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(54) Title: BREAST ENDOTHELIAL CELL EXPRESSION PATTERNS

(57) Abstract: To gain a better understanding of breast tumor angiogenesis, breast endothelial cells (ECs) were isolated and evaluated for gene expression patterns. When transcripts from breast ECs derived from normal and malignant breast tissues were compared, genes that were specifically elevated in tumor-associated breast endothelium were revealed. These results confirm that neoplastic and normal endothelium in human breast are distinct at the molecular level, and have significant implications for the development of anti-angiogenic therapies in the future.

WO 2004/091383 A2

BREAST ENDOTHELIAL CELL EXPRESSION PATTERNS

[01] This application claims priority to provisional U.S. Application Ser. No. 60/458,960, filed April 1, 2003.

TECHNICAL FIELD OF THE INVENTION

[02] This invention is related to the area of angiogenesis and anti-angiogenesis. In particular, it relates to genes which are characteristically expressed in breast tumor endothelial cells.

BACKGROUND OF THE INVENTION

[03] To date, global gene expression profiles from endothelial cell-specific populations is limited to normal and tumorigenic colon tissue [St Croix, 2000]. There is a need in the art for analysis of endothelial cells from other tissue, so that diagnostic and therapeutic agents for non-colonic tumors can be developed.

SUMMARY OF THE INVENTION

[04] According to one embodiment of the invention a method is provided to aid in diagnosing breast tumors. An expression product (protein or RNA) of at least one gene in a first breast tissue sample suspected of being neoplastic is detected. The at least one gene is selected from the group consisting of hypothetical protein DKFZp434G171; heat shock 70kDa protein 1A; jagged 1 (Alagille syndrome); cyclin-dependent kinase 3; 6-phosphogluconolactonase; likely homolog of rat and mouse retinoid-inducible serine carboxypeptidase; plasmalemma vesicle associated protein; NADH:ubiquinone oxidoreductase MLRQ subunit homolog; HIF-1 responsive RTP801; ribosomal protein L27; secreted protein, acidic, cysteine-rich (osteonectin); hexokinase 1; ribosomal protein L13a; collagen, type IV, alpha 1; insulin-like growth

factor binding protein 7; collagen, type III, alpha 1 (Ehlers-Danlos syndrome type IV, autosomal dominant); heat shock 10kDa protein 1 (chaperonin 10); calcium channel, voltage-dependent, alpha 1H subunit; CD9 antigen (p24); TEM17; TEM13, Thy-1 cell surface antigen; Tax interaction protein 1; dysferlin, limb girdle muscular dystrophy 2B (autosomal recessive); hypothetical protein MGC34648; putative translation initiation factor; insulin-like growth factor binding protein 4; matrix metalloproteinase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase); heterogeneous nuclear ribonucleoprotein R; bHLH factor Hes4; collagen, type VI, alpha 2; T-box 2; glyceraldehyde-3-phosphate dehydrogenase; G protein-coupled receptor 4; collagen, type I, alpha 1; ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1); ribosomal protein, large, P1; TEM10, COL1A2 involved in tissue remodeling; heat shock 70kDa protein 8; KIAA0152 gene product; Ca2+-promoted Ras inactivator; serine/arginine repetitive matrix 2; hypoxia-inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor); benzodiazapine receptor (peripheral); ectonucleoside triphosphate diphosphohydrolase 1; heparan sulfate proteoglycan 2 (perlecan); fibromodulin; hairy/enhancer-of-split related with YRPW motif 1; collagen, type V, alpha 3; hairy/enhancer-of-split related with YRPW motif-like; hypothetical protein MGC2731; amino-terminal enhancer of split; mitogen-activated protein kinase 9; regulator of G-protein signalling 5; prothymosin, alpha (gene sequence 28); tubulin, beta, 2; protease, serine, 23; hypothetical protein FLJ20898; calpain 1, (mu/I) large subunit; interferon, alpha-inducible protein (clone IFI-6-16); ESTs, Weakly similar to T25031 hypothetical protein T20D3.3 - Caenorhabditis elegans [C.elegans]; major histocompatibility complex, class I, C; hypoxia up-regulated 1; complement component 4B; prefoldin 2; cytoskeleton-associated protein 1; Rho GTPase activating protein 4; Homo sapiens clone FLC1492 PRO3121 mRNA, complete cds; transducin-like enhancer of split 2 (E(sp1) homolog, Drosophila); ribosomal protein L37; hypothetical protein MGC4677; ESTs, Highly similar to MT1A_HUMAN METALLOTHIONEIN-IA (MT-1A) [H.sapiens]; TEM11, nidogen (enactin); guanine nucleotide binding protein (G protein), gamma 5; matrix Gla protein; heat shock 105kD; GNAS complex locus; Homo sapiens cDNA FLJ11658 fis, clone HEMBA1004577; H19, imprinted maternally expressed

untranslated mR NA; protein tyrosine phosphatase type IVA, member 3; snail homolog 1 (Drosophila); integrin-binding sialoprotein (bone sialoprotein, bone sialoprotein II); tissue inhibitor of metalloproteinase 1 (erythroid potentiating activity, collagenase inhibitor); peptidylprolyl isomerase B (cyclophilin B); MARCKS-like protein; FAST kinase; protease, serine, 11 (IGF binding); beta-2-microglobulin; delta sleep inducing peptide, immunoreactor; collagen, type IV, alpha 2; immediate early response 3; cadherin 5, type 2, VE-cadherin (vascular epithelium); RGC32 protein; guanylate cyclase 1, soluble, beta 3; major histocompatibility complex, class I, B; ribonuclease, RNase A family, 1 (pancreatic); collagen, type XVIII, alpha 1; v-jun sarcoma virus 17 oncogene homolog (avian); Homo sapiens mRNA; cDNA DKFZp686G1610 (from clone DKFZp686G1610); nucleolin; lectin, galactoside-binding, soluble, 3 binding protein; Lysosomal-associated multispanning membrane protein-5; ribosomal protein S16; guanine nucleotide binding protein (G protein), gamma 12; serine (or cysteine) proteinase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1; biglycan; DnaJ (Hsp40) homolog, subfamily B, member 1; tumor rejection antigen (gp96) 1; interferon, alpha-inducible protein (clo ne IFI-15K); solute carrier family 21 (prostaglandin transporter), member 2; CD74 antigen (invariant polypeptide of major histocompatibility complex, class II antigen-associated); serum/glucocorticoid regulated kinase; mitogen-activated protein kinase; receptor (calcitonin) activity modifying protein 3; sema domain, immunoglobulin domain (Ig); benzodiazapine receptor (peripheral) – mitochondrial; C1 domain-containing phosphatase & tensin-like; and Notch homolog 3 (Drosophila). Expression of the at least one gene in the first breast tissue sample is compared to expression of the at least one gene in a second breast tissue sample which is normal. Increased expression of the at least one gene in the first breast endothelial tissue sample relative to the second tissue sample identifies the first breast tissue sample as likely to be neoplastic.

[05] According to another embodiment of the invention a method is provided of treating a breast tumor. Cells of the breast tumor are contacted with an antibody. The antibody

specifically binds to an extracellular epitope of a protein selected from the group consisting of benzodiazapine receptor (peripheral); cadherin 5, type 2, VE-cadherin (vascular epithelium); calcium channel, voltage-dependent, alpha 1H subunit; CD74 antigen (invariant polypeptide of major histocompatibility complex, class II antigen-associated); CD9 antigen (p24); dysferlin, limb girdle muscular dystrophy 2B (autosomal recessive); ectonucleoside triphosphate diphosphohydrolase 1; G protein-coupled receptor 4; hypothetical protein FLJ20898; hypoxia up-regulated 1; immediate early response 3; interferon, alpha-inducible protein (clone IFI-6-16); jagged 1 (Alagille syndrome); KIAA0152 gene product; Lysosomal-associated multispanning membrane protein-5; major histocompatibility complex, class I, B; major histocompatibility complex, class I, C; NADH:ubiquinone oxidoreductase MLRQ subunit homolog; Notch homolog 3 (Drosophila); plasmalemma vesicle associated protein; solute carrier family 21 (prostaglandin transporter), member 2; TEM13, Thy-1 cell surface antigen; receptor (calcitonin) activity modifying protein 3; sema domain, immunoglobulin domain (Ig); benzodiazapine receptor (peripheral) – mitochondrial; and TEM17. Immune destruction of cells of the breast tumor is thereby triggered.

[06] According to still another embodiment of the invention a method is provided for identifying a test compound as a potential anti-cancer or anti-breast tumor drug. A test compound is contacted with a cell which expresses at least one gene selected from the group consisting of: hypothetical protein DKFZp434G171; heat shock 70kDa protein 1A; jagged 1 (Alagille syndrome); cyclin-dependent kinase 3; 6-phosphogluconolactonase; likely homolog of rat and mouse retinoid-inducible serine carboxypeptidase; plasmalemma vesicle associated protein; NADH:ubiquinone oxidoreductase MLRQ subunit homolog; HIF-1 responsive RTP801; ribosomal protein L27; secreted protein, acidic, cysteine-rich (osteonectin); hexokinase 1; ribosomal protein L13a; collagen, type IV, alpha 1; insulin-like growth factor binding protein 7; collagen, type III, alpha 1 (Ehlers-Danlos syndrome type IV, autosomal dominant); heat shock 10kDa protein 1 (chaperonin 10); calcium channel, voltage-

dependent, alpha 1H subunit; CD9 antigen (p24); TEM17; TEM13, Thy-1 cell surface antigen; Tax interaction protein 1; dysferlin, limb girdle muscular dystrophy 2B (autosomal recessive); hypothetical protein MGC34648; putative translation initiation factor; insulin-like growth factor binding protein 4; matrix metalloproteinase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase); heterogeneous nuclear ribonucleoprotein R; bHLH factor Hes4; collagen, type VI, alpha 2; T-box 2; glyceraldehyde-3-phosphate dehydrogenase; G protein-coupled receptor 4; collagen, type I, alpha 1; ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1); ribosomal protein, large, P1; TEM10, COL1A2 involved in tissue remodeling; heat shock 70kDa protein 8; KIAA0152 gene product; Ca2+-promoted Ras inactivator; serine/arginine repetitive matrix 2; hypoxia-inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor); benzodiazapine receptor (peripheral); ectonucleoside triphosphate diphosphohydrolase 1; heparan sulfate proteoglycan 2 (perlecan); fibromodulin; hairy/enhancer-of-split related with YRPW motif 1; collagen, type V, alpha 3; hairy/enhancer-of-split related with YRPW motif-like; hypothetical protein MGC2731; amino-terminal enhancer of split; mitogen-activated protein kinase 9; regulator of G-protein signalling 5; prothymosin, alpha (gene sequence 28); tubulin, beta, 2; protease, serine, 23; hypothetical protein FLJ20898; calpain 1, (mu/I) large subunit; interferon, alpha-inducible protein (clone IFI-6-16); ESTs, Weakly similar to T25031 hypothetical protein T20D3.3 - Caenorhabditis elegans [C.elegans]; major histocompatibility complex, class I, C; hypoxia up-regulated 1; complement component 4B; prefoldin 2; cytoskeleton-associated protein 1; Rho GTPase activating protein 4; Homo sapiens clone FLC1492 PRO3121 mRNA, complete cds; transducin-like enhancer of split 2 (E(sp1) homolog, Drosophila); ribosomal protein L37; hypothetical protein MGC4677; ESTs, Highly similar to MT1A_HUMAN METALLOTHIONEIN-IA (MT-1A) [H.sapiens]; TEM11, nidogen (enactin); guanine nucleotide binding protein (G protein), gamma 5; matrix Gla protein; heat shock 105kD; GNAS complex locus; Homo sapiens cDNA FLJ11658 fis, clone HEMBA1004577; H19, imprinted maternally expressed untranslated mR NA; protein tyrosine phosphatase type IVA, member 3; snail homolog 1 (Drosophila); integrin-binding sialoprotein (bone sialoprotein, bone

