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(54) **METHODS AND SYSTEMS OF USING EXOSOMES FOR DETERMINING PHENOTYPES**

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(57) **ABSTRACT**

Exosomes can be used for detecting biomarkers for diagnostic, therapy-related or prognostic methods to identify phenotypes, such as a condition or disease, for example, the stage or progression of a disease. Cell-of-origin exosomes can be used in profiling of physiological states or determining phenotypes. Biomarkers or markers from cell-of-origin specific exosomes can be used to determine treatment regimens for diseases, conditions, disease stages, and stages of a condition, and can also be used to determine treatment efficacy. Markers from cell-of-origin specific exosomes can also be used to identify conditions of diseases of unknown origin.

FIG. 1a

Cancer Lineage, Group Comparison, Disease State	Antigens	References
Breast	BCA-225	Cerani et al., 1985
Breast	BCA-225	Mesa-Tejada et al., 1988
Breast	BCA-225	Loy et al., 1991
Breast	BCA-225	Ma et al., 1993
Breast	hsp70	Wolfers et al. 2001 Nat Med 793: 297
Breast	MART-1	Wolfers et al. 2001 Nat Med 793: 297
Breast	ER	Oldenhuis CN et al., Eur J Cancer. 2008 May;44(7):946-53. Epub 2008 Apr 7; Payne SJ et al., Histopathology. 2008 Jan;52(1):82-90
Breast	Class III b-tubulin	Galmarini CM et al., Clin Cancer Res. 2008 Jul 15;14(14):4511-6
Breast	VEGFA	Linderholm BK et al., Cancer Res. 2001 Mar 1;61(5):2256-60
Breast	HER2/neu (for Her2+BC)	De Laurentiis M et al., Ann Oncol. 2005 May;16 Suppl 4:iv7-13.
Breast	GPR30	Filardo EJ et al., Steroids. 2008 Oct;73(9-10):870-3.
Breast	ErbB4(JM) isoform	Määttä JA et al., Mol Biol Cell. 2006 Jan;17(1):67-79.
Breast	MPR8	Bera TK et al., Molecular Medicine 7(8): 509-516, 2001
Breast	MISIIR	Jamie N Bakkum-Gamez et al., Gynecologic oncology (Gynecol Oncol) Vol. 108 Issue 1 Pg. 141-8
Ovarian	CA125 (0C125)#	Bast et al., 1981
Ovarian	CA125	Dabawat S, et al., 1983
Ovarian	CA125	Davis H et al., 1986
Ovarian	CA125	Nouwen E, et al., 1986
Ovarian	CA125	Quirk J, et al., 1988
Ovarian	CA-125	Fukazawa I et al., 1988
Ovarian	VEGFA	Osada R et al., Hum Pathol. 2006 Nov;37(11):1414-25.
Ovarian	VEGFR2	Chen BY et al., Zhonghua Zhong Liu Za Zhi. 2005 Jan;27(1):33-7
Ovarian	HER2	Steffensen KD et al., Int J Oncol. 2008 Jul;33(1):195-204
Ovarian	MISIIR	Jamie N Bakkum-Gamez et al., Gynecologic oncology (Gynecol Oncol) Vol. 108 Issue 1 Pq. 141-8
Lung	CYFRA 21-1	Kulpa J, et al., C Clin Chem 48: 1931-1937 (2002)
Lung	TPA-M	Kulpa J, et al., *supra.*
Lung	TPS	Kulpa J, et al., *supra.*
Lung	CEA	Kulpa J, et al., *supra.*
Lung	SCC-Ag	Kulpa J, et al., *supra.*
Lung	XAGE-1b	Kikuchi et al., Cancer Immunity, 8:13 (2008)
Lung	HLA class I	Kikuchi et al., *supra.*
Lung	TA-MUC1	Kuemmel et al., Lung Cancer Jun 6, 2008
Lung	KRAS	Zhang Z et al., Cancer Biol Ther. 2006 Nov;5(11):1481-6
Lung	hENT1	Oguri T et al., Cancer Lett. 2007 Oct 18;256(1):112-9.
Lung	kinin B1 receptor	Chee J et al., Biol Chem. 2008 Sep;389(9):1225-33.

FIG. 1b

Cancer Lineage, Group Comparison, Disease State	Antigens	References
Lung	kinin B2 receptor	Chee J et al., Biol Chem. 2008 Sep;389(9):1225-33.
Lung	TSC403	Ozaki K et al., CANCER RESEARCH 58, 3499-3503, August 15, 1998
Lung	HTI56	Dobbs LG et al., JHC Volume 47(2): 129-137, 1999
Lung	DC-LAMP	Salaun B et al., American Journal of Pathology. 2004;164:861-871
Colon	CEA	Park et al., 2002
Colon	MUC2	Park et al., 2002
Colon	GPA33	Huber et al., 2005
Colon	CEACAM5	Huber et al., 2005
Colon	ENFB1	Huber et al., 2006
Colon	CCSA-3	Leman et al., 2007
Colon	CCSA-4	Leman et al., 2008
Colon	ADAM 10	Choi et al., 2007, J Ethnopharmacol 110(1): 49-55.
Colon	CD44	Choi et al., 2007, J Ethnopharmacol 110(1): 49-55.
Colon	NG2	Choi et al., 2007, J Ethnopharmacol 110(1): 49-55.
Colon	ephrin-B1	Choi et al., 2007, J Ethnopharmacol 110(1): 49-55.
Colon	plakoglobin	Choi et al., 2007, J Ethnopharmacol 110(1): 49-55.
Colon	galectin-4	Choi et al., 2007, J Ethnopharmacol 110(1): 49-55.
Colon	RACK1	Choi et al., 2007, J Ethnopharmacol 110(1): 49-55
Colon	tetraspanin-8	Choi et al., 2007, J Ethnopharmacol 110(1): 49-55
Colon	FasL	Choi et al., 2007, J Ethnopharmacol 110(1): 49-55
Colon	A33	Choi et al., 2007, J Ethnopharmacol 110(1): 49-55
Colon	CEA	Choi et al., 2007, J Ethnopharmacol 110(1): 49-55
Colon	EGFR	Choi et al., 2007, J Ethnopharmacol 110(1): 49-55
Colon	dipeptidase 1	Choi et al., 2007, J Ethnopharmacol 110(1): 49-55
Colon	PTEN	Frattini et al., 2007
Colon	Na(+)-dependent glucose transporter	Wang Y et al., Pediatr Res. 1994 Oct;36(4):514-21.
Colon	UDP-glucuronosyltransferase 1A	Gong QH et al., Pharmacogenetics 11:357-368(2001).
Benign Prostatic Hyperplasia	KIA1	Ueda T, et al., 1996
Benign Prostatic Hyperplasia	Intact Fibronectin	Janković MM, Kosanović MM, Dis Markers. 2008;25(1):49-58.
Prostate	PSA	Nurmikko P et al., 2000
Prostate	TMPRSS2	Wilson S et al., Biochem J. 2005 Jun 15;388(Pt 3):967-72.
Prostate	FASLG	Huber et al., 2005, Gastroenterol Nurs 28(6): 510-1.
Prostate	TNFSF10	Huber et al., 2005, Gastroenterol Nurs 28(6): 510-1
Prostate	PSMA	Pinto JT et al., Clin Cancer Res. 1996 Sep;2(9):1445-51.
Prostate	NGEP	Das S et al., Cancer Res. 2007 Feb 15;67 (4):1594-1601
Prostate	IL-7R1	Haudenschild DR et al., Prostate. 2006 Sep 1;66(12):1268-74.

FIG. 1c

Cancer Lineage, Group Comparison, Disease State	Antigens	References
Prostate	CSCR4	Chinni SR et al., Mol Cancer Res. 2008 Mar;6(3):446-57.
Prostate	CysLT1R	Matsuyama M et al., Oncol Rep. 2007 Jul;18(1):99-104.
Prostate	TRPM8	Bidaux G et al., J Clin Invest. 2007 Jun;117(6):1647-57.
Prostate	Kv1.3	Prevarskaya N et al., Cell Death Differ. 2007 Jul;14(7):1295-304.
Prostate	TRPV6	Prevarskaya N et al., Cell Death Differ. 2007 Jul;14(7):1295-304.
Prostate	TRPM8	Prevarskaya N et al., Cell Death Differ. 2007 Jul;14(7):1295-304.
Prostate	PSGR	Xu LL et al., Cancer Res. 2000 Dec 1;60(23):6568-72.
Prostate	MISIIR	Bakkum-Gamez J.N. et al., Gynecol Oncol Vol. 108 Issue 1 Pg. 141-8
Melanoma	TYRP1	Mears et al., 2004
Melanoma	SILV	Mears et al., 2004
Melanoma	MLANA	Mears et al., 2004
Melanoma	MCAM	Mears et al., 2004
Melanoma	CD63	Azorsa et al. 1991
Melanoma	CD63	Barrio et al. 1998
Melanoma	CD63	Demetrick et al., 1992
Melanoma	CD63	Mete et al., 2005
Melanoma	CD63	Kwon et al., 2007
Melanoma	Alix	Mears et al., 2004, Proteomics 4(12): 4019-31.
Melanoma	hsp70	Mears et al., 2004, Proteomics 4(12): 4019-31
Melanoma	moesin	Mears et al., 2004, Proteomics 4(12): 4019-31.
Melanoma	p120 catenin	Mears et al., 2004, Proteomics 4(12): 4019-31
Melanoma	PGRL	Mears et al., 2004, Proteomics 4(12): 4019-31
Melanoma	syntaxin-binding protein 1 & 2	Mears et al., 2004, Proteomics 4(12): 4019-31
Melanoma	DUSP1	
Brain	PRMT8	Lee et al., 2005
Brain	BDNF	Binder and Scharfman, 2004
Brain	EGFR	Hicke et al., J. Biol. Chem. 276, 48644-48654, 2001; Daniels et al., PNAS 100, 15416-15421, 2003
Brain	DPPX	Kim et al., J. Biochem, 2001, Vol. 129, No. 2 289-295
Brain	Elk	Lhotak V et al., MOLECULAR AND CELLULAR BIOLOGY, May 1991, p. 2496-2502
Brain	Densin-180	Apperson ML et al., Journal of Neuroscience Volume 16, Number 21, Issue of November 1, 1996 pp. 6839-6852
Brain	BAI2	Shiratsuchi T et al., Cytogenet Cell Genet. 1997;79(1-2):103-8.
Brain	BAI3	Shiratsuchi T et al., Cytogenet Cell Genet. 1997;79(1-2):103-8.
Psoriasis	flt-1	Detmar M, et al., 1994
Psoriasis	VPF receptors	Detmar M, et al., 1994
Psoriasis	kdr	Detmar M, et al., 1994
CVD	FATP6	Gimeno RE et al., J Biol Chem. 2003 May 2;278(18):16039-44.
Hematological malignancies	CD44	Liu J and Jiang G, Il Mol Immunol. 2006 Oct;3(5):359-65.

FIG. 1d

Cancer Lineage, Group Comparison, Disease State	Antigens	References
Hematological malignancies	CD58	Kroger N, et al., 1997
Hematological malignancies	CD31	Kroger N, et al., 1998
Hematological malignancies	CD11a	Kroger N, et al., 1999
Hematological malignancies	CD49d	Kroger N, et al., 2000
Hematological malignancies	GARP	Wang R et al., PLoS ONE. 2008 Jul 16;3(7):e2705.
Hematological malignancies	BTS	Suenaga T et al., Eur J Immunol. 2007 Nov;37(11):3197-207.
Hematological malignancies	Raftlin	Saeki K et al., The EMBO Journal (2003) 22, 3015-3026
Hepatocellular Carcinoma	HBxAg	Wang W, et al., 1991
Hepatocellular Carcinoma	HBsAg	Wang W, et al., 1991
Hepatocellular Carcinoma	NLT	Simonson GD et al., Journal of Cell Science 107, 1065-1072 (1994)
Cervical Cancer	MCT-1	Pinheiro C, et al., 2008
Cervical Cancer	MCT-2	Pinheiro C, et al., 2008
Cervical Cancer	MCT-4	Pinheiro C, et al., 2008
Head and Neck Cancer	EGFR	Sheikh Ali MA et al., Cancer Sci. 2008 Aug;99(8):1589-94
Head and Neck Cancer	EphB4	Yavrouian EJ et al., Arch Otolaryngol Head Neck Surg. 2008 Sep;134(9):985-91.
Head and Neck Cancer	EphrinB2	Yavrouian EJ et al., Arch Otolaryngol Head Neck Surg. 2008 Sep;134(9):985-91.
Endometrial Cancer	AlphaV Beta6 integrin	Hecht JL et al., Appl Immunohistochem Mol Morphol. 2008 Aug 11.
Autoimmune Disease	Tim-2	Chakravarti S, et al., 2005
Irritable Bowel Disease	Il-16	Seegert D, et al., 2001
Irritable Bowel Disease	5-HT	Kerckhoffs AP et al., Neurogastroenterol Motil. 2008 Aug;20(8):900-7.
Irritable Bowel Disease	Il-1beta	Seegert D, et al., 2001
Irritable Bowel Disease	Il-12	Seegert D, et al., 2001
Irritable Bowel Disease	TNF-alpha	Seegert D, et al., 2001
Irritable Bowel Disease	interferon gamma	Seegert D, et al., 2001

FIG. 1e

Cancer Lineage, Group Comparison, Disease State	Antigens	References
Irritable Bowel Disease	Il-6	Seegert D, et al., 2001
Irritable Bowel Disease	Rantes	Seegert D, et al., 2001
Irritable Bowel Disease	MCP-1	Seegert D, et al., 2001
Diabetes	IL-6	Pradhan A, et al., 2001
Diabetes	CRP	Pradhan A, et al., 2001
Diabetes	RBP4	Lee SJ et al., Anal Chem. 2008 Apr 15;80(8):2867-73.
Barrett's Esophagus	p53	Hamelin R, et al., 1994
Barrett's Esophagus	MUC1	Burjonrappa SC et al., Indian J Cancer. 2007 Jan-Mar;44(1):1-5.
Barrett's Esophagus	MUC6	Glickman JN et al., Am J Surg Pathol. 2003 Oct;27(10):1357-65
Fibromyalgia	neopterin	Bonaccorso S, et al., 1997
Fibromyalgia	gp130	Maes M et al., 1999
Stroke	S-100	Missler U, et al., 1997
Stroke	Neuron specific enolase	Missler U, et al., 1997
Stroke	PARK7	Allard L, et al., 2005
Stroke	NDKA	Allard L, et al., 2005
Stroke	ApoC-I	Allard L, et al., 2005
Stroke	ApoC-III	Allard L, et al., 2003
Stroke	SAA	Allard L, et al., 2003
Stroke	AT-III fragment	Allard L, et al., 2003
Stroke	Lp-PLA2	http://www.doctorslounge.com/neurology/news/stroke_lp-pla2_crp.shtml; Gorelick PB, Am J Cardiol. 2008 Jun 16;101(12A):34F-40F
Stroke	hs-CRP	http://www.doctorslounge.com/neurology/news/stroke_lp-pla2_crp.shtml
Multiple Sclerosis	B7	Ferrante P, et al., 1998
Multiple Sclerosis	B7-2	Ferrante P, et al., 1998
Multiple Sclerosis	CD-95(fas)	Ferrante P, et al., 1998
Multiple Sclerosis	Apo-1/Fas	Ferrante P, et al., 1998
Parkinsons Disease	PARK2	Shimura H, eat al., 2000
Parkinsons Disease	Ceruloplasmin	Shi M et al., Neurobiol Dis. 2008 Sep 26.
Parkinsons Disease	VDBP	Zhang et al., 2008 Am. J. Clin. Pathol. 129, 526-9.,
Parkinsons Disease	tau	Zhang et al., 2008 Am. J. Clin. Pathol. 129, 526-9; Mollenhauer B et al., Dement Geriatr Cogn Disord; 2006;22(3):200-8; Davidsson P and Sjögren M, Dis Markers. 2005;21(2):81-92.
Parkinsons Disease	DJ-1	Waragai et al., 2007 Neurosci. Lett. 425, 18-22 & Waragai et at 2006 Biochem. Biophys. Res. Commun. 345, 967-72
Rheumatic Disease	Citrulinated fibrin a-chain	Skriner et al., 2006
Rheumatic Disease	CD5 antigen-like fibrinogen fragment D	Skriner et al., 2006

FIG. 1f

Cancer Lineage, Group Comparison, Disease State	Antigens	References
Rheumatic Disease	CD5 antigen-like fibrinogen fragment B	Skriner et al., 2006
Rheumatic Disease	TNFalpha	Anderson AK et al., Arthritis Res Ther. 2008;10(2):204. Epub 2008 Mar 14.
Alzheimers Disease	APP695	Rebeck G, et al., 2001
Alzheimers Disease	APP751	Rebeck G, et al., 2001
Alzheimers Disease	APP770	Rebeck G, et al., 2001
Alzheimers Disease	BACE1	Hebert SS et al., 2008. Proc Natl Acad Sci U.S.A., 105(17): 6415-20
Alzheimers Disease	Cystatin C	Simonsen et al., 2008 Neurobiol. Aging. 29, 961-8
Alzheimers Disease	Amyloid Beta	Simonsen et al., 2008 Neurobiol. Aging. 29, 961-8
Alzheimers Disease	t-Tau	Simonsen et al., 2008 Neurobiol. Aging. 29, 961-8
Alzheimers Disease	Complement factor H	Hye et al., 2006 Brain. 129, 3042-50
Alzheimers Disease	alpha-2-macroglobulin	Hye et al., 2006 Brain. 129, 3042-50
Alzheimers Disease	APOE4	Albert MS, Proc Natl Acad Sci U S A. 1996 Nov 26;93(24):13547-51.
Prion Diseases	PrPSc	Takemura K et al., Exp Biol Med (Maywood) Feb;231(2)204-14, 2006
Prion Diseases	14-3-3 zeta	Kubler E et at , British Medical Bulletin 66:267-279, 2003
Prion Diseases	S-100	Kubler E et al , British Medical Bulletin 66:267-279, 2003
Prion Diseases	AQP-4	Kubler E et al , British Medical Bulletin 66:267-279, 2003
Chronic Neuropathic Pain	Chemokine receptor (CCR2/4)	White FA et al., Proc Natl Acad Sci U S A. 2007 Dec 18;104(51):20151-8
Peripheral Neuropathic Pain	OX42 (rodent)	Blackbeard J et al., J Neurosci Methods. 2007 Aug 30;164(2):207-17
Peripheral Neuropathic Pain	ED9 (rodent)	Blackbeard J et al., J Neurosci Methods. 2007 Aug 30;164(2):207-17
Schizophrenia	ATP5B	Altar CA, Neuropsychopharmacology. 2008 Oct 15.
Schizophrenia	ATP5H	Altar CA, Neuropsychopharmacology. 2008 Oct 15.
Schizophrenia	ATP6V1B	Altar CA, Neuropsychopharmacology. 2008 Oct 15.
Schizophrenia	DNM1	Altar CA, Neuropsychopharmacology. 2008 Oct 15.
GIST	PDGFRA	Yang J et al., ncer. 2008 Oct 1;113(7):1532-43
GIST	c-kit	Yang J et al., ncer. 2008 Oct 1;113(7):1532-43
GIST	NHE-3	Kulaksiz H et al., Cell Tissue Res. 2001 Mar;303(3):337-43.
Renal Cell Carcinoma	HIF1alpha	Rathmell WK, Chen S, Expert Rev Anticancer Ther. 2008 Jan;8(1):63-73.
Renal Cell Carcinoma	VEGF	Rathmell WK, Chen S, Expert Rev Anticancer Ther. 2008 Jan;8(1):63-74.
Renal Cell Carcinoma	PDGFRA	Rathmell WK, Chen S, Expert Rev Anticancer Ther. 2008 Jan;8(1):63-74.
Cirrhosis	NLT	Simonson GD et al., Journal of Cell Science 107,1065-1072 (1994)
Cirrhosis	HBsAg	Wang, W. et al., 1991
Esophageal cancer	CaSR	Justinich CJ et al., Am J Physiol Gastrointest Liver Physiol. 2008 Jan;294(1):G120-9.

FIG. 1g

Cancer Lineage, Group Comparison, Disease State	Antigens	References
Influenza	Hemmaglutanin	Verma RK and Jain Amita, FEMS Immunol Med Microbiol 51 (2007) 453-461
Influenza	Neurominidase	Verma RK and Jain Amita, *supra.*
TB	Antigen 60	Verma RK and Jain Amita, *supra.*
TB	HSP antigen	Verma RK and Jain Amita, *supra.*
TB	Lipoarabinoman nan antigen	Verma RK and Jain Amita, *supra.*
TB	Antigen of acylated trehalose family	Verma RK and Jain Amita, *supra.*
TB	DAT antigen	Verma RK and Jain Amita, *supra.*
TB	Sulfolipid antigen	Verma RK and Jain Amita, *supra.*
TB	TAT antigen	Verma RK and Jain Amita, *supra.*
TB	Trehalose 6,6-dimycolate (cord-factor) antigen	Verma RK and Jain Amita, *supra.*
HIV	Gp41	Phogat S et al., J Intern Med. 2007 July ; 262(1): 26-43.
HIV	gp120	Phogat S et al., J Intern Med. 2007 July ; 262(1): 26-43.
Autism	VIP	Nelson KB et al Annals of Neurology 2001, 49:597-606..
Autism	PACAP	Nelson KB et al Annals of Neurology 2001, 49:597-606.
Autism	CGRP	Nelson KB et al Annals of Neurology 2001, 49:597-606.
Autism	NT3	Nelson KB et al Annals of Neurology 2001, 49:597-606.
Asthma	YKL-40	Scot, I., Thorax 2008;63:365, A New Biomarker in Asthma
Asthma	S-nitrosothiols	Holgate, ST., Lancet. 1998 May 2;351(9112):1317-9.
Asthma	SCCA2	Izuhara, K., Allergol Int. 2006 Dec ;55 (4):361-7.
Asthma	PAI	Izuhara, K., Allergol Int. 2006 Dec ;55 (4):361-7.
Asthma	amphiregulin	Izuhara, K., Allergol Int. 2006 Dec ;55 (4):361-7.
Asthma	Periostin	Izuhara, K., Allergol Int. 2006 Dec ;55 (4):361-7.
Lupus	TNFR	Suh CH and Kim HA, Expert Rev Mol Diagn. 2008 Mar;8(2):189-98
Vulnerable plaque	Alpha v Beta 3 integrin	Burtea C et al., Cardiovasc Res. 2008 Apr 1;78(1):148-57.
Vulnerable plaque	MMP9	Blankenberg S et al., 2003 Circulation 107:1579-1585.

FIG. 2a

Cancer Lineage, Group Comparison, Other Significant Disease State	Binding Agents	Select Reference(s)
Breast	Herceptin (Trastuzumab)	Adams GP, Weiner LM, Nat Biotechnol. 2005 Sep;23(9):1147-57.
Breast	CCND1 PNA	Tian et al , NAR 24(5-7):1085-91, 2005; Tian et al., Ann NY Acad Sci 1059, 106-44, 2005
Breast	MYC PNA	Tian et at , NAR 24(5-7):1085-91, 2005; Tian et al., Ann NY Acad Sci 1059, 106-44, 2005
Breast	IGF-1 PNA	Tian et al , J. of Nucl Med 48(10), 1699-707, 20007
Breast	MYC PNA	Tian et al., Bioconjug Chem 16)1)70-9, 2005
Breast	SC4 aptamer (Ku)	Zhang et al. 2004
Breast	All-7 aptamer (ERB2)	Kunz et al., MolecularCancer Research(4) 983998, 2006
Breast	Galectin -3 binding agent	Cancer Invest 26(6)615-23, 2008
Breast	mucin-type O-glycans binding agent	Cancer Invest 26(6)615-23, 2008
Breast	L-PHA binding agent	Abbott et al., J Proteome Res 7(4)1470-80, 2008
Breast	Galectin-9 binding agent	Yamaguchi et al., Breast J 5(2), 2006
Breast	ER	Payne SJ et al., Histopathology. 2008 Jan;52(1):82-90.
Breast	PR	Payne SJ et al., Histopathology. 2008 Jan;52(1):82-90.
Ovarian	(90)Y-muHMFG1 binding agent	Oei et al 2008
Ovarian	OC125 (anti-CA125 antibody)	Matsuoka et al 1987
Ovarian	monoclonal antibodies (HMFG1, HMFG2, H317, and H17E2), Hu2PLAP	Kosmas et al , Oncology 55 (5),435-446, 1998
Lung	SCLC specific aptamer HCA 12	Chen et at , Chem Med Chem (3)991-1001, 2008
Lung	SCLC specific aptamer HCC03	Chen et al , Chem Med Chem (3)991-1001, 2008
Lung	SCLC specific aptamer HCH07	Chen et al , Chem Med Chem (3)991-1001, 2008
Lung	SCLC specific aptamer HCH01	Chen et at , Chem Med Chem (3)991-1001, 2008
Lung	A-p50 aptamer (NF-KB)	Mi et al., Mol Ther 16(1)66-73, 2008
Lung	Cetuximab	Rossi A et al., Rev Recent Clin Trials. 2008 Sep;3(3):217-27
Lung	Panitumumab	Rossi A et al., Rev Recent Clin Trials. 2008 Sep;3(3):217-27
Lung	Bevacizumab	Gettinger S et al., Semin Respir Crit Care Med. 2008 Jun;29(3):291-301
Lung	L19 antibody	Pedretti et al., Lung Cancer Sep 15, 2008
Lung	F16 antibody	Pedretti et al., Lung Cancer Sep 15, 2008
Lung	anti-CD45 (anti-ICAM-1 antibody, aka UV3)	Brooks et al., Int J Cancer 2438(10)2438-45, 2008
Lung	L2G7 Ab (anti-HGF antibody)	Stabile et al., Mol Cancer Ther 7(7)1913-22, 2008
Colon	angiopoietin 2 specific aptamer	Sarraf-Yazdi et al., J SURG Res 146(1)16-23, 2008.

FIG. 2b

Cancer Lineage, Group Comparison, Other Significant Disease State	Binding Agents	Select Reference(s)
Colon	beta-catenin aptamer	Lee et al., Cancer Research 66(21)10560-6, 2006.
Colon	TCF1 aptamer	Choi et al., Mol Caner Therapy (9)2428-34, 2006.
Colon	anti-Derlin1 antibody	Ran et al., Clin Cancer Res 14(206538-45, 2008
Colon	anti-RAGE antibody	Turovskaya et al., Carcinogenesis 29(10)2035-2043, 2008.
Colon	monoclonal antibody gb3.1	Turovskaya et al., Carcinogenesis 29(10)2035-2043, 2008.
Colon	Galectin-3 binding agent	Greco et al., Glycobiology 14(9)783-92, 2004.
Colon	Cetuximab	Giuliani F, Colucci G et al., Int J Biol Markers. 2007 Jan-Mar;22(1 Suppl 4):S62-70
Colon	Panitumumab	Chua YJ, Cunningham D, Clin Colorectal Cancer. 2005 Nov;5 Suppl 2:S81-8.
Colon	Matuzumab	Chua YJ, Cunningham D, Clin Colorectal Cancer. 2005 Nov;5 Suppl 2:S81-8.
Colon	Bevacizumab	Majer M et al., Anticancer Agents Med Chem. 2007 Sep;7(5):492-503
Colon	Mac-2 binding agent	Lotz MM et al., Proc Natl Acad Sci U S A. 1993 90(18): 8319-23, "Mitogen-activated protein kinases p42mapk and p44mapk are required for fibroblast proliferation."
Adenoma versus CRC	Complement C3	Qui et al , J of Proteome Res 7(4)1693-1703, 2008
Adenoma versus CRC	histidine-rich glycoprotein binding agent	Qui et al , J of Proteome Res 7(4)1693-1703, 2008
Adenoma versus CRC	kininogen-1 binding agent	Qui et al , J of Proteome Res 7(4)1693-1703, 2008
Adenoma versus CRC	Galectin-3 binding agent	Schoeppner HL et al., Cancer. 1995 Jun 15;75(12):2818-26.
Adenoma with low grade versus high grade dysplasia	Galectin-3 binding agent	Schoeppner HL et al., Cancer. 1995 Jun 15;75(12):2818-26.
CRC versus normal	anti-ODC monoclonal antibody	Hu HY et al., World J Gastroenterol. 2005 Apr 21;11(15):2244-8.
CRC versus normal	anti-CEA monoclonal antibody	Zhang HZ et al., Cancer Res. 1989 Oct 15;49(20):5766-73.
CRC versus normal	Mac-2 binding agent	Lotz MM et al., Proc Natl Acad Sci U S A. 1993 Apr 15;90(8):3466-70.
Prostate	PSA binding agent	Nurmikko P et al., 2000, Clin Chem 46(10): 1610-8.
Prostate	PSMA binding agent	Aggarwal S et al., Cancer Res. 2006 Sep 15;66(18):9171-7.
Prostate	TMPRSS2 binding agent	Wilson S et al., Biochem J. 2005 Jun 15;388(Pt 3):967-72.
Prostate	monoclonal antibody 5D4	Sawant et al., J Drug Target 16(7)601-4, 2008.
Prostate	XPSM-A9	Lupold et al., Cancer Research 62(14): 4029-4033, 2002.
Prostate	XPSM-A10	Lupold et al., Cancer Research 62(14): 4029-4033, 2002.
Prostate	Galectin-3 binding agent	Califice et al., Int J Oncol 25(4)983-92, 2004
Prostate	E-selectin binding agent	Bhaskar et al., Cancer Research 63(19(6387-94, 2003.

FIG. 2c

Cancer Lineage, Group Comparison, Other Significant Disease State	Binding Agents	Select Reference(s)
Prostate	Galectin-1 binding agent	van den Brule et al., J Pathology 193(1)80-7, 2001
Prostate	E4 (IgG2a kappa)	Nilsson S et al., Cancer Biother Radiopharm. 1997 Dec;12(6):395-403.
Melanoma	Tremelimumab (anti-CTLA4 antibody)	Camacho LH, Expert Opin Investig Drugs 17(3)371-85, 2008.
Melanoma	1pilimumumab (anti-CTLA4 antibody)	Lens M et al., Recent Patents Anticancer Drug Discovery Jun3(2)105-13, 2008.
Melanoma	CTLA-4 aptamers	Santulli-Marotto et al., Cancer Research 63(21)7483-9, 2003.
Melanoma	STAT-3 peptide aptamers	Nagel Wolfrum et al., Molecular Cancer Research 2:170-182, 2004
Melanoma	Galectin-1 binding agent	Mathieu et al., J Invest Dermatol 127(10)2399-410, 2007, Le Mercier et al., J Neuropathol Exp Neurol. 67(5)456-69, 2008.
Melanoma	Galectin-3 binding agent	Prieto et al., Clin Cancer Res 12(22)6709-15, 2006; Vereecken et al., Arch Dermatol Res 296(8)353-8, 2005
Melanoma	PNA	Dore et al., Pigment Cell Res 7(6)461-4, 1994.
Pancreatic	H38-15 (HGF aptamer)	Saito T and Tomida M, DNA Cell Biol. 2005 Oct;24(10):624-33.
Pancreatic	H38-21(HGF aptamer)	Saito T and Tomida M, DNA Cell Biol. 2005 Oct;24(10):624-33.
Pancreatic	Matuzumab	Kleepspeies A et al., Clin Cancer Res. 2008 Sep 1;14(17):5426-36
Pancreatic	Cetuximanb	Burris H 3rd et al., Oncologist. 2008 Mar;13(3):289-98.
Pancreatic	Bevacizumab	Burris H 3rd et al., Oncologist. 2008 Mar;13(3):289-98.
Brain	aptamer 111.1 (pigpen)	Blank Met al., JBC May 11; 276(19)16464-8, 2001
Brain	TTA1 (Tenascin-C) aptamer	Hicke et al., J. Biol. Chem. 276, 48644-48654, 2001; Daniels et al., PNAS 100, 15416-15421, 2003
Psoriasis	E-selectin binding agent	Rottman JB et al., Lab Invest. 2001 Mar;81(3):335-47.
Psoriasis	ICAM-1 binding agent	Rottman JB et al., Lab Invest. 2001 Mar;81(3):335-47.
Psoriasis	VLA-4 binding agent	Rottman JB et al., Lab Invest. 2001 Mar;81(3):335-47.
Psoriasis	VCAM-1 binding agent	Rottman JB et al., Lab Invest. 2001 Mar;81(3):335-47.
Psoriasis	alphaEbeta7 binding agent	Rottman JB et al., Lab Invest. 2001 Mar;81(3):335-47.
Cardiovascular Disease	RB007 (factor IXA aptamer)	Chan MY et al., Circulation. 2008 Jun 3;117(22):2865-74. Epub 2008 May 27
Cardiovascular Disease	ARC1779 (anti VWF) aptamer	Gilbert JC et al., Circulation. 2007 Dec 4;116(23):2678-86. Epub 2007 Nov 19
Cardiovascular Disease	LOX1 binding agent	Dunn S et al., Biochem J. 2008 Jan 15;409(2):349-55.
Hematological malignancies	anti-CD20	Ravandi F et al., Clin Cancer Res. 2003 Feb;9(2):535.
Hematological malignancies	anti-CD52	Ravandi F et al., Clin Cancer Res. 2003 Feb;9(2):535.
B-Cell Chronic Lymphocytic Leukemias	Rituximab	Robak T, Leuk Lymphoma. 2004 Feb;45(2):205-19.

FIG. 2d

Cancer Lineage, Group Comparison, Other Significant Disease State	Binding Agents	Select Reference(s)
B-Cell Chronic Lymphocytic Leukemias	Alemtuzumab	Robak T, Leuk Lymphoma. 2004 Feb;45(2):205-19.
B-Cell Chronic Lymphocytic Leukemias	Apt48 (BCL6)	Chattopadhyay et al 2006, J Assoc Physicians India 54: 547.
B-Cell Chronic Lymphocytic Leukemias	R0-60 aptamer	Wu CC et al., Hum Gene Ther. 2003 Jun 10;14(9):849-60.
B-Cell Chronic Lymphocytic Leukemias	D-R15-8 aptamer	Wu CC et al., Hum Gene Ther. 2003 Jun 10;14(9):849-60.
B-cell lymphoma	Ibritumomab	Cheson BD, Leonard JP, N Engl J Med. 2008 Aug 7;359(6):613-26.
B-cell lymphoma	Tositumomab	Cheson BD, Leonard JP, *supra.*
B-cell lymphoma	Anti-CD20 Antibodies	Cheson BD, Leonard JP, *supra.*
B-cell lymphoma	Alemtuzumab	Cheson BD, Leonard JP, *supra.*
B-cell lymphoma	Galiximab	Cheson BD, Leonard JP, *supra.*
B-cell lymphoma	Anti-CD40 Antibodies	Cheson BD, Leonard JP, *supra.*
B-cell lymphoma	Epratuzumab	Cheson BD, Leonard JP, *supra..*
B-cell lymphoma	Lumiliximab	Cheson BD, Leonard JP, *supra.*
B-cell lymphoma	Monoclonal antibody Hu1D10	Cheson BD, Leonard JP, *supra.*
B-cell lymphoma-DLBCL	Galectin-3 binding agent	D'Haene N et al., Int J Immunopathol Pharmacol. 2005 Jul-Sep;18(3):431-43.
B-cell lymphoma	Apt48	Chattopadhyay A et al., Oncogene. 2006 Apr 6;25(15):2223-33.
Burkitt's lymphoma	TD05 aptamer	Mallikaratchy P et al., Mol Cell Proteomics Dec; 6(12)2230-8, 2007.
Burkitt's lymphoma	IgM monoclonal antibody (38-13)	Wiels J et al., Cancer Res. 1984 Jan;44(1):129- 33.
Cervical Cancer	Galectin-9 binding agent	Liang et al., Clin Oncol 134(8)899-907, 2008.
Cervical Cancer	HPVE7 aptamer	Nauenburg S et al., FASEB J. 2001 Mar;15(3):592-4. Epub 2001 Jan 19.
Endometrial Cancer	Galectin-1 binding agent	Mylonas I et al., Anticancer Res. 2007 JulAug;27(4A):1975-80.
Head and Neck Cancer	(111)In-cMAb U36	Sandstrom K et al., Tumour Biol. 2008;29(3):137-44.
Head and Neck Cancer	anti-LOXL4 antibody	Weise JB et al., Eur J Cancer. 2008 Jun;44(9):1323-31.
Head and Neck Cancer	U36 monoclonal antibody	Verel I et al., Int J Cancer. 2002 May 20;99(3):396-402.
Head and Neck Cancer	BIWA-1 monoclonal antibody	Verel I et al., Int J Cancer. 2002 May 20;99(3):396-402.

FIG. 2e

Cancer Lineage, Group Comparison, Other Significant Disease State	Binding Agents	Select Reference(s)
Head and Neck Cancer	BIWA-2 monoclonal antibody	Verel I et al., Int J Cancer. 2002 May 20;99(3):396-402.
Head and Neck Cancer	BIWA-4 monoclonal antibody	Verel I et al., Int J Cancer. 2002 May 20;99(3):396-402.
Head and Neck Cancer	BIWA-8 monoclonal antibody	Verel I et al., Int J Cancer. 2002 May 20;99(3):396-402.
Irritable Bowel Disease	ACCA (anti-glycan antibody)	Li X et al., World J Gastroenterol. 2008 Sep 7;14(33):5115-24.
Irritable Bowel Disease	ALCA(anti-glycan antibody)	Li X et al., World J Gastroenterol. 2008 Sep 7;14(33):5115-24.
Irritable Bowel Disease	AMCA (anti-glycan antibody)	Li X et al., World J Gastroenterol. 2008 Sep 7;14(33):5115-24.
Diabetes	RBP4 aptamer	Lee SJ et al., Anal Chem. 2008 Apr 15;80(8):2867-73.
Fibromyalgia	L-selectin binding agent	Macedo JA et al., J Neuroimmunol. 2007 Aug;188(1-2):159-66,.
Multiple Sclerosis	Natalizumab (Tysabri)	Goodin DS et al., Neurology. 2008 Sep 2;71(10):766-73.
Rheumatic Disease	Rituximab (anti-CD20 antibody)	Anderson AK et al., Arthritis Res Ther. 2008;10(2):204. Epub 2008 Mar 14.
Rheumatic Disease	Keliximab (anti-CD4 antibody)	Anderson AK et al., Arthritis Res Ther. 2008;10(2):204. Epub 2008 Mar 14.
Alzheimers Disease	TH14-BACE1 aptamers	Rentmeister A et al., RNA. 2006 Sep;12(9):1650-60. Epub 2006 Aug 3
Alzheimers Disease	S10-BACE1 aptamers	Rentmeister A et al., RNA. 2006 Sep;12(9):1650-60. Epub 2006 Aug 3
Alzheimers Disease	anti-Abeta monoclonal antibody	Geylis V et al., Autoimmun Rev. 2006 Jan;5(1):33-9. Epub 2005 Aug 1. Review.
Alzheimers Disease	Bapineuzumab (AAB-001) - Elan	Hock C et al., Neuron. 2003 May 22;38(4):54754
Alzheimers Disease	LY2062430 (anti-amyloid beta Ab)-Eli Lilly	Irena Melnikova, Nature Reviews Drug Discovery 6, 341-342 (May 2007)
Alzheimers Disease	BACE1-Anti sense	Faghihi MA et al., Nat Med. 2008 Jul;14(7):723- 30. Epub 2008 Jun 29
Prion Diseases	rhuPrP© aptamer	Takemura K et al., Exp Biol Med (Maywood) Feb;231(2)204-14, 2006
Prion Diseases	DP7 aptamer	Proske D et al., Chembiochem. 2002 Aug 2;3(8):717-25.
Prion Diseases	Thioaptamer 97	King DJ et al., J Mol Biol. 2007 Jun 15;369(4):1001-14. Epub 2007 Feb 9
Prion Diseases	SAF-93 aptamer	Rhie A et al., J Biol Chem. 2003 Oct 10;278(41):39697-705. Epub 2003 Aug 5
Prion Diseases	15B3 (anti-PrPSc antibody)	Korth C et al., Nature 390:74-77, 1997
Prion Diseases	monoclonal anti PrPSc antibody P1:1	Jones M et al., Brain Pathol. 2008 May 26.
Prion Diseases	1.5D7, 1.6F4 antibodies	Cordes H, J Immunol Methods Sep 15;337(2)106-20, 2008

FIG. 2f

Cancer Lineage, Group Comparison, Other Significant Disease State	Binding Agents	Select Reference(s)
Prion Diseases	monoclonal antibody 14D3	Krasemann S et al., Mol Med. 1996 Nov;2(6):725-34
Prion Diseases	monoclonal antibody 4F2	Krasemann S et al., Mol Med. 1996 Nov;2(6):725-34
Prion Diseases	monoclonal antibody 8G8	Krasemann S et al., Mol Med. 1996 Nov;2(6):725-34
Prion Diseases	monoclonal antibody 12F10	Krasemann S et al., Mol Med. 1996 Nov;2(6):725-34
Sepsis	HA-1A monoclonal antibody	Cross AS and Opal S Journal of Endotoxin Research, Vol. 1, No. 1, 57-69 (1994)
Sepsis	E-5 monoclonal antibody	Cross AS and Opal S Journal of Endotoxin Research, Vol. 1, No. 1, 57-69 (1994)
Sepsis	TNF-alpha monoclonal antibody	Abraham E et al., JAMA Vol. 273 No. 12, March 22, 1995
Sepsis	Afelimomab	Vincent JL Int J Clin Pract. 2000 Apr;54(3):190- 3
Sepsis	E-selectin binding agent	Tsokos M et al., Int Journal of Legal Medicine, Volume 113, Number 6:338-342, 2000
Schizophrenia	L-selectin binding agent	Iwata Y et al., Schizophr Res. 2007 Jan;89(1- 3):154-60. Epub 2006 Oct 17
Schizophrenia	N-CAM binding agent	Vawter MP et al., Exp Neurol. 1998 Feb;149(2):424-32
Depression	GPIb binding agent	Walsh MT et al., Life Sci. 2002 May 17;70(26):3155-65
GIST	anti-DOG1 antibody	Espinosa F et al., Am J Surg Pathol Feb;32(2)210-8, 2008
Esophageal cancer	CaSR binding agent	Justinich CJ et al., Am J Physiol Gastrointest Liver Physiol. 2008 Jan;294(1):G120-9.
Gastric cancer	Calpain nCL-2 binding agent	Hata et al., J. Biol. Chem., Vol. 281, Issue 16, 11214-11224, April 21, 2006
Gastric cancer	drebrin binding agent	Keon BH et al., Journal of Cell Science, Vol 113, Issue 2 325-336
Osteoarthritis	DDR-2 binding agent	Xu et al., Arthritis Rheum. 2007 Aug;56(8):2663-73.
COPD	CXCR3 binding agent	Freeman CM et al., Am J Pathol. 2007 Sep;171(3):767-76.
COPD	CCR5 binding agent	Freeman CM et al., Am J Pathol. 2007 Sep;171(3):767-76.
COPD	CXCR6 binding agent	Freeman CM et al., Am J Pathol. 2007 Sep;171(3):767-76.
Asthma	VIP binding agent	Nelson KB et alAnnals of Neurology 2001, 49:597-606.
Asthma	PACAP binding agent	Nelson KB et alAnnals of Neurology 2001, 49:597-606..
Asthma	CGRP binding agent	Nelson KB et alAnnals of Neurology 2001, 49:597-606..
Asthma	NT3 binding agent	Nelson KB et alAnnals of Neurology 2001, 49:597-606..
Asthma	YKL-40 binding agent	Scot, I., Thorax 2008;63:365, A New Biomarker in Asthma
Asthma	S-nitrosothiols	Holgate, ST., Lancet. 1998 May 2;351(9112):1317-9.
Asthma	SCCA2 binding agent	Izuhara, K., Allergol Int. 2006 Dec ;55 (4):3617.
Asthma	PAI binding agent	Izuhara, K., Allergol Int. 2006 Dec ;55 (4):3617.
Asthma	amphiregulin binding agent	Izuhara, K., Allergol Int. 2006 Dec ;55 (4):3617.
Asthma	Periostin binding agent	Izuhara, K., Allergol Int. 2006 Dec ;55 (4):3617.
Vulnerable plaque	Gd-DTPA-g-mimRGD (Alpha v Beta 3 integrin binding peptide)	Burtea C et al., Cardiovasc Res. 2008 Apr 1;78(1):148-57.
Vulnerable plaque	MMP-9 binding agent	Blankenberg S et al., 2003 Circulation 107:1579-1585.

