial tissues. To minimize the number of LCM-ed cells required, this analysis could conceivably be performed under multiple-reaction monitoring (MRM) mode on a triple-quadrupole or linear ion trap instrument, which has long been used for mallmolecule quantification in the pharmaceutical industry. Such monitoring would target the transitions specific to the peptides of interest from the PCMs. The increased sampling time afforded by MRM would result in superior sensitivity, thus requiring less protein or fewer cancerous cells.

Table 1

Differentially Expressed Proteins in Endometrial Malignancies/Cancer

Protein	***Gene name***	***Accession Numbers***	***Expression in EmCa***
WAP four-disulfide core domain 2 (WFDC2)	WFDC2	GeneID: 10406 CAG33258, NP_006094, NP_542772, NP_542773, NP_542774 (protein) NM_006103, NM_080734, NM_080735, NM_080736 (mRNA) and SEQ ID NOs. 1 to 9.	Up in secretory phase; higher levels in Type I
Clusterin	CLU	GeneID: 1191 NP_001822, NP_976084 (protein) NM_001831, NM_203339 (mRNA) and SEQ ID NOs. 10 to 13.	Up

(continued)

Differentially Expressed Proteins in Endometrial Malignancies/Cancer

Protein	*Gene name*	*Accession Numbers*	*Expression in EmCa*
Mucin 5B	MUC5B	GeneID: 4587 AAG33673.1, CAA06167.1, AAC51344.1, CAA70926.1, CAA96577.1, AAC67545.1, AAF64523.1, AAB35930.1, AAB61398.1, AAC51343.1, AAB65151.1,CAA52408.1, CAA52910.1, Q14879,Q93043, Q9HC84, Q9NYE4 (protein) AC061979.17 (11065..50111, AF107890.1, AJ004862.1, U78554.1 Y09788.2, Z72496.1, AF086604.1, AF253321.1 S80993.1, U63836.1, U78551.1, U95031.1,X74370.1, X74955.1 (mRNA) and SEQ ID NO. 14.	Under
leucine aminopeptidase 3 (LAP3)	LAP3	Gene ID. 51056 NP_056991 (protein) NM_015907 (mRNA) and SEQ ID NOs. 15 and 16.	Up
Macrophage capping protein; gelsolin-like capping protein (CAP-G)	CAP-G	Gene ID: 822 NP_001738 (protein) NM_001747 (mRNA) and SEQ ID NOs. 17 and 18.	Up
Progestagen-associated endometrial protein (PAEP) (pregnancy- ' associated endometrial alpha-2-globulin, placental protein 14 glycodelin)	PAEP	Gene ID:5047 NP_002562 and NP_001018059 (protein) NM_001018049 and NM_002571 (mRNA) and SEQ ID NOs. 19, 20 and 21.	

Table 2

Differentially Expressed Proteins in Endometrial Malignancies/Cancer

Protein	*Gene name*	*Accession Nos.*	*Expression in EmCa*
Chaperonin 10 (Cpn10)	HSPE1	Gene ID:3336 Q04984 and AAH23518 NP_002148	Up
Calgranulin A		[SEQ ID NO. 32] NM_002157 and U07550 [SEQ ID NOs. 32 and 33]	
	S100A8	Gene ID: 6279 NP_002955, P05109 [SEQ ID NO. 34] A12027 [SEQ ID NO. 35] NM_002964 [SEQ ID NO. 36]	Up
Calgranulin B	S100A9	Gene ID: 6280 NM_002965 (mRNA) NP_002956 (protein) P06702 [SEQ ID NO. 37] X06233 [SEQ ID NO. 38] M21064 [SEQ ID NO. 39]	Up
Polymeric-immunoglobulin Receptor precursor	PIGR	Gene ID:5284 NP_002635, P01833 or Q81 ZY7 [SEQ ID NO. 40] NM 002644 [SEQ ID NO. 41]	Up
Phosphatidylethanolamine-binding protein	PBP PEBP-1	Gene ID: 5037 NP_002558 P30086 [SEQ ID NO. 42] (PEBP) NM_002567[SEQ ID NO. 43]	Up

(continued)

Differentially Expressed Proteins in Endometrial Malignancies/Cancer

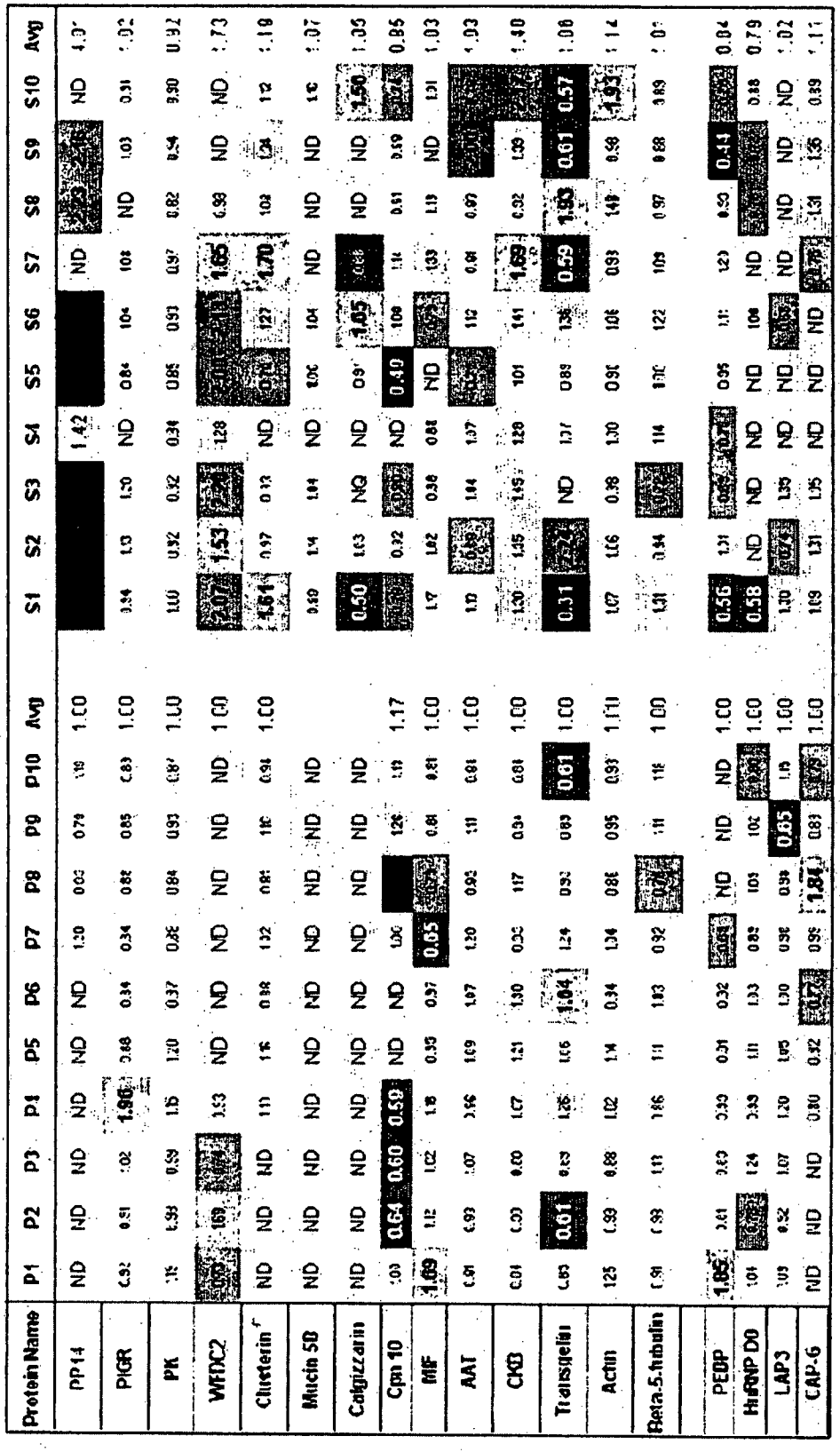
Protein	*Gene name*	*Accession Nos.*	*Expression in EmCa*
Acidic leucine-rich nuclear phosphoprotein 32 family member A	ANP32A	GeneID: 8125 NP_006296 P39687 [SEQ ID NO. 44] NM_006305 [SEQ ID NO. 45]	Up
Heat shock 70 kDa protein 6	HSPA6	GeneID: 3310 P17066 [SEQ ID 46] NM_002155 [SEQ ID NO. 47] X51757 [SEQ ID NO. 48]	Up
Macrophage migration Inhibitory factor (MIF)	MIF	GeneID: 4282 NP_002406 P14174 [SEQ ID NO. 49] NM_002415 [SEQ ID NO. 50] L19686 [SEQ ID NO. 51]	Up
Calgizzarin (S100C protein)	S100A11	GeneID:6282 NP_005611 P31949 [SEQ ID NO. 52] NM_005620 and D38583[SEQ ID NO. 53]	Up
Triosephosphate isomerase	TPI1	GeneID: 7167 P00938 and NP_000356[SEQ ID NO. 54] NM_000365 [SEQ ID NO. 55] X69723 [SEQ ID NO. 56]	Up
Alpha-1-antitrypsin precursor	SERPINA1 (AAT)	GeneID: 5265 NP_000286 NP_001002235 NP_001002236 (protein) NM_001002235 NM_001002236 (mRNA) gi/1703025 ITHU and P01009 [SEQ ID NO. 57] NM_000295[SEQ ID NO. 58] K02212 [SEQ ID NO. 59]	Under
Creatine kinase B (B-CK)	CKB	GeneID: 1152 gi/125294, NP_001814 P12277[SEQ ID NO. 60] NM_001823 [SEQ ID NO. 61] X 15334 [SEQ ID NO. 62]	Under
Pyruvate kinase, M1 or M2 isozyme	PKM2	GeneID: 5315 NM_002654 NM_182470 NM_182471 (mRNA) NP_002645 NP_872270 NP_872271 (protein) gi/20178296; gi/125604; P14618, KPY1_HUMAN [SEQ ID NO. 63]	Up
Transgelin (smooth muscle protein 22-alpha)	TAGLN	X56494 [SEQ ID NO. 64] GeneID: 6876 NM_001001522 NM_003186 (mRNA) NP_001001522 NP_003177 (proteint) gi/3123283 Q01995 [SEQ ID NO. 65] D84342 [SEQ ID NO. 66]	Under
Heterologous nuclear ribonucleoprotein D	hnRPD	GeneID:3184 NM_001003810 NM_002138 NM_031369 NM_031370 (mRNA) NP_001003810 NP_002129 NP_112737 NP_112738 (protein) ROD_HUMAN (Q14103) [SEQ ID NO.67] AF026126 [SEQ ID NO. 68]	Up
Actin	ACT gamma 1	Gene ID. 71 (gamma 1)	

(continued)

Differentially Expressed Proteins in Endometrial Malignancies/Cancer

Protein	*Gene name*	*Accession Nos.*	*Expression in EmCa*
	ACT gamma 2	NP_001605 (protein) NM_001614 (mRNA) Gene ID. 72 (gamma 2) NP_001606 (protein) NM_001615 (mRNA) [SEQ ID NOs. 28, 29, 30, and 31.]	
Beta-5 tubulin	TUBB	Gene ID. 203068 NP_821133 (protein) NM_178014 (mRNA) [SEQ ID NOs. 26 and 27.]	
Hn RNP-DO	RALY	GeneID: 22913 NP_031393, NP_057951 (protein) NM_016732 NM_007367(mRNA) [SEQ ID NOs. 22, 23, 24, and 25.]	

Table 3


Normal proliferative samples
Normal secretory samples
Protein Name
P1
P2
P3
P4
P5
P6
P7
P8
P9
P10
Avg
S1
S2
S3
S4
S5
S6
S7
S8
S9
S10
Avg
PP14
PIGR
PK
WFDC2
Clusterin
Mucin 5B
Calgizzarin
Cpn 10
MIF
AAT
CKB
Transgelin
Actin
Beta-5-tubulin
PEDF
HnRNP D0
LAP3
CAP-6
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<0.5
<0.67
<0.8
>1.25
>1.5
>2.0
>2.5

Table 3 Continued

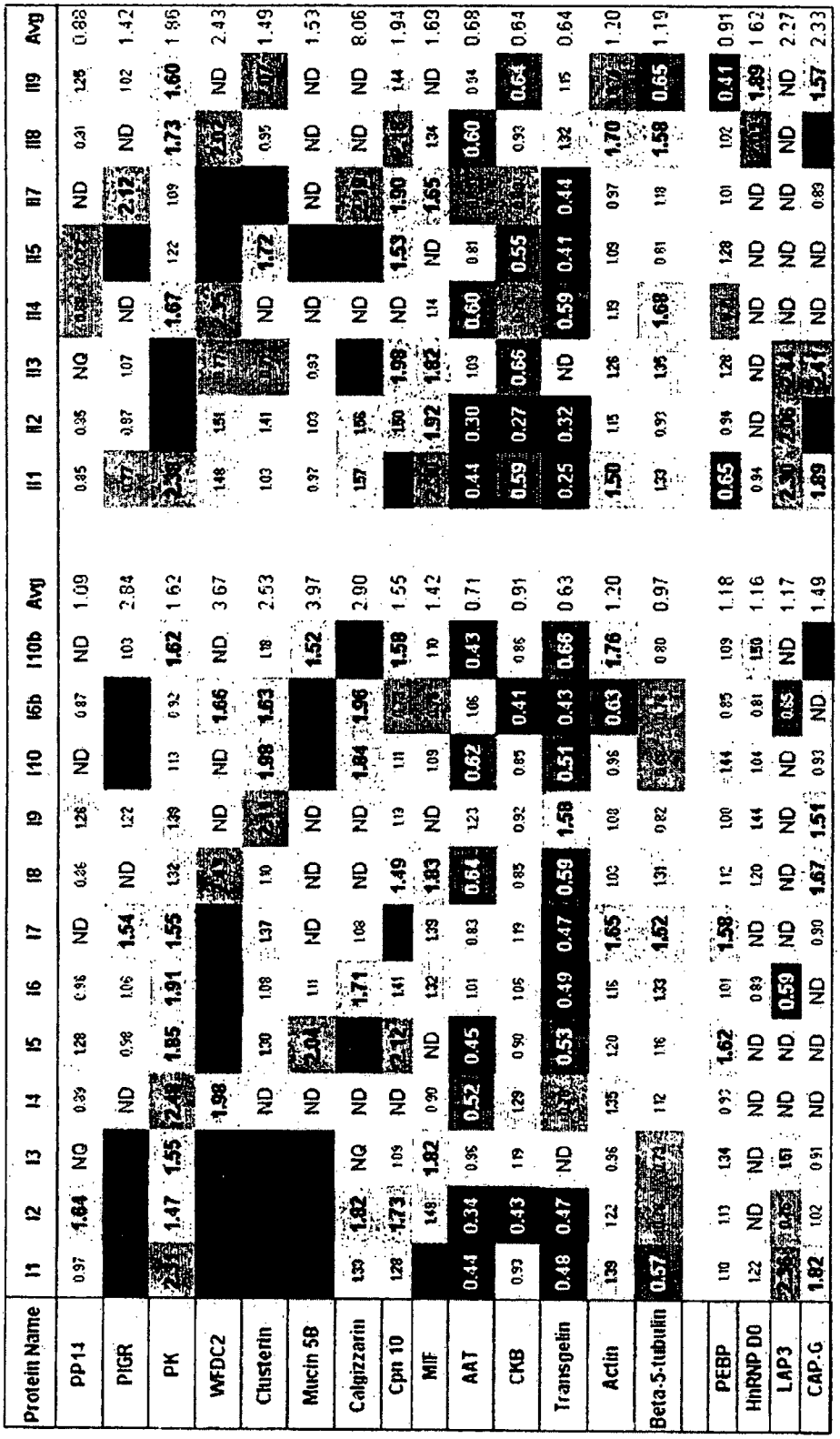

Table 4

Run number	S1 (S:P)	S2 (S:P)	S3 (S:P)	S4 (S:P)	S5 (S:P)	S6 (S:P)	S7 (S:P)	S8 (S:P)	S9 (S:P)	S10 (S:P)
R1	0.81	1.00	1.00	0.84	0.80	1.02	1.04	1.04	0.76	1.03

(continued)

Run number	S1 (S:P)	S2 (S:P)	S3 (S:P)	S4 (S:P)	S5 (S:P)	S6 (S:P)	S7 (S:P)	S8 (S:P)	S9 (S:P)	S10 (S:P)
R2	0.80	0.91	0.89	0.82	0.96	1.09	ND	0.93	0.83	1.11
R3	0.91	0.91	0.89	0.79	0.88		1.05	0.85	0.75	
Avg	0.84	0.94	0.93	0.82	0.88	1.06	1.05	0.94	0.78	1.07
SD	0.06	0.05	0.06	0.03	0.08	0.05	0.01	0.10	0.04	0.06

	S1 (I:P)	S2 (I:P)	S3 (I:P)	S4 (I:P)	S5 (I:P)	S6 (I:P)	S7 (I:P)	S8 (I:P)	S9 (I:P)	S10 (I:P)	S6 (I:P)	S10 (I:P)
R1	1.79	1.45	1.78	2.47	2.31	2.19	1.54	1.67	1.04	1.38	1.16	1.99
R2	2.24	1.60	1.57	2.30	1.83	2.17	ND	1.51	1.39	1.30	0.93	1.85
R3	1.80	1.45	1.33	1.69	1.59		1.80	1.37	1.02			
Avg	1.94	1.50	1.56	2.15	1.91	2.18	1.67	1.52	1.15	1.34	1.05	1.92
SD	0.26	0.09	0.23	0.41	0.37	0.01	0.18	0.15	0.21	0.06	0.16	0.10

	S1 (II:P)	S2 (II:P)	S3 (II:P)	S4 (II:P)	S5 (II:P)	S7 (II:P)	S8 (II:P)	S9 (II:P)
R1	1.90	2.75	3.47	1.51	1.41	1.12	2.19	1.15
R2	2.31	2.96	2.24	1.51	1.23	ND	1.79	1.54
R3	1.79	2.12	2.11	1.33	1.13	1.23	1.99	1.32
Avg	2.00	2.61	2.61	1.45	1.26	1.18	1.99	1.34
SD	0.27	0.44	0.75	0.10	0.14	0.08	0.20	0.20

Table 5

	split 1	**split 2**	**split 3**	**split 4**	**split 5**	**split 6**	**split 7**	**split 8**	**split 9**	**split 10**
Training Set										
true pos	12	11	12	11	12	12	12	12	12	12
false pos	0	1	0	1	0	2	1	1	1	1
true negs	13	12	13	12	13	11	12	12	12	12
false negs	1	2	1	2	1	1	1	1	1	1
Test Set										
true pos	6	7	6	7	6	7	7	7	7	7
false pos	1	0	1	0	1	1	1	0	0	0
true negs	6	7	6	7	6	6	6	7	7	7
false negs	1	0	1	0	1	0	0	0	0	0

[0360] Below full citations are set out for references.