sialoprotein II); tissue inhibitor of metalloproteinase 1 (erythroid potentiating activity, collagenase inhibitor); peptidylprolyl isomerase B (cyclophilin B); MARCKS-like protein; FAST kinase; protease, serine, 11 (IGF binding); beta-2-microglobulin; delta sleep inducing peptide, immunoreactor; collagen, type IV, alpha 2; immediate early response 3; cadherin 5, type 2, VE-cadherin (vascular epithelium); RGC32 protein; guanylate cyclase 1, soluble, beta 3; major histocompatibility complex, class I, B; ribonuclease, RNase A family, 1 (pancreatic); collagen, type XVIII, alpha 1; v-jun sarcoma virus 17 oncogene homolog (avian); Homo sapiens mRNA; cDNA DKFZp686G1610 (from clone DKFZp686G1610); nucleolin; lectin, galactoside-binding, soluble, 3 binding protein; Lysosomal-associated multispanning membrane protein-5; ribosomal protein S16; guanine nucleotide binding protein (G protein), gamma 12; serine (or cysteine) proteinase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1; biglycan; DnaJ (Hsp40) homolog, subfamily B, member 1; tumor rejection antigen (gp96) 1; interferon, alpha-inducible protein (clo ne IFI-15K); solute carrier family 21 (prostaglandin transporter), member 2; CD74 antigen (invariant polypeptide of major histocompatibility complex, class II antigen-associated); serum/glucocorticoid regulated kinase; mitogen-activated protein kinase; receptor (calcitonin) activity modifying protein 3; sema domain, immunoglobulin domain (Ig); benzodiazapine receptor (peripheral) – mitochondrial; C1 domain-containing phosphatase & tensin-like; and Notch homolog 3 (Drosophila). An expression product of the at least one gene is monitored. The test compound is identified as a potential anti-cancer drug if it decreases the expression of the at least one gene.

[07] Still another embodiment of the invention is a method to induce an immune response to a breast tumor. A protein or nucleic acid encoding a protein is administered to a mammal, preferably a human. The protein is selected from the group consisting of: hypothetical protein DKFZp434G171; heat shock 70kDa protein 1A; jagged 1 (Alagille syndrome); cyclin-dependent kinase 3; 6-phosphogluconolactonase; likely homolog of rat and mouse retinoid-inducible serine carboxypeptidase; plasmalemma

vesicle associated protein; NADH:ubiquinone oxidoreductase MLRQ subunit homolog; HIF-1 responsive RTP801; ribosomal protein L27; secreted protein, acidic, cysteine-rich (osteonectin); hexokinase 1; ribosomal protein L13a; collagen, type IV, alpha 1; insulin-like growth factor binding protein 7; collagen, type III, alpha 1 (Ehlers-Danlos syndrome type IV, autosomal dominant); heat shock 10kDa protein 1 (chaperonin 10); calcium channel, voltage-dependent, alpha 1H subunit; CD9 antigen (p24); TEM17; TEM13, Thy-1 cell surface antigen; Tax interaction protein 1; dysferlin, limb girdle muscular dystrophy 2B (autosomal recessive); hypothetical protein MGC34648; putative translation initiation factor; insulin-like growth factor binding protein 4; matrix metalloproteinase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase); heterogeneous nuclear ribonucleoprotein R; bHLH factor Hes4; collagen, type VI, alpha 2; T-box 2; glyceraldehyde-3-phosphate dehydrogenase; G protein-coupled receptor 4; collagen, type I, alpha 1; ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1); ribosomal protein, large, P1; TEM10, COL1A2 involved in tissue remodeling; heat shock 70kDa protein 8; KIAA0152 gene product; Ca2+-promoted Ras inactivator; serine/arginine repetitive matrix 2; hypoxia-inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor); benzodiazapine receptor (peripheral); ectonucleoside triphosphate diphosphohydrolase 1; heparan sulfate proteoglycan 2 (perlecan); fibromodulin; hairy/enhancer-of-split related with YRPW motif 1; collagen, type V, alpha 3; hairy/enhancer-of-split related with YRPW motif-like; hypothetical protein MGC2731; amino-terminal enhancer of split; mitogen-activated protein kinase 9; regulator of G-protein signalling 5; prothymosin, alpha (gene sequence 28); tubulin, beta, 2; protease, serine, 23; hypothetical protein FLJ20898; calpain 1, (mu/I) large subunit; interferon, alpha-inducible protein (clone IFI-6-16); ESTs, Weakly similar to T25031 hypothetical protein T20D3.3 - Caenorhabditis elegans [C.elegans]; major histocompatibility complex, class I, C; hypoxia up-regulated 1; complement component 4B; prefoldin 2; cytoskeleton-associated protein 1; Rho GTPase activating protein 4; Homo sapiens clone FLC1492 PRO3121 mRNA, complete cds; transducin-like enhancer of split 2 (E(sp1) homolog, Drosophila); ribosomal protein L37; hypothetical protein MGC4677; ESTs, Highly similar to MT1A_HUMAN

METALLOTHIONEIN-IA (MT-1A) [H.sapiens]; TEM11, nidogen (enactin); guanine nucleotide binding protein (G protein), gamma 5; matrix Gla protein; heat shock 105kD; GNAS complex locus; Homo sapiens cDNA FLJ11658 fis, clone HEMBA1004577; H19, imprinted maternally expressed untranslated mR NA; protein tyrosine phosphatase type IVA, member 3; snail homolog 1 (Drosophila); integrin-binding sialoprotein (bone sialoprotein, bone sialoprotein II); tissue inhibitor of metalloproteinase 1 (erythroid potentiating activity, collagenase inhibitor); peptidylprolyl isomerase B (cyclophilin B); MARCKS-like protein; FAST kinase; protease, serine, 11 (IGF binding); beta-2-microglobulin; delta sleep inducing peptide, immunoreactor; collagen, type IV, alpha 2; immediate early response 3; cadherin 5, type 2, VE-cadherin (vascular epithelium); RGC32 protein; guanylate cyclase 1, soluble, beta 3; major histocompatibility complex, class I, B; ribonuclease, RNase A family, 1 (pancreatic); collagen, type XVIII, alpha 1; v-jun sarcoma virus 17 oncogene homolog (avian); Homo sapiens mRNA; cDNA DKFZp686G1610 (from clone DKFZp686G1610); nucleolin; lectin, galactoside-binding, soluble, 3 binding protein; Lysosomal-associated multispanning membrane protein-5; ribosomal protein S16; guanine nucleotide binding protein (G protein), gamma 12; serine (or cysteine) proteinase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1; biglycan; DnaJ (Hsp40) homolog, subfamily B, member 1; tumor rejection antigen (gp96) 1; interferon, alpha-inducible protein (clo ne IFI-15K); solute carrier family 21 (prostaglandin transporter), member 2; CD74 antigen (invariant polypeptide of major histocompatibility complex, class II antigen-associated); serum/glucocorticoid regulated kinase; mitogen-activated protein kinase; receptor (calcitonin) activity modifying protein 3; sema domain, immunoglobulin domain (Ig); benzodiazapine receptor (peripheral) – mitochondrial; C1 domain-containing phosphatase & tensin-like; and Notch homolog 3 (Drosophila). An immune response to the protein is thereby induced.

[08] The present invention thus provides the art with methods of diagnosing and treating breast tumors.

DETAILED DESCRIPTION OF THE INVENTION

[09] Using SAGE (Serial Analysis of Gene Expression) profiling, the present inventors were able to identify previously unrecognized, angiogenesis-specific markers that discriminate between non-proliferative and pathologic endothelial cells. In addition, a set of previously identified angiogenesis-specific markers from other tumor types (colon and/or brain) were found to be expressed in breast tumor endothelium as well. We identified 111 human genes that were expressed at significantly higher levels in breast tumor endothelium than in normal breast endothelium. See Table1. Additional such genes which can be used similarly to the 11 human genes are shown in Table 2. We have named these markers BEMs (breast tumor endothelial markers). BEMs that are expressed in both colon and breast tumor epithelium are identified in Table 3. BEMs that are expressed in both brain and breast tumor epithelium are identified in Table 4. BEMs that are expressed in each of brain, colon, and breast tumor epithelium are identified in Table 5.

Table 1—111 Breast Markers

Unigene ID	*Function*	*OMIMID*	*Protein*
Hs.8728	hypothetical protein DKFZp434G171		CAB61365
Hs.8997	heat shock 70kDa protein 1A	140550	NP_005336
Hs.91143	jagged 1 (Alagille syndrome)	601920	NP_000205
Hs.100009	cyclin-dependent kinase 3	123828	
Hs.100071	6-phosphogluconolactonase	604951	NP_036220
Hs.106747	likely homolog of rat and mouse retinoid-inducible serine carboxypeptidase		NP_067639
Hs.107125	plasmalemma vesicle associated protein		NP_112600
Hs.110024	NADH:ubiquinone oxidoreductase MLRQ subunit homolog		NP_064527
Hs.111244	HIF-1 responsive RTP801		NP_061931
Hs.111611	ribosomal protein L27	607526	NP_000979
Hs.111779	secreted protein, acidic, cysteine-rich (osteonectin)	182120	NP_003109
Hs.118625	hexokinase 1	142600	NP_277035
Hs.119122	ribosomal protein L13a		
Hs.119129	collagen, type IV, alpha 1	120130	NP_001836
Hs.119206	insulin-like growth factor binding protein 7	602867	NP_001544
Hs.119571	collagen, type III, alpha 1 (Ehlers-Danlos syndrome type IV, autosomal dominant)	120180	NP_000081
Hs.1197	heat shock 10kDa protein 1 (chaperonin 10)	600141	NP_002148
Hs.122359	calcium channel, voltage-dependent, alpha 1H subunit		NP_066921
Hs.1244	CD9 antigen (p24)	143030	NP_001760
Hs.125036	TEM17	606826	NP_065138
Hs.125359	TEM13, Thy-1 cell surface antigen	188230	NP_006279
Hs.12956	Tax interaction protein 1		NP_055419
Hs.143897	dysferlin, limb girdle muscular dystrophy 2B (autosomal recessive)	603009	NP_003485
Hs.146360	hypothetical protein MGC34648		NP_689873
Hs.150580	putative translation initiation factor		NP_005792
Hs.1516	insulin-like growth factor binding protein 4	146733	NP_001543
Hs.151738	matrix metalloproteinase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase)	120361	NP_004985
Hs.15265	heterogeneous nuclear ribonucleoprotein R	607201	NP_005817
Hs.154029	bHLH factor Hes4		NP_066993
Hs.159263	collagen, type VI, alpha 2	120240	NP_001840
Hs.168357	T-box 2	600747	NP_005985
Hs.169476	glyceraldehyde-3-phosphate dehydrogenase	138400	NP_002037
Hs.17170	G protein-coupled receptor 4	600551	NP_005273
Hs.172928	collagen, type I, alpha 1	120150	NP_000079
Hs.173737	ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1)	602048	