FIG. 3a

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins Ligands Peptides	snoRNA	Select Reference(s)
Breast	miR-21	let-7					Iorio et al., Cancer Research 65, 7065-7070, August 15, 2005.
Breast	miR-155	miR-10b					Iorio et al., *supra.*
Breast	miR-206	miR-125a					Iorio et al., *supra.*
Breast	miR-122a	miR-125b					Iorio et al., *supra.*
Breast	miR-210	miR-145					Iorio et al., *supra.*
Breast		miR-143					Michael et al.Mol Cancer Res 1: 882-891, 2003.
Breast		miR-145					Michael et al.*supra*
Breast		miR-16					Michael et al.*supra*
Breast		let-7					Michael et al.*supra.*
Breast	miR-21	let-7					Lu et al. Nature 435: 834-838, 2005.
Breast	miR-21	let-7					Volinia et al. Proc Natl Acad Sci USA 103: 2257-2261, 2006.
Breast	miR-155	miR-10b					Volinia et al. *supra.*
Breast	miR-206	miR-125a					Volinia et al. *supra.*
Breast	miR-122a	miR-125b					Volinia et al. *supra.*
Breast	miR-210	miR-145					Volinia et al. *supra.*
Breast	miR-21						Si et al. Oncogene 26: 2799-2803, 2006.
Breast					hsp70		Wolfers et al. 2001 Nat Med 793): 297-302.
Breast					MART-1		Wolfers et al. 2001 Nat Med 793): 297-302.
Breast					TRP		Wolfers et al. 2001 Nat Med 793): 297-302.
Breast					HER2		Wolfers et al. 2001 Nat Med 793): 297-302.
Breast					hsp70		Koga et al., 2005, Antican, Res 25(6A):3703-5
Breast					MART-1		Koga et al., *supra.*
Breast					TRP		Koga et al., *supra.*
Breast					HER2		Koga et al., *supra.*
Breast	.				GASS		Mourtada-Maarabouni et at 2008
Breast			ER		ER		Oldenhuls CN et al., Eur J Cancer. 2008 May;44(7):946- 53. Epub 2008 Apr 7; Payne SJ et al., Histopathology. 2008 Jan;52(1):82-90
Breast			PR		PR		Oldenhuis et al., *supra.*; Payne et al., *supra.*
Breast			HER2				Oldenhuis et al., *supra.*; Payne et al., *supra*

FIG. 3b

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins Ligands Peptides	snoRNA	Select Reference(s)
Breast			MUC1				Singh R, Bandyopadhyay D, Cancer Biol Ther. 2007 Apr;6(4):481-6
Breast					Class III b-tubulin		Galmarini CM et al., Clin Cancer Res. 2008 Jul 15;14(14):4511-6
Breast			EGFR				Rajkumar T, Gullick WJ, Breast Cancer Res Treat. 1994 Jan;29(1):3-9
Breast				KRAS			Hollestelle A et al., Mol Cancer Res. 2007 Feb;5(2):195-201
Breast					VEGFA		Linderholm BK et al., Cancer Res. 2001 Mar 1:61(5):2256-60
Breast				B-Raf			Hollestelle A et al., Mol Cancer Res. 2007 Feb;5(2):195-201
Breast				CYP2D6			Punglia RS et al., J Natl Cancer Inst. 2008 May 7;100(9):642-8

FIG. 4a

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins Ligands Peptides	snoRNA	Select Reference(s)
Ovarian			ERCC1				Rosell R "et al., Drugs Today (Barc). 2003 Oct;39(10):775-86
Ovarian			ER				Geisler JP et al., Eur J Gynaecol Oncol. 2008;29(2):126-8; Fujimoto J et al., J Steroid Biochem Mol Biol. 2007 May;104(3-5):301-4
Ovarian			TOP01				Naniwa, J et al., . Int J Gynecol Cancer, 2007. 17(1): p. 76-82
Ovarian			TOP2A				Chekerov R et al., Neoplasia. 2006 Jan;8(1):38-45.
Ovarian			AR				Ito K et al., Int J Cancer. 2002 Jun 10;99(5):652-7; Akahira JI et al., Jpn J Cancer Res. 2001 Sep;92(9):926-32
Ovarian			PTEN				Chen Y et al., Chin Med Sci J. 2004 Mar;19(1):25-30
Ovarian			HER2/ neu				Mileo AM et al., Int J Biol Markers. 1992 Jan-Mar;7(1):47-51
Ovarian			EGFR				Vermeij J et al., BMC Cancer. 2008 Jan 8;8:3; Lassus H et al., J Mol Med. 2006 Aug;84(8):671-81
Ovarian				KRAS			Mayr D et al., Gynecol Oncol. 2006 Dec;103(3):883-7
Ovarian					VEGFA		Osada R et al., Hum Pathol. 2006 Nov;37(11):1414-25.
Ovarian					VEGFR2		Chen BY et al., Zhonghua Zhong Liu Za Zhi. 2005 Jan;27(1):33-7
Ovarian				B-Raf			Sieben NL et al., J Pathol. 2004 Mar;202(3):336-40
Ovarian	miR-200a	miR-199a					lorio el al. Cancer Res. 2007; 67: (18). September 15, 2007
Ovarian	miR-141	miR-140					lorio el al. *Supra.*
Ovarian	miR-200c	miR-145					lorio el al. *Supra.*
Ovarian	miR-200b	miR-125b-1					lorio el al. *Supra.*
Ovarian					HER2		Steffensen KD et al., Int J Oncol. 2008 Jul;33(1):195-204

FIG. 4b

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins Ligands Peptides	snoRNA	Select Reference(s)
Ovarian	miR-21						Taylor et al., Gynecologic Oncology 110 (2008) 13-21.
Ovarian	miR-141						Taylor et al., *supra.*
Ovarian	miR-200a						Taylor et al., *supra.*
Ovarian	miR-200b						Taylor et al., *supra.*
Ovarian	mIR-200c						Taylor et al., *supra.*
Ovarian	miR-203						Taylor et al., *supra..*
Ovarian	miR-205						Taylor et al., *supra..*
Ovarian	miR-214						Taylor et al., *supra.*
Ovarian	miR-215						Taylor et al., *supra..*

FIG. 5

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins Ligands Peptides	snoRNA	Select Reference(s)
Lung	miR-21						Markou A et al., Clin Chem. 2008 Oct;54(10):1696-704
Lung	miR-205						Markou A et al., *supra.*
Lung	miR-221						Garofalo M et al., Oncogene. 2008 Jun 19;27(27):3845-55
Lung	miR-221 (protective)						Yu SL et al., Cancer Cell. 2008 Jan;13(1):48-57
Lung	Let-7a(protective)						Yu SL et al., *supra.*
Lung	miR-137 (risky)						Yu SL et al., *supra.*
Lung	miR-372(risky)						Yu SL et al., *supra.*
Lung	miR-122a(risky)						Yu SL et al., *supra.*
Lung			EGFR				Rosell R et al., Clin Cancer Res. 2006 12(24):7222-31
Lung					KRAS		Zhang Z et al., Cancer Biol Ther. 2006 Nov;5(11):1481-6
Lung			PTEN				Sos ML et al., J Thorac Oncol. 2008 Feb;3(2):170-3
Lung			RRM1				Souglakos et al., 2008; Rosell et al., 2004
Lung			RRM2				Souglakos et al., 2008
Lung					hENT1		Oguri T et al., Cancer Lett. 2007 Oct 18;256(1):112-9.
Lung			ABCB1				Sekine I et al., J Thorac Oncol. 2006 Jan;1(1):31-7; Ushijima R et al., Anticancer Res. 2007 Nov-Dec;27(6C):4351-8
Lung			ABCG2				Nakano H et al., Cancer. 2008 Mar 1;112(5):1122-30
Lung			LRP				Paredes Lario A et al., Arch Bronconeumol. 2007 Sep;43(9):479-84
Lung			class III b-tubulin				Sève P et al., Clin Cancer Res. 2005 Aug 1;11(15):5481-6; Sève P, Clin Cancer Res. 2007 Feb 1;13(3):994-9
Lung				EGFR			Rosell R et al., Clin Cancer Res. 2006 Dec 15;12(24):7222-31
Lung				KRAS			Massarelli E et al., Clin Cancer Res, 2007. 13(10): p. 2890-6
Lung				B-Raf			Yousem SA et al., Am J Surg Pathol. 2008 Sep;32(9):1317-21.
Lung				UGT1A1			Han JY et al., J Clin Oncol. 2006 May 20;24(15):2237-44
Lung			VEGFR 2/3				PCT Publication No. WO/2009/105223

FIG. 6a

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins Ligands Peptides	snoRNA	Select Reference(s)
Colon		miR-143					Michael et al., 2003, Mol Cancer Res 1(12): 882-91
Colon		miR-145					Michael et al., 2003, *supra.*
Colon		miR-143					Akao et al., 2006, Oncol Rep 16(4): 845-50
Colon		miR-126					Guo et al., 2008, Plant Physiol 165(16): 1745-55
Colon		miR-34b					Toyota et al., 2008, Cancer Res 68(11): 4123-31
Colon		miR-34c					Toyota et al., 2008, *supra.*
Colon		let-7					Akao et al., 2006, Oncol Rep, 16(4): 845-50
Colon	miR-24-1						Volinia et al. Proc Natl Acad Sci USA 103: 2257-2261, 2006.
Colon	miR-29b-2						Volinia et al. *supra.*
Colon	miR-20a						Volinia et al. *supra.*
Colon	miR-10a		.				Volinia et al. *supra.*"
Colon	miR-32						Volinia et al. *supra.*
Colon	miR-203						Volinia et al. *supra.*
Colon	miR-106a						Volinia et al. *supra.*
Colon	miR-17-5p						Volinia et al. *supra.*
Colon	miR-30c						Volinia et al. *supra.*
Colon	miR-223						Volinia et al. *supra.*
Colon	miR-126						Volinia et al. *supra.*"
Colon	miR-128b						Volinia et al. *supra.*
Colon	miR-21						Volinia et al. *supra.*
Colon	miR-24-2						Volinia et al. *supra.*
Colon	miR-99b						Volinia et al. *supra.*
Colon	miR-155						Volinia et al. *supra.*
Colon	miR-213						Volinia et al. *supra.*
Colon	miR-150						Volinia et al. *supra.*
Colon	miR-107						Volinia et al. *supra.*
Colon	miR-191						Volinia et al. *supra.*"
Colon	miR-221						Volinia et al. *supra.*
Colon		miR-9-3					Volinia et al. *supra.*
Colon		miR-34a					Tazawa et al., 2007, J Urol, 156(3): 967-71
Colon		miR-145					Schepeler et al., 2008, Cancer Res, 68(15): 6416-23
Colon		miR-455					Schepeler et al., *supra.*
Colon		miR-484					Schepeler et al., *supra.*
Colon		miR-101					Schepeler et al., *supra.*
Colon	miR-20a						Schepeler et al., *supra.*
Colon	MiR-510						Schepeler et al., *supra.*
Colon	miR-92						Schepeler et al., *supra.*
Colon	miR-513						Schepeler et al., *supra.*

FIG. 6b

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins Ligands Peptides	snoRNA	Select Reference(s)
Colon	miR-19a						Bandres et al., 2006, Mol Cancer, 5:29
Colon	miR-21						Bandres et al., *supra.*
Colon	miR-20						Bandres et al., *supra.*
Colon	miR-183						Bandres et al., *supra.*
Colon	miR-96						Bandres et al., *supra.*
Colon	miR-135b						Bandres et al., *supra.*
Colon	miR-31						Bandres et al., *supra.*
Colon		miR-145					Bandres et al., *supra.*36
Colon		miR-133b					Bandres et al., *supra.*
Colon		miR-129					Bandres et al., *supra.*
Colon		miR-124a					Bandres et al., *supra.*
Colon		miR-30-3p					Bandres et al., *supra.*
Colon		miR-328					Bandres et al., *supra.*
Colon		miR-106a					Diaz et al., 2008, Br J Anaesth, 101(2): 161-4
Colon		miR-17-5p					Diaz et al., *supra.*
Colon	mIR-21						Schetter et al. 2008, JAMA, 299(4): 425
Colon	miR-92						Schetter et al. *supra.*
Colon	miR-222						Schetter et al. *supra.*
Colon	miR-181b						Schetter et al. *supra.*
Colon	miR-210						Schetter et al. *supra.*
Colon	miR-20a						Schetter et al. *supra.*
Colon	miR-106a						Schetter et al. *supra.*
Colon	miR-93						Schetter et al. *supra.*
Colon	miR-335						Schetter et al. *supra.*
Colon	miR-338						Schetter et al. *supra.*
Colon	miR-133b						Schetter et al. *supra.*
Colon	miR-346						Schetter et al. *supra.*
Colon	miR-106b						Schetter et al. *supra.*
Colon	miR-153a						Schetter et al. *supra.*
Colon	miR-219						Schetter et al. *supra.*
Colon	miR-34a						Schetter et al. *supra.*
Colon	miR-99b						Schetter et al. *supra.*
Colon	miR-185						Schetter et al. *supra.*
Colon	miR-223						Schetter et al. *supra.*
Colon	miR-211						Schetter et al. *supra.*
Colon	miR-135a						Schetter et al. *supra.*
Colon	miR-127						Schetter et al. *supra.*
Colon	miR-203						Schetter et al. *supra.*
Colon	miR-212						Schetter et al. *supra.*
Colon	miR-95						Schetter et al. *supra.*
Colon	miR-17-5p						Schetter et al. *supra.*
Colon		miR-342					Schetter et al. *supra.*
Colon		miR-192					Schetter et al. *supra.*
Colon		miR-1					Schetter et al. *supra.*
Colon		miR-34b					Schetter et al. *supra.*

FIG. 6c

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins Ligands Peptides	snoRNA	Select Reference(s)
Colon		miR-215					Schetter et al. *supra.*
Colon		miR-192					Schetter et al. *supra.*
Colon		miR-301					Schetter et al. *supra.*
Colon		miR-324-5p					Schetter et al. *supra.*
Colon		miR-30a-3p					Schetter et al. *supra.*
Colon		miR-34c					Schetter et al. *supra.*
Colon		miR-331					Schetter et al. *supra.*
Colon		miR-148b					Schetter et al. *supra.*
Colon					AFRs		Choi et al., 2007, J Ethnopharmacol 110(1): 49-55.
Colon					Rabs		Choi et al., *supra.*
Colon					ADAM10		Choi et al., *supra.*
Colon					CD44		Choi et al., *supra.*
Colon					NG2		Choi et al., *supra..*
Colon					ephrin-B1		Choi et al., *supra.*
Colon					MIF		Choi et al., *supra.*
Colon					b-catenin		Choi et al., *supra.*
Colon					Junction		Choi et al., *supra.*
Colon					plakoglobin		Choi et al., *supra.*
Colon					glalectin-4		Choi et al., *supra.*
Colon					RACK1		Choi et al., *supra.*
Colon					tetrspanin-8		Choi et al., *supra.*
Colon					FastL		Choi et al., *supra.*
Colon					TRAIL		Choi et al., *supra.*
Colon					A33		Choi et al., *supra.*
Colon					CEA		Choi et al., *supra.*
Colon					EGFR		Choi et al., *supra.*
Colon					dipeptidase 1		Choi et al., *supra.*
Colon					hsc-70		Choi et al., *supra.*
Colon					tetraspanins		Choi et al., *supra.*
Colon					ESCRT		Choi et al., *supra.*
Colon			EFNB1				Huber et al., 2005, Gastroenterol Nurs 28(6): 510-1.
Colon			ERCC1				Shirota Y et al., J Clin Oncol, 2001. 19(23): p. 4298-304
Colon					TS		Cascinu S et al., Ann Oncol, 2001. 12(2): p. 239-44; Ciaparrone M et al., Oncology, 2006. 70(5): p. 366-77
Colon					PTEN		Frattini et al., 2007

FIG. 6d

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins Ligands Peptides	snoRNA	Select Reference(s)
Colon					TOPO1		Braun MS et al., J Clin Oncol, 2008. 26(16): p. 2690-8
Colon			HER2				Ochs AM et al., Clin Colorectal Cancer. 2004 Nov;4(4):262-7
Colon			VEGF				Ochs AM et al., *supra.*
Colon			EGFR				Cappuzo et al 2008, Sartore-Bianche et al 2007
Colon				EGFR			Zhang X et al., Oncol Rep. 2008 Jun;19(6):1541-4; Riese DJ 2nd et al., Bioessays. 2007 Jun;29(6):558-65
Colon				KRAS			Amado RG et al., J Clin Oncol, 2008. 26(10): p. 1626-34; De Roock W et al., Ann Oncol, 2008. 19(3): p. 508-15.
Colon				VEGFA			Uthoff SM et al., Int J Cancer. 2002 Sep 1;101(1):32-6.
Colon				B-Raf			Ogino S et al., Gut. 2008 Oct 2; Matos P et al., Gastroenterology. 2008 Sep;135(3):899-906
Colon				APC			Conlin A et al., Gut, 2005. 54(9): p. 1283-6
Colon				p53			Conlin A et al., *supra.*

FIG. 7

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins Ligands Peptides	snoRNA	Select Reference(s)
Adenoma versus Hyperplastic Polyp			ABCA8			did not find any	Galamb et al., 2008,Cancer Epidemiol Biomarkers Prev 17(10): 2835-45
Adenoma versus Hyperplastic Polyp			KIAA1199				Galamb et al., *supra.*
Adenoma versus Hyperplastic Polyp			GCG				Galamb et al., *supra.*
Adenoma versus Hyperplastic Polyp			MAMDC2				Galamb et al., *supra.*
Adenoma versus Hyperplastic Polyp			C2orf32				Galamb et al., *supra.*
Adenoma versus Hyperplastic Polyp			229670_at				Galamb et al., *supra.*
Adenoma versus Hyperplastic Polyp			IGF1				Galamb et al., *supra.*
Adenoma versus Hyperplastic Polyp			PCDH7				Galamb et al., *supra.*
Adenoma versus Hyperplastic Polyp			PRDX6				Galamb et al., *supra.*
Adenoma versus Hyperplastic Polyp				BRAF			Kim YH et al., Int J Cancer. 2008 Dec 1;123(11):2587-93
Adenoma versus Hyperplastic Polyp				KRAS			Rashid A et al., Gastroenterology. 2000 Aug;119(2)•323-32
Adenoma versus Hyperplastic Polyp			PCNA				Barletta A et al., Anticancer Res. 1998 May-Jun;18(3A):1677-82
Adenoma versus Hyperplastic Polyp			COX2				McLean MH et al., Histopathology. 2008 Jun;52(7):806-15. Epub 2008 May 6.
Adenoma versus Hyperplastic Polyp			MUC6				Owens SR et al., Mod Pathol. 2008 Jun;21(6):660-9.
Adenoma versus Hyperplastic Polyp					hTERT		Oka S et al., Scand J Gastroenterol. 2002 Oct;37(10):1194-200

FIG. 8

Cancer Lineage, Group Comparison, Other Significant Disease State	**Up-regulated miRs**	**Down-regulated miRs**	**mRNAs**	**Mutational Analysis**	**Proteins Ligands Peptides**	**snoRNA**	**Select Reference(s)**
IBD versus normal			REG1A				Galamb et al., 2008, "Inflammation, Adenoma and Cancer Objective Classification of Colon Biopsy Specimens with Gene Expression Signature", Dis Markers, 25(1): 1-16
IBD versus normal			MMP3				Galamb et al., *supra.*

FIG. 9a

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins Ligands Peptides	snoRNA	Select Reference(s)
Adenoma versus CRC			GREM1				Galamb et al., 2008, Dis Markers, 25(1): 1-16.
Adenoma versus CRC			DDR2				Galamb et al., *supra.*
Adenoma versus CRC			GUCY1A3				Galamb et al., *supra.*
Adenoma versus CRC			TNS1				Galamb et al., *supra.*
Adenoma versus CRC			ADAMTS1				Galamb et al., *supra.*
Adenoma versus CRC			FBLN1				Galamb et al., *supra.*
Adenoma versus CRC			FLJ38028				Galamb et al., *supra.*
Adenoma versus CRC			RDX				Galamb et al., *supra.*
Adenoma versus CRC			FAM129A				Galamb et al., *supra.*
Adenoma versus CRC			ASPN				Galamb et al., *supra.*
Adenoma versus CRC			FRMD6				Galamb et al., *supra.*
Adenoma versus CRC			MCC				Galamb et al., *supra.*
Adenoma versus CRC			RBMS1				Galamb et al., *supra.*
Adenoma versus CRC			SNAI2				Galamb et al., *supra.*
Adenoma versus CRC			MEIS1				Galamb et al., *supra.*
Adenoma versus CRC			DOCK10				Galamb et al., *supra.*
Adenoma versus CRC			PLEKHC1				Galamb et al., *supra.*
Adenoma versus CRC			FAM126A				Galamb et al., *supra.*
Adenoma versus CRC			TBC1D9				Galamb et al., *supra.*
Adenoma versus CRC			VWF				Galamb et al., *supra.*
Adenoma versus CRC			DCN				Galamb et al., *supra.*
Adenoma versus CRC			ROBO1				Galamb et al., *supra.*
Adenoma versus CRC			MSRB3				Galamb et al., *supra.*
Adenoma versus CRC			LATS2				Galamb et al., *supra.*

FIG. 9b

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins Ligands Peptides	snoRNA	Select Reference(s)
Adenoma versus CRC			MEF2C				Galamb et al., *supra.*
Adenoma versus CRC			IGFBP3				Galamb et al., *supra.*
Adenoma versus CRC			GNB4				Galamb et al., *supra.*
Adenoma versus CRC			RCN3				Galamb et al., *supra.*
Adenoma versus CRC			AKAP12				Galamb et al., *supra.*
Adenoma versus CRC			RFTN1				Galamb et al., *supra.*
Adenoma versus CRC			226834_at				Galamb et al., *supra.*
Adenoma versus CRC			COL5A1				Galamb et al., *supra.*
Adenoma versus CRC			GNG2				Galamb et al., *supra.*
Adenoma versus CRC			NR3C1				Galamb et al., *supra.*
Adenoma versus CRC			SPARCL1				Galamb et al., *supra.*
Adenoma versus CRC			MAB21L2				Galamb et al., *supra.*
Adenoma versus CRC			AXIN2				Galamb et al., *supra.*
Adenoma versus CRC			236894_at				Galamb et al., *supra.*
Adenoma versus CRC			AEBP1				Galamb et al., *supra.*
Adenoma versus CRC			AP1S2				Galamb et al., *supra.*
Adenoma versus CRC			C10orf56				Galamb et al., *supra.*
Adenoma versus CRC			LPHN2				Galamb et al., *supra.*
Adenoma versus CRC			AKT3				Galamb et al., *supra.*
Adenoma versus CRC			FRMD6				Galamb et al., *supra.*
Adenoma versus CRC			COL15A1				Galamb et al., *supra.*
Adenoma versus CRC			CRYAB				Galamb et al., *supra.*
Adenoma versus CRC			COL14A1				Galamb et al., *supra.*
Adenoma versus CRC			LOC286167				Galamb et al., *supra.*

FIG. 9c

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins Ligands Peptides	snoRNA	Select Reference(s)
Adenoma versus CRC			QKI				Galamb et al., *supra.*
Adenoma versus CRC			WWTR1				Galamb et al., *supra.*
Adenoma versus CRC			GNG11				Galamb et al., *supra.*
Adenoma versus CRC			PAPPA				Galamb et al., *supra.*
Adenoma versus CRC			ELDT1				Galamb et al., *supra.*

FIG. 10

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins Ligands Peptides	snoRNA	Select Reference(s)
IBD versus CRC			227458_at				Galamb et al., 2008, Helicobacter, 13(2); 112-26.
IBD versus CRC			INDO				Galamb et al., *supra.*
IBD versus CRC			CXCL9				Galamb et al., *supra.*
IBD versus CRC			CCR2				Galamb et al., *supra.*
IBD versus CRC			CD38				Galamb et al., *supra.*
IBD versus CRC			RARRES3				Galamb et al., *supra.*
IBD versus CRC			CXCL10				Galamb et al., *supra.*
IBD versus CRC			FAM26F				Galamb et al., *supra.*
IBD versus CRC			TNIP3				Galamb et al., *supra.*
IBD versus CRC			NOS2A				Galamb et al., *supra.*
IBD versus CRC			CCRL1				Galamb et al., *supra.*
IBD versus CRC			TLR8				Galamb et al., *supra.*
IBD versus CRC			IL18BP				Galamb et al., *supra.*
IBD versus CRC			FCRL5				Galamb et al., *supra.*
IBD versus CRC			SAMD9L				Galamb et al., *supra.*
IBD versus CRC			ECGF1				Galamb et al., *supra.*
IBD versus CRC			TNFSF13B				Galamb et al., *supra.*
IBD versus CRC			GBP5				Galamb et al., *supra.*
IBD versus CRC			GBP1				Galamb et al., *supra.*

FIG. 11a

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins Ligands Peptides	snoRNA	Select Reference(s)
CRC Dukes B versus Dukes C-D			TMEM37*				Galamb et al., 2008, Helicobacter, 13(2); 112-26.
CRC Dukes B versus Dukes C-D			IL33				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-D			CA4				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-D			CCDC58				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-D			CLIC6				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-D			VSNL1				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-D			ESPN				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-D			APCDDI				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-D			C13orf18				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-D			CYP4X1				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-D			ATP2A3				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-D			LOC646627				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-D			MUPCDH				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-D			ANPEP				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-D			C1orf115				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-D			HSD3B2				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-I)			GBA3				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-D			GABRB2				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-13			GYLTL1 B				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-D			LYZ				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-D			SPC25				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-D			CDKN2B				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-D			FAM89A				Galamb et al., *supra.*

FIG. 11b

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins Ligands Peptides	snoRNA	Select Reference(s)
CRC Dukes B versus Dukes C-D			MOGAT2				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-D			SEMA6D				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-D			229376_at				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-D			TSPAN5				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-D			IL6R				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-D			SLC26A2				Galamb et al., *supra.*
CRC Dukes B versus Dukes C-D					PAR4		Madoz-Gúrpide et al., Mol. Cell. Prot. 6:2150-64, 2007
CRC Dukes B versus Dukes C-D					DIABLO		Madoz-Gúrpide J et al., *supra.*
CRC Dukes B versus Dukes C-D					caspase-3		Madoz-Gúrpide J et al., *supra*
CRC Dukes B versus Dukes C-D					p53		Madoz-Gúrpide J et al., *supra*
CRC Dukes B versus Dukes C-D					TRF1		Madoz-Gúrpide J et al., *supra*
CRC Dukes B versus Dukes C-D					c-myc		Madoz-Gúrpide J et al., *supra*

FIG. 12a

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Adenoma with low grade versus high grade dysplasia			SI				Galamb et al., 2008, Dis Markers, 25(1): 1-16
Adenoma with low grade versus high grade dysplasia			DMBT1				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			CFI*				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			AQP1				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			APOD				Galamb et al. *supra..*
Adenoma with low grade versus high grade dysplasia			TNFRSF17				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			CXCL10				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			CTSE				Galamb et al. *supra..*
Adenoma with low grade versus high grade dysplasia			IGHA1				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			SLC9A3				Galamb et al. *supra..*
Adenoma with low grade versus high grade dysplasia			SLC7A1				Galamb et al. *supra..*
Adenoma with low grade versus high grade dysplasia			BATF2				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			SOCS1				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			DOCK2				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			NOS2A				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			HK2				Galamb et al. *supra.*

FIG. 12b

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Adenoma with low grade versus high grade dysplasia			CXCL2				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			IL15RA				Galamb et al. *supra..*
Adenoma with low grade versus high grade dysplasia			POU2AF1				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			CLEC3B				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			ANI3BP				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			MGC13057				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			LCK*				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			C4BPA				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			HOXC6				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			GOLT1A				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			C2orf32				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			IL10RA				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			240856_at				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			SOCS3				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			MEIS3P1				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			HIPK1				Galamb et al. *supra.*

FIG. 12c

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Adenoma with low grade versus high grade dysplasia			GLS				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			CPLX1				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			236045_x_at				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			GALC				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			AMN				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			CCDC69				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			CCL28				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			CPA3				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			TRIB2				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			HMGA2				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			PLCL2				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			NR3C1				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			EIF5A				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			LARP4				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			RP5-1022P6.2				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			PHLDB2				Galamb et al. *supra.*

FIG. 12d

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Adenoma with low grade versus high grade dysplasia			FKBP1B				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			INDO				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			CLDN8				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			CNTN3				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			PBEF1				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			SLC16A9				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			CDC25B				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			TPSB2				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			PBEF1				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			ID4				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			GJB5				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			CHN2				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			LIMCH1				Galamb et al. *supra.*
Adenoma with low grade versus high grade dysplasia			CXCL9				Galamb et al. *supra.*

FIG. 13a

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
UC vs CD			IFITM1				Wu F., et al., 2007, Inflamm Bowel Dis, 13(7): 807-21.
UC vs CD			IFITM3				Wu F., et al., 2007 *supra.*
UC vs CD			STAT1				Wu F., et al., 2007 *supra*
UC vs CD			STAT3				Wu F., et al., 2007 *supra*
UC vs CD			TAP1		•		Wu F., et al., 2007 *supra*
UC vs CD			PSME2				Wu F., et al., 2007 *supra*
UC vs CD			PSMB8				Wu F., et al., 2007 *supra*
UC vs CD			HNF4G				Wu F., et al., 2007 *supra*
UC vs CD			KLF5				Wu F., et al., 2007 *supra*
UC vs CD			AQP8				Wu F., et al., 2007 *supra*
UC vs CD			APT2B1				Wu F., et al., 2007 *supra*
UC vs CD			SLC16A				Wu F., et al., 2007 *supra*
UC vs CD			MFAP4				Galamb et al., 2008, Helicobacter, 13(2); 112-26.
UC vs CD			CCNG2				Galamb et al., *supra.*
UC vs CD			SLC44A4				Galamb et al., *supra.*
UC vs CD			DDAH1				Galamb et al., *supra.*
UC vs CD			TOB1				Galamb et al., *supra.*
UC vs CD			231152_at				Galamb et al., *supra.*
UC vs CD			MKNK1				Galamb et al., *supra.*
UC vs CD			CEACAM7*				Galamb et al., *supra.*
UC vs CD			1562836_at				Galamb et al., *supra.*
UC vs CD			CDC42SE2				Galamb et al., *supra.*
UC vs CD			PSD3				Galamb et al., *supra.*
UC vs CD			231169_at				Galamb et al., *supra.*
UC vs CD			IGL@*				Galamb et al., *supra.*
UC vs CD			GSN				Galamb et al., *supra.*
UC vs CD			GPM6B				Galamb et al., *supra.*
UC vs CD			CDV3*				Galamb et al., *supra.*
UC vs CD			PDPK1				Galamb et al., *supra.*
UC vs CD			ANP32E				Galamb et al., *supra.*
UC vs CD			ADAM9				Galamb et al., *supra.*
UC vs CD			CDH1				Galamb et al., *supra.*
UC vs CD			NLRP2				Galamb et al., *supra.*
UC vs CD			215777_at				Galamb et al., *supra.*
UC vs CD			OSBPL1				Galamb et al., *supra.*
UC vs CD			VNN1				Galamb et al., *supra.*
UC vs CD			RABGAP1L				Galamb et al., *supra.*
UC vs CD			PHACTR2				Galamb et al., *supra.*
UC vs CD			ASH1L				Galamb et al., *supra.*
UC vs CD			213710_s_at				Galamb et al., *supra.*
UC vs CD			CDH1				Galamb et al., *supra.*
UC vs CD			NLRP2				Galamb et al., *supra.*
UC vs CD			215777_at				Galamb et al., *supra.*
UC vs CD			OSBPLI				Galamb et al., *supra.*

FIG. 13b

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
UC vs CD			VNN1				Galamb et al., *supra.*
UC vs CD			RABGAP1L				Galamb et al., *supra.*
UC vs CD			PHACTR2				Galamb et al., *supra.*
UC vs CD			ASH1				Galamb et al., *supra.*
UC vs CD			213710_s_at				Galamb et al., *supra.*
UC vs CD			ZNF3				Galamb et al., *supra.*
UC vs CD			FUT2				Galamb et al., *supra.*
UC vs CD			IGHA1				Galamb et al., *supra.*
UC vs CD			EDEM1				Galamb et al., *supra.*
UC vs CD			GPR171				Galamb et al., *supra.*
UC vs CD			229713_at				Galamb et al., *supra.*
UC vs CD			LOC643187				Galamb et al., *supra.*
UC vs CD			FLVCRI				Galamb et al., *supra.*
UC vs CD			SNAP23*				Galamb et al., *supra.*
UC vs CD			ETNK1				Galamb et al., *supra.*
UC vs CD			LOC728411				Galamb et al., *supra.*
UC vs CD			POSTN				Galamb et al., *supra.*
UC vs CD			MUC12				Galamb et al., *supra.*
UC vs CD			HOXA5				Galamb et al., *supra.*
UC vs CD			SIGLEC1				Galamb et al., *supra.*
UC vs CD			LARP5				Galamb et al., *supra.*
UC vs CD			PIGR				Galamb et al., *supra.*
UC vs CD			SPTBN1				Galamb et al., *supra.*
UC vs CD			UFM1				Galamb et al., *supra.*
UC vs CD			C6orf62				Galamb et al., *supra.*
UC vs CD			WDR90				Galamb et al., *supra.*
UC vs CD			ALDH1A3				Galamb et al., *supra.*
UC vs CD			F2RL1				Galamb et al., *supra.*
UC vs CD			IGHV1-69				Galamb et al., *supra.*
UC vs CD			DUOX2				Galamb et al., *supra.*
UC vs CD			RAB5A				Galamb et al., *supra.*
UC vs CD			CP				Galamb et al., *supra.*
UC vs CD				CARD15			Radford-Smith et al 2007, Gastroenterology 132(7): 2313-9.
UC vs CD					(P)ASCA		Li X et al., World J Gastroenterol. 2008 Sep 7;14(33):5115-24.

FIG. 14

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Hyperplastic polyp versus normal			SLC6A14				Galamb et al., 2008, Cancer Epidemiol Biomarkers Prev, 17(10): 2835-45
Hyperplastic polyp versus normal			ARHGEF10				Galamb et al., *supra.*
Hyperplastic polyp versus normal			ALS2				Galamb et al., *supra.*
Hyperplastic polyp versus normal			IL1RN				Galamb et al., *supra.*
Hyperplastic polyp versus normal			SPRY4				Galamb et al., *supra.*
Hyperplastic polyp versus normal			PTGER3				Galamb et al., *supra.*
Hyperplastic polyp versus normal			TRIM29				Galamb et al., *supra.*
Hyperplastic polyp versus normal			SERPINB5				Galamb et al., *supra.*
Hyperplastic polyp versus normal			1560327_at				Galamb et al., *supra.*
Hyperplastic polyp versus normal			ZAK				Galamb et al., *supra.*
Hyperplastic polyp versus normal			BAG4				Galamb et al., *supra.*
Hyperplastic polyp versus normal			TRIB3				Galamb et al., *supra.*
Hyperplastic polyp versus normal			TTL				Galamb et al., *supra.*
Hyperplastic polyp versus normal			FOXQ1				Galamb et al., *supra.*

FIG. 15

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Adenoma with low grade dysplasia versus normal			UGT2A3				Galamb et al., 2008, Dis Markers, 25(1): 1-16.
Adenoma with low grade dysplasia versus normal			KLK11				Galamb et al., *supra.*
Adenoma with low grade dysplasia versus normal			KIAA1199				Galamb et al., *supra.*
Adenoma with low grade dysplasia versus normal			FOXQ1				Galamb et al., *supra.*
Adenoma with high grade dysplasia versus normal			CLDN8				Galamb et al., *supra.*
Adenoma with high grade dysplasia versus normal			ABCA8				Galamb et al., *supra.*
Adenoma with high grade dysplasia versus normal			PYY				Galamb et al., *supra.*

FIG. 16

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Adenoma versus normal			KIAA1199				Galamb et al., 2008, Dis Markers, 25(1): 1-16.
Adenoma versus normal			FOXQ1				Galamb et al., *supra.*
Adenoma versus normal			CA7				Galamb et al., *supra.*
Adenoma versus normal					Clusterin		Chen X et al., Proc Natl Acad Sci U S A. 2003 Aug 5;100(16):9530-5.

FIG. 17

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
CRC versus normal			VWF				Galamb et al., 2008, Dis Markers, 25(1): 1-16
CRC versus normal			IL8				Galamb et al., *supra.*
CRC versus normal			CHI3L1				Galamb et al., *supra.*
CRC versus normal			S100A8				Galamb et al., *supra.*
CRC versus normal			GREM1				Galamb et al., *supra.*
CRC versus normal			ODC				Hu HY et al., World J Gastroenterol. 2005 Apr 21;11(15):2244-8.
CRC versus normal				KRAS			Amado RG et al., J Clin Oncol, 2008.26(10): p. 1626-34; De Roock W et al., Ann Oncol, 2008. 19(3): p. 508-15.
CRC versus normal				BRAF			Ogino S et al., Gut. 2008 Oct 2; Matos P et al., Gastroenterology. 2008 Sep;135(3):899-906.
CRC versus normal				APC			Conlin A et al., Gut, 2005. 54(9): p. 1283-6.
CRC versus normal				MSH2			Davidson NO, Keio J Med. 2007 Mar;56(1):14-20.
CRC versus normal				MLH1			Davidson NO, Keio *supra.*
CRC versus normal					cytokeratin 13		Madoz-Gúrpide J et al., Molecular & Cellular Proteomics 6:2150-2164, 2007.
CRC versus normal					calcineurin		Madoz-Gúrpide J et al., *supra.*
CRC versus normal					CHK1		Madoz-Gúrpide J et al., *supra.*
CRC versus normal					clathrin light chain		Madoz-Gúrpide J et al., *supra.*
CRC versus normal					phospho-ERK		Madoz-Gúrpide J et al., *supra.*
CRC versus normal					phospho-PTK2		Madoz-Gúrpide J et al., *supra.*
CRC versus normal					MDM2		Madoz-Gúrpide J et al., *supra.*

FIG. 18

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Benign Prostatic Hyperplasia					Intact Fibronectin		Janković MM, Kosanović MM, Dis Markers, 2008;25(1):49-58.

FIG. 19a

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Prostate					FASLG		Huber et al., 2005, Gastroenterol Nurs 28(6): 510-1.
Prostate					TNFSF10		Huber et al., 2005, *supra.*
Prostate					FASLG		Adreola et al., JEM 195:10 1303-1316 (2002)
Prostate					TNFSF10		Adreola et al., *supra.*
Prostate					FASLG		Abusamra et al., 2005, Blood Cells Mol Dis, 35(2): 169-73
Prostate					TNFSF10		Abusamra et al., 2005, *supra.*
Prostate					FASLG		Kim et al., Int J Cancer. 2008 Dec 1;123(11):2587-93.
Prostate					TNFSF10		Kim et al., *supra.*
Prostate					FASLG		Taylor et al., 2003, Int J Oncol 22(6): 1311-7
Prostate					TNFSF10		Taylor et al., *supra.*
Prostate		let-7a					Porkka et al., 2007, Cancer Res, 67(13): 6130-5
Prostate		let-7b					Porkka et al., *supra.*
Prostate		let-7c					Porkka et al., *supra.*
Prostate		let-7d					Porkka et al., *supra.*
Prostate		let-7g					Porkka et al., *supra.*
Prostate		miR-16					Porkka et al., *supra.*
Prostate		miR-23a					Porkka et al., *supra.*
Prostate		miR-23b					Porkka et al., *supra.*
Prostate		miR-26a					Porkka et al., *supra.*
Prostate		miR-92					Porkka et al., *supra.*
Prostate		miR-99a					Porkka et al., *supra.*
Prostate		miR-103					Porkka et al., *supra.*
Prostate		miR-125a					Porkka et al., *supra.*
Prostate		miR-125b					Porkka et al., *supra.*
Prostate		miR-143					Porkka et al., *supra.*
Prostate		miR-145					Porkka et al., *supra.*
Prostate		miR-195					Porkka et al., *supra.*
Prostate		miR-199					Porkka et al., *supra.*
Prostate		miR-221					Porkka et al., *supra.*
Prostate		miR-222					Porkka et al., *supra.*
Prostate		miR-497					Porkka et al., *supra.*
Prostate		let-7f					Porkka et al., *supra.*
Prostate		miR-19b					Porkka et al., *supra.*
Prostate		miR-22					Porkka et al., *supra.*
Prostate		miR-26b					Porkka et al., *supra.*
Prostate		miR-27a					Porkka et al., *supra.*

FIG. 19b

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Prostate		miR-27b					Porkka et al., *supra.*
Prostate		miR-29a					Porkka et al., *supra.*
Prostate		miR-29b					Porkka et al., *supra.*
Prostate		miR-30_5p					Porkka et al., *supra.*
Prostate		miR-30c					Porkka et al., *supra.*
Prostate		miR-100					Porkka et al., *supra.*
Prostate		miR-141					Porkka et al., *supra.*
Prostate		miR-148a					Porkka et al., *supra.*
Prostate		miR-205					Porkka et al., *supra.*
Prostate	miR-202						Porkka et al., *supra.*
Prostate	miR-210						Porkka et al., *supra.*
Prostate	miR-296						Porkka et al., *supra.*
Prostate	miR-320						Porkka et al., *supra.*
Prostate	miR-370						Porkka et al., *supra.*
Prostate	miR-373						Porkka et al., *supra.*
Prostate	miR-498						Porkka et al., *supra.*
Prostate	miR-503						Porkka et al., *supra.*
Prostate	miR-184						Porkka et al., *supra.*
Prostate	miR-198						Porkka et al., *supra.*
Prostate	miR-302c						Porkka et al., *supra.*
Prostate	miR-345						Porkka et al., *supra.*5
Prostate	miR-491						Porkka et al., *supra.*
Prostate	miR-513						Porkka et al., *supra.*
Prostate	miR-32						Ambs et al., 2008, Cancer Res, 68(15): 6162-70
Prostate	miR-182						Ambs et al., *supra.*
Prostate	miR-31						Ambs et al., *supra.*
Prostate	miR-26a-1/2						Ambs et al., *supra.*-70
Prostate	miR-200c						Ambs et al., *supra.*
Prostate	miR-375						Ambs et al., *supra.*
Prostate	miR-196a-1/2						Ambs et al., *supra.*
Prostate	miR-370						Ambs et al., *supra.*
Prostate	miR-425						Ambs et al., *supra.*
Prostate	miR-425						Ambs et al., *supra.*
Prostate	miR-194-1/2						Ambs et al., *supra.*
Prostate	miR-181a-1/2						Ambs et al., *supra.*
Prostate	miR-34b						Ambs et al., *supra.*

FIG. 19c

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Prostate	let-7i						Ambs et al., *supra.*
Prostate	miR-188						Ambs et al., *supra.*
Prostate	miR-25						Ambs et al., *supra.*
Prostate	miR-106b						Ambs et al., *supra.*
Prostate	miR-449						Ambs et al., *supra.*
Prostate	miR-99b						Ambs et al., *supra.*
Prostate	miR-93						Ambs et al., *supra.*
Prostate	miR-92-1/2						Ambs et al., *supra.*
Prostate	miR-125a						Ambs et al., *supra.*
Prostate		miR-520h					Ambs et al., *supra.*
Prostate		miR-494					Ambs et al., *supra.*
Prostate		miR-490					Ambs et al., *supra.*
Prostate		miR-133a-1					Ambs et al., *supra.*
Prostate		miR-1-2					Ambs et al., *supra.*
Prostate		miR-218-2					Ambs et al., *supra.*
Prostate		miR-220					Ambs et al., *supra.*
Prostate		miR-128a					Ambs et al., *supra.*
Prostate		miR-221					Ambs et al., *supra.*
Prostate		miR-499					Ambs et al., *supra.*
Prostate		miR-329					Ambs et al., *supra.*
Prostate		miR-340					Ambs et al., *supra.*
Prostate		miR-345					Ambs et al., *supra.*
Prostate		miR-410					Ambs et al., *supra.*
Prostate		miR-126					Ambs et al., *supra.*
Prostate		miR-205.					Ambs et al., *supra.*
Prostate		miR-7-1/2					Ambs et al., *supra.*
Prostate		miR-145					Ambs et al., *supra.*
Prostate		miR-34a					Ambs et al., *supra.*
Prostate		miR-487					Ambs et al., *supra.*
Prostate		let-7b					Ambs et al., *supra.*
Prostate						U50	Dong et al., 2008, Prostate 68(4): 381-99.
Prostate			AR				
Prostate	miR-141						Mitchell et al. PNAS 2008
Prostate			PCA3				Marks et. Al, Urology 69: 532-535, 2007.

FIG. 20a

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Melanoma					Alix		Mears et al., 2004, Proteomics 4(12): 4019-31.
Melanoma					hsp70		Mears et al., *supra.*
Melanoma					Gib2		Mears et al., *supra.*
Melanoma					Gia		Mears et al., *supra.*
Melanoma					moesin		Mears et al., *supra.*
Melanoma					GAPDH		Mears et al., *supra.*
Melanoma					malate dehydro-genase		Mears et al., *supra.*
Melanoma					p120 catenin		Mears et al., *supra.*
Melanoma					PGRL		Mears et al., *supra.*
Melanoma					syntaxin-binding protein 1 & 2		Mears et al., *supra.*
Melanoma					septin-2		Mears et al., *supra.*
Melanoma					WD-repeat containing protein 1		Mears et al., *supra.*
Melanoma		miR-9					Schultz et al., 2008, Cell Res 18(5): 549-57.
Melanoma		miR-15a					Schultz et al., *supra.*
Melanoma		miR-17-3p					Schultz et al., *supra.*
Melanoma	miR-19a						Schultz et al., *supra.*
Melanoma		miR-23b					Schultz et al., *supra.*
Melanoma		miR-27a					Schultz et al., *supra.*
Melanoma		miR-28					Schultz et al., *supra.*
Melanoma		miR-29b					Schultz et al., *supra.*
Melanoma		miR-30b					Schultz et al., *supra.*
Melanoma		miR-31					Schultz et al., *supra.*
Melanoma		miR-34b					Schultz et al., *supra.*
Melanoma		m1R-34c					Schultz et al., *supra.*
Melanoma		miR-95					Schultz et al., *supra.*
Melanoma		miR-96					Schultz et al., *supra.*
Melanoma		miR-100		•			Schultz et al., *supra.*
Melanoma		miR-104					Schultz et al., *supra.*
Melanoma		miR-105					Schultz et al., *supra.*
Melanoma		miR-106a					Schultz et al., *supra.*
Melanoma		miR-107					Schultz et al., *supra.*
Melanoma		miR-122a					Schultz et al., *supra.*
Melanoma		miR-124a					Schultz et al., *supra.*

FIG. 20b

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Melanoma		miR-125b					Schultz et al., *supra.*
Melanoma		miR-127					Schultz et al., *supra.*
Melanoma		miR-128a					Schultz et al., *supra.*
Melanoma		miR-128b					Schultz et al., *supra.*
Melanoma		miR-129 .					Schultz et al., *supra.*
Melanoma		miR-135a					Schultz et al., *supra.*
Melanoma		miR-135b					Schultz et al., *supra.*
Melanoma		miR-137					Schultz et al., *supra.*
Melanoma		miR-138					Schultz et al., *supra.*
Melanoma		miR-139					Schultz et al., *supra.*
Melanoma		miR-140					Schultz et al., *supra.*
Melanoma		miR-141					Schultz et al., *supra.*
Melanoma	miR-144						Schultz et al., *supra.*
Melanoma		miR-149					Schultz et al., *supra.*
Melanoma		miR-154					Schultz et al., *supra.*
Melanoma		miR-154#3					Schultz et al., *supra.*
Melanoma		miR-181a					Schultz et al., *supra.*
Melanoma		miR-182					Schultz et al., *supra.*
Melanoma		miR-183					Schultz et al., *supra.*
Melanoma		miR-184					Schultz et al., *supra.*
Melanoma		miR-185					Schultz et al., *supra.*
Melanoma		miR-189					Schultz et al., *supra.*
Melanoma		miR-190					Schultz et al., *supra.*
Melanoma		miR-199					Schultz et al., *supra.*
Melanoma		miR-199b					Schultz et al., *supra.*
Melanoma		miR-200a					Schultz et al., *supra.*
Melanoma		miR-200b					Schultz et al., *supra.*
Melanoma	miR-200c						Schultz et al., *supra.*
Melanoma		miR-204					Schultz et al., *supra.*
Melanoma	miR-211						Schultz et al., *supra.*
Melanoma		miR-213					Schultz et al., *supra.*
Melanoma		miR-215					Schultz et al., *supra.*
Melanoma		miR-216					Schultz et al., *supra.*
Melanoma		miR-219					Schultz et al., *supra.*
Melanoma		miR-222					Schultz et al., *supra.*
Melanoma		miR-224					Schultz et al., *supra.*
Melanoma		miR-299					Schultz et al., *supra.*
Melanoma		miR-302a					Schultz et al., *supra.*
Melanoma		miR-302b					Schultz et al., *supra.*
Melanoma		miR-302c					Schultz et al., *supra.*
Melanoma		miR-302d					Schultz et al., *supra.*
Melanoma		miR-323					Schultz et al., *supra.*

FIG. 20c

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Melanoma	miR-324-5p						Schultz et al., *supra.*
Melanoma		miR-325					Schultz et al., *supra.*
Melanoma	miR-331			•			Schultz et al., *supra.*
Melanoma	miR-374						Schultz et al., *supra.*
Melanoma		let-7a					Schultz et al., *supra.*
Melanoma		let-7b					Schultz et al., *supra.*
Melanoma		let-7d					Schultz et al., *supra.*
Melanoma		let-7e					Schultz et al., *supra.*
Melanoma		let-7g					Schultz et al., *supra.*
Melanoma				CDK4			Castelli et al., J Cell Physiology 182(3)323-31, 2000.
Melanoma			MUM-1				Castelli et al., *supra.*
Melanoma			beta-catenin				Castelli et al., *supra.*
Melanoma			Nop/5/Sik				Nakamoto et al., American Journal of Pathology 159(4), 2001.
Melanoma						H/ACA (U107f)	Luo and Li, 2007, J Ind Microbiol Biotechnol 34(2): 117-22.
Melanoma						SNO RA11D	Yang et al., nar 34:5112-5123, 2006
Melanoma					DUSP-1		

FIG. 21a

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Pancreatic	miR-221						Bloomston et al., 2008, J Gastrointest Surg. Dec;11(12):1680-5.
Pancreatic	miR-181a						Bloomston et al., *supra.*
Pancreatic	miR-155						Bloomston et al., *supra*
Pancreatic	miR-210						Bloomston et al., *supra*
Pancreatic	miR-213						Bloomston et al., *supra.*
Pancreatic	miR-181b						Bloomston et al., *supra*
Pancreatic	miR-222						Bloomston et al., *supra.*
Pancreatic	miR-181b-2						Bloomstom et al., *supra.*
Pancreatic	miR-21						Bloomstom et al., *supra.*
Pancreatic	miR-181b-1						Bloomstom et al., *supra.*
Pancreatic	miR-181c						Bloomstom et al., *supra.*
Pancreatic	miR-220						Bloomstom et al., *supra.*
Pancreatic	miR-181d						Bloomstom et al., *supra.*
Pancreatic	miR-223						Bloomstom et al., *supra.*
Pancreatic	miR-100-1/2						Bloomstom et al., *supra.*
Pancreatic	miR-125a						Bloomstom et al., *supra.*
Pancreatic	miR-143						Bloomstom et al., *supra.*
Pancreatic	miR-10a						Bloomstom et al., *supra.*
Pancreatic	mi R-146						Bloomstom et al., *supra.*
Pancreatic	miR-99						Bloomstom et al., *supra.*
Pancreatic	miR-100						Bloomstom et al., *supra.*
Pancreatic	miR-199a-1						Bloomstom et al., *supra.*
Pancreatic	miR-10b						Bloomstom et al., *supra.*
Pancreatic	miR-199a-2						Bloomstom et al., *supra.*
Pancreatic	miR-107						Bloomstom et al., *supra.*
Pancreatic	miR-103-2						Bloomstom et al., *supra.*
Pancreatic	miR-125b-1						Bloomstom et al., *supra.*
Pancreatic	miR-205						Bloomstom et al., *supra.*
Pancreatic	miR-23a						Bloomstom et al., *supra.*
Pancreatic		miR-148a					Bloomstom et al., *supra.*
Pancreatic		mIR-148b					Bloomstom et al., *supra.*
Pancreatic		miR-375					Bloomstom et al., *supra.*
Pancreatic	miR-221						Lee et al., 2006, J Biol Chem 281(5): 2649-53.
Pancreatic	miR-424						Lee at al., *supra.*

FIG. 21b

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Pancreatic	miR-301						Lee at al., *supra.*
Pancreatic	miR-100						Lee at al., *supra.*
Pancreatic	miR-376a						Lee at al., *supra.*
Pancreatic	miR-125b-1						Lee at al., *supra.*
Pancreatic	miR-21						Lee at al., *supra.*
Pancreatic		miR-345					Lee at al., *supra.*
Pancreatic	miR-16-1						Lee at al., *supra.*
Pancreatic	miR-181a						Lee at al., *supra.*
Pancreatic	miR-181c						Lee at al., *supra.*
Pancreatic	miR-92						Lee at al., *supra.*
Pancreatic	miR-15						Lee at al., *supra.*
Pancreatic		miR-142					Lee at al., *supra.*
Pancreatic	miR-155						Lee at al., *supra.*
Pancreatic	let-7f-1						Lee at al., *supra.*
Pancreatic	miR-212						Lee at al., *supra.*
Pancreatic	miR-107						Lee at al., *supra.*
Pancreatic	miR-024-1/2						Lee at al., *supra.*
Pancreatic	let-7d						Lee at al., *supra.*
Pancreatic		miR-139					Lee at al., *supra.*
Pancreatic				KRAS			Shibata D et al., Baillieres Clin Gastroenterol. 1990 Mar;4(1):151-69.
Pancreatic				CTNNLB1			Shi C et al., Adv Anat Pathol. 2008 Jul;15(4):185-95.
Pancreatic			.	AKT			Kang SP and Siaf MW, JOP. J Pancreas (Online) 2008; 9(3):251-266.
Pancreatic				NCOA3			Kang SP and Siaf MW, *supra.*
Pancreatic				B-RAF			Kang SP and Siaf MW, *supra*
Pancreatic			PSCA				Koorstra JB et al., Pancreatology. 2008;8(2)110-25. Epub 2008 Apr 1.
Pancreatic			Meso-thelin				Koorstra JB et al., *supra.*
Pancreatic			Osteo-pontin				Koorstra JB et al., *supra.*

FIG. 22

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Brain	miR-21						Mathupala et al., 2007, DNA Cell Biol, 26(5): 301-10
Brain	miR-10b						Ciafre et al., 2005, Biochem Biophys Res 2005 Sep 9;334(4):1351.
Brain	miR-130a						Ciafre et al., *supra.*
Brain	miR-221						Ciafre et al., *supra.*
Brain	miR-125b-1						Ciafre et al., *supra.*
Brain	miR-125b-2						Ciafre et al., *supra.*
Brain	miR-9-2						Ciafre et al., *supra.*
Brain	miR-21						Ciafre et al., *supra.*
Brain	miR-25						Ciafre et al., *supra.*
Brain	miR-23						Ciafre et al., *supra.*
Brain		miR-128a					Ciafre et al., *supra.*
Brain		miR-181c					Ciafre et al., *supra.*
Brain		miR-181a					Ciafre et al., *supra.*
Brain		miR-181b					Ciafre et al., *supra.*
Brain			MGMT				Blank M et al., JBC May 11; 276(19)16464-8, 2001
Brain					EGFR		Hicke et al., J. Biol. Chem. 276, 48644-48654, 2001; Daniels et al., PNAS 100, 15416-15421, 2003

FIG. 23a

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Psoriasis	miR-146b						Sonkoly et al., 2007, PLoS ONE, 2(7): e610
Psoriasis	miR-20a						Sonkoly et al., *supra.*
Psoriasis	miR-146a						Sonkoly et al., *supra.*
Psoriasis	miR-31						Sonkoly et al., *supra.*
Psoriasis	miR-200a						Sonkoly et al., *supra.*
Psoriasis	miR-17-5p						Sonkoly et al., *supra.*
Psoriasis	miR-30e-5p						Sonkoly et al., *supra.*
Psoriasis	miR-141						Sonkoly et al., *supra.*
Psoriasis	miR-203						Sonkoly et al., *supra.*
Psoriasis	miR-142-3p						Sonkoly et al., *supra.*
Psoriasis	miR-21						Sonkoly et al., *supra.*
Psoriasis	miR-106a						Sonkoly et al., *supra.*
Psoriasis		miR-125b					Sonkoly et al., *supra.*
Psoriasis		miR-99b					Sonkoly et al., *supra.*
Psoriasis		miR-122a					Sonkoly et al., *supra.*
Psoriasis		miR-197					Sonkoly et al., *supra.*
Psoriasis		miR-100					Sonkoly et al., *supra.*
Psoriasis		miR-381					Sonkoly et al., *supra.*
Psoriasis		miR-518b					Sonkoly et al., *supra.*
Psoriasis		miR-524					Sonkoly et al., *supra.*
Psoriasis		let-7e					Sonkoly et al., *supra.*
Psoriasis		miR-30c					Sonkoly et al., *supra.*
Psoriasis		miR-365					Sonkoly et al., *supra.*
Psoriasis		miR-133b					Sonkoly et al., *supra.*
Psoriasis		miR-10a					Sonkoly et al., *supra.*
Psoriasis		miR-133a	•				Sonkoly et al., *supra.*
Psoriasis		miR-22					Sonkoly et al., *supra.*
Psoriasis		miR-326					Sonkoly et al., *supra.*
Psoriasis		miR-215					Sonkoly et al., *supra.*
Psoriasis			IL-20				Stenderup K et al., Ann N Y Acad Sci. 2007 Sep;1110:368-81.
Psoriasis			VEGFR-1				Man XY et al., J Cell Mol Med. 2008 Apr;12(2):649-60
Psoriasis			VEGFR-2				Man XY et al., *supra.*
Psoriasis			VEGFR-3				Man XY et al., *supra.*

FIG. 23b

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Psoriasis			EGR1				Fang M et al., Genomic Med. 2007;1(1-2):75-85. Epub 2007 Jul 25
Psoriasis				MGST2			Yan KL et al., J Invest Dermatol. 2006 May;126(5):1003-5.