Full Citations for References

[0361]

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Sequence Listing

[0362]

SEQ ID NO. 1
WAP four-disulfide core domain 2 isoform 1 precursor [Homo sapiens]
NP_006094

```
1 mpacrlgpla aalllslllf gftlvsgtga ektgvcpelq adqnctqecv sdsecadnlk
61 ccsagcatfc slpndkegsc pqvninfpql glcrdqcqvd sqcpgqmkcc rngcgkvscv
121 tpnf
```

SEQ ID NO.2
WAP four-disulfide core domain 2 isoform 4 precursor [Homo sapiens]
NP_542772

```
1 mpacrlgpla aalllslllf gftlvsdkeg scpqvninfp qlglcrdqcq vdsqcpgqmk
61 ccrngcgkvs cvtpnf
```

SEQ ID NO. 3
WAP four-disulfide core domain 2 isoform 5 [Homo sapiens]
NP_542773

```
1 mlqvqvnlpv splptypysf fypdkegscp qvninfpqlg lcrdqcqvds qcpgqmkccr
61 ngcgkvscvt pnf
```

SEQ ID NO. 4
WAP four-disulfide core domain 2 isoform 2 precursor [Homo sapiens].
NP_542774

```
1 mpacrlgpla aalllslllf gftlvsgtga ektgvcpelq adqnctqecv sdsecadnlk
61 ccsagcatfc slpnalfhwh lktrrlweis gprprrptwd ss
```

SEQ ID NO.5
Homo sapiens WAP four-disulfide core domain 2 (WFDC2), transcript variant 1, mRNA.
NM_006103

```
1 cacctgcacc ccgcccgggc atagcaccat gcctgcttgt cgcctaggcc cgctagccgc
61 cgccctcctc ctcagcctgc tgctgttcgg cttcacccta gtctcaggca caggagcaga
121 gaagactggc gtgtgccccg agctccaggc tgaccagaac tgcacgcaag agtgcgtctc
181 ggacagcgaa tgcgccgaca acctcaagtg ctgcagcgcg ggctgtgcca ccttctgctc
241 tctgcccaat gataaggagg gttcctgccc ccaggtgaac attaactttc cccagctcgg
301 cctctgtcgg gaccagtgcc aggtggacag ccagtgtcct ggccagatga aatgctgccg
361 caatggctgt gggaaggtgt cctgtgtcac tcccaatttc tgagctccag ccaccaccag
421 gctgagcagt gaggagagaa agtttctgcc tggccctgca tctggttcca gcccacctgc
481 cctccccttt ttcgggactc tgtattccct cttgggctga ccacagcttc tccctttccc
541 aaccaataaa gtaaccactt tcagcaaaaa
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SEQ ID NO. 6
Homo sapiens WAP four-disulfide core domain 2 (WFDC2), transcript variant 4, mRNA.
NM_080734

```
1 cacctgcacc ccgcccgggc atagcaccat gcctgcttgt cgcctaggcc cgctagccgc
61 cgccctcctc ctcagcctgc tgctgttcgg cttcacccta gtctcagata aggagggttc
121 ctgcccccag gtgaacatta actttcccca gctcggcctc tgtcgggacc agtgccaggt
181 ggacagccag tgtcctggcc agatgaaatg ctgccgcaat ggctgtggga aggtgtcctg
241 tgtcactccc aatttctgag gtccagccac caccaggctg agcagtgagg agagaaagtt
301 tctgcctggc cctgcatctg gttccagccc acctgccctc ccctttttcg ggactctgta
361 ttccctcttg ggctgaccac agcttctccc tttcccaacc aataaagtaa ccactttcag
421 c
```

SEQ ID NO.7

Homo sapiens WAP four-disulfide core domain 2 (WFDC2), transcript variant 5, mRNA.
NM_080735

```
1 agcccagtga ggggcagtgg gggggccatg ctgcaggtac aagttaatct ccctgtatcg
61 cctctgccca cttaccctta ctccttttтc tacccagata aggagggttc ctgcccccag
121 gtgaacatta actttcccca gctcggcctc tgtcgggacc agtgccaggt ggacagccag
181 tgtcctggcc agatgaaatg ctgccgcaat ggctgtggga aggtgtcctg tgtcactccc
241 aatttctgag gtccagccac caccaggctg agcagtgagg agagaaagtt tctgcctggc
301 cctgcatctg gttccagccc acctgccctc ccctttttcg ggactctgta ttccctcttg
361 ggctgaccac agcttctccc tttcccaacc aataaagtaa ccactttcag c
```

SEQ ID NO. 8

Homo sapiens WAP four-disulfide core domain 2 (WFDC2), transcript variant 2, mRNA.
NM_080736

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1 cacctgcacc ccgcccgggc atagcaccat gcctgcttgt cgcctaggcc cgctagccgc
61 cgccctcctc ctcagcctgc tgctgttcgg cttcacccta gtctcaggca caggagcaga
121 gaagactggc gtgtgccccg agctccaggc tgaccagaac tgcacgcaag agtgcgtctc
181 ggacagcgaa tgcgccgaca acctcaagtg ctgcagcgcg ggctgtgcca ccttctgctc
241 tctgcccaat gcactgttcc actggcacct aaagacacgg aggctctggg agatttctgg
301 ccctaggcca cgaaggccca cttgggactc aagctgaggt cctgtgattc catttggg
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SEQ ID NO. 9

WFDC2 Homo sapiens
CAG33258

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1 mpacrlgpla aalllslllf gftlvsgtga ektgvcpelq adqnctqecv sdsecadnlk
61 ccsagcatfc slpndkegsc pqvninfpql glcrdqcqvd sqcpgqmkcc rngcgkvscv
121 tpnf
```

SEQ ID NO. 10

clusterin isoform 1 [Homo sapiens].
NP_001822

```
1 mqvcsqpqrg cvreqsaint appsahnaas pggarghrvp lteackdsri ggmmktlllf
61 vgllltwesg qvlgdqtvsd nelqemsnqg skyvnkeiqn avngvkqikt liektneerk
121 tllsnleeak kkkedalnet resetklkel pgvcnetmma lweeckpclk qtcmkfyarv
181 crsgsglvgr qleeflnqss pfyfwmngdr idsllendrq qthmldvmqd hfsrassiid
241 elfqdrfftr epqdtyhylp fslphrrphf ffpksrivrs lmpfspyepl nfhamfqpfl
301 emiheaqqam dihfhspafq hpptefireg dddrtvcrei rhnstgclrm kdqcdkcrei
361 lsvdcstnnp sqaklrreld eslqvaerlt rkynellksy qwkmlntssl leqlneqfnw
421 vsrlanltqg edqyylrvtt vashtsdsdv psgvtevvvk lfdsdpitvt vpvevsrknp
481 kfmetvaeka lqeyrkkhre e
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SEQ ID NO. 11

clusterin isoform 2 [Homo sapiens].
NP_976084

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1 mmktlllfvg llltwesgqv lgdqtvsdne lqemsnqgsk yvnkeiqnav ngvkqiktli
61 ektneerktl lsnleeakkk kedalnetre setklkelpg vcnetmmalw eeckpclkqt
121 cmkfyarvcr sgsglvgrql eeflnqsspf yfwmngdrid sllendrqqt hmldvmqdhf
181 srassiidel fqdrfftrep qdtyhylpfs lphrrphfff pksrivrslm pfspyeplnf
241 hamfqpflem iheaqqamdi hfhspafqhp ptefiregdd drtvcreirh nstgclrmkd
301 qcdkcreils vdcstnnpsq aklrreldes lqvaerltrk ynellksyqw kmlntsslle
361 qlneqfnwvs rlanltqged qyylrvttva shtsdsdvps gvtevvvklf dsdpitvtvp
421 vevsrknpkf metvaekalq eyrkkhree
```

SEQ ID NO. 12
Homo sapiens clusterin (CLU), transcript variant 1, mRNA.
NM_001831

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1 ctttccgcgg cattctttgg gcgtgagtca tgcaggtttg cagccagccc caaagggggt
61 gtgtgcgcga gcagagcgct ataaatacgg cgcctcccag tgcccacaac gcggcgtcgc
121 caggaggagc gcgcgggcac agggtgccgc tgaccgaggc gtgcaaagac tccagaattg
181 gaggcatgat gaagactctg ctgctgtttg tggggctgct gctgacctgg gagagtgggc
241 aggtcctggg ggaccagacg gtctcagaca atgagctcca ggaaatgtcc aatcagggaa
301 gtaagtacgt caataaggaa attcaaaatg ctgtcaacgg ggtgaaacag ataaagactc
361 tcatagaaaa aacaaacgaa gagcgcaaga cactgctcag caacctagaa gaagccaaga
421 agaagaaaga ggatgcccta aatgagacca gggaatcaga gacaaagctg aaggagctcc
481 caggagtgtg caatgagacc atgatggccc tctgggaaga gtgtaagccc tgcctgaaac
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601 agcttgagga gttcctgaac cagagctcgc ccttctactt ctggatgaat ggtgaccgca
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1021 acgatgaccg gactgtgtgc cgggagatcc gccacaactc cacgggctgc
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tcctccttgc
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1321 aagaccagta ctatctgcgg gtcaccacgg tggcttccca cacttctgac
tcggacgttc
```

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gagaaagcgc
1501 tgcaggaata ccgcaaaaag caccgggagg agtgagatgt ggatgttgct
tttgcaccta
1561 cgggggcatc tgagtccagc tccccccaag atgagctgca gccccccaga
gagagctctg
1621 cacgtcacca agtaaccagg ccccagcctc caggccccca actccgccca
gcctctcccc
1681 gctctggatc ctgcactcta acactcgact ctgctgctca tgggaagaac
agaattgctc
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aggcaggggg
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ctgtcatacc
1921 agtgaagaat aaaagggtga agaataaaag ggatatgatg acaaggttga
tccacttcaa
1981 gaattgcttg ctttcaggaa gagagatgtg tttcaacaag ccaactaaaa
tatattgctg
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cagaagtcca
2221 aattatcagt tttatttgta agagctattg cttttgcagc ggttttattt
gtaaaagctg
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tggcatttcc
2341 tgtccaccgc cggtttatat gatcttcata cctttccctg gaccacaggc
gtttctcggc
2401 ttttagtctg aaccatagct gggctgcagt accctacgct gccagcaggt
ggccatgact
2461 acccgtggta ccaatctcag tcttaaagct caggcttttc gttcattaac
attctctgat
2521 agaattctgg tcatcagatg tactgcaatg gaacaaaact catctggctg
catcccaggt
2581 gtgtagcaaa gtccacatgt aaatttatag cttagaatat tcttaagtca
ctgtcccttg
2641 tctctctttg aagttataaa caacaaactt aaagcttagc ttatgtccaa
ggtaagtatt
2701 ttagcatggc tgtcaaggaa attcagagta aagtcagtgt gattcactta
atgatataca
2761 ttaattagaa ttatggggtc agaggtattt gcttaagtga tcataattgt
aaagtatatg
2821 tcacattgtc acattaatgt caaaaaaaaa aaaaaaaaa
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SEQ ID NO. 13

Homo sapiens clusterin (CLU), transcript variant 2, mRNA
NM_203339

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1 gggcagcctg ctgtcggctt agaggggatg ggcagtgtgg agggcctggc agagcaagag
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121 tctctactct ccgaagggaa ttgtccttcc tggcttccac tacttccacc cctgaatgca
181 caggcagccc ggcccaagtc tcccactagg gatgcagatg gattcggtgt gaagggctgg
241 ctgctgttgc ctccggctct tgaaagtcaa gttcagaggc gtgcaaagac tccagaattg
```

301 gaggcatgat gaagactctg ctgctgtttg tggggctgct gctgacctgg gagagtgggc
361 aggtcctggg ggaccagacg gtctcagaca atgagctcca ggaaatgtcc aatcagggaa
421 gtaagtacgt caataaggaa attcaaaatg ctgtcaacgg ggtgaaacag ataaagactc
481 tcatagaaaa aacaaacgaa gagcgcaaga cactgctcag caacctagaa gaagccaaga
541 agaagaaaga ggatgcccta aatgagacca gggaatcaga gacaaagctg aaggagctcc
601 caggagtgtg caatgagacc atgatggccc tctgggaaga gtgtaagccc tgcctgaaac
661 agacctgcat gaagttctac gcacgcgtct gcagaagtgg ctcaggcctg gttggccgcc
721 agcttgagga gttcctgaac cagagctcgc ccttctactt ctggatgaat ggtgaccgca
781 tcgactccct gctggagaac gaccggcagc agacgcacat gctggatgtc atgcaggacc
841 acttcagccg cgcgtccagc atcatagacg agctcttcca ggacaggttc ttcacccggg
901 agccccagga tacctaccac tacctgccct tcagcctgcc ccaccggagg cctcacttct
961 tctttcccaa gtcccgcatc gtccgcagct tgatgccctt ctctccgtac gagcccctga
1021 acttccacgc catgttccag cccttccttg agatgataca cgaggctcag
caggccatgg
1081 acatccactt ccatagcccg gccttccagc acccgccaac agaattcata
cgagaaggcg
1141 acgatgaccg gactgtgtgc cgggagatcc gccacaactc cacgggctgc
ctgcggatga
1201 aggaccagtg tgacaagtgc cgggagatct tgtctgtgga ctgttccacc
aacaacccct
1261 cccaggctaa gctgcggcgg gagctcgacg aatccctcca ggtcgctgag
aggttgacca
1321 ggaaatacaa cgagctgcta aagtcctacc agtggaagat gctcaacacc
tcctccttgc
1381 tggagcagct gaacgagcag tttaactggg tgtcccggct ggcaaacctc
acgcaaggcg
1441 aagaccagta ctatctgcgg gtcaccacgg tggcttccca cacttctgac
tcggacgttc
1501 cttccggtgt cactgaggtg gtcgtgaagc tctttgactc tgatcccatc
actgtgacgg
1561 tccctgtaga agtctccagg aagaacccta aatttatgga gaccgtggcg
gagaaagcgc
1621 tgcaggaata ccgcaaaaag caccgggagg agtgagatgt ggatgttgct
tttgcaccta
1681 cgggggcatc tgagtccagc tccccccaag atgagctgca gccccccaga
gagagctctg
1741 cacgtcacca agtaaccagg ccccagcctc caggcccccа actccgccca
gcctctcccc
1801 gctctggatc ctgcactcta acactcgact ctgctgctca tgggaagaac
agaattgctc
1861 ctgcatgcaa ctaattcaat aaaactgtct tgtgagctga tcgcttggag
ggtcctcttt
1921 ttatgttgag ttgctgcttc ccggcatgcc ttcattttgc tatggggggc
aggcaggggg
1981 gatggaaaat aagtagaaac aaaaaagcag tggctaagat ggtataggga
ctgtcatacc
2041 agtgaagaat aaaagggtga agaataaaag ggatatgatg acaaggttga
tccacttcaa
2101 gaattgcttg ctttcaggaa gagagatgtg tttcaacaag ccaactaaaa
tatattgctg
2161 caaatggaag cttttctgtt ctattataaa actgtcgatg tattctgacc
aaggtgcgac
2221 aatctcctaa aggaatacac tgaaagttaa ggagaagaat cagtaagtgt
aaggtgtact
2281 tggtattata atgcataatt gatgttttcg ttatgaaaac atttggtgcc
cagaagtcca
2341 aattatcagt tttatttgta agagctattg cttttgcagc ggttttattt
gtaaaagctg
2401 ttgatttcga gttgtaagag ctcagcatcc caggggcatc ttcttgactg
tggcatttcc

2461 tgtccaccgc cggtttatat gatcttcata cctttccctg gaccacaggc gtttctcggc
2521 ttttagtctg aaccatagct gggctgcagt accctacgct gccagcaggt ggccatgact
2581 acccgtggta ccaatctcag tcttaaagct caggcttttc gttcattaac attctctgat
2641 agaattctgg tcatcagatg tactgcaatg gaacaaaact catctggctg catcccaggt
2701 gtgtagcaaa gtccacatgt aaatttatag cttagaatat tcttaagtca ctgtcccttg
2761 tctctctttg aagttataaa caacaaactt aaagcttagc ttatgtccaa ggtaagtatt
2821 ttagcatggc tgtcaaggaa attcagagta aagtcagtgt gattcactta atgatataca
2881 ttaattagaa ttatggggtc agaggtattt gcttaagtga tcataattgt aaagtatatg
2941 tcacattgtc acattaatgt caaaaaaaaa aaaaaaaaa

SEQ ID NO. 14

mucin 5B [Homo sapiens]
AAG33673

1 mgapsacrtl vlalaamlvv pqaetqgpve pswgnaghtm dggaptsspt rrvsfvppvt
61 vfpslsplnp ahngrvcstw gdfhyktfdg dvfrfpglcn yvfsehcraa yedfnvqlrr
121 glvgsrpvvt rvvikaqglv lkasngsvli ngqreelpys rtgllveqsg dyikvsirlv
181 ltflwngeds alleldpkya nqtcglcgdf nglpafnefy ahnarltplq fgnlqkldgp
241 teqcpdplpl pagnctdeeg ichrtllgpa faechalvds taylaacaqd lcrcptcpca
301 tfveysrqca haggqprnwr cpelcprtcp lnmqhqecgs pctdtcsnpq raqlcedhcv
361 dgcfcppgst vlddithsgc lplgqcpcth ggrtyspgts fnttcssctc sgglwqcqdl
421 pcpgtcsvqg gahistydek lydlhgdcsy vlskkcadss ftvlaelrkc gltdnenclk
481 avtlsldggd tairvqadgg vflnsiytql plsaanitlf tpssffivvq tglglqllvq
541 lvplmqvfvr ldpahqgqmc glcgnfnqnq addftalsgv veatgaafan twkaqaacan
601 arnsfedpcs lsvenenyar hwcsrltdpn safsrchsii npkpfhsncm fdtcncerse
661 dclcaalssy vhacaakgvq lsdwrdgvct kymqncpksq ryayvvdacq ptcrglsead
721 vtcsvsfvpv dgctcpagtf lndagacvpa qecpcyahgt vlapgevvhd egavcsctgg
781 klsclgaslq kstgcaapmv yldcsnssag tpgaeclrsc htldvgcfst hcvsgcvcpp
841 glvsdgsggc iaeedcpcvh neatykpget irvdcntctc rnrrwecshr lclgtcvayg
901 dghfitfdgd rysfegscey ilaqdycgdn tthgtfrivt enipcgttgt tcskaiklfv
961 esyelilqeg tfkavargpg gdppykirym giflviethg mavswdrkts vfirlhqdyk
1021 grvcglcgnf ddnaindfat rsrsvvgdal efgnswklsp scpdalapkd pctanpfrks
1081 waqkqcsilh gptfaacrsq vdstkyyeac vndacacdsg gdcecfctav aayaqachda
1141 glcvswrtpd tcplfcdfyn phggcewhyq pcgapclktc rnpsghclvd lpglegcypk
1201 cppsqpffne dqmkcvaqcg cydkdgnyyd vgarvptaen cqscnctpsg iqcahsleac
1261 tctyedrtys yqdviynttd glgacliaic gsngtiirka vacpgtpatt pftfttawvp
1321 hsttspalpv stvcvrevcr wsswynghrp epglgggdfe tfenlrqrgy qvcpvladie
1381 craaqlpdmp leelgqqvdc drmrglmcan sqqspplchd yelrvlccey vpcgpspapg
1441 tspqpslsas tepavptptq ttatekttlw vtpsirstaa ltsqtgsssg pvtvtpsapg
1501 tttcqprcqw tewfdedypk seqlggdves ydkiraaggh lcqqpkdiec qaesfpnwtl
1561 aqvgqkvhcd vhfglvcrnw eqegvfkmcy nyri