Unigene ID	Function	OMIMID	Protein
Hs.177592	ribosomal protein, large, P1	180520	
Hs.179573	TEM10, COL1A2 involved in tissue remodeling	120160	NP_000080
Hs.180414	heat shock 70kDa protein 8	600816	NP_006588
Hs.181418	KIAA0152 gene product		NP_055545
Hs.184367	Ca2+-promoted Ras inactivator		BAA25464
Hs.197114	serine/arginine repetitive matrix 2	606032	NP_057417
Hs.197540	hypoxia-inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor)	603348	NP_001521
Hs.202	benzodiazapine receptor (peripheral)	109610	NP_000705
Hs.205353	ectonucleoside triphosphate diphosphohydrolase 1	601752	NP_001767
Hs.211573	heparan sulfate proteoglycan 2 (perlecan)	142461	NP_005520
Hs.230	Fibromodulin	600245	NP_002014
Hs.234434	hairy/enhancer-of-split related with YRPW motif 1	602953	NP_036390
Hs.235368	collagen, type V, alpha 3	120216	NP_056534
Hs.23823	hairy/enhancer-of-split related with YRPW motif-like		NP_055386
Hs.240170	hypothetical protein MGC2731		NP_076973
Hs.244	amino-terminal enhancer of split	600188	
Hs.246857	mitogen-activated protein kinase 9	602896	NP_620708
Hs.24950	regulator of G-protein signalling 5	603276	NP_003608
Hs.250655	prothymosin, alpha (gene sequence 28)	188390	NP_002814
Hs.251653	tubulin, beta, 2	602660	NP_006079
Hs.25338	protease, serine, 23		
Hs.25549	hypothetical protein FLJ20898		NP_078876
Hs.2575	calpain 1, (mu/I) large subunit	114220	NP_005177
Hs.265827	interferon, alpha-inducible protein (clone IFI-6-16)	147572	NP_075011
Hs.267200	ESTs, Weakly similar to T25031 hypothetical protein T20D3.3 - Caenorhabditis elegans [C.elegans]		
Hs.277477	major histocompatibility complex, class I, C	142840	NP_002108
Hs.277704	hypoxia up-regulated 1	601746	NP_006380
Hs.278625	complement component 4B	120820	NP_000583
Hs.298229	prefoldin 2		NP_036526
Hs.31053	cytoskeleton-associated protein 1	601303	NP_001272
Hs.3109	Rho GTPase activating protein 4	300023	NP_001657
Hs.327412	Homo sapiens clone FLC1492 PRO3121 mRNA, complete cds		
Hs.332173	transducin-like enhancer of split 2 (E(sp1) homolog, Drosophila)	601041	NP_003251
Hs.337445	ribosomal protein L37	604181	NP_000988
Hs.337986	hypothetical protein MGC4677		NP_443103
Hs.353882	ESTs, Highly similar to MT1A_HUMAN METALLOTHIONEIN-IA (MT-1A) [H.sapiens]		
Hs.356624	TEM11, nidogen (enactin)	131390	NP_002499
Hs.356668	guanine nucleotide binding protein (G protein), gamma 5	600874	NP_005265
Hs.365706	matrix Gla protein	154870	NP_000891

Unigene ID	Function	OMIMID	Protein
Hs.36927	heat shock 105Kd		NP_006635
Hs.374523	GNAS complex locus	139320	NP_536350
Hs.380824	Homo sapiens cDNA FLJ11658 fis, clone HEMBA1004577		
Hs.406410	H19, imprinted maternally expressed untranslated mRNA	103280	BAB71280
Hs.43666	protein tyrosine phosphatase type IVA, member 3	606449	NP_116000
Hs.48029	snail homolog 1 (Drosophila)	604238	NP_005976
Hs.49215	integrin-binding sialoprotein (bone sialoprotein, bone sialoprotein II)	147563	NP_004958
Hs.5831	tissue inhibitor of metalloproteinase 1 (erythroid potentiating activity, collagenase inhibitor)	305370	NP_003245
Hs.699	peptidylprolyl isomerase B (cyclophilin B)	123841	NP_000933
Hs.75061	MARCKS-like protein	602940	NP_075385
Hs.75087	FAST kinase	606965	NP_079372
Hs.75111	protease, serine, 11 (IGF binding)	602194	NP_002766
Hs.75415	beta-2-microglobulin	109700	NP_004039
Hs.75450	delta sleep inducing peptide, immunoreactor	602960	
Hs.75617	collagen, type IV, alpha 2	120090	NP_001837
Hs.76095	immediate early response 3	602996	NP_434702
Hs.76206	cadherin 5, type 2, VE-cadherin (vascular epithelium)	601120	NP_001786
Hs.76640	RGC32 protein		
Hs.77890	guanylate cyclase 1, soluble, beta 3	139397	NP_000848
Hs.77961	major histocompatibility complex, class I, B	142830	NP_005505
Hs.78224	ribonuclease, RNase A family, 1 (pancreatic)	180440	AAH05324
Hs.78409	collagen, type XVIII, alpha 1	120328	NP_085059
Hs.78465	v-jun sarcoma virus 17 oncogene homolog (avian)	165160	NP_002219
Hs.7869	Homo sapiens mRNA; cDNA DKFZp686G1610 (from clone DKFZp686G1610)		
Hs.79110	Nucleolin	164035	NP_005372
Hs.79339	lectin, galactoside-binding, soluble, 3 binding protein	600626	NP_005558
Hs.79356	Lysosomal-associated multispanning membrane protein-5	601476	NP_006753
Hs.80617	ribosomal protein S16	603675	
Hs.8107	guanine nucleotide binding protein (G protein), gamma 12		
Hs.82085	serine (or cysteine) proteinase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1	173360	NP_000593
Hs.821	Biglycan	301870	NP_001702
Hs.82646	DnaJ (Hsp40) homolog, subfamily B, member 1	604572	NP_006136
Hs.82689	tumor rejection antigen (gp96) 1	191175	NP_003290
Hs.833	interferon, alpha-inducible protein (clone IFI-15K)	147571	NP_005092

Unigene ID	Function	OMIMID	Protein
Hs.83974	solute carrier family 21 (prostaglandin transporter), member 2	601460	NP_005621
Hs.84298	CD74 antigen (invariant polypeptide of major histocompatibility complex, class II antigen-associated)	142790	NP_004346
Hs.8546	Notch homolog 3 (Drosophila)	600276	NP_000426

Table 2—Additional Tumor Endothelial Markers in Breast

Unigene ID	Function	OMIMID	Protein
Hs.296323	serum/glucocorticoid regulated kinase	602958	NP_005618
Hs.246857	mitogen-activated protein kinase	602896	NP_620708
Hs.25691	receptor (calcitonin) activity modifying protein 3	605155	NP_005847
Hs.9598	sema domain, immunoglobulin domain (Ig)	---	BAB21836
Hs.202	benzodiazapine receptor (peripheral) – mitochondrial	109610	NP_000715
Hs.6147	C1 domain-containing phosphatase & tensin-like	---	NP_056134

Table 3—Markers in Colon and Breast Tumor Epithelium

Unigene ID	*Function*	*OMIMID*	*Protein*
Hs.8997	heat shock 70kDa protein 1A	140550	NP_005336
Hs.110024	NADH:ubiquinone oxidoreductase MLRQ subunit homolog		NP_064527
Hs.111779	secreted protein, acidic, cysteine-rich (osteonectin)	182120	NP_003109
Hs.119129	collagen, type IV, alpha 1	120130	NP_001836
Hs.119206	insulin-like growth factor binding protein 7	602867	NP_001544
Hs.119571	collagen, type III, alpha 1 (Ehlers-Danlos syndrome type IV, autosomal dominant)	120180	NP_000081
Hs.1197	heat shock 10kDa protein 1 (chaperonin 10)	600141	NP_002148
Hs.125036	TEM17	606826	NP_065138
Hs.125359	TEM13, Thy-1 cell surface antigen	188230	NP_006279
Hs.151738	matrix metalloproteinase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase)	120361	NP_004985
Hs.159263	collagen, type VI, alpha 2	120240	NP_001840
Hs.168357	T-box 2	600747	NP_005985
Hs.172928	collagen, type I, alpha 1	120150	NP_000079
Hs.179573	TEM10, COL1A2 involved in tissue remodeling	120160	NP_000080
Hs.230	Fibromodulin	600245	NP_002014
Hs.23823	hairy/enhancer-of-split related with YRPW motif-like		NP_055386
Hs.24950	regulator of G-protein signalling 5	603276	NP_003608
Hs.265827	interferon, alpha-inducible protein (clone IFI-6-16)	147572	NP_075011
Hs.327412	Homo sapiens clone FLC1492 PRO3121 mRNA, complete cds		
Hs.337986	hypothetical protein MGC4677		NP_443103
Hs.356624	TEM11, nidogen (enactin)	131390	NP_002499
Hs.36927	heat shock 105kD		NP_006635
Hs.43666	protein tyrosine phosphatase type IVA, member 3	606449	NP_116000
Hs.5831	tissue inhibitor of metalloproteinase 1 (erythroid potentiating activity, collagenase inhibitor)	305370	NP_003245
Hs.699	peptidylprolyl isomerase B (cyclophilin B)	123841	NP_000933
Hs.75617	collagen, type IV, alpha 2	120090	NP_001837
Hs.77890	guanylate cyclase 1, soluble, beta 3	139397	NP_000848
Hs.78409	collagen, type XVIII, alpha 1	120328	NP_085059
Hs.78465	v-jun sarcoma virus 17 oncogene homolog (avian)	165160	NP_002219
Hs.821	Biglycan	301870	NP_001702
Hs.82646	DnaJ (Hsp40) homolog, subfamily B, member 1	604572	NP_006136
Hs.8546	Notch homolog 3 (Drosophila)	600276	NP_000426

Table 4—Markers in Brain and Breast Tumor Epithelium

Unigene ID	*Function*	*OMIMID*	*Protein*
Hs.107125	plasmalemma vesicle associated protein		NP_112600
Hs.111611	ribosomal protein L27	607526	NP_000979
Hs.111779	Secreted protein, acidic, cysteine-rich (osteonectin)	182120	NP_003109
Hs.119129	Collagen, type IV, alpha 1	120130	NP_001836
Hs.119571	Collagen, type III, alpha 1 (Ehlers-Danlos syndrome type IV, autosomal dominant)	120180	NP_000081
Hs.125359	TEM13, Thy-1 cell surface antigen	188230	NP_006279
Hs.143897	Dysferlin, limb girdle muscular dystrophy 2B (autosomal recessive)	603009	NP_003485
Hs.151738	matrix metalloproteinase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase)	120361	NP_004985
Hs.159263	Collagen, type VI, alpha 2	120240	NP_001840
Hs.172928	Collagen, type I, alpha 1	120150	NP_000079
Hs.179573	TEM10, COL1A2 involved in tissue remodeling	120160	NP_000080
Hs.211573	Heparan sulfate proteoglycan 2 (perlecan)	142461	NP_005520
Hs.277477	major histocompatibility complex, class I, C	142840	NP_002108
Hs.327412	Homo sapiens clone FLC1492 PRO3121 mRNA, complete cds		
Hs.332173	transducin-like enhancer of split 2 (E(sp1) homolog, Drosophila)	601041	NP_003251
Hs.337986	hypothetical protein MGC4677		NP_443103
Hs.365706	matrix Gla protein	154870	NP_000891
Hs.75061	MARCKS-like protein	602940	NP_075385
Hs.75111	Protease, serine, 11 (IGF binding)	602194	NP_002766
Hs.75617	collagen, type IV, alpha 2	120090	NP_001837
Hs.77961	major histocompatibility complex, class I, B	142830	NP_005505
Hs.79356	Lysosomal-associated multispanning membrane protein-5	601476	NP_006753
Hs.82085	serine (or cysteine) proteinase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1	173360	NP_000593
Hs.821	Biglycan	301870	NP_001702

Table 5—Breast, Brain, and Colon Tumor Endothelial Markers

Unigene ID	*Function*	*OMIMID*	*Protein*
Hs.111779	secreted protein, acidic, cysteine-rich (osteonectin)	182120	NP_003109
Hs.119129	collagen, type IV, alpha 1	120130	NP_001836
Hs.119571	collagen, type III, alpha 1 (Ehlers-Danlos syndrome type IV, autosomal dominant)	120180	NP_000081
Hs.125359	TEM13, Thy-1 cell surface antigen	188230	NP_006279
Hs.151738	matrix metalloproteinase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase)	120361	NP_004985
Hs.159263	collagen, type VI, alpha 2	120240	NP_001840
Hs.172928	collagen, type I, alpha 1	120150	NP_000079
Hs.179573	TEM10, COL1A2 involved in tissue remodeling	120160	NP_000080
Hs.327412	Homo sapiens clone FLC1492 PRO3121 mRNA, complete cds		
Hs.337986	hypothetical protein MGC4677		NP_443103
Hs.75617	collagen, type IV, alpha 2	120090	NP_001837
Hs.821	biglycan	301870	NP_001702

[10] Endothelial cells (ECs) represent only a minor fraction of the total cells within normal or tumor tissues, and only those EC transcripts expressed at the highest levels would be expected to be represented in libraries constructed from unfractionated tissues. The genes described in the current study should therefore provide a valuable resource for basic and clinical studies of human breast angiogenesis in the future.