FIG. 24a

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Cardiovascular Disease					CK-MB		Wu AH et al., 1996, Clin Chem, 42(4): 651-2
Cardiovascular Disease					cTnI (cardiac troponin)		Wu AH et al., *supra.*
Cardiovascular Disease					C-reactive protein		Rifai N and Ridker PM, Clin Chem. 2001 Mar;47(3):403-11.
Cardiovascular Disease					cardiac Troponin (cTn)		O'Brien PJ, Toxicology. 2008 Mar 20;245(3):206-18.
Cardiovascular Disease					IL-6		Ikonomidis I et al., Atherosclerosis. 2008 Jul;199(1):3-11.
Cardiovascular Disease					MCSF		Ikonomidis I et al., *supra.*
Cardiovascular Disease					BNP		Wang TJ et al., N Engl J Med. 350 (7): 655-63
Cardiovascular Disease		miR-1					van Rooij et al., 2008, Circ. Res, 103(9): 919-28
Cardiovascular Disease	miR-195						van Rooij et al., *supra.*
Cardiovascular Disease	miR-208						van Rooij et al., *supra.*
Cardiovascular Disease		miR-1					Ikeda et al., 2007, Physiol Genomics 31(3): 367-73.
Cardiovascular Disease	miR-214						Ikeda et al., 2007, *supra.*
Cardiovascular Disease	let-7b						Ikeda et al., *supra.*
Cardiovascular Disease	let-7c						Ikeda et al., *supra.*
Cardiovascular Disease	let-7e						Ikeda et al., *supra.*
Cardiovascular Disease		miR-10a					Ikeda et al., *supra.*
Cardiovascular Disease	miR-15b						Ikeda et al., *supra.*
Cardiovascular Disease		miR-17-5p					Ikeda et al., *supra.*
Cardiovascular Disease		miR-19a					Ikeda et al., *supra.*
Cardiovascular Disease		miR-19b					Ikeda et al., *supra.*
Cardiovascular Disease		miR-20a					Ikeda et al., *supra.*
Cardiovascular Disease		miR-20b					Ikeda et al., *supra.*

FIG. 24b

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Cardiovascular Disease	miR-23a						Ikeda et al., *supra.*
Cardiovascular Disease	miR-24						Ikeda et al., *supra.*
Cardiovascular Disease		miR-26b					Ikeda et al., *supra.*
Cardiovascular Disease	miR-27a						Ikeda et al., *supra.*
Cardiovascular Disease	miR-27b						Ikeda et al., *supra.*
Cardiovascular Disease		miR-28					Ikeda et al., *supra.*
Cardiovascular Disease		miR-30e-5p					Ikeda et al., *supra.*
Cardiovascular Disease	miR-93						Ikeda et al., *supra.*
Cardiovascular Disease	miR-99b						Ikeda et al., *supra.*
Cardiovascular Disease	miR-100						Ikeda et al., *supra.*
Cardiovascular Disease		miR-101					Ikeda et al., *supra.*
Cardiovascular Disease	miR-103						Ikeda et al., *supra.*
Cardiovascular Disease		miR-106a					Ikeda et al., *supra.*
Cardiovascular Disease	miR-125b						Ikeda et al., *supra.*
Cardiovascular Disease		miR-126					Ikeda et al., *supra.*
Cardiovascular Disease	miR-140						Ikeda et al., *supra.*
Cardiovascular Disease	miR-145						Ikeda et al., *supra.*
Cardiovascular Disease	miR-181a						Ikeda et al., *supra.*
Cardiovascular Disease	miR-191						Ikeda et al., *supra.*
Cardiovascular Disease	miR-195						Ikeda et al., *supra.*
Cardiovascular Disease	miR-199a						Ikeda et al., *supra.*
Cardiovascular Disease		miR-222					Ikeda et al., *supra.*
Cardiovascular Disease	miR-320						Ikeda et al., *supra.*
Cardiovascular Disease	miR-342						Ikeda et al., *supra.*

FIG. 24c

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Cardiovascular Disease		miR-374					Ikeda et al., *supra.*
Cardiovascular Disease		miR-422b					Ikeda et al., *supra.*
Cardiovascular Disease		miR-423					Ikeda et al., *supra.*
Cardiovascular Disease	miR-451						Ikeda et al., *supra.*
Cardiovascular Disease	miR-499						Ikeda et al., *supra.*
Cardiovascular Disease				MYH7			Buvoli M et al., Trends Cardiovasc Med. 2008 May;18(4):141-9.
Cardiovascular Disease				SCN5A			Makita N et al., J Clin Invest. 2008 Jun;118(6):2219-29,.
Cardiovascular Disease				CHRM2			Zhang L et al., Circ Res. 2008 Jun 6;102(11):1426-32. Epub 2008 May 1.
Cardiovascular Disease			MRP14				Healy AM et al., Circulation 113:2278-2284, 2006.
Cardiovascular Disease			CD69				Healy AM et al., *supra.*
Cardiovascular Disease					CRP		Moura LM et al., Expert Rev Cardiovasc Ther. 2008 Aug;6(7):945-54.
Cardiovascular Disease					BPN		Moura LM et al., *supra.*
Cardiovascular Disease					CD40 & CD4OL		Ferroni P and Guadagni F, Cardiovasc Hematol Disord Drug Targets. 2008 Sep;8(3):194-202.

FIG. 25

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Hematological malignancies – TALL			HOX11				Fernando et al., Cancer Cell, 1: 75-87, 2002.
Hematological malignancies – TALL			TAL1				Fernando et al., Cancer Cell, 1: 75-87, 2002.
Hematological malignancies – TALL			LY1				Fernando et al., Cancer Cell, 1: 75-87, 2002.
Hematological malignancies – TALL			LMO1				Fernando et al., Cancer Cell, 1: 75-87, 2002.
Hematological malignancies – TALL			LMO2				Fernando et al., Cancer Cell, 1: 75-87, 2002.
Hematological malignancies				c-kit			Ravandi F et al., Clin Cancer Res. 2003 Feb;9(2):535-52
Hematological malignancies				PDGFR			Ravandi F et al., Clin Cancer Res. 2003 Feb;9(2):535-53
Hematological malignancies				ABL			Ravandi F et al., Clin Cancer Res. 2003 Feb;9(2):535-54

FIG. 26a

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
B-Cell Chronic Lymphocytic Leukemias		miR-213					Calin et al., 2004, Proc Natl Acad Sci U S A 101(32): 11755-60.
B-Cell Chronic Lymphocytic Leukemias	miR-183-prec						Calin et al., *supra.*
B-Cell Chronic Lymphocytic Leukemias	miR-190						Calin et al., *supra.*
B-Cell Chronic Lymphocytic Leukemias	miR-24-1-prec						Calin et al., *supra.*
B-Cell Chronic Lymphocytic Leukemias	miR-33						Calin et al., *supra.*
B-Cell Chronic Lymphocytic Leukemias	miR-19a						Calin et al., *supra.*
B-Cell Chronic Lymphocytic Leukemias	miR-140						Calin et al., *supra.*
B-Cell Chronic Lymphocytic Leukemias	miR-123						Calin et al., *supra.*
B-Cell Chronic Lymphocytic Leukemias	miR-10b						Calin et al., *supra.*
B-Cell Chronic Lymphocytic Leukemias	miR-15b-prec						Calin et al., *supra.*
B-Cell Chronic Lymphocytic Leukemias	miR-92-1						Calin et al., *supra.*
B-Cell Chronic Lymphocytic Leukemias	miR-188						Calin et al., *supra.*
B-Cell Chronic Lymphocytic Leukemias	miR-154						Calin et al., *supra.*
B-Cell Chronic Lymphocytic Leukemias		miR-220					Calin et al., *supra.*
B-Cell Chronic Lymphocytic Leukemias	miR-217						Calin et al., *supra.*
B-Cell Chronic Lymphocytic Leukemias	miR-101						Calin et al., *supra.*
B-Cell Chronic Lymphocytic Leukemias	miR-141-prec						Calin et al., *supra.*
B-Cell Chronic Lymphocytic Leukemias	miR-153-prec						Calin et al., *supra.*
B-Cell Chronic Lymphocytic Leukemias	miR-196-2						Calin et al., *supra.*
B-Cell Chronic Lymphocytic Leukemias	miR-134						Calin et al., *supra.*
B-Cell Chronic Lymphocytic Leukemias	miR-141						Calin et al., *supra.*
B-Cell Chronic Lymphocytic Leukemias	miR-132						Calin et al., *supra.*
B-Cell Chronic Lymphocytic Leukemias	miR-192						Calin et al., *supra.*

FIG. 26b

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
B-Cell Chronic Lymphocytic Leukemias	miR-181b-prec						Calin et al., *supra.*
B-Cell Chronic Lymphocytic Leukemias			ZAP70	IGHV			Plass C et al., 2007 British Journal of Haematology, 139, 744-752, "
B-Cell Chronic Lymphocytic Leukemias				P53			Plass C et al., *supra.*
B-Cell Chronic Lymphocytic Leukemias				ATM			Plass C et al., *supra.*
B-Cell Chronic Lymphocytic Leukemias			AdipoR1				Molica S et al., 2008 Sep 27, Leuk Lymphoma 49(1): 62-7.

FIG. 27

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
B-cell lymphoma						U50	Tanaka et al., Genes Cells 5(4)277-87, 2000.
B-cell lymphoma	miR-17-92 polycistron						Inomata M et al., Blood. 2008 Oct 21.
B-cell lymphoma-DLBCL	miR-155						Lawrie CH et al., Br J Haematol. 2008 May;141(5):672-5.
B-cell lymphoma-DLBCL	miR-210						Lawrie CH et al., Br J Haematol. 2008 May;141(5):672-5.
B-cell lymphoma-DLBCL	miR-21						Lawrie CH et al., Br J Haematol. 2008 May;141(5):672-5.

FIG. 28

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
B-cell lymphoma-DLBCL-germinal center-like			A-myb				Rosenwald et al., 2002, Semin Oncol 29(3): 258-63.
B-cell lymphoma-DLBCL-germinal center-like			LMO2				Rosenwald et al., *supra.*
B-cell lymphoma-DLBCL-germinal center-like			JNK3				Rosenwald et al., *supra*
B-cell lymphoma-DLBCL-germinal center-like			CD10				Rosenwald et al., *supra*
B-cell lymphoma-DLBCL-germinal center-like			bcl-6				Rosenwald et al., *supra*
B-cell lymphoma-DLBCL-activated B-cell-like			Cyclin D2				Rosenwald et al., *supra*
B-cell lymphoma-DLBCL-activated B-cell-like			IRF4				Rosenwald et al., *supra.*
B-cell lymphoma-DLBCL-activated B-cell-like			Flip				Rosenwald et al., *supra*
B-cell lymphoma-DLBCL-activated B-cell-like			CD44				Rosenwald et al., *supra*
B-cell lymphoma-DLBCL	miR-155						Lawrie CH et al., Br J Haematol. 2008 May;141(5):672-5.
B-cell lymphoma-DLBCL	miR-210						Lawrie CH et al., *supra.*
B-cell lymphoma-DLBCL	miR-21						Lawrie CH et al., *supra.*

FIG. 29

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Burkitt's lymphoma		pri-miR-155					Kluiver J et al., Oncogene. 2007 May 31;26(26):3769-76.
Burkitt's lymphoma					BCL6		Rosenwald, A & G. Ott, Ann Oncol. 2008 Jun;19 Suppl 4:iv67-9.
Burkitt's lymphoma					KI-67		Rosenwald, A & G. Ott, *supra.*
Burkitt's lymphoma			MYC				Dave SS et al., N Engl J Med. 2006 Jun 8;354(23):2431-42.
Burkitt's lymphoma			TERT				Dave et al., *supra.*
Burkitt's lymphoma			NS				Dave et al., *supra.*
Burkitt's lymphoma			NP				Dave et al., *supra.*
Burkitt's lymphoma			MAZ				Dave et al., *supra.*
Burkitt's lymphoma			RCF3				Dave et al., *supra.*
Burkitt's lymphoma			BYSL				Dave et al., *supra.*
Burkitt's lymphoma			IDES				Dave et al., *supra.*
Burkitt's lymphoma			CDC7				Dave et al., *supra.*
Burkitt's lymphoma			TCL1A				Dave et al., *supra.*
Burkitt's lymphoma			AUTS2				Dave et al., *supra.*
Burkitt's lymphoma			MYBL1				Dave et al., *supra.*
Burkitt's lymphoma			BMP7				Dave et al., *supra.*
Burkitt's lymphoma			ITPR3				Dave et al., *supra.*
Burkitt's lymphoma			CDC2				Dave et al., *supra.*
Burkitt's lymphoma			BACK2				Dave et al., *supra.*
Burkitt's lymphoma			TTK				Dave et al., *supra.*
Burkitt's lymphoma			MME				Dave et al., *supra.*
Burkitt's lymphoma			ALOX5				Dave et al., *supra.*
Burkitt's lymphoma			TOP1				Dave et al., *supra.*

FIG. 30a

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Hepatocellular Carcinoma		let-7a-1					Gramantieri et al., 2007, Cancer Res 67(13): 6092-9
Hepatocellular Carcinoma		let-7a-2					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		let-7a-3					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		let-7b					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		let-7c					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		let-7d					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		let-7e					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		let-7f-2					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		let-fg					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		miR-122a					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		miR-124a-2					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		miR-130a					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		miR-132					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		miR-136					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		miR-141					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		miR-142					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		miR-143					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		miR-145					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		miR-146					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		miR-150					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		miR-155(BIC)					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		miR-181a-1					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		miR-181a-2					Gramantieri et al., *supra.*

FIG. 30b

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Hepatocellular Carcinoma		miR-181c					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		miR-195					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		miR-199a-1-5p					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		miR-199a-2-5p					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		miR-199b					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		miR-200b					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		miR-214					Gramantieri et al., *supra.*
Hepatocellular Carcinoma	miR-221						Gramantieri et al., *supra.*
Hepatocellular Carcinoma		miR-223					Gramantieri et al., *supra.*
Hepatocellular Carcinoma		pre-mIR-594					Gramantieri et al., *supra.*
Hepatocellular Carcinoma			FAT10				Lukasiak S et al., Methods Mol Biol. 2008;429:59-72.

FIG. 31

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Cervical Cancer			HPV E6				Liang et al., Clin Oncol 134(8)899-907, 2008, "Galectin-9
Cervical Cancer			HPV E7				
Cervical Cancer			p53				

FIG. 32

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Endometrial Cancer	miR-185	miR-71				N/A	Boren T et al., Gynecologic Oncology 110 (2008) 206-215.
Endometrial Cancer	miR-106a	miR-221					Boren et al., *supra.*
Endometrial Cancer	miR-181a	miR-193					Boren et al., *supra.*
Endometrial Cancer	miR-210	miR-152					Boren et al., *supra.*
Endometrial Cancer	miR-423	miR-30c					Boren et al., *supra.*
Endometrial Cancer	miR-103				-		Boren et al., *supra.*
Endometrial Cancer	miR-107						Boren et al., *supra.*
Endometrial Cancer	let-7c						Boren et al., *supra.*
Endometrial Cancer				PTEN			Doll A et al., J Steroid Biochem Mol Biol. 2008 Feb;108(3-5):221-9.
Endometrial Cancer				K-RAS			Doll et al., *supra.*
Endometrial Cancer				B-catenin			Doll et al., *supra.*
Endometrial Cancer				p53			Doll et al., *supra.*
Endometrial Cancer				Her2/neu			Doll et al., *supra.*
Endometrial Cancer					NLRP7		Ohno S et al., Anticancer Res. 2008 Jul-Aug;28(4C):2493-7.
Endometrial Cancer					AlphaV Beta6 integrin		Hecht JL et al., Appl Immunohistochem Mol Morphol. 2008 Aug 11.

FIG. 33a

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Head and Neck Cancer			HPV E6			N/A	Ragin CC et al., J Dent Res. 2007 Feb;86(2):104-14
Head and Neck Cancer			HPV E7				Ragin CC et al., *supra.*
Head and Neck Cancer			p53				van Houten VM et al., J Pathol. 2002 Dec;198(4):476-86.
Head and Neck Cancer	miR-21	miR-494					Chang SS et al., Int J Cancer. 2008 Sep 16;123(12):2791¬2797.
Head and Neck Cancer	let-7						Chang SS et al., *supra.*
Head and Neck Cancer	miR-18						Chang SS et al., *supra.*
Head and Neck Cancer	miR-29c						Chang SS et al., *supra.*
Head and Neck Cancer	miR-142-3p						Chang SS et al., *supra.*
Head and Neck Cancer	miR-155						Chang SS et al., *supra.*
Head and Neck Cancer	miR-146b						Chang SS et al., *supra.*
Head and Neck Cancer	miR-205						Tran N et al., Biochem Biophys Res Commun. 2007 Jun 22;358(1):12-7.
Head and Neck Cancer	miR-21						Tran N et at, *supra.*
Head and Neck Cancer				GSTM1			Rusin P et al., Postepy Hg Med Dosw (Online). 2008 Sep 23;62:490-501.
Head and Neck Cancer				GSTT1			Rusin P et al., Postepy Hig Med Dosw (Online). 2008 Sep 23;62:490-501.
Head and Neck Cancer				GSTP1			Rusin P et al., *supra.*
Head and Neck Cancer				OGG1			Rusin P et al., *supra.*
Head and Neck Cancer				XRCC1			Rusin P et al., *supra.*
Head and Neck Cancer				XPD			Rusin P et al., *supra.*
Head and Neck Cancer				RAD51			Rusin P et al., *supra.*

FIG. 33b

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Head and Neck Cancer			IL-8				Palka KT et al., 2008, Semin Oncol 35(3): 198-210.
Head and Neck Cancer			SAT				Palka KT et al., *supra.*
Head and Neck Cancer			H3FA3				Palka KT et al., *supra.*
Head and Neck Cancer			EGFR	EGFR	EGFR		Sheikh Ali MA et al., Cancer Sci. 2008 Aug;99(8):1589-94
Head and Neck Cancer				p53			Kanatas A and Harris A , Tumori 94(3): 444; author reply 444.
Head and Neck Cancer							Ferris RL and Grandis JR, Clinical Cancer Research 13, 5663-5664, October 1, 2007."
Head and Neck Cancer					EphB4		Yavrouian EJ et al., Arch Otolaryngol Head Neck Surg. 2008 Sep;134(9):985-91.
Head and Neck Cancer					EphrinB2		Yavrouian EJ et al., *supra.*

FIG. 34

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Irritable Bowel Disease					Il-16		Seegert D, et al., 2001, Gut, 48(3): 326-32
Irritable Bowel Disease					Il-1 beta		Seegert D, et al., *supra.*
Irritable Bowel Disease					Il-12		Seegert D, et al., *supra*
Irritable Bowel Disease					TNF-alpha		Seegert D, et al., *supra*
Irritable Bowel Disease					interferon gamma		Seegert D, et al., *supra*
Irritable Bowel Disease					Il-6		Seegert D, et al., *supra*
Irritable Bowel Disease					Rantes		Seegert D, et al., *supra*
Irritable Bowel Disease					MCP-1		Seegert D, et al., *supra*
Irritable Bowel Disease				CARD 15			Li X et al., World J Gastroenterol. 2008 Sep 7;14(33):5115-24.
Irritable Bowel Disease					Resistin		Li X et al., *supra.*
Irritable Bowel Disease			Trypsinogen IV				Kerckhoffs AP et al., Neurogastroenterol Motil. 2008 Aug;20(8):900-7.."
Irritable Bowel Disease					5-HT		Kerckhoffs AP et al., *supra.*

FIG. 35

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Diabetes			IL-8				Nair S et al., Diabetologia. 2005 September; 48(9): 1784-1788.
Diabetes			CTSS				Nair S et al., *supra.*
Diabetes			ITGB2				Nair S et al., *supra.*
Diabetes			HLA-DRA				Nair S et al., *supra.*
Diabetes			CD53				Nair S et al., *supra.*
Diabetes			PLAG27				Nair S et al., *supra.*
Diabetes			MMP9				Nair S et al., *supra.*
Diabetes					RBP4	.	Nair S et al., *supra.*

FIG. 36

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Barrett's Esophagus				p53	p53		Hamelin R, et al., 1994, Gastroenterology, 107(4): 1012-8
Barrett's Esophagus	miR-21						Watson DI, et al., 2007, World J Surg 31(3): 447-9.
Barrett's Esophagus	miR-143						Watson DI, et al., *supra*..
Barrett's Esophagus	miR-145						Watson DI, et al., *supra*..
Barrett's Esophagus	miR-194						Watson DI, et al., *supra*..
Barrett's Esophagus	miR-215						Watson DI, et al., *supra*..
Barrett's Esophagus					MUC1		Burjonrappa SC et al., Indian J Cancer. 2007 Jan-Mar;44(1):1-5.
Barrett's Esophagus					MUC2		Burjonrappa SC et al., *supra*.
Barrett's Esophagus					MUC6		Glickman JN et al., Am J Surg Pathol. 2003 Oct;27(10):1357- 65
Barrett's Esophagus			S100A2				Lee OJ et al., Neoplasia. 2006 Oct;8(10):843-50
Barrett's Esophagus			S100A4				Lee OJ et al., *supra*.

FIG. 37

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Fibromyalgia			NR2D				Kim SH et al., J Rheumatol. 2006 Apr;33(4):785-8.

FIG. 38

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Stroke			MMP9				Sharp FR et al., Stroke. 2007 Feb;38(2 Suppl):691-3.
Stroke			S100-P				Sharp FR et al., *supra.*
Stroke			S100A12				Sharp FR et al., *supra.*
Stroke			S100A9				Sharp FR et al., *supra.*
Stroke			coag factor V				Sharp FR et al., *supra.*
Stroke			Arginasel				Sharp FR et al., *supra.*
Stroke			CA-IV				Sharp FR et al., *supra.*
Stroke			monocarboxylic acid transporter				Sharp FR et al., *supra.*
Stroke			ets-2				Sharp FR et al., *supra.*
Stroke			EIF2alpha				Sharp FR et al., *supra.*
Stroke			cytoskeleton associated protein 4				Sharp FR et al., *supra.*
Stroke			N-formylpeptide receptor				Sharp FR et al., *supra.*
Stroke			Ribonuclease2				Sharp FR et al., *supra.*
Stroke			N-acetylneuraminate pyruvate lyase				Sharp FR et al., *supra.*
Stroke			BCL-6				Sharp FR et al., *supra.*
Stroke			Glycogen phosphorylase				Sharp FR et al., *supra.*
Stroke					Lp-PLA2		http://www.doctorslounge.com/neurology/news/stroke_lp-pla2_crp.shtml; Gorelick PB, Am J Cardiol. 2008 Jun 16;101(12A):34F-40F
Stroke					hs-CRP		http://www.doctorslounge.com/neurology/news/stroke_lp-pla2_crp.shtml

FIG. 39

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Multiple Sclerosis			IL-6				Kinter J et al., Int MS J. 2008 Jun;15(2):51-8.
Multiple Sclerosis			IL-17				Tajouri L et al., Curr Genomics. 2007 May:8(3):181-9..
Multiple Sclerosis			PAR-3				Tajouri L et al., *supra.*
Multiple Sclerosis			IL-17				Tajouri L et al., *supra*
Multiple Sclerosis			T1/ST2				Tajouri L et al., *supra*
Multiple Sclerosis			JunD				Tajouri L et al., *supra*
Multiple Sclerosis			5-LO				Tajouri L et al., *supra*
Multiple Sclerosis			LTA4H				Tajouri L et al., *supra*
Multiple Sclerosis			MBP				Tajouri L et al., *supra*
Multiple Sclerosis			PLP				Tajouri L et al., *supra*
Multiple Sclerosis			alpha-beta crystallin				Tajouri L et al., *supra*

FIG. 40a

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Parkinsons Disease		miR-133b					Kim J. et al., Science. 2007 Aug 31;317(5842):1220-4.
Parkinsons Disease				FGF20			Wang G. et al., 2008, FEBS Lett 582 (25-26): 3663-8
Parkinsons Disease				alpha-synuclein			Mizuta I. et al., 2008, Hum Genet, 124(1): 89-94
Parkinsons Disease				FGF20			Mizuta I. et al., *supra.*
Parkinsons Disease				NDUFV2			Mizuta I. et al., *supra.*
Parkinsons Disease				FGF2			Mizuta I. et al., *supra.*
Parkinsons Disease				CALB1			Mizuta I. et al., *supra.v*
Parkinsons Disease				B2M			Mizuta I. et al., *supra.*
Parkinsons Disease			Nurr1				Altar CA, Neuropsychopharm. 2008 Oct 15.
Parkinsons Disease			BDNF				Altar CA, *supra.*
Parkinsons Disease			TrkB				Altar CA, *supra.*
Parkinsons Disease			gstml				Altar CA, *supra.*
Parkinsons Disease			S100 beta				Altar CA, *supra.*
Parkinsons Disease					apo-H		Shi M et al., Neurobiol Dis. 2008 Sep 26.
Parkinsons Disease					Ceruloplas min		Shi M et al., *supra.*
Parkinsons Disease					BDNF		Zhang et al., 2008 Am. J. Clin. Pathol. 129, 526-9.
Parkinsons Disease					IL-8		Zhang et al., *supra.*
Parkinsons Disease					Beta2-microglobul in		Zhang et al., *supra*
Parkinsons Disease					apoAll		Zhang et al., *supra*
Parkinsons Disease					tau		Zhang et al., *supra*
Parkinsons Disease					ABeta1-42		Zhang et al., *supra*

FIG. 40b

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Parkinsons Disease					DJ-1		Waragai et al., 2007 Neurosci. Lett. 425, 18¬22 & Waragai et al 2006 Biochem. Biophys. Res. Commun. 345, 967-72.

FIG. 41

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Rheumatic Disease	miR-146a						Pauley KM et al., Arthritis Res Ther. 2008 Aug 29;10(4):R101. [Epub ahead of print]; Stanczyk J et al., Arthritis Rheum. 2008 Apr;58(4):1001-9.
Rheumatic Disease	miR-155						Pauley KM et al., *supra.*; Stanczyk J et al., *supra.*
Rheumatic Disease	mIR-132						Pauley KM et al., *supra.*; Stanczyk J et al., *supra.*
Rheumatic Disease	mIR-16						Pauley KM et al., *supra.*;Stanczyk J et al., *supra.*
Rheumatic Disease	miR-181						TiNat Clin Pract Rheumatol. 2008 Oct;4(10):534- 41. Epub 2008 Aug 26.ii E et al.,
Rheumatic Disease			HOXD10				Galligan CL et al., Genes Immun. 2007 Sep;6(6):480-91. Epub 2007 Jun 14 .
Rheumatic Disease			HOXD11				Galligan CL et al., *supra.*
Rheumatic Disease			HOXD13				Galligan CL et al., *supra*
Rheumatic Disease			CCL8				Galligan CL et al., *supra*
Rheumatic Disease			LIM homeobox2				Galligan CL et al., *supra*
Rheumatic Disease			CENP-E				Kullmann F et al., Arthritis Res. 1999;1(1):71-80. Epub 1999 Oct 26.
Rheumatic Disease							Anderson AK et al., Arthritis Res Ther. 2008;10(2):204. Epub 2008 Mar 14.
Rheumatic Disease					TNFalpha		Anderson AK et al., *supra.*

FIG. 42a

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Alzheimers Disease				APP			Vassar et al., 2005 Subcell. Biochem. 38, pp. 79-103.
Alzheimers Disease				presenilin1			Vassar et al., *supra.*
Alzheimers Disease				presenilin2			Vassar et al., *supra.*
Alzheimers Disease		miR-107					Wang WX et al., 2008, FEBS Lett. 582(25-26): 3663-8
Alzheimers Disease		miR-29a					Hebert SS et al., 2008, Proc Natl Aced Sci U.S.A., 105(17): 6415-20
Alzheimers Disease		miR-29b-1					Hebert SS et al., *supra.*
Alzheimers Disease		miR-9					Hebert SS et al., *supra.*
Alzheimers Disease					BACE1		Hebert SS et al., *supra.*
Alzheimers Disease			HIF-1alpha				Zhang et al., 2008 Am. J. Clin. Pathol. 129, 526-9.
Alzheimers Disease			BACE1				Zhang et al., *supra.*
Alzheimers Disease				APOE4			Thomas P and Fenech M, Mutagenesis. 2007 Jan;22(1):15-33. Epub 2006 Dec 8
Alzheimers Disease	.		Reelin		Reelin		Botella-Lopez A et al., Proc Nail Acad Sci U S A. 2006 Apr 4;103(14):5573-8. Epub 2006 Mar 27
Alzheimers Disease			CHRNA 7				Altar CA, Neuropsychopharmacology. 2008 Oct 15.
Alzheimers Disease			3Rtau/4 Rtau				Altar CA, *supra.*
Alzheimers Disease					Cystatin C		Simonsen et al., 2008 Neurobiol. Aging. 29, 961-8
Alzheimers Disease					Truncated Cystatin C		Simonsen et al., *supra.*
Alzheimers Disease					Amyloid Beta		Simonsen et al., *supra.*
Alzheimers Disease					C3a		Simonsen et al., *supra.*

FIG. 42b

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Alzheimers Disease					t-Tau		Simonsen et al., *supra.*
Alzheimers Disease					Complement factor H		Hye et al., 2006 Brain. 129, 3042-50
Alzheimers Disease					Alpha-2-macroglobulin		Hye et al., *supra.*

FIG. 43

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Prion Diseases					PrP©		Takemura K et al., Exp Biol Med (Maywood) Feb;231(2)204-14, 2006
Prion Diseases					14-3-3		Kubler E et al , British Medical Bulletin 66:267-279, 2003
Prion Diseases					NSE		Kubler E et al , British Medical Bulletin 66:267-279, 2003
Prion Diseases					S-100		Kubler E et al , British Medical Bulletin 66:267-279, 2003
Prion Diseases					Tau		Kubler E et al , British Medical Bulletin 66:267-279, 2003
Prion Diseases					AQP-4		Kubler E et al , British Medical Bulletin 66:267-279, 2003
Prion Diseases			Amyloid B4				Tamguney G et al., J Gen Virol. 2008 Jul;89(Pt 7):1777-88
Prion Diseases			App				Tamguney G et al., J Gen Virol. 2008 Jul;89(Pt 7):1777-88
Prion Diseases			IL-1R1				Tamguney G et al., J Gen Virol. 2008 Jul;89(Pt 7):1777-88
Prion Diseases			SOD1				Tamguney G et al., J Gen Virol. 2008 Jul;89(Pt 7):1777-88

FIG. 44

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Sepsis			15-Hydroxy-PG dehydrogenase (up)				Tang MP et al., Am J Respir Crit Care Med 176:676-684, 2007
Sepsis			LAIR1 (up)				Tang MP et al., *supra.*
Sepsis			NFKB1A (up)				Tang MP et al., *supra.*
Sepsis			TLR2				Johnson SB et al., Annals of Surgery 245,Number 4, April 2007, 245(4): 611-21.
Sepsis			PGLYPRI			•	Johnson SB et al., *supra.*
Sepsis			TLR4				Johnson SB et al., *supra.*
Sepsis			MD2				Johnson SB et al., *supra.*
Sepsis			TLR5				Johnson SB et al., *supra.*
Sepsis			IFNAR2				Johnson SB et al., *supra.*
Sepsis			IRAK2				Johnson SB et al., *supra.*
Sepsis			IRAK3				Johnson SB et al., *supra.*
Sepsis			IRAK4				Johnson SB et al., *supra.*
Sepsis			PI3K				Johnson SB et al., *supra.*
Sepsis			PI3KCB	•			Johnson SB et al., *supra.*
Sepsis			MAP2K6				Johnson SB et al., *supra.*
Sepsis			MAPK14				Johnson SB et al., *supra.*
Sepsis			NFKBIA				Johnson SB et al., *supra.*
Sepsis			NFKB1				Johnson SB et al., *supra.*
Sepsis			IL1R1				Johnson SB et al., *supra.*
Sepsis			MAP2K1IP1				Johnson SB et al., *supra.*
Sepsis			MKNK1				Johnson SB et al., *supra.*
Sepsis			FAS				Johnson SB et al., *supra.*
Sepsis			CASP4				Johnson SB et al., *supra.*
Sepsis			GADD45B				Johnson SB et al., *supra.*
Sepsis			SOCS3				Johnson SB et al., *supra.*
Sepsis			TNFSF10				Johnson SB et al., *supra.*
Sepsis			TNFSF13B				Johnson SB et al., *supra.*
Sepsis			OSM				Johnson SB et al., *supra.*
Sepsis			HGF				Johnson SB et al., *supra.*
Sepsis			IL18R1				Johnson SB et al., *supra.*

FIG. 45

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Chronic Neuropathic Pain			ICAM-1 (rodent)				Rodriguez Parkitna J et al., J Physiol Pharmacol. 2006 Sep;57(3):401-14.
Chronic Neuropathic Pain			CGRP (rodent)				Rodriguez Parkitna J et al., J Physiol Pharmacol. 2006 Sep;57(3):401-14.
Chronic Neuropathic Pain			TIMP-1 (rodent)				Rodriguez Parkitna J et al., J Physiol Pharmacol. 2006 Sep;57(3):401-14.
Chronic Neuropathic Pain			CLR-1 (rodent)				Rodriguez Parkitna J et al., J Physiol Pharmacol. 2006 Sep;57(3):401-14.
Chronic Neuropathic Pain			HSP-27 (rodent)				Kim DS et al., Neuroreport. 2001 Oct 29;12(15):3401-5
Chronic Neuropathic Pain			FABP (rodent)				Kim DS et al., Neuroreport. 2001 Oct 29;12(15):3401-5
Chronic Neuropathic Pain			Apolipo-protein D (rodent)				Kim DS et al., Neuroreport. 2001 Oct 29;12(15):3401-5
Chronic Neuropathic Pain					Chemokines		White FA et al., Proc Natl Acad Sci U S A. 2007 Dec 18;104(51):20151-8
Chronic Neuropathic Pain					Chemokine receptor (CCR2/4)		White FA et al., Proc Natl Acad Sci U S A. 2007 Dec 18;104(51):20151-8

FIG. 46

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Periperhal Neuropathic Pain					OX42 (rodent)		Blackbeard J et al., J Neurosci Methods. 2007 Aug 30;164(2):207-17
Periperhal Neuropathic Pain					ED9 (rodent)		Blackbeard J et al., J Neurosci Methods. 2007 Aug 30;164(2):207-17

FIG. 47

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Schizophrenia			IFITM3		ATP5B		Altar CA, Neuropsychopharm. 2008 Oct 15.
Schizophrenia			SERPINA3		ATP5H		Altar CA, *supra.*
Schizophrenia			GLS		ATP6V1B		Altar CA, *supra.*
Schizophrenia			ALDH7A1B ASP1		DNM1		Altar CA, *supra.*
Schizophrenia					NDUFV2		Altar CA, *supra.*
Schizophrenia					NSF		Altar CA, *supra.*
Schizophrenia					PDHB		Altar CA, *supra.*
Schizophrenia	miR-181b						Beveridge NJ et al., Hum Moi Genet. 2008 Apr 15;17(8):1156-68. Epub 2008 Jan 9
Schizophrenia		miR-7					Perkins DO et al., Genome Biol. 2007;8(2):R27.
Schizophrenia		miR-24					Perkins DO et al., *supra.*
Schizophrenia		miR-26b					Perkins DO et al., *supra*
Schizophrenia		miR-29b					Perkins DO et al., *supra*
Schizophrenia		miR-30b					Perkins DO et al., *supra*
Schizophrenia		miR-30e					Perkins DO et al., *supra*
Schizophrenia		miR-92					Perkins DO et al., *supra*
Schizophrenia		miR-195					Perkins DO et al., *supra*
Schizophrenia				DISCI			Millar JK et al., J Physiol. 2007 Oct 15;584(Pt 2):401-5.
Schizophrenia				dysbindin			Chen XW et al., J Cell Biol. 2008 Jun 2;181(5):791-801
Schizophrenia				neuregulin-1			Harrison PJ, Novartis Found Symp. 2007;288:246-55; discussion 255-9, 276-81
Schizophrenia				seratonin 2a receptor			Erdmann J et al., Volume 97, Number 5 / March, 1996 614-619
Schizophrenia				NURR1			Buervenich Set al., Volume 96 Issue 6, Pages 808- 813

FIG. 48

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Bipolar Disorder			FGF2				Altar CA, Neuropsychopharm. 2008 Oct 15.
Bipolar Disorder			ALDH7A1				Altar CA, *supra.*
Bipolar Disorder			AGXT2L1				Altar CA, *supra.*
Bipolar Disorder			AQP4				Altar CA, *supra.*
Bipolar Disorder			PCNT2				Anitha A et al., Biol Psychiatry. 2008 Apr 1;63(7):678-85. Epub 2007 Sep 20
Bipolar Disorder				Dysbindin			Goes FS et al., Curr Psychiatry Rep. 2008 Apr;10(2):178-89 "The genetics of psychotic bipolar disorder."
Bipolar Disorder				DAOA/G30			Goes FS et al., Curr Psychiatry Rep. 2008 Apr;10(2):178-89.
Bipolar Disorder				DISCI			Goes FS et al., Curr Psychiatry Rep. 2008 Apr;10(2):178-89.
Bipolar Disorder				neuregulin-1			Goes FS et al., Curr Psychiatry Rep, 2008 Apr;10(2):178-89.

FIG. 49

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Depression			FGFR1				Altar CA, Neuropsychopharinacology. 2008 Oct 15.
Depression			FGFR2				Altar CA, Neuropsychopharmacology. 2008 Oct 15.
Depression			FGFR3				Altar CA, Neuropsychopharmacology. 2008 Oct 15.
Depression			AQP4				Altar CA, Neuropsychopharmacology. 2008 Oct 15.

FIG. 50

Cancer Lineage, Group Comparison, Other Significant Disease State	**Up-regulated miRs**	**Down-regulated miRs**	**mRNAs**	**Mutational Analysis**	**Proteins, Ligands, Peptides**	**snoRNA**	**Select Reference(s)**
GIST					PDGFRA		Yang J et al., Cancer. 2008 Oct 1;113(7):1532-43
GIST					c-kit		Yang J et al., *supra.*
GIST			DOG-1				Espinosa F et al., Am J Surg Pathol Feb;32(2)210-8, 2008
GIST			PKC-theta	PKC-theta			Blay P et al., CM Cancer Res. 2004 Jun 15;10(12 Pt 1):4089-95
GIST			KIT				Allander SV et al., Cancer Res. 2001 Dec 15;61(24):8624-8.
GIST			GPR20				Allander SV et al., *supra.*
GIST			PRKCQ				Allander SV et al., *supra*
GIST			KCNK3				Allander SV et al., *supra*
GIST			KCNH2				Allander SV et al., *supra*
GIST			SCG2				Allander SV et al., *supra*
GIST			TNFRSF 6B				Allander SV et al., *supra*
GIST			CD34				Allander SV et al., *supra*

FIG. 51a

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
RCC		Mir-141					Nakada C et al., J Pathol. 2008 Aug 28
RCC		Mir200c					Nakada C et al., *supra.*
RCC			laminin receptor 1				Ohno Y et al., Oncol Rep. 2008 Sep;20(3):501-9.
RCC		.	betaig-h3				Ohno Y et al., *supra.*
RCC				VHL			Nickerson ML et al., Clin Cancer Res. 2008 Aug 1;14(15):4726-34
RCC					HIF1alpha		Rathmell WK, Chen S, Expert Rev Anticancer Ther. 2008 Jan;8(1):63-73.
RCC					VEGF		Rathmell WK, Chen S, *supra.*
RCC					PDGFRA		Rathmell WK, Chen S, *supra.*
RCC			Galectin-1				Young AN, Am J Pathol. 2001 May;158(5):1639-51.
RCC			a-2 Macroglobulin				Young AN, *supra.*
RCC			Adipophilin				Young AN, *supra.*
RCC			Angiopoietin 2				Young AN, *supra.*
RCC		.	Caldesmon 1				Young AN, *supra.*
RCC			Class II MHC-associated invariant chain (CD74)				Young AN, *supra.*
RCC			Collagen IV-a1				Young AN, *supra.*
RCC			Complement component				Young AN, *supra.*
RCC			Complement component 3				Young AN, *supra.*

FIG. 51b

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
RCC			Cytochrome P450, subfamily IIJ polypeptide 2				Young AN, *supra.*
RCC			Delta sleep-Inducing peptide				Young AN, *supra.*
RCC			Fc g receptor illa (CD16)				Young AN, *supra.*
RCC			HLA-B				Young AN, *supra.*
RCC			HLA-DR a				Young AN, *supra.*
RCC			HLA-DR b				Young AN, *supra.*
RCC			HLA-SB				Young AN, *supra.*
RCC			IFN-induced transmembrane protein 3				Young AN, *supra.*
RCC			IFN-induced transmembrane protein 1				Young AN, *supra.*
RCC			Lysyl Oxidase				Young AN, *supra.*

FIG. 52

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Cirrhosis			NLT				Simonson GD et al., Journal of Cell Science 107, 1065-1072 (1994)
Cirrhosis					NLT		Simonson GD et al., *supra.*
Cirrhosis					HBsAg		Wang, W. et al., Hepatology. 1991 Jul;14(1):29-37.
Cirrhosis					AST		Wai CT, et al. Hepatology. 2003;38:518-526.
Cirrhosis					YKL-40		Patel K, et al., Gastroenterology. 2004;126 (suppl 2):A-708. [S1645]
Cirrhosis					Hyaluronic acid		Patel K, et al., *supra.*
Cirrhosis					TIMP-1		Patel K, et al., *supra.*
Cirrhosis					alpha 2 macroglobulin		Patel K, et al., *supra.*
Cirrhosis					a-1-antitrypsin PI Z allele		*Hum Hered* 1992;42:235-241
Cirrhosis					haptoglobin		*Hum Hered* 1992;42:235-241
Cirrhosis					acid phosphatase ACP AC		*Hum Hered* 1992;42:235-241

FIG. 53

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Esphageal cancer (adeno)	miR-192	miR-27b					Feber A et al., J Thorac Cardiovasc Surg. 2008 Feb;135(2):255-60
Esphageal cancer (adeno)	miR-194	miR-205					Feber A et al., *supra.*
Esphageal cancer (adeno)	miR-21	miR-203					Feber A et al., *supra.*
Esphageal cancer (adeno)	miR-200c	miR-342					Feber A et al., *supra.*
Esphageal cancer (adeno)	miR-93	let-7c					Feber A et al., *supra.*
Esphageal cancer (adeno)		miR-125b					Feber A et al., *supra.*
Esphageal cancer (adeno)		miR-100					Feber A et al., *supra.*
Esphageal cancer (adeno)		miR-152					Feber A et al., *supra.*
Esphageal cancer (squamous)	miR-342	miR-192					Feber A et al., *supra.*
Esphageal cancer (squamous)	miR-152	miR-194					Feber A et al., *supra.*
Esphageal cancer (squamous)	miR-93	miR-27b					Feber A et al., *supra.*
Esphageal cancer (squamous)		miR-205					Feber A et al., *supra.*
Esphageal cancer (squamous)		miR-203					Feber A et al., *supra.*
Esphageal cancer (squamous)		miR-200c					Feber A et al., *supra.*
Esphageal cancer (squamous)		let-7c					Feber A et al., *supra.*
Esphageal cancer (squamous)		miR-100					Feber A et al., *supra.*
Esphageal cancer	miR-25	miR-100					Guo Y et al., Cancer Res. 2008 Jan 1;68(1):26-33.
Esphageal cancer	miR-424	miR-99a					Guo Y et al., *supra.*
Esphageal cancer	miR-151	miR-29c					Guo Y et al., *supra.*
Esphageal cancer		miR-140					Guo Y et al., *supra.*
Esphageal cancer		miR-103					Guo Y et al., *supra.*
Esphageal cancer		miR-107					Guo Y et al., *supra.*
Esphageal cancer			MTHFR				Höfler H et al., Adv Exp Med Biol. 2006;587:115-20.

FIG. 54

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Gastric cancer	miR-106a						Xiao B et al., Clin Chim Acta. 2008 Oct 30.
Gastric cancer	miR-21						Zhang Z et al., Lab Invest. 2008 Sep 15.
Gastric cancer		let-7a					Zhang HH et al., World J Gastroenterol. 2007 May 28;13(20):2883-8.
Gastric cancer	miR-21						Volinia S et al., Proc Natl Acad Sci U S A. 2006 Feb 14;103(7):2257-61.
Gastric cancer	miR-191						Volinia S et al., Proc Natl Acad Sci U S A. 2006 Feb 14;103(7):2257-61.
Gastric cancer	miR-223						Volinia S et al., Proc Natl Acad Sci U S A. 2006 Feb 14;103(7):2257-61.
Gastric cancer	miR-24-1						Volinia S et al., Proc Natl Acad Sci U S A. 2006 Feb 14;103(7):2257-61.
Gastric cancer	miR-24-2						Volinia S et al., Proc Natl Acad Sci U S A. 2006 Feb 14;103(7):2257-61.
Gastric cancer	miR-107						Volinia S et al., Proc Natl Acad Sci U S A. 2006 Feb 14;103(7):2257-61.
Gastric cancer	miR-92-2						Volinia S et al., Proc Natl Acad Sci U S A. 2006 Feb 14;103(7):2257-61.
Gastric cancer	miR-214						Volinia S et al., Proc Natl Acad Sci U S A. 2006 Feb 14;103(7):2257-61.
Gastric cancer	miR-25						Volinia S et al., Proc Natl Acad Sci U S A. 2006 Feb 14;103(7):2257-61.
Gastric cancer	miR-221						Volinia S et al., Proc Natl Acad Sci U S A. 2006 Feb 14;103(7):2257-61.
Gastric cancer			RRM2				Kolesar J et al., Cancer Chemother Pharmacol. 2008 Oct 22.
Gastric cancer			EphA4		EphA4		Oki M et al., World J Gastroenterol. 2008 Oct 7;14(37):5650-6
Gastric cancer			survivin				Yie SM et al., Ann Surg Oncol. 2008 Nov;15(11):3073-82.
Gastric cancer				APC			Lea IA et al., Carcinogenesis. 2007 September;28(9): 1851-1858.

FIG. 55

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Autism					GM1		Lekman et al., Acta Paediatrica 1995, vol. 84, no7, pp. 787-790.
Autism					GDIa		Lekman et al., *supra.*
Autism					GDIb		Lekman et al., *supra*
Autism					GTIb		Lekman et al., *supra*
Autism	miR-484						Ablu-Elneel, Liu et al., Neurogenetics (2008) 9:153-161
Autism	miR-21						Ablu-Elneel, Liu et al., *supra.*
Autism	miR-212						Ablu-Elneel, Liu et al., *supra.*
Autism	miR-23a						Ablu-Elneel, Liu et al., *supra.*
Autism	miR-598						Ablu-Elneel, Liu et al., *supra.*
Autism	miR-95						Ablu-Elneel, Liu et al., *supra.*
Autism	miR-129						Ablu-Elneel, Liu et al., *supra.*
Autism	miR-431						Ablu-Elneel, Liu et al., *supra.*
Autism	miR-7						Ablu-Elneel, Liu et al., *supra.*
Autism	miR-15a						Ablu-Elneel, Liu et al., *supra.*
Autism	miR-27a						Ablu-Elneel, Liu et al., *supra.*
Autism	miR-15b						Ablu-Elneel, Liu et al., *supra.*
Autism	miR-148b						Ablu-Elneel, Liu et al., *supra.*
Autism	miR-132						Ablu-Elneel, Liu et al., *supra.*
Autism	miR-128						Ablu-Elneel, Liu et al., *supra.*
Autism		miR-93					Ablu-Elneel, Liu et al., *supra.*
Autism		miR-106a					Ablu-Elneel, Liu et al., *supra.*
Autism		miR-539					Ablu-Elneel, Liu et al., *supra.*
Autism		miR-652					Ablu-Elneel, Liu et al., *supra.*
Autism		miR-550					Ablu-Elneel, Liu et al., *supra.*
Autism		miR-432					Ablu-Elneel, Liu et al., *supra.*
Autism		miR-193b					Ablu-Elneel, Liu et al., *supra.*
Autism		miR-181d					Ablu-Elneel, Liu et al., *supra.*
Autism		miR-146b					Ablu-Elneel, Liu et al., *supra.*
Autism		miR-140					Ablu-Elneel, Liu et al., *supra.*
Autism		miR-381					Ablu-Elneel, Liu et al., *supra.*
Autism		miR-320a					Ablu-Elneel, Liu et al., *supra.*
Autism		miR-106b					Ablu-Elneel, Liu et al., *supra.*

FIG. 56

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Organ Rejection					matrix metallo-protein-9		American Physiological Society (2006, November 4). Proteins May Predict Lung Transplant Rejection. ScienceDaily. Retrieved
Organ Rejection					proteinase 3		American Physiological Society, *supra.*
Organ Rejection					HNP		American Physiological Society, *supra.*
Organ Rejection	miR-658						W. Sui et al., Transplant Immunology 19 (2008) 81-85
Organ Rejection	miR-125a						W. Sui et al.., *supra.*
Organ Rejection	miR-320						W. Sui et al.., *supra.*
Organ Rejection	miR-381						W. Sui et al.., *supra.*
Organ Rejection	miR-628						W. Sui et al.., *supra.*
Organ Rejection	miR-602						W. Sui et al.., *supra.*
Organ Rejection	miR-629						W. Sui et al.., *supra.*
Organ Rejection	miR-125a						W. Sui et al.., *supra.*
Organ Rejection		miR-324-3p					W. Sui et al.., *supra.*
Organ Rejection		miR-611					W. Sui et al.., *supra.*
Organ Rejection		miR-654					W. Sui et al.., *supra.*
Organ Rejection		miR-330_MM1					W. Sui et al.., *supra.*
Organ Rejection		miR-524					W. Sui et al.., *supra.*
Organ Rejection		miR-17-3p_MM1					W. Sui et al.., *supra.*
Organ Rejection		miR-483					W. Sui et al.., *supra.*
Organ Rejection		miR-663					W. Sui et al.., *supra.*
Organ Rejection		miR-516-5p					W. Sui et al.., *supra.*
Organ Rejection		miR-326					W. Sui et al.., *supra.*
Organ Rejection		miR-197_MM2					W. Sui et al.., *supra.*
Organ Rejection		miR-346					W. Sui et al.., *supra.*

FIG. 57

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
methicillin-resistant Staphylococcus aureus					ETA		M. Ben Nejma et al.., Diagnostic Microbiology and Infectious Disease 55 (2006) 21– 25
methicillin-resistant Staphylococcus aureus					ETB		M. Ben Nejma et al. / Diagnostic Microbiology and Infectious Disease 55 (2006) 21– 26
methicillin-resistant Staphylococcus aureus					TSST-1		M. Ben Nejma et al. / Diagnostic Microbiology and Infectious Disease 55 (2006) 21– 27
methicillin-resistant Staphylococcus aureus					leukocidins		M. Ben Nejma et al. / Diagnostic Microbiology and Infectious Disease 55 (2006) 21– 28
methicillin-resistant Staphylococcus aureus				mecA			M. Ben Nejma et al. / Diagnostic Microbiology and Infectious Disease 55 (2006) 21– 29
methicillin-resistant Staphylococcus aureus				Protein A SNPs			Frénay HM et al., J Clin Microbiol. 1994 Mar;32(3):846-7.
methicillin-resistant Staphylococcus aureus			TSST-1				Chini V et al., Lett Appl Microbiol. 2007 Nov;45(5):479-84.

FIG. 58

Cancer Lineage, Group Comparison, Other Significant Disease State	Up-regulated miRs	Down-regulated miRs	mRNAs	Mutational Analysis	Proteins, Ligands, Peptides	snoRNA	Select Reference(s)
Vulnerable plaque					IL-6		Maier W et al., 2005 Circulation 111:1355-1361.
Vulnerable plaque					MMP-9		Blankenberg S et al., 2003 Circulation 107:1579-1585.
Vulnerable plaque					PAPP-A		Elesber AA et al., 2006 Eur Heart J 27:1678-1684.
Vulnerable plaque					D-dimer		Danesh j et al., JAMA 2005, 294:1799-1809, Danesh J, Circulation 2001, 103:2323-2327
Vulnerable plaque					fibrinogen		Danesh et al. 2005, Danesh et al. 2001
Vulnerable plaque					Lp-PLA2		Zalewski A et al., Arterioscler Thromb Vasc Biol. 2005;25:923-931
Vulnerable plaque					SCD40L		Koenig W and Khuseyinova N, Arterioscler Thromb Vasc Biol. 2007;27:15-26.
Vulnerable plaque					IL-18		Koenig W and Khuseyinova N, Arterioscler Thromb Vasc Biol. 2007;27:15-26.
Vulnerable plaque					oxLDL		Koenig W and Khuseyinova N, Arterioscler Thromb Vasc Biol. 2007;27:15-26.
Vulnerable plaque					GPx-1		Koenig W and Khuseyinova N, Arterioscler Thromb Vasc Biol. 2007;27:15-26.
Vulnerable plaque					MCP-1		Koenig W and Khuseyinova N, Arterioscler Thromb Vasc Biol. 2007;27:15-26.
Vulnerable plaque					PIGF		Koenig W and Khuseyinova N, Arterioscler Thromb Vasc Biol. 2007;27:15-26.
Vulnerable plaque					CRP		Koenig W and Khuseyinova N, Arterioscler Thromb Vasc Biol. 2007;27:15-26.