SEQ ID NO. 15
NP_056991
leucine aminopeptidase 3 [Homo sapiens]

```
1 mfllplpaag rvvvrrlavr rfgsrslsta dmtkglvlgi yskekeddvp qftsagenfd
61 kllagklret lnisgpplka gktrtfyglh qdfpsvvlvg lgkkaagide qenwhegken
121 iraavaagcr qiqdlelssv evdpcgdaqa aaegavlgly eyddlkqkkk mavsaklygs
181 gdqeawqkgv lfasgqnlar qlmetpanem tptrfaeiie knlksasskt evhirpkswi
241 eeqamgsfls vakgsdeppv fleihykgsp nanepplvfv gkgitfdsgg isikasanmd
301 lmradmggaa ticsaivsaa klnlpiniig laplcenmps gkankpgdvv raknqktiqv
361 dntdaegrli ladalcyaht fnpkvilnaa tltgamdval gsgatgvftn sswlwnklfe
421 asietgdrvw rmplfehytr qvvdcqladv nnigkyrsag actaaaflke fvthpkwahl
481 diagvmtnkd evpylrkgmt grptrtlief llrfsqdna
```

SEQ ID NO. 16
NM_015907
Homo sapiens leucine aminopeptidase 3 (LAP3), mRNA.

```
1 ctgcccatcc gtcccgcccc ctagacgcac gtccgctcgc ccggcgcccg agccagtccg
61 cgcgcacgcc gtctgcgccc cgaaagcccc gccccaaggc gcgcccgccc accgctctcc
121 acgtgctcgc tggagggcgg tgcgaggggc cgagccgaca agatgttctt gctgcctctt
181 ccggctgcgg ggcgagtagt cgtccgacgt ctggccgtga gacgtttcgg gagccggagt
241 ctctccaccg cagacatgac gaagggcctt gttttaggaa tctattccaa agaaaaagaa
301 gatgatgtgc cacagttcac aagtgcagga gagaattttg ataaattgtt agctggaaag
361 ctgagagaga ctttgaacat atctggacca cctctgaagg cagggaagac tcgaaccttt
421 tatggtctgc atcaggactt ccccagcgtg gtgctagttg gcctcggcaa aaaggcagct
481 ggaatcgacg aacaggaaaa ctggcatgaa ggcaaagaaa acatcagagc tgctgttgca
541 gcggggtgca ggcagattca agacctggag ctctcgtctg tggaggtgga tccctgtgga
601 gacgctcagg ctgctgcgga gggagcggtg cttggtctct atgaatacga tgacctaaag
661 caaaaaaaga agatggctgt gtcggcaaag ctctatggaa gtggggatca ggaggcctgg
721 cagaaaggag tcctgtttgc ttctgggcag aacttggcac gccaattgat ggagacgcca
781 gccaatgaga tgacgccaac cagatttgct gaaattattg agaagaatct caaaagtgct
841 agtagtaaaa ccgaggtcca tatcagaccc aagtcttgga ttgaggaaca ggcaatggga
901 tcattcctca gtgtggccaa aggatctgac gagcccccag tcttcttgga aattcactac
961 aaaggcagcc ccaatgcaaa cgaaccaccc ctggtgtttg ttgggaaagg aattaccttt
1021 gacagtggtg gtatctccat caaggcttct gcaaatatgg acctcatgag
ggctgacatg
1081 ggaggagctg caactatatg ctcagccatc gtgtctgctg caaagcttaa
tttgcccatt
1141 aatattatag gtctggcccc tctttgtgaa aatatgccca gcggcaaggc
caacaagccg
1201 ggggatgttg ttagagccaa aaacgggaag accatccagg ttgataacac
tgatgctgag
1261 gggaggctca tactggctga tgcgctctgt tacgcacaca cgtttaaccc
gaaggtcatc
1321 ctcaatgccg ccaccttaac aggtgccatg gatgtagctt tgggatcagg
tgccactggg
1381 gtctttacca attcatcctg gctctggaac aaactcttcg aggccagcat
tgaaacaggg
1441 gaccgtgtct ggaggatgcc tctcttcgaa cattatacaa gacaggttgt
agattgccag
1501 cttgctgatg ttaacaacat tggaaaatac agatctgcag gagcatgtac
agctgcagca
1561 ttcctgaaag aattcgtaac tcatcctaag tgggcacatt tagacatagc
aggcgtgatg
1621 accaacaaag atgaagttcc ctatctacgg aaaggcatga ctgggaggcc
cacaaggact
```

1681 ctcattgagt tcttacttcg tttcagtcaa gacaatgctt agttcagata
ctcaaaaatg
1741 tcttcactct gtcttaaatt ggacagttga acttaaaagg tttttgaata
aatggatgaa
1801 aatcttttaa cggagacaaa ggatggtatt taaaaatgta gaacacaatg
aaatttgtat
1861 gccttgattt ttttttcatt tcacacaaag atttataaag gtaaagttaa
tatcttactt
1921 gataaggatt tttaagatac tctataaatg attaaaattt ttagaacttc
ctaatcactt
1981 ttcagagtat atgtttttca ttgagaagca aaattgtaac tcagatttgt
gatgctagga
2041 acatgagcaa actgaaaatt actatgcact tgtcagaaac aataaatgca
acttgttgtg

SEQ ID NO. 17
NP_001738
gelsolin-like capping protein [Homo sapiens].

1 mytaipqsgs pfpgsvqdpg lhvwrveklk pvpvaqenqg vffsgdsylv lhngpeevsh
61 lhlwigqqss rdeqgacavl avhlntllge rpvqhrevqg nesdlfmsyf prglkyqegg
121 vesafhktst gapaaikkly qvkgkknira teralnwdsf ntgdcfildl gqnifawcgg
181 ksnilernka rdlalairds erqgkaqvei vtdgeepaem iqvlgpkpal kegnpeedlt
241 adkanaqaaa lykvsdatgq mnltkvadss pfalellisd dcfvldnglc gkiyiwkgrk
301 anekerqaal qvaegfisrm qyapntqvei lpqghespif kqffkdwk

SEQ ID NO. 18
NM_001747
Homo sapiens capping protein (actin filament), gelsolin-like CAPG), mRNA.

1 gacggcctgg catacccact gcccacccca gtgactgctc ttctgcttca ggcctgctgg
61 cctcccagca ctgcctgccc ctccctgtcg ggggacatcg cctccacacc ggctggggaa
121 ggagcccagg ggtggggctg gtgggtgggg ctggtggttg gggcagccag agaagtaaga
181 gggaagtgag aagccgggtg gggcaggctg gaaggaagac gaacctacga agcagagatc
241 tgaagacagc atgtacacag ccattcccca gagtggctct ccattcccag gctcagtgca
301 ggatccaggc ctgcatgtgt ggcgggtgga gaagctgaag ccggtgcctg tggcgcaaga
361 gaaccagggc gtcttcttct cgggggactc ctacctagtg ctgcacaatg gcccagaaga
421 ggtttcccat ctgcacctgt ggataggcca gcagtcatcc cgggatgagc agggggcctg
481 tgccgtgctg gctgtgcacc tcaacacgct gctgggagag cggcctgtgc agcaccgcga
541 ggtgcagggc aatgagtctg acctcttcat gagctacttc ccacggggcc tcaagtacca
601 ggaaggtggt gtggagtcag catttcacaa gacctccaca ggagccccag ctgccatcaa
661 gaaactctac caggtgaagg ggaagaagaa catccgtgcc accgagcggg cactgaactg
721 ggacagcttc aacactgggg actgcttcat cctggacctg ggccagaaca tcttcgcctg
781 gtgtggtgga aagtccaaca tcctggaacg caacaaggcg agggacctgg ccctggccat
841 ccgggacagt gagcgacagg gcaaggccca ggtggagatt gtcactgatg gggaggagcc
901 tgctgagatg atccaggtcc tgggccccaa gcctgctctg aaggagggca accctgagga
961 agacctcaca gctgacaagg caaatgccca ggccgcagct ctgtataagg tctctgatgc
1021 cactggacag atgaacctga ccaaggtggc tgactccagc ccatttgccc
ttgaactgct
1081 gatatctgat gactgctttg tgctggacaa cgggctctgt ggcaagatct
atatctggaa
1141 ggggcgaaaa gcgaatgaga aggagcggca ggcagccctg caggtggccg
agggcttcat
1201 ctcgcgcatg cagtacgccc cgaacactca ggtggagatt ctgcctcagg
gccatgagag
1261 tcccatcttc aagcaatttt tcaaggactg gaaatgaggg tgggcgtctt
cctgccccat

```
1321 gctcccctgc cccccaccac ctgcctgctt gcttctctgg ctgcctggtc
agtgcagagg
1381 tgcccccctgc agatgttcaa taaaggagac aagtgctttc ccagctcttt
tcctgcacca
1441 ccaaaaaaaa aaaaaaaaaa
```

SEQ ID NO. 19
glycodelin precursor (PP14) [Homo sapiens]
NP_002562 and NP_001018059

```
1 mlcllltlgv alvcgvpamd ipqtkqdlel pklagtwhsm amatnnislm atlkaplrvh
61 itsllptped nleivlhrwe nnscvekkvl gektenpkkf kinytvanea tlldtdydnf
121 lflclqdttt piqsmmcqyl arvlveddei mqgfirafrp lprhlwylld lkqmeepcrf
```

SEQ ID NO. 20
Homo sapiens progestagen-associated endometrial protein (placental protein 14, pregnancy-associated endometrial alpha-2-globulin, alpha uterine protein) (PAEP), transcript variant 1, mRNA
NM_001018049

```
1 catccctctg gctccagagc tcagagccac ccacagccgc agccatgctg tgcctcctgc
61 tcaccctggg cgtggccctg gtctgtggtg tcccggccat ggacatcccc cagaccaagc
121 aggacctgga gctcccaaag ttggcaggga cctggcactc catggccatg gcgaccaaca
181 acatctccct catggcgaca ctgaaggccc ctctgagggt ccacatcacc tcactgttgc
241 ccacccccga ggacaacctg gagatcgttc tgcacagatg ggagaacaac agctgtgttg
301 agaagaaggt ccttggagag aagactgaga atccaaagaa gttcaagatc aactatacgg
361 tggcgaacga ggccacgctg ctcgatactg actacgacaa tttcctgttt ctctgcctac
421 aggacaccac cacccccatc cagagcatga tgtgccagta cctggccaga gtcctggtgg
481 aggacgatga gatcatgcag ggattcatca gggctttcag gcccctgccc aggcacctat
541 ggtacttgct ggacttgaaa cagatggaag agccgtgccg tttctaggtg agctcctgcc
601 tggtcctgcc tcctggctca cctccgcctc caggaagacc agactcccac ccttccacac
661 ctccagagca gtgggacttc ctcctgccct ttcaaagaat aaccacagct cagaagacga
721 tgacgtggtc atctgtgtcg ccatcccctt cctgctgcac acctgcacca cggccatggg
781 gaggctgctc cctgggggca gagtctctgg cagaggttat taataaaccc ttggagcatg
841 aaaaaaaaaa aaaaaaa
```

SEQ ID NO. 21
NM_002577
Homo sapiens progestagen-associated endometrial protein (placental protein 14, pregnancy-associated endometrial alpha-2-globulin, alpha uterine protein) (PAEP), transcript variant 2, mRNA.

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1 catccctctg gctccagagc tcagagccac ccacagccgc agccatgctg tgcctcctgc
61 tcaccctggg cgtggccctg gtctgtggtg tcccggccat ggacatcccc cagaccaagc
121 aggacctgga gctcccaaag ttggcaggga cctggcactc catggccatg gcgaccaaca
181 acatctccct catggcgaca ctgaaggccc ctctgagggt ccacatcacc tcactgttgc
241 ccacccccga ggacaacctg gagatcgttc tgcacagatg ggagaacaac agctgtgttg
301 agaagaaggt ccttggagag aagactgaga atccaaagaa gttcaagatc aactatacgg
361 tggcgaacga ggccacgctg ctcgatactg actacgacaa tttcctgttt ctctgcctac
421 aggacaccac cacccccatc cagagcatga tgtgccagta cctggccaga gtcctggtgg
481 aggacgatga gatcatgcag ggattcatca gggctttcag gcccctgccc aggcacctat
541 ggtacttgct ggacttgaaa cagatggaag agccgtgccg tttctagctc acctccgcct

601 ccaggaagac cagactccca cccttccaca cctccagagc agtgggactt cctcctgccc
661 tttcaaagaa taaccacagc tcagaagacg atgacgtggt catctgtgtc gccatccccc
721 tcctgctgca cacctgcacc acggccatgg ggaggctgct ccctgggggc agagtctctg
781 gcagaggtta ttaataaacc cttggagcat gaaaaaaaaa aaaaaaaa
```

SEQ ID NO. 22

RNA binding protein (autoantigenic, hnRNP-associated with lethal yellow) short isoform [Homo sapiens].
NP_031393

```
1 mslklqasnv tnkndpksin srvfignlnt alvkksdvet ifskygrvag csvhkgyafv
61 qysnerhara avlgengrvl agqtldinma gepkpdrpkg lkraasaiyr lfdyrgrlsp
121 vpvpravpvk rprvtvplvr rvktnvpvkl farstavtts sakiklksse lqaikteltq
181 iksnidalls rleqiaaeqk anpdgkkkgd gggagggggg ggsggggsgg gggggssrpp
241 apqenttsea glpqgeartr ddgdeegllt hseeelehsq dtdaddgalq
```

SEQ ID NO. 23
RNA binding protein (autoantigenic, hnRNP-associated with lethal yellow) long isoform [Homo sapiens].
NP_057951

```
1 mslklqasnv tnkndpksin srvfignlnt alvkksdvet ifskygrvag csvhkgyafv
61 qysnerhara avlgengrvl agqtldinma gepkpdrpkg lkraasaiys gyifdydyyr
121 ddfydrlfdy rgrlspvpvp ravpvkrprv tvplvrrvkt nvpvklfars tavttssaki
181 klksselqai kteltqiksn idallsrleq iaaeqkanpd gkkkgdggga gggggggsg
241 gggsgggggg gssrppapqe nttseaglpq geartrddgd eeglltheee elehsqdtda
301 ddgalq
```

SEQ ID NO. 24
Homo sapiens RNA binding protein, autoantigenic (hnRNP-associated with lethal yellow homolog (mouse)) (RALY), transcript variant 2, mRNA
NM_007367

```
1 cgcgcgagcg gcgccagctc ggggcagcgg aacccagaga agctgagggg gcggtagcgg
61 cggcgacggc gacgacgacg actcccgcgc gtgtgcccag cctcttcccg ccgcagccgc
121 ccttttcctc cctcccttac gtccccgagt gcggcagtac cgcctccttc ccagccgcgc
181 ggcttcctcc agacctctcg gcgcgggtga gccctattcc cagaggcagg tggtgctgac
241 cctgtaaccc aaaggaggaa acagctggct aagctcatca ttgttactgg tgggcaccat
301 gtccttgaag cttcaggcaa gcaatgtaac caacaagaat gaccccaagt ccatcaactc
361 tcgagtcttc attggaaacc tcaacacagc tctggtgaag aaatcagatg tggagaccat
421 cttctctaag tatggccgtg tggccggctg ttctgtgcac aagggctatg cctttgttca
481 gtactccaat gagcgccatg cccgggcagc tgtgctggga gagaatgggc gggtgctggc
541 cgggcagacc ctggacatca acatggctgg agagcctaag cctgacagac ccaaggggct
601 aaagagagca gcatctgcca tatacaggct cttcgactac cggggccgtc tgtcgcccgt
661 gccagtgccc agggcggtcc ctgtgaagcg accccgggtc acagtccctt tggtccggcg
721 tgtcaaaact aacgtacctg tcaagctctt tgcccgctcc acagctgtca ccaccagctc
781 agccaagatc aagttaaaga gcagtgagct gcaggccatc aagacggagc tgacacagat
841 caagtccaat atcgatgccc tgctgagccg cttggagcag atcgctgcgg agcaaaaggc
901 caatccagat ggcaagaaga agggtgatgg aggtggcgcc ggcggcggcg gcggtggtgg
961 tggcagcggt ggcggtggca gtggtggtgg cggtggcggt ggcagcagcc ggccaccagc
1021 cccccaagag aacacaactt ctgaggcagg cctgccccag ggggaagcac
ggacccgaga
```

1081 cgacggcgat gaggaagggc tcctgacaca cagcgaggaa gagctggaac acagccagga
1141 cacagacgcg gatgatgggg ccttgcagta agcagcctga caggagcaat ggccaccagc
1201 aggtgaaggg catcgctgcc ccaggcctca agccgggcac ccaaccctgg atgccacccc
1261 ccagcgggta ccagaggaaa gctggcagca ggcgcctcct cccccaacgc atcccagcca
1321 gtgccatgtc ctctgcaggt ggagttactg gcctactcct tccccatgag ccctccctgt
1381 ctgcactgcc caggccagag ggtagagcac aggggtttcc ccatactacc tcccctcccc
1441 aggacactcc caggcttggg ttttttctat aggtttggcg gggggccaca gggaggggac
1501 cctgacaata aagagattgg atcccaaaaa aaaaaaaaaa a

SEQ ID NO. 25

Homo sapiens RNA binding protein, autoantigenic (hnRNP-associated with lethal yellow homolog (mouse)) (RALY), transcript variant 1, mRNA.

NM_016732

1 cgcgcgagcg gcgccagctc ggggcagcgg aacccagaga agctgagggg gcggtagcgg
61 cggcgacggc gacgacgacg actcccgcgc gtgtgcccag cctcttcccg ccgcagccgc
121 ccttttcctc cctcccttac gtccccgagt gcggcagtac cgcctccttc ccagccgcgc
181 ggcttcctcc agacctctcg gcgcgggtga gccctattcc cagaggcagg tggtgctgac
241 cctgtaaccc aaaggaggaa acagctggct aagctcatca ttgttactgg tgggcaccat
301 gtccttgaag cttcaggcaa gcaatgtaac caacaagaat gaccccaagt ccatcaactc
361 tcgagtcttc attggaaacc tcaacacagc tctggtgaag aaatcagatg tggagaccat
421 cttctctaag tatggccgtg tggccggctg ttctgtgcac aagggctatg cctttgttca
481 gtactccaat gagcgccatg cccgggcagc tgtgctggga gagaatgggc gggtgctggc
541 cgggcagacc ctggacatca acatggctgg agcctaag cctgacagac ccaaggggct
601 aaagagagca gcatctgcca tatacagtgg ctacatcttt gactatgatt actaccggga
661 cgacttctac gacaggctct tcgactaccg gggccgtctg tcgcccgtgc cagtgcccag
721 ggcggtccct gtgaagcgac cccgggtcac agtccctttg gtccggcgtg tcaaaactaa
781 cgtacctgtc aagctctttg cccgctccac agctgtcacc accagctcag ccaagatcaa
841 gttaaagagc agtgagctgc aggccatcaa gacggagctg acacagatca agtccaatat
901 cgatgccctg ctgagccgct tggagcagat cgctgcggag caaaaggcca atccagatgg
961 caagaagaag ggtgatggag gtggcgccgg cggcggcggc ggtggtggtg gcagcggtgg
1021 cggtggcagt ggtggtggcg gtggcggtgg cagcagccgg ccaccagccc cccaagagaa
1081 cacaacttct gaggcaggcc tgccccaggg ggaagcacgg acccgagacg acggcgatga
1141 ggaagggctc ctgacacaca gcgaggaaga gctggaacac agccaggaca cagacgcgga
1201 tgatggggcc ttgcagtaag cagcctgaca ggagcaatgg ccaccagcag gtgaagggca
1261 tcgctgcccc aggcctcaag ccgggcaccc aaccctggat gccacccccc agcgggtacc
1321 agaggaaagc tggcagcagg cgcctcctcc cccaacgcat cccagccagt gccatgtcct
1381 ctgcaggtgg agttactggc ctactccttc cccatgagcc ctccctgtct gcactgccca
1441 ggccagaggg tagagcacag gggtttcccc atactacctc ccctccccag gacactccca
1501 ggcttgggtt ttttctatag gtttggcggg gggccacagg gaggggaccc tgacaataaa
1561 gagattggat cccaaaaaaa aaaaaaaaa

SEQ ID NO. 26

NP_821133
Amino acid
tubulin, beta polypeptide [Homo sapiens].