[11] Isolated and purified nucleic acids, according to the present invention are those which are not linked to those genes to which they are linked in the human genome. Moreover, they are not present in a mixture such as a library containing a multitude of distinct sequences from distinct genes. They may be, however, linked to other genes such as vector sequences or sequences of other genes to which they are not naturally adjacent.

[12] The nucleic acids may represent either the sense or the anti-sense strand. Nucleic acids and proteins although disclosed herein with sequence particularity, may be derived from a single individual. Allelic variants which occur in the population of humans are included within the scope of such nucleic acids and proteins. Those of skill in the art are well able to identify allelic variants as being the same gene or protein. Given a nucleic acid, one of ordinary skill in the art can readily determine an open reading frame present, and consequently the sequence of a polypeptide encoded by the open reading frame and, using techniques well known in the art, express such protein in a suitable host. Proteins comprising such polypeptides can be the naturally occurring proteins, fusion proteins comprising exogenous sequences from other genes from humans or other species, epitope tagged polypeptides, etc. Isolated and purified proteins are not in a cell, and are separated from the normal cellular constituents, such as nucleic acids, lipids, etc. Typically the protein is purified to such an extent that it comprises the predominant species of protein in the composition, such as greater than 50, 60 70, 80, 90, or even 95% of the proteins present.

[13] Using the proteins according to the invention, one of ordinary skill in the art can readily generate antibodies which specifically bind to the proteins. Such antibodies can be monoclonal or polyclonal. They can be chimeric, humanized, or totally human. Any functional fragment or derivative of an antibody can be used including Fab, Fab', Fab2, Fab'2, and single chain variable regions. So long as the fragment or derivative retains specificity of binding for the endothelial marker protein it can be used. Antibodies can be tested for specificity of binding by comparing binding to appropriate antigen to binding to irrelevant antigen or antigen mixture under a given set of conditions. If the antibody binds to the appropriate antigen at least 2, 5, 7, and preferably 10 times more than to irrelevant antigen or antigen mixture then it is considered to be specific.

[14] Techniques for making such partially to fully human antibodies are known in the art and any such techniques can be used. According to one particularly preferred embodiment, fully human antibody sequences are made in a transgenic mouse which has been engineered to express human heavy and light chain antibody genes. Multiple strains of such transgenic mice have been made which can produce different classes of antibodies. B cells from transgenic mice which are producing a desirable antibody can be fused to make hybridoma cell lines for continuous production of the desired antibody. See for example, Nina D. Russel, Jose R. F. Corvalan, Michael L. Gallo, C. Geoffrey Davis, Liise-Anne Pirofski. Production of Protective Human Antipneumococcal Antibodies by Transgenic Mice with Human Immunoglobulin Loci *Infection and Immunity* April 2000, p. 1820-1826; Michael L. Gallo, Vladimir E. Ivanov, Aya Jakobovits, and C. Geoffrey Davis. The human immunoglobulin loci introduced into mice: V (D) and J gene segment usage similar to that of adult humans *European Journal of Immunology* 30: 534-540, 2000; Larry L. Green. Antibody engineering via genetic engineering of the mouse: XenoMouse strains are a vehicle for the facile generation of therapeutic human monoclonal antibodies *Journal of Immunological Methods 231* 11-23, 1999; Yang X-D, Corvalan JRF, Wang P, Roy

CM-N and Davis CG. Fully Human Anti-interleukin-8 Monoclonal Antibodies: Potential Therapeutics for the Treatment of Inflammatory Disease States. *Journal of Leukocyte Biology* Vol. 66, pp401-410 (1999); Yang X-D, Jia X-C, Corvalan JRF, Wang P, CG Davis and Jakobovits A. Eradication of Established Tumors by a Fully Human Monoclonal Antibody to the Epidermal Growth Factor Receptor without Concomitant Chemotherapy. *Cancer Research* Vol. 59, Number 6, pp1236-1243 (1999) ; Jakobovits A. Production and selection of antigen-specific fully human monoclonal antibodies from mice engineered with human Ig loci. *Advanced Drug Delivery Reviews* Vol. 31, pp: 33-42 (1998); Green L and Jakobovits A. Regulation of B cell development by variable gene complexity in mice reconstituted with human immunoglobulin yeast artificial chromosomes. *J. Exp. Med.* Vol. 188, Number 3, pp: 483-495 (1998); Jakobovits A. The long-awaited magic bullets: therapeutic human monoclonal antibodies from transgenic mice. *Exp. Opin. Invest. Drugs* Vol. 7(4), pp : 607-614 (1998) ; Tsuda H, Maynard-Currie K, Reid L, Yoshida T, Edamura K, Maeda N, Smithies O, Jakobovits A. Inactivation of Mouse HPRT locus by a 203-bp retrotransposon insertion and a 55-kb gene-targeted deletion: establishment of new HPRT-Deficient mouse embryonic sBEM cell lines. *Genomics* Vol. 42, pp: 413-421 (1997) ; Sherman-Gold, R. Monoclonal Antibodies: The Evolution from '80s Magic Bullets To Mature, Mainstream Applications as Clinical Therapeutics. *Genetic Engineering* News Vol. 17, Number 14 (August 1997); Mendez M, Green L, Corvalan J, Jia X-C, Maynard-Currie C, Yang X-d, Gallo M, Louie D, Lee D, Erickson K, Luna J, Roy C, Abderrahim H, Kirschenbaum F, Noguchi M, Smith D, Fukushima A, Hales J, Finer M, Davis C, Zsebo K, Jakobovits A. Functional transplant of megabase human immunoglobulin loci recapitulates human antibody response in mice. *Nature Genetics* Vol. 15, pp: 146-156 (1997); Jakobovits A. Mice engineered with human immunoglobulin YACs: A new technology for production of fully human antibodies for autoimmunity therapy. *Weir's Handbook of Experimental Immunology, The Integrated Immune System* Vol. IV, pp: 194.1-194.7 (1996) ; Jakobovits A. Production of fully human antibodies by transgenic mice. *Current Opinion in Biotechnology* Vol. 6, No. 5, pp: 561-566 (1995) ; Mendez M, Abderrahim H, Noguchi M, David N, Hardy M, Green L, Tsuda H, Yoast S, Maynard-Currie C,

Garza D, BEMmill R, Jakobovits A, Klapholz S. Analysis of the structural integrity of YACs comprising human immunoglobulin genes in yeast and in embryonic sBEM cells. *Genomics* Vol. 26, pp: 294-307 (1995); Jakobovits A. YAC Vectors: Humanizing the mouse genome. *Current Biology* Vol. 4, No. 8, pp: 761-763 (1994); Arbones M, Ord D, Ley K, Ratech H, Maynard-Curry K, Otten G, Capon D, Tedder T. Lymphocyte homing and leukocyte rolling and migration are impaired in L-selectin-deficient mice. *Immunity* Vol. 1, No. 4, pp: 247-260 (1994); Green L, Hardy M, Maynard-Curry K, Tsuda H, Louie D, Mendez M, Abderrahim H, Noguchi M, Smith D, Zeng Y, et. al. Antigen-specific human monoclonal antibodies from mice engineered with human Ig heavy and light chain YACs. *Nature Genetics* Vol. 7, No. 1, pp: 13-21 (1994); Jakobovits A, Moore A, Green L, Vergara G, Maynard-Curry K, Austin H, Klapholz S. Germ-line transmission and expression of a human-derived yeast artificial chromosome. *Nature* Vol. 362, No. 6417, pp: 255-258 (1993) ; Jakobovits A, Vergara G, Kennedy J, Hales J, McGuinness R, Casentini-Borocz D, Brenner D, Otten G. Analysis of homozygous mutant chimeric mice: deletion of the immunoglobulin heavy-chain joining region blocks B-cell development and antibody production. *Proceedings of the National Academy of Sciences USA* Vol. 90, No. 6, pp: 2551-2555 (1993); Kucherlapati et al., U.S. Patent 6,l075,181.

[15] Antibodies can also be made using phage display techniques. Such techniques can be used to isolate an initial antibody or to generate variants with altered specificity or avidity characteristics. Single chain Fv can also be used as is convenient. They can be made from vaccinated transgenic mice, if desired. Antibodies can be produced in cell culture, in phage, or in various animals, including but not limited to cows, rabbits, goats, mice, rats, hamsters, guinea pigs, sheep, dogs, cats, monkeys, chimpanzees, apes.

[16] Antibodies can be labeled with a detectable moiety such as a radioactive atom, a chromophore, a fluorophore, or the like. Such labeled antibodies can be used for diagnostic techniques, either *in vivo*, or in an isolated test sample. Antibodies can also

be conjugated, for example, to a pharmaceutical agent, such as chemotherapeutic drug or a toxin. They can be linked to a cytokine, to a ligand, to another antibody. Suitable agents for coupling to antibodies to achieve an anti-tumor effect include cytokines, such as interleukin 2 (IL-2) and Tumor Necrosis Factor (TNF); photosensitizers, for use in photodynamic therapy, including aluminum (III) phthalocyanine tetrasulfonate, hematoporphyrin, and phthalocyanine; radionuclides, such as iodine-131 (^{131}I), yttrium-90 (^{90}Y), bismuth-212 (^{212}Bi), bismuth-213 (^{213}Bi), technetium-99m (^{99m}Tc), rhenium-186 (^{186}Re), and rhenium-188 (^{188}Re); antibiotics, such as doxorubicin, adriamycin, daunorubicin, methotrexate, daunomycin, neocarzinostatin, and carboplatin; bacterial, plant, and other toxins, such as diphtheria toxin, pseudomonas exotoxin A, staphylococcal enterotoxin A, abrin-A toxin, ricin A (deglycosylated ricin A and native ricin A), TGF-alpha toxin, cytotoxin from chinese cobra (naja naja atra), and gelonin (a plant toxin); ribosome inactivating proteins from plants, bacteria and fungi, such as restrictocin (a ribosome inactivating protein produced by *Aspergillus restrictus*), saporin (a ribosome inactivating protein from *Saponaria officinalis*), and RNase; tyrosine kinase inhibitors; ly207702 (a difluorinated purine nucleoside); liposomes containing antitumor agents (*e.g.*, antisense oligonucleotides, plasmids which encode for toxins, methotrexate, etc.); and other antibodies or antibody fragments, such as F(ab).