FIG. 59a

5' Upstream Fusion Gene Partner	3' downstream Fusion Gene Partner	Cancer Lineage
ACSL3	ETV1	Prostate cancer
AKAP9	BRAF	Papillary thyroid carcinoma
Alpha	TFEB	Renal cell carcinoma
ARHGAP20	BRWD3	B-cell chronic lymphocytic leukemia (B-CLL)
ASPSCR1	TFE3	Renal-cell carcinoma
ATIC	ALK	Anaplastic large cell lymphoma (ALCL)
BCL11B	TLX3	T-cell acute lymphoblastic / lymphocytic leukemia (T-ALL)
BCL3	MYC	B-cell chronic lymphocytic leukemia (B-CLL)
BCL7A	MYC	B-cell chronic lymphocytic leukemia (B-CLL)
BCR	ABL1	Chronic myelogenous leukemia (CML)
BCR	FGFR1	CML-like Myeoproliferative disorder (MPD)
BCR	JAK2	Chronic myelogenous leukemia (CML)
BCR	PDGFRA	Atypical CML
BIRC3	MALT1	B-cell non Hodgkin lymphoma, MALT-lymphomas
BRD4	NUT	Poorly differenitated epithelial carcinoma (Aggressive midline carcinoma)
BRWD3	ARHGAP20	B-cell chronic lymphocytic leukemia (B-CLL)
BTG1	MYC	B-cell chronic lymphocytic leukemia (B-CLL)
CARS	ALK	Inflammatory myofibroblastic tumor
CANT1	ETV4	Prostate cancer
CBFB	MYH11	Acute myelogenous leukemia (AML)
CCDC6	PDGFRB	Philadelphia chr negative Myeoproliferative disorder (MPD)
CCDC6	RET	Pappilary thyroid carcinoma
CCND1	FSTL3	Chronic myelogenous leukemia (CML)
CD74	ROS1	Non small cell lung carcinoma (NSCLC)
CDH11	USP6	Aneurysmal bone cyst
CDK6	EVI1	Myeolid leukemia
CDK6	MLL	Acute lymphoblastic / lymphocytic leukemia (ALL)
CDK6	TLX3	Acute lymphoblastic / lymphocytic leukemia (ALL)
CEP110	FGFR1	Myeloproliferative disorder (Myeoproliferative disorder (MPD))
CHCHD7	PLAG1	Pleomorphic salivary gland adenomas (PA) (Head and Neck)
CHIC2	ETV6	Acute myelogenous leukemia (AML)
CIITA	BCL6	Diffuse large B-cell lymphoma (DLBCL)
CLTC	ALK	Diffuse large B-cell lymphoma (DLBCL)
CLTC	TFE3	Pediatric renal adenocarcinoma
C15ORF21	ETV1	Prostate cancer
COL1A1	PDGFB	Dermatofibrosarcoma protuberans
COL1A1	USP6	Aneurysmal bone cyst
COL1A2	PLAG1	Lipoblastoma

FIG. 59b

5' Upstream Fusion Gene Partner	3' downstream Fusion Gene Partner	Cancer Lineage
CRC1	MAML2	Mucoepidermoid carcinoma
CRTC1	MAML2	Mucoepidermoid carcinomas , Warthin's tumor
CRTC3	MAML2	Mucoepidermoid carcinoma
CTNNB1	PLAG1	Pleomorphic salivary gland adenomas (PA) (Head and Neck)
DDX5	ETV4	Prostate cancer
EIF4A2	BCL6	Non-Hodgkin lymphoma (NHL)
EML1	ABL1	T-cell acute lymphoblastic / lymphocytic leukemia (T-ALL)
EML4	ALK	Non small cell lung carcinoma (NSCLC)
EPC1	PHF1	Endometiral stromal sarcoma
ERC1	RET	Papillary thyroid carcinoma
ETV6	ABL1	Chronic myelogenous leukemia (CML), Acute myelogenous leukemia (AML), Acute lymphoblastic / lymphocytic leukemia (ALL)
ETV6	ABL2	T-cell acute lymphoblastic / lymphocytic leukemia (T-ALL), Acute myelogenous leukemia (AML)
ETV6	ACSL6	Polycythemia vera
ETV6	ARNT	Acute myelogenous leukemia (AML)
ETV6	CDX2	Acute myelogenous leukemia (AML)
ETV6	EVI1	Chronic myelogenous leukemia (CML)
ETV6	FGFR3	Peripheral T-cell lymphoma
ETV6	FLT3	ALL, Myeoproliferative disorder (MPD)
ETV6	HLXB9	Acute myelogenous leukemia (AML)
ETV6	JAK2	Philadelphia chr negative Myeoproliferative disorder (MPD), B cell malignancies
ETV6	MDS2	Myelodisplastic syndrome
ETV6	MN1	Chronic myelogenous leukemia (CML)
ETV6	NTRK3	Secretory breast cancer
ETV6	PDGFRB	Chronic myelomonocytic leukemia (CMML)
ETV6	PER1	Acute myelogenous leukemia (AML)
ETV6	RUNX1	Acute lymphoblastic / lymphocytic leukemia (ALL)
ETV6	SYK	Myelodisplastic syndrome
ETV6	TCBA1	Chronic myelogenous leukemia (CML)
ETV6	TTL	Acute lymphoblastic / lymphocytic leukemia (ALL)
EWSR1	ATF1	Soft tissue sarcoma
EWSR1	DDIT3	Myxoid liposarcoma
EWSR1	ERG	Ewing sarcomas
EWSR1	ETV1	Ewing sarcomas
EWSR1	ETV4	Ewing sarcomas
EWSR1	FEV	Ewing sarcomas
EWSR1	FLI1	Ewing sarcomas

FIG. 59c

5' Upstream Fusion Gene Partner	3' downstream Fusion Gene Partner	Cancer Lineage
EWSR1	NR4A3	Malignant tumor of soft tissue origin
EWSR1	POU5F1	Undifferentiated bone tumor
EWSR1	TEC	Ewing sarcomas
EWSR1	WT1	Soft tissue sarcoma
EWSR1	ZNF278	Small round cell sarcoma
EWSR1	ZNF384	Acute lymphoblastic leukemia
FGFR1OP	FGFR1	Stem-cell myeloproliferative disorder characterized by myeloid hyperplasia, T -cell lymphoblastic leukemia/lymphoma and peripheral blood eosinophilia, and it generally progresses to acute myeloid leukemia;
FGFR1OP2	FGFR1	Myeoproliferative disorder (MPD) is characterized by myeloid hyperplasia, eosinophilia and T-cell or B-cell lymphoblastic lymphoma
FHIT	HMGA2	Pleomorphic salivary gland adenomas (PA) (Head and Neck)
FIP1L1	PDGFRA	Hypereosinophilia
FLT3	ETV6	Hypereosinophilia
FLJ35294	ETV1	Prostate cancer
FUS	ATF1	Angiomatoid fibrous histiocytoma (AFH)
FUS	CREB3L1	Fibromyxoid sarcoma
FUS	CREB3L2	Low-grade fibromyxoid sarcoma (LGFMS)
FUS	DDIT3	Myxoid liposarcoma
FUS	DDIT3	The Myxoid/Round Cell Liposarcoma
FUS	ERG	Ewing sarcomas
GAPDH	BCL6	B-cell non hodgkin lymphoma (B-NHL), Diffuse large B-cell lymphoma (DLBCL)
GOLGA5	RET	Papillary thyroid carcinoma
GOPC	ROS1	Glioblastoma
HAS2	PLAG1	Lipoblastoma
HERV	ETV1	Prostate cancer
HIP1	PDGFRB	Chronic myelomonocytic leukemia (CMML)
HIST1H4I	BCL6	B-cell Non-Hodgkin lymphoma (NHL) (NHL)
HMGA1	LAMA4	Pulmonary chondroid hamartoma
HMGA2	CCNB1IP1	Benign mesenchymal tumors
HMGA2	COX6C	Uterine leiomyoma
HMGA2	CXCR7	Lipoma
HMGA2	FHIT	Pleomorphic salivary gland adenomas (PA) (Head andNeck)
HMGA2	LHFP	Solitary lipomas
HMGA2	LPP	Lipoma, parosteal lipoma, and pulmonary chondroid hamartoma
HMGA2	NFIB	Pleomorphic salivary gland adenomas (PA) (Head and Neck)
HMGA2	RAD51L1	Uterine leiomyomata

FIG. 59d

5' Upstream Fusion Gene Partner	3' downstream Fusion Gene Partner	Cancer Lineage
HNRPA2B1	ETV1	Prostate cancer
HOOK3	RET	Pappilary thyroid carcinoma
HRH4	RET	Pappilary thyroid carcinoma
HSP90AA1	BCL6	B cell Non-Hodgkin lymphoma (NHL) (B-NHL)
HSP90AB1	BCL6	B-cell tumors
IGH	MYC	Burkitt's lymphoma
IKZF1	BCL6	Diffuse large B-cell lymphoma (DLBCL)
IL2	TNFRSF17	T-cell acute lymphoblastic leukemia (T-ALL)
IL21R	BCL6	Diffuse large B-cell lymphoma (DLBCL)
ITK	SYK	Unspecified peripheral T-cell lymphoma
JAZF1	PHF1	Endometrial stromal sarcomas
JAZF1	SUZ12	endometrial stromal tumors and endometrial stromal sarcoma
KIAA1509	PDGFRA	Chronic eosinophilic leukemia (CEL)
KIAA1618	ALK	Anaplastic large-cell lymphoma (ALCL)
KLK2	ETV4	Prostate cancer
KTN1	RET	Papillary thyroid carcinoma
LCP1	BCL6	Non Hodgkin follicular, Burkitt lymphomas
LIFR	PLAG1	Pleomorphic salivary gland adenomas (PA) (Head and Neck)
MALAT1	TFEB	Pediatric renal neoplasm
MEF2D	DAZAP1	Acute myelogenous leukemia (AML)
MLL	ABI1	acute non lymphoblastic leukemia
MLL	AFF1	Acute lymphoblastic / lymphocytic leukemia (ALL), Acutemyelogenous leukemia (AML)
MLL	AFF3	Acute lymphoblastic / lymphocytic leukemia (ALL)
MLL	AFF4	Acute lymphoblastic / lymphocytic leukemia (ALL)
MLL	ARHGAP26	Acute monocytic leukemia (Acute myelogenous leukemia (AML) (M5b)
MLL	ARHGEF12	Acute myelogenous leukemia (AML)
MLL	CASC5	Acute myelogenous leukemia (AML)
MLL	CBL	Acute myelogenous leukemia (AML)
MLL	CLP1	Monoblastic leukemia
MLL	CREBBP	Acute myelogenous leukemia (AML)
MLL	CXXC6	Acute lymphoblastic / lymphocytic leukemia (ALL)
MLL	DAB2IP	Acute myelogenous leukemia (AML)
MLL	ELL	Acute myelogenous leukemia (AML)
MLL	EP300	Acute myelogenous leukemia (AML)
MLL	EPS15	Acute myelogenous leukemia (AML)
MLL	FNBP1	Acute myelogenous leukemia (AML)
MLL	FOXO3A	Acute myelogenous leukemia (AML)

FIG. 59e

5' Upstream Fusion Gene Partner	3' downstream Fusion Gene Partner	Cancer Lineage
MLL	GAS7	Acute lymphoblastic / lymphocytic leukemia (ALL)
MLL	GMPS	Acute myelogenous leukemia (AML)
MLL	GPHN	Acute myelogenous leukemia (AML)
MLL	LASP1	Infant acute myeloid leukemia Acute myelogenous leukemia (AML)-M4
MLL	LPP	Secondary acute leukemia
MLL	MAPRE1	Pro-B acute lymphoblastic leukemia
MLL	MLL	Acute myeloid and lymphoid leukemia
MLL	MLLT1	Acute myelogenous leukemia (AML)
MLL	MLLT10	Pediatric acute megakaryoblastic leukemia AND acute monoblastic leukemia
MLL	MLLT11	Acute myelogenous leukemia (AML)
MLL	MLLT3	Acute myelogenous leukemia (AML)
MLL	MLLT4	M4/M5 ANLL
MLL	MLLT6	Acute myelogenous leukemia (AML)
MLL	MLLT7	Acute leukemias
MLL	MYO1F	Acute myelogenous leukemia (AML)
MLL	PICALM	Acute myelogenous leukemia (AML)
MLL	RARA	M5 acute non lymphocytic leukemia (ANLL)
MLL	SEPT11	Chronic neutrophilic leukemia
MLL	SEPT2	Acute myelogenous leukemia (AML), therapy-related myelodysplastic syndrome
MLL	SEPT5	De novo acute non lymphocytic leukemia
MLL	SEPT6	Acute myelogenous leukemia (AML)
MLL	SEPT9	Myeloid neoplasia
MLL	SH3GL1	Acute leukemia
MLL	SORBS2	Acute myelogenous leukemia (AML)
MLL	ZFYVE19	Acute myelogenous leukemia (AML)
MSI2	HOXA9	Chronic myelogenous leukemia (CML)
MSN	ALK	Anaplastic large cell lymphoma (ALCL)
MYC	BCL7A	High-grade B cell Non-Hodgkin lymphoma (NHL)
MYC	BTG1	B-cell chronic lymphocytic leukemia (B-CLL)
MYH9	ALK	Anaplastic large cell lymphoma (ALCL)
MYST3	ASXL2	Therapy-related myelodysplastic syndrome
MYST3	CREBBP	Acute myelogenous leukemia (AML)
MYST3	EP300	Acute myelomonocytic or monocytic leukaemia (M4 or M5 Acute myelogenous leukemia (AML))
MYST3	NCOA2	Acute leukemia
MYST4	CREBBP	Acute myelogenous leukemia (AML)
NACA	BCL6	Non-Hodgkin lymphoma (NHL)

FIG. 59f

5' Upstream Fusion Gene Partner	3' downstream Fusion Gene Partner	Cancer Lineage
NCOA4	RET	Papillary thyroid carcinoma
NIN	PDGFRB	Chronic myeloprolifetrative disorder with eosinophilia
NONO	TFE3	Renal cell carcinoma
NPM1	ALK	Anaplastic large-cell lymphomas (ALCL)
NPM1	MLF1	Acute myelogenous leukemia (AML)
NPM1	RARA	Acute promyelocytic leukemia (APML)
NUMA1	RARA	Atypical M3 acute non lyphoblastic leukemia (ANLL)
NUP214	ABL1	T-cell acute lymphoblastic / lymphocytic leukemia (T-ALL)
NUP214	DEK	Acute myelogenous leukemia (AML) and myelodysplastic syndrome
NUP214	SET	Acute undifferentiated leukemia (AUL)
NUP98	ADD3	T-cell acute lymphoblastic leukemia with biphenotipic characteristics (T/myeloid)
NUP98	CCDC28A	Acute megakaryoblastic leukemia, AND T cell acute lymphoblastic leukaemia (T-ALL)
NUP98	DDX10	De novo or secondary myeloid malignancies
NUP98	HOXA11	Juvenile myelomonocytic leukemia (JMML)
NUP98	HOXA13	Acute myelogenous leukemia (AML)
NUP98	HOXA9	Acute myelogenous leukemia (AML)
NUP98	HOXC11	Acute myelogenous leukemia (AML)
NUP98	HOXC13	Acute myelogenous leukemia (AML)
NUP98	HOXD11	Acute myelomonocytic leukaemia
NUP98	HOXD13	Acute myelogenous leukemia (AML)
NUP98	JARID1A	Acute leukemia
NUP98	NSD1	Childhood acute myelogenous leukemia (AML)
NUP98	PRRX1	M2-ANLL, Non hodgkin lymphoma (NHL)
NUP98	PRRX2	Acute myelogenous leukemia (AML)
NUP98	PSIP1	Acute non lymphoblastic leukemia
NUP98	RAP1GDS1	T acute lymphoblastic leukaemia
NUP98	TOP1	Acute myelogenous leukemia (AML)
NUP98	WHSC1L1	Acute myelogenous leukemia (AML)
NUT	BRD4	Midline carcinoma
OMD	USP6	Aneurysmal bone cyst
PAX3	FOXO1	Rhabdomyosarcoma
PAX5	ETV6	Acute lymphoblastic / lymphocytic leukemia (ALL)
PAX7	FOXO1	Alveolar rhabdomyosarcomas
PAX8	PPARγ	Follicular thyroid carcinoma
PCM1	JAK2	Myeloproliferative disorder (MPD) and acute erythroid leukemia
PCM1	RET	Papillary thyroid carcinoma
PDE4DIP	PDGFRB	Chronic eosinophilic leukemia (CEL)

FIG. 59g

5' Upstream Fusion Gene Partner	3' downstream Fusion Gene Partner	Cancer Lineage
PICALM	MLLT10	CML, Acute myelogenous leukemia (AML)
PIM1	BCL6	Diffuse large B-cell lymphoma (DLBCL)
PML	RARA	Acute promyelocytic leukemia (APML)
POU2AF1	BCL6	Non-Hodgkin lymphoma (NHL)
PRCC	TFE3	Renal cell carcinoma
PRDM16	EVI1	MDS and Acute myelogenous leukemia (AML)
PRKAR1A	RET	Papillary thyroid carcinoma
RABEP1	PDGFRB	Myeloproliferative disorder (MPD) and Acute myelogenousleukemia (AML),
RANBP2	ALK	Inflammatory myofibroblastic tumors (IMT)
RBM15	MKL1	Acute myelogenous leukemia (AML)
RFG	RET	Papillary thyroid carcinoma
RFG9	RET	Papillary thyroid carcinoma
RHOH	BCL6	Follicular centrocytic-centroblastic lymphoma.
Ria	RET	Papillary thyroid carcinoma
RLF	MYCL1	Small-cell lung cancer (SCLC)
RPN1	EVI1	Acute non lymphocytic leukemia (ANLL), Myelodysplastic syndrome
RUNX1	CBFA2T3	Myeloid malignancies.
RUNX1	EVI1	Acute myelogenous leukemia (AML), therapy-related MDS and chronic myeloid leukemia in blastic phase
RUNX1	MDS1	Acute myelogenous leukemia (AML), therapy-related MDS and chronic myeloid leukemia in blastic phase
RUNX1	RPL22	Acute myelogenous leukemia (AML)
RUNX1	RUNX1T1	Acute myelogenous leukemia (AML)
RUNX1	SH3D19	Acute myelogenous leukemia (AML)
RUNX1	USP42	Acute myelogenous leukemia (AML)
RUNX1	YTHDF2	Acute myelogenous leukemia (AML)
RUNX1	ZNF687	Acute myelogenous leukemia (AML)
SEC31A	ALK	Diffuse large B-cell lymphoma (DLBCL)
SENP6	TCBA1	T-cell lymphoma
SFPQ	TFE3	Renal cell carcinoma
SFRS3	BCL6	Follicular lymphoma
SLC5A3	ERG	Prostate cancer
SLC45A3	ETV1	Prostate cancer
SLC45A3	ETV5	Prostate cancer
SPECC1	PDGFRB	Juvenile myelomonocytic leukemia
SS18	SSX1	Synovial sarcoma
SS18	SSX2	Synovial sarcoma
SS18	SSX4	Synovial sarcoma

FIG. 59h

5' Upstream Fusion Gene Partner	3' downstream Fusion Gene Partner	Cancer Lineage
SS18L1	SSX1	Synovial sarcoma
STAT5B	RARA	Acute promyelocytic leukemia (APML)
TAF15	NR4A3	Ewing's sarcoma/primitive neuroectodermal tumor
TAF15	TEC	Ewing sarcomas
TAF15	ZNF384	Acute myelogenous leukemia (AML)
TAL1	STIL	T-cell malignancies (T-ALL)
TCBA1	ETV6	Acute lymphoblastic / lymphocytic leukemia (ALL)
TCEA1	PLAG1	Pleomorphic salivary gland adenomas (PA) (Head and Neck)
TCF12	NR4A3	Extraskeletal myxoid chondrosarcoma
TCF12	TEC	Extraskeletal myxoid chondrosarcoma
TCF3	HLF	pre-B-cell acute lymphoblastic leukemia
TCF3	PBX1	Acute lymphoblastic / lymphocytic leukemia (ALL)
TCF3	TFPT	Acute lymphoblastic / lymphocytic leukemia (ALL)
TFG	ALK	Anaplastic large cell lymphoma (ALCL), Non small cell lung carcinoma (NSCLC)
TFG	NR4A3	Extraskeletal myxoid chondrosarcoma
TFG	NTRK1	Papillary thyroid carcinoma
TFRC	BCL6	B-cell non hodgkin lymphoma (B-NHL), Diffuse large B-cell lymphoma (DLBCL)
THRAP3	USP6	Aneurysmal bone cysts
TIAF1	FGFR1	Myeoproliferative disorder (MPD)
TMPRSS2	ERG	Prostate cancer
TMPRSS2	ETV1	Prostate cancer
TMPRSS2	ETV4	Prostate cancer
TMPRSS2	ETV5	Prostate cancer
TP53BP1	PDGFRB	CML-like disorder associated with eosinophilia
TPM3	ALK	Anaplastic large cell lymphoma (ALCL)
TPM3	NTRK1	Papillary thyroid carcinoma
TPM3	PDGFRB	Chronic eosinophilic leukemia (CEL)
TPM3	TPR	Papillary thyroid carcinoma
TPM4	ALK	Inflammatory Myofibroblastic Tumors
TPR	MET	Papillary thyroid carcinoma
TPR	NTRK1	Papillary thyroid carcinoma
TRIM24	FGFR1	Myeoproliferative disorder (MPD)
TRIM24	RARA	Myeoproliferative disorder (MPD)
TRIM24	RET	Papillary thyroid carcinoma
TRIM27	RET	Papillary thyroid carcinoma
TRIM33	RET	Papillary thyroid carcinoma
TRIP11	PDGFRB	Acute myelogenous leukemia (AML)

FIG. 59i

5' Upstream Fusion Gene Partner	3' downstream Fusion Gene Partner	Cancer Lineage
TTL	ETV6	Acute lymphoblastic / lymphocytic leukemia (ALL)
ZBTB16	RARA	Acute promyelocytic leukemia (APML)
ZMYM2	FGFR1	Stem cell leukemia lymphoma syndrome (SCLL).

FIG. 60a

Gene	miRNA Associated with Gene
Androgen receptor	miR-124a, miR-130a, miR-130b,miR-143, miR-149, miR-194, miR-29b, miR-29c, miR-301, miR-30a-5p, miR-30d, miR-30e-5p, miR-337, miR-342, miR-368, miR-488, miR-493-5p, miR-506, miR-512-5p, miR-644, miR-768-5p, miR-801
DNMT3B	miR-618, miR-1253, miR-765, miR-561, miR-330-5p, miR-326, miR-188, miR-203, miR-221, miR-222, miR-26a, miR-26b, miR-29a, miR-29b, miR-29c, miR-370, miR-379, miR-429, miR-519e*, miR-598, miR-618, miR-635
GART	miR-101, miR-141, miR-144, miR-182, miR-189, miR-199a , miR-199b, miR-200a, miR-200b, miR-202, miR-203, miR-223, miR-329, miR-383, miR-429, miR-433, miR-485-5p, miR-493-5p, miR-499, miR-519a, miR-519b, miR-519c, miR-569, miR-591, miR-607, miR-627, miR-635, miR-659
MGMT	miR-122a, miR-142-3p, miR-17-3p, miR-181a, miR-181b, miR-181c, miR-181d, miR-199b, miR-200a*, miR-217, miR-302b*, miR-32, miR-324-3p, miR-34a, miR-371, miR-425-5p, miR-496, miR-514, miR-515-3p, miR-516-3p, miR-574, miR-597, miR-603, miR-653, miR-655, miR-92, miR-92b, miR-99a
Top2B	miR-548f, miR-548a-3p, miR-548g, miR-513a-3p, miR-548c-3p, miR-101, miR-653, miR-548d-3p, miR-575, miR-297, miR-576-3p, miR-548b-3p, miR-624, miR-548n, miR-758, miR-1253, miR-1324, miR-23b, miR-320a, miR-320b, miR-1183, miR-1244, miR-23a, miR-451, miR-568, miR-1276 , miR-548e, miR-590-3p, miR-1, miR-101, miR-126, miR-126*, miR-129, miR-136, miR-140, miR-141, miR-144, miR-147, miR-149, miR-18, miR-181b, miR-181c, miR-182, miR-184 , miR-186, miR-189, miR-191, miR-19a, miR-19b, miR-200a, miR-206, miR-210, miR-218, miR-223, miR-23a, miR-23b , miR-24, miR-27a, miR-302, miR-30a, miR-31, miR-320, miR, 23, miR-362, miR-374, miR-383, miR-409-3p, miR-451, miR-489, miR-493-3p, miR-514, miR-542-3p, miR-544, miR-548a, miR-548b, miR-548c, miR-548d, miR-559, miR-568, miR-575, miR-579, miR-585, miR-591, miR-598, miR-613, miR-649, miR-651, miR-758, miR-768-3p, miR-9*
HSP90	miR-1, miR-513a-3p, miR-548d-3, miR-642, miR-206, miR-450b-3p, miR-152, miR-148, miR-148b, miR-188-3p, miR-23a, miR-23b, miR-578, miR-653, miR-1206, miR-192, miR-215, miR-181b, miR-181d, miR-223, miR-613, miR-769-3p, miR-99a, miR-100, miR-454, miR-548n, miR-640, miR-99b, miR-150, miR-181a, miR-181c, miR-522, miR-624, miR-1, miR-130a, miR-130b, miR-146, miR-148a, miR-148b, miR-152, miR-181a, miR-181b, miR-181c, miR-204, miR-206, miR-211, miR-212, miR-215, miR-223, miR-23a, miR-23b, miR-301, miR-31, miR-325, miR-363*, miR-566, miR-9, miR-99b
ASPM	miR-1, miR-122a, miR-135a, miR-135b, miR-137, miR-153, miR-190, miR-206, miR-320, miR-380-3p, miR-382, miR-433, miR-453, miR-493-5p, miR-496, miR-499, miR-507, miR-517b, miR-548a, miR-548c, miR-567, miR-568, miR-580, miR-602, miR-651, miR-653, miR-758, miR-9*
SPARC	miR-768-5p, miR-203, miR-196, miR-569, miR-187, miR-641, miR-1275, miR-432, miR-622, miR-296-3p, miR-646, miR-96b, miR-499-5p, miR-590-5p, miR-495, miR-625, miR-1244, miR-512-5p, miR-1206, miR-1303, miR-186, miR-302d, miR-494, miR-562, miR-573, miR-10a, miR-203, miR-204, miR-211, miR-29a, miR-29b, miR-29c, miR-29c, miR-339, miR-433, miR-452, miR-515-5p, miR-517a, miR-517b, miR-517c, miR-592, miR-96

FIG. 60b

Gene	miRNA Associated with Gene
PFKB3	miR-513a-3p, miR-1286, miR-488, miR-539, miR-658, miR-524-5p, miR-1258, miR-150, miR-216b, miR-377, miR-135a, miR-26a, miR-548a-5p, miR-26b, miR-520d-5p , miR-224, miR-1297, miR-1197, miR-182, miR-452, miR-509-3-5p, miR-548m, miR-625, miR-509-5p, miR-1266, miR-135b , miR-190b, miR-496, miR-616, miR-621, miR-650, miR-105, miR-19a, miR-346, miR-620, miR-637, miR-651, miR-1283, miR-590-3p, miR-942, miR-1185, miR-577, miR-602, miR-1305, miR-220c, miR-1270, miR-1282, miR-432, miR-491-5p, miR-548n, miR-765, miR-768-3p, miR-924
HMMR	miR-936, miR-656, miR-105, miR-361-5p, miR-194, miR-374a, miR-590-3p, miR-186, miR-769-5p, miR-892a, miR-380, miR-875-3p, miR-208a, miR-208b, miR-586, miR-125a-3p, miR-630, miR-374b, miR-411, miR-629, miR-1286, miR-1185, miR-16, miR-200b, miR-671-5p, miR-95, miR-421, miR-496, miR-633, miR-1243, miR-127-5p, miR-143, miR-15b, miR-200c, miR-24, miR-34c-3p
CENPF	miR-30c, miR-30b, miR-190, miR-508-3p, miR-384, miR-512-5p, miR-548p, miR-297, miR-520f, miR-376a, miR-1184, miR-577, miR-708, miR-205, miR-376b, miR-520g, miR-520h, miR-519d, miR-596, miR-768-3p, miR-340, miR-620, miR-539, miR-567, miR-671-5, miR-1183, miR-129-3p, miR-636, miR-106a, miR-1301, miR-17, miR-20a, miR-570, miR-656, miR-1263, miR-1324, miR-142-5p, miR-28-5p, miR-302b, miR-452, miR-520d-3p, miR-548o, miR-892b, miR-302d, miR-875-3p, miR-106b, miR-1266, miR-1323, miR-20b, miR-221, miR-520e, miR-664, miR-920, miR-922, miR-93, miR-1228, miR-1271, miR-30e, miR-483-3p, miR-509-3-5p, miR-515-3p, miR-519e, miR-520b, miR-520c-3p, miR-582-3p
NCAPG2	miR-876-5p, miR-1260, miR-1246, miR-548c-3p, miR-1224-3p, miR-619, miR-605, miR-490-5p, miR-186, miR-448, miR-129-5p, miR-188-3p, miR-516b, miR-342-3p, miR-127, miR-548k, miR-654-3p, miR-1290, miR-656, miR-34b, miR-520g, miR-1231, miR-1289, miR-1229, miR-23a, miR-23b, miR-616, miR-620
EGFR	miR-105, miR-128a, miR-128b, miR-140, miR-141, miR-146a, miR-146b, miR-27a, miR-27b, miR-302a, miR-302d, miR-370, miR-548c,miR-574, miR-587, miR-7
SSTR3	miR-125a, miR-125b, miR-133a, miR-133b, miR-136, miR-150, miR-21, miR-380-5p, miR-504,miR-550, miR-671, miR-766, miR-767-3p

FIG. 61

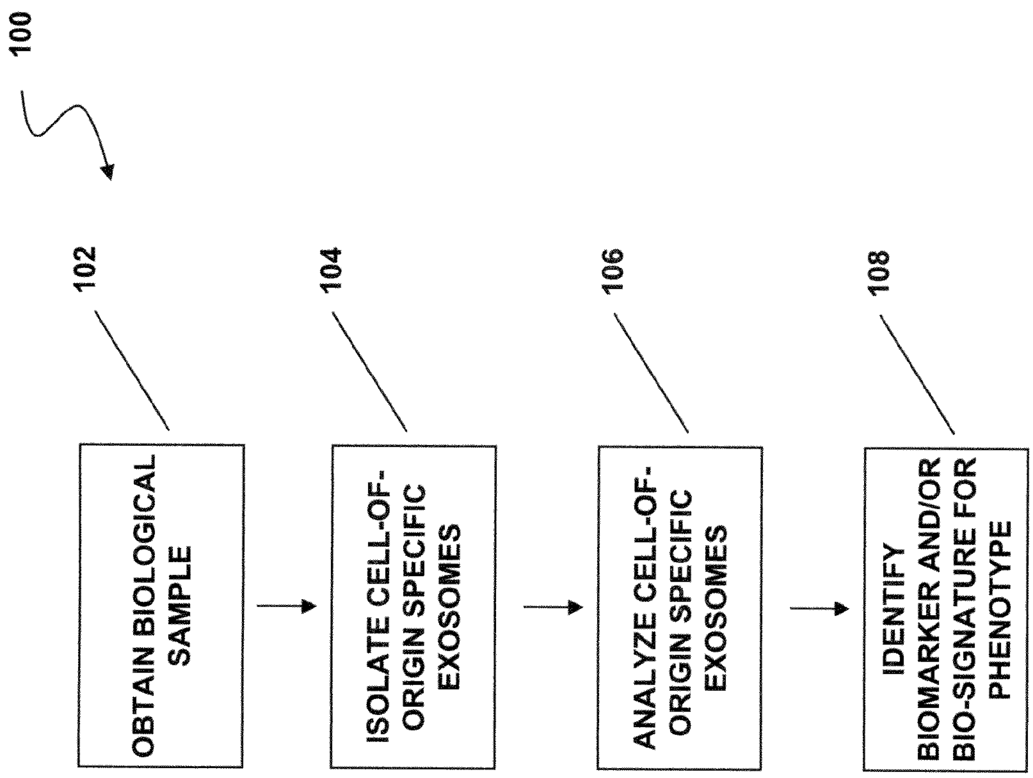

100
102
104
106
108
OBTAIN BIOLOGICAL SAMPLE
ISOLATE CELL-OF-ORIGIN SPECIFIC EXOSOMES
ANALYZE CELL-OF-ORIGIN SPECIFIC EXOSOMES
IDENTIFY BIOMARKER AND/OR BIO-SIGNATURE FOR PHENOTYPE

FIG. 62

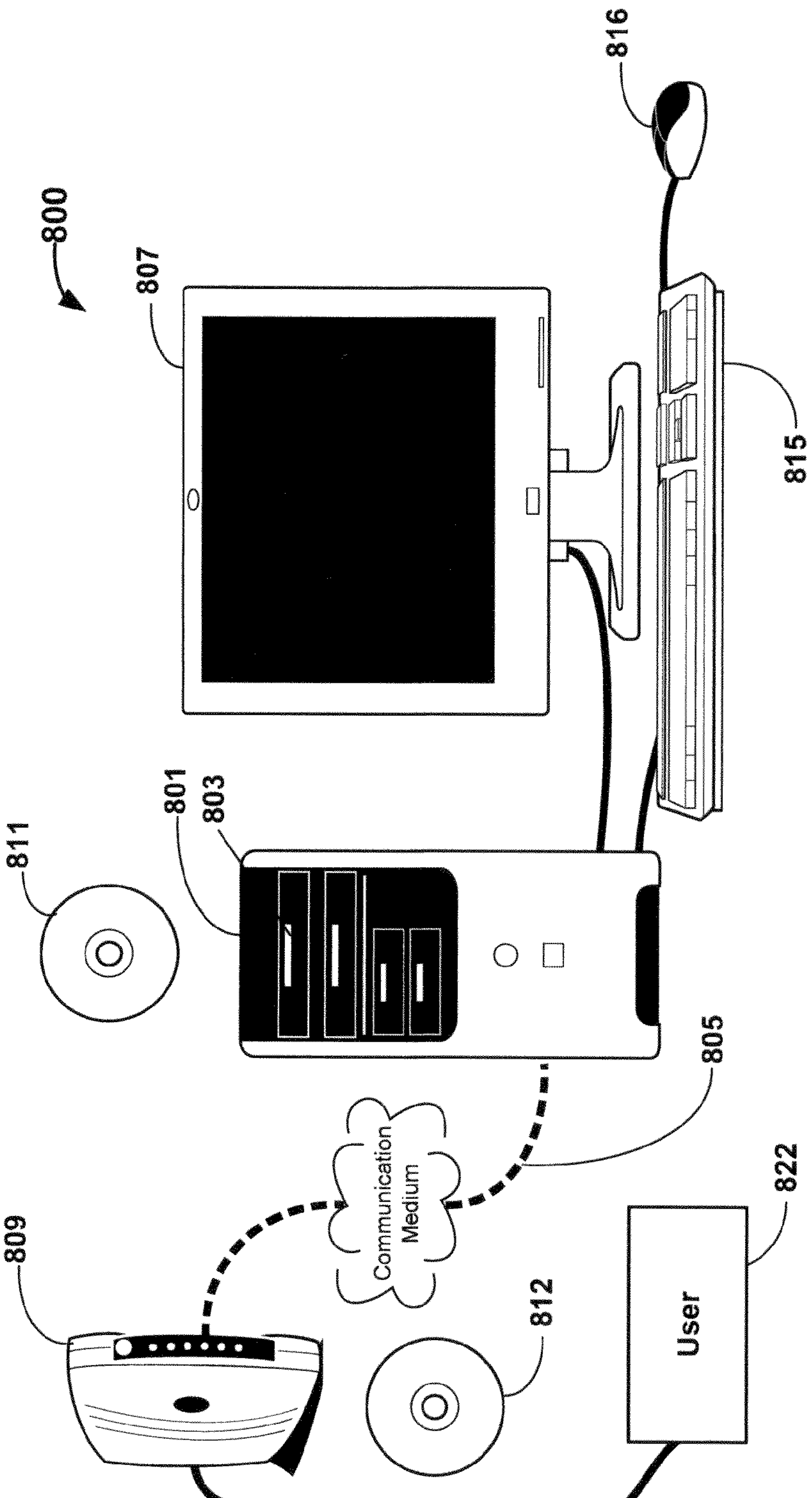

800
807
816
815
811
801
803
805
809
812
822
Communication Medium
User

FIG. 63

Protein Name	vcap average	lncap average	normalaverage
Biotin	33236	40207	52224
bcl-XL	19205	24857	9458
Estriol	16066	23435	16560
Heat Shock Protein 27/hsp27	10172	22822	43471
CD45RO	15037	20251	10114
CNPase	11269	19646	11675
ERCC1	15292	19036	1597
Keratin 15	13459	17580	9325
CD81/TAPA-1	4967	17031	194
Laminin B1/b1	4609	14848	10241
MyoD1	7144	12472	15022
HPV 16	12742	11185	15094
Gai1	4163	10716	1361
CD9	7009	10146	191
Epithelial Specific Antigen	10850	9754	1275
Cyclin E	5111	9068	6280
MHC II (HLA-DP and DR)	6936	8943	4757
E2F-2	2890	8801	3094
CD63	4591	8501	2783
Amyloid Beta (APP)	4663	7896	5893
Streptavidin	6348	7658	7909
Mast Cell Chymase	1818	7582	433
AIF (Apoptosis Inducing Factor)	4263	7322	7686
CD42b	1717	6787	10836
MHC II (HLA-DP and DR)	6936	8943	4757
Calmodulin	3353	4722	1861

FIG. 64A

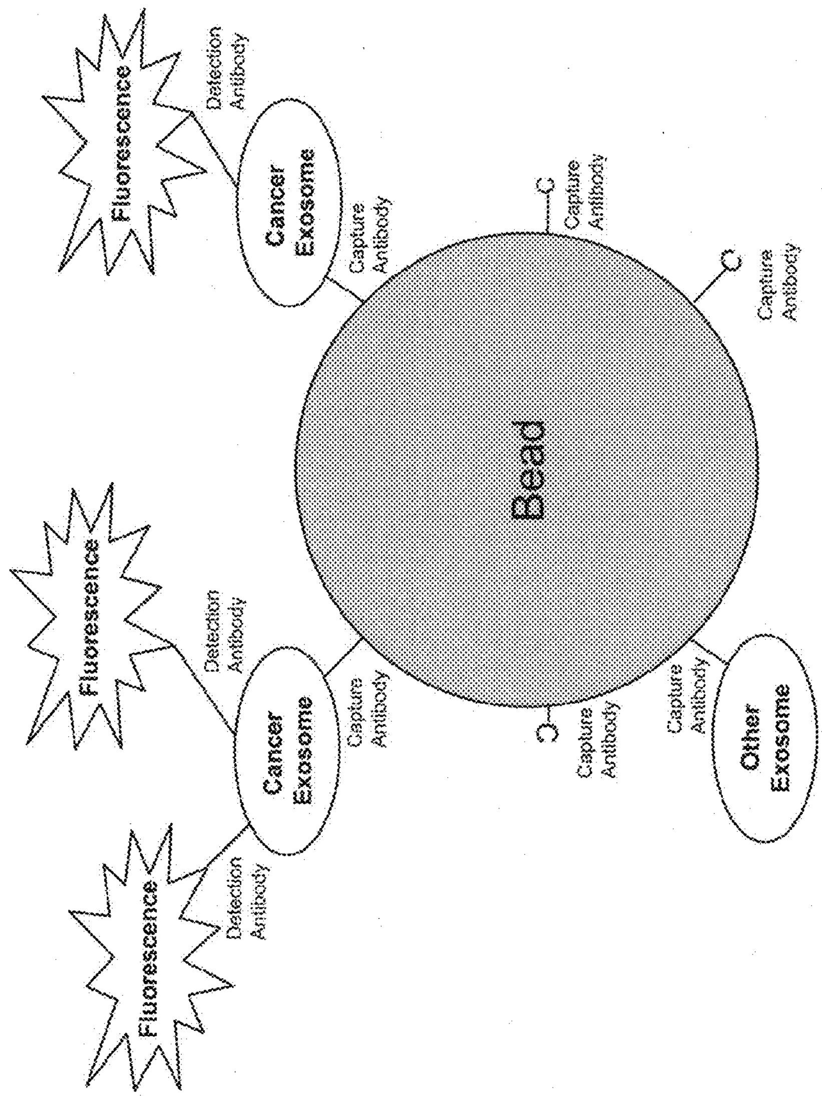

Bead
Fluorescence
Fluorescence
Fluorescence
Detection Antibody
Detection Antibody
Detection Antibody
Cancer Exosome
Cancer Exosome
Other Exosome
Capture Antibody
Capture Antibody
Capture Antibody
Capture Antibody
Capture Antibody
Capture Antibody

FIG. 64B

Screening Scheme

5 Detection Antibodies X 20 Capture Antibodies = 100 Combinations Screened

Detection Antibodies	Capture Antibodies	
CD63	CD9	Rab
CD9	PSCA	IgG
CD81	TNFR	CD81
B7H3	CD63 2X	STEAP
EpCam	B7H3	PCSA
	Rab IgG	PSM
	MFG-E8	5T4
	Epcam 2X	
	CD63	

black: exosome antibodies
red: prostate antibodies
green: Colon antibodies
blue: Cancer antibodies
orange: Control

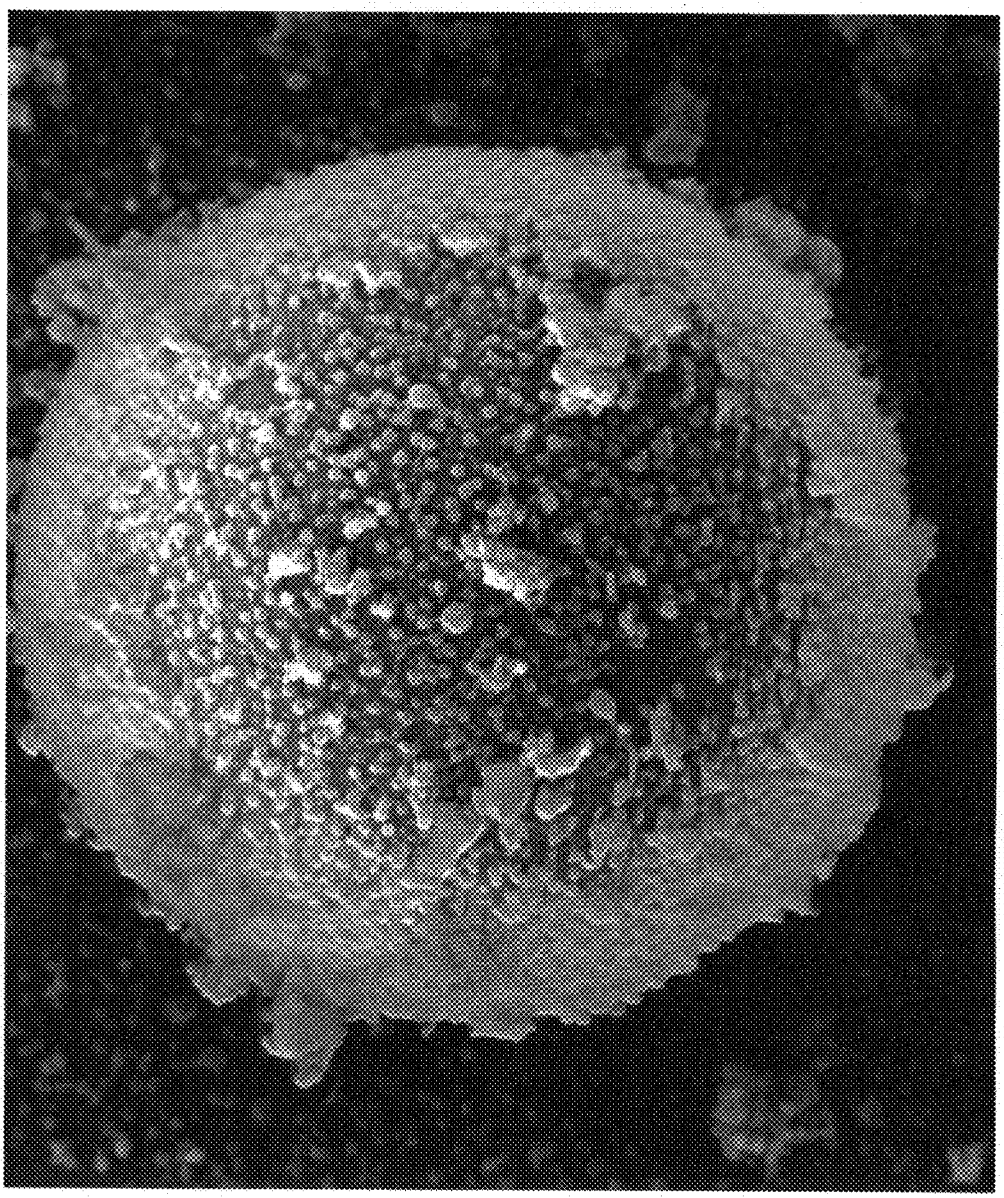


FIG. 65A

FIG. 65B

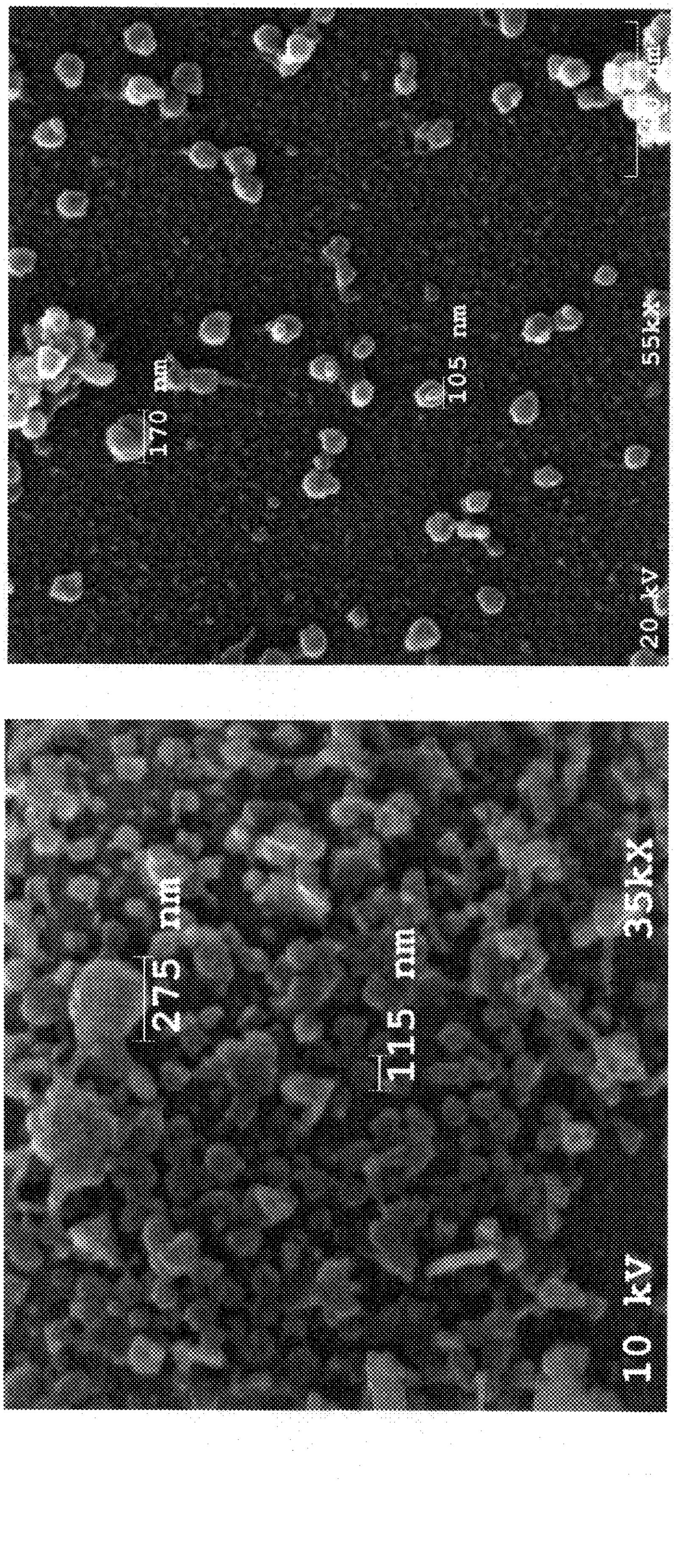


FIG. 66

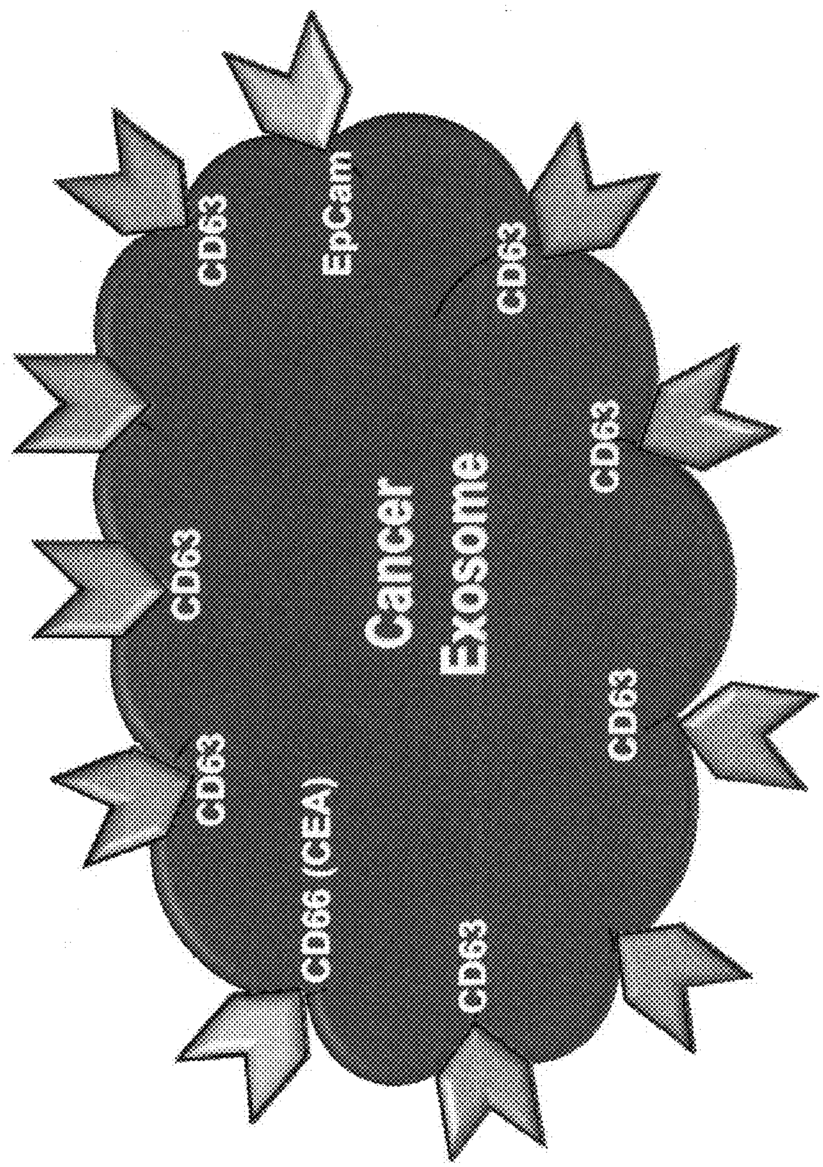

Cancer Exosome
CD63
EpCam
CD63
CD63
CD63
CD63
CD63
CD66 (CEA)
CD63

FIG. 67A

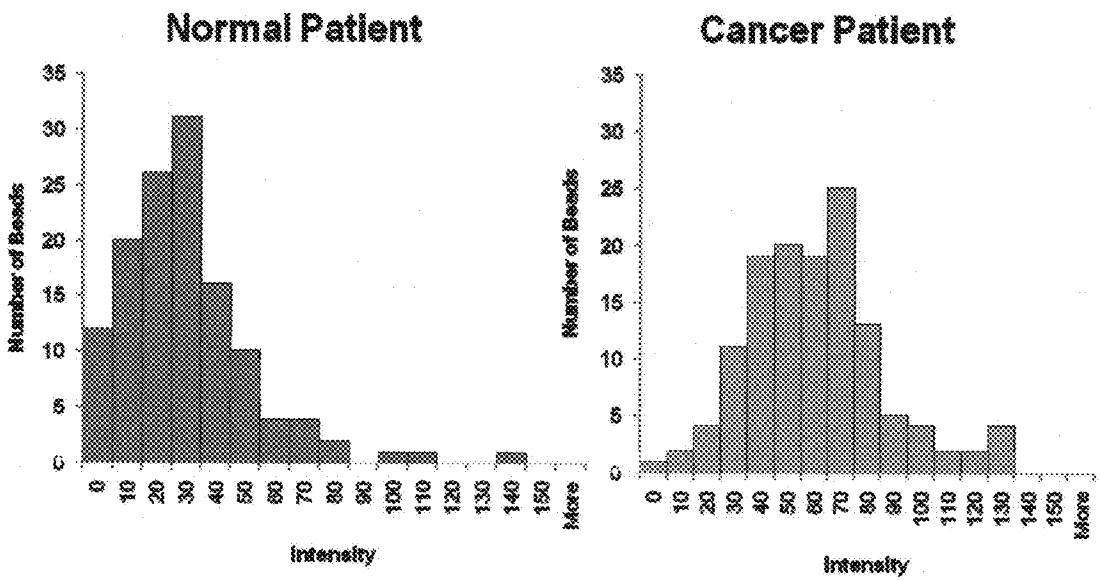

Normal Patient
Number of Beads
Intensity
0
5
10
15
20
25
30
35
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
More
Cancer Patient
Number of Beads
Intensity