```
1 mreivhiqag qcgnqigakf wevisdehgi dptgtyhgds dlqldrisvy yneatggkyv
61 prailvdlep gtmdsvrsgp fgqifrpdnf vfgqsgagnn wakghytega elvdsvldvv
121 rkeaescdcl qgfqlthslg ggtgsgmgtl liskireeyp drimntfsvv pspkvsdtvv
181 epynatlsvh qlventdety cidnealydi cfrtlklttp tygdlnhlvs atmsgvttcl
241 rfpgqlnadl rklavnmvpf prlhffmpgf apltsrgsqq yraltvpelt qqvfdaknmm
301 aacdprhgry ltvaavfrgr msmkevdeqm lnvqnknssy fvewipnnvk tavcdipprg
361 lkmavtfign staiqelfkr iseqftamfr rkaflhwytg egmdemefte aesnmndlvs
421 eyqqyqdata eeeedfgeea eeea
```

SEQ ID NO. 27
NM_178014
mRNA
Homo sapiens tubulin, beta (TUBB), mRNA.

```
1 gcacctcgct gctccagcct ctggggcgca ttccaacctt ccagcctgcg acctgcggag
61 aaaaaaaatt acttattttc ttgccccata cataccttga ggcgagcaaa aaaattaaat
121 tttaaccatg agggaaatcg tgcacatcca ggctggtcag tgtggcaacc agatcggtgc
181 caagttctgg gaggtgatca gtgatgaaca tggcatcgac cccaccggca cctaccacgg
241 ggacagcgac ctgcagctgg accgcatctc tgtgtactac aatgaagcca caggtggcaa
301 atatgttcct cgtgccatcc tggtggatct agaacctggg accatggact ctgttcgctc
361 aggtcctttt ggccagatct ttagaccaga caactttgta tttggtcagt ctggggcagg
421 taacaactgg gccaaaggcc actacacaga gggcgccgag ctggttgatt ctgtcctgga
481 tgtggtacgg aaggaggcag agagctgtga ctgcctgcag ggcttccagc tgacccactc
541 actgggcggg ggcacaggct ctggaatggg cactctcctt atcagcaaga tccgagaaga
601 ataccctgat cgcatcatga ataccttcag tgtggtgcct tcacccaaag tgtctgacac
661 cgtggtcgag ccctacaatg ccaccctctc cgtccatcag ttggtagaga atactgatga
721 gacctattgc attgacaacg aggccctcta tgatatctgc ttccgcactc tgaagctgac
781 cacaccaacc tacggggatc tgaaccacct tgtctcagcc accatgagtg gtgtcaccac
841 ctgcctccgt ttccctggcc agctcaatgc tgacctccgc aagttggcag tcaacatggt
901 ccccttccca cgtctccatt tctttatgcc tggctttgcc cctctcacca gccgtggaag
961 ccagcagtat cgagctctca cagtgccgga actcacccag caggtcttcg atgccaagaa
1021 catgatggct gcctgtgacc cccgccacgg ccgatacctc accgtggctg
ctgtcttccg
1081 tggtcggatg tccatgaagg aggtcgatga gcagatgctt aacgtgcaga
acaagaacag
1141 cagctacttt gtggaatgga tccccaacaa tgtcaagaca gccgtctgtg
acatcccacc
1201 tcgtggcctc aagatggcag tcaccttcat tggcaatagc acagccatcc
aggagctctt
1261 caagcgcatc tcggagcagt tcactgccat gttccgccgg aaggccttcc
tccactggta
1321 cacaggcgag ggcatggacg agatggagtt caccgaggct gagagcaaca
tgaacgacct
1381 cgtctctgag tatcagcagt accaggatgc caccgcagaa gaggaggagg
atttcggtga
1441 ggaggccgaa gaggaggcct aaggcagagc ccccatcacc tcaggcttct
cagttccctt
1501 agccgtctta ctcaactgcc cctttcctct ccctcagaat ttgtgtttgc
tgcctctatc
1561 ttgttttttg ttttttcttc tggggggggt ctagaacagt gcctggcaca
tagtaggcgc
1621 tcaataaata cttgtttgtt gaatgtctcc tctctctttc cactctggga
aacctaggtt
```

```
1681 tctgccattc tgggtgaccc tgtatttctt tctggtgccc attccatttg
tccagttaat
1741 acttcctctt aaaaatctcc aagaagctgg gtctccagat cccatttaga
accaaccagg
1801 tgctgaaaac acatgtagat aatggccatc atcctaagcc caaagtagaa
aatggtagaa
1861 ggtagtgggt agaagtcact atataaggaa ggggatggga ttttccattc
taaaagtttt
1921 ggagagggaa atccaggcta ttaaagtcac taaatttcta agtatgtcca
tttcccatct
1981 cagcttcaag ggaggtgtca gcagtattat ctccactttc aatctccctc
caagctctac
2041 tctggaggag tctgtcccac tctgtcaagt ggaatccttc cctttccaac
tctacctccc
2101 tcactcagct cctttccccc gatcagagaa agggatcaag ggggttggga
gggggggaaag
2161 agaccagcct tggtccctaa gcctccagaa acgtcttctt aatccccacc
ttttcttact
2221 cccaaaaaag aatgaacacc cctgactctg gagtggtgta tactgccaca
tcagtgtttg
2281 agtcagtccc cagaggagag gggaaccctc ctccatcttt tttgcaacat
ctcatttctt
2341 ccttttgctg ttgcttcccc cctcacacac ttggttttgt tctatcctac
atttgagatt
2401 tctattttat gttgaacttg ctgctttttt tcatattgaa aagatgacat
cgccccaaga
2461 gccaaaaata aatgggaatt gaaaaaaaaa aaaaaaaaaa aaaaaaaaaa
```

SEQ ID NO. 28

NP_001605

Amino acid

actin, gamma 1 propeptide [Homo sapiens].

```
1 meeeiaalvi dngsgmckag fagddaprav fpsivgrprh qgvmvgmgqk dsyvgdeaqs
61 krgiltlkyp iehgivtnwd dmekiwhhtf ynelrvapee hpvllteapl npkanrekmt
121 qimfetfntp amyvaiqavl slyasgrttg ivmdsgdgvt htvpiyegya lphailrldl
181 agrdltdylm kiltergysf tttaereivr dikeklcyva ldfeqemata asssslekky
241 elpdgqviti gnerfrcpea lfqpsflgme scgihettfn simkcdvdir kdlyantvls
301 ggttmypgia drmqkeital apstmkikii apperkysvw iggsilasls tfqqmwiskq
361 eydesgpsiv hrkcf
```

SEQ ID NO. 29

NM_001614

Homo sapiens actin, gamma 1 (ACTG1), mRNA.

```
1   gtctcagtcg ccgctgccag ctctcgcact ctgttcttcc gccgctccgc cgtcgcgttt
61  ctctgccggt cgcaatggaa gaagagatcg ccgcgctggt cattgacaat ggctccggca
121 tgtgcaaagc tggttttgct ggggacgacg ctccccgagc cgtgtttcct tccatcgtcg
181 ggcgccccag acaccagggc gtcatggtgg gcatgggcca gaaggactcc tacgtgggcg
241 acgaggccca gagcaagcgt ggcatcctga ccctgaagta ccccattgag catggcatcg
301 tcaccaactg ggacgacatg gagaagatct ggcaccacac cttctacaac gagctgcgcg
361 tggccccgga ggagcaccca gtgctgctga ccgaggcccc cctgaacccc aaggccaaca
421 gagagaagat gactcagatt atgtttgaga ccttcaacac cccggccatg tacgtggcca
481 tccaggccgt gctgtccctc tacgcctctg ggcgcaccac tggcattgtc atggactctg
541 gagacggggt cacccacacg gtgcccatct acgagggcta cgccctcccc cacgccatcc
601 tgcgtctgga cctggctggc cgggacctga ccgactacct catgaagatc ctcactgagc
661 gaggctacag cttcaccacc acggccgagc gggaaatcgt gcgcgacatc aaggagaagc
721 tgtgctacgt cgccctggac ttcgagcagg agatggccac cgccgcatcc tcctcttctc
```

781 tggagaagag ctacgagctg cccgatggcc aggtcatcac cattggcaat gagcggttcc
841 ggtgtccgga ggcgctgttc cagccttcct tcctgggtat ggaatcttgc ggcatccacg
901 agaccacctt caactccatc atgaagtgtg acgtggacat ccgcaaagac ctgtacgcca
961 acacggtgct gtcgggcggc accaccatgt acccgggcat tgccgacagg atgcagaagg
1021 agatcaccgc cctggcgccc agcaccatga agatcaagat catcgcaccc
ccagagcgca
1081 agtactcggt gtggatcggt ggctccatcc tggcctcact gtccaccttc
cagcagatgt
1141 ggattagcaa gcaggagtac gacgagtcgg gcccctccat cgtccaccgc
aaatgcttct
1201 aaacggactc agcagatgcg tagcatttgc tgcatgggtt aattgagaat
agaaatttgc
1261 ccctggcaaa tgcacacacc tcatgctagc ctcacgaaac tggaataagc
cttcgaaaag
1321 aaattgtcct tgaagcttgt atctgatatc agcactggat tgtagaactt
gttgctgatt
1381 ttgaccttgt attgaagtta actgttcccc ttggtatttg tttaataccc
tgtacatatc
1441 tttgagttca acctttagta cgtgtggctt ggtcacttcg tggctaaggt
aagaacgtgc
1501 ttgtggaaga caagtctgtg gcttggtgag tctgtgtggc cagcagcctc
tgatctgtgc
1561 agggtattaa cgtgtcaggg ctgagtgttc tgggatttct ctagaggctg
gcaagaacca
1621 gttgttttgt cttgcgggtc tgtcagggtt ggaaagtcca agccgtagga
cccagtttcc
1681 tttcttagct gatgtctttg gccagaacac cgtgggctgt tacttgcttt
gagttggaag
1741 cggtttgcat ttacgcctgt aaatgtattc attcttaatt tatgtaaggt
ttttttttgta
1801 cgcaattctc gattctttga agagatgaca acaaattttg gttttctact
gttatgtgag
1861 aacattaggc cccagcaaca cgtcattgtg taaggaaaaa taaaagtgct gccgtaacc

SEQ ID NO. 30

NM_001615

homo sapiens actin, gamma 2, smooth muscle, enteric (ACTG2), mRNA.

1 gcctctgggg ttttatattg ctctggtatt catgccaaag acacaccagc cctcagtcac
61 tgggagaaga acctctcata ccctcggtgc tccagtcccc agctcactca gccacacaca
121 ccatgtgtga agaggagacc accgcgctcg tgtgtgacaa tggctctggc ctgtgcaagg
181 caggcttcgc aggagatgat gcccccgggg ctgtcttccc ctccattgtg ggccgccctc
241 gccaccaggg tgtgatggtg ggaatgggcc agaaagacag ctatgtgggg gatgaggctc
301 agagcaagcg agggatccta actctcaaat accccattga acacggcatc atcaccaact
361 gggatgacat ggagaagatc tggcaccact ccttctacaa tgagctgcgt gtagcacctg
421 aagagcaccc caccctgctc acagaggctc ccctaaatcc caaggccaac agggaaaaga
481 tgacccagat catgtttgaa accttcaatg tcccctgccat gtacgtcgcc attcaagctg
541 tgctctccct ctatgcctct ggccgcacga caggcatcgt cctggattca ggtgatggcg
601 tcacccacaa tgtccccatc tatgaaggct atgccctgcc ccatgccatc atgcgcctgg
661 acttggctgg ccgtgacctc acggactacc tcatgaagat cctcacagag agaggctatt
721 cctttgtgac cacagctgag agagaaattg tgcgagacat caaggagaag ctgtgctatg
781 tggccctgga ttttgagaat gagatggcca cagcagcttc ctcttcctcc ctggagaaga
841 gctatgagct gccagatggg caggttatca ccattggcaa tgagcgcttc cgctgccctg
901 agaccctctt ccagccttcc tttattggca tggagtccgc tggaattcat gagacaacct
961 acaattccat catgaagtgt gacattgaca tccgtaagga cttatatgcc aacaatgtcc
1021 tctctggggg caccaccatg taccctggca ttgctgacag gatgcagaag
gagatcacag

```
1081 ccctggcccc cagcaccatg aagatcaaga ttattgctcc cccagagcgg
aagtactcag
1141 tctggatcgg gggctctatc ctggcctctc tctccacctt ccagcagatg
tggatcagca
1201 agcctgagta tgatgaggca gggccctcca ttgtccacag gaagtgcttc
taaagtcaga
1261 acaggttctc caaggatccc ctcgagacta ctctgttacc agtcatgaaa
cattaaaacc
1321 tacaagcctt aaaaaaaaaa aaaaa
```

SEQ ID NO. 31
NP_001606
actin, gamma 2 propeptide [Homo sapiens].

```
1 mceeettalv cdngsglcka gfagddapra vfpsivgrpr hqgvmvgmgq kdsyvgdeaq
61 skrgiltlky piehgiitnw ddmekiwhhs fynelrvape ehptllteap lnpkanrekm
121 tqimfetfnv pamyvaiqav lslyasgrtt givldsgdgv thnvpiyegy alphaimrld
181 lagrdltdyl mkiltergys fvttaereiv rdikeklcyv aldfenemat aasssskeks
241 yelpdgqvit ignerfrcpe tlfqpsfigm esagihetty nsimkcdidi rkdlyannvl
301 sggttmypgi adrmqkeita lapstmkiki iapperkysv wiggsilasl stfqqmwisk
361 peydeagpsi vhrkcf
```

SEQ ID NO. 32
Q04984 and AAH23518
Chaperonin 10
1 magqafrkfl plfdrvlver saaetvtkgg imlpeksqgk vlqatvvavg sgskgkggei 61 qpvsvkvgdk vllpeyggtk vvlddkdyfl frdgdilgky vd

SEQ ID NO. 33
NM_002157 and U07550
Human chaperonin 10 mRNA, complete cds

```
  1  gctacactag agcagagtac gagtctgagg cggagggagt aatggcagga caagcgttta
 61  gaaagtttct tccactcttt gaccgagtat tggttgaaag gagtgctgct gaaactgtaa
121 ccaaaggagg cattatgctt ccagaaaaat ctcaaggaaa agtattgcaa gcaacagtag
181 tcgctgttgg atcgggttct aaaggaaagg gtggagagat tcaaccagtt agcgtgaaag
241 ttggagataa agttcttctc ccagaatatg gaggcaccaa agtagttcta gatgacaagg
301 attatttcct atttagagat ggtgacattc ttggaaagta cgtagactga aataagtcac
361 tattgaaatg gcatcaacat gatgctgccc attccactga agttctgaaa tctttcgtca
421 tgtaaataat ttccatattt ctcttttata ataaactaat gataactaat gacatccagt
481 gtctccaaaa ttgtttcctt gtactgatat aaacacttcc aaataaaaat atgtaaat
```

SEQ ID NO. 34
P05109
Calgranulin A

```
 1 mltelekaln siidvyhkys likgnfhavy rddlkkllet ecpqyirkkg advwfkeldi
61 ntdgavnfqe flilvikmgv aahkkshees hke
```

SEQ ID NO. 35
A12027
Macrophage migration inhibition factor (MRP-14)cDNA from Human placenta (formula v)

```
1    cttgggttgc ttccaccttt tggctcttgt aaataatgct gctatgaaca tgaatgtaca
61   aacatctgtt tgaatccctg cattcaattc ttttgcatat atacccagga gcagaatgat
121  ggatcatatg gtaattctgt gtttatttat ttgaggaaca aacttgccgt tttccataac
181  agctgcacta ttttacattc ccactaacag tgcattaggc ttccaattct ctatgccctc
241  accaacactt gttttctggg ttttaaaaga agtagtagtc atccttgtag gtgtcaggtg
301  gtatctcatt gtcgttttgc ttcatgtttt cctaaagatt agtaattttc atatgcttat
361  tgaccatttg tatatcttct tcggagaagt gtctatttga gtctttcccc aattttgatt
421  ggtttgtttg ttttttgttg ttgagttgta gggattcttt tatattctgg atattaatcc
481  cttatcagat atttgtttta caaatatttt ctttgtaaca acagaaacac accacagtct
541  tcaaggttgg aagccagtta atctgagtag cattttgtta gtggtgggga gaggatttgt
601  tcctcctgaa atcctgggga attggccacc tcctcttctc ctcttaggca tgaagcgcgt
661  ctggcttctc caaagaactc ttcccctcca ctacctcaga gttagcttcc tctcttcagc
721  cagtgatcct ggggtcccag acacaataat taaccaagag agggtgaaag gctccctgct
781  gtgtttatgc aatggctcag gcccttgtga agtgccgagg gaccccaagc agcctccatc
841  tcccagggca tggtccatcc ccagctttca cagaacagga aagctgtgga ggagtgtggg
901  cagcagggta ggaatggata tagcccttgg caacaacaca tttccccaca aagcacccac
961  ccaaaagaac aacaacgata gttttagttt ttagtaatga gaacaatagt tctcatgact
1021 aaaagccatc agccaggaca ctgttctcaa ccctttgcg gtctttggac
cctttgaaac
1081 tctgacagaa gccatggagg aatgttctca ctgagtgcat gcactcaaaa
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1141 aacttcaatt cagtttcagg gatgtatggc ctgaccacca atgcagggga
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1201 caatagtgga gagggcatgg gagtgggaat ctggctggat caagcaagtg
gatgccagca
1261 gcccagaaaa agagcccccc tacctgcttt ttccttcctg ggcactattg
cccagcaaat
1321 gccttcctct ttccgcttct cctacctccc cacccaaaat tttcattctg
cacagtgatt
1381 gccacattca ctggttgaga aacagagact gtagcaactc tggcagggag
aagctgtctc
1441 tgatggcctg aagctgtggg cagctggcca agcctaaccg ctataaaaag
gagctgcctc
1501 tcagccctgc atgtctcttg tcagctgtct ttcagaagac ctggtaagtg
ggactgtctg
1561 ggttggcccc gcactttggg cttctcttgg ggagggtcag ggaagtggag
cagccttcct
1621 gagagaggag agagaaagct cagggaggtc tggagcaaag atactcctgg
aggtggggag
1681 tgaggcaggg ataaggaagg agagtatcct ccagcacctt ccagtgggta
agggcacatt
1741 gtctcctagg ctggactttt cttgagcaga gggtggggtg gtaaggaaag
tctacgggcc
1801 cccgtgtgtg tgcacatgtc tctgtgtgaa tggacccttc cccttcccac
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1861 ctatcatccc acccttccca ccagaggcca tagccatctg ctggtttggt
tatttgagag
1921 tgcaggccag gacaaggcca tcgcttgggg catgaatcct ctgcgtactg
ccctggccag
1981 atgcaaattc cctgccatgg gattccccag aaggttctgt ttttcaggtg
gggcaagttc
2041 cgtgggcatc atgttgaccg agctggagaa agccttgaac tctatcatcg
acgtctacca
2101 caagtactcc ctgataaagg ggaatttcca tgccgtctac agggatgacc
tgaagaaatt
```

2161 gctagagacc gagtgtcctc agtatatcag ggtgaggagg ggctgggtgt ggcgggggct
2221 ctctgcctgg tcctggggct gccctgggcc agcggtcctc cctgccaccc ttcatagatg
2281 ctatgcctcg gctctctctg agatctttaa actctggctt cttcctcctc aatcttgaca
2341 gaaaaagggt gcagacgtct ggttcaaaga gttggatatc aacactgatg gtgcagttaa
2401 cttccaggag ttcctcattc tggtgataaa gatgggcgtg gcagcccaca aaaaaagcca
2461 tgaagaaagc cacaaagagt agctgagtta ctgggcccag aggctgggcc cctggacatg
2521 tacctgcaga ataataaagt catcaatacc tcatgcctct ctcttatgct tttgtggaat
2581 gaggttcctc ggtgtggagg gagggttgga aaacccaaag gaagaaaaag aaatctatgt
2641 tatcccaccc tacctctcac aagcctttcc tgctttaccc ctcacctggc ctctgcccca
2701 cattccttca gcccctcatt tcgagcattg gatttgaggc ttaaggattc aaaaagtcgt
2761 catgaatata gctgatgatt ttatagtggt tctgaaatgg gtcggggatt tgggaacagg
2821 gtggtagtat aagaacaact gatactgttc tctaagctaa atcttagctt ccagctacct
2881 gtcttagatg tggctcttgg gaaccttaga gtgatagcta catagaagtg tgtgggtgtg
2941 tgtgtgtgtg tctgtgtgtg tgtgtgtgag agagagacag acagaaagag agcaagagag
3001 ggaaggggggg agaggctgat tgtgtgtgtg gtgtgatgta ggtggacaat gttcagagtc
3061 ctccattaac aggataatcc tcacacctgt ccacatacct gtagtttgtc cttggggatt
3121 ttgaaaattt ttcctccctc tccactccca aactcccaac tcaattaaat gataaaggaa
3181 taggcaaata ggaaaataaa ttagtaaaac ttaagtcaaa gaataggtta ttcatacgct
3241 gcctatggga ttctatgctt tgtgatcaga aaattatcta aaaaatactt cccaagggct
3301 ggtacaaggg aggccagaag acgagtggtt cttctctgag gtggacatta aaaaaagaag
3361 aaaatgaagg ggaacctttt gacaagaatg tcaccccaaa ctggattttc atgctgtggt
3421 gtggggaatt ttctgttgtc ctcacttagg tgctggggca gtggtgttag tgatgggtaa
3481 aaaggtagga agctgtcaca gaatcactaa accagggttc ttaacttgtc tgtctataca
3541 tctctgaaat tgggttgaag ttgtgtgcat cattttgagt gacgcactga gaacattcct
3601 ccacggcttc catcgagagt ctcgaaaagg cccaacacct caaaaaggtt aagaacactt
3661 gtcctgctta ctggttttta gtaacaaatg gcagagtatt tctctctgtc tctctctctt
3721 ttttttttt ttttttgag acacagggtc ttgtctgtca cgtggactag agtacaatgg
3781 gcatgatcat gggctcactg tagcctcgaa cacctgggct caagtaatcc tcccacctca
3841 gcctctttag tagctgggac tacagcatga gccactgccc ttggctaatt tttaaattat
3901 ttttttgtag agatggaaac ttgctatgtt gcccaggcta gtctcaaact cctggactca