[17] Those of skill in the art will readily understand and be able to make such antibody derivatives, as they are well known in the art. The antibodies may be cytotoxic on their own, or they may be used to deliver cytotoxic agents to particular locations in the body. The antibodies can be administered to individuals in need thereof as a form of passive immunization.

[18] Characterization of extracellular regions for the cell surface and secreted proteins from the protein sequence is based on the prediction of signal sequence, transmembrane domains and functional domains. Antibodies are preferably

specifically immunoreactive with membrane associated proteins, particularly to extracellular domains of such proteins or to secreted proteins. Such targets are readily accessible to antibodies, which typically do not have access to the interior of cells or nuclei. However, in some applications, antibodies directed to intracellular proteins may be useful as well. Moreover, for diagnostic purposes, an intracellular protein may be an equally good target since cell lysates may be used rather than a whole cell assay.

[19] Computer programs can be used to identify extracellular domains of proteins whose sequences are known. Such programs include SMART software (Schultz et al., Proc. Natl. Acad. Sci. USA *95:* 5857-5864, 1998) and Pfam software (BaBEMan et al., Nucleic acids Res. *28:* 263-266, 2000) as well as PSORTII. Typically such programs identify transmembrane domains; the extracellular domains are identified as immediately adjacent to the transmembrane domains. Prediction of extracellular regions and the signal cleavage sites are only approximate. It may have a margin of error + or – 5 residues. Signal sequence can be predicted using three different methods (Nielsen et al, *Protein Engineering* 10: 1-6 ,1997, Jagla et. al, Bioinformatics 16: 245-250 , 2000, Nakai, K and Horton, P. Trends in Biochem. Sci. 24:34-35, 1999) for greater accuracy. Similarly transmembrane (TM) domains can be identified by multiple prediction methods. (Pasquier, et. al, Protein Eng. 12:381-385, 1999, Sonnhammer et al., In Proc. of Sixth Int. Conf. on Intelligent Systems for Molecular Biology, p. 175-182 , Ed J. Glasgow, T. Littlejohn, F. Major, R. Lathrop, D. Sankoff, and C. Sensen Menlo Park, CA: AAAI Press, 1998 , Klein, et.al, Biochim. Biophys. Acta, 815:468, 1985, Nakai and Kanehisa Genomics, 14: 897-911 , 1992). In ambiguous cases, locations of functional domains in well characterized proteins are used as a guide to assign a cellular localization.

[20] Putative functions or functional domains of novel proteins can be inferred from homologous regions in the database identified by BLAST searches (Altschul et. al.

Nucleic Acid Res. 25: 3389-3402, 1997) and/or from a conserved domain database such as Pfam (BaBEMan et.al, Nucleic Acids Res. 27:260-262 1999) BLOCKS (Henikoff, et. al, Nucl. Acids Res. 28:228-230, 2000) and SMART (Ponting, et. al, Nucleic Acid Res. 27,229-232, 1999). Extracellular domains include regions adjacent to a transmembrane domain in a single transmembrane domain protein (out–in or type I class). For multiple transmembrane domains proteins, the extracellular domain also includes those regions between two adjacent transmembrane domains (in-out and out-in). For type II transmembrane domain proteins, for which the N-terminal region is cytoplasmic, regions following the transmembrane domain is generally extracellular. Secreted proteins on the other hand do not have a transmembrane domain and hence the whole protein is considered as extracellular.

[21] Membrane associated proteins can be engineered to delete the transmembrane domains, thus leaving the extracellular portions which can bind to ligands. Such soluble forms of transmembrane receptor proteins can be used to compete with natural forms for binding to ligand. Thus such soluble forms act as inhibitors and can be used therapeutically as anti-angiogenic agents, as diagnostic tools for the quantification of natural ligands, and in assays for the identification of small molecules which modulate or mimic the activity of a BEM:ligand complex.

[22] Alternatively, the endothelial markers themselves can be used as vaccines to raise an immune response in the vaccinated animal or human. For such uses, a protein, or immunogenic fragment of such protein, corresponding to the intracellular, extracellular or secreted BEM of interest is administered to a subject. The immogenic agent may be provided as a purified preparation or in an appropriately expressing cell. The administration may be direct, by the delivery of the immunogenic agent to the subject, or indirect, through the delivery of a nucleic acid encoding the immunogenic agent under conditions resulting in the expression of the immunogenic agent of interest in the subject. The BEM of interest may be delivered in an expressing cell,

such as a purified population of breast tumor endothelial cells or a population of fused breast tumor endothelial and dendritic cells. Nucleic acids encoding the BEM of interest may be delivered in a viral or non-viral delivery vector or vehicle. Non-human sequences encoding the human BEM of interest or other mammalian homolog can be used to induce the desired immunologic response in a human subject. For several of the BEMs of the present invention, mouse, rat or other ortholog sequences can be obtained from the literature or using techniques well within the skill of the art.

[23] Endothelial cells can be identified using the markers which are disclosed herein as being endothelial cell specific. Antibodies specific for such markers can be used to identify such cells, by contacting the antibodies with a population of cells containing some endothelial cells. The presence of cross-reactive material with the antibodies identifies particular cells as endothelial. Similarly, lysates of cells can be tested for the presence of cross-reactive material. Any known format or technique for detecting cross-reactive material can be used including, immunoblots, radioimmunoassay, ELISA, immunoprecipitation, and immunohistochemistry. In addition, nucleic acid probes for these markers can also be used to identify endothelial cells. Any hybridization technique known in the art including Northern blotting, RT-PCR, microarray hybridization, and in situ hybridization can be used.

[24] One can identify breast tumor endothelial cells for diagnostic purposes, testing cells suspected of containing one or more BEMs. One can test both tissues and bodily fluids of a subject. For example, one can test a patient's blood for evidence of intracellular and membrane associated BEMs, as well as for secreted BEMs. Of particular interest in this context is the testing of breast duct fluid. Intracellular and/or membrane associated BEMs may be present in bodily fluids as the result of high levels of expression of these factors and/or through lysis of cells expressing the BEMs.

[25] Populations of various types of endothelial cells can also be made using the antibodies to endothelial markers of the invention. The antibodies can be used to purify cell populations according to any technique known in the art, including but not limited to fluorescence activated cell sorting. Such techniques permit the isolation of populations which are at least 50, 60, 70, 80, 90, 92, 94, 95, 96, 97, 98, and even 99 % the type of endothelial cell desired, whether normal, tumor, or pan-endothelial. Antibodies can be used to both positively select and negatively select such populations. Preferably at least 1, 5, 10, 15, 20, or 25 of the appropriate markers are expressed by the endothelial cell population.

[26] Populations of endothelial cells made as described herein, can be used for screening drugs to identify those suitable for inhibiting the growth of tumors by virtue of inhibiting the growth of the tumor vasculature.

[27] Populations of endothelial cells made as described herein, can be used for screening candidate drugs to identify those suitable for modulating angiogenesis, such as for inhibiting the growth of tumors by virtue of inhibiting the growth of endothelial cells, such as inhibiting the growth of the tumor or other undesired vasculature, or alternatively, to promote the growth of endothelial cells and thus stimulate the growth of new or additional large vessel or microvasculature.

[28] Inhibiting the growth of endothelial cells means either regression of vasculature which is already present, or the slowing or the absence of the development of new vascularization in a treated system as compared with a control system. By stimulating the growth of endothelial cells, one can influence development of new (neovascularization) or additional vasculature development (revascularization). A variety of model screening systems are available in which to test the angiogenic and/or anti-angiogenic properties of a given candidate drug. Typical tests involve assays measuring the endothelial cell response, such as proliferation, migration,

differentiation and/or intracellular interaction with a given candidate drug. By such tests, one can study the signals and effects of the test stimuli. Some common screens involve measurement of the inhibition of heparanase, endothelial tube formation on Matrigel, scratch induced motility of endothelial cells, platelet-derived growth factor driven proliferation of vascular smooth muscle cells, and the rat aortic ring assay (which provides an advantage of capillary formation rather than just one cell type).

[29] Drugs can be screened for the ability to mimic or modulate, inhibit or stimulate, growth of tumor endothelium cells and/or normal endothelial cells. Drugs can be screened for the ability to inhibit tumor endothelium growth but not normal endothelium growth or survival. Similarly, human cell populations, such as normal endothelium populations or breast tumor endothelial cell populations, can be contacted with test substances and the expression of breast tumor endothelial markers and/or normal endothelial markers determined. Test substances that decrease the expression of breast tumor endothelial markers (BEMs) are candidates for inhibiting angiogenesis and the growth of tumors. In cases where the activity of a BEM is known, agents can be screened for their ability to decrease or increase the activity.

[30] For those breast tumor endothelial markers identified as containing transmembrane regions, it is desirable to identify drug candidates capable of binding to the BEM receptors found at the cell surface. For some applications, the identification of drug candidates capable of blocking the BEM receptor from its native ligand will be desired. For some applications, the identification of a drug candidate capable of binding to the BEM receptor may be used as a means to deliver a therapeutic or diagnostic agent. For other applications, the identification of drug candidates capable of mimicking the activity of the native ligand will be desired. Thus, by manipulating the binding of a transmembrane BEM receptor:ligand complex, one may be able to promote or inhibit further development of endothelial cells and hence, vascularization.

[31] For those breast tumor endothelial markers identified as being secreted proteins, *i.e.*, extracellular, it is desirable to identify drug candidates capable of binding to the secreted BEM protein. For some applications, the identification of drug candidates capable of interfering with the binding of the secreted BEM it is native receptor. For other applications, the identification of drug candidates capable of mimicking the activity of the native receptor will be desired. Thus, by manipulating the binding of the secreted BEM:receptor complex, one may be able to promote or inhibit futher development of endothelial cells, and hence, vascularization.

[32] Expression can be monitored according to any convenient method. Protein or mRNA can be monitored. Any technique known in the art for monitoring specific genes' expression can be used, including but not limited to ELISAs, SAGE, microarray hybridization, Western blots. Changes in expression of a single marker may be used as a criterion for significant effect as a potential pro-angiogenic, anti-angiogenic or anti-tumor agent. However, it also may be desirable to screen for test substances that are able to modulate the expression of at least 5, 10, 15, or 20 of the relevant markers, such as the tumor or normal endothelial markers. Inhibition of BEM protein activity can also be used as a drug screen.

[33] Test substances for screening can come from any source. They can be libraries of natural products, combinatorial chemical libraries, biological products made by recombinant libraries, etc. The source of the test substances is not critical to the invention. The present invention provides means for screening compounds and compositions that may previously have been overlooked in other screening schemes. Nucleic acids and the corresponding encoded proteins of the markers of the present invention can be used therapeutically in a variety of modes. BEMs can be used to stimulate the growth of vasculature, such as for wound healing or to circumvent a blocked vessel. The nucleic acids and encoded proteins can be administered by any means known in the art. Such methods include, using liposomes, nanospheres, viral vectors, non-viral vectors comprising polycations, etc. Suitable viral vectors include

adenovirus, retroviruses, and sindbis virus. Administration modes can be any known in the art, including parenteral, intravenous, intramuscular, intraperitoneal, topical, intranasal, intrarectal, intrabronchial, etc.