FIG. 67B

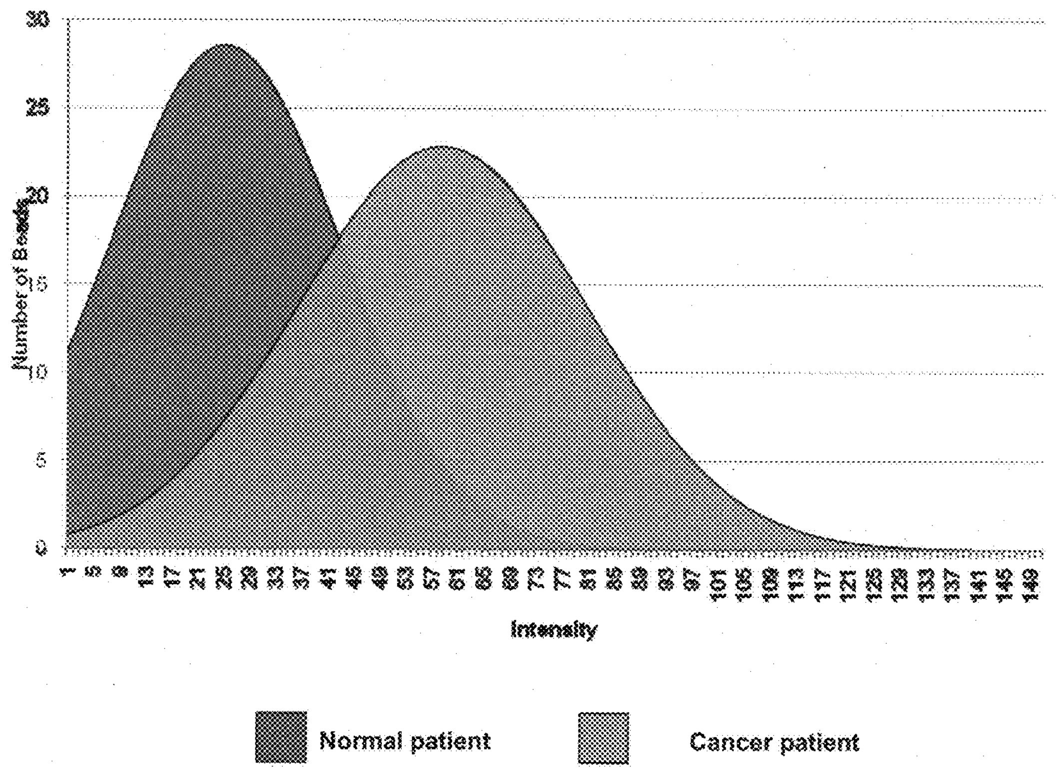

30
25
20
15
10
5
0
Number of Beads
1
5
9
13
17
21
25
29
33
37
41
45
49
53
57
61
65
69
73
77
81
85
89
93
97
101
105
109
113
117
121
125
129
133
137
141
145
149
Intensity
Normal patient
Cancer patient

FIG. 68A

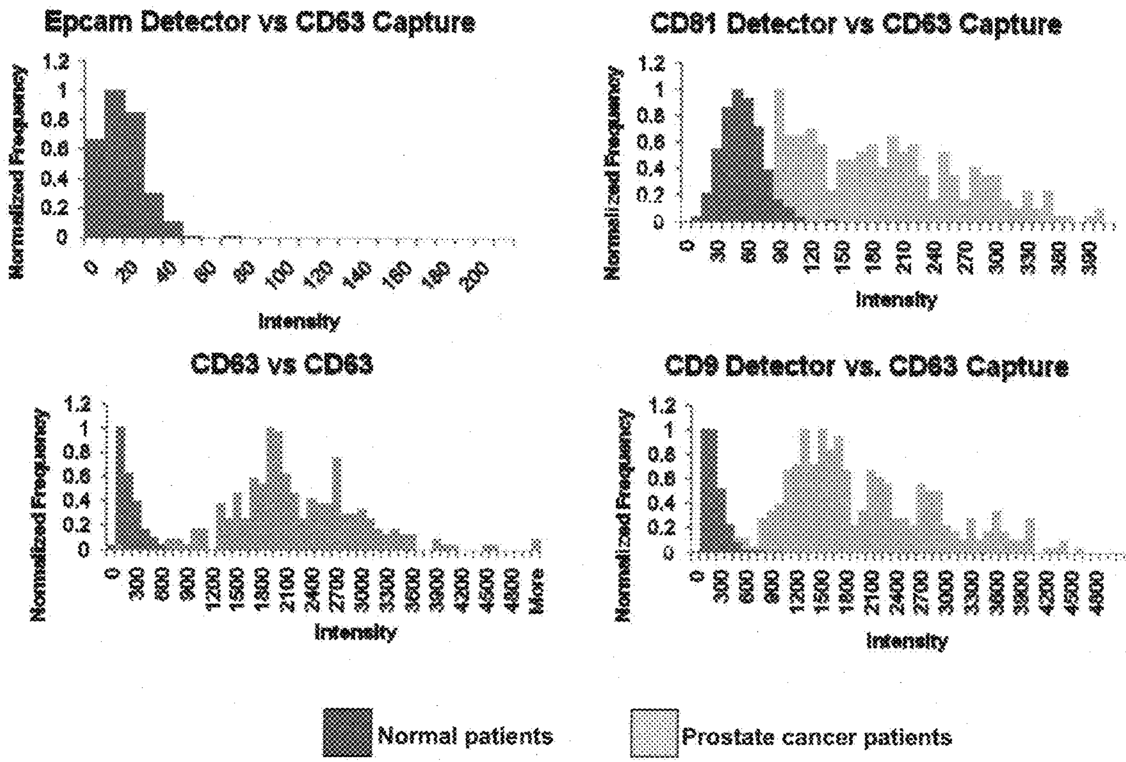

Epcam Detector vs CD63 Capture
CD81 Detector vs CD63 Capture
CD63 vs CD63
CD9 Detector vs. CD63 Capture
Normalized Frequency
Intensity
Normal patients
Prostate cancer patients

FIG. 68B

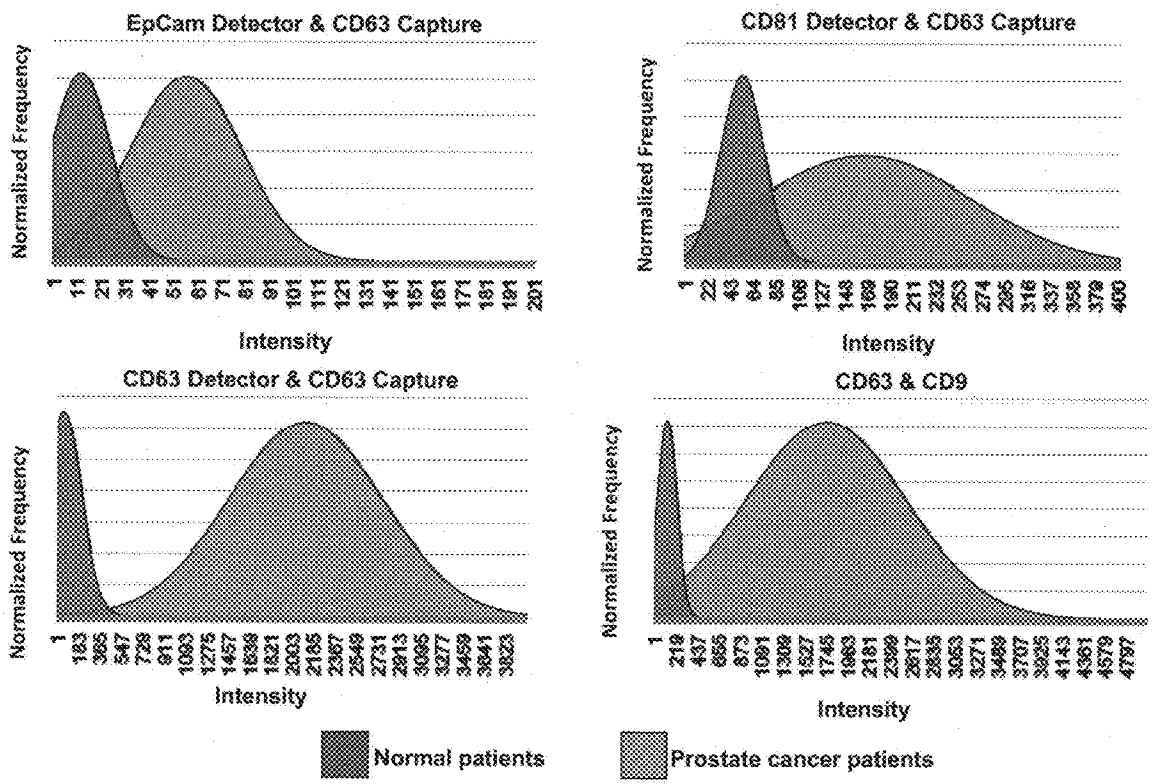

EpCam Detector & CD63 Capture
CD81 Detector & CD63 Capture
CD63 Detector & CD63 Capture
CD63 & CD9
Normalized Frequency
Intensity
Normal patients
Prostate cancer patients

FIG. 68C

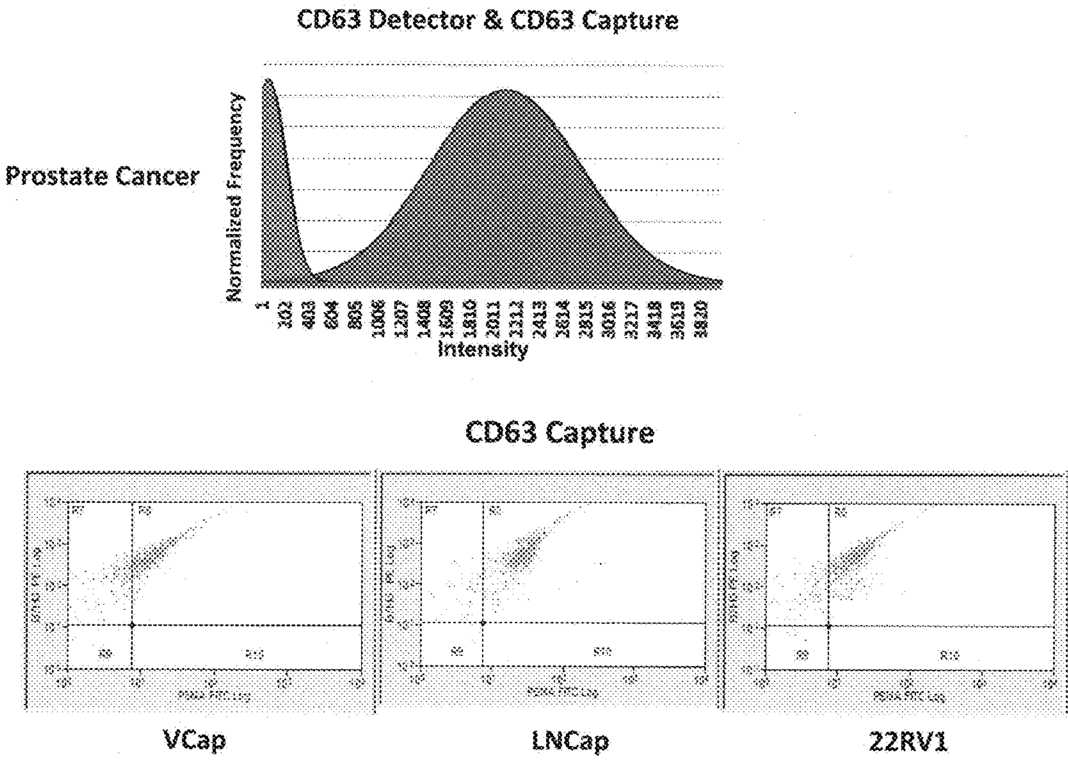

CD63 Detector & CD63 Capture
Prostate Cancer
Normalized Frequency
1
202
403
604
805
1006
1207
1408
1609
1810
2011
2212
2413
2614
2815
3016
3217
3418
3619
3820
Intensity
CD63 Capture
VCap
LNCap
22RV1

FIG. 68D

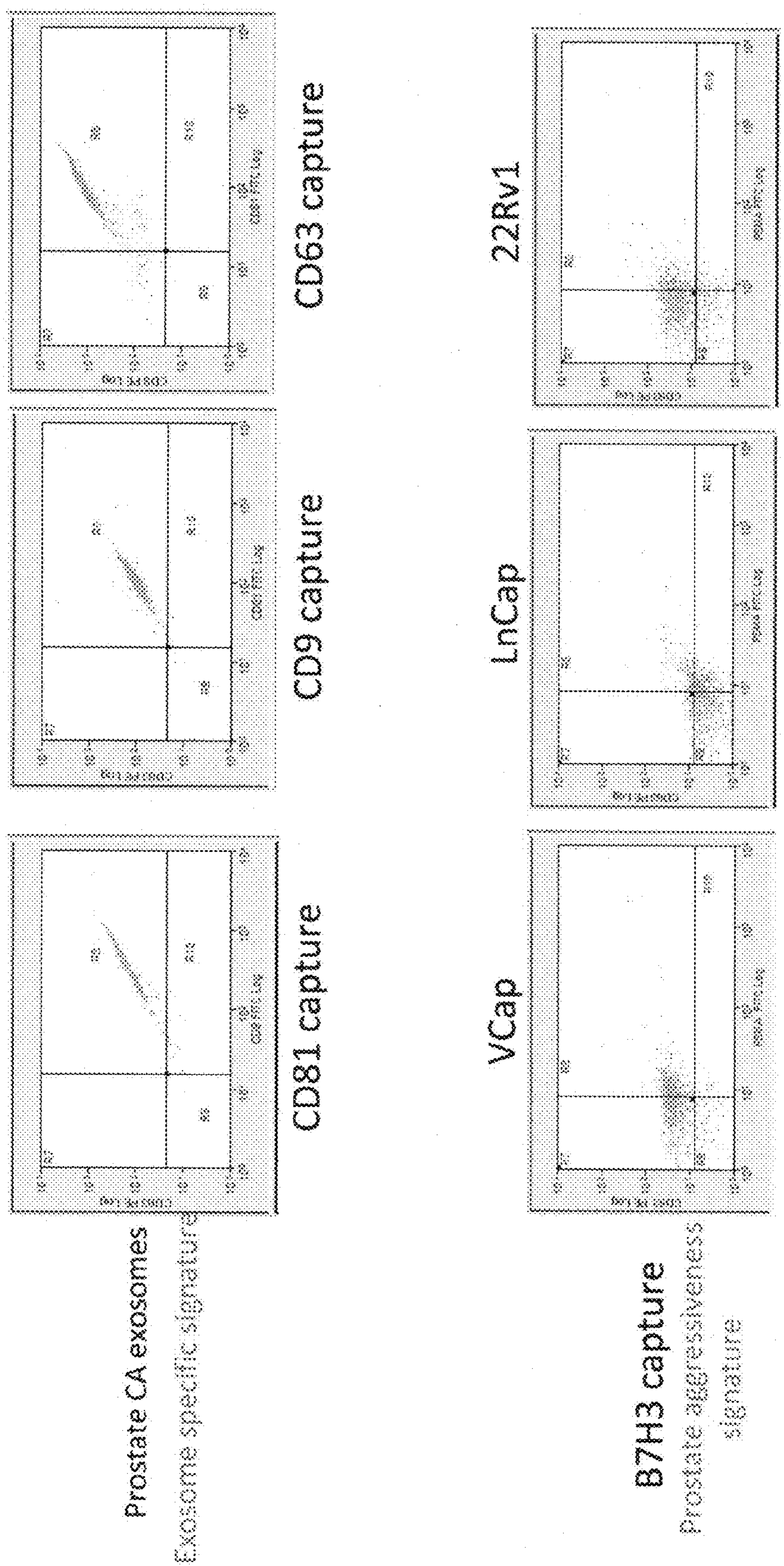

CD63 capture
CD9 capture
CD81 capture
22Rv1
LnCap
VCap
Prostate CA exosomes
Exosome specific signature
B7H3 capture
Prostate aggressiveness
signature

FIG. 69A

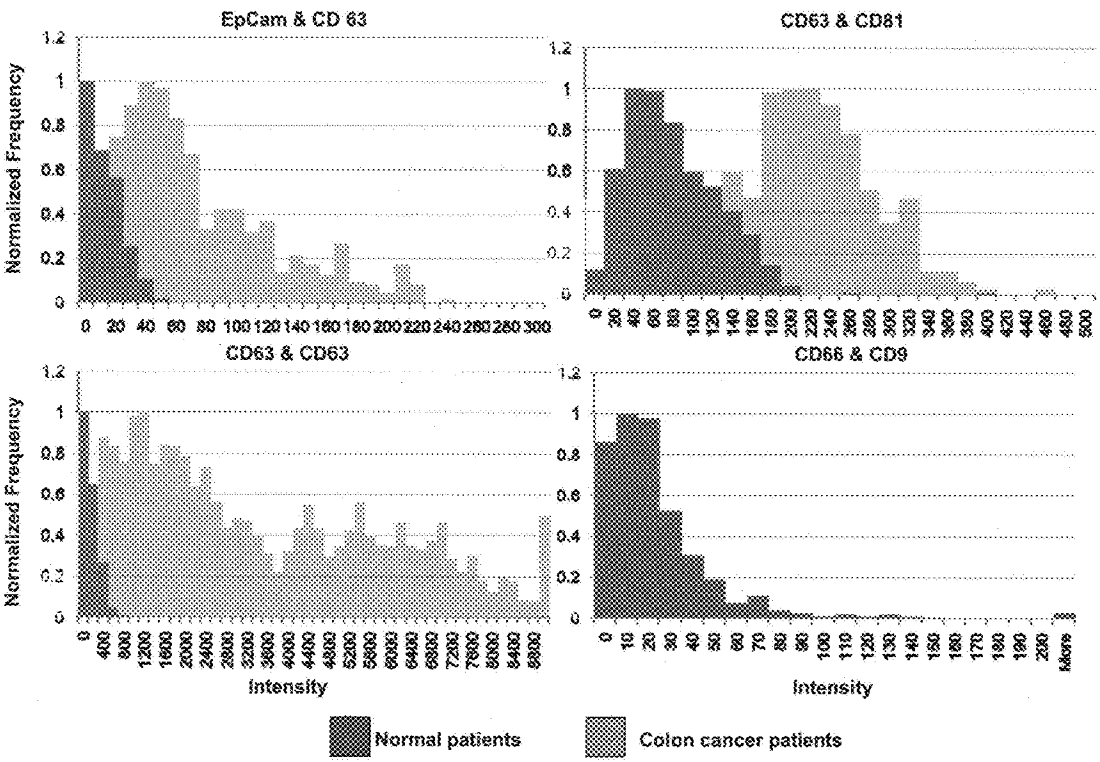

EpCam & CD 63
CD63 & CD81
CD63 & CD63
CD66 & CD9
Normalized Frequency
Intensity
Normal patients
Colon cancer patients

FIG. 69B

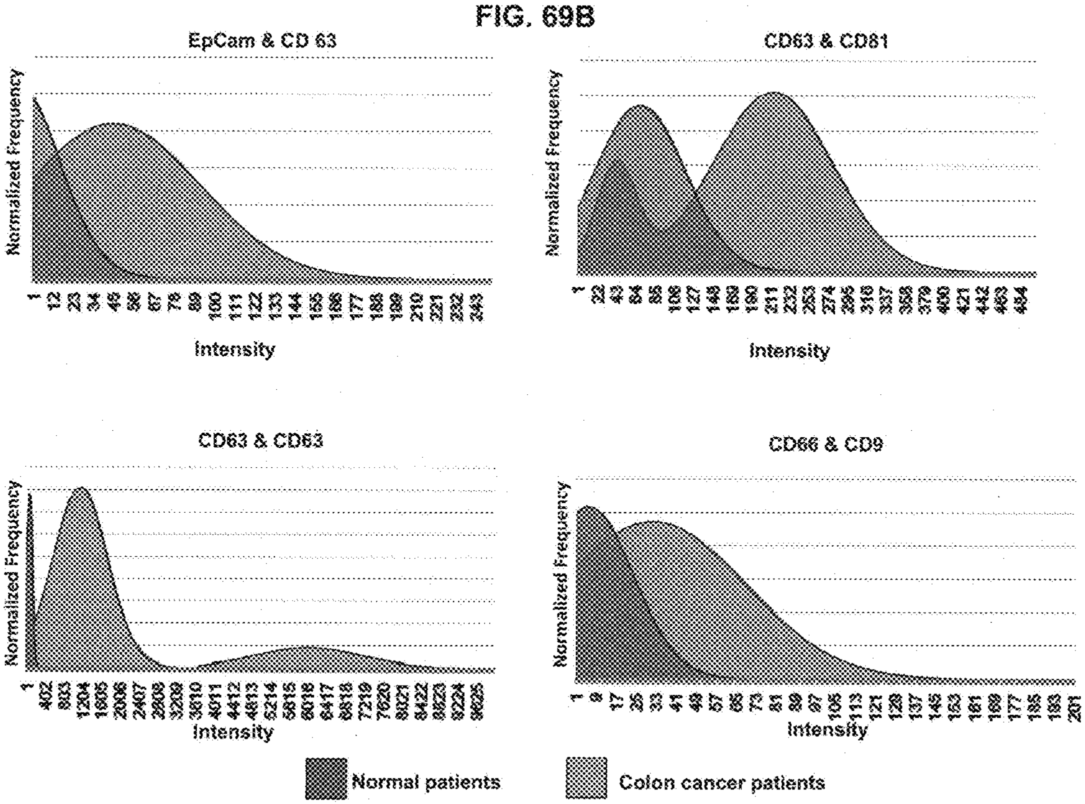
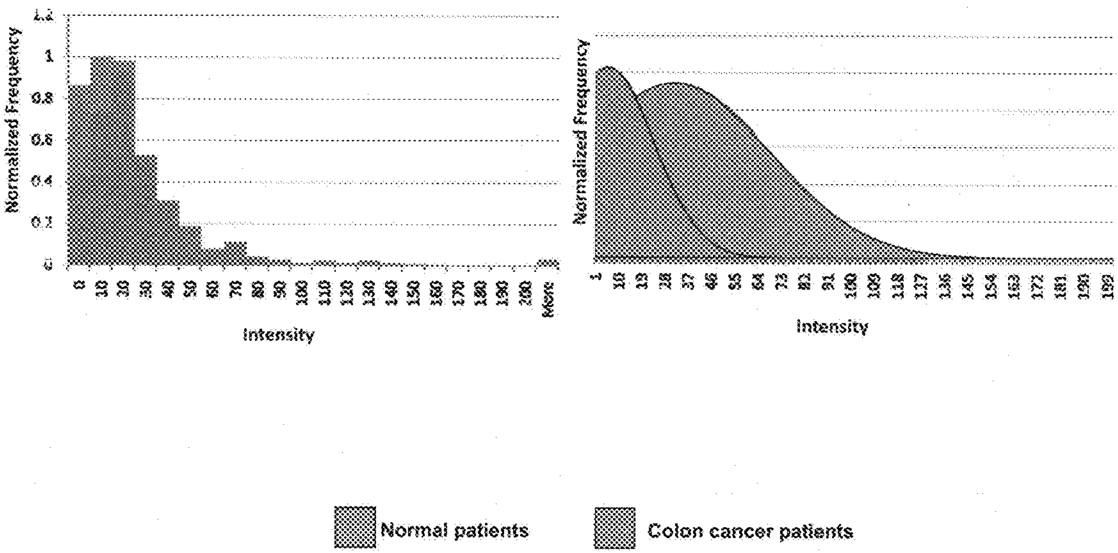

EpCam & CD 63
Normalized Frequency
Intensity
CD63 & CD81
Normalized Frequency
Intensity
CD63 & CD63
Normalized Frequency
Intensity
CD66 & CD9
Normalized Frequency
Intensity
Normal patients
Colon cancer patients

FIG. 69C



Normalized Frequency
Intensity
Normalized Frequency
Intensity
Normal patients
Colon cancer patients

FIG. 70A

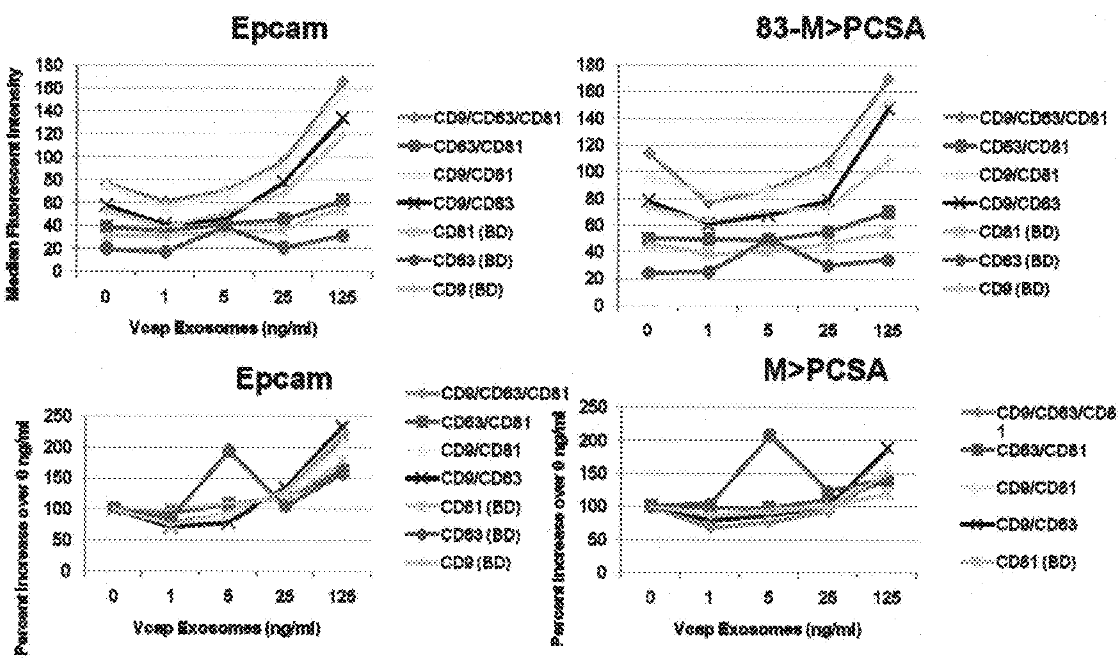

Epcam
Median Fluorescent Intensity
Vcap Exosomes (ng/ml)
CD9/CD63/CD81
CD63/CD81
CD9/CD81
CD9/CD63
CD81 (BD)
CD63 (BD)
CD9 (BD)
83-M>PCSA
Epcam
Percent Increase over 0 ng/ml
M>PCSA

FIG. 70B

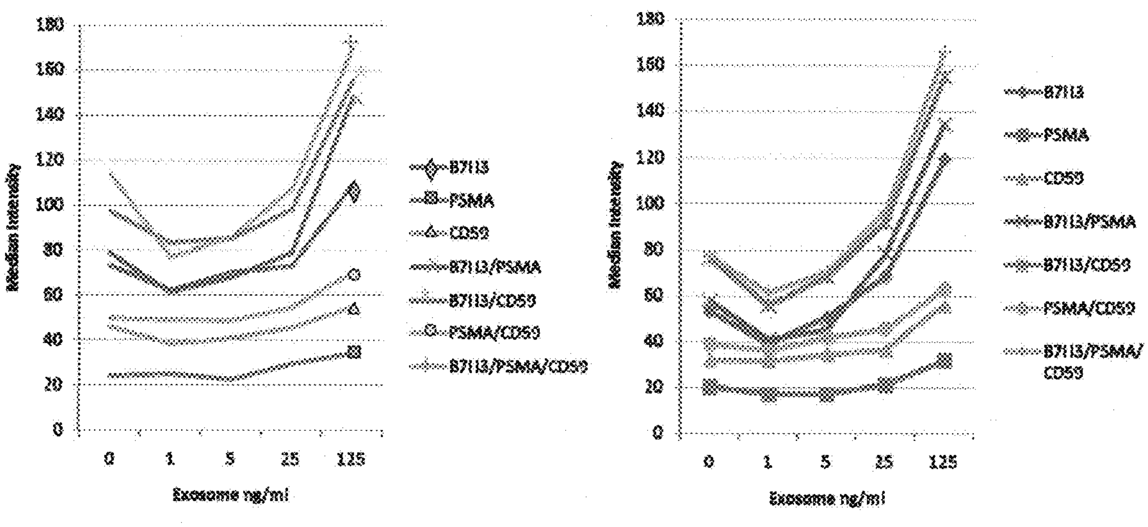

Median Intensity
Exosome ng/ml
B7H3
PSMA
CD59
B7H3/PSMA
B7H3/CD59
PSMA/CD59
B7H3/PSMA/CD59

FIG. 71A

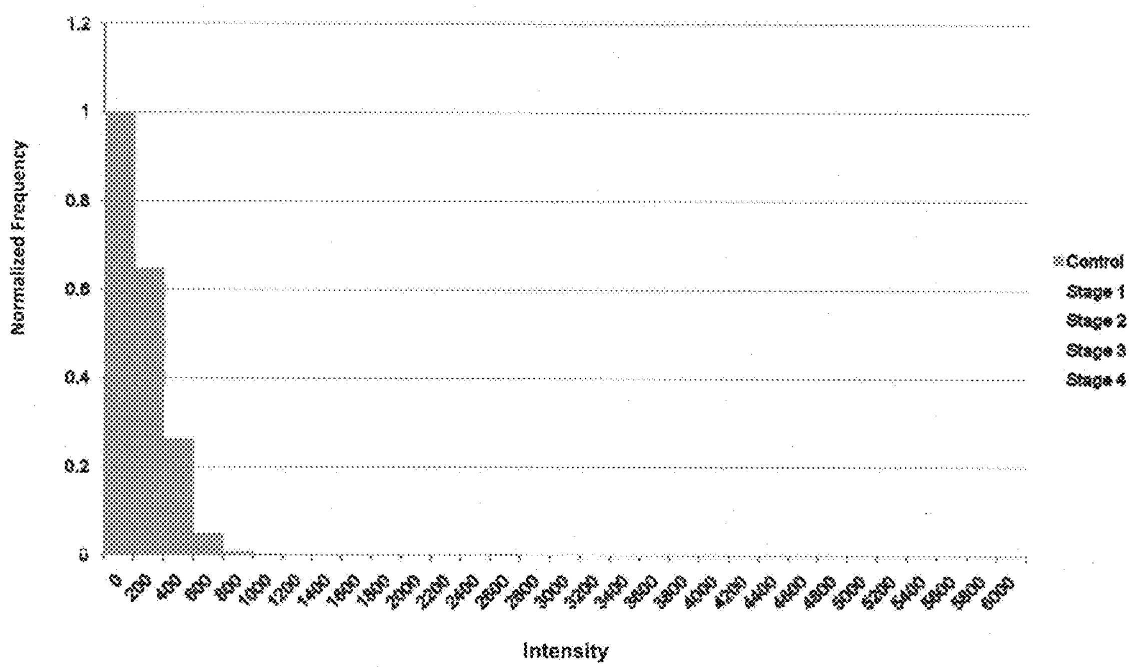

1.2
1
0.8
0.6
0.4
0.2
0
Normalized Frequency
0
200
400
600
800
1000
1200
1400
1600
1800
2000
2200
2400
2600
2800
3000
3200
3400
3600
3800
4000
4200
4400
4600
4800
5000
5200
5400
5600
5800
6000
Intensity
Control
Stage 1
Stage 2
Stage 3
Stage 4

FIG. 71B

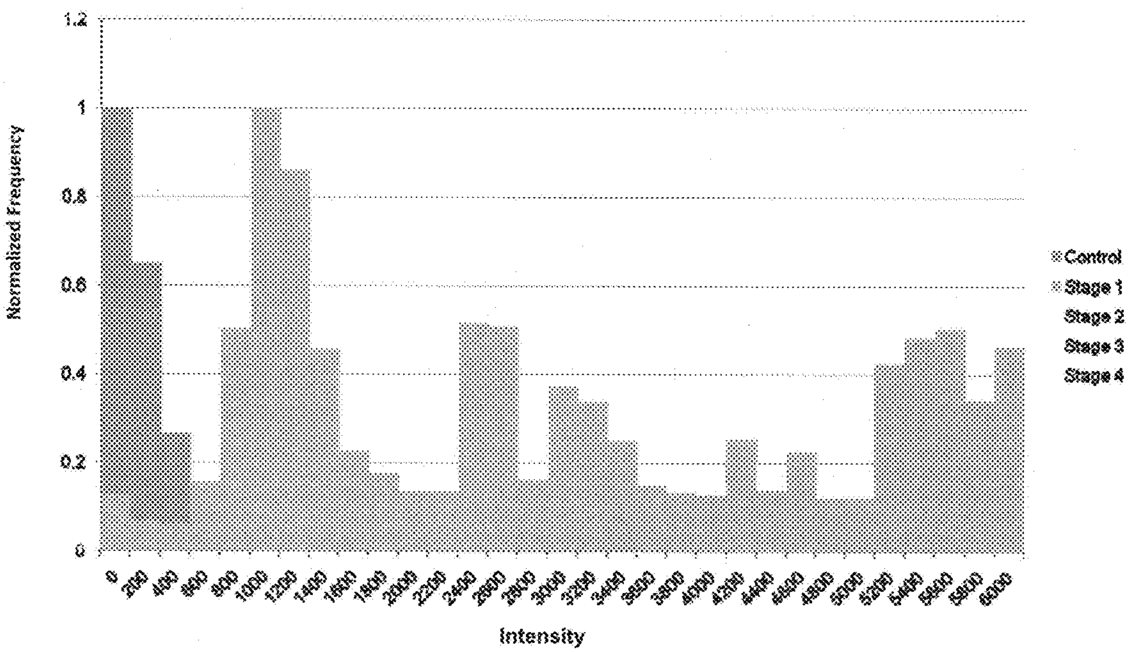

1.2
1
0.8
0.6
0.4
0.2
0
Normalized Frequency
0
200
400
600
800
1000
1200
1400
1600
1800
2000
2200
2400
2600
2800
3000
3200
3400
3600
3800
4000
4200
4400
4600
4800
5000
5200
5400
5600
5800
6000
Intensity
Control
Stage 1
Stage 2
Stage 3
Stage 4

FIG. 71C

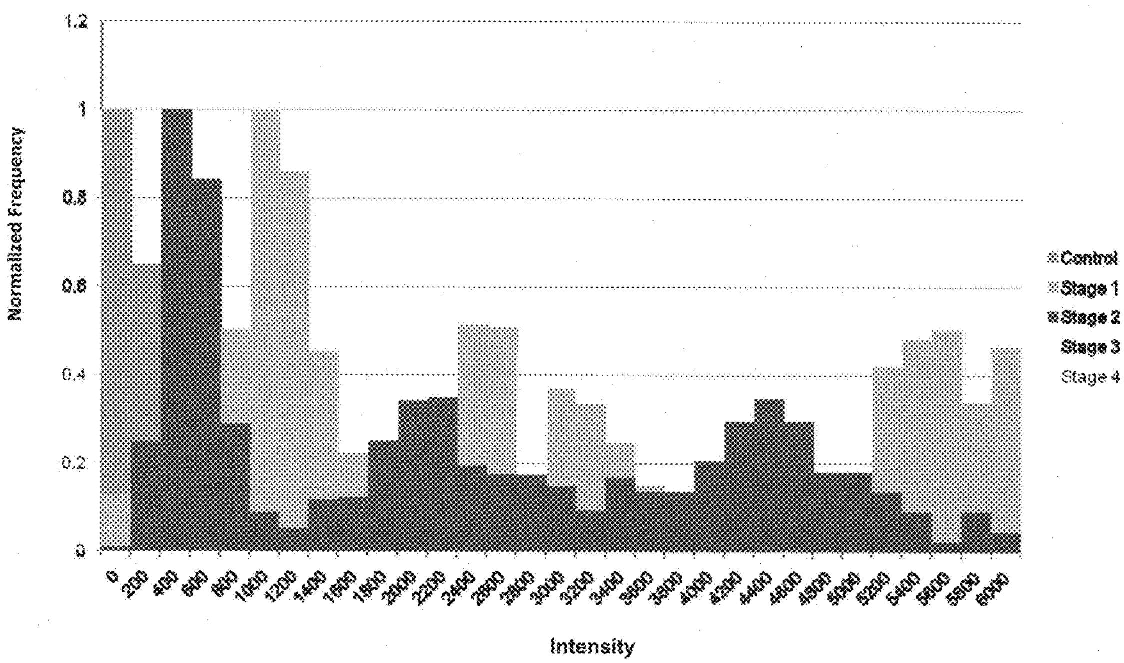

1.2
1
0.8
0.6
0.4
0.2
0
Normalized Frequency
0
200
400
600
800
1000
1200
1400
1600
1800
2000
2200
2400
2600
2800
3000
3200
3400
3600
3800
4000
4200
4400
4600
4800
5000
5200
5400
5600
5800
6000
Intensity
Control
Stage 1
Stage 2
Stage 3
Stage 4

FIG. 71D

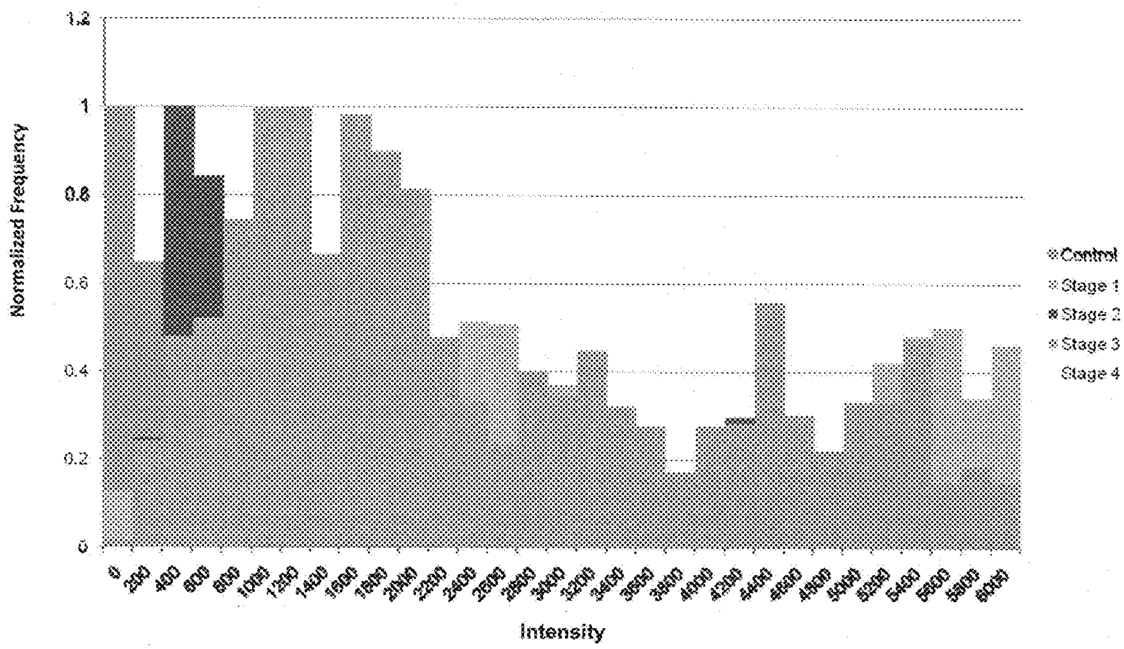

1.2
1
0.8
0.6
0.4
0.2
0
Normalized Frequency
0
200
400
600
800
1000
1200
1400
1600
1800
2000
2200
2400
2600
2800
3000
3200
3400
3600
3800
4000
4200
4400
4600
4800
5000
5200
5400
5600
5800
6000
Intensity
Control
Stage 1
Stage 2
Stage 3
Stage 4

FIG. 71E

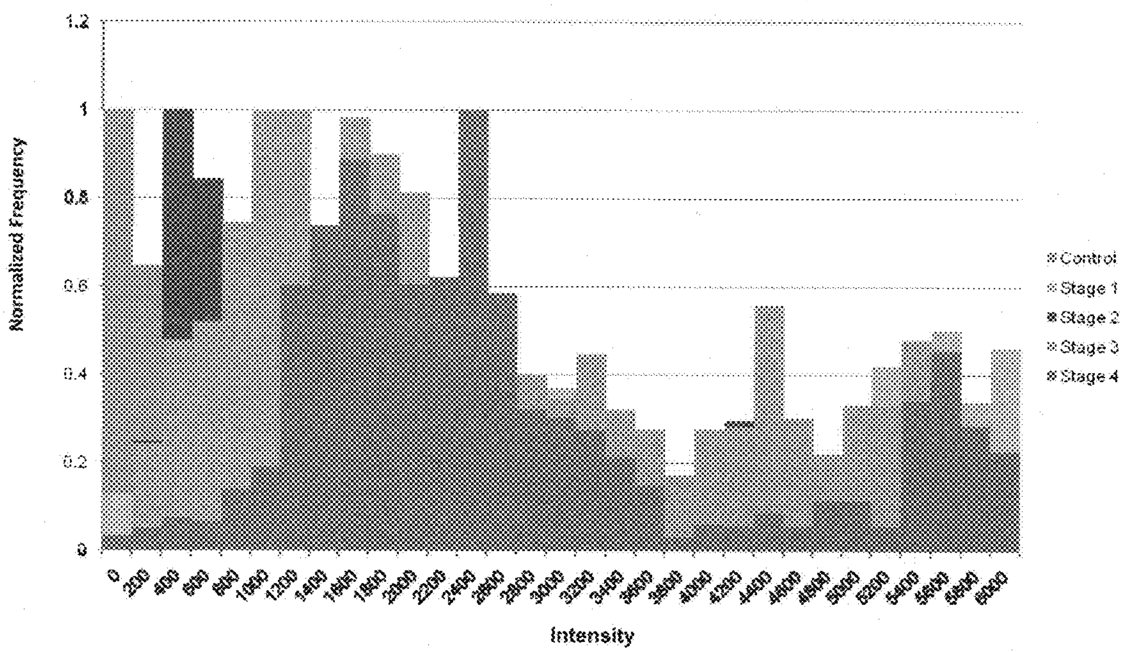

1.2
1
0.8
0.6
0.4
0.2
0
Normalized Frequency
0
200
400
600
800
1000
1200
1400
1600
1800
2000
2200
2400
2600
2800
3000
3200
3400
3600
3800
4000
4200
4400
4600
4800
5000
5200
5400
5600
5800
6000
Intensity
Control
Stage 1
Stage 2
Stage 3
Stage 4

FIG. 71F

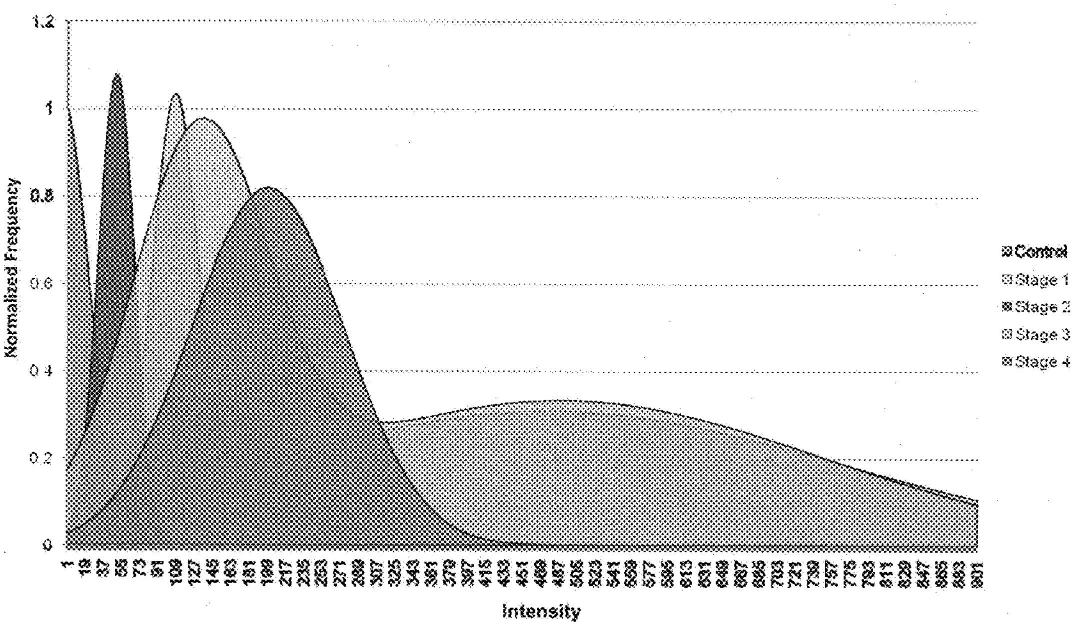

1.2
1
0.8
0.6
0.4
0.2
0
Normalized Frequency
Intensity
Control
Stage 1
Stage 2
Stage 3
Stage 4

FIG. 72A

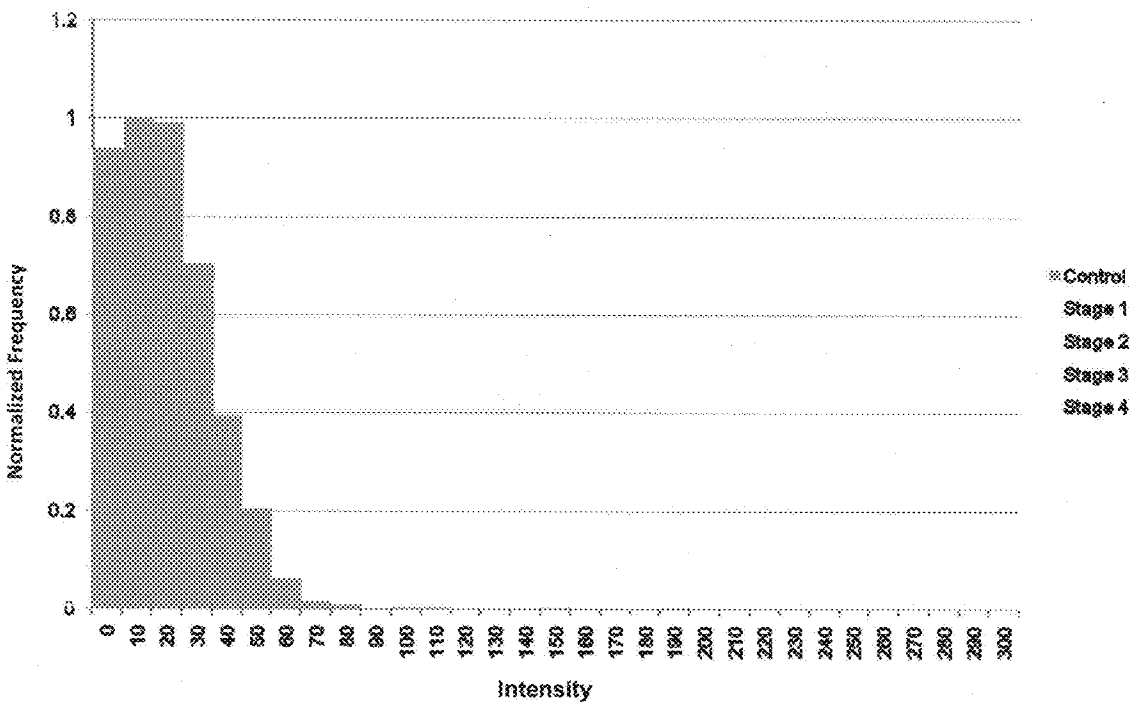
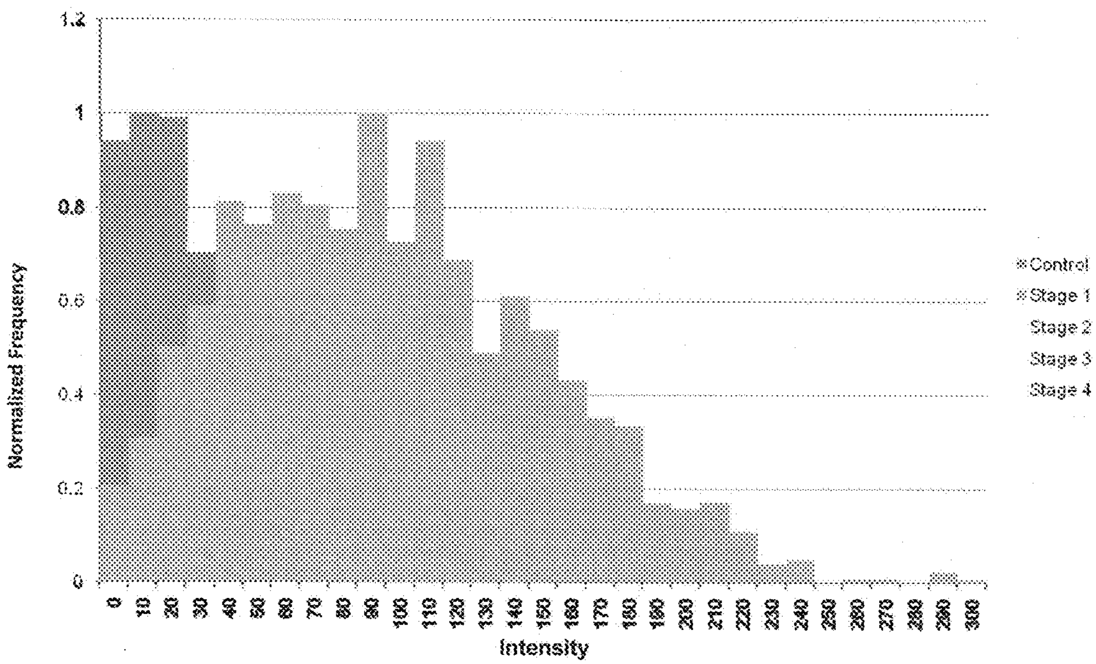

1.2
1
0.8
0.6
0.4
0.2
0
Normalized Frequency
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
240
250
260
270
280
290
300
Intensity
Control
Stage 1
Stage 2
Stage 3
Stage 4