```
3961 agcgatcctc ctaccttggc ctcccaaagt gctgagatta cagtgtgatc
cacaccacac
4021 ctggccaaag attggagtat ttttattgct attgttgtgc tgggtgggtg
ggtgggtgta
4081 tgctttgtgg ggacgtgtgt tgttgccaag ggctaaatca gttcctaccc
tgctgcccac
4141 agtcctccac agctttcctg ctctgtgaag ctaaggatac accccgatga
taagctgtca
4201 acata
```

SEQ ID NO. 36

NM_002964

Homo sapiens S100 calcium binding protein A8 (calgranulin A) S100A8, mRNA

```
   1 atgtctcttg tcagctgtct ttcagaagac ctggtggggc aagtccgtgg gcatcatgtt
  61 gaccgagctg gagaaagcct tgaactctat catcgacgtc taccacaagt actccctgat
 121 aaaggggaat ttccatgccg tctacaggga tgacctgaag aaattgctag agaccgagtg
 181 tcctcagtat atcaggaaaa agggtgcaga cgtctggttc aaagagttgg atatcaacac
 241 tgatggtgca gttaacttcc aggagttcct cattctggtg ataaagatgg gcgtggcagc
 301 ccacaaaaaa agccatgaag aaagccacaa agagtagctg agttactggg cccagaggct
 361 gggcccctgg acatgtacct gcagaataat aaagtcatca atacctcaaa aaaaaaaaaa
 421 aaaaaaaa
```

SEQ ID NO. 37

P06702

Calgranulin B/MRP-14

```
   1 mtckmsqler nietiintfh qysvklghpd tlnqgefkel vrkdlqnflk kenknekvie
  61 himedldtna dkqlsfeefi mlmarltwas hekmhegdeg pghhhkpglg egtp
```

SEQ ID NO. 38

X06233

Human mRNA for calcium-binding protein in macrophages (RP-14) macrophage migration inhibitory factor (MIF)-related protein

```
aaaacactct gtgtggctcc tcggctttga cagagtgcaa gacgatgact tgcaaaatgt
cgcagctgga acgcaacata gagaccatca tcaacacctt ccaccaatac tctgtgaagc
tggggcaccc agacaccctg aaccaggggg aattcaaaga gctggtgcga aaagatctgc
aaaatttttct caagaaggag aataagaatg aaaaggtcat agaacacatc atggaggacc
tggacacaaa tgcagacaag cagctgagct tcgaggagtt catcatgctg atggcgaggc
taacctgggc ctcccacgag aagatgcacg agggtgacga gggccctggc caccaccata
agccaggcct cggggagggc acccccctaag accacagtgg ccaagatcac agtggccacg
gccacggcca cagtcatggt ggccacggcc acagccaccc at
```

SEQ ID NO. 39

M21064

Human migration inhibitory factor-related protein 14 (MRP14) gene, complete cds

```
   1 atcactgtgg agtaggggaa gggcactcct ggggtggcaa ggtgggaggt
gggccctgtg
```

61 ttcccacagt gggcagggag gtagtgaaag ggaagctggc cggacaggaa gggccattcc
121 aagagggctt tgtgcgcagg gctaagccaa gctttctcca taggcaatgg ggagcaactg
181 gaggttcgta gcaggagaag gacacatcaa gcccaccagg aggctaagta aaaacagttg
241 tctcccaagt tataagttcc tggaaccctt gctgggagca ggatttagaa aaatgatgct
301 gagagatgct agaaacatat tcgccctgag gctctctcac tcagactgca agaggaaggt
361 atcatcagaa ttgcccttaa ccaggaacca gaatagctgg gtccccttcc tgccaagtca
421 gcaaccagct atgtgacctt gctcaggtcc atctccgggt gtcagtttct tcatctacaa
481 tgcaagaggg ttgcccacct ctgagaaccc ttctaacccc aaatctcacc ctatgaatct
541 aagaacacaa cccctcgcca tcctaagtat cacagagcca ggcaagcatg ggtgagagct
601 cagaccatcc ttgttggact aaaaggaagg ggcagactgc catgggggc agccgagagg
661 gtcaggcccc cataggtcct cagcctgctt caacctcaaa ggggatgggg ggctgagtgg
721 tgccagagga gcagcaggct cgctcgggga gagtagggcc ttaggataga agggaaatga
781 actaaacaac cagcttcctg caaaccagtt tcaggccagg gctgggaatt tcacaaaaaa
841 gcagaaggcg ctctgtgaac atttcctgcc ccgccccagc cccttcctg gcagcattag
901 cacactgctc acctgtgaag caatcttccg gagacagggc caaagggcaa gtgccccagt
961 caggagctgc ctataaatgc cgagcctgca cagctctggc aaacactctg tgtggctcct
1021 cggctttggt aagtgagctg ccagcttccc caggcagaag cctgcctgcc gattccttct
1081 ttccttccct gacccaactt ccttccaaat cctcctccta gaagccctcc ttggttggcc
1141 ctgcctactt taaagcttct ttcacatttt cttaggtcat gttcccctgg ggcctcctgc
1201 cctcaaatgc tttgcttttt ggcactctgt agatattcta aaaaatcatt ttgtacatgt
1261 gtgtgacagg ccatctccca gttaagttgc agcctgtgct ttctttttat tttgcacttc
1321 ccccactatt tctgtgagtg cttagtagga agtgtcaaag aagcttgaca gcattttctt
1381 ctaagtgtcc caactcttgg ttttccatta cacagacaga gtgcaagacg atgacttgca
1441 aaatgtcgca gctggaacgc aacatagaga ccatcatcaa caccttccac caatactctg
1501 tgaagctggg gcacccagac accctgaacc agggggaatt caaagagctg gtgcgaaaag
1561 atctgcaaaa ttttctcaag gtagggctgg actctggcag gtctgaccca gcctcaccgc
1621 agtttgggtt gacaagggag gatgggagta tgggctacag caatcaaggg gaagatttga
1681 gctcctggag cccagcccca agacgcagcg agtgtcctgt tatacagggc aggtgctcac
1741 agttacacag gacgacaggg tcaagaaatt gctcaattga acacctgcta tttgtcgggc
1801 cctgttctgg gcagagggat gtagtggtaa atgggagccc actattccat gaggagacac

1861 acagtaaagt tgttggccaa taaagagcac agataaagcc aaatgccaat aagtgcctgg
1921 aagaaaatga gatagagtgc gctgtgggca atggggctgg gtggggtgga ggtgaccagt
1981 tagggtacat gagaagggcc tctttgagga ggtaacattt gagctgagcc ccgaatgttg
2041 gggagggaag cccctgagga tgacacttgg cacaaagctg aggagaccct aagcctcagg
2101 gcgaacttgg ggtggaagac ttgggggctt ttctaatcct aagggtctgc ggtggaaaat
2161 gaatgcataa agagcacatg gagagcacct gcacagcact cagggaactg ggaggttttt
2221 cccccgctcc aaaaatgatt aggcagttct aagaaaaagg ctgagcactt ccaacagcct
2281 ttttgttttc ttttcaaatt tggggaaagt cgggaaacag aggcctgcat taagaagggt
2341 ggaacacatg ggtctcagtc tcagttccag tcccggagcc agacatcctg gggtaggtcc
2401 ccagccctcc cagtgccccc ccctccgcct tggtaaggtg gagaattgca gccttcagag
2461 ttaggggccc tgacagctct ccataggtgg aggcctcagg caggcaggat gctgggtggg
2521 gtaggcaaga aagggcccag cagagaggcc gcatcggaaa actatcctcc atgtgacccc
2581 ctatgcccgc ttcacccccc acctgacatc ccccaccaga agcaaagcga tgctgtggga
2641 aaggaagcag agcctcatgg atgggctgca caggagagtg ctcgcattgg ctgggtaccc
2701 cacaggttct gggaggggac ttagcgaggt gactcagtgc ctcggcctcc caaagtgctg
2761 ggattacaag catgagccac cctgtccgac catctccccc tttatacttt atcacaccct
2821 tgaggtcagc ggagcacata ctctgctctc tgaccctcca tctcccctgc ccacacctag
2881 gtttttctag tgtttccccg ttgtattggt tgaaataagt ttcactaatt ggtaacctcc
2941 agagggaagg gaagggaggg caggggaagg agtgaagtgc agaggggtag cagagtggaa
3001 ctggcctcta agtcagatct gaatttgcat gccctcaata gtcaagcctg tgaaaactaa
3061 tgaccctctc taggactggt ttcaagtctt cctccaggaa gataccattc ctagctgtta
3121 aagttgttat aaggaccaaa tgaggtgaca tttccaggct tactcatgcc atgaccaggg
3181 caagaccctg gaactcagct tcctcttcta taaatagaga atcagcaccc aagtcacagg
3241 gtcatggagg gaataaactg gagagcgttt ggtatgtgct cagtgtctgc tccattgtgc
3301 gcactcagcc tatggtcatt tttaattttt aaatccagcc ccagggtcga ggcttccttg
3361 tacatttgcc agctggtcat ttactgtgct cccagtcccc acctctggcc acacccagct
3421 ctcacagcct tctctcccca cccgcagaag gagaataaga atgaaaaggt catagaacac
3481 atcatggagg acctggacac aaatgcagac aagcagctga gcttcgagga gttcatcatg
3541 ctgatggcga ggctaacctg ggcctcccac gagaagatgc acgagggtga cgagggccct
3601 ggccaccacc ataagccagg cctcggggag ggcacccccc aagaccacag tggccaagat

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3661 cacagtggcc acggccacgg ccacagtcat ggtggccacg gccacaggcc
actaatcagg
3721 aggccaggcc accctgcctc tacccaacca gggccccggg gctgttatgt
caaactgtct
3781 tggctgtggg gctaggggct ggggcaaata agtctcttcc tccaagtcag
tgctctgtgt
3841 gcttcttcca cctcttctcc aaccctgcct tcccagggct ctggcattta
gacagccctg
3901 tccttatctg tgactcagcc ccctcattca gtattaacaa aatgagaagc
agcaaaacat
3961 gggtctgtgc tgggcccctt ggctcacctc cctgaccatg tcctcacctc
tgacttcagg
4021 ccccactgtt cagatcccag gctccctgcc ccatctcaga caccctgtcc
agcctgtcca
4081 gcctgacaaa tggcccttgt cactgtacac tgtagaaagc aaaaaggcat
atctctaccc
4141 cttgatatgc ctgctacctc accaaccagc cccaagcctg tcttcaccca
tcactgtcta
4201 cacagccctc tctctctcct aacagaattc tattcctctg aaagtcttca
gaaactggac
4261 ctagatagtg ccatgtctgg ggaggaatat ggcaccaggc agtggaaaca
aggacagatc
4321 ggtgtgttat ctcacatttg atcagagagc atgatctctc ttaacagacc
tgccacccta
4381 atcaacggga gtgctcacac aagtgggagt ctgagagctt agccctatgc ccaccctgg
```

SEQ ID NO. 40

P01833 and Q81ZY7

Polymeric-immunoglobulin receptor (precursor)

```
  1 mllfvltcll avfpaistks pifgpeevns vegnsvsitc yypptsvnrh trkywcrqga
 61 rggcitliss egyvsskyag ranltnfpen gtfvvniaql sqddsgrykc glginsrgls
121 fdvslevsqg pgllndtkvy tvdlgrtvti ncpfktenaq krkslykqig lypvlvidss
181 gyvnpnytgr irldiqgtgq llfsvvinql rlsdagqylc qagddsnsnk knadlqvlkp
241 epelvyedlr gsvtfhcalg pevanvakfl crqssgencd vvvntlgkra pafegrilln
301 pqdkdgsfsv vitglrkeda grylcgahsd gqlqegspiq awqlfvnees tiprsptvvk
361 gvagssvavl cpynrkesks ikywclwega qngrcpllvd segwvkaqye grlslleepg
421 ngtftvilnq ltsrdagfyw cltngdtlwr ttveikiieg epnlkvpgnv tavlgetlkv
481 pchfpckfss yekywckwnn tgcqalpsqd egpskafvnc densrlvslt lnlvtradeg
541 wywcgvkqgh fygetaavyv aveerkaags rdvslakada apdekvldsg freienkaiq
601 dprlfaeeka vadtrdqadg srasvdsgss eeqggssral vstlvplglv lavgavavgv
661 ararhrknvd rvsirsyrtd ismsdfensr efgandnmga ssitqetslg gkeefvatte
721 sttetkepkk akrsskeeae maykdfllqs stvaaeaqdg pqea
```

SEQ ID NO. 41

NM_002644

Homo sapiens polymeric immunoglobulin receptor (PIGR), mRNA

```
   1 agagtttcag ttttggcagc agcgtccagt gccctgccag tagctcctag
agaggcaggg
  61 gttaccaact ggccagcagg ctgtgtccct gaagtcagat caacgggaga
gaaggaagtg
 121 gctaaaacat tgcacaggag aagtcggcct gagtggtgcg gcgctcggga
cccaccagca
 181 atgctgctct tcgtgctcac ctgcctgctg gcggtcttcc cagccatctc
cacgaagagt
```

241 cccatatttg gtcccgagga ggtgaatagt gtggaaggta actcagtgtc catcacgtgc
301 tactacccac ccacctctgt caaccggcac acccggaagt actggtgccg gcagggagct
361 agaggtggct gcataaccct catctcctcg gagggctacg tctccagcaa atatgcaggc
421 agggctaacc tcaccaactt cccggagaac ggcacatttg tggtgaacat tgcccagctg
481 agccaggatg actccgggcg ctacaagtgt ggcctgggca tcaatagccg aggcctgtcc
541 tttgatgtca gcctggaggt cagccagggt cctgggctcc taaatgacac taaagtctac
601 acagtggacc tgggcagaac ggtgaccatc aactgccctt tcaagactga gaatgctcaa
661 aagaggaagt ccttgtacaa gcagataggc ctgtaccctg tgctggtcat cgactccagt
721 ggttatgtaa atcccaacta tacaggaaga atacgccttg atattcaggg tactggccag
781 ttactgttca gcgttgtcat caaccaactc aggctcagcg atgctgggca gtatctctgc
841 caggctgggg atgattccaa tagtaataag aagaatgctg acctccaagt gctaaagccc
901 gagcccgagc tggtttatga agacctgagg ggctcagtga ccttccactg tgccctgggc
961 cctgaggtgg caaacgtggc caaatttctg tgccgacaga gcagtgggga aaactgtgac
1021 gtggtcgtca acaccctggg gaagagggcc ccagcctttg agggcaggat cctgctcaac
1081 ccccaggaca aggatggctc attcagtgtg gtgatcacag gcctgaggaa ggaggatgca
1141 gggcgctacc tgtgtggagc ccattcggat ggtcagctgc aggaaggctc gcctatccag
1201 gcctggcaac tcttcgtcaa tgaggagtcc acgattcccc gcagccccac tgtggtgaag
1261 ggggtggcag gaggctctgt ggccgtgctc tgcccctaca accgtaagga aagcaaaagc
1321 atcaagtact ggtgtctctg ggaaggggcc cagaatggcc gctgcccccc gctggtggac
1381 agcgaggggt gggttaaggc ccagtacgag ggccgcctct ccctgctgga ggagccaggc
1441 aacggcacct tcactgtcat cctcaaccag ctcaccagcc gggacgccgg cttctactgg
1501 tgtctgacca acggcgatac tctctggagg accaccgtgg agatcaagat tatcgaagga
1561 gaaccaaacc tcaaggtacc agggaatgtc acggctgtgc tgggagagac tctcaaggtc
1621 ccctgtcact ttccatgcaa attctcctcg tacgagaaat actggtgcaa gtggaataac
1681 acgggctgcc aggccctgcc cagccaagac gaaggcccca gcaaggcctt cgtgaactgt
1741 gacgagaaca gccggcttgt ctccctgacc ctgaacctgg tgaccagggc tgatgagggc
1801 tggtactggt gtggagtgaa gcagggccac ttctatggag agactgcagc cgtctatgtg
1861 gcagttgaag agaggaaggc agcggggtcc cgcgatgtca gcctagcgaa ggcagacgct
1921 gctcctgatg agaaggtgct agactctggt tttcgggaga ttgagaacaa agccattcag
1981 gatcccaggc tttttgcaga ggaaaaggcg gtggcagata caagagatca agccgatggg