[34] Specific biological antagonists of BEMs can also be used to therapeutic benefit. For example, antibodies, T cells specific for a BEM, antisense to a BEM, interferance RNA to a BEM, and ribozymes specific for a BEM can be used to restrict, inhibit, reduce, and/or diminish tumor or other abnormal or undesirable vasculature growth. Such antagonists can be administered as is known in the art for these classes of antagonists generally. Anti-angiogenic drugs and agents can be used to inhibit tumor growth, as well as to treat diabetic retinopathy, rheumatoid arthritis, psoriasis, polycystic kidney disease (PKD), and other diseases requiring angiogenesis for their pathologies.

[35] Mouse counterparts to human BEMs can be used in mouse cancer models or in cell lines or *in vitro* to evaluate potential anti-angiogenic or anti-tumor compounds or therapies. Their expression can be monitored as an indication of effect. Mouse BEMs can be used as antigens for raising antibodies which can be tested in mouse tumor models. Mouse BEMs with transmembrane domains are particularly preferred for this purpose. Mouse BEMs can also be ued as vaccines to raise an immunological response in a human to the human ortholog.

[36] The above disclosure generally describes the present invention. All references disclosed herein are expressly incorporated by reference in their entireties. A more complete understanding can be obtained by reference to the following specific examples which are provided herein for purposes of illustration only, and are not intended to limit the scope of the invention.

EXAMPLE 1

[37] Function of BEM proteins was determined using bioinformatics tools. BEMs that are putative functional receptors with short cytoplasmic tails make particularly interesting targets.

Breast Tumor Endothelial Putative Functional Receptors with Short Cytoplasmic Tails

Unigene ID	*Function*	*OMIMID*	*Protein*
Hs.181418	KIAA0152 gene product	---	055545
Hs.25691	receptor (calcitonin) activity modifying protein 3	605155	005847
Hs.9598	sema domain	---	BAB212835

EXAMPLE 2

[38] Protein kinases were identified among the BEMs. These are particularly good druggable targets, especially for small molecules.

Protein Kinases

Unigene ID	*Function*	*OMIMID*	*Protein*
Hs.100009	cyclin-dependent kinase 3	123828	
Hs.143897	dysferlin, limb girdle muscular dystrophy 2B (autosomal recessive)	603009	NP_003485
Hs.184367	Ca2+-promoted Ras inactivator		BAA25464
Hs.246857	mitogen-activated protein kinase 9	602896	NP_620708
Hs.75087	FAST kinase	606965	NP-079372
Hs.296323	serum/glucocorticoid regulated kinase	602958	NP_005618
Hs.246857	mitogen-activated protein kinase	602986	NP_620708

EXAMPLE 3

[39] Kinases with non-protein substrates were also identified. These similarly are believed to be exceedingly good druggable targets.

Kinases with non-protein substrates

Unigene ID	*Function*	*OMIMID*	*Protein*
Hs.118625	hexokinase 1	142600	NP_277035
Hs.82689	tumor rejection antigen (gp96) 1	191175	NP_003290

EXAMPLE 4

[40] Growth factors were identified among the BEMs:

Growth factors

Unigene ID	*Function*	*OMIMID*	*Protein*
Hs.91143	jagged 1 (Alagille syndrome)	601920	NP_000205
Hs.119206	insulin-like growth factor binding protein 7	602867	NP_001544
Hs.1516	insulin-like growth factor binding protein 4	146733	NP_001543
Hs.211573	heparan sulfate proteoglycan 2 (perlecan)	142461	NP_005520
Hs.75111	protease, serine, 11 (IGF binding)	602194	NP_002766
Hs.8546	Notch homolog 3 (Drosophila)	600276	NP_000426

EXAMPLE 5

[41] Phosphatases, like kinases, are readily amenable to screening for inhibitors, especially small molecule inhibitors:

Phosphatases

Unigene ID	*Function*	*OMIMID*	*Protein*
Hs.8997	ı a protein 1A	140550	NP_005336
Hs.205353	riphosphate diphosphohydrolase	601752	NP_001767
Hs.43666	phosphatase type IVA, member	606449	NP_116000
Hs.6147	e C1 domain-containing ıophosphatase & tensin-like	---	NP_056134

EXAMPLE 6

[42] GPCRs were identified among the BEMs:

GPCRs

Unigene ID	*Function*	*OMIMID*	*Protein*
Hs.17170	G protein-coupled receptor 4	600551	NP_005273

EXAMPLE 7

[43] The cellular location of the BEMs was determined to be either cytoplasmic, etracellular, membrane, or nuclear, as shown below.

Extracellular Proteins

Unigene ID	*Function*	*OMIMID*	*Protein*
Hs.75415	Beta-2-microglobulin	109700	NP_004039
Hs.821	Biglycan	301870	NP_001702
Hs.172928	collagen, type I, alpha 1	120150	NP_000079
Hs.119571	collagen, type III, alpha 1 (Ehlers-Danlos syndrome type IV, autosomal dominant)	120180	NP_000081
Hs.119129	collagen, type IV, alpha 1	120130	NP_001836
Hs.75617	collagen, type IV, alpha 2	120090	NP_001837
Hs.235368	collagen, type V, alpha 3	120216	NP_056534
Hs.159263	collagen, type VI, alpha 2	120240	NP_001840
Hs.78409	collagen, type XVIII, alpha 1	120328	NP_085059
Hs.278625	complement component 4B	120820	NP_000583
Hs.230	Fibromodulin	600245	NP_002014
Hs.211573	heparan sulfate proteoglycan 2 (perlecan)	142461	NP_005520
Hs.1516	insulin-like growth factor binding protein 4	146733	NP_00154

Unigene ID	*Function*	*OMIMID*	*Protein*
Hs.119206	insulin-like growth factor binding protein 7	602867	NP_001544
Hs.49215	integrin-binding sialoprotein (bone sialoprotein, bone sialoprotein II)	147563	NP_004958
Hs.79339	lectin, galactoside-binding, soluble, 3 binding protein	600626	NP_005558
Hs.106747	likely homolog of rat and mouse retinoid-inducible serine carboxypeptidase		NP_067639
Hs.365706	matrix Gla protein	154870	NP_000891
Hs.151738	matrix metalloproteinase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase)	120361	NP_004985
Hs.699	peptidylprolyl isomerase B (cyclophilin B)	123841	NP_000933
Hs.75111	protease, serine, 11 (IGF binding)	602194	NP_002766
Hs.25338	protease, serine, 23		
Hs.78224	ribonuclease, RNase A family, 1 (pancreatic)	180440	AAH05324
Hs.111779	secreted protein, acidic, cysteine-rich (osteonectin)	182120	NP_003109
Hs.82085	serine (or cysteine) proteinase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1	173360	NP_000593
Hs.179573	TEM10, COL1A2 involved in tissue remodeling	120160	NP_000080
Hs.356624	TEM11, nidogen (enactin)	131390	NP_002499
Hs.5831	tissue inhibitor of metalloproteinase 1 (erythroid potentiating activity, collagenase inhibitor)	305370	NP_003245
Hs.82689	tumor rejection antigen (gp96) 1	191175	NP_003290

Membrane Proteins

Unigene ID	*Function*	*Protein*	*TM Domains*	*TM Location*	*Orientation of N-terminus*
Hs.202	benzodiazapine receptor (peripheral)	NP_000705	3	107-129,78-100,133-155	OUT
Hs.76206	cadherin 5, type 2, VE-cadherin (vascular epithelium)	NP_001786	1	598-620	Unsure
Hs.122359	calcium channel, voltage-dependent, alpha 1H subunit	NP_066921	19	1370-1392,1614-1636,1533-1555,141-163,915-937,396-418,1651-1673,1745-1767,990-1012,234-256,1430-1452,1333-1355,1680-1702,855-877,1295-1316,826-848,100-122,1840-1862,364-386	IN
Hs.84298	CD74 antigen (invariant polypeptide of major histocompatibility complex, class II antigen-associated)	NP_004346	1	49-71	IN
Hs.1244	CD9 antigen (p24)	NP_001760	4	59-81,88-110,12-34,194-216	IN
Hs.143897	dysferlin, limb girdle muscular dystrophy 2B (autosomal recessive)	NP_003485	1	2045-2067	Unsure

Unigene ID	Function	Protein	TM Domains	TM Location	Orientation of N-terminus
Hs.205353	ectonucleoside triphosphate diphosphohydrolase 1	NP_001767	1	477-499	IN
Hs.17170	G protein-coupled receptor 4	NP_005273	5	55-77,92-113,20-42,225-244,183-205	OUT
Hs.25549	hypothetical protein FLJ20898	NP_078876	3	102-124,139-161,168-190	Unsure
Hs.277704	hypoxia up-regulated 1	NP_006380	1	13-35	IN
Hs.76095	Immediate early response 3	NP_434702	1	123-145	Unsure
Hs.265827	interferon, alpha-inducible protein (clone IFI-6-16)	NP_075011	2	5-24,44-66	IN
Hs.91143	jagged 1 (Alagille syndrome)	NP_000205	1	1069-1091	Unsure
Hs.181418	KIAA0152 gene product	NP_055545	1	271-290	OUT
Hs.79356	Lysosomal-associated multispanning membrane protein-5	NP_006753	5	63-85,100-121,142-164,15-37,184-206	Unsure
Hs.77961	major histocompatibility complex, class I, B	NP_005505	1	308-330	OUT
Hs.277477	major histocompatibility complex, class I, C	NP_002108	1	308-330	OUT
Hs.110024	NADH:ubiquinone oxidoreductase MLRQ subunit homolog	NP_064527	1	20-42	Unsure
Hs.8546	Notch homolog 3 (Drosophila)	NP_000426	3	1641-1663,1496-1518,20-42	Unsure
Hs.107125	plasmalemma vesicle associated protein	NP_112600	1	42-64	IN
Hs.83974	solute carrier family 21 (prostaglandin transporter), member 2	NP_005621	12	256-278,363-385,397-419,100-122,208-230,326-348,173-195,514-536,71-93,557-576,606-628,25-47	Unsure
Hs.125359	TEM13, Thy-1 cell surface antigen	NP_006279	1	140-161	Unsure
Hs.125036	TEM17	NP_065138	1	425-447	OUT

Unigene ID	Function	Protein	TM Domains	TM Location	Orientation of N-terminus
Hs.9598	sema domain, immunoglobulin domain (Ig)	BAB21836	1	727-794	OUT
Hs.202	Benzodiazapine receptor (peripheral)-mitochondrial	NP_00715	3	107-129, 78-100, 133-155	OUT

Nuclear Proteins

Unigene ID	*Function*	*OMIMID*	*Protein*
Hs.244	amino-terminal enhancer of split	600188	
Hs.154029	bHLH factor Hes4		NP_066993
Hs.75450	delta sleep inducing peptide, immunoreactor	602960	
Hs.75087	FAST kinase	606965	NP_079372
Hs.356668	guanine nucleotide binding protein (G protein), gamma 5	600874	NP_005265
Hs.406410	H19, imprinted maternally expressed untranslated mRNA	103280	BAB71280
Hs.234434	hairy/enhancer-of-split related with YRPW motif 1	602953	NP_036390
Hs.23823	hairy/enhancer-of-split related with YRPW motif-like		NP_055386
Hs.15265	heterogeneous nuclear ribonucleoprotein R	607201	NP_005817
Hs.8728	hypothetical protein DKFZp434G171		CAB61365
Hs.240170	hypothetical protein MGC2731		NP_076973
Hs.146360	hypothetical protein MGC34648		NP_689873
Hs.337986	hypothetical protein MGC4677		NP_443103
Hs.197540	hypoxia-inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor)	603348	NP_001521
Hs.75061	MARCKS-like protein	602940	NP_075385
Hs.246857	mitogen-activated protein kinase 9	602896	NP_620708
Hs.79110	Nucleolin	164035	NP_005372
Hs.298229	prefoldin 2		NP_036526
Hs.250655	prothymosin, alpha (gene sequence 28)	188390	NP_002814
Hs.24950	regulator of G-protein signalling 5	603276	NP_003608
Hs.76640	RGC32 protein		
Hs.3109	Rho GTPase activating protein 4	300023	NP_001657
Hs.337445	ribosomal protein L37	604181	NP_000988
Hs.197114	serine/arginine repetitive matrix 2	606032	NP_057417
Hs.48029	snail homolog 1 (Drosophila)	604238	NP_005976
Hs.168357	T-box 2	600747	NP_005985
Hs.332173	transducin-like enhancer of split 2 (E(sp1) homolog, Drosophila)	601041	NP_003251
Hs.78465	v-jun sarcoma virus 17 oncogene homolog (avian)	165160	NP_002219