FIG. 72B



1.2
1
0.8
0.6
0.4
0.2
0
Normalized Frequency
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
240
250
260
270
280
290
300
Intensity
Control
Stage 1
Stage 2
Stage 3
Stage 4

FIG. 72C

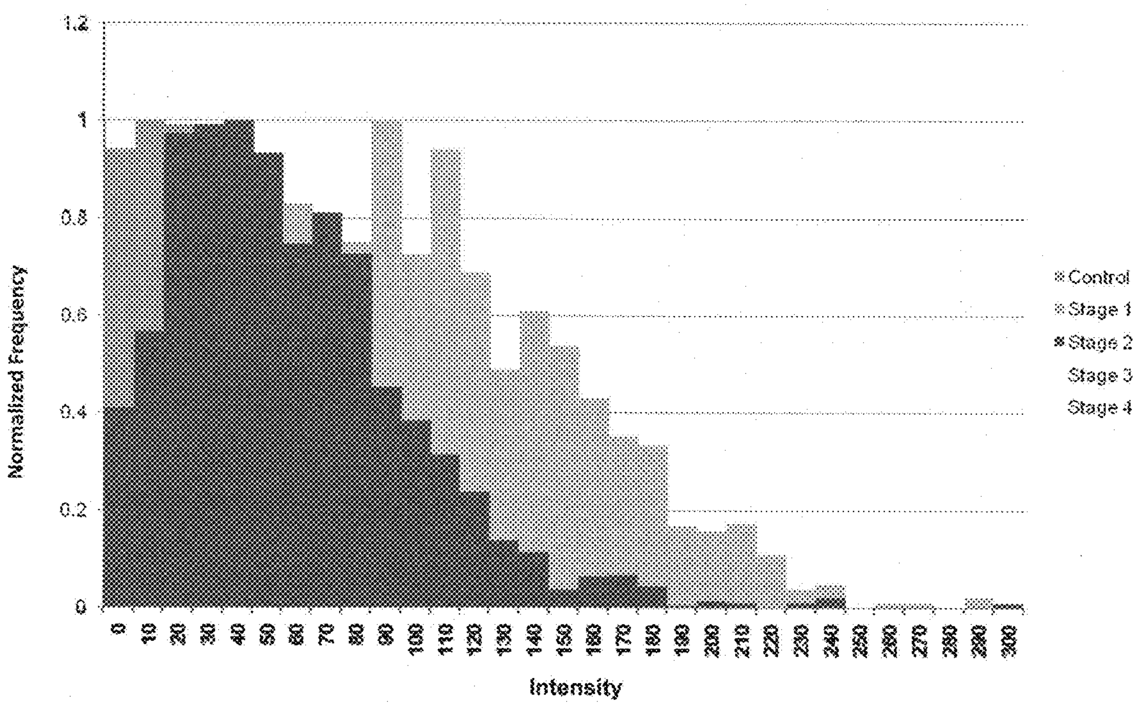

1.2
1
0.8
0.6
0.4
0.2
0
Normalized Frequency
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
240
250
260
270
280
290
300
Intensity
Control
Stage 1
Stage 2
Stage 3
Stage 4

FIG. 72D

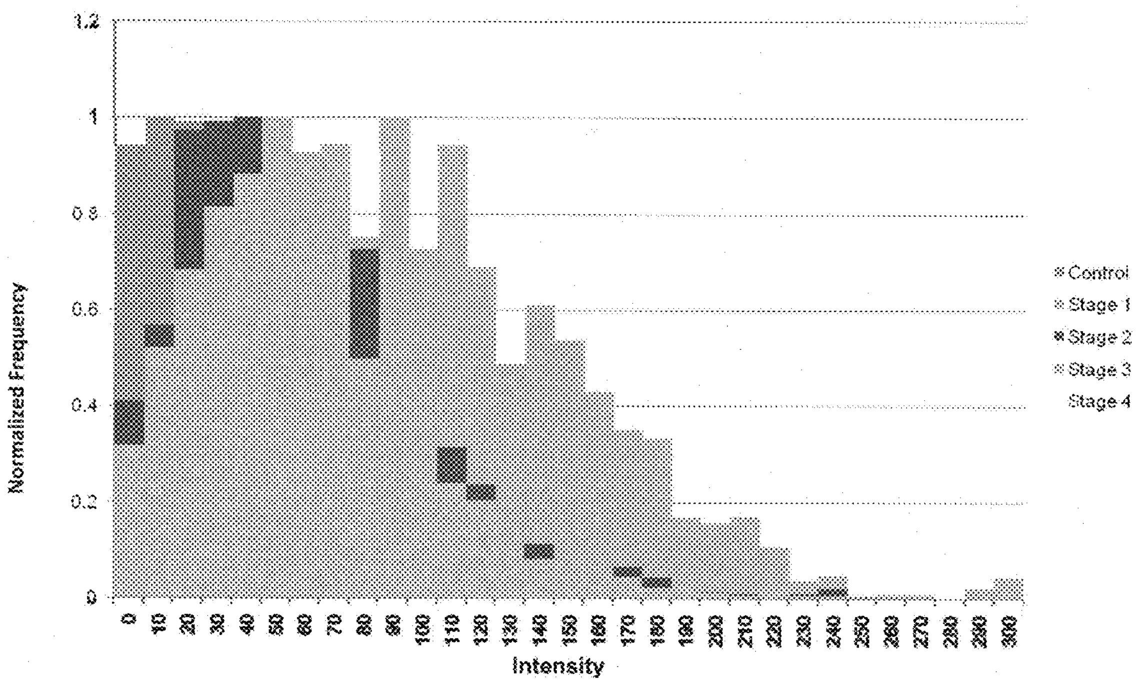

1.2
1
0.8
0.6
0.4
0.2
0
Normalized Frequency
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
240
250
260
270
280
290
300
Intensity
Control
Stage 1
Stage 2
Stage 3
Stage 4

FIG. 72E

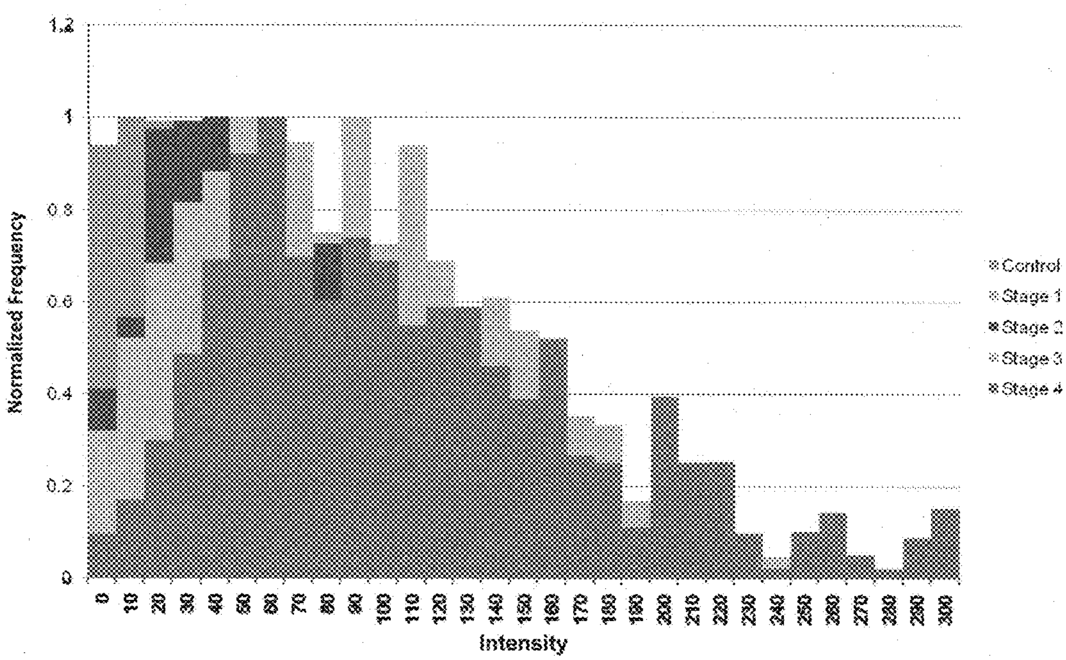

1.2
1
0.8
0.6
0.4
0.2
0
Normalized Frequency
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
240
250
260
270
280
290
300
Intensity
Control
Stage 1
Stage 2
Stage 3
Stage 4

FIG. 72F

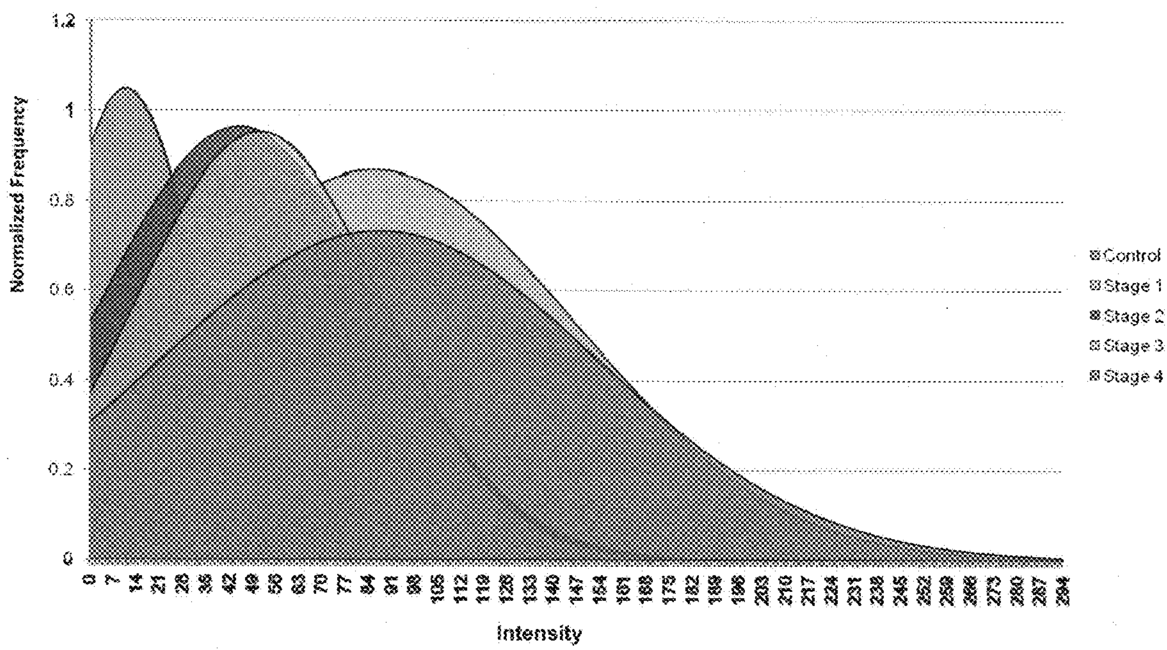

1.2
1
0.8
0.6
0.4
0.2
0
Normalized Frequency
0
7
14
21
28
35
42
49
56
63
70
77
84
91
98
105
112
119
126
133
140
147
154
161
168
175
182
189
196
203
210
217
224
231
238
245
252
259
266
273
280
287
294
Intensity
Control
Stage 1
Stage 2
Stage 3
Stage 4

FIG. 73A

	Sensitivity	Specificity	Confidence
EpCam vs CD63	87.5%	80%	99%
CD63 vs CD81	90%	100%	99%
CD63 vs CD63	60%	80%	99%
CD9 vs CD63	60%	80%	99%

FIG. 73B-E

B. EpCam vs. CD63

True Positive	7	8	True Negative
False Negative	1	2	False Positive

C. CD81 vs. CD63

True Positive	4	10	True Negative
False Negative	1	0	False Positive

D. CD63 vs. CD63

True Positive	3	8	True Negative
False Negative	2	2	False Positive

E. CD9 vs. CD63

True Positive	3	8	True Negative
False Negative	2	2	False Positive

FIG. 74A

Detector vs Capture	Sensitivity	Specificity	Confidence
Epcam vs CD63	95%	ND	99%
Epcam vs CD9	90%	ND	99%
CD63 vs CD63	100%	ND	99%
CD9 vs CD63	100%	ND	99%
CD66 vs CD9	85%	ND	99%

FIG. 74 B-F

B. EpCam vs. CD63

True Positive	19	6	True Negative
False Negative	1	ND	False Positive

C. CD81 vs. CD63

True Positive	18	6	True Negative
False Negative	2	ND	False Positive

D. CD63 vs. CD63

True Positive	20	6	True Negative
False Negative	0	ND	False Positive

E. CD9 vs. CD63

True Positive	20	6	True Negative
False Negative	0	ND	False Positive

F. CD66 vs. CD63

True Positive	17	6	True Negative
False Negative	3	ND	False Positive

FIG. 75A

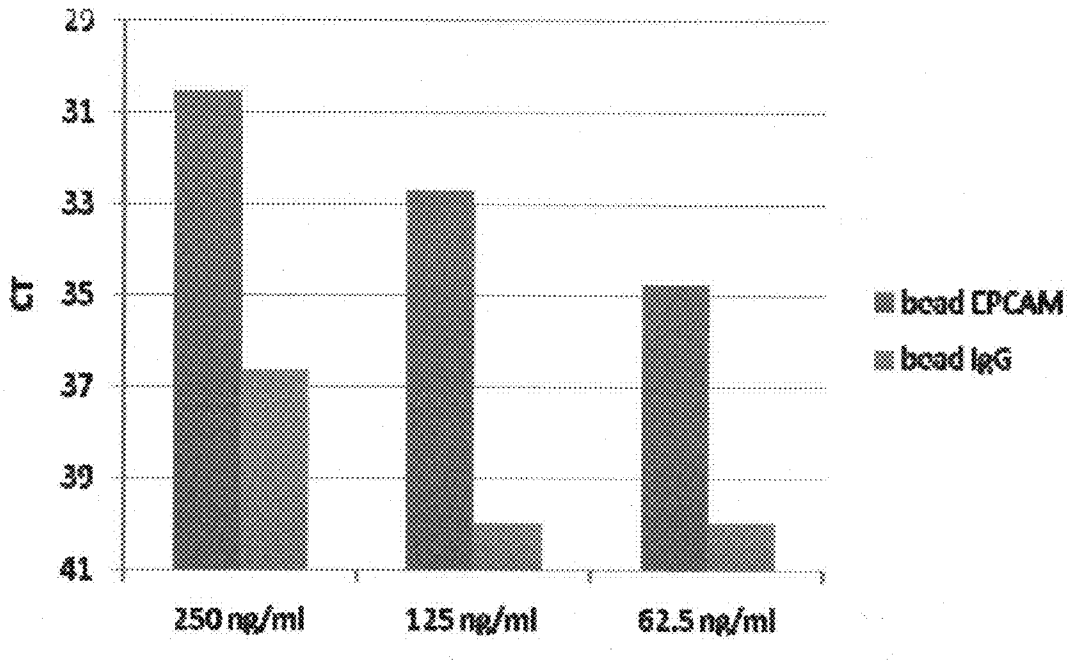

29
31
33
35
37
39
41
CT
250 ng/ml
125 ng/ml
62.5 ng/ml
bead EPCAM
bead IgG

FIG. 75B

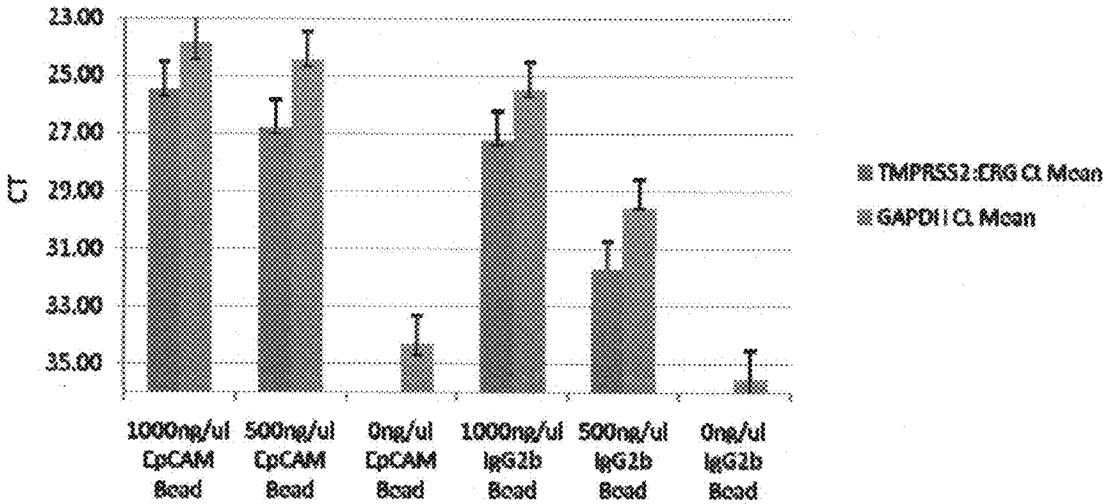

23.00
25.00
27.00
29.00
31.00
33.00
35.00
CT
TMPRSS2:ERG Ct Mean
GAPDH Ct Mean
1000ng/ul EpCAM Bead
500ng/ul EpCAM Bead
0ng/ul EpCAM Bead
1000ng/ul IgG2b Bead
500ng/ul IgG2b Bead
0ng/ul IgG2b Bead

FIG. 75C

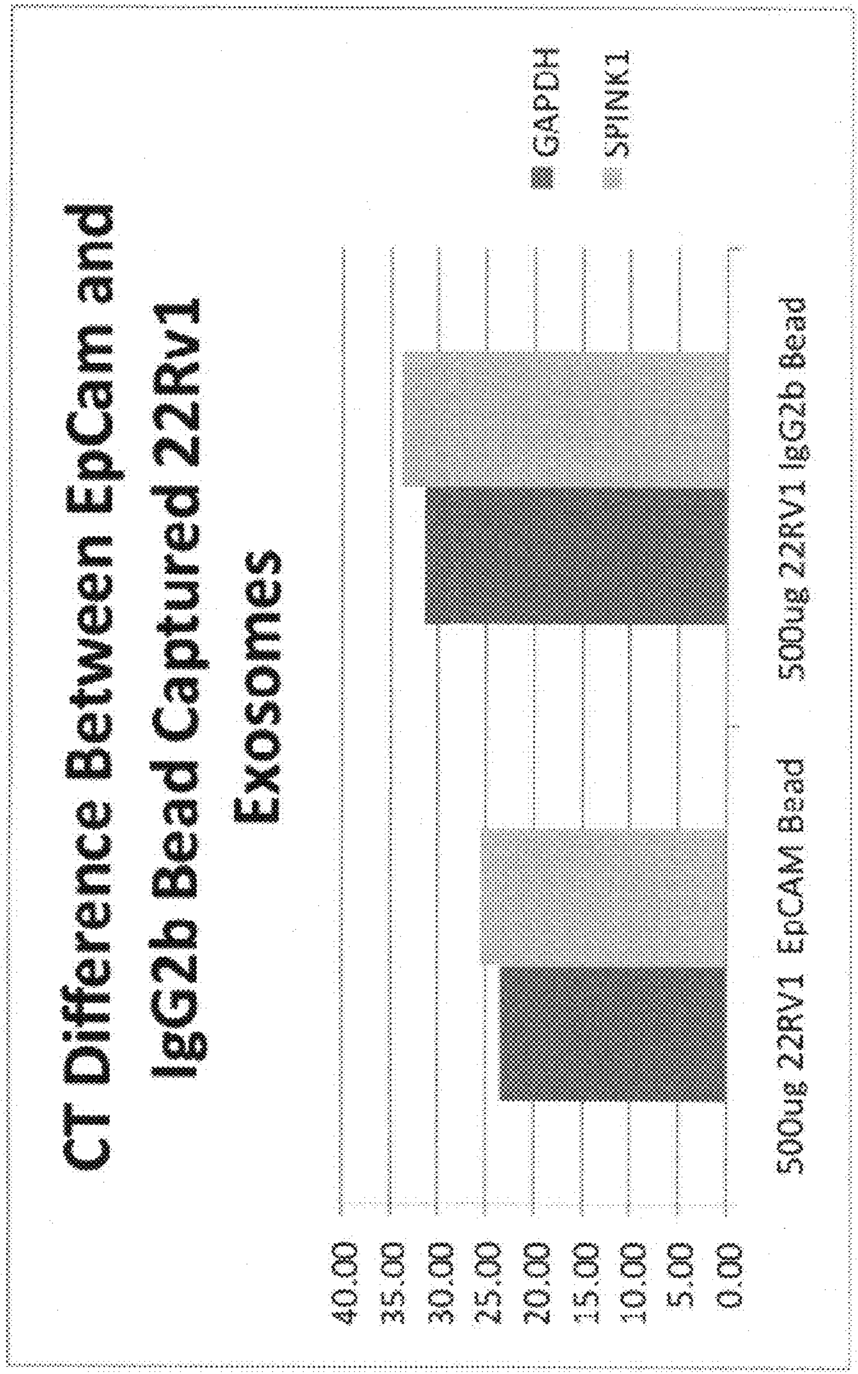

CT Difference Between EpCam and IgG2b Bead Captured 22Rv1 Exosomes
40.00
35.00
30.00
25.00
20.00
15.00
10.00
5.00
0.00
500ug 22RV1 EpCAM Bead
500ug 22RV1 IgG2b Bead
GAPDH
SPINK1

FIG. 76A

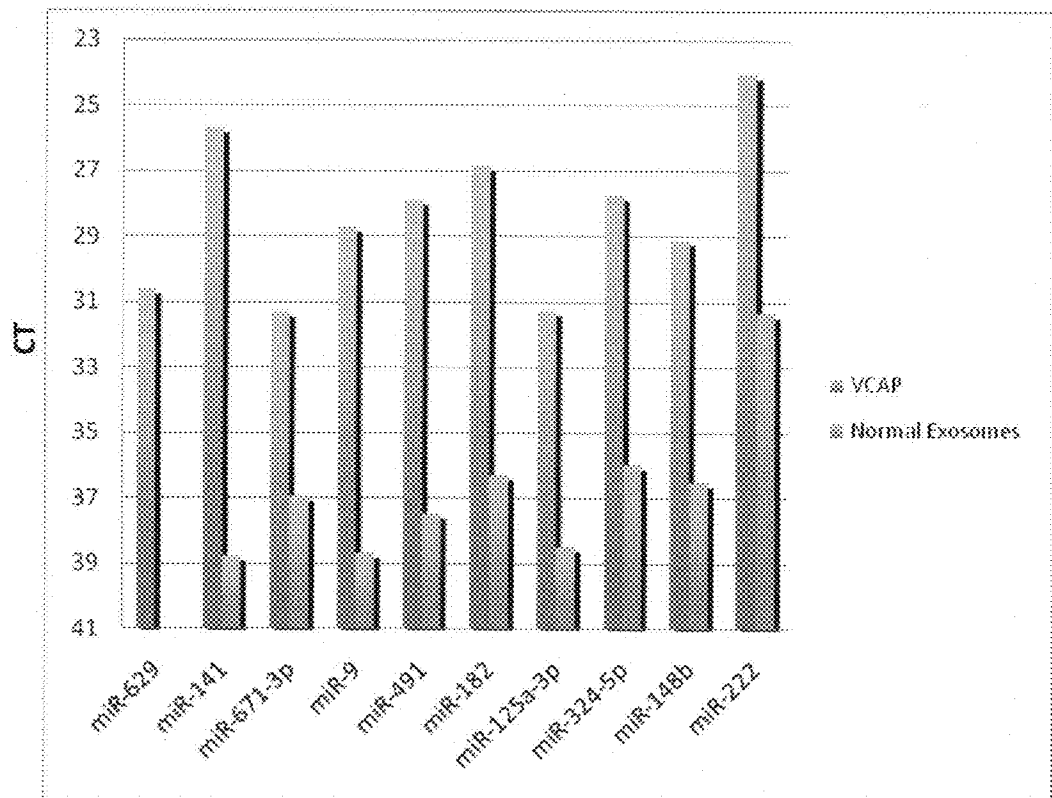

23
25
27
29
31
33
35
37
39
41
CT
VCAP
Normal Exosomes
miR-629
miR-141
miR-671-3p
miR-9
miR-491
miR-182
miR-125a-3p
miR-324-5p
miR-148b
miR-222

FIG. 76B

	VCAP Exosomes avg CT	Normal Plasma Exosomes avg ct
miR-629	30.63	
miR-141	25.69	38.78
miR-671-3p	31.31	36.93
miR-9	28.72	38.69
miR-491	27.89	37.47
miR-182	26.83	36.3
miR-125a-3p	31.26	38.51
miR-324-5p	27.74	35.98
miR-148b	29.11	36.51
miR-222	24.06	31.33

FIG. 77

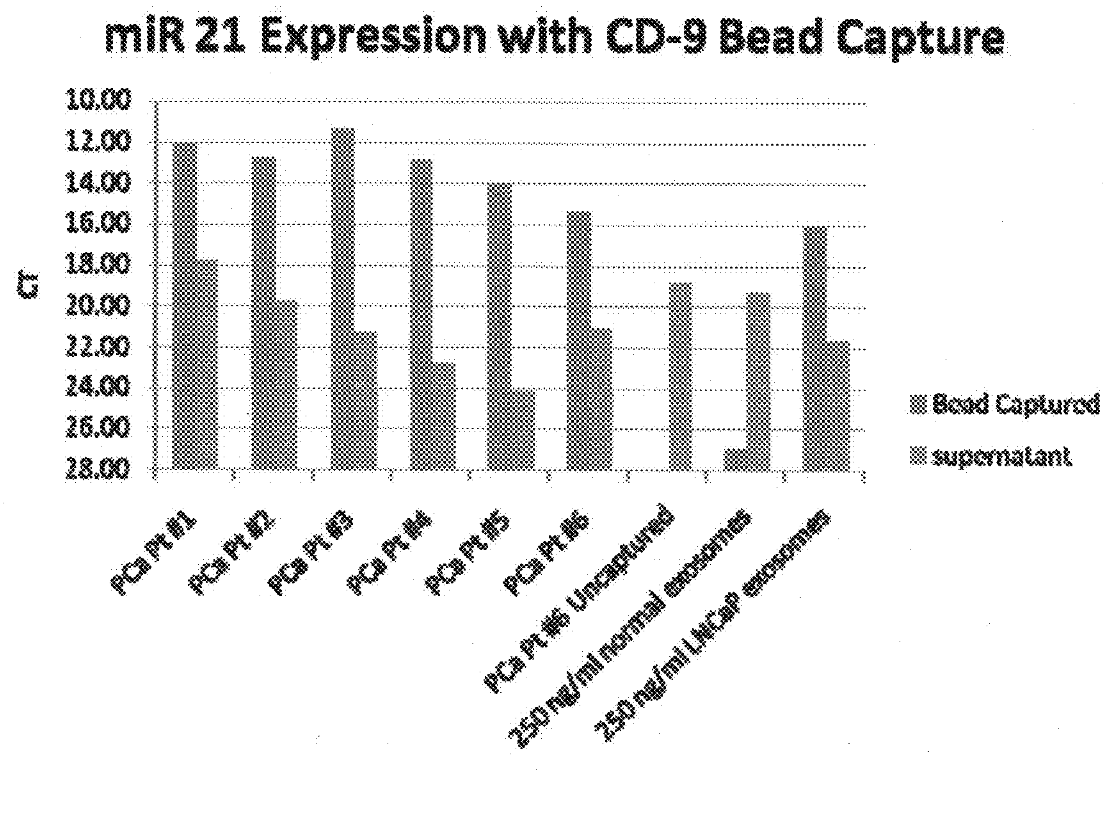

miR 21 Expression with CD-9 Bead Capture
10.00
12.00
14.00
16.00
18.00
20.00
22.00
24.00
26.00
28.00
CT
Bead Captured
supernatant
PCa Pt #1
PCa Pt #2
PCa Pt #3
PCa Pt #4
PCa Pt #5
PCa Pt #6
PCa Pt #6 Uncaptured
250 ng/ml normal exosomes
250 ng/ml LNCaP exosomes

FIG. 78

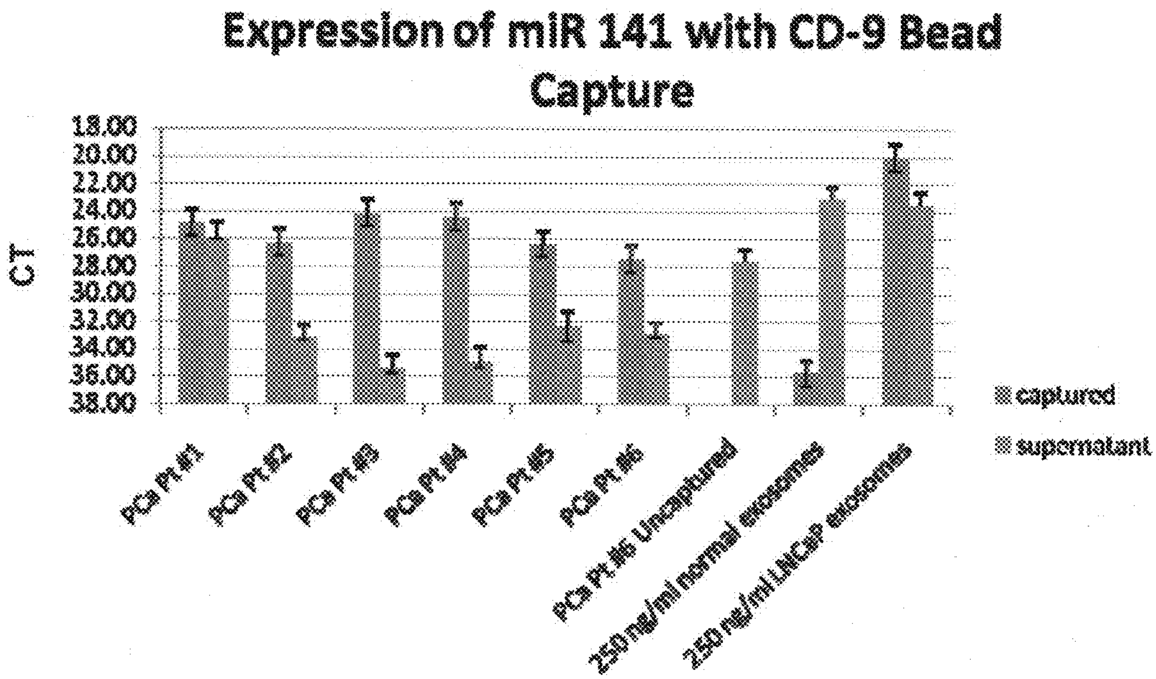

Expression of miR 141 with CD-9 Bead Capture
CT
18.00
20.00
22.00
24.00
26.00
28.00
30.00
32.00
34.00
36.00
38.00
captured
supernatant
PCa Pt #1
PCa Pt #2
PCa Pt #3
PCa Pt #4
PCa Pt #5
PCa Pt #6
PCa Pt #6 Uncaptured
250 ng/ml normal exosomes
250 ng/ml LNCaP exosomes

FIG. 79

Exosome	Prostate	Cancer-1	Cancer-2	Cancer-3	QC-1	QC-2	Sensitivity	Specificity	Sensitivity	Specificity
							With BPH	With BPH	Without BPH	Without BPH
3000	100	na	200	na	4000	na	85.70%	58.00%	85.70%	71.40%
3000	100	350	100	na	4000	na	85.70%	74.10%	85.70%	85.70%
3000	100	125	125	50	4000	na	71.40%	83.00%	71.40%	90.40%
3000	100	100	100	50	4000	8000	71.40%	87.00%	71.40%	90.40%
3000	100	100	150	50	4000	na	64.30%	90.30%	64.20%	90.40%
3000	100	100	150	150	4000	na	35.70%	93.40%	35.70%	95.20%

METHODS AND SYSTEMS OF USING EXOSOMES FOR DETERMINING PHENOTYPES

CROSS-REFERENCE

[0001] This application is a continuation of U.S. patent application Ser. No. 12/591,226, filed Nov. 12, 2009, which claims the benefit of U.S. Provisional Application Nos. 61/114,045, filed Nov. 12, 2008; 61/114,058, filed Nov. 12, 2008; 61/114,065, filed Nov. 13, 2008; 61/151,183, filed Feb. 9, 2009; 61/278,049, filed Oct. 2, 2009; 61/250,454, filed Oct. 9, 2009; and 61/253,027 filed Oct. 19, 2009, of which each is incorporated herein by reference in its entirety. This application is also related to U.S. application Ser. No. 12/609,847, filed Oct. 30, 2009, which claims the benefit of U.S. Provisional Application Nos. 61/109,742, filed Oct. 30, 2008; 61/112,571, filed Nov. 7, 2008; 61/114,045, filed Nov. 12, 2008; 61/114,058, filed Nov. 12, 2008; 61/114,065, filed Nov. 13, 2008; 61/151,183, filed Feb. 9, 2009; 61/278,049, filed Oct. 2, 2009; 61/250,454, filed Oct. 9, 2009, and 61/253,027 filed Oct. 19, 2009, each of which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] A critical need for disease detection, prognostic prediction, monitoring, and therapeutic decisions is improved assay sensitivity and specificity. At present, biomarkers (proteins, peptides, lipids, RNAs, DNA and modifications thereof for disease-associated molecular alterations) for conditions and diseases, such as cancer, rely almost exclusively on obtaining samples from tissue to identify the condition or disease. Methods to obtain these tissues of interest for analysis are often invasive, costly and pose complication risks for the patient. Furthermore, use of bodily fluids to isolate or detect biomarkers often significantly dilutes a biomarker resulting in readouts that lack requisite sensitivity. Additionally, most biomarkers are produced in low or moderate amounts in normal tissues other than the diseased tissue and thus this lack of specificity can also be problematic.

[0003] The identification of specific biomarkers, such as DNA, RNA and proteins can provide bio-signatures that are used for the diagnosis, prognosis, or theranosis of a condition or disease. Exosomes are a good source for assessing one or more biomarkers that are present in or on the surface of an exosome. Furthermore, identifying particular characteristics of an exosome (e.g., size, surface antigens, cell-of-origin) can itself provide a diagnostic, prognostic or theranostic readout.

[0004] The secretion of exosomes by cancerous cells, other diseased cells, or at certain times of a physiological process (e.g., pregnancy), can be leveraged to aid in diagnosis as well as individualized treatment decisions. Exosomes have been found in a number of body fluids, including blood plasma, breast milk, bronchoalveolar lavage fluid and urine. Exosomes also take part in the communication between cells, as transport vehicles for proteins, RNAs, DNAs, viruses, and prions.

[0005] The present inventions provide an improvement to prior art assays. Products and process are provided for improved assay sensitivity and specificity, allowing for disease detection, prognostic prediction, disease monitoring, disease staging, and therapeutic decision-making, as well as physiological state identification. Products and processes include cell-of-origin specific selection of exosomes and analysis of their protein composition, RNA composition, DNA composition, lipid profile, and relevant metabolic and/or epigenetic modifications of these analytes. Also provided herein are methods of determining biomarkers and bio-signatures for exosomes without prior concentration or purification of the exosomes from a sample.

SUMMARY

[0006] Disclosed herein are methods and compositions for characterizing a phenotype by analyzing an exosome. Characterizing a phenotype for a subject or individual may include, but is not limited to, the diagnosis of a disease or condition, the prognosis of a disease or condition, the determination of a disease stage or a condition stage, a drug efficacy, a physiological condition, organ distress or organ rejection, disease or condition progression, therapy-related association to a disease or condition, or a specific physiological or biological state.

[0007] The method can include determining a bio-signature of an exosome in a biological sample from a subject and characterizing a phenotype in said subject based on the bio-signature. Characterizing can also be based on determining the amount of exosomes in a biological sample. The characterization of the phenotype can be performed with at least 70, 80 or 90% sensitivity, specificity, or both.

[0008] The exosome can be isolated or concentrated prior to determining an exosomal bio-signature. The bio-signature can comprise an expression level, presence, absence, mutation, copy number variation, truncation, duplication, insertion, modification, sequence variation, or molecular association of a biomarker. The bio-signature can also comprise quantification of isolated exosomes, temporal evaluation of the variation in exosomal half-life, circulating exosomal half-life, exosomal metabolic half-life, or the activity of an exosome.

[0009] The exosome can be a cell-of-origin specific exosome. The exosome can be derived from a tumor or cancer cell. The cell-of-origin for an exosome can be a lung, pancreas, stomach, intestine, bladder, kidney, ovary, testis, skin, colorectal, breast, prostate, brain, esophagus, liver, placenta, or fetal cell.

[0010] One or more biomarkers of an exosome can be assessed for characterizing a phenotype. The biomarker can be a nucleic acid, peptide, protein, lipid, antigen, carbohydrate or proteoglycan, such as DNA or RNA. The RNA can be mRNA, miRNA, snoRNA, snRNA, rRNAs, tRNAs, siRNA, hnRNA, or shRNA. The biomarker can be an antigen selected from FIG. **1**, or a biomarker selected from a table listed in FIG. **3-60**. One or more biomarkers can be assessed and used to characterize a phenotype. The bio-signature can comprise one or more miRNAs selected from the group consisting of: miR-9, miR-629, miR-141, miR-671-3p, miR-491, miR-182, miR-125a-3p, miR-324-5p, miR-148b, and miR-222. The bio-signature can be used to characterize a phenotype, such as prostate cancer. Other biomarkers can be selected from the group consisting of: CD9, PSCA (prostate stem cell antigen), TNFR, CD63, MFG-E8, EpCam, Rab, CD81, STEAP, PCSA (prostate cell surface antigen), PSM (or PSMA, prostate specific membrane antigen), 5T4, CD59, CD66, CD24 and B7H3. Detecting a plurality of biomarkers can provide greater sensitivity or specificity as compared to detecting less than a plurality of biomarkers.

[0011] Methods of multiplexing, or multiplex analysis of, a plurality of exosomes are also provided. Multiplexing a plurality of exosomes can comprise applying said plurality of exosomes to a plurality of particles, wherein each particle of a subset of the plurality of particles is coupled to a different capture agent, capturing a subset of said plurality of exosomes; and, detecting one or more biomarkers of the captured exosomes. Multiplexing can also be performed using an array, wherein the capture agents are attached to an array instead of particles or beads.

[0012] Also provided herein are isolated exosomes. The isolated exosome can comprise any one or more biomarkers disclosed herein, such as a specific combination of biomarkers. Compositions comprising the one or more isolated exosomes are also provided. The composition can comprise a substantially enriched population of exosomes. The population of exosomes can be substantially homogeneous for one or more specific biomarkers, for a particular bio-signature, or derived from a specific cell type.

[0013] Detection systems, microfluidic devices, and kits for assessing one or more exosomes, such as for the isolation, separation, or detection of one or more exosomes, are also provided.

INCORPORATION BY REFERENCE

[0014] All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] FIG. **1** (*a*)-(g) represents a table which lists exemplary cancers by lineage, group comparisons of cells/tissue, and specific disease states and antigens specific to those cancers, group cell/tissue comparisons and specific disease states. Furthermore, the antigen can be a biomarker. The one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0016] FIG. **2** (*a*)-(f) represents a table which lists exemplary cancers by lineage, group comparisons of cells/tissue, and specific disease states and binding agents specific to those cancers, group cell/tissue comparisons and specific disease states.

[0017] FIG. **3** (*a*)-(b) represents a table which lists exemplary breast cancer biomarkers that can be derived and analyzed from exosomes specific to breast cancer to create a breast cancer specific exosome bio-signature. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0018] FIG. **4** (*a*)-(b) represents a table which lists exemplary ovarian cancer biomarkers that can be derived from and analyzed from exosomes specific to ovarian cancer to create an ovarian cancer specific exosome bio-signature. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0019] FIG. **5** represents a table which lists exemplary lung cancer biomarkers that can be derived from and analyzed from exosomes specific to lung cancer to create a lung cancer specific exosome bio-signature. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0020] FIG. **6** (*a*)-(d) represents a table which lists exemplary colon cancer biomarkers that can be derived from and analyzed from exosomes specific to colon cancer to create a colon cancer specific exosome bio-signature. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0021] FIG. **7** represents a table which lists exemplary biomarkers specific to an adenoma versus a hyperplastic polyp that can be derived and analyzed from exosomes specific to adenomas versus hyperplastic polyps. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0022] FIG. **8** is a table which lists exemplary biomarkers specific to inflammatory bowel disease (IBD) versus normal tissue that can be derived and analyzed from exosomes specific to inflammatory bowel disease versus normal tissue. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0023] FIG. **9**(*a*)-(c) represents a table which lists exemplary biomarkers specific to an adenoma versus colorectal cancer (CRC) that can be derived and analyzed from exosomes specific to adenomas versus colorectal cancer. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0024] FIG. **10** represents a table which lists exemplary biomarkers specific to IBD versus CRC that can be derived and analyzed from exosomes specific to IBD versus CRC. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0025] FIG. **11** (*a*)-(b) represents a table which lists exemplary biomarkers specific to CRC Dukes B versus Dukes C-D that can be derived and analyzed from exosomes specific to CRC Dukes B versus Dukes C-D. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0026] FIG. **12**(*a*)-(d) represents a table which lists exemplary biomarkers specific to an adenoma with low grade dysplasia versus an adenoma with high grade dysplasia that can be derived and analyzed from exosomes specific to an adenoma with low grade dysplasia versus an adenoma with high grade dysplasia. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0027] FIG. **13**(*a*)-(b) represents a table which lists exemplary biomarkers specific to ulcerative colitis (UC) versus Crohn's Disease (CD) that can be derived and analyzed from exosomes specific to UC versus CD. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0028] FIG. **14** represents a table which lists exemplary biomarkers specific to a hyperplastic polyp versus normal tissue that can be derived and analyzed from exosomes specific to a hyperplastic polyp versus normal tissue. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0029] FIG. **15** is a table which lists exemplary biomarkers specific to an adenoma with low grade dysplasia versus normal tissue that can be derived and analyzed from exosomes specific to an adenoma with low grade dysplasia versus normal tissue. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0030] FIG. **16** is a table which lists exemplary biomarkers specific to an adenoma versus normal tissue that can be derived and analyzed from exosomes specific to an adenoma versus normal tissue. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0031] FIG. **17** represents a table which lists exemplary biomarkers specific to CRC versus normal tissue that can be derived and analyzed from exosomes specific to CRC versus normal tissue. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0032] FIG. **18** is a table which lists exemplary biomarkers specific to benign prostatic hyperplasia that can be derived from and analyzed from exosomes specific to benign prostatic hyperplasia. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0033] FIG. **19**(*a*)-(c) represents a table which lists exemplary prostate cancer biomarkers that can be derived from and analyzed from exosomes specific to prostate cancer to create a prostate cancer specific exosome bio-signature. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0034] FIG. **20**(*a*)-(c) represents a table which lists exemplary melanoma biomarkers that can be derived from and analyzed from exosomes specific to melanoma to create a melanoma specific exosome bio-signature. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0035] FIG. **21**(*a*)-(b) represents a table which lists exemplary pancreatic cancer biomarkers that can be derived from and analyzed from exosomes specific to pancreatic cancer to create a pancreatic cancer specific exosome bio-signature. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0036] FIG. **22** is a table which lists exemplary biomarkers specific to brain cancer that can be derived from and analyzed from exosomes specific to brain cancer to create a brain cancer specific exosome bio-signature. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0037] FIG. **23**(*a*)-(b) represents a table which lists exemplary psoriasis biomarkers that can be derived from and analyzed from exosomes specific to psoriasis to create a psoriasis specific exosome bio-signature. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0038] FIG. **24**(*a*)-(c) represents a table which lists exemplary cardiovascular disease biomarkers that can be derived from and analyzed from exosomes specific to cardiovascular disease to create a cardiovascular disease specific exosome bio-signature. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0039] FIG. **25** is a table which lists exemplary biomarkers specific to hematological malignancies that can be derived from and analyzed from exosomes specific to hematological malignancies to create a specific exosome bio-signature for hematological malignancies. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0040] FIG. **26**(*a*)-(b) represents a table which lists exemplary biomarkers specific to B-Cell Chronic Lymphocytic Leukemias that can be derived from and analyzed from exosomes specific to B-Cell Chronic Lymphocytic Leukemias to create a specific exosome bio-signature for B-Cell Chronic Lymphocytic Leukemias. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0041] FIG. **27** is a table which lists exemplary biomarkers specific to B-Cell Lymphoma and B-Cell Lymphoma-DLBCL that can be derived from and analyzed from exosomes specific to B-Cell Lymphoma and B-Cell Lymphoma-DLBCL. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0042] FIG. **28** represents a table which lists exemplary biomarkers specific to B-Cell Lymphoma-DLBCL-germinal center-like and B-Cell Lymphoma-DLBCL-activated B-cell-like and B-cell lymphoma-DLBCL that can be derived from and analyzed from exosomes specific to B-Cell Lymphoma-DLBCL-germinal center-like and B-Cell Lymphoma-DLBCL-activated B-cell-like and B-cell lymphoma-DLBCL. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0043] FIG. **29** represents a table which lists exemplary Burkitt's lymphoma biomarkers that can be derived from and analyzed from exosomes specific to Burkitt's lymphoma to create a Burkitt's lymphoma specific exosome bio-signature. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0044] FIG. **30**(*a*)-(b) represents a table which lists exemplary hepatocellular carcinoma biomarkers that can be derived from and analyzed from exosomes specific to hepatocellular carcinoma to create a specific exosome bio-signature for hepatocellular carcinoma. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0045] FIG. **31** is a table which lists exemplary biomarkers for cervical cancer that can be derived from and analyzed from exosomes specific to cervical cancer. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0046] FIG. **32** represents a table which lists exemplary biomarkers for endometrial cancer that can be derived from and analyzed from exosomes specific to endometrial cancer to create a specific exosome bio-signature for endometrial cancer. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0047] FIG. **33**(*a*)-(b) represents a table which lists exemplary biomarkers for head and neck cancer that can be derived from and analyzed from exosomes specific to head and neck cancer to create a specific exosome bio-signature for head and neck cancer. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0048] FIG. **34** represents a table which lists exemplary biomarkers for inflammatory bowel disease (IBD) that can be derived from and analyzed from exosomes specific to IBD to create a specific exosome bio-signature for IBD. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0049] FIG. **35** is a table which lists exemplary biomarkers for diabetes that can be derived from and analyzed from exosomes specific to diabetes to create a specific exosome bio-signature for diabetes. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0050] FIG. **36** is a table which lists exemplary biomarkers for Barrett's Esophagus that can be derived from and analyzed from exosomes specific to Barrett's Esophagus to create a specific exosome bio-signature for Barrett's Esophagus. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0051] FIG. **37** is a table which lists exemplary biomarkers for fibromyalgia that can be derived from and analyzed from exosomes specific to fibromyalgia. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0052] FIG. **38** represents a table which lists exemplary biomarkers for stroke that can be derived from and analyzed from exosomes specific to stroke to create a specific exosome bio-signature for stroke. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0053] FIG. **39** is a table which lists exemplary biomarkers for Multiple Sclerosis (MS) that can be derived from and analyzed from exosomes specific to MS to create a specific exosome bio-signature for MS. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0054] FIG. **40**(*a*)-(b) represents a table which lists exemplary biomarkers for Parkinson's Disease that can be derived from and analyzed from exosomes specific to Parkinson's Disease to create a specific exosome bio-signature for Parkinson's Disease. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0055] FIG. **41** represents a table which lists exemplary biomarkers for Rheumatic Disease that can be derived from and analyzed from exosomes specific to Rheumatic Disease to create a specific exosome bio-signature for Rheumatic Disease. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0056] FIG. **42**(*a*)-(b) represents a table which lists exemplary biomarkers for Alzheimers Disease that can be derived from and analyzed from exosomes specific to Alzheimers Disease to create a specific exosome bio-signature for Alzheimers Disease. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0057] FIG. **43** is a table which lists exemplary biomarkers for Prion Diseases that can be derived from and analyzed from exosomes specific to Prion Diseases to create a specific exosome bio-signature for Prion Diseases. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0058] FIG. **44** represents a table which lists exemplary biomarkers for sepsis that can be derived from and analyzed from exosomes specific to sepsis to create a specific exosome bio-signature for sepsis. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0059] FIG. **45** is a table which lists exemplary biomarkers for chronic neuropathic pain that can be derived from and analyzed from exosomes specific to chronic neuropathic pain. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0060] FIG. **46** is a table which lists exemplary biomarkers for peripheral neuropathic pain that can be derived from and analyzed from exosomes specific to peripheral neuropathic pain. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0061] FIG. **47** represents a table which lists exemplary biomarkers for Schizophrenia that can be derived from and analyzed from exosomes specific to Schizophrenia to create a specific exosome bio-signature for Schizophrenia. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0062] FIG. **48** is a table which lists exemplary biomarkers for bipolar disorder or disease that can be derived from and analyzed from exosomes specific to bipolar disorder to create a specific exosome bio-signature for bipolar disorder. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0063] FIG. **49** is a table which lists exemplary biomarkers for depression that can be derived from and analyzed from exosomes specific to depression to create a specific exosome bio-signature for depression. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0064] FIG. **50** is a table which lists exemplary biomarkers for gastrointestinal stromal tumor (GIST) that can be derived from and analyzed from exosomes specific to GIST to create a specific exosome bio-signature for GIST. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0065] FIG. **51**(*a*)-(b) represent sa table which lists exemplary biomarkers for renal cell carcinoma (RCC) that can be derived from and analyzed from exosomes specific to RCC to create a specific exosome bio-signature for RCC. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0066] FIG. **52** is a table which lists exemplary biomarkers for cirrhosis that can be derived from and analyzed from exosomes specific to cirrhosis to create a specific exosome bio-signature for cirrhosis. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0067] FIG. **53** is a table which lists exemplary biomarkers for esophageal cancer that can be derived from and analyzed from exosomes specific to esophageal cancer to create a specific exosome bio-signature for esophageal cancer. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0068] FIG. **54** is a table which lists exemplary biomarkers for gastric cancer that can be derived from and analyzed from exosomes specific to gastric cancer to create a specific exosome bio-signature for gastric cancer. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0069] FIG. **55** is a table which lists exemplary biomarkers for autism that can be derived from and analyzed from exosomes specific to autism to create a specific exosome bio-signature for autism. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0070] FIG. **56** is a table which lists exemplary biomarkers for organ rejection that can be derived from and analyzed from exosomes specific to organ rejection to create a specific exosome bio-signature for organ rejection. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0071] FIG. **57** is a table which lists exemplary biomarkers for methicillin-resistant *staphylococcus aureus* that can be derived from and analyzed from exosomes specific to methicillin-resistant *staphylococcus aureus* to create a specific exosome bio-signature for methicillin-resistant *staphylococcus aureus*. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0072] FIG. **58** is a table which lists exemplary biomarkers for vulnerable plaque that can be derived from and analyzed from exosomes specific to vulnerable plaque to create a specific exosome bio-signature for vulnerable plaque. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified.

[0073] FIG. **59**(*a*)-(i) is a table which lists exemplary gene fusions that can be derived from, or analyzed from exosomes. The gene fusion can be biomarker, and can be present or absent, underexpressed or overexpressed, or modified, such as epigentically modified or post-translationally modified.

[0074] FIG. **60**(*a*)-(b) is a table of genes and their associated miRNAs, of which the gene, such as the mRNA of the gene, their associated miRNAs, or any combination thereof, can be used as one or more biomarkers that can be analyzed from exosomes. Furthermore, the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified.

[0075] FIG. **61** is a flow chart of an exemplary method disclosed herein.

[0076] FIG. **62** illustrates a computer system that can be used in some exemplary embodiments of the invention.

[0077] FIG. **63** illustrates results obtained from screening for proteins on exosomes, which can be used a biomarkers for the exosomes and antibodies to the proteins can be used as binding agents. Examples of the proteins identified include Bcl-XL, ERCC1, Keratin 15, CD81/TAPA-1, CD9, Epithelial Specific Antigen (ESA), and Mast Cell Chymase. The one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified.

[0078] FIG. **64** illustrates a particle based method of isolating exosomes. (A) is a schematic of a bead coated with a capture antibody, which captures exosomes expressing that protein. In this schematic, the capture antibody is for an exosomal protein that is not specific for exosomes derived from cancer cells ("cancer exosome"). The detection antibody binds to the captured exosome and fluoresces a signal. The detection antibody in this example detects an antigen that is associated with cancer exosomes. (B) is an example of a screening scheme that can be performed by multiplexing using the beads as shown in (A).