2041 agcagagcat ctgtggattc cggcagctct gaggaacaag gtggaagctc cagagcgctg
2101 gtctccaccc tggtgcccct gggcctggtg ctggcagtgg gagccgtggc tgtgggggtg
2161 gccagagccc ggcacaggaa gaacgtcgac cgagtttcaa tcagaagcta caggacagac
2221 attagcatgt cagacttcga gaactccagg gaatttggag ccaatgacaa catgggagcc
2281 tcttcgatca ctcaggagac atccctcgga ggaaaagaag agtttgttgc caccactgag
2341 agcaccacag agaccaaaga acccaagaag gcaaaaaggt catccaagga ggaagccgag
2401 atggcctaca aagacttcct gctccagtcc agcaccgtgg ccgccgaggc ccaggacggc
2461 ccccaggaag cctagacggt gtcgccgcct gctccctgca cccatgacaa tcaccttcag
2521 aatcatgtcg atcctggggc cctcagctcc tggggacccc actccctgct ctaacacctg
2581 cctaggtttt tcctactgtc ctcagaggcg tgctggtccc ctcctcagtg acatcaaagc
2641 ctggcctaat tgttcctatt ggggatgagg gtggcatgag gaggtcccac ttgcaacttc
2701 tttctgttga gagaacctca ggtacggaga agaatagagg tcctcatggg tcccttgaag
2761 gaagagggac cagggtggga gagctgattg cagaaaggag agacgtgcag cgcccctctg
2821 cacccttatc atgggatgtc aacagaattt ttccctccac tccatccctc cctcccgtcc
2881 ttccccctct cttctttcct tccatcaaaa gatgtatttg aattcatact agaattcagg
2941 tgctttgcta gatgctgtga caggtatgcc accaacactg ctcacagcct ttctgaggac
3001 accagtgaaa gaagccacag ctcttcttgg cgtatttata ctcactgagt cttaactttt
3061 caccaggggt gctcacctct gcccctattg ggagaggtca taaaatgtct cgagtcctaa
3121 ggccttaggg gtcatgtatg atgagcatac acacaggtaa ttataaaccc acattcttac
3181 catttcacac ataagaaaat tgaggtttgg aagagtgaag cgtttttctt tttctttttt
3241 ttttttgaga cggagtctct cactgtcgcc caggctggag tgcagtggcg caatctcggc
3301 tcactgcaac ctccgcctcc caggttgaca ccattctcct gcctcaccct cccaagtagc
3361 tgggactaca ggcgcctgcc agcacgcctg gctaattttt tgtatttta gtagagacag
3421 ggtttcaccg tgttagccag gatggtctcg atctcctgac ctcgtgatcc gcctgcctct
3481 gcctcccaaa gtgctgggat tacaggcgtg agccaccgcg tccggcctct ttttttcttt
3541 tctttttttt gagacaaagt ctcactgtgt cacccagact ggaatgcagt gacacaatct
3601 cggctcactg aaacctctgc cttccaggtt caagctattc tcatgcctca gcctctcaag
3661 tagctgggac tacagatgtg ggccaccatg tctggctaat tttttttttt ttttttttt
3721 tttgtagaga cagggtttcg ccatgttgac gagactggtc tcgaactcct ggcctcaagt
3781 gatctgccgc ctcagcttct caaagtactg ggattatata ggcatgagcc actgagcctg

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3841 gccctgaagc gtttttctca aaggccctca gtgagataaa ttagatttgg
catctcctgt
3901 cctgggccag ggatctctct acaagagccc ctgcccctct gttggaggca
cagttttaga
3961 ataaggagga ggagggagaa gagaaaatgt aaaggaggga gatctttccc
aggccgcacc
4021 atttctgtca ctcacatgga cccaagataa aagaatggcc aaaccctcac
aacccctgat
4081 gtttgaagag ttccaagttg aagggaaaca aagaagtgtt tgatggtgcc
agagaggggc
4141 tgctctccag aaagctaaaa tttaatttct tttttcctct gagttctgta
cttcaaccag
4201 cctacaagct ggcacttgct aacaaatcag aaatatgaca attaatgatt
aaagactgtg
4261 attgcc
```

SEQ ID NO. 42

P30086 - Homo sapiens

Phosphatidylethanolamine binding protein (PEBP)

```
  1 mpvdlskwsg plslqevdeq pqhplhvtya gaavdelgkv ltptqvknrp tsiswdglds
 61 gklytlvltd pdapsrkdpk yrewhhflvv nmkgndissg tvlsdyvgsg ppkgtglhry
121 vwlvyeqdrp lkcdepilsn rsgdhrgkfk vasfrkkyel rapvagtcyq aewddyvpkl
181 yeqlsgk
```

SEQ ID NO. 43

NM_002567

Homo sapiens prostatic binding protein (PBP), mRNA

```
  1 tgggcggcgg ctgaggcgcg tgctctcgcg tggtcgctgg gtctgcgtct
tcccgagcca
 61 gtgtgctgag ctctccgcgt cgcctctgtc gcccgcgcct ggcctaccgc
ggcactcccg
121 gctgcacgct ctgcttggcc tcgccatgcc ggtggacctc agcaagtggt
ccgggccctt
181 gagcctgcaa gaagtggacg agcagccgca gcacccgctg catgtcacct
acgccggggc
241 ggcggtggac gagctgggca aagtgctgac gcccacccag gttaagaata
gacccaccag
301 catttcgtgg gatggtcttg attcagggaa gctctacacc ttggtcctga
cagacccgga
361 tgctcccagc aggaaggatc ccaaatacag agaatggcat catttcctgg
tggtcaacat
421 gaagggcaat gacatcagca gtggcacagt cctctccgat tatgtgggct
cggggcctcc
481 caagggcaca ggcctccacc gctatgtctg gctggtttac gagcaggaca
ggccgctaaa
541 gtgtgacgag cccatcctca gcaaccgatc tggagaccac cgtggcaaat
tcaaggtggc
601 gtccttccgt aaaaagtatg agctcagggc cccggtggct ggcacgtgtt
accaggccga
661 gtgggatgac tatgtgccca aactgtacga gcagctgtct gggaagtagg
gggttagctt
721 ggggacctga actgtcctgg aggccccaag ccatgttccc cagttcagtg
ttgcatgtat
781 aatagatttc tcctcttcct gccccccttg gcatgggtga gacctgacca
gtcagatggt
```

```
 841 agttgagggt gacttttcct gctgcctggc ctttataatt ttactcactc
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 901 atgttttgat caaatttgaa cttcattttg gggggtattt tggtactgtg
atggggtcat
 961 caaattatta atctgaaaat agcaacccag aatgtaaaaa agaaaaaact
gggggggaaaa
1021 agaccaggtc tacagtgata gagcaaagca tcaaagaatc tttaagggag
gtttaaaaaa
1081 aaaaaaaaaa aaaaagattg gttgcctctg cctttgtgat cctgagtcca
gaatggtaca
1141 caatgtgatt ttatggtgat gtcactcacc tagacaacca gaggctggca
ttgaggctaa
1201 cctccaacac agtgcatctc agatgcctca gtaggcatca gtatgtcact
ctggtccctt
1261 taaagagcaa tcctggaaga agcaggaggg agggtggctt tgctgttgtt
gggacatggc
1321 aatctagacc ggtagcagcg ctcgctgaca gcttgggagg aaacctgaga
tctgtgtttt
1381 ttaaattgat cgttcttcat gggggtaaga aaagctggtc tggagttgct
gaatgttgca
1441 ttaattgtgc tgtttgcttg tagttgaata aaaatagaaa cctgaatgaa
gaaaaaaaaa
1501 aaaaaaa
```

SEQ ID NO. 44

P39687 - Homo sapiens

Acidic leucine-rich nuclear phosphoprotein 32 family member A

```
  1 memgrrihle lrnrtpsdvk elvldnsrsn egklegltde feeleflsti nvgltsianl
 61 pklnklkkle lsdnrvsggl evlaekcpnl thlnlsgnki kdlstieplk klenlksldl
121 fncevtnlnd yrenvfkllp qltyldgydr ddkeapdsda egyvegldde eededeeeyd
181 edaqvvedee dedeeeegee edvsgeeeed eegyndgevd deedeeelge eergqkrkre
241 pedegeddd
```

SEQ ID NO. 45

NM_006305

Homo sapiens acidic (leucine-rich) nuclear phosphoprotein 32 family, member A (ANP32A), mRNA

```
  1 cgggtgctgg gggctcgaga accgagcgga gctggttgag ccttcaaagt
cctaaaacgc
 61 gcggccgtgg gttcggggtt tattgattga attccgccgg cgcgggagcc
tctgcagaga
121 gagagcgcga gagatggaga tgggcagacg gattcattta gagctgcgga
acaggacgcc
181 ctctgatgtg aaagaacttg tcctggacaa cagtcggtcg aatgaaggca
aactcgaagg
241 cctcacagat gaatttgaag aactggaatt cttaagtaca atcaacgtag
gcctcacctc
301 aatcgcaaac ttaccaaagt taaacaaact taagaagctt gaactaagcg
ataacagagt
361 ctcaggggge ctggaagtat tggcagaaaa gtgtccgaac ctcacgcatc
taaatttaag
421 tggcaacaaa attaaagacc tcagcacaat agagccactg aaaaagttag
aaaacctcaa
481 gagcttagac cttttcaatt gcgaggtaac caacctgaac gactaccgag
aaaatgtgtt
```

```
 541 caagctcctc ccgcaactca catatctcga cggctatgac cgggacgaca
aggaggcccc
 601 tgactcggat gctgagggct acgtggaggg cctggatgat gaggaggagg
atgaggatga
 661 ggaggagtat gatgaagatg ctcaggtagt ggaagacgag gaggacgagg
atgaggagga
 721 ggaaggtgaa gaggaggacg tgagtggaga ggaggaggag gatgaagaag
gttataacga
 781 tggagaggta gatgacgagg aagatgaaga agagcttggt gaagaagaaa
ggggtcagaa
 841 gcgaaaacga gaacctgaag atgagggaga agatgatgac taagtggaat
aacctatttt
 901 gaaaaattcc tattgtgatt tgactgtttt tacccatatc ccctctcccc
ccccctcca
 961 atcctgcccc ctgaaactta tttttttctg attgtaacgt tgctgtggga
acgagagggg
1021 aagagtgtac tgggggttgc gggggggaggg atggcgggtg ggggtggaat
aaaatactat
1081 ttttactgcc actctttaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaa
```

SEQ ID NO. 46

P17066 - Homo sapiens

Heat shock 70kDa protein

```
  1 mqaprelavg idlgttyscv gvfqqgrvei landqgnrtt psyvaftdte rlvgdaaksq
 61 aalnphntvf dakrligrkf adttvqsdmk hwpfrvvseg gkpkvrvcyr gedktfypee
121 issmvlskmk etaeaylgqp vkhavitvpa yfndsqrqat kdagaiagln vlriinepta
181 aaiaygldrr gagernvlif dlgggtfdvs vlsidagvfe vkatagdthl ggedfdnrlv
241 nhfmeefrrk hgkdlsgnkr alrrlrtace rakrtlssst qatleidslf egvdfytsit
301 rarfeelcsd lfrstlepve kalrdakldk aqihdvvlvg gstripkvqk llqdffngke
361 lnksinpdea vaygaavqaa vlmgdkcekv qdlllldvap lslgletagg vmttliqrna
421 tiptkqtqtf ttysdnqpgv fiqvyegera mtkdnnllgr felsgippap rgvpqievtf
481 didangilsv tatdrstgka nkititndkg rlskeeverm vheaeqykae deaqrdrvaa
541 knsleahvfh vkgslqeesl rdkipeedrr kmqdkcrevl awlehnqlae keeyehqkre
601 leqicrpifs rlyggpgvpg gsscgtqarq gdpstgpiie evd
```

SEQ ID NO. 47

NM_002155

Homo sapiens heat shock 70kDa protein 6 (HSP70B') (HSPA6), mRNA.

```
   1 agagccagcc cggaggagct agaaccttcc ccgcatttct ttcagcagcc
tgagtcagag
  61 gcgggctggc ctggcgtagc cgcccagcct cgcggctcat gccccgatct
gcccgaacct
 121 tctcccgggg tcagcgccgc gccgcgccac ccggctgagt cagcccgggc
gggcgagagg
 181 ctctcaactg ggcgggaagg tgcgggaagg tgcggaaagg ttcgcgaaag
ttcgcggcgg
 241 cgggggtcgg gtgaggcgca aaaggataaa aagcccgtgg aagcggagct
gagcagatcc
 301 gagccgggct ggctgcagag aaaccgcagg gagagcctca ctgctgagcg
cccctcgacg
 361 gcggagcggc agcagcctcc gtggcctcca gcatccgaca agaagcttca
gccatgcagg
 421 ccccacggga gctcgcggtg ggcatcgacc tgggcaccac ctactcgtgc
gtgggcgtgt
```

481 ttcagcaggg ccgcgtggag atcctggcca acgaccaggg caaccgcacc acgcccagct
541 acgtggcctt caccgacacc gagcggctgg tcggggacgc ggccaagagc caggcggccc
601 tgaaccccca caacaccgtg ttcgatgcca agcggctgat cgggcgcaag ttcgcggaca
661 ccacggtgca gtcggacatg aagcactggc ccttccgggt ggtgagcgag ggcggcaagc
721 ccaaggtgcg cgtatgctac cgcggggagg acaagacgtt ctaccccgag gagatctcgt
781 ccatggtgct gagcaagatg aaggagacgg ccgaggcgta cctgggccag cccgtgaagc
841 acgcagtgat caccgtgccc gcctatttca atgactcgca gcgccaggcc accaaggacg
901 cggggccat cgcggggctc aacgtgttgc ggatcatcaa tgagcccacg gcagctgcca
961 tcgcctatgg gctggaccgg cggggcgcgg gagagcgcaa cgtgctcatt tttgacctgg
1021 gtgggggcac cttcgatgtg tcggttctct ccattgacgc tggtgtcttt gaggtgaaag
1081 ccactgctgg agatacccac ctgggaggag aggacttcga caaccggctc gtgaaccact
1141 tcatggaaga attccggcgg aagcatggga aggacctgag cgggaacaag cgtgccctgc
1201 gcaggctgcg cacagcctgt gagcgcgcca agcgcaccct gtcctccagc acccaggcca
1261 ccctggagat agactccctg ttcgagggcg tggacttcta cacgtccatc actcgtgccc
1321 gctttgagga actgtgctca gacctcttcc gcagcaccct ggagccggtg gagaaggccc
1381 tgcgggatgc caagctggac aaggcccaga ttcatgacgt cgtcctggtg gggggctcca
1441 ctcgcatccc caaggtgcag aagttgctgc aggacttctt caacggcaag gagctgaaca
1501 agagcatcaa ccctgatgag gctgtggcct atggggctgc tgtgcaggcg gccgtgttga
1561 tgggggacaa atgtgagaaa gtgcaggatc tcctgctgct ggatgtggct cccctgtctc
1621 tggggctgga gacagcaggt ggggtgatga ccacgctgat ccagaggaac gccactatcc
1681 ccaccaagca gacccagact ttcaccacct actcggacaa ccagcctggg gtcttcatcc
1741 aggtgtatga gggtgagagg gccatgacca aggacaacaa cctgctgggg cgttttgaac
1801 tcagtggcat ccctcctgcc ccacgtggag tcccccagat agaggtgacc tttgacattg
1861 atgctaatgg catcctgagc gtgacagcca ctgacaggag cacaggtaag gctaacaaga
1921 tcaccatcac caatgacaag ggccggctga gcaaggagga ggtggagagg atggttcatg
1981 aagccgagca gtacaaggct gaggatgagg cccagaggga cagagtggct gccaaaaact
2041 cgctggaggc ccatgtcttc catgtgaaag gttctttgca agaggaaagc cttagggaca
2101 agattcccga agaggacagg cgcaaaatgc aagacaagtg tcgggaagtc cttgcctggc
2161 tggagcacaa ccagctggca gagaaggagg agtatgagca tcagaagagg gagctggagc
2221 aaatctgtcg ccccatcttc tccaggctct atgggggcc tggtgtccct gggggcagca

```
2281 gttgtggcac tcaagcccgc cagggggacc ccagcaccgg ccccatcatt
gaggaggttg
2341 attgaatggc ccttcgtgat aagtcagctg tgactgtcag ggctatgcta
tgggccttct
2401 agactgtctt ctatgatcct gcccttcaga gatgaacttt ccctccaaag
ctagaacttt
2461 cttcccagga taactgaagt cttttgactt tttgggggga gggcggttca
tcctcttctg
2521 cttcaaataa aaagtcatta atttattaaa acttgtgtgg cactttaaca
ttgctttcac
2581 ctatattttg tgtactttgt tacttgcatg tatgaatttt gttatgtaaa
atatagttat
2641 agacctaaat aaaaaaaaaa aaaa
```

SEQ ID NO. 48

X51757

Human heat-shock protein HSP70B gene

```
   1 cccgggcggg cgagaggctc tcaactgggc gggaaggtgc gggaaggtgc
ggaaaggttc
  61 gcgaaagttc gcggcggcgg gggtcgggtg aggcgcaaaa ggataaaaag
cccgtggaag
 121 cggagctgag cagatccgag ccgggctggc tgcagagaca ccgcagggag
agcctcactg
 181 ctgagcgccc ctcgacggcg gacgggcagc agcctccgtg gcctccagca
tccgacaaga
 241 agcttcagcc atgcaggccc cacgggagct cgcggtgggc atcgacctgg
gcaccaccta
 301 ctcgtgcgtg ggcgtgtttc agcagggccg cgtggagatc ctggccaacg
accagggcaa
 361 ccgcaccacg cccagctacg tggccttcac cgacaccgag cggctggtcg
gggacgcggc
 421 caagagccag gcggccctga acccccacaa caccgtgttc gatgccaagc
ggctgatcgg
 481 gcgcaagttc gcggacacca cggtgcagtc ggacatgaag cactggccct
tccgggtggt
 541 gagcgagggc ggcaagccca aggtgccggt atcgtaccgc ggggaggaca
agacgttcta
 601 ccccgaggag atctcgtcca tggtgctgag caagatgaag gagacggccg
aggcgtacct
 661 gggccagccc gtgaagcacg cagtgatcac cgtgcccgcc tatttcaatg
actcgcagcg
 721 ccaggccacc aaggacgcgg gggccatcgc ggggctcaac gtgttgcgga
tcatcaatga
 781 gcccacggca gctgccatcg cctatgggct ggaccggcgg ggcgcgggag
agcgcaacgt
 841 gctcattttt gacctgggtg ggggcacctt cgatgtgtcg gttctctcca
ttgacgctgg
 901 tgtctttgag gtgaaagcca ctgctggaga tacccacctg ggaggagagg
acttcgacaa
 961 ccggctcgtg aaccacttca tggaagaatt ccggcggaag catgggaagg
acctgagcgg
1021 gaacaagcgt gccctcggca ggctgcgcac agcctgtgag cgcgccaagc
gcaccctgtc
1081 ctccagcacc caggccaccc tggagataga ctccctgttc gagggcgtgg
acttctacac
1141 gtccatcact cgtgcccgct ttgaggaact gtgctcagac ctcttccgca
gcaccctgga
```