Cytoplasmic proteins

Unigene ID	*Function*	*OMIMID*	*Protein*
Hs.184367	Ca2+-promoted Ras inactivator		BAA25464
Hs.2575	calpain 1, (mu/I) large subunit	114220	NP_005177
Hs.100009	cyclin-dependent kinase 3	123828	
Hs.31053	cytoskeleton-associated protein 1	601303	NP_001272
Hs.82646	DnaJ (Hsp40) homolog, subfamily B, member 1	604572	NP_006136
Hs.169476	glyceraldehyde-3-phosphate dehydrogenase	138400	NP_002037
Hs.77890	guanylate cyclase 1, soluble, beta 3	139397	NP_000848
Hs.36927	heat shock 105Kd		NP_006635
Hs.1197	heat shock 10kDa protein 1 (chaperonin 10)	600141	NP_002148
Hs.8997	heat shock 70kDa protein 1A	140550	NP_005336
Hs.180414	heat shock 70kDa protein 8	600816	NP_006588
Hs.118625	hexokinase 1	142600	NP_277035
Hs.327412	Homo sapiens clone FLC1492 PRO3121 mRNA, complete cds		
Hs.833	interferon, alpha-inducible protein (clone IFI-15K)	147571	NP_005092
Hs.150580	putative translation initiation factor		NP_005792
Hs.173737	ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1)	602048	
Hs.119122	ribosomal protein L13a		
Hs.111611	ribosomal protein L27	607526	NP_000979
Hs.177592	ribosomal protein, large, P1	180520	
Hs.12956	Tax interaction protein 1		NP_055419
Hs.251653	tubulin, beta, 2	602660	NP_006079

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We claim:

1. A method to aid in diagnosing breast tumor, comprising the steps of:

detecting an expression product of at least one gene in a first brain tissue sample suspected of being neoplastic wherein said at least one gene is selected from the group consisting of hypothetical protein DKFZp434G171; heat shock 70kDa protein 1A; jagged 1 (Alagille syndrome); cyclin-dependent kinase 3; 6-phosphogluconolactonase; likely homolog of rat and mouse retinoid-inducible serine carboxypeptidase; plasmalemma vesicle associated protein; NADH:ubiquinone oxidoreductase MLRQ subunit homolog; HIF-1 responsive RTP801; ribosomal protein L27; secreted protein, acidic, cysteine-rich (osteonectin); hexokinase 1; ribosomal protein L13a; collagen, type IV, alpha 1; insulin-like growth factor binding protein 7; collagen, type III, alpha 1 (Ehlers-Danlos syndrome type IV, autosomal dominant); heat shock 10kDa protein 1 (chaperonin 10); calcium channel, voltage-dependent, alpha 1H subunit; CD9 antigen (p24); TEM17; TEM13, Thy-1 cell surface antigen; Tax interaction protein 1; dysferlin, limb girdle muscular dystrophy 2B (autosomal recessive); hypothetical protein MGC34648; putative translation initiation factor; insulin-like growth factor binding protein 4; matrix metalloproteinase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase); heterogeneous nuclear ribonucleoprotein R; bHLH factor Hes4; collagen, type VI, alpha 2; T-box 2; glyceraldehyde-3-phosphate dehydrogenase; G protein-coupled receptor 4; collagen, type I, alpha 1; ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1); ribosomal protein, large, P1; TEM10, COL1A2 involved in tissue remodeling; heat shock 70kDa protein 8; KIAA0152 gene product; Ca2+-promoted Ras inactivator; serine/arginine repetitive matrix 2; hypoxia-inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor); benzodiazapine receptor (peripheral); ectonucleoside triphosphate diphosphohydrolase 1; heparan sulfate proteoglycan 2 (perlecan); fibromodulin;

hairy/enhancer-of-split related with YRPW motif 1; collagen, type V, alpha 3; hairy/enhancer-of-split related with YRPW motif-like; hypothetical protein MGC2731; amino-terminal enhancer of split; mitogen-activated protein kinase 9; regulator of G-protein signalling 5; prothymosin, alpha (gene sequence 28); tubulin, beta, 2; protease, serine, 23; hypothetical protein FLJ20898; calpain 1, (mu/I) large subunit; interferon, alpha-inducible protein (clone IFI-6-16); ESTs, Weakly similar to T25031 hypothetical protein T20D3.3 - Caenorhabditis elegans [C.elegans]; major histocompatibility complex, class I, C; hypoxia up-regulated 1; complement component 4B; prefoldin 2; cytoskeleton-associated protein 1; Rho GTPase activating protein 4; Homo sapiens clone FLC1492 PRO3121 mRNA, complete cds; transducin-like enhancer of split 2 (E(sp1) homolog, Drosophila); ribosomal protein L37; hypothetical protein MGC4677; ESTs, Highly similar to MT1A_HUMAN METALLOTHIONEIN-IA (MT-1A) [H.sapiens]; TEM11, nidogen (enactin); guanine nucleotide binding protein (G protein), gamma 5; matrix Gla protein; heat shock 105kD; GNAS complex locus; Homo sapiens cDNA FLJ11658 fis, clone HEMBA1004577; H19, imprinted maternally expressed untranslated mR NA; protein tyrosine phosphatase type IVA, member 3; snail homolog 1 (Drosophila); integrin-binding sialoprotein (bone sialoprotein, bone sialoprotein II); tissue inhibitor of metalloproteinase 1 (erythroid potentiating activity, collagenase inhibitor); peptidylprolyl isomerase B (cyclophilin B); MARCKS-like protein; FAST kinase; protease, serine, 11 (IGF binding); beta-2-microglobulin; delta sleep inducing peptide, immunoreactor; collagen, type IV, alpha 2; immediate early response 3; cadherin 5, type 2, VE-cadherin (vascular epithelium); RGC32 protein; guanylate cyclase 1, soluble, beta 3; major histocompatibility complex, class I, B; ribonuclease, RNase A family, 1 (pancreatic); collagen, type XVIII, alpha 1; v-jun sarcoma virus 17 oncogene homolog (avian); Homo sapiens mRNA; cDNA DKFZp686G1610 (from clone DKFZp686G1610); nucleolin; lectin, galactoside-binding, soluble, 3 binding protein; Lysosomal-associated multispanning membrane protein-5; ribosomal

protein S16; guanine nucleotide binding protein (G protein), gamma 12; serine (or cysteine) proteinase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1; biglycan; DnaJ (Hsp40) homolog, subfamily B, member 1; tumor rejection antigen (gp96) 1; interferon, alpha-inducible protein (clone IFI-15K); solute carrier family 21 (prostaglandin transporter), member 2; CD74 antigen (invariant polypeptide of major histocompatibility complex, class II antigen-associated); serum/glucocorticoid regulated kinase; mitogen-activated protein kinase; receptor (calcitonin) activity modifying protein 3; sema domain, immunoglobulin domain (Ig); benzodiazapine receptor (peripheral) – mitochondrial; C1 domain-containing phosphatase & tensin-like; and Notch homolog 3 (Drosophila);

and

comparing expression of the at least one gene in the first breast tissue sample with expression of the at least one gene in a second breast tissue sample which is normal, wherein increased expression of the at least one gene in the first breast tissue sample relative to the second tissue sample identifies the first breast tissue sample as likely to be neoplastic.

2. The method of claim 1 wherein the increased expression of the at least one gene in the first breast tissue sample relative to the second tissue sample is at least two-fold higher.
3. The method of claim 1 wherein the increased expression of the at least one gene in the first breast tissue sample relative to the second tissue sample is at least five-fold higher.
4. The method of claim 1 wherein the increased expression of the at least one gene in the first breast tissue sample relative to the second tissue sample is at least ten-fold higher.
5. The method of claim 1 wherein the expression product is RNA.
6. The method of claim 1 wherein the expression product is protein.

7. The method of claim 1 wherein the first and second tissue samples are from a human.
8. The method of claim 1 wherein the first and second tissue samples are from the same human.
9. The method of claim 1 wherein the step of detecting is performed using a Western blot.
10. The method of claim 1 wherein the step of detecting is performed using an immunoassay.
11. The method of claim 1 wherein the step of detecting is performed using an immunohistochemical assay.
12. The method of claim 1 wherein the step of detecting is performed using SAGE.
13. The method of claim 1 wherein the step of detecting is performed using hybridization to a microarray.
14. A method of treating a breast tumor, comprising the step of:

contacting cells of the breast tumor with an antibody, wherein the antibody specifically binds to an extracellular epitope of a protein selected from the group consisting of benzodiazapine receptor (peripheral); cadherin 5, type 2, VE-cadherin (vascular epithelium); calcium channel, voltage-dependent, alpha 1H subunit; CD74 antigen (invariant polypeptide of major histocompatibility complex, class II antigen-associated); CD9 antigen (p24); dysferlin, limb girdle muscular dystrophy 2B (autosomal recessive); ectonucleoside triphosphate diphosphohydrolase 1; G protein-coupled receptor 4; hypothetical protein FLJ20898; hypoxia up-regulated 1; immediate early response 3; interferon, alpha-inducible protein (clone IFI-6-16); jagged 1 (Alagille syndrome); KIAA0152 gene product; Lysosomal-associated multispanning membrane protein-5; major histocompatibility complex, class I, B; major histocompatibility complex, class I, C; NADH:ubiquinone oxidoreductase MLRQ subunit homolog; Notch homolog 3 (Drosophila); plasmalemma vesicle associated protein; solute carrier family 21 (prostaglandin transporter), member 2; TEM13, Thy-1 cell surface antigen; receptor (calcitonin) activity modifying protein 3; sema domain, immunoglobulin domain (Ig);

benzodiazapine receptor (peripheral) – mitochondrial; and TEM17; whereby immune destruction of cells of the breast tumor is triggered.