[0079] FIG. **65** depicts scanning electron micrographs (SEMs) of EpCam conjugated beads that have been incubated with VCaP exosomes. (A) A glass slide was coated with poly-L-lysine and incubated with the bead solution. After attachment, the beads were (i) fixed sequentially with glutaraldehyde and osmium tetroxide, 30 min per fix step with a few washes in between; (ii) gradually dehydrated in acetone, 20% increments, about 5-7 min per step; (iii) critical-point dried; and (iv) sputter-coated with gold. (B) Left: depicts a higher magnification of exosomes on an EpCam coated bead as in (A). Right: depicts exosomes isolated by ultracentrifugation and adhered to a poly-L-lysine coated glass slide and fixed and stained as in (A).

[0080] FIG. **66** is a schematic of an exosome protein expression patterns. Different proteins are typically not distributed evenly or uniformly on exosome shell. Exosome-specific proteins are typically more common, while cancer-specific proteins are less common. Exosome capture can be more easily accomplished using a more common, less cancer-specific protein, and cancer-specific proteins used in the detection phase.

[0081] FIG. **67** illustrates the method of depicting the results using the bead based method of detecting exosomes from a subject. (A) For an individual patient, a graph of the bead enumeration and signal intensity using a screening scheme as depicted in FIG. **64**B, where ~100 capture beads are used for each capture/detection combination assay per patient. For a given patient, the output shows number of beads detected vs. intensity of signal. The number of beads captured at a given intensity is an indication of how frequently an exosome expresses the detection protein at that intensity. The more intense the signal for a given bead, the greater the expression of the detection protein. (B) is a normalized graph obtained by combining normal patients into one curve and cancer patients into another, and using bio-statistical analysis to differentiate the curves. Data from each individual is normalized to account for variation in the number of beads read by the detection machine, added together, and then normalized again to account for the different number of samples in each population.

[0082] FIG. **68** illustrates prostate cancer bio-signatures. (A) is a histogram of intensity values collected from a multiplexing experiment using the Luminex platform, where beads were functionalized with CD63 antibody, incubated with exosomes purified from patient plasma, and then labeled with a phycoerythrin (PE) conjugated EpCam antibody. The darker shaded bars (blue) represent the population from 12 normal subjects and the lighter shaded bars (green) are from 7 stage 3 prostate cancer patients. (B) is a normalized graph for each of the histograms shown in (A), as described in FIG. **67**. The distributions are of a Gaussian fit to intensity values from the Luminex results of (A) for both prostate patient samples and normal samples. (C) is an example of one of the prostate bio-signatures shown in (B), the CD63 versus CD63 bio-signature (upper graph) where CD63 is used as the detector and capture antibody. The lower three panels show the results of flow cytometry on three prostate cancer cell lines (VCaP, LNcap, and 22RV1). Points above the horizontal line indicate beads that captured exosomes with CD63 that contain B7H3. Beads to the right of the vertical line indicate beads that have captured exosomes with CD63 that have PSMA. Those beads that are above and to the right of the lines have all three antigens. CD63 is a surface protein that is associated with exosomes, PSMA is surface protein that is associated with prostate cells, and B7H3 is a surface protein that is associated with aggressive cancers (specifically prostate, ovarian, and non-small-cell lung). The combination of all three antigens together identifies exosomes that are from cancer prostate cells. The majority of CD63 expressing prostate cancer exosomes also have prostate-specific membrane antigen, PSMA, and B7H3 (implicated in regulation of tumor cell migration and invasion and an indicator of aggressive cancer as well as clinical outcome). (D) is a prostate cancer exosome topography. The upper panels show the results of capturing and labeling with CD63, CD9, and CD81 in various combinations. Almost all points are in the upper right quadrant indicating that these three markers are highly coupled. If an exosome has one of them, it typically has all three. The lower row depicts the results of capturing cell line exosomes with B7H3 and labeling with CD63 and PSMA. Both VCaP and 22RV1 show that most exosomes captured with B7H3 also have CD63, and that there are two populations, those with PSMA and those without. The presence of B7H3 may be an indication of how aggressive the cancer is, as LNcap does not have a high amount of B7H3 containing exosomes (not many spots with CD63). LnCap is an earlier stage prostate cancer analogue cell line.

[0083] FIG. **69**: illustrates colon cancer bio-signatures. (A) shows histograms of intensity values collected from various multiplexing experiments using the Luminex platform, where beads were functionalized with a capture antibody, incubated with exosomes purified form patient plasma, and then labeled with a detector antibody. The darker shaded bars (blue) represent the population from normals and the lighter shaded bars (green) are from colon cancer patients. (B) shows a normalized graph for each of the histograms shown in (A). (C) shows a histogram of intensity values collected from a Luminex experiment where beads where functionalized with CD66 antibody (the capture antibody), incubated with exosomes purified from patient plasma, and then labeled with a PE conjugated EpCam antibody (the detector antibody). The red population is from 6 normals and the green is from 21 colon cancer patients. Data from each individual was normalized to account for variation in the number of beads read by the Luminex machine, added together, and then normalized again to account for the different number of samples in each population.

[0084] FIG. **70** illustrates multiple detectors can increase the signal of exosome detection. (A) Median intensity values are plotted as a function of purified exosome concentration from the VCaP cell line when labeled with a variety of prostate specific PE conjugated antibodies. Exosomes captured with EpCam (left graphs) or PCSA (right graphs) and the various proteins detected by the detector antibody are listed to the right of each graph. In both cases the combination of CD9 and CD63 gives the best increase in signal over background (bottom graphs depicting percent increase). The combination of CD9 and CD63 gave about 200% percent increase over background. (B) further illustrates prostate cancer/prostate exosome-specific marker multiplexing improves detection of prostate cancer cell derived exosomes. Median intensity values are plotted as a function of purified exosome concentration from the VCaP cell line when labeled with a variety of prostate specific PE conjugated antibodies. Exosomes captured with PCSA (left) and exosomes captured with EpCam (right) are depicted. In both cases the combination of B7H3 and PSMA gives the best increase in signal over background.

[0085] FIG. **71** illustrates a colon cancer bio-signature for colon cancer by stage, using CD63 detector and CD63 capture. The histograms of intensities from exosomes captured with CD63 coated beads and labeled with CD63 conjugated PE. There are 6 patients in the control group (A), 4 in stage I (B), 5 in stage 11 (C), 8 in stage III (D), and 4 stage 1V (E). Data from each individual was normalized to account for variation in the number of beads read by the Luminex machine, added together, and then normalized again to account for the different number of samples in each population (F).

[0086] FIG. **72**: illustrates colon cancer bio-signature for colon cancer by stage, using EpCam detector and CD9 capture. The histograms of intensities are from exosomes captured with CD9 coated beads and labeled with EpCam. There are patients in the (A) control group, (B) stage I, (C) stage II, (D) stage III, and (E) stage 1V. Data from each individual was normalized to account for variation in the number of beads read by the Luminex machine, added together, and then normalized again to account for the different number of samples in each population (F).

[0087] FIG. **73**: illustrates (A) the sensitivity and specificity, and the confidence level, for detecting prostate cancer using antibodies to the listed proteins listed as the detector and capture antibodies. CD63, CD9, and CD81 are general exosome markers and EpCam is a cancer marker. The individual results are depicted in (B) for EpCam versus CD63, with 99% confidence, 100% (n=8) cancer patient samples were different from the Generalized Normal Distribution and with 99% confidence, 77% (n=10) normal patient samples were not different from the Generalized Normal Distribution; (C) for CD81 versus CD63, with 99% confidence, 90% (n=5) cancer patient samples were different from the Generalized Normal Distribution; with 99% confidence, 77% (n=10) normal patient samples were not different from the Generalized Normal Distribution; (D) for CD63 versus CD63, with 99% confidence, 60% (n=5) cancer patient samples were different from the Generalized Normal Distribution; with 99% confidence, 80% (n=10) normal patient samples were not different from the Generalized Normal Distribution; (E) for CD9 versus CD63, with 99% confidence, 90% (n=5) cancer patient samples were different from the Generalized Normal Distribution; with 99% confidence, 77% (n=10) normal patient samples were not different from the Generalized Normal Distribution.

[0088] FIG. **74** illustrates (A) the sensitivity and the confidence level for detecting colon cancer using antibodies to the listed proteins listed as the detector and capture antibodies. CD63, CD9 are general exosome markers, EpCam is a cancer marker, and CD66 is a colon marker. The individual results are depicted in (B) for EpCam versus CD63, with 99% confidence, 95% (n=20) cancer patient samples were different from the Generalized Normal Distribution; with 99% confidence, 100% (n=6) normal patient samples were not different from the Generalized Normal Distribution; (C) for EpCam versus CD9, with 99% confidence, 90% (n=20) cancer patient samples were different from the Generalized Normal Distribution; with 99% confidence, 77% (n=6) normal patient samples were not different from the Generalized Normal Distribution; (D) for CD63 versus CD63, with 99% confidence, 60% (n=20) cancer patient samples were different from the Generalized Normal Distribution; with 99% confidence, 80% (n=6) normal patient samples were not different from the Generalized Normal Distribution; (E) for CD9 versus CD63, with 99% confidence, 90% (n=20) cancer patient samples were different from the Generalized Normal Distribution; with 99% confidence, 77% (n=6) normal patient samples were not different from the Generalized Normal Distribution; (F) for CD66 versus CD9, with 99% confidence, 90% (n=20) cancer patient samples were different from the Generalized Normal Distribution; with 99% confidence, 77% (n=6) normal patient samples were not different from the Generalized Normal Distribution.

[0089] FIG. **75** illustrates the capture of prostate cancer cells-derived exosomes from plasma with EpCam by assessing TMPRSS2-ERG expression. (A) Graduated amounts of VCAP purified exosomes were spiked into normal plasma. Exosomes were isolated using Dynal beads with either EPCAM antibody or its isotype control. RNA from the exosomes was isolated and the expression of the TMPRSS2:ERG fusion transcript was measured using qRT-PCR. (B) VCaP purified exosomes were spiked into normal plasma and then incubated with Dynal magnetic beads coated with either the EpCam or isotype control antibody. RNA was isolated directly from the Dynal beads. Equal volumes of RNA from each sample were used for RT-PCR and subsequent Taqman assays. (C) Cycle threshold (CT) differences of the SPINK1 and GAPDH transcripts between 22RV1 exosomes captured with EpCam and IgG2 isotype negative control beads. Higher CT values indicate lower transcript expression.

[0090] FIG. **76**: illustrates the top ten differentially expressed microRNAs between VCaP prostate cancer cell derived exosomes and normal plasma exosomes. VCAP cell line exosomes and exosomes from normal plasma were isolated via ultracentrifugation followed by RNA isolation. MicroRNAs were profiled using qRT-PCR analysis. Prostate cancer cell line derived exosomes have higher levels (lower CT values) of the indicated microRNAs as depicted in the bar graph (A) and table (B).

[0091] FIG. **77** depicts a bar graph of miR-21 expression with CD9 bead capture. 1 ml of plasma from prostate cancer patients, 250 ng/ml of LNCaP, or normal purified exosomes was incubated with CD9 coated Dynal beads. The RNA was isolated from the beads and the bead supernatant. One sample (#6) was also uncaptured for comparison. MiR-21 expression was measured with qRT-PCR and the mean CT values for each sample compared. CD9 capture improves the detection of miR-21 in prostate cancer samples.

[0092] FIG. **78** depicts a bar graph of miR-141 expression with CD9 bead capture. The experiment was performed as in FIG. **77**, with miR-141 expression measured with qRT-PCR instead of miR-21.

[0093] FIG. **79** depicts a table of the sensitivity and specificity for different prostate signatures. “Exosome” lists the threshold value or reference value of exosome levels, “Prostate” lists the threshold value or reference value used for prostate exosomes, “Cancer-1,” “Cancer-2,” and “Cancer-3” lists the threshold values or reference values for the three different bio-signatures for prostate cancer, the “QC-1” and “QC-2” columns list the threshold values or reference values for quality control, or reliability, and the last four columns list the specificities and sensitivities for benign prostate hyperplasia (BPH).

DETAILED DESCRIPTION

[0094] Disclosed herein are products and processes for characterizing a phenotype of an individual by analyzing exosomes. A phenotype can be any observable characteristic or trait of a subject, such as a disease or condition, a disease stage or condition stage, susceptibility to a disease or condition, prognosis of a disease stage or condition, a physiological state; or response to therapeutics. A phenotype can result from a subject’s gene expression as well as the influence of environmental factors and the interactions between the two, as well as from epigenetic modifications to nucleic acid sequences

[0095] A phenotype in a subject can be characterized by obtaining a biological sample from said subject and analyzing one or more exosomes from the sample. For example, characterizing a phenotype for a subject or individual may include detecting a disease or condition (including pre-symptomatic early stage detecting), determining the prognosis, diagnosis, or theranosis of a disease or condition, or determining the stage or progression of a disease or condition. Characterizing a phenotype can also include identifying appropriate treatments or treatment efficacy for specific diseases, conditions, disease stages and condition stages, predictions and likelihood analysis of disease progression, particularly disease recurrence, metastatic spread or disease relapse. A phenotype can also be a clinically distinct type or subtype of a condition or disease, such as a cancer or tumor. Phenotype determination can also be a determination of a physiological condition, or an assessment of organ distress or organ rejection, such as post-transplantation. The products and processes described herein allow assessment of a subject on an individual basis, which can provide benefits of more efficient and economical decisions in treatment.

[0096] The phenotype can be a disease or condition such as listed in Table 1. For example, the phenotype can be a tumor, neoplasm, or cancer. A cancer detected or assessed by products or processes described herein includes, but is not limited to, breast cancer, ovarian cancer, lung cancer, colon cancer, hyperplastic polyp, adenoma, colorectal cancer, high grade dysplasia, low grade dysplasia, prostatic hyperplasia, prostate cancer, melanoma, pancreatic cancer, brain cancer (such as a glioblastoma), hematological malignancy, hepatocellular carcinoma, cervical cancer, endometrial cancer, head and neck cancer, esophageal cancer, gastrointestinal stromal tumor (GIST), renal cell carcinoma (RCC) or gastric cancer. The colorectal cancer can be CRC Dukes B or Dukes C-D. The hematological malignancy can be B-Cell Chronic Lymphocytic Leukemia, B-Cell Lymphoma-DLBCL, B—Cell Lymphoma-DLBCL-germinal center-like, B-Cell Lymphoma-DLBCL-activated B-cell-like, and Burkitt's lymphoma. The phenotype may also be a premalignant condition, such as Barrett's Esophagus.

[0097] The phenotype can also be an inflammatory disease, immune disease, or autoimmune disease. For example, the disease may be inflammatory bowel disease (IBD), Crohn's disease (CD), ulcerative colitis (UC), pelvic inflammation, vasculitis, psoriasis, diabetes, autoimmune hepatitis, Multiple Sclerosis, Myasthenia Gravis, Type I diabetes, Rheumatoid Arthritis, Psoriasis, Systemic Lupus Erythematosis (SLE), Hashimoto's Thyroiditis, Grave's disease, Ankylosing Spondylitis Sjogrens Disease, CREST syndrome, Scleroderma, Rheumatic Disease, organ rejection, Primary Sclerosing Cholangitis, or sepsis.

[0098] The phenotype can also be a cardiovascular disease, such as atherosclerosis, congestive heart failure, vulnerable plaque, stroke, or ischemia. The cardiovascular disease or condition can be high blood pressure, stenosis, vessel occlusion or a thrombotic event.

[0099] The phenotype can also be a neurological disease, such as Multiple Sclerosis (MS), Parkinson's Disease (PD), Alzheimer's Disease (AD), schizophrenia, bipolar disorder, depression, autism, Prion Disease, Pick's disease, dementia, Huntington disease (HD), Down's syndrome, cerebrovascular disease, Rasmussen's encephalitis, viral meningitis, neurospsychiatric systemic lupus erythematosus (NPSLE), amyotrophic lateral sclerosis, Creutzfeldt-Jacob disease, Gerstmann-Straussler-Scheinker disease, transmissible spongiform encephalopathy, ischemic reperfusion damage (e.g. stroke), brain trauma, microbial infection, or chronic fatigue syndrome. The phenotype may also be a condition such as fibromyalgia, chronic neuropathic pain, or peripheral neuropathic pain.

[0100] The phenotype may also be an infectious disease, such as a bacterial, viral or yeast infection. For example, the disease or condition may be Whipple's Disease, Prion Disease, cirrhosis, methicillin-resistant *staphylococcus aureus*, HIV, hepatitis, syphilis, meningitis, malaria, tuberculosis, or influenza. Viral proteins, such as HIV or HCV-like particles can be assessed in an exosome, to characterize a viral condition.

[0101] The phenotype can also be a perinatal or pregnancy related condition (e.g. preeclampsia or preterm birth), metabolic disease or condition, such as a metabolic disease or condition associated with iron metabolism. For example, hepcidin can be assayed in an exosome to characterize an iron deficiency. The metabolic disease or condition can also be diabetes, inflammation, or a perinatal condition.

[0102] Subject

[0103] One or more phenotypes of a subject can be determined by analyzing exosomes in a biological sample obtained from the subject. A subject or patient can include, but is not limited to, mammals such as bovine, avian, canine, equine, feline, ovine, porcine, or primate animals (including humans and non-human primates). A subject may also include mammals of importance due to being endangered, such as Siberian tigers; or economic importance, such as animals raised on farms for consumption by humans, or animals of social importance to humans such as animals kept as pets or in zoos. Examples of such animals include but are not limited to: carnivores such as cats and dogs; swine including pigs, hogs and wild boars; ruminants or ungulates such as cattle, oxen, sheep, giraffes, deer, goats, bison, camels or horses. Also included are birds that are endangered or kept in zoos, as well as fowl and more particularly domesticated fowl, i.e. poultry, such as turkeys and chickens, ducks, geese, guinea fowl. Also included are domesticated swine and horses (including race horses). In addition, any animal species connected to commercial activities are also included such as those animals connected to agriculture and aquaculture and other activities in which disease monitoring, diagnosis, and therapy selection are routine practice in husbandry for economic productivity and/or safety of the food chain.

[0104] The subject can have a pre-existing disease or condition, such as cancer. Alternatively, the subject may not have any known pre-existing condition. The subject may also be non-responsive to an existing or past treatment, such as a treatment for cancer.

[0105] Samples

[0106] The biological sample obtained from the subject may be any bodily fluid. For example, the biological sample can be peripheral blood, sera, plasma, ascites, urine, cerebrospinal fluid (CSF), sputum, saliva, bone marrow, synovial fluid, aqueous humor, amniotic fluid, cerumen, breast milk, broncheoalveolar lavage fluid, semen (including prostatic fluid), Cowper's fluid or pre-ejaculatory fluid, female ejaculate, sweat, fecal matter, hair, tears, cyst fluid, pleural and peritoneal fluid, pericardial fluid, lymph, chyme, chyle, bile, interstitial fluid, menses, pus, sebum, vomit, vaginal secretions, mucosal secretion, stool water, pancreatic juice, lavage fluids from sinus cavities, bronchopulmonary aspirates or other lavage fluids. A biological sample may also include the blastocyl cavity, umbilical cord blood, or maternal circulation which may be of fetal or maternal origin. The biological sample may also be a tissue sample or biopsy, from which exosomes may be obtained. For example, if the sample is a solid sample, cells from the sample can be cultured and exosome product induced (see for example, Example 1).

[0107] Table 1 provides a list of examples of diseases, conditions, or biological states and a corresponding list of biological samples from which exosomes may be analyzed.

TABLE 1

Examples of Biological Samples for Exosome Analysis for Various Diseases. Conditions, or Biological States

Disease, Condition or Biological State	Biological Samples
Cancers/neoplasms affecting the following tissue types/bodily systems: breast, lung, ovarian, colon, rectal, prostate, pancreatic, brain, bone, connective tissue, glands, skin, lymph, nervous system, endocrine, germ cell, genitourinary, hematologic/blood, bone marrow, muscle, eye, esophageal, fat tissue, thyroid, pituitary, spinal cord, bile duct, heart, gall bladder, bladder, testes, cervical, endometrial, renal, ovarian, digestive/gastrointestinal, stomach, head and neck, liver, leukemia, respiratory/thorasic, cancers of unknown primary	Blood, serum, cerebrospinal fluid (CSF), urine, sputum, ascites, synovial fluid, semen, nipple aspirates, saliva, bronchoalveolar lavage fluid, tears, oropharyngeal washes, feces, peritoneal fluids, pleural effusion, sweat, tears, aqueous humor, pericardial fluid, lymph, chyme, chyle, bile, stool water, amniotic fluid, breast milk, pancreatic juice, cerumen, Cowper's fluid or pre-ejaculatory fluid, female ejaculate, interstitial fluid, menses, mucus, pus, sebum, vaginal lubrication, vomit
Neurodegenerative/neurological disorders: Parkinson's disease, Alzheimer's Disease and multiple sclerosis, Schizophrenia, and bipolar disorder, spasticity disorders, epilepsy	Blood, serum, CSF, urine
Cardiovascular Disease: atherosclerosis, cardiomyopathy, endocarditis, vunerable plaques, infection	Blood, serum, CSF, urine
Stroke: ischemic, intracerebral hemorrhage, subarachnoid hemorrhage, transient ischemic attacks (TIA)	Blood, serum, CSF, urine
Pain disorders: peripheral neuropathic pain and chronic neuropathic pain, and fibromyalgia,	Blood, serum, CSF, urine
Autoimmune disease: systemic and localized diseases, rheumatic disease, Lupus, Sjogren's syndrome	Blood, serum, CSF, urine, synovial fluid
Digestive system abnormalities: Barrett's esophagus, irritable bowel syndrome, ulcerative colitis, Crohn's disease, Diverticulosis and Diverticulitis, Celiac Disease	Blood, serum, CSF, urine
Endocrine disorders: diabetes mellitus, various forms of Thyroiditis,, adrenal disorders, pituitary disorders	Blood, serum, CSF, urine
Diseases and disorders of the skin: psoriasis	Blood, serum, CSF, urine, synovial fluid, tears
Urological disorders: benign prostatic hypertrophy (BPH), polycystic kidney disease, interstitial cystitis	Blood, serum, urine
Hepatic disease/injury: Cirrhosis, induced hepatotoxicity (due to exposure to natural or synthetic chemical sources)	Blood, serum, urine
Kidney disease/injury: acute, sub-acute, chronic conditions, Podocyte injury, focal segmental glomerulosclerosis	Blood, serum, urine
Endometriosis	Blood, serum, urine, vaginal fluids
Osteoporosis	Blood, serum, urine, synovial fluid
Pancreatitis	Blood, serum, urine, pancreatic juice
Asthma	Blood, serum, urine, sputum, bronchiolar lavage fluid
Allergies	Blood, serum, urine, sputum, bronchiolar lavage fluid
Prion-related diseases	Blood, serum, CSF, urine
Viral Infections: HIV/AIDS	Blood, serum, urine
Sepsis	Blood, serum, urine, tears, nasal lavage
Organ rejection/transplantation	Blood, serum, urine, various lavage fluids
Differentiating conditions: adenoma versus hyperplastic polyp, irritable bowel syndrome (IBS) versus normal, classifying Dukes stages A, B, C, and/or D of colon cancer, adenoma with low-grade hyperplasia versus high-grade hyperplasia, adenoma versus normal, colorectal cancer versus normal, IBS versus, ulcerative colitis (UC) versus Crohn's disease (CD),	Blood, serum, urine, sputum, feces, colonic lavage fluid
Pregnancy related physiological states, conditions, or affiliated diseases: genetic risk, adverse pregnancy outcomes	Maternal serum, amniotic fluid, cord blood

[0108] The biological samples may be obtained through a third party, such as a party not performing the analysis of the exosome. For example, the sample may be obtained through a clinician, physician, or other health care manager of a subject from which the sample is derived. Alternatively, the biological sample may obtained by the same party analyzing the exosomes.

[0109] The volume of the biological sample used for analyzing an exosome can be in the range of between 0.1-20 mL, such as less than about 20, 15, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 0.1 mL.

[0110] Furthermore, analysis of one or more exosomes in a biological sample can be used to determine whether an additional biological sample should be obtained for analysis. For example, analysis of one or more exosomes in a serum sample can be used to determine whether a biopsy should be obtained.

Exosomes

[0111] The exosomes from a biological sample for analysis are used to determine a phenotype. Exosomes are small vesicles that are released into the extracellular environment from a variety of different cells such as but not limited to, cells that originate from, or are derived from, the ectoderm, endoderm, or mesoderm including any such cells that have undergone genetic, environmental, and/or any other variations or alterations (e.g. Tumor cells or cells with genetic mutations). An exosome is typically created intracellularly when a segment of the cell membrane spontaneously invaginates and is ultimately exocytosed (see for example, Keller et al., *Immunol. Lett.* 107 (2): 102-8 (2006)). Exosomes can have, but not be limited to, a diameter of greater than about 10, 20, or 30 nm. They can have a diameter of about 30-1000 nm, about 30-800 nm, about 30-200 nm, or about 30-100 nm. In some embodiments, the exosomes can have, but not be limited to, a diameter of less than about 10,000 nm, 1000 nm, 800 nm, 500 nm, 200 nm, 100 nm or 50 nm. As used throughout, the term "about," when referring to a value or to an amount is meant to encompass variations in some embodiments±10% from the specified amount, as such variations are appropriate.

[0112] Exosomes may also be referred to as microvesicles, nanovesicles, vesicles, dexosomes, bleb, blebby, prostasomes, microparticles, intralumenal vesicles, endosomal-like vesicles or exocytosed vehicles. As used herein, exosomes can also include any shed membrane bound particle that is derived from either the plasma membrane or an internal membrane. Exosomes can also include cell-derived structures bounded by a lipid bilayer membrane arising from both herniated evagination (blebbing) separation and sealing of portions of the plasma membrane or from the export of any intracellular membrane-bounded vesicular structure containing various membrane-associated proteins of tumor origin, including surface-bound molecules derived from the host circulation that bind selectively to the tumor-derived proteins together with molecules contained in the exosome lumen, including but not limited to tumor-derived microRNAs or intracellular proteins. Blebs and blebbing are further described in Charras et al., *Nature Reviews Molecular and Cell Biology, Vol.* 9, No. 11, p. 730-736 (2008). Exosomes can also include membrane fragments. Circulating tumor-derived exosomes (CTEs) as referenced herein are exosomes that are shed into circulation or bodily fluids from tumor cells. CTEs, as with cell-of-origin specific exosomes, typically have unique biomarkers that permit their isolation from bodily fluids in a highly specific manner.

[0113] Exosomes can be directly assayed from the biological samples, such that the level of exosomes is determined or the one or more biomarkers of the exosomes is determined without prior isolation, purification, or concentration of the exosomes. Alternatively, exosomes may be isolated, purified, or concentrated from a sample prior to analysis.

Isolation of Exosomes

[0114] An exosome may be purified or concentrated prior to analysis. Analysis of an exosome can include quantitiating the amount one or more exosome populations of a biological sample. For example, a heterogeneous population of exosomes can be quantitated, or a homogeneous population of exosomes, such as a population of exosomes with a particular biomarker profile, a particular bio-signature, or derived from a particular cell type (cell-of-origin specific exosomes) can be isolated from a heterogeneous population of exosomes and quantitated. Analysis of an exosome can also include detecting, quantitatively or qualitatively, a particular biomarker profile or a bio-signature, of an exosome, as described below.

[0115] An exosome can be stored and archived, such as in a bio-fluid bank and retrieved for analysis as necessary. An exosome may also be isolated from a biological sample that has been previously harvested and stored from a living or deceased subject. In addition, an exosome may be isolated from a biological sample which has been collected as described in King et al., *Breast Cancer Res* 7(5): 198-204 (2005). An exosome may be isolated from an archived or stored sample. Alternatively, an exosome may be isolated from a biological sample and analyzed without storing or archiving of the sample. Furthermore, a third party may obtain or store the biological sample, or obtain or store the exosomes for analysis.

[0116] An enriched population of exosomes can be obtained from a biological sample. For example, exosomes may be concentrated or isolated from a biological sample using size exclusion chromatography, density gradient centrifugation, differential centrifugation, nanomembrane ultrafiltration, immunoabsorbent capture, affinity purification, microfluidic separation, or combinations thereof.

[0117] Size exclusion chromatography, such as gel permeation columns, centrifugation or density gradient centrifugation, and filtration methods can be used. For example, exosomes can be isolated by differential centrifugation, anion exchange and/or gel permeation chromatography (for example, as described in U.S. Pat. Nos. 6,899,863 and 6,812, 023), sucrose density gradients, organelle electrophoresis (for example, as described in U.S. Pat. No. 7,198,923), magnetic activated cell sorting (MACS), or with a nanomembrane ultrafiltration concentrator. Various combinations of isolation or concentration methods can be used.

[0118] Highly abundant proteins, such as albumin and immunoglobulin, may hinder isolation of exosomes from a biological sample. For example, exosomes may be isolated from a biological sample using a system that utilizes multiple antibodies that are specific to the most abundant proteins found in blood. Such a system can remove up to several proteins at once, thus unveiling the lower abundance species such as cell-of-origin specific exosomes.

[0119] This type of system can be used for isolation of exosomes from biological samples such as blood, cerebrospinal fluid or urine. The isolation of exosomes from a biological sample may also be enhanced by high abundant protein removal methods as described in Chromy et al. *J. Proteome Res* 2004; 3:1120-1127. In another embodiment, the isolation of exosomes from a biological sample may also be enhanced by removing serum proteins using glycopeptide capture as described in Zhang et al, *Mol Cell Proteomics* 2005; 4:144-155. In addition, exosomes from a biological sample such as urine may be isolated by differential centrifugation followed by contact with antibodies directed to cytoplasmic or anti-cytoplasmic epitopes as described in Pisitkun et al., *Proc Natl Acad Sci USA,* 2004; 101:13368-13373.

[0120] Isolation or enrichment of exosomes from biological samples can also be enhanced by use of sonication (for example, by applying ultrasound), or the use of detergents, other membrane-active agents, or any combination thereof. For example, ultrasonic energy can be applied to a potential tumor site, and without being bound by theory, release of exosomes from the tissue can be increased, allowing an enriched population of exosomes that can be analyzed or assessed from a biological sample using one or more methods disclosed herein.

Binding Agents

[0121] A binding agent is an agent that binds to an exosomal component, such as a biomarker of an exosome. The binding agent can be a capture agent. A capture agent captures the exosome by binding to an exosomal target, such as a biomarker on the exosome. For example, the capture agent can be a capture antibody that binds to an antigen on the exosome. The capture agent can be coupled to a substrate and used to isolate the exosome, such as described herein.

[0122] A binding agent can be used after exosomes are concentrated or isolated from a biological sample. For example, exosomes can first be isolated from a biological sample before exosomes with a specific biomarker are isolated using a binding agent for the biomarker. Thus, exosomes with the specific biomarker is isolated from a heterogeneous population of exosomes. Alternatively, a binding agent may be used on a biological sample comprising exosomes without a prior isolation step or concentration of exosomes. For example, a binding agent is used to isolate an exosome with a specific biomarker from a biological sample.

[0123] A binding agent can be DNA, RNA, monoclonal antibodies, polyclonal antibodies, Fabs, Fab', single chain antibodies, synthetic antibodies, aptamers (DNA/RNA), peptoids, zDNA, peptide nucleic acids (PNAs), locked nucleic acids (LNAs), lectins, synthetic or naturally occurring chemical compounds (including but not limited to drugs, labeling reagents), dendrimers, or combinations thereof. For example, the binding agent can be a capture antibody.

[0124] In some instances, a single binding agent can be employed to isolate an exosome. In other instances, a combination of different binding agents may be employed to isolate an exosome. For example, at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 50, 75 or 100 different binding agents may be used to isolate an exosome from a biological sample. Furthermore, the one or more different binding agents for an exosome can form the bio-signature of the exosome, further described below.

[0125] Different binding agents can also be used for multiplexing. For example, isolation of more than one population of exosomes (for example, exosomes from specific cell types) can be performed by isolating each exosome population with a different binding agent. Different binding agents can be bound to different particles, wherein the different particles are labeled. In another embodiment, an array comprising different binding agents can be used for multiplex analysis, wherein the different binding agents are differentially labeled or can be ascertained based on the location of the binding agent on the array. Multiplexing can be accomplished up to the resolution capability of the labels or detection method, such as described below.

[0126] The binding agent can be an antibody. For example, an exosome may be isolated using one or more antibodies specific for one or more antigens present on the exosome. For example, an exosome can have CD63 on its surface, and an antibody, or capture antibody, for CD63 can be used to isolate the exosome. Alternatively, an exosome derived from a tumor cell can express EpCam, the exosome can be isolated using an antibody for EpCam and CD63. Other antibodies for isolating exosomes can include an antibody, or capture antibody, to CD9, PSCA, TNFR, CD63, B7H3, MFG-E8, EpCam, Rab, CD81, STEAP, PCSA, PSMA, or 5T4.

[0127] The antibodies disclosed herein can be immunoglobulin molecules or immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that specifically binds an antigen and synthetic antibodies. The immunoglobulin molecules can be of any class (e.g., IgG, IgE, IgM, IgD or IgA) or subclass of immunoglobulin molecule. Antibodies include, but are not limited to, polyclonal, monoclonal, bispecific, synthetic, humanized and chimeric antibodies, single chain antibodies, Fab fragments and $F(ab')_2$ fragments, Fv or Fv' portions, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies, or epitope-binding fragments of any of the above. An antibody, or generally any molecule, "binds specifically" to an antigen (or other molecule) if the antibody binds preferentially to the antigen, and, e.g., has less than about 30%, 20%, 10%, 5% or 1% cross-reactivity with another molecule.

[0128] The binding agent can also be a polypeptide or peptide. Polypeptide is used in its broadest sense and may include a sequence of subunit amino acids, amino acid analogs, or peptidomimetics. The subunits may be linked by peptide bonds. The polypeptides may be naturally occurring, processed forms of naturally occurring polypeptides (such as by enzymatic digestion), chemically synthesized or recombinantly expressed. The polypeptides for use in the methods of the present invention may be chemically synthesized using standard techniques. The polypeptides may comprise D-amino acids (which are resistant to L-amino acid-specific proteases), a combination of D- and L-amino acids, β amino acids, or various other designer or non-naturally occurring amino acids (e.g., (β-methyl amino acids, Cα-methyl amino acids, and Nα-methyl amino acids, etc.) to convey special properties. Synthetic amino acids may include ornithine for lysine, and norleucine for leucine or isoleucine. In addition, the polypeptides can have peptidomimetic bonds, such as ester bonds, to prepare polypeptides with novel properties. For example, a polypeptide may be generated that incorporates a reduced peptide bond, i.e., $R_1—CH_2—NH—R_2$, where R_1 and R_2 are amino acid residues or sequences. A reduced peptide bond may be introduced as a dipeptide subunit. Such a polypeptide would be resistant to protease activity, and would possess an extended half-live in vivo. Polypeptides can also include peptoids (N-substituted glycines), in which the side chains are appended to nitrogen atoms along the molecule's backbone, rather than to the α-carbons, as in amino acids. Polypeptides and peptides are intended to be used interchangeably throughout this application, i.e. where the term peptide is used, it may also include polypeptides and where the term polypeptides is used, it may also include peptides.

[0129] An exosome may be isolated using a known binding agent. For example, the binding agent can be an agent that binds exosomal "housekeeping proteins," or general exosome biomarkers, such as CD63, CD9, CD81, CD82, CD37, CD53, or Rab-5b. The binding agent can also be an agent that binds to exosomes derived from specific cell types, such as tumor cells (e.g. binding agent for EpCam) or specific cell-of-origins, such as described below. For example, the binding agent used to isolate an exosome may be a binding agent for an antigen selected from FIG. **1**. The binding agent for an exosome can also be selected from those listed in FIG. **2**. For example, the binding agent can be for an antigen such as 5T4, B7H3, caveolin, CD63, CD9, E-Cadherin, MFG-E8, PSCA, PSMA, Rab-5B, STEAP, TNFR1, CD81, EpCam, CD59, or CD66. One or more binding agents, such as one or more binding agents for two or more of the antigens, can be used for isolating an exosome. The binding agent used can be selected based on the desire of isolating exosomes derived from particular cell types, or cell-of-origin specific exosomes.

[0130] A binding agent can also be linked directly or indirectly to a solid surface or substrate. A solid surface or substrate can be any physically separable solid to which a binding agent can be directly or indirectly attached including, but not limited to, surfaces provided by microarrays and wells, particles such as beads, columns, optical fibers, wipes, glass and modified or functionalized glass, quartz, mica, diazotized membranes (paper or nylon), polyformaldehyde, cellulose, cellulose acetate, paper, ceramics, metals, metalloids, semiconductive materials, quantum dots, coated beads or particles, other chromatographic materials, magnetic particles; plastics (including acrylics, polystyrene, copolymers of styrene or other materials, polypropylene, polyethylene, polybutylene, polyurethanes, TEFLON™, etc.), polysaccharides, nylon or nitrocellulose, resins, silica or silica-based materials including silicon and modified silicon, carbon, metals, inorganic glasses, plastics, ceramics, conducting polymers (including polymers such as polypyrole and polyindole); micro or nanostructured surfaces such as nucleic acid tiling arrays, nanotube, nanowire, or nanoparticulate decorated surfaces; or porous surfaces or gels such as methacrylates, acrylamides, sugar polymers, cellulose, silicates, or other fibrous or stranded polymers. In addition, as is known the art, the substrate may be coated using passive or chemically-derivatized coatings with any number of materials, including polymers, such as dextrans, acrylamides, gelatins or agarose. Such coatings can facilitate the use of the array with a biological sample.

[0131] For example, an antibody used to isolate an exosome can be bound to a solid substrate such as a well, such as commercially available plates (e.g. from Nunc, Milan Italy). Each well can be coated with the antibody. In some embodiments, the antibody used to isolate an exosome can be bound to a solid substrate such as an array. The array can have a predetermined spatial arrangement of molecule interactions, binding islands, biomolecules, zones, domains or spatial arrangements of binding islands or binding agents deposited within discrete boundaries. Further, the term array may be used herein to refer to multiple arrays arranged on a surface, such as would be the case where a surface bore multiple copies of an array. Such surfaces bearing multiple arrays may also be referred to as multiple arrays or repeating arrays.

[0132] A binding agent can also be bound to particles such as beads or microspheres. For example, an antibody specific for an exosomal component can be bound to a particle, and the antibody-bound particle is used to isolate exosomes from a biological sample. In some embodiments, the microspheres may be magnetic or fluorescently labeled. In addition, a binding agent for isolating exosomes can be a solid substrate itself. For example, latex beads, such as aldehyde/sulfate beads (Interfacial Dynamics, Portland, Oreg.) can be used.

[0133] A binding agent bound to a magnetic bead can also be used to isolate an exosome. For example, a biological sample such as serum from a patient can be collected for colon cancer screening. The sample can be incubated with anti-CCSA-3 (Colon Cancer-Specific Antigen) coupled to magnetic microbeads. A low-density microcolumn can be placed in the magnetic field of a MACS Separator and the column is then washed with a buffer solution such as Tris-buffered saline. The magnetic immune complexes can then be applied to the column and unbound, non-specific material can be discarded. The CCSA-3 selected exosomes can be recovered by removing the column from the separator and placing it on a collection tube. A buffer can be added to the column and the magnetically labeled exosomes can be released by applying the plunger supplied with the column. The isolated exosomes can be diluted in IgG elution buffer and the complex can then be centrifuged to separate the microbeads from the exosomes. The pelleted isolated cell-of-origin specific exosomes can be resuspended in buffer such as phosphate-buffered saline and quantitated. Alternatively, due to the strong adhesion force between the antibody captured cell-of-origin specific exosomes and the magnetic microbeads, a proteolytic enzyme such as trypsin can be used for the release of captured exosomes without the need for centrifugation. The proteolytic enzyme can be incubated with the antibody captured cell-of-origin specific exosomes for at least a time sufficient to release the exosomes.

[0134] A binding agent, such as an antibody, for isolating an exosome is preferably contacted with the biological sample comprising the exosome of interest for at least a time sufficient for the binding agent to bind to an exosomal component. For example, an antibody may be contacted with a biological sample for various intervals ranging from seconds days, including but not limited to, about 10 minutes, 30 minutes, 1 hour, 3 hours, 5 hours, 7 hours, 10 hours, 15 hours, 1 day, 3 days, 7 days or 10 days.

[0135] A binding agent, such as an antibody specific to an antigen listed in FIG. **1**, or a binding agent listed in FIG. **2**, can be labeled with, including but not limited to, a magnetic label, a fluorescent moiety, an enzyme, a chemiluminescent probe, a metal particle, a non-metal colloidal particle, a polymeric dye particle, a pigment molecule, a pigment particle, an electrochemically active species, semiconductor nanocrystal or other nanoparticles including quantum dots or gold particles. The label can be, but not be limited to, fluorophores, quantum dots, or radioactive labels. For example, the label can be a radioisotope (radionuclides), such as ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{32}P, ^{35}S, ^{64}Cu, ^{68}Ga, ^{86}Y, ^{99}Tc, ^{111}In, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{133}Xe, ^{177}Lu, ^{211}At, or ^{213}Bi. The label can be a fluorescent label, such as a rare earth chelate (europium chelate), fluorescein type, such as, but not limited to, FITC, 5-carboxyfluorescein, 6-carboxy fluorescein; a rhodamine type, such as, but not limited to, TAMRA; dansyl; Lissamine; cyanines; phycoerythrins; Texas Red; and analogs thereof.

[0136] A binding agent can be directly or indirectly labeled, e.g., the label is attached to the antibody through biotin-streptavidin. Alternatively, an antibody is not labeled, but is later contacted with a second antibody that is labeled after the first antibody is bound to an antigen of interest.

[0137] For example, various enzyme-substrate labels are available or disclosed (see for example, U.S. Pat. No. 4,275,149). The enzyme generally catalyzes a chemical alteration of a chromogenic substrate that can be measured using various techniques. For example, the enzyme may catalyze a color change in a substrate, which can be measured spectrophotometrically. Alternatively, the enzyme may alter the fluorescence or chemiluminescence of the substrate. Examples of enzymatic labels include luciferases (e.g., firefly luciferase and bacterial luciferase; U.S. Pat. No. 4,737,456), luciferin, 2,3-dihydrophthalazinediones, malate dehydrogenase, urease, peroxidase such as horseradish peroxidase (HRP), alkaline phosphatase (AP), β-galactosidase, glucoamylase, lysozyme, saccharide oxidases (e.g., glucose oxidase, galactose oxidase, and glucose-6-phosphate dehydrogenase), heterocyclic oxidases (such as uricase and xanthine oxidase), lactoperoxidase, microperoxidase, and the like. Examples of enzyme-substrate combinations include, but are not limited to, horseradish peroxidase (HRP) with hydrogen peroxidase as a substrate, wherein the hydrogen peroxidase oxidizes a dye precursor (e.g., orthophenylene diamine (OPD) or 3,3',5, 5'-tetramethylbenzidine hydrochloride (TMB)); alkaline phosphatase (AP) with para-nitrophenyl phosphate as chromogenic substrate; and β-D-galactosidase ((β-D-Gal) with a chromogenic substrate (e.g., p-nitrophenyl-(β-D-galactosidase) or fluorogenic substrate 4-methylumbelliferyl-β-D-galactosidase.

[0138] Depending on the method of isolation used, the binding agent may be linked to a solid surface or substrate, such as arrays, particles, wells and other substrates described above. Methods for direct chemical coupling of antibodies, to the cell surface are known in the art, and may include, for example, coupling using glutaraldehyde or maleimide activated antibodies. Methods for chemical coupling using multiple step procedures include biotinylation, coupling of trinitrophenol (TNP) or digoxigenin using for example succinimide esters of these compounds. Biotinylation can be accomplished by, for example, the use of D-biotinyl-N-hydroxysuccinimide. Succinimide groups react effectively with amino groups at pH values above 7, and preferentially between about pH 8.0 and about pH 8.5. Biotinylation can be accomplished by, for example, treating the cells with dithiothreitol followed by the addition of biotin maleimide.

[0139] Flow Cytometry

[0140] Isolation of exosomes using particles such as beads or microspheres can also be performed using flow cytometry. Flow cytometry can be used for sorting microscopic particles suspended in a stream of fluid. As particles pass through they can be selectively charged and on their exit can be deflected into separate paths of flow. It is therefore possible to separate populations from an original mix, such as a biological sample, with a high degree of accuracy and speed. Flow cytometry allows simultaneous multiparametric analysis of the physical and/or chemical characteristics of single cells flowing through an optical/electronic detection apparatus. A beam of light, usually laser light, of a single frequency (color) is directed onto a hydrodynamically focused stream of fluid. A number of detectors are aimed at the point where the stream passes through the light beam; one in line with the light beam (Forward Scatter or FSC) and several perpendicular to it (Side Scatter or SSC) and one or more fluorescent detectors.

[0141] Each suspended particle passing through the beam scatters the light in some way, and fluorescent chemicals in the particle may be excited into emitting light at a lower frequency than the light source. This combination of scattered and fluorescent light is picked up by the detectors, and by analyzing fluctuations in brightness at each detector (one for each fluorescent emission peak), it is possible to deduce various facts about the physical and chemical structure of each individual particle. FSC correlates with the cell size and SSC depends on the inner complexity of the particle, such as shape of the nucleus, the amount and type of cytoplasmic granules or the membrane roughness. Some flow cytometers have eliminated the need for fluorescence and use only light scatter for measurement.

[0142] Flow cytometers can analyze several thousand particles every second in "real time" and can actively separate out and isolate particles having specified properties. They offer high-throughput automated quantification, and separation, of the set parameters for a high number of single cells during each analysis session. Modern instruments have multiple lasers and fluorescence detectors, for example up to 4 lasers and 18 fluorescence detectors, allowing multiple labels to be used to more precisely specify a target population by their phenotype.

[0143] The data resulting from flow-cytometers can be plotted in 1 dimension to produce histograms or seen in 2 dimensions as dot plots or in 3 dimensions with newer software. The regions on these plots can be sequentially separated by a series of subset extractions which are termed gates. Specific gating protocols exist for diagnostic and clinical purposes especially in relation to hematology. The plots are often made on logarithmic scales. Because different fluorescent dye's emission spectra overlap, signals at the detectors have to be compensated electronically as well as computationally. Fluorophores for labeling biomarkers may include those described in Ormerod, *Flow Cytometry* 2nd ed., Springer-Verlag, New York (1999), and in Nida et al., *Gynecologic Oncology* 2005; 4 889-894 which is incorporated herein by reference.

[0144] Multiplexing

[0145] Different binding agents can be used for multiplexing different exosome populations. Different exosome populations can be isolated or detected using different binding agents. Each exosome population in a biological sample can be labeled with a different signaling label, such as fluorophores, quantum dots, or radioactive labels, such as described above. The label can be directly conjugated to a binding agent or indirectly used to detect a binding agent. The number of populations detected in a multiplexing assay is dependent on the resolution capability of the labels and the summation of signals, as more than two differentially labeled exosome populations that bind two or more affinity elements can produce summed signals.

[0146] Multiplexing of at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 50, 75 or 100 different exosome populations may be performed. For example, one population of exosomes specific to a cell-of-origin can be assayed along with a second population of exosomes specific to a different cell-of-origin, where each population is labeled with a different label. Alternatively, a population of exosomes with a particular biomarker or bio-signature can be assayed along with a second population of exosomes with a different biomarker or bio-signature.

[0147] In one embodiment, multiplex analysis is performed by applying a plurality of exosomes comprising more than one population of exosomes to a plurality of substrates, such as beads. Each bead is coupled to one or more capture agents. The plurality of beads is divided into subsets, where beads with the same capture agent or combination of capture agents form a subset of beads, such that each subset of beads has a different capture agent or combination of capture agents than another subset of beads. The beads can then be used to capture exosomes that comprises a component that binds to the capture agent. The different subsets can be used to capture different populations of exosomes. The captured exosomes can then be analyzed by detecting one or more biomarkers of the exosomes.

[0148] Flow cytometry can be used in combination with a particle-based or bead based assay. Multiparametric immunoassays or other high throughput detection assays using bead coatings with cognate ligands and reporter molecules with specific activities consistent with high sensitivity automation can be used. For example, beads in each subset can be differentially labeled from another subset. For example, in a particle based assay system, a binding agent or capture agent for an exosome, such as a capture antibody, can be immobilized on addressable beads or microspheres. Each binding agent for each individual binding assay (such as an immunoassay when the binding agent is an antibody) can be coupled to a distinct type of microsphere (i.e., microbead) and the binding assay reaction takes place on the surface of the microspheres. Microspheres can be distinguished by different labels, for example, a microsphere with a specific capture agent would have a different signaling label as compared to another microsphere with a different capture agent. For example, microspheres can be dyed with discrete fluorescence intensities such that the fluorescence intensity of a microsphere with a specific binding agent is different than that of another microsphere with a different binding agent.

[0149] The microsphere can be labeled or dyed with at least 2 different labels or dyes. In some embodiments, the microsphere is labeled with at least 3, 4, 5, 6, 7, 8, 9, or 10 different labels. Different microspheres in a plurality of microspheres can have more than one label or dye, wherein various subsets of the microspheres have various ratios and combinations of the labels or dyes permitting detection of different microspheres with different binding agents. For example, the various ratios and combinations of labels and dyes can permit different fluorescent intensities. Alternatively, the various ratios and combinations maybe used to generate different detection patters to identify the binding agent. The microspheres can be labeled or dyed externally or may have intrinsic fluorescence or signaling labels. Beads can be loaded separately with their appropriate binding agents and thus, different exosome populations can be isolated based on the different binding agents on the differentially labeled microspheres to which the different binding agents are coupled.

[0150] In another embodiment, multiplex analysis can be performed using a planar substrate, wherein the said substrate comprises a plurality of capture agents. The plurality of capture agents can capture one or more populations of exosomes, and one or more biomarkers of the captured exosomes detected. The planar substrate can be a microarray or other substrate as further described herein.

[0151] Novel Binding Agents

[0152] An exosome may be isolated using a binding agent for a novel component of an exosome, such as an antibody for a novel antigen specific to an exosome of interest. Novel antigens that are specific to exosomes of interest may be isolated or identified using different test compounds of known composition bound to a substrate, such as an array or a plurality of particles, which can allow a large amount of chemical/structural space to be adequately sampled using only a small fraction of the space. The novel antigen identified can also serve as a biomarker for the exosome. For example, a novel antigen identified for a cell-of-origin specific exosome can be a biomarker for that particular cell-of-origin specific exosome.

[0153] A binding agent can be identified by screening either a homogeneous or heterogeneous exosome population against test compounds. Since the composition of each test compound on the substrate surface is known, this constitutes a screen for affinity elements. For example, a test compound array comprises test compounds at specific locations on the substrate addressable locations, and can be used to identify one or more binding agents for an exosome. The test compounds can all be unrelated or related based on minor variations of a core sequence or structure. The different test compounds may include variants of a given test compound (such as polypeptide isoforms), test compounds that are structurally or compositionally unrelated, or a combination thereof.

[0154] Test compounds can be peptoids, polysaccharides, organic compounds, inorganic compounds, polymers, lipids, nucleic acids, polypeptides, antibodies, proteins, polysaccharides, or other compounds. The test compounds can be natural or synthetic. The test compounds can comprise or consist of linear or branched heteropolymeric compounds based on any of a number of linkages or combinations of linkages (e.g., amide, ester, ether, thiol, radical additions, metal coordination, etc.), dendritic structures, circular structures, cavity structures or other structures with multiple nearby sites of attachment that serve as scaffolds upon which specific additions are made. These test compounds can be spotted on the substrate or synthesized in situ, using standard methods in the art. In addition, the test compounds can be spotted or synthesized in situ in combinations in order to detect useful interactions, such as cooperative binding.