```
1201 gccggtggag aaggccctgc gggatgccaa gctggacaag gcccagattc
atgacgtcgt
1261 cctggtgggg ggctccactc gcatccccaa ggtgcagaag ttgctgcagg
acttcttcaa
1321 cggcaaggag ctgaacaaga gcatcaaccc tgatgaggct gtggcctatg
gggctgctgt
1381 gcaggcggcc gtgttgatgg gggacaaatg tgagaaagtg caggatctcc
tgctgctgga
1441 tgtggctccc ctgtctctgg ggctggagac agcaggtggg gtgatgacca
cgctgatcca
1501 gaggaacgcc actatcccca ccaagcagac ccagactttc accacctact
cggacaacca
1561 gcctggggtc ttcatccagg tgtatgaggg tgagagggcc atgaccaagg
acaacaacct
1621 gctggggcgt tttgaactca gtggcatccc tcctgcccca cgtggagtcc
cccagataga
1681 ggtgaccttt gacattgatg ctaatggcat cctgagcgtg acagccactg
acaggagcac
1741 aggtaaggct aacaagatca ccatcaccaa tgacaagggc cggctgagca
aggaggaggt
1801 ggagaggatg gttcatgaag ccgagcagta caaggctgag gatgaggccc
agagggacag
1861 agtggctgcc aaaaactcgc tggaggccca tgtcttccat gtgaaaggtt
ctttgcaaga
1921 ggaaagcctt agggacaaga ttcccgaaga ggacaggcgc aaaatgcaag
acaagtgtcg
1981 ggaagtcctt gcctggctgg agcacaacca gctggcagag aaggaggagt
atgagcatca
2041 gaagagggag ctggagcaaa tctgtcgccc catcttctcc aggctctatg
gggggcctgg
2101 tgtccctggg ggcagcagtt gtggcactca agcccgccag ggggacccca
gcaccggccc
2161 catcattgag gaggttgatt gaatggccct tcgtgataag tcagctgtga
ctgtcagggc
2221 tatgctatgg gccttctaga ctgtcttcta tgatcctgcc cttcagagat
gaactttccc
2281 tccaaagcta gaactttctt cccaggataa ctgaagtctt ttgacttttt
gcggggaggg
2341 cggttcatcc tcttctgctt caaataaaaa gtcattaatt tattaaaact
tgtgtggcac
2401 tttaacattg ctttcaccta tattttgtgt actttgttac ttgcatgtat
gaattttgtt
2461 atgtaaaata tagttataga cctaaataag ct
```

SEQ ID NO. 49

P14174

macrophage migration inhibitory factor - Homo Sapiens

```
  1 mpmfivntnv prasvpdgfl seltqqlaqa tgkppqyiav hvvpdqlmaf ggssepcalc
 61 slhsigkigg aqnrsyskll cgllaerlri spdrvyinyy dmnaanvgwn nstfa
```

SEQ ID NO. 50

NM_002415 - Homo Sapiens

Homo sapiens macrophage migration inhibitory factor (glycosylation-inhibiting factor) (MIF), mRNA

```
  1 accacagtgg tgtccgagaa gtcaggcacg tagctcagcg gcggccgcgg cgcgtgcgtc
```

```
 61 tgtgcctctg cgcgggtctc ctggtccttc tgccatcatg ccgatgttca tcgtaaacac
121 caacgtgccc cgcgcctccg tgccggacgg gttcctctcc gagctcaccc agcagctggc
181 gcaggccacc ggcaagcccc cccagtacat cgcggtgcac gtggtcccgg accagctcat
241 ggccttcggc ggctccagcg agccgtgcgc gctctgcagc ctgcacagca tcggcaagat
301 cggcggcgcg cagaaccgct cctacagcaa gctgctgtgc ggcctgctgg ccgagcgcct
361 gcgcatcagc ccggacaggg tctacatcaa ctattacgac atgaacgcgg ccaatgtggg
421 ctggaacaac tccaccttcg cctaagagcc gcagggaccc acgctgtctg cgctggctcc
481 acccgggaac ccgccgcacg ctgtgttcta ggcccgccca ccccaacctt ctggtgggga
541 gaaataaacg gtttagagac t
```

SEQ ID NO. 51

L19686

Homo sapiens macrophage migration inhibitory factor (MIF) gene, complete cds

```
   1 ctgcaggaac caatacccat aggctatttg tataaatggg ccatggggcc
tcccagctgg
  61 aggctggctg gtgccacgag ggtcccacag gcatgggtgt ccttcctata
tcacatggcc
 121 ttcactgaga ctggtatatg gattgcacct atcagagacc aaggacagga
cctccctgga
 181 aatctctgag gacctggcct gtgatccagt tgctgccttg tcctcttcct
gctatgtcat
 241 ggcttatctt ctttcaccca ttcattcatt cattcattca ttcagcagta
ttagtcaatg
 301 tctcttgata tgcctggcac ctgctagatg gtccccgagt ttaccattag
tggaaaagac
 361 atttaagaaa ttcaccaagg gctctatgag aggccataca cggtggacct
gactagggtg
 421 tggcttccct gaggagctga agttgcccag aggcccagag aaggggagct
gagcacgttt
 481 gaaccactga acctgctctg gacctcgcct ccttccttcg gtgcctccca
gcatcctatc
 541 ctctttaaag agcaggggtt cagggaagtt ccctggatgg tgattcgcag
gggcagctcc
 601 cctctcacct gccgcatgac taccccgccc catctcaaac acacaagctc
acgcatgcgg
 661 gactggagcc cttgaggaca tgtggcccaa agacaggagg tacaggggct
cagtgcgtgc
 721 agtggaatga actgggcttc atctctggaa gggtaagggg ccatcttccg
ggttcaccgc
 781 cgcatcccca cccccggcac agcgcctcct ggcgactaac atcggtgact
tagtgaaagg
 841 actaagaaag acccgaggcg aggccggaac aggccgattt ctagccgcca
agtggagaac
 901 aggttggagc ggtgcgccgg gcttagcggc ggttgctgga ggaacgggcg
gagtcgccca
 961 gggtcctgcc ctgcgggggt cgagccgagg caggcggtga cttccccact
cggggcggag
1021 ccgcagcctc gcgggggcgg ggcctggcgc cggcggtggc gtcacaaaag
gcgggaccac
1081 agtggtgtcc gagaagtcag gcacgtagct cagcggcggc cgcggcgcgt
gcgtctgtgc
1141 ctctgcgcgg gtctcctggt ccttctgcca tcatgccgat gttcatcgta
aacaccaacg
1201 tgccccgcgc ctccgtgccg gacgggttcc tctccgagct cacccagcag
ctggcgcagg
1261 ccaccggcaa gccccccag gtttgccggg aggggacagg aagaggggg
tgcccaccgg
```

```
1321 acgaggggtt ccgcgctggg agctggggag gcgactcctg aacggagctg
ggggggcggg
1381 cgggggggagg acggtggctc gggcccgaag tggacgttcg gggcccgacg
aggtcgctgg
1441 ggcgggctga ccgcgccctt tcctcgcagt acatcgcggt gcacgtggtc
ccggaccagc
1501 tcatggcctt cggcggctcc agcgagccgt gcgcgctctg cagcctgcac
agcatcggca
1561 agatcggcgg cgcgcagaac cgctcctaca gcaagctgct gtgcggcctg
ctggccgagc
1621 gcctgcgcat cagcccggac aggtacgcgg agtcgcggag gggcggggga
ggggcggcgg
1681 cgcgcggcca ggcccgggac tgagccaccc gctgagtccg gcctcctccc
cccgcagggt
1741 ctacatcaac tattacgaca tgaacgcggc caatgtgggc tggaacaact
ccaccttcgc
1801 ctaagagccg cagggaccca cgctgtctgc gctggctcca cccgggaacc
cgccgcacgc
1861 tgtgttctag gcccgcccac cccaaccttc tggtggggag aaataaacgg
tttagagact
1921 aggagtgcct cggggttcct tggcttgcgg gaggaattgg tgcagagccg
ggacattggg
1981 gagcgaggtc gggaaacggt gttgggggcg ggggtcaggg ccgggttgct
ctcctcgaac
2041 ctgctgttcg ggagcccttt tgtccagcct gtcctcctta cgctcctaac
agaggagccc
2101 cagtgtcttt ccattctatg gcgtacgaag ggatgaggag aagttggcac
tctgccctgg
2161 gctgcag
```

SEQ ID NO. 52

P31949

Calgizzarin - Homo sapiens

1 makissptet erciesliav fqkyagkdgy nytlsktefl sfmntelaaf tknqkdpgvl 61 drmmkkldtn sdgqldfsef lnligglama chdsflkavp sqkrt

SEQ ID NO. 53

NM_005620 and D38583 - Homo sapiens

Homo sapiens S100 calcium binding protein A11 (calgizzarin)(S100A11), mRNA

```
   1 gggcaaggct gggccgggaa gggcgtgggt tgaggagagg ctccagaccc gcacgccgcg
  61 cgcacagagc tctcagcgcc gctcccagcc acagcctccc gcgcctcgct cagctccaac
 121 atggcaaaaa tctccagccc tacagagact gagcggtgca tcgagtccct gattgctgtc
 181 ttccagaagt atgctggaaa ggatggttat aactacactc tctccaagac agagttccta
 241 agcttcatga atacagaact agctgccttc acaaagaacc agaaggaccc tggtgtcctt
 301 gaccgcatga tgaagaaact ggacaccaac agtgatggtc agctagattt ctcagaattt
 361 cttaatctga ttggtggcct agctatggct tgccatgact ccttcctcaa ggctgtccct
 421 tcccagaagc ggacctgagg acccccttggc cctggccttc aaacccaccc cctttccttc
 481 cagcctttct gtcatcatct ccacagccca cccatccccc gagcacacta accacctcat
 541 gcaggcccca cctgccaata gtaataaagc aatgtcactt ttttaaaaca tgaaa
```

SEQ ID NO. 54

P00938 and NP_000356 - Homo sapiens

Triosephosphate isomerase

```
   1 mapsrkffvg gnwkmngrkq slgeligtln aakvpadtev vcapptayid farqkldpki
  61 avaaqncykv tngaftgeis pgmikdcgat wvvlghserr hvfgesdeli gqkvahalae
 121 glgviacige kldereagit ekvvfeqtkv iadnvkdwsk vvlayepvwa igtgktatpq
 181 qaqevheklr gwlksnvsda vaqstriiyg gsvtgatcke lasqpdvdgf lvggaslkpe
 241 fvdiinakq
```

SEQ ID NO. 55

NM_000365

Homo sapiens triosephosphate isomerase 1 (TPI1), mRNA

```
   1 ccttcagcgc ctcggctcca gcgccatggc gccctccagg aagttcttcg
ttgggggaaa
  61 ctggaagatg aacgggcgga agcagagtct gggggagctc atcggcactc
tgaacgcggc
 121 caaggtgccg gccgacaccg aggtggtttg tgctcccccc actgcctata
tcgacttcgc
 181 ccggcagaag ctagatccca agattgctgt ggctgcgcag aactgctaca
aagtgactaa
 241 tggggctttt actggggaga tcagccctgg catgatcaaa gactgcggag
ccacgtgggt
 301 ggtcctgggg cactcagaga gaaggcatgt ctttggggag tcagatgagc
tgattgggca
 361 gaaagtggcc catgctctgg cagagggact cggagtaatc gcctgcattg
gggagaagct
 421 agatgaaagg gaagctggca tcactgagaa ggttgttttc gagcagacaa
aggtcatcgc
 481 agataacgtg aaggactgga gcaaggtcgt cctggcctat gagcctgtgt
gggccattgg
 541 tactggcaag actgcaacac cccaacaggc ccaggaagta cacgagaagc
tccgaggatg
 601 gctgaagtcc aacgtctctg atgcggtggc tcagagcacc cgtatcattt
atggaggctc
 661 tgtgactggg gcaacctgca aggagctggc cagccagcct gatgtggatg
gcttccttgt
 721 gggtggtgct tccctcaagc ccgaattcgt ggacatcatc aatgccaaac
aatgagcccc
 781 atccatcttc cctacccttc ctgccaagcc agggactaag cagcccagaa
gcccagtaac
 841 tgccctttcc ctgcatatgc ttctgatggt gtcatctgct ccttcctgtg
gcctcatcca
 901 aactgtatct tcctttactg tttatatctt caccctgtaa tggttgggac
caggccaatc
 961 ccttctccac ttactataat ggttggaact aaacgtcacc aaggtggctt
ctccttggct
1021 gagagatgga aggcgtggtg ggatttgctc ctgggttccc taggccctag
tgagggcaga
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1141 tgctgccctc tcccatggtg cccgtgcctc tgtgctgtgt atgtgaacca
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1201 ggaataaacc tggcactagg aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaa
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SEQ ID NO. 56

X69723

H.sapiens TPI1 gene for triosephosphate isomerase.

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gttttcactc
 121 aggtagactc cctgggtaca agggtgcctg ctcagcagtc gggcatgagc
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agtgggcgat
 241 ctgggctacg gccaagttgc caccagctag ttccgcttga aaaccacttc
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 301 ggggactcaa gtcgccaagc gagggttccc ctgagcgccg gagctcacag
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ggcggcggca
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 541 ggaggcggag ttccacttcg cggcgctcta tataagtggg cagtggccgc
gactgcgcgc
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 661 tgggggaaac tggaagatga acgggcggaa gcagagtctg ggggagctca
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3601 tggttgggac caggccaatc ccttctccac ttactataat ggttggaact aaacgtcacc
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4921 tgcccatcct tcttttggac ctgtacatca aacccagtac ctaaccgttt gcacctcttg
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SEQ ID NO. 57

ITHU and P01009 - Homo sapiens

α-1-antitrypsin precursor

mpssvswgil llaglcclvp vslaedpqgd aaqktdtshh dqdhptfnki tpnlaefafs
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qellrtlnqp dsqlqlttgn glflseglkl vdkfledvkk lyhseaftvn fgdteeakkq
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SEQ ID NO. 58

NM_000295

Homo sapiens serine (or cysteine) proteinase inhibitor, clade A(alpha-1 antiproteinase, antitrypsin), member 1 (SERPINA1), transcript variant 1, mRNA

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121 aactggggtg accttggtta atattcacca gcagcctccc ccgttgcccc tctggatcca
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SEQ ID NO. 59

K02212

Human alpha-1-antitrypsin gene (S variant), complete cds

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121 ctgctgctca ctcagttcca caggtgggag gaacagcagg gcttagagtg ggggtcattg
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6121 tgaaacatgt attcctcact ggcctatcac ctgaagcctt tgaatttgca acacctgcca
6181 acccctccct caaaagagtt gccctctcta gatccttttg atgtaaggtt tggtgttgag
6241 acttatttca ctaaattctc atacataaac atcactttat gtatgaggca aaatgaggac
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6361 tcctaggtct atctgaagtt aaaagaggtg tcttttcact tcccacctcc tccatctact
6421 ttaaagcagc acaaacccct gctttcaagg agagatgagc gtctctaaag cccctgacag
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8581 aatgccaggg tcctgggggc cccagggcat tctaagccag ctcccactgt cccaggaaaa
8641 cagcataggg gaggggaggt gggaggcaag gccaggggct gcttcctcca ctctgaggct
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8761 aaagtcctgg ctctgctgtg gccttagtgg gggcccaggt ccctctccag ccccagtctc
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9361 cttccaaacc ttcactcacc cctggtgatg cccaccttcc cctctctcca ggcaaatggg
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9661 tcctggaaaa tgaagacaga aggtgattcc ccaacctgag ggtgaccaag aagctgccca

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9781 gaaccccaca tccctgggtc actgctactc tgtataaact tggcttccag aatgaggcca
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11461 tgaatgattt cagctaaagt gacacttatt ttggaaaact aaaggcgacc aatgaacaac

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tctatccccc
12001 ccgaggtcaa gttcaacaaa ccctttgtct tcttaatgat tgaacaaaat
accaagtctc
12061 ccctcttcat gggaaaagtg gtgaatccca cccaaaaata actgcctctc
gctcctcaac
12121 ccctcccctc catccctggc cccctccctg gatgacatta aagaagggtt
gagctggtcc
12181 ctgcctgcat gtgatctgta aatccctggg atgttttctc tg
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SEQ ID NO. 60

gi/125294, P12277 - Homo sapiens
Creatine kinase, B chain (B-CK)

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vdnpghpyim tvgcvagdee syevfkdlfd piiedrhggy kpsdehktdl npdnlqggdd
ldpnyvlssr vrtgrsirgf clpphcsrge rraieklave alssldgdla gryyalksmt
eaeqqqlidd hflfdkpvsp lllasgmard wpdargiwhn dnktflvwvn eedhlrvism
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SEQ ID NO. 61

NM_001823 Homo sapiens creatine kinase, brain (CKB), mRNA Creatine kinase, B chain (B-CK)

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121 tcccggccga ggacgagttc cccgacctga gcgcccacaa caaccacatg gccaaggtgc
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841 gcaccggcct cacccagatt gaaactctct tcaagtctaa ggactatgag ttcatgtgga
901 accctcacct gggctacatc ctcacctgcc catccaacct gggcaccggg ctgcgggcag
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1141 tggacggagt gaagctgctc atcgagatgg agcagcggct ggagcagggc
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1321 cccttagcct tgctgtagag acttccgtca cccttggtag agtttatttt
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1381 aagatactgc tgatgctgaa ataaactagg gttttggcct gcctgcgtct g
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SEQ ID NO. 62

X15334

Human gene for creatine kinase B (EC 2.7.3.2).