15. The method of claim 14 wherein the antibody is conjugated to a diagnostic or therapeutic reagent.
16. The method of claim 14 wherein the breast tumor is multidrug-sensitive.
17. The method of claim 14 wherein the reagent is a chemotherapeutic agent.
18. The method of claim 14 wherein the reagent is a cytotoxin.
19. The method of claim 14 wherein the reagent is a non-radioactive label.
20. The method of claim 14 wherein the reagent is a radioactive compound.
21. The method of claim 14 wherein the breast tumor is in a human.
22. A method of identifying a test compound as a potential anti-cancer or anti-breast tumor drug, comprising the step of:

contacting a test compound with a cell which expresses at least one gene selected from the group consisting of hypothetical protein DKFZp434G171; heat shock 70kDa protein 1A; jagged 1 (Alagille syndrome); cyclin-dependent kinase 3; 6-phosphogluconolactonase; likely homolog of rat and mouse retinoid-inducible serine carboxypeptidase; plasmalemma vesicle associated protein; NADH:ubiquinone oxidoreductase MLRQ subunit homolog; HIF-1 responsive RTP801; ribosomal protein L27; secreted protein, acidic, cysteine-rich (osteonectin); hexokinase 1; ribosomal protein L13a; collagen, type IV, alpha 1; insulin-like growth factor binding protein 7; collagen, type III, alpha 1 (Ehlers-Danlos syndrome type IV, autosomal dominant); heat shock 10kDa protein 1 (chaperonin 10); calcium channel, voltage-dependent, alpha 1H subunit; CD9 antigen (p24); TEM17; TEM13, Thy-1 cell surface antigen; Tax interaction protein 1; dysferlin, limb girdle muscular dystrophy 2B (autosomal recessive); hypothetical protein MGC34648; putative translation initiation factor; insulin-like growth factor binding protein 4; matrix metalloproteinase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase); heterogeneous nuclear ribonucleoprotein R; bHLH factor Hes4; collagen, type VI, alpha 2; T-box 2; glyceraldehyde-3-phosphate dehydrogenase; G protein-coupled receptor 4; collagen, type I, alpha 1; ras-related C3 botulinum toxin

substrate 1 (rho family, small GTP binding protein Rac1); ribosomal protein, large, P1; TEM10, COL1A2 involved in tissue remodeling; heat shock 70kDa protein 8; KIAA0152 gene product; Ca2+-promoted Ras inactivator; serine/arginine repetitive matrix 2; hypoxia-inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor); benzodiazapine receptor (peripheral); ectonucleoside triphosphate diphosphohydrolase 1; heparan sulfate proteoglycan 2 (perlecan); fibromodulin; hairy/enhancer-of-split related with YRPW motif 1; collagen, type V, alpha 3; hairy/enhancer-of-split related with YRPW motif-like; hypothetical protein MGC2731; amino-terminal enhancer of split; mitogen-activated protein kinase 9; regulator of G-protein signalling 5; prothymosin, alpha (gene sequence 28); tubulin, beta, 2; protease, serine, 23; hypothetical protein FLJ20898; calpain 1, (mu/I) large subunit; interferon, alpha-inducible protein (clone IFI-6-16); ESTs, Weakly similar to T25031 hypothetical protein T20D3.3 - Caenorhabditis elegans [C.elegans]; major histocompatibility complex, class I, C; hypoxia up-regulated 1; complement component 4B; prefoldin 2; cytoskeleton-associated protein 1; Rho GTPase activating protein 4; Homo sapiens clone FLC1492 PRO3121 mRNA, complete cds; transducin-like enhancer of split 2 (E(sp1) homolog, Drosophila); ribosomal protein L37; hypothetical protein MGC4677; ESTs, Highly similar to MT1A_HUMAN METALLOTHIONEIN-IA (MT-1A) [H.sapiens]; TEM11, nidogen (enactin); guanine nucleotide binding protein (G protein), gamma 5; matrix Gla protein; heat shock 105kD; GNAS complex locus; Homo sapiens cDNA FLJ11658 fis, clone HEMBA1004577; H19, imprinted maternally expressed untranslated mR NA; protein tyrosine phosphatase type IVA, member 3; snail homolog 1 (Drosophila); integrin-binding sialoprotein (bone sialoprotein, bone sialoprotein II); tissue inhibitor of metalloproteinase 1 (erythroid potentiating activity, collagenase inhibitor); peptidylprolyl isomerase B (cyclophilin B); MARCKS-like protein; FAST kinase; protease, serine, 11 (IGF binding); beta-2-microglobulin; delta sleep inducing peptide, immunoreactor; collagen, type IV, alpha 2; immediate early response 3; cadherin 5, type 2, VE-cadherin (vascular epithelium); RGC32 protein; guanylate cyclase 1, soluble, beta 3; major histocompatibility complex, class I, B; ribonuclease, RNase A family, 1 (pancreatic); collagen, type XVIII, alpha 1; v-

jun sarcoma virus 17 oncogene homolog (avian); Homo sapiens mRNA; cDNA DKFZp686G1610 (from clone DKFZp686G1610); nucleolin; lectin, galactoside-binding, soluble, 3 binding protein; Lysosomal-associated multispanning membrane protein-5; ribosomal protein S16; guanine nucleotide binding protein (G protein), gamma 12; serine (or cysteine) proteinase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1; biglycan; DnaJ (Hsp40) homolog, subfamily B, member 1; tumor rejection antigen (gp96) 1; interferon, alpha-inducible protein (clo ne IFI-15K); solute carrier family 21 (prostaglandin transporter), member 2; CD74 antigen (invariant polypeptide of major histocompatibility complex, class II antigen-associated); serum/glucocorticoid regulated kinase; mitogen-activated protein kinase; receptor (calcitonin) activity modifying protein 3; sema domain, immunoglobulin domain (Ig); benzodiazapine receptor (peripheral) – mitochondrial; C1 domain-containing phosphatase & tensin-like; and Notch homolog 3 (Drosophila);

monitoring an expression product of the at least one gene; and

identifying the test compound as a potential anti-cancer drug if it decreases the expression of the at least one gene.

23. The method of claim 22 wherein the cell is a human cell.
24. The method of claim 22 wherein the cell is a breast tumor cell.
25. The method of claim 22 wherein the cell is a human breast tumor cell.
26. The method of claim 22 wherein the expression product is RNA.
27. The method of claim 22 wherein the expression product is protein.
28. The method of claim 22 wherein the cell overexpresses the at least one gene relative to a normal cell of the same tissue.
29. The method of claim 22 wherein expression of at least two of said genes is monitored.
30. The method of claim 22 wherein expression of at least three of said genes is monitored.
31. The method of claim 22 wherein expression of at least four of said genes is monitored.

32. The method of claim 22 wherein the test compound is identified if the decrease in expression is at least two-fold.

33. The method of claim 22 wherein the test compound is identified if the decrease in expression is at least five-fold.

34. The method of claim 22 wherein the decrease in expression is at least ten-fold.

35. The method of claim 22 wherein the test compound is identified as an anti-breast tumor drug.

36. A method to induce an immune response to a breast tumor, comprising:

administering to a mammal a protein or nucleic acid encoding a protein selected from the group consisting of: hypothetical protein DKFZp434G171; heat shock 70kDa protein 1A; jagged 1 (Alagille syndrome); cyclin-dependent kinase 3; 6-phosphogluconolactonase; likely homolog of rat and mouse retinoid-inducible serine carboxypeptidase; plasmalemma vesicle associated protein; NADH:ubiquinone oxidoreductase MLRQ subunit homolog; HIF-1 responsive RTP801; ribosomal protein L27; secreted protein, acidic, cysteine-rich (osteonectin); hexokinase 1; ribosomal protein L13a; collagen, type IV, alpha 1; insulin-like growth factor binding protein 7; collagen, type III, alpha 1 (Ehlers-Danlos syndrome type IV, autosomal dominant); heat shock 10kDa protein 1 (chaperonin 10); calcium channel, voltage-dependent, alpha 1H subunit; CD9 antigen (p24); TEM17; TEM13, Thy-1 cell surface antigen; Tax interaction protein 1; dysferlin, limb girdle muscular dystrophy 2B (autosomal recessive); hypothetical protein MGC34648; putative translation initiation factor; insulin-like growth factor binding protein 4; matrix metalloproteinase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase); heterogeneous nuclear ribonucleoprotein R; bHLH factor Hes4; collagen, type VI, alpha 2; T-box 2; glyceraldehyde-3-phosphate dehydrogenase; G protein-coupled receptor 4; collagen, type I, alpha 1; ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1); ribosomal protein, large, P1; TEM10, COL1A2 involved in tissue remodeling; heat shock 70kDa protein 8; KIAA0152 gene product; Ca2+-promoted Ras inactivator; serine/arginine repetitive matrix 2; hypoxia-inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor);

benzodiazapine receptor (peripheral); ectonucleoside triphosphate diphosphohydrolase 1; heparan sulfate proteoglycan 2 (perlecan); fibromodulin; hairy/enhancer-of-split related with YRPW motif 1; collagen, type V, alpha 3; hairy/enhancer-of-split related with YRPW motif-like; hypothetical protein MGC2731; amino-terminal enhancer of split; mitogen-activated protein kinase 9; regulator of G-protein signalling 5; prothymosin, alpha (gene sequence 28); tubulin, beta, 2; protease, serine, 23; hypothetical protein FLJ20898; calpain 1, (mu/I) large subunit; interferon, alpha-inducible protein (clone IFI-6-16); ESTs, Weakly similar to T25031 hypothetical protein T20D3.3 - Caenorhabditis elegans [C.elegans]; major histocompatibility complex, class I, C; hypoxia up-regulated 1; complement component 4B; prefoldin 2; cytoskeleton-associated protein 1; Rho GTPase activating protein 4; Homo sapiens clone FLC1492 PRO3121 mRNA, complete cds; transducin-like enhancer of split 2 (E(sp1) homolog, Drosophila); ribosomal protein L37; hypothetical protein MGC4677; ESTs, Highly similar to MT1A_HUMAN METALLOTHIONEIN-IA (MT-1A) [H.sapiens]; TEM11, nidogen (enactin); guanine nucleotide binding protein (G protein), gamma 5; matrix Gla protein; heat shock 105kD; GNAS complex locus; Homo sapiens cDNA FLJ11658 fis, clone HEMBA1004577; H19, imprinted maternally expressed untranslated mR NA; protein tyrosine phosphatase type IVA, member 3; snail homolog 1 (Drosophila); integrin-binding sialoprotein (bone sialoprotein, bone sialoprotein II); tissue inhibitor of metalloproteinase 1 (erythroid potentiating activity, collagenase inhibitor); peptidylprolyl isomerase B (cyclophilin B); MARCKS-like protein; FAST kinase; protease, serine, 11 (IGF binding); beta-2-microglobulin; delta sleep inducing peptide, immunoreactor; collagen, type IV, alpha 2; immediate early response 3; cadherin 5, type 2, VE-cadherin (vascular epithelium); RGC32 protein; guanylate cyclase 1, soluble, beta 3; major histocompatibility complex, class I, B; ribonuclease, RNase A family, 1 (pancreatic); collagen, type XVIII, alpha 1; v-jun sarcoma virus 17 oncogene homolog (avian); Homo sapiens mRNA; cDNA DKFZp686G1610 (from clone DKFZp686G1610); nucleolin; lectin, galactoside-binding, soluble, 3 binding protein; Lysosomal-associated multispanning membrane protein-5; ribosomal protein S16; guanine nucleotide binding protein (G protein), gamma 12; serine

(or cysteine) proteinase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1; biglycan; DnaJ (Hsp40) homolog, subfamily B, member 1; tumor rejection antigen (gp96) 1; interferon, alpha-inducible protein (clo ne IFI-15K); solute carrier family 21 (prostaglandin transporter), member 2; CD74 antigen (invariant polypeptide of major histocompatibility complex, class II antigen-associated); serum/glucocorticoid regulated kinase; mitogen-activated protein kinase; receptor (calcitonin) activity modifying protein 3; sema domain, immunoglobulin domain (Ig); benzodiazapine receptor (peripheral) – mitochondrial; C1 domain-containing phosphatase & tensin-like; and Notch homolog 3 (Drosophila), whereby an immune response to the protein is induced.

37. The method of claim 36 wherein a protein is administered.
38. The method of claim 36 wherein a nucleic acid is administered.
39. The method of claim 38 wherein the nucleic acid is administered intramuscularly.
40. The method of claim 36 further comprising administering an immune adjuvant to the mammal.
41. The method of claim 36 wherein the mammal has a breast tumor.
42. The method of claim 36 wherein the mammal has had a breast tumor surgically removed.