[0155] The test compounds can be polypeptides with known amino acid sequences, thus, detection a test compound binding with an exosome can lead to identification of a polypeptide of known amino sequence that can be used as a binding agent. For example, a homogenous population of exosomes can be applied to a spotted array on a slide containing between a few and 1,000,000 test polypeptides having a length of variable amino acids. The polypeptides can be attached to the surface through the C-terminus. The sequence of the polypeptides can be generated randomly from 19 amino acids, excluding cysteine. The binding reaction can include a non-specific competitor, such as excess bacterial proteins labeled with another dye such that the specificity ratio for each polypeptide binding target can be determined. The polypeptides with the highest specificity and binding can be selected. The identity of the polypeptide on each spot is known, and thus can be readily identified. Once the novel antigens specific to the homogeneous exosome population, such as a cell-of-origin specific exosome is identified, such cell-of-origin specific exosomes may subsequently be isolated using such antigens in methods described hereafter.

[0156] Arrays can also be used for identifying antibodies for isolating exosomes. Test antibodies can be attached to an array and screened against a heterogeneous population of exosomes to identify antibodies that can be used to isolate, and identify, an exosome. A homogeneous population of exosomes, such as cell-of-origin specific exosomes, can also be screened with an antibody array. Other than identifying antibodies to isolate the homogeneous population of exosomes, one or more protein biomarkers specific to the homogenous exosome population can be identified. Commercially available platforms with test antibodies pre-selected, or custom selection of test antibodies attached to the array, can be used. For example, an antibody array from Full Moon Biosystems can be screened using prostate cancer cell derived exosomes, identifying antibodies to Bcl-XL, ERCC1, Keratin 15, CD81/TAPA-1, CD9, Epithelial Specific Antigen (ESA), and Mast Cell Chymase as binding agents (see for example, FIG. **63**), and the proteins identified can be used as biomarkers for the exosomes.

[0157] An antibody or synthetic antibody to be used as a binding agent can also be identified through a peptide array. Another method is the use of synthetic antibody generation through antibody phage display. M13 bacteriophage libraries of antibodies (e.g. Fabs) are displayed on the surfaces of phage particles as fusions to a coat protein. Each phage particle displays a unique antibody and also encapsulates a vector that contains the encoding DNA. Highly diverse libraries can be constructed and represented as phage pools, which can be used in antibody selection for binding to immobilized antigens. Antigen-binding phages are retained by the immobilized antigen, and the nonbinding phages are removed by washing. The retained phage pool can be amplified by infection of an *Escherichia coli* host and the amplified pool can be used for additional rounds of selection to eventually obtain a population that is dominated by antigen-binding clones. At this stage, individual phase clones can be isolated and subjected to DNA sequencing to decode the sequences of the displayed antibodies. Through the use of phase display and other methods known in the art, high affinity designer antibodies for exosomes can be generated.

[0158] Bead-based assays can also be used to identify novel binding agents to isolate exosomes. A test antibody or peptide can be conjugated to a particle. For example, a bead can be conjugated to an antibody or peptide and used to detect and quantify the proteins expressed on the surface of a population of exosomes in order to discover and specifically select for novel antibodies that can target exosomes from specific tissue or tumor types. Any molecule of organic origin can be successfully conjugated to a polystyrene bead through use of a commercially available kit according to manufacturer's instructions. Each bead set can be colored a certain detectable wavelength and each can be linked to a known antibody or peptide which can be used to specifically measure which beads are linked to exosomal proteins matching the epitope of previously conjugated antibodies or peptides. The beads can be dyed with discrete fluorescence intensities such that each bead with a different intensity has a different binding agent as described above.

[0159] For example, a purified exosome preparation can be diluted in assay buffer to an appropriate concentration according to empirically determined dynamic range of assay. A sufficient volume of coupled beads can be prepared and approximately 1 μl of the antibody-coupled beads can be aliqouted into a well and adjusted to a final volume of approximately 50 μl. Once the antibody-conjugated beads have been added to a vacuum compatible plate, the beads can be washed to ensure proper binding conditions: An appropriate volume of exosomal preparation can then be added to each well being tested and the mixture incubated, such as for 15-18 hours. A sufficient volume of detection antibodies using detection antibody diluent solution can be prepared and incubated with the mixture for 1 hour or for as long as necessary. The beads can then be washed before the addition of detection antibody (biotin expressing) mixture composed of streptavidin phycoereythin. The beads can then be washed and vacuum aspirated several times before analysis on a suspension array system using software provided with an instrument. The identity of antigens that can be used to selectively extract the exosomes can then be elucidated from the analysis.

[0160] Assays using imaging systems can be utilized to detect and quantify proteins expressed on the surface of an exosome in order to discover and specifically select for and enrich exosomes from specific tissue or tumor types. Antibodies, peptides or cells conjugated to multiple well multiplex carbon coated plates can be used. Simultaneous measurement of many analytes in a well can be achieved through the use of capture antibodies arrayed on the patterned carbon working surface. Analytes can then be detected with antibodies labeled with reagents in electrode wells with an enhanced electro-chemiluminescent plate. Any molecule of organic origin can be successfully conjugated to the carbon coated plate. Proteins expressed on the surface of exosomes can be identified from this assay and can be used as targets to specifically select for and enrich exosomes from specific tissue or tumor types.

[0161] The binding agent can also be a novel aptamer. An aptamer for a target can be identified using systematic evolution of ligands by exponential enrichment (SELEX) (Tuerk & Gold, *Science* 249:505-510, 1990; Ellington & Szostak, *Nature* 346:818-822, 1990), such as described in U.S. Pat. No. 5,270,163. A library of nucleic acids can be contacted with a target exosome, and those nucleic acids specifically bound to the target are partitioned from the remainder of nucleic acids in the library which do not specifically bind the target. The partitioned nucleic acids are amplified to yield a ligand-enriched pool. Multiple cycles of binding, partitioning, and amplifying (i.e., selection) result in identification of one or more aptamers with the desired activity. Another method for identifying an aptamer to isolate exosomes is described in U.S. Pat. No. 6,376,19, which describes increasing or decreasing frequency of nucleic acids in a library by their binding to a chemically synthesized peptide. Modified methods, such as Laser SELEX or deSELEX as described in U.S. Patent Publication No. 20090264508 can also be used.

[0162] Microfluidics

[0163] The methods for isolating or identifying exosomes can be used in combination with microfluidic devices. The methods of isolating exosomes disclosed herein can be performed using microfluidic devices. Microfluidic devices, which may also be referred to as "lab-on-a-chip" systems, biomedical micro-electro-mechanical systems (bioMEMs), or multicomponent integrated systems, can be used for isolating, and analyzing, exosomes. Such systems miniaturize and compartmentalize processes that allow for binding of exosomes, detection of exosomal biomarkers, and other processes.

[0164] A microfluidic device can also be used for isolation of an exosome through size differential or affinity selection. For example, a microfluidic device can use one more channels for isolating an exosome from a biological sample based on size, or by using one or more binding agents for isolating an exosome, from a biological sample. A biological sample can be introduced into one or more microfluidic channels, which selectively allows the passage of exosomes. The selection can be based on a property of the exosomes, for example, size, shape, deformability, biomarker profile, or bio-signature.

[0165] Alternatively, a heterogeneous population of exosomes can be introduced into a microfluidic device, and one or more different homogeneous populations of exosomes can be obtained. For example, different channels can have different size selections or binding agents to select for different exosome populations. Thus, a microfluidic device can isolate a plurality of exosomes, wherein at least a subset of the plurality of exosomes comprises a different bio-signature from another subset of said plurality of exosomes. For example, the microfluidic device can isolate at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, or 100 different subsets of exosomes, wherein each subset of exosomes comprises a different bio-signature.

[0166] In some embodiments, the microfluidic device can comprise one or more channels that permit further enrichment or selection of exosomes. A population of exosomes that has been enriched after passage through a first channel can be introduced into a second channel, which allows the passage of the desired exosome population to be further enriched, such as through binding agents present in the second channel.

[0167] Array-based assays and bead-based assays can be used with microfluidic device. For example, the binding agent can be coupled to beads and the binding reaction between the beads and exosomes can be performed in a microfluidic device. Multiplexing can also be performed using a microfluidic device. Different compartments can comprise different binding agents for different populations of exosomes, where each population is of a different cell-of-origin specific exosome population or each population has a different bio-signature. The hybridization reaction between the microspheres and exosomes can be performed in a microfluidic device and the reaction mixture can be delivered to a detection device. The detection device, such as a dual or multiple laser detection system can be part of the microfluidic system and can use a laser to identify each bead or microsphere by its color-coding, and another laser can detect the hybridization signal associated with each bead.

[0168] Examples of microfluidic devices that may be used, or adapted for use with exosomes, include but are not limited to those described in U.S. Pat. Nos. 7,591,936, 7,581,429, 7,579,136, 7,575,722, 7,568,399, 7,552,741, 7,544,506, 7,541,578, 7,518,726, 7,488,596, 7,485,214, 7,467,928, 7,452,713, 7,452,509, 7,449,096, 7,431,887, 7,422,725, 7,422,669, 7,419,822, 7,419,639, 7,413,709, 7,411,184, 7,402,229, 7,390,463, 7,381,471, 7,357,864, 7,351,592, 7,351,380, 7,338,637, 7,329,391, 7,323,140, 7,261,824, 7,258,837, 7,253,003, 7,238,324, 7,238,255, 7,233,865, 7,229,538, 7,201,881, 7,195,986, 7,189,581, 7,189,580, 7,189,368, 7,141,978, 7,138,062, 7,135,147, 7,125,711, 7,118,910, and 7,118,661.

Cell-of-Origin and Disease-Specific Exosomes

[0169] The bindings agents disclosed herein can be used to isolate a heterogeneous population of exosomes from a sample or can be used to isolate or identify a homogeneous population of exosomes, such as cell-of-origin specific exosomes or exosomes with specific bio-signatures. A homogeneous population of exosomes, such as cell-of-origin specific exosomes, can be analyzed and used to characterize a phenotype for a subject. Cell-of-origin specific exosomes are exosomes derived from specific cell types, which can include, but are not limited to, cells of a specific tissue, cells from a specific tumor of interest or a diseased tissue of interest, circulating tumor cells, or cells of maternal or fetal origin. The exosomes may be derived from tumor cells or lung, pancreas, stomach, intestine, bladder, kidney, ovary, testis, skin, colorectal, breast, prostate, brain, esophagus, liver, placenta, or fetal cells. The isolated exosomes can also be from a particular sample type, such as urinary exosomes.

[0170] Cell-of-origin specific exosomes from a biological sample can be isolated using one or more binding agents that are specific to a cell-of-origin. Exosomes for analysis of a disease or condition can be isolated using one or more binding agents specific for biomarkers for that disease or condition.

[0171] The exosomes can be concentrated prior to isolation of cell-of-origin specific exosomes, such as through centrifugation, chromatography, or filtration, as described above, to produce a heterogeneous population of exosomes prior to isolation of cell-of-origin specific exosomes. Alternatively, the exosomes are not concentrated, or the biological sample is not enriched for exosomes, prior to isolation of cell-of-origin exosomes.

[0172] FIG. **61** illustrates a flowchart which depicts one method **100** for isolating or identifying cell-of-origin specific exosomes. First, a biological sample is obtained from a subject in step **102**. The sample can be obtained from a third party or from the same party performing the analysis. Next, cell-of-origin specific exosomes are isolated from the biological sample in step **104**. The isolated cell-of-origin specific exosomes are then analyzed in step **106** and a biomarker or bio-signature for a particular phenotype is identified in step **108**. The method may be used for a number of phenotypes. In some embodiments, prior to step **104**, exosomes are concentrated or isolated from a biological sample to product a heterogeneous population of exosomes. For example, heterogeneous population of exosomes may be isolated using centrifugation, chromatography, filtration, or other methods as described above, prior to use of one or more binding agents specific for isolating or identifying exosomes derived from specific cell types, or cell-of-origin specific exosomes.

[0173] Cell-of-origin specific exosomes can be isolated from a biological sample of a subject by employing one or more binding agents that bind with high specificity to the cell-of-origin specific exosomes. In some instances, a single binding agent can be employed to isolate cell-of-origin specific exosomes. In other instances, a combination of binding agents may be employed to isolate cell-of-origin specific exosomes. For example, at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 50, 75, or 100 different binding agents may be used to isolate cell-of-origin exosomes. Therefore, an exosome population (e.g., exosomes having the same binding agent profile) can be identified by utilizing a single or a plurality of binding agents.

[0174] One or more binding agents can be selected based on their specificity for a target antigen(s) that is specific to a cell-of-origin, tumor or disease. Non-limiting examples of antigens which may be used singularly, or in combination, to isolate a cell-of-origin specific exosome, disease specific exosome, or tumor specific exosome is shown in FIG. **1** and are also described below. The antigen may be membrane bound antigens which are accessible to binding agents. The antigen can also be a biomarker for the phenotype.

[0175] Breast Cancer

[0176] An exosome derived from a breast cancer cell can be isolated using a binding agent (e.g., antibody), that is specific for an antigen that is associated with a cell of breast cancer origin (e.g., cells of glandular or stromal origin). An exosome derived from a breast cancer cell can be isolated using an antigen including, but not limited to, BCA-225, hsp70, MART1, ER, VEGFA, Class III b-tubulin, HER2/neu (for Her2+BC), GPR30, ErbB4 (JM) isoform, MPR8, MISIIR, fragments thereof, any combination thereof, or any combination of antigens that are specific for a breast cancer cell.

[0177] Ovarian Cancer

[0178] An exosome derived from an ovarian cancer cell can be isolated using an antibody, or any other binding agent, for an antigen that is specific for a cell of ovarian cancer origin including, but not limited to, CA125, VEGFR2, HER2, MISIIR, VEGFA, CD24, fragments thereof, any combination thereof, or any combination of antigens that is specific for an ovarian cancer cell.

[0179] Lung Cancer

[0180] An exosome derived from a lung cancer cell can be isolated using an antibody, or any other binding agent, for an antigen that is specific for a cell of lung cancer origin including, but not limited to, CYFRA21-1, TPA-M, TPS, CEA, SCC-Ag, XAGE-1b, HLA Class 1, TA-MUC1, KRAS, hENT1, kinin B1 receptor, kinin B2 receptor, TSC403, HTI56, DC-LAMP, fragments thereof, any combination thereof, or any combination of antigens that is specific for a lung cancer cell.

[0181] Colon Cancer

[0182] An exosome derived from a colon cancer cell can be isolated using an antibody, or any other binding agent, for an antigen that is specific for a cell of colon cancer origin including, but not limited to, CEA, MUC2, GPA33, CEACAM5, ENFB1, CCSA-3, CCSA-4, ADAM10, CD44, NG2, ephrin B1, plakoglobin, galectin 4, RACK1, tetraspanin-8, FASL, A33, CEA, EGFR, dipeptidase 1, PTEN, Na(+)-dependent glucose transporter, UDP-glucuronosyltransferase 1A, fragments thereof, any combination thereof, or any combination of antigens that is specific for a colon cancer cell.

[0183] Prostate Cancer

[0184] An exosome derived from a prostate cancer cell can be isolated using an antibody, or any other binding agent, for an antigen that is specific for a cell of prostate cancer origin including, but not limited to, PSA, TMPRSS2, FASLG, TNFSF10, PSMA, NGEP, Il-7RI, CSCR4, CysLT1R, TRPM8, Kv1.3, TRPV6, TRPM8, PSGR, MISIIR, galectin-3, PCA3, TMPRSS2:ERG, fragments thereof, any combination thereof, or any combination of antigens that is specific for a prostate cancer cell.

[0185] Brain Cancer

[0186] An exosome derived from brain cancer cell can be isolated using an antibody, or any other binding agent, for an antigen that is specific for a cell of brain cancer origin including, but not limited to, PRMT8, BDNF, EGFR, DPPX, Elk, Densin-180, BAI2, BAI3, fragments thereof, any combination thereof, or any combination of antigens that is specific for a brain cancer cell.

[0187] Blood Cancer

[0188] An exosome derived from a hematological malignancy cell can be isolated using an antibody, or any other binding agent, for an antigen that is specific for a cell of hematological malignancy origin including, but not limited to, CD44, CD58, CD31, CD11a, CD49d, GARP, BTS, Raftlin, fragments thereof, any combination thereof, or any combination of antigens that is specific for a hematological malignancy cell.

[0189] Melanoma

[0190] An exosome derived from a melanoma cell can be isolated using an antibody, or any other binding agent, for an antigen that is specific for a cell of melanoma origin including, but not limited to, DUSP1, TYRP1, SILV, MLANA, MCAM, CD63, Alix, hsp70, meosin, p120 catenin, PGRL, syntaxin binding protein 1 &2, caveolin, fragments thereof, any combination thereof, or any combination of antigens that is specific for a melanoma cell.

[0191] Liver Cancer

[0192] An exosome derived from a hepatocellular carcinoma cell can be isolated using an antibody, or any other binding agent, for an antigen that is specific for a cell of hepatocellular carcinoma origin including, but not limited to, HBxAg, HBsAg, NLT, fragments thereof, any combination thereof, or any combination of antigens that is specific for a hepatocellular carcinoma cell.

[0193] Cervical Cancer

[0194] An exosome derived from a cervical cancer cell can be isolated using an antibody, or any other binding agent, for an antigen that is specific for a cell of cervical cancer origin including, but not limited to, MCT-1, MCT-2, MCT-4, fragments thereof, any combination thereof, or any combination of antigens that is specific for a cervical cancer cell.

[0195] Endometrial Cancer

[0196] An exosome derived from an endometrial cancer cell can be isolated using an antibody, or any other binding agent, for an antigen that is specific for a cell of endometrial cancer origin including, but not limited to, Alpha V Beta 6 integrin, fragments thereof, any combination thereof, or any combination of antigens that is specific for an endometrial cancer cell.

[0197] Psoriasis

[0198] An exosome for characterizing psoriasis can be isolated using an antibody, or any other binding agent, for an antigen that is specific for psoriasis including, but not limited to, flt-1, VPF receptors, kdr, fragments thereof, any combination thereof, or any combination of antigens that is specific to psoriasis.

[0199] Autoimmune Disease

[0200] An exosome for characterizing an autoimmune disease can be isolated using an antibody, or any other binding agent, for an antigen that is specific for an autoimmune disease including, but not limited to, Tim-2, fragments thereof, or any combination of antigens that is specific to an autoimmune disease.

[0201] Irritable Bowel Disease

[0202] An exosome for characterizing irritable bowel disease (IBD) or syndrome (IBS) can be isolated using an antibody, or any other binding agent, for an antigen that is specific for IBD or IBS including, but not limited to, IL-16, IL-1beta, IL-12, TNF-alpha, interferon-gamma, IL-6, Rantes, 11-12, MCP-1, 5HT, fragments thereof, or any combination of antigens that is specific to IBD or IBS.

[0203] Diabetes

[0204] An exosome derived from a pancreatic cell can be isolated using an antibody, or any other binding agent, for an antigen that is specific for a cell of pancreatic origin including, but not limited to, IL-6, CRP, RBP4, fragments thereof, any combination thereof, or any combination of antigens that is specific for a pancreatic cell.

[0205] Barrett's Esophagus

[0206] An exosome for characterizing Barrett's Esophagus can be isolated using an antibody, or any other binding agent, for an antigen that is specific for Barrett's Esophagus including, but not limited to, p53, MUC1, MUC6, fragments thereof, any combination thereof, or any combination of antigens that is specific to Barrett's Esophagus.

[0207] Fibromyalgia

[0208] An exosome for characterizing fibromyalgia can be isolated using an antibody, or any other binding agent, for an antigen that is specific for fibromyalgia including, but not limited to, neopterin, gp130, fragments thereof, any combination thereof, or any combination of antigens that is specific to fibromyalgia.

[0209] Prostatic Hyperplasia

[0210] An exosome derived from a benign prostatic hyperplasia (BPH) cell can be isolated using an antibody, or any other binding agent, for an antigen that is specific for a cell of BPH origin including, but not limited to, KIA1, intact fibronectin, fragments thereof, any combination thereof, or any combination of antigens that is specific for a BPH cell.

[0211] Multiple Sclerosis

[0212] An exosome for characterizing multiple sclerosis (MS) can be isolated using an antibody, or any other binding agent, for an antigen that is specific for MS including, but not limited to, B7, B7-2, CD-95 (fas), Apo-1/Fas, fragments thereof, any combination thereof, or any combination of antigens that is specific to MS.

[0213] Parkinson's Disease

[0214] An exosome for characterizing Parkinson's disease can be isolated using an antibody, or any other binding agent, for an antigen that is specific for Parkinson's disease including, but not limited to, PARK2, ceruloplasmin, VDBP, tau, DJ-1, fragments thereof, any combination thereof, or any combination of antigens that is specific to Parkinson's disease.

[0215] Rheumatic Disease

[0216] An exosome for characterizing rheumatic disease can be isolated using an antibody, or any other binding agent, for an antigen that is specific for rheumatic disease including, but not limited to, Citrulinated fibrin a-chain, CD5 antigen-like fibrinogen fragment D, CD5 antigen-like fibrinogen fragment B, TNF alpha, fragments thereof, any combination thereof, or any combination of antigens that is specific to rheumatic disease.

[0217] Alzheimer's Disease

[0218] An exosome derived from a neuron of a patient suffering from Alzheimer's disease can be further isolated using an antibody, or any other binding agent, for an antigen that including, but not limited to, APP695, APP751 or APP770, BACE1, cystatin C, amyloid β, T-tau, complement factor H or alpha-2-macroglobulin, fragments thereof, any combination thereof, or any combination of antigens that are specific for Alzheimer's.

[0219] Head and Neck Cancer

[0220] An exosome derived from a head and neck cancer cell can be isolated using an antibody, or any other binding agent, for an antigen that is specific for a cell of head and neck cancer origin including, but not limited to, EGFR, EphB4 or Ephrin B2, fragments thereof, any combination thereof, or any combination of antigens that is specific for a head and neck cancer cell.

[0221] Gastrointestinal Stromal Tumor

[0222] An exosome derived from a gastrointestinal stromal tumor (GIST) cell can be isolated using an antibody, or any other binding agent, for an antigen that is specific for a cell of GIST origin including, but not limited to, c-kit PDGFRA, NHE-3, fragments thereof, any combination thereof, or any combination of antigens that is specific for a GIST cell.

[0223] Renal Cell Carcinoma

[0224] An exosome derived from a renal cell carcinomas (RCC) cell can be isolated using an antibody, or any other binding agent, for an antigen that is specific for a cell of RCC origin including, but not limited to, c PDGFRA, VEGF, HIF 1 alpha, fragments thereof, any combination thereof, or any combination of antigens that is specific for a RCC cell.

[0225] Schizophrenia

[0226] An exosome for characterizing schizophrenia can be isolated using an antibody, or any other binding agent, for an antigen that is specific for schizophrenia including, but not limited to, ATP5B, ATP5H, ATP6V1B, DNM1, fragments thereof, any combination thereof, or any combination of antigens that is specific to schizophrenia.

[0227] Peripheral Neuropathic Pain

[0228] An exosome derived from a nerve cell of a patient suffering from peripheral neuropathic pain can be isolated using an antibody, or any other binding agent, for an antigen that is specific for peripheral neuropathic pain including, but not limited to, OX42, ED9, fragments thereof, any combination thereof, or any combination of antigens that is specific for peripheral neuropathic pain.

[0229] Chronic Neuropathic Pain

[0230] An exosome derived from a nerve cell of a patient suffering from chronic neuropathic pain can be isolated using an antibody, or any other binding agent, for an antigen that is specific for chronic neuropathic pain including, but not limited to, chemokine receptor (CCR2/4), fragments thereof, or any combination of antigens that is specific for chronic neuropathic pain.

[0231] Prion Disease

[0232] An exosome derived from a cell of a patient suffering from prion disease can be isolated using an antibody, or any other binding agent, for an antigen that is specific for prion disease including, but not limited to, PrPSc, 14-3-3 zeta, S-100, AQP4, fragments thereof, or any combination of antigens that is specific for prion disease.

[0233] Stroke

[0234] An exosome for characterizing stroke can be isolated using an antibody, or any other binding agent, for an antigen that is specific for stroke including, but not limited to, S-100, neuron specific enolase, PARK7, NDKA, ApoC-I, ApoC-III, SAA or AT-III fragment, Lp-PLA2, hs-CRP, fragments thereof, any combination thereof, or any combination of antigens that is specific to stroke.

[0235] Cardiovascular Disease

[0236] An exosome for characterizing a cardiovascular disease can be isolated using an antibody, or any other binding agent, for an antigen that is specific for a cardiovascular disease including, but not limited to, FATP6, fragments thereof, or any combination of antigens that is specific to a cardiovascular disease or cardiac cell.

[0237] Esophageal Cancer

[0238] An exosome derived from an esophageal cancer cell can be isolated using an antibody, or any other binding agent, for an antigen that is specific for a cell of esophageal cancer origin including, but not limited to, CaSR, fragments thereof, or any combination of antigens that is specific for an esophageal cancer cell.

[0239] Tuberculosis

[0240] An exosome for characterizing tuberculosis (TB) can be isolated using an antibody, or any other binding agent, for an antigen that is specific for TB including, but not limited to, antigen 60, HSP, Lipoarabinomannan, Sulfolipid, antigen of acylated trehalose family, DAT, TAT, Trehalose 6,6-dimycolate (cord-factor) antigen, fragments thereof, any combination thereof, or any combination of antigens that is specific to TB.

[0241] HIV

[0242] An exosome for characterizing HIV can be isolated using an antibody, or any other binding agent, for an antigen that is specific for HIV including, but not limited to, gp41, gp120, fragments thereof, any combination thereof, or any combination of antigens that is specific to HIV.

[0243] Autism

[0244] An exosome for characterizing autism can be isolated using an antibody, or any other binding agent, for an antigen that is specific for autism including, but not limited to, VIP, PACAP, CGRP, NT3, fragments thereof, any combination thereof, or any combination of antigens that is specific to autism.

[0245] Asthma

[0246] An exosome for characterizing asthma can be isolated using an antibody, or any other binding agent, for an antigen that is specific for asthma including, but not limited to, YKL-40, S-nitrosothiols, SSCA2, PAI, amphiregulin, periostin, fragments thereof, any combination thereof, or any combination of antigens that is specific to asthma.

[0247] Lupus

[0248] An exosome for characterizing lupus can be isolated using an antibody, or any other binding agent, for an antigen that is specific for lupus including, but not limited to, TNFR, fragments thereof, or any combination of antigens that is specific to lupus.

[0249] Cirrhosis

[0250] An exosome for characterizing cirrhosis can be isolated using an antibody, or any other binding agent, for an antigen that is specific for cirrhosis including, but not limited to, NLT, HBsAg, fragments thereof, any combination thereof, or any combination of antigens that is specific to cirrhosis.

[0251] Influenza

[0252] An exosome for characterizing influenza can be isolated using an antibody, or any other binding agent, for an antigen that is specific for influenza including, but not limited to, hemagglutinin, neurominidase, fragments thereof, any combination thereof, or any combination of antigens that is specific to influenza.

[0253] Vulnerable Plaque

[0254] An exosome for characterizing vulnerable plaque can be isolated using an antibody, or any other binding agent, for an antigen that is specific for vulnerable plaque including, but not limited to, Alpha v. Beta 3 integrin, MMP9, fragments thereof, any combination thereof, or any combination of antigens that is specific to vulnerable plaque.

[0255] A cell-of-origin specific exosome may be isolated using novel binding agents, using methods as described above. Furthermore, a cell-of-origin specific exosome can also be isolated from a biological sample using isolation methods based on cellular binding partners or binding agents of such exosomes. Such cellular binding partners can include but are not limited to peptides, proteins, RNA, DNA, apatmers, cells or serum-associated proteins that only bind to such exosomes when one or more specific biomarkers are present. Isolation of a cell-of-origin specific exosome can be carried out with a single binding partner or binding agent, or a combination of binding partners or binding agents whose singular application or combined application results in cell-of-origin specific isolation. Non-limiting examples of such binding agents are provided in FIG. 2. For example, an exosome for characterizing breast cancer can be isolated with one or more binding agents including, but not limited to, estrogen, progesterone, Herceptin (Trastuzumab), CCND1, MYC PNA, IGF-1 PNA, MYC PNA, SC4 aptamer (Ku), AII-7 aptamer (ERB2), Galectin-3, mucin-type O-glycans, L-PHA, Galectin-9, or any combination thereof.

[0256] A binding agent may also be used for isolating the cell-of-origin specific exosome based on i) the presence of antigens specific for cell-of-origin specific exosomes cells, ii) the absence of markers specific for cell-of-origin specific exosomes, or iii) expression levels of biomarkers specific for cell-of-origin specific exosomes. A heterogeneous population of exosomes is applied to a surface coated with specific binding agents designed to rule out or identify the cell-of-origin characteristics of the exosomes. Various binding agents, such as antibodies, can be arrayed on a solid surface or substrate and the heterogeneous population of exosomes is allowed to contact the solid surface or substrate for a sufficient time to allow interactions to take place. Specific binding or non-binding to given antibody locations on the array surface or substrate can then serve to identify antigen specific characteristics of the exosome population that are specific to a given cell-of-origin.

[0257] A cell-of-origin specific exosome can be enriched or isolated using one or more binding agents using a magnetic capture method, fluorescence activated cell sorting or laser cytometry as described above. Magnetic capture methods can include, but are not limited to, the use of magnetically activated cell sorter (MACS) microbeads or magnetic columns. Examples of immunoaffinity and magnetic particle methods that can be used is described in U.S. Pat. No. 4,551,435, 4,795,698, 4,925,788, 5,108,933, 5,186,827, 5,200,084 or 5,158,871. A cell-of-origin specific exosome can also be isolated following the general methods described in U.S. Pat. No. 7,399,632, by using combination of antigens specific to an exosome.

[0258] Any other method for isolating or otherwise enriching the cell-of-origin specific exosomes with respect to a biological sample may also be used in combination with the present invention. For example, size exclusion chromatography such as gel permeation columns, centrifugation or density gradient centrifugation, and filtration methods can be used in combination with the antigen selection methods described herein. The cell-of-origin specific exosomes may also be isolated following the methods described in Koga et al., *Anticancer Research,* 25:3703-3708 (2005), Taylor et al., *Gynecologic Oncology,* 110:13-21 (2008), Nanjee et al., *Clin Chem,* 2000; 46:207-223 or U.S. Pat. No. 7,232,653.

Exosome Assessment

[0259] A phenotype can be characterized for a subject by analyzing a biological sample from the subject and determining the level, amount, or concentration of one or more populations of exosomes in the sample. An exosome can be purified or concentrated prior to determining the amount of exosomes. Alternatively, the amount of exosomes can be directly assayed from a sample, without prior purification or concentration. The exosomes can be cell-of-origin specific exosomes or exosomes with a specific biomarker or combination of biomarkers. The amount of exosomes can be used to characterize a phenotype, such as a diagnosis, theranosis or prognosis of a condition or disease. The amount may be used to determine a physiological or biological state, such as pregnancy or the stage of pregnancy. The amount of exosomes can also be used to determine treatment efficacy, stage of a disease or condition, or progression of a disease or condition. For example, the amount of exosomes can be proportional to an increase in disease stage or progression.

[0260] The exosomes can be evaluated by comparing the level of exosomes with a reference level or value of exosomes. The reference value can be particular to physical or temporal endpoint. For example, the reference value can be from the same subject from whom a sample is assessed for an exosome, or the reference value can be from a representative population of samples (e.g., samples from normal subjects not exhibiting a symptom of disease). Therefore, a reference value can provide a threshold measurement which is compared to a subject sample's readout for one or more exosome populations assayed in a given sample. Such reference values may be set according to data pooled from groups of sample corresponding to a particular cohort, including but not limited to age (e.g., newborns, infants, adolescents, young, middle-aged adults, seniors and adults of varied ages), racial/ethnic groups, normal versus diseased subjects, smoker v. non-smoker, subject receiving therapy versus untreated subject, different time points of treatment for a particular individual or group of subjects similarly diagnosed or treated or combinations thereof.

[0261] A reference value may be based on samples assessed from the same subject so to provide individualized tracking. Frequent testing of a patient may provide better comparisons to the reference values previously established for a particular patient and would allow a physician to more accurately assess the patient's disease stage or progression, and to inform a better decision for treatment. The reduced intraindividual variance of exosomes levels would allow a more specific and individualized threshold to be defined for the patient. Temporal intrasubject variation allows each individual to serve as a longitudinal control for optimum analysis of disease or physiological state.

[0262] Reference values can be established for unaffected individuals (of varying ages, ethnic backgrounds and sexes) without a particular phenotype by determining the amount of exosomes in an unaffected individual. For example, a reference value for a reference population can be utilized as a baseline for detection of one or more exosome populations in a test subject. If a sample from a subject has a level or value that is similar to the reference, the subject can be identified to not have the disease, or of having a low likelihood of developing a disease.

[0263] Alternatively, reference values or levels can be established for individuals with a particular phenotype by determining the amount of one or more populations of exosomes in an individual with the phenotype. In addition, an index of values can be generated for a particular phenotype. For example, different disease stages can have different values, such as obtained from individuals with the different disease stages. A subject's value can be compared to the index and a diagnosis or prognosis of the disease can be determined, such as the disease stage or progression. In other embodiments, an index of values is generated for therapeutic efficacies. For example, the level of exosomes of individuals with a particular disease can be generated and noted what treatments were effective for the individual. The levels can be used to generate values of which is a subject's value is compared, and a treatment or therapy can be selected for the individual.

[0264] For example, a reference value can be determined for individuals unaffected with a particular cancer, by isolating exosomes with an antigen that specifically targets for the particular cancer. For example, individuals with varying stages of colorectal cancer and noncancerous polyps can be surveyed using the same techniques described for unaffected individuals and the levels of circulating exosomes for each group defined as means±standard deviations from at least two separate experiments performed in triplicate. Comparisons between these groups can be made using statistical applications such as one-way ANOVA, followed by Tukey's multiple comparisons post-test comparing each population.

[0265] Reference values can also be established for disease recurrence monitoring (or exacerbation phase in MS), or for therapeutic response monitoring.

[0266] The values can be a quantitative or qualitative value. The values can be a direct measurement of the level of exosomes (example, mass per volume), or an indirect measure, such as the amount of a specific exosomal marker. The values can be a quantitative, such as a numerical value. In other embodiments, the value is qualitiative, such as no exosomes, low level of exosomes, medium level, or high level of exosomes, or variations thereof.

[0267] The reference values can be stored in a database and used as a reference for the diagnosis, prognosis, or theranosis of a disease or condition based on the level or amount of exosomes, such as total amount of exosomes, or the amount of a specific population of exosomes, such as cell-of-origin specific exosomes or exosomes with one or more specific biomarkers.

[0268] Exosome levels may be characterized using mass spectrometry or flow cytometry. Analysis may also be carried out on exosomes by immunocytochemical staining, Western blotting, electrophoresis, chromatography or x-ray crystallography in accordance with procedures well known in the art. Exosomes may be characterized and quantitatively measured using flow cytometry as described in Clayton et al., *Journal of Immunological Methods* 2001; 163-174, which is herein incorporated by reference in its entirety. Exosome levels may be determined using binding agents as described above. For example, a binding agent to exosomes can be labeled and the label detected and used to determine the amount of exosomes in a sample. The binding agent can be bound to a substrate, such as arrays or particles, such as described above. Alternatively, the exosomes may be labeled directly.

[0269] Electrophoretic tags or eTags can also be used to determine the amount of exosomes. eTags are small fluorescent molecules linked to nucleic acids or antibodies and are designed to bind one specific nucleic acid sequence or protein, respectively. After the eTag binds its target, an enzyme is used to cleave the bound eTag from the target. The signal generated from the released eTag, called a "reporter," is proportional to the amount of target nucleic acid or protein in the sample. The eTag reporters can be identified by capillary electrophoresis. The unique charge-to-mass ratio of each eTag reporter—that is, its electrical charge divided by its molecular weight—makes it show up as a specific peak on the capillary electrophoresis readout. Thus by targeting a specific biomarker of an exosome with an eTag, the amount or level of exosomes can be determined.

[0270] The exosome levels can determined from a heterogeneous population of exosomes, such as the total population of exosomes in a sample. Alternatively, the exosomes level is determined from a homogenous population, or substantially homogenous population of exosomes, such as the level of specific cell-of-origin exosomes, such as exosomes from prostate cancer cells. In yet other embodiments, the level is determined for exosomes with a particular biomarker or combination of biomarkers, such as a biomarker specific for prostate cancer. Determining the level of exosome can be performed in conjunction with determining the biomarker or combination of biomarkers of an exosome. Alternatively, determining the amount of exosome may be performed prior to or subsequent to determining the biomarker or combination of biomarkers of the exosomes.

[0271] Determining the amount of exosomes can be assayed in a multiplexed manner. For example, determining the amount of more than one population of exosomes, such as different cell-of-origin specific exosomes or exosomes with different biomarkers or combination of biomarkers, can be performed, such as those disclosed herein.

[0272] Specificity and Sensitivity

[0273] The level of exosomes as determined using one or more processes disclosed herein can be used to characterize a phenotype with increased sensitivity and the specificity. The sensitivity can be determined by: (number of true positives)/(number of true positives+number of false negatives). The specificity can be determined by: (number of true negatives)/(number of true negatives+number of false positives).

[0274] The level of exosomes as determined using one or more processes disclosed herein can be used to characterize a phenotype with at least 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, or 70% sensitivity, such as with at least 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, or 87% sensitivity. For example, the phenotype can be characterized with at least 87.1, 87.2, 87.3, 87.4, 87.5, 87.6, 87.7, 87.8, 87.9, 88.0, or 89% sensitivity, such as with at least 90% sensitivity. The phenotype can be characterized with at least 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% sensitivity.

[0275] The phenotype of a subject can also be characterized with at least 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, or 97% specificity, such as with at least 97.1, 97.2, 97.3, 97.4, 97.5, 97.6, 97.7, 97.8, 97.8, 97.9, 98.0, 98.1, 98.2, 98.3, 98.4, 98.5, 98.6, 98.7, 98.8, 98.9, 99.0, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, 99.9 or 100% specificity.

[0276] The phenotype can also be characterized with at least 70% sensitivity and at least 80, 90, 95, 99, or 100% specificity; at least 75% sensitivity and at least 80, 90, 95, 99, or 100% specificity; at least 80% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 85% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 86% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 87% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 88% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 89% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 90% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 95% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 99% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; or at least 100% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity.

[0277] Furthermore, the confidence level for determining the specificity, sensitivity, or both, may be with at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% confidence.

Bio-Signatures

[0278] A bio-signature of an exosome from a subject can be used to characterize a phenotype. A bio-signature can reflect the particular antigens or biomarkers that are present on an exosome. In addition, a bio-signature can also reflect one or more biomarkers that are carried in an exosome. Alternatively, a bio-signature can comprise a combination of one or more antigens or biomarkers that are present on an exosome with one or more biomarkers that are detected in the exosome.

[0279] The exosome can be purified or concentrated prior to determining the bio-signature of the exosome. Alternatively, the bio-signature of the exosome can be directly assayed from a sample, without prior purification or concentration. An exosome can also be isolated prior to assaying. For example, a cell-of-origin specific exosome can be isolated and its bio-signature determined. The bio-signature is used to determine a diagnosis, prognosis, or theranosis of a disease or condition. Therefore, a bio-signature can also be used to determine treatment efficacy, stage of a disease or condition, or progression of a disease or condition. Furthermore, a bio-signature may be used to determine a physiological state, such as pregnancy.

[0280] An exosomal characteristic in and of itself can be assessed to determine a bio-signature. The exosomal characteristic can be used to diagnose, detect or determine a disease stage or progression, the therapeutic implications of a disease or condition, or characterize a physiological state. An exosomal characteristic can include, but is not limited to, the level or amount of exosomes, temporal evaluation of the variation in exosomal half-life, circulating exosomal half-life or exosomal metabolic half-life, or the activity of an exosome.

[0281] In addition, a bio-signature can also correspond to an expression level, presence, absence, mutation, variant, copy number variation, truncation, duplication, modification, or molecular association of one or more biomarkers. A biomarker may be any exosomal component and can form its own signature. For example, the biomarker may be the RNA content of the exosome, such that the RNA signature includes one or more RNA species, such as, but not limited to, mRNA, miRNA, snoRNA, snRNA, rRNAs, tRNAs, siRNA, hnRNA, shRNA, or a combination thereof. Therefore, an exosome can be assayed to determine a RNA signature.

[0282] Other biomarkers include, but are not limited to, one or more proteins or peptides (e.g., providing a protein signature), nucleic acids (e.g. RNA signature as described, or a DNA signature), lipids (e.g. lipid signature), or combinations thereof. In some embodiments, the bio-signature can also comprise the type or amount of drug or drug metabolite present in an exosome (e.g. drug signature), as such drug may be taken by a subject from which the biological sample is obtained from, resulting in an exosome carrying such drug, or metabolites of such drug.

[0283] An RNA signature or DNA signature can also include a mutational, epigenetic modification, or genetic variant analysis of the RNA or DNA present in the exosome. In addition, a protein signature can include, but is not limited to, the mutation, modification, overexpression, underexpression, presence or absence of antigens, peptides, proteins or combinations thereof.

[0284] A bio-signature of an exosome can comprise one or more miRNA signatures combined with one or more additional signatures including, but not limited to, an mRNA signature, DNA signature, protein signature, peptide signature, antigen signature, or any combination thereof. For example, the bio-signature can comprise one or more miRNA biomarkers with one or more DNA biomarkers, one or more mRNA biomarkers, one or more snoRNA biomarkers, one or more protein biomarkers, one or more peptide biomarkers, one or more antigen biomarkers, one or more antigen biomarkers, one or more lipid biomarkers, or any combination thereof.

[0285] A bio-signature can comprise a combination of one or more antigens or binding agents (such as ability to bind one or more binding agents), such as listed in FIGS. **1** and **2**, respectively. The bio-signature can further comprise one or more other biomarkers, such as, but not limited to, miRNA, DNA (e.g. single stranded DNA, complementary DNA, or noncoding DNA), or mRNA. For example, the bio-signature of an exosome can comprise a combination of one or more antigens, such as shown in FIG. **1**, one or more binding agents, such as shown in FIG. **2**, and one or more biomarkers for a condition or disease, such as listed in FIGS. **3-60**. The bio-signature can comprise one or more biomarkers, for example miRNA, with one or more antigens specific for a cancer cell (for example, as shown in FIG. **1**).

[0286] An exosome can have a bio-signature that is specific to the cell-of-origin and, as such, can be utilized to derive disease-specific or biological state specific diagnostic, prognostic or therapy-related bio-signatures representative of the cell-of-origin. An exosome may also have a bio-signature that is specific to a given disease or physiological condition that may be different from the bio-signature of the cell-of-origin, but no less important to the diagnosis, prognosis, staging, therapy-related determinations or physiological state characterization.

[0287] The bio-signature of an exosome, such as a cell-of-origin specific exosome described herein, can be used clinically in making decisions concerning treatment modalities, including therapeutic intervention, diagnostic criteria such as disease staging, disease monitoring, and disease stratification, and surveillance for detection, metastasis or recurrence or progression of disease. The bio-signature of an exosome, such as an isolated cell-of-origin specific exosome can further be used clinically to make treatment decisions, including whether to perform surgery or what treatment standards should be utilized along with surgery (e.g., either pre-surgery or post-surgery).

[0288] An exosome bio-signature can also be used in therapy related diagnostics to provide tests useful to diagnose a disease or choose the correct treatment regimen, as well as monitor a subject's response. Therapy related tests are useful to predict and assess drug response in individual subjects, i.e., to provide personalized medicine. Therapy related tests are also useful to select a subject for treatment who is particularly likely to benefit from the treatment or to provide an early and objective indication of treatment efficacy in an individual subject. For example, a treatment can be altered without the great expense of delaying beneficial treatment as well as the great financial cost of administering an ineffective drug(s).

[0289] Therapy related diagnostics are also useful in clinical diagnosis and management of a variety of diseases and disorders, which include, but are not limited to cardiovascular disease, cancer, infectious diseases, sepsis, neurological diseases, central nervous system related diseases, endovascular related diseases, and autoimmune related diseases or the prediction of drug toxicity, drug resistance or drug response. Therapy related tests may be developed in any suitable diagnostic testing format, which include, but are not limited to, e.g., immunohistochemical tests, clinical chemistry, immunoassay, cell-based technologies, nucleic acid tests or body imaging methods. Therapy related tests can further include but are not limited to, testing that aids in the determination of therapy, testing that monitors for therapeutic toxicity, or response to therapy testing. For example, a bio-signature can determine whether a particular disease or condition is resistant to a drug, and therefore, a physician need not waste valuable time with hit-and-miss treatment. Instead, to obtain early validation of a drug choice or treatment regimen, a bio-signature is determined for an exosome obtained from a subject, which then determines whether the particular subject's disease has the biomarker associated with drug resistance. Therefore, such a determination enables doctors to devote critical time as well as the patient's financial resources to effective treatments.

[0290] Moreover, an exosome bio-signature may be used to assess whether a subject is afflicted with disease, is at risk for developing disease or to assess the stage or progression of the disease. For example, a bio-signature can be used to assess whether a subject has prostate cancer (for example, FIGS. **68**, **73**) or colon cancer (for example, FIGS. **69**, **74**). Furthermore, a bio-signature can be used to determine a stage of a disease or condition, such as colon cancer (for example, FIGS. **71**, **72**).

[0291] Furthermore, determining the amount of exosomes, such a heterogeneous population of exosomes, and the amount of one or more homogeneous population of exosomes, such as a population of exosomes with the same bio-signature, can be used to characterize a phenotype. For example, determination of the total amount of exosomes in a sample (i.e. not cell-type specific) and determining the presence of one or more different cell-of-origin specific exosomes (such as cell-of-origin specific exosomes) can be used to characterize a phenotype. Threshold values, or reference values or amounts can be determined based on comparisons of normal subjects and subjects with the phenotype of interest, as further described below, and criteria based on the threshold or reference values determined. The different criteria can be used to characterize a phenotype.

[0292] For example, one criterion can be based on the amount of a heterogeneous population of exosomes in a sample. If the amount is lower than a threshold value or reference value, the criterion is met. Alternatively, the criterion can be based on whether the amount of exosomes is higher than a threshold or reference value. Another criterion can be the amount of exosomes with a specific bio-signature or biomarker. If the amount of exosomes with the specific bio-signature or biomarker is lower, or higher, than a threshold or reference value, the criterion is met. A criterion can also be based on the amount of exosomes derived from a particular cell type. If the amount is lower, or higher, than a threshold or reference value, the criterion is met. Another criterion can be based on whether the amount of exosomes derived from a cancer cell or comprising one or more cancer specific biomarkers. If the amount is lower, or higher, than a threshold or reference value, the criterion is met. A criterion can also be the reliability of the result, such as meeting a quality control measure or value.

[0293] A phenotype for a subject can be characterized based on meeting at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 criteria. For example, for the characterizing of a cancer, a number of different criteria can be used: 1) if the amount of exosomes in a sample from a subject is higher than a reference value; 2) if the amount of a cell type (ie. derived from a specific tissue or organ) specific exosomes is higher than a reference value; and 3) if the amount of exosomes with one or more cancer specific biomarkers is higher than a reference value, the subject is diagnosed with a cancer. The method can further include a quality control measure, such that the results are provided for the subject if the samples meet the quality control measure.

[0294] A bio-signature can be determined by comparing the amount of exosomes, the structure of an exosome, (using transmission electron microscopy, see for example, Hansen et al., *Journal of Biomechanics* 31, *Supplement* 1: 134-134(1) (1998), or scanning electron microscopy), or any other exosomal characteristic. Various combinations of methods and techniques or analyzing one or more exosomes can be used to determine a phenotype for a subject.

[0295] An exosome characteristic can include, but is not limited to the presence or absence, copy number, expression level, or activity level of a biomarker. The presence of a mutation (e.g., mutations which affect activity of the biomarker, such as substitution, deletion, or insertion mutations), variant, or post-translation modification of a biomarker, such as a protein biomarker, can include, but not be limited to, acylation, acetylation, phosphorylation, ubiquitination, deacetylation, alkylation, methylation, amidation, biotinylation, gamma-carboxylation, glutamylation, glycosylation, glycyation, hydroxylation, covalent attachment of heme moiety, iodination, isoprenylation, lipoylation, prenylation, GPI anchor formation, myristoylation, farnesylation, geranylgeranylation, covalent attachment of nucleotides or derivatives thereof, ADP-ribosylation, flavin attachment, oxidation, palmitoylation, pegylation, covalent attachment of phosphatidylinositol, phosphopantetheinylation, polysialylation, pyroglutamate formation, racemization of proline by prolyl isomerase, tRNA-mediation addition of amino acids such as arginylation, sulfation, the addition of a sulfate group to a tyrosine, or selenoylation of the biomarker can also be an exosomal characteristic.

[0296] The methods described above can be used to identify an exosome bio-signature that is associated with a disease, condition or physiological state.

[0297] The bio-signature can also be utilized to determine if a subject is afflicted with cancer or is at risk for developing cancer. A subject at risk of developing cancer can include those who may be predisposed or who have pre-symptomatic early stage disease.

[0298] A bio-signature can also be utilized to provide a diagnostic or theranostic determination for other diseases including but not limited to autoimmune diseases, inflammatory bowel diseases, Alzheimer's disease, Parkinson's disease, Multiple Sclerosis, sepsis or pancreatitis or any disease, conditions or symptoms listed in FIGS. **3-58**.

[0299] The bio-signature can also be used to identify a given pregnancy state from the peripheral blood, umbilical cord blood, or amniotic fluid (e.g. miRNA signature specific to Downs Syndrome) or adverse pregnancy outcome such as pre-eclampsia, pre-term birth, premature rupture of membranes, intrauterine growth restriction or recurrent pregnancy loss. The bio-signature can also be used to indicate the health of the mother, the fetus at all developmental stages, the pre-implantation embryo or a newborn.

[0300] A bio-signature can be utilized for pre-symptomatic diagnosis. Furthermore, the bio-signature can be utilized to detect disease, determine disease stage or progression, determine the recurrence of disease, identify treatment protocols, determine efficacy of treatment protocols or evaluate the physiological status of individuals related to age and environmental exposure.

[0301] Monitoring the bio-signature of an exosome can also be used to identify toxic exposures in a subject including, but not limited to, situations of early exposure or exposure to an unknown or unidentified toxic agent. Without being bound by any one specific theory for mechanism of action, exosomes are shed from damaged cells and in the process compartmentalize specific contents of the cell including both membrane components and engulfed cytoplasmic contents. Cells exposed to toxic agents/chemicals may increase exosome shedding to expel toxic agents or metabolites thereof, thus resulting in increased exosome levels. Thus, monitoring an exosome and/or bio-signature allows assessment of an individual's response to potential toxic agent(s).

[0302] Furthermore, an exosome can be used to identify states of drug-induced toxicity or the organ injured, by detecting one or more specific antigen, binding agent, biomarker, or any combination thereof of the exosome. Therefore, the exosome, or exosome bio-signature can be used to monitor an individual for acute, chronic, or occupational exposures to any number of toxic agents including, but not limited to, drugs, antibiotics, industrial chemicals, toxic antibiotic metabolites, herbs, household chemicals, and chemicals produced by other organisms, either naturally occurring or synthetic in nature.

[0303] In addition, an exosome bio-signature can be used to identify conditions or diseases, including cancers of unknown origin, also known as cancers of unknown primary (CUP). For example, an exosome may be isolated from a biological sample as previously described to arrive at a heterogeneous population of exosomes. The heterogeneous population of exosomes can then be applied to surfaces coated with specific binding agents designed to rule out or identify antigen specific characteristics of the exosome population that are specific to a given cell-of-origin. Further, as described above, the bio-signature of a specific cell-of-origin exosome can correlate with the cancerous state of cells. Compounds that inhibit cancer in a subject may cause a change, e.g., a change in bio-signature of specific cell-of-origin exosome, which can be monitored by serial isolation of a cell-of-origin exosome over time and treatment course.

[0304] Alternatively, an exosome bio-signature can be used to assess the efficacy of a therapy, e.g., chemotherapy, radiation therapy, surgery, or any other therapeutic approach useful for inhibiting cancer in a subject. In addition, an exosome bio-signature can