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ctgcgaagag
 121 ggcccagggt tggggtctgg aaactccgag gctgcacttg ccagcggcct
cttaaggcca
 181 cagcgtcccc gtggtttctg gctcgcagcc ccccgagacc caggacttgt
ccaaggtcag
 241 ggcaccgcgg gtgcccccgg gctgggccgc agcagactgc gcttcccgcg
cgccttcgct
 301 ttgcaccagg atcgcccagg aaatgcctgc gggcaccttg aggaaggtcg
gcggctccgg
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cggccgagga
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1201 cgagttcccc gacctgagcg cccacaacaa ccacatggcc aaggtgctga
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2761 ctccaggggc agggctccta cccccactgt gggggggcggg tcgggctgtc
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2941 ctcctgggca tggcagggag cagcacctca gggacttggg aagttccttt
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3001 cggcctgggg ctttttttctg ggtatgccct gagaccagcc ctcccgcagg
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caggtgccag
3181 ggacggggca ggcccagacc ccagggcccc agcagggatg tgggtgcccc
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SEQ ID NO. 63

P14618 - Homo sapiens

Pyruvate kinase M1 or M2 isozyme

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fasfirkasd vhevrkvlge kgknikiisk ienhegvrrf deileasdgi mvargdlgie
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SEQ ID NO. 64

X56494

H.sapiens M gene for M1-type and M2-type pyruvate kinase

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SEQ ID NO. 65

Q01995 - Homo sapiens

Transgelin

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SEQ ID NO. 66

D84342

Homo sapiens DNA for SM22 alpha, complete cds

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SEQ ID NO. 67

Q14103 - human

Heterogeneous nuclear ribonucleoprotein

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gevvdctlkl dpitgrsrgf gfvlfkeses vdkvmdqkeh klngkvidpk rakamktkep
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SEQ ID NO. 68

AF026126

Homo sapiens heterogeneous nuclear ribonucleoprotein D (HNRPD) gene, complete cds

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13801 ttactgaata attttaacta tttattcttc taaggataca gcttgtctct ggattttcca
13861 gtcttaattt tatattttat taatctattt taatgcttgc ttttcccatt tatagacgtt
13921 gtagcagtaa ttgcaagaag ttcttgagct gaattcctgt tgtgacaact tcctataatt
13981 acagtagata acttttctt ttagtcgtat ataacttttc tataacttgt gatggacaag
14041 agatatgctt atccaataaa ataagcttaa atattagatg ctcttgggtc aaaatgtcct
14101 tttaccaaat tgacctttt atgagttctt tgggtaaata ctttaaagct ttttatattt
14161 taaagaatac ttgtaaaagc atatcacatc ttaaaccagt ggtgcacatg tggatttaca
14221 gctcatggac tctactgttc agctttaatt tataaaacat atcacacatt taatgttata
14281 cagtatttac atatagtgga acatagggat aactcagttt tatgtaaatt tttgttaagt
14341 gttgtagcct gcccagagtg acttctattt tttcttcttt gtctccaggt ggtgaagcag
14401 tattttccaa tttgaagatt catttgaagg tggctcctgc cacctgctaa tagcagttca
14461 aactaaattt tttgtatcaa gtccctgaat ggaagtatga cgttgggtcc ctctgaagtt
14521 taattctgag ttctcattaa aagaaatttg ctttcattgt tttatttctt aattgctatg
14581 cttcagaatc aatttgtgtt ttatgccctt tcccccagta ttgtagagca agtcttgtgt
14641 taaaagccca gtgtgacagt gtcatgatgt agtagtgtct tactggtttt ttaataaatc
14701 cttttgtata aaaatgtatt ggctctttta tcatcagaat aggaaaaaat tgtcatggat

```
14761 tcaagttatt aaaagcataa gtttggaaga caggcttgcc gaaattgagg
acatgattaa
14821 aattgcagtg aagtttgaaa tgtttttagc aaaatctaat ttttgccata
atgtgtcctc
14881 cctgtccaaa ttgggaatga cttaatgtca atttgtttgt tggttgtttt
aataatactt
14941 ccttatgtag ccattaagat ttatatgaat attttcccca atg
```

Claims

1. A method for detecting at least one endometrial marker associated with an endometrium phase in a human subject, wherein the at least one endometrial marker comprises WAP four-disulfide core domain 2 polypeptide (WFDC2), the method comprising:

   (a) in a biological sample obtained from the subject, the biological sample being derived from endometrial tissue or blood, measuring the amount of the at least one endometrial marker in the biological sample; and,
   (b) comparing the measured amount with a standard amount, wherein a difference between the measured amount and the standard amount is indicative of the presence of the endometrium phase.

2. The method of claim 1, wherein the standard amount is an amount of the at least one marker in non-receptive uterine tissue and a higher measured amount relative to the standard amount is indicative of uterine receptivity.

3. The method of claim 1, wherein the non-receptive uterine tissue is in a proliferative phase.

4. The method according to any one of claims 1 to 3, wherein step (a) comprises:

   (a) contacting the biological sample with at least one binding agent, such as an antibody, that specifically binds to the at least one endometrial marker or a part thereof; and
   (b) measuring the amount of the at least one endometrial cancer marker that binds to the at least one binding agent.

5. Use of a diagnostic composition for detecting an endometrium phase in a method for determining endometrial phase in humans, the composition comprising an agent that is capable of binding to at least one endometrial marker listed in Table 1, wherein the at least one marker comprises WFDC2.

6. The method according to any one of claims 1 to 4, wherein the at least one endometrial marker comprises, in addition to WFDC2, one or more of: clusterin, mucin 5B, leucine aminopeptidase 3 (LAP3), macrophage capping protein (CAP-G), pyruvate kinase M1/M2 (PK), chaperonin 10 (Cpn10) or α-1-antitrypsin (ATT).

7. Use of a set of endometrial markers in a method for determining endometrial phase in humans, the set of endometrial markers comprising WAP four-disulfide core domain 2 polypeptide (WFDC2) and at least 1, 2, 3, 4, or 5 of the other markers listed in Table 1.

8. The use of claim 7, further comprising 2 to 16 of the markers listed in Table 2.

9. Use of a kit for conducting the method as claimed in any one of claims 1 to 3 or 5, comprising at least one binding agent that specifically binds to at least one endometrial marker listed in Table 1, wherein the at least one marker includes WAP four-disulfide core domain 2 polypeptide (WFDC2), and at least one of instructions, compounds, reagents, and containers for using the kit, wherein the binding agent comprises: a detectable substance; a substance that binds directly or indirectly to a detectable substance.

10. The use of claim 9, wherein the binding agent comprises antibodies or fragments of antibodies that bind specifically to an epitope to at least one endometrial marker.

11. The method according to any one of claims 1-4 or 6, wherein the endometrial tissue is diseased endometrial tissue.

Patentansprüche

1. Verfahren zum Bestimmen von mindestens einem endometrialen Marker, der mit einer endometrialen Phase in einem menschlichen Subjekt assoziiert ist, wobei der mindestens eine endometriale Marker WAP Vier-Disulfid-Kerndomänenpolypeptid 2 (WFDC2) umfasst, das Verfahren umfassend:

   (a) in einer biologischen Probe, die von dem Subjekt erhalten wurde, wobei die biologische Probe aus endometrialem Gewebe oder Blut abgeleitet ist, Messen der Menge von dem mindestens einen endometrialen Marker in der biologischen Probe; und
   (b) Vergleichen der gemessenen Menge mit einer Standard-Menge, wobei ein Unterschied zwischen der gemessenen Menge und der Standard-Menge auf die Anwesenheit der endometrialen Phase hinweist.

2. Verfahren nach Anspruch 1, wobei die Standard-Menge eine Menge des mindestens einen Markers in nicht-empfänglichem Gebärmuttergewebe ist und eine höhere gemessene Menge im Vergleich zur Standard-Menge auf Gebärmutter-Empfänglichkeit hinweist.

3. Verfahren nach Anspruch 1, wobei das nicht-empfängliche Gebärmuttergewebe in einer Proliferationsphase ist.

4. Verfahren nach einem der Ansprüche 1 bis 3, wobei Schritt (a) umfasst:

   (a) Kontaktieren der biologischen Probe mit mindestens einem Bindungs-Agens, wie einem Antikörper, der spezifisch an den mindestens einen endometrialen Marker oder einen Teil davon bindet; und
   (b) Messen der Menge des mindestens einen endometrialen Krebs-Markers, der an das mindestens eine Bindungs-Agens bindet.

5. Verwendung einer diagnostischen Zusammensetzung zum Bestimmen einer endometrialen Phase in einem Verfahren zum Bestimmen der endometrialen Phase beim Menschen, wobei die Zusammensetzung ein Mittel umfasst, das in der Lage ist an mindestens einen in Tabelle 1 aufgelisteten endometrialen Marker zu binden, wobei der mindestens eine Marker WFDC2 umfasst.

6. Verfahren nach einem der Ansprüche 1 bis 4, wobei der mindestens eine endometriale Marker, zusätzlich zu WFDC2, einen oder mehrere aus Clusterin, Mucin 5B, Leucin Aminopeptidase 3 (LAP3), Makrophagen-Capping Protein (CAP-G), Pyruvatkinase M1/M2 (PK), Chaperonin 10 (Cpn10) oder α-1-Antitrypsin (ATT) umfasst.

7. Verwendung eines Sets von endometrialen Markern in einem Verfahren zum Bestimmen der endometrialen Phase beim Menschen, wobei das Set von endometrialen Markern WAP Vier-Disulfid-Kerndomänenpolypeptid 2 (WFDC2) und mindestens 1, 2, 3, 4 oder 5 von den anderen in Tabelle 1 aufgeführten Markern umfasst.

8. Verwendung nach Anspruch 7, ferner umfassend 2 bis 16 der in Tabelle 2 aufgeführten Marker.

9. Verwendung eines Kits zum Durchführen des Verfahrens nach einem der Ansprüche 1 bis 3 oder 5, umfassend mindestens ein Bindungs-Agens, das spezifisch an mindestens einen in Tabelle 1 aufgeführten endometrialen Marker bindet, wobei der mindestens eine Marker WAP Vier-Disulfid-Kerndomänenpolypeptid 2 (WFDC2) und mindestens einen aus Instruktionen, Verbindungen, Reagenzien und Behälter zum Verwenden des Kits enthält, wobei das Bindungs-Agens eine nachweisbare Substanz, eine Substanz, die direkt oder indirekt an die nachweisbare Substanz bindet, umfasst.

10. Verwendung nach Anspruch 9, wobei das Bindungs-Agens Antikörper oder Fragmente von Antikörpern umfasst, die spezifisch an ein Epitop des mindestens einen endometrialen Markers bindet.

11. Verfahren nach einem der Ansprüche 1-4 oder 6, wobei das endometriale Gewebe erkranktes endometriales Gewebe ist.

Revendications

1. Procédé de détection d'au moins un marqueur de l'endomètre associé à une phase de l'endomètre chez un sujet humain, dans lequel l'au moins un marqueur de l'endomètre comprend le polypeptide de la protéine WAP à 2 domaines centraux à 4 ponts disulfure (WFDC2), le procédé comprenant les étapes consistant à :

   (a) mesurer, dans un échantillon biologique obtenu du sujet, l'échantillon biologique étant dérivé du tissu de l'endomètre ou du sang, la quantité de l'au moins un marqueur de l'endomètre dans l'échantillon biologique ; et,
   (b) comparer la quantité mesurée à une quantité standard, dans lequel une différence entre la quantité mesurée et la quantité standard indique la présence de la phase de l'endomètre.

2. Procédé selon la revendication 1, dans lequel la quantité standard est une quantité de l'au moins un marqueur dans un tissu utérin non réceptif et une quantité mesurée supérieure par rapport à la quantité standard indique une réceptivité utérine.

3. Procédé selon la revendication 1, dans lequel le tissu utérin non réceptif est dans une phase proliférative.

4. Procédé selon l'une quelconque des revendications 1 à 3, dans lequel l'étape (a) comprend les étapes consistant à :

   (a) mettre en contact l'échantillon biologique avec au moins un agent de liaison, tel qu'un anticorps, qui se lie de façon spécifique à l'au moins un marqueur de l'endomètre ou à une partie de celui-ci ; et
   (b) mesurer la quantité de l'au moins un marqueur du cancer de l'endomètre qui se lie à l'au moins un agent de liaison.

5. Utilisation d'une composition de diagnostic pour détecter une phase de l'endomètre dans un procédé pour déterminer une phase de l'endomètre chez des humains, la composition comprenant un agent qui est capable de se lier à au moins un marqueur de l'endomètre répertorié au tableau 1, dans laquelle l'au moins un marqueur comprend WFDC2.

6. Procédé selon l'une quelconque des revendications 1 à 4, dans lequel l'au moins un marqueur de l'endomètre comprend, en plus de WFDC2, un ou plusieurs parmi : la clusterine, la mucine 5B, la leucine aminopeptidase 3 (LAP3), une protéine de coiffe des macrophages (CAP-G), la pyruvate kinase M1/M2 (PK), la chaperonine 10 (Cpn10) ou l'α-1-antitrypsine (ATT).

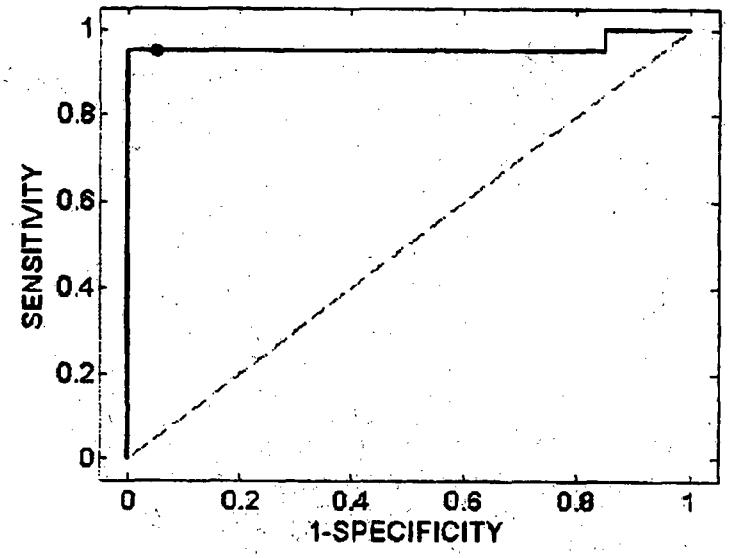
7. Utilisation d'un ensemble de marqueurs de l'endomètre dans un procédé de détermination de la phase de l'endomètre chez les humains, l'ensemble de marqueurs de l'endomètre comprenant le polypeptide de la protéine WAP à 2 domaines centraux à 4 ponts disulfure (WFDC2) et au moins 1, 2, 3, 4, ou 5 des autres marqueurs répertoriés au Tableau 1.

8. Utilisation selon la revendication 7, comprenant en outre 2 à 16 des marqueurs répertoriés au Tableau 2.

9. Utilisation d'un nécessaire pour mener le procédé tel que revendiqué dans l'une quelconque des revendications 1 à 3 ou 5, comprenant au moins un agent de liaison qui se lie spécifiquement à au moins un marqueur de l'endomètre répertorié au Tableau 1, dans laquelle l'au moins un marqueur inclut le polypeptide de la protéine WAP à 2 domaines centraux à 4 ponts disulfure (WFDC2), et au moins un parmi des instructions, des composés, des réactifs, et des conteneurs pour utiliser le nécessaire, dans laquelle l'agent de liaison comprend : une substance détectable ; une substance qui se lie directement ou indirectement à une substance détectable.

10. Utilisation selon la revendication 9, dans laquelle l'agent de liaison comprend des anticorps ou des fragments d'anticorps qui se lient spécifiquement à un épitope à au moins un marqueur de l'endomètre.

11. Procédé selon l'une quelconque des revendications 1 à 4 ou 6, dans lequel le tissu de l'endomètre est un tissu de l'endomètre malade.



3-marker panel

Sensitivity	0.95	19/20
Specificity	0.95	19/20
AUC	0.958	
PV	0.95	38/40
PPV	0.95	19/20

FIGURE 1

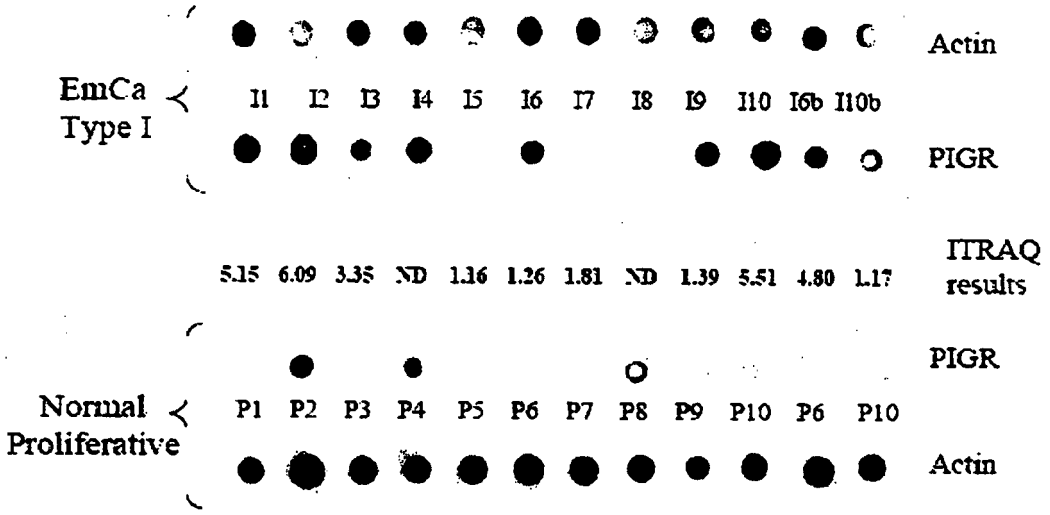

Actin
EmCa Type I
I1 I2 I3 I4 I5 I6 I7 I8 I9 I10 I6b I10b
PIGR
5.15 6.09 3.35 ND 1.16 1.26 1.81 ND 1.39 5.51 4.80 1.17
ITRAQ results
PIGR
Normal Proliferative
P1 P2 P3 P4 P5 P6 P7 P8 P9 P10 P6 P10
Actin

FIGURE 2

Figure 3

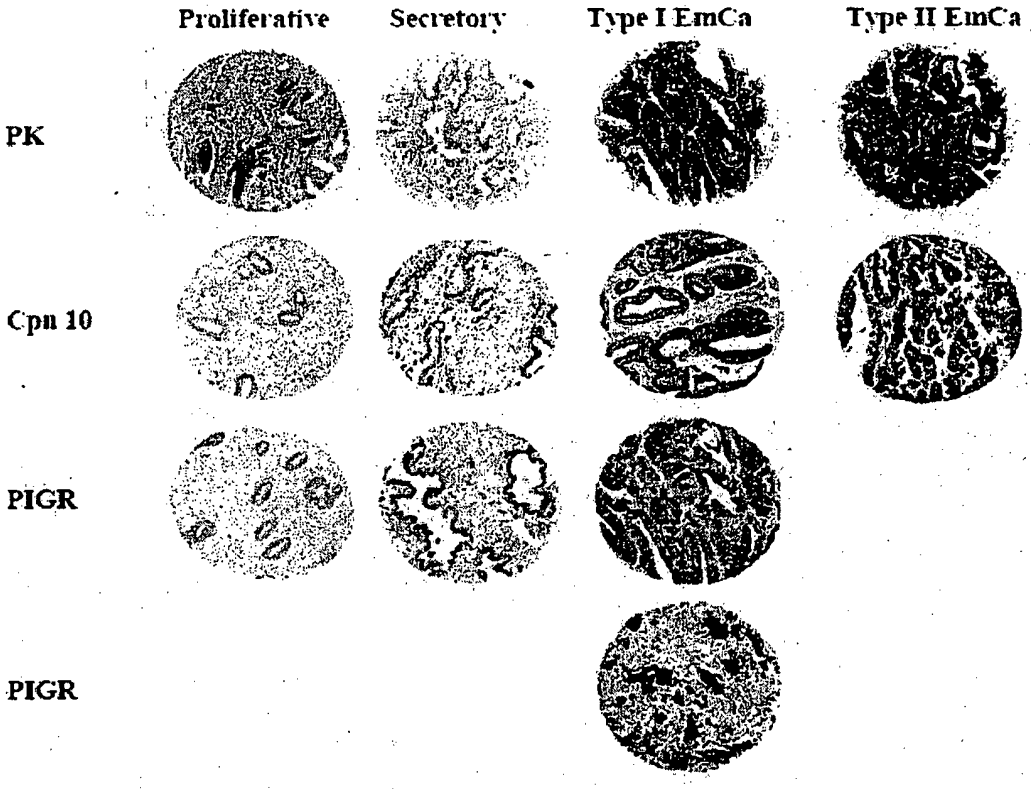


FIGURE 3

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摘要(译)

描述了用于检测受试者中的子宫内膜疾病或子宫内膜期的方法，包括测量来自受试者的样品中的编码标志物的子宫内膜标志物或多核苷酸。本发明还提供了子宫内膜疾病的定位或成像方法，以及用于实施本发明方法的试剂盒。本发明还涉及使用子宫内膜标志物，编码标志物的多核苷酸和/或标志物的结合剂的子宫内膜疾病的治疗应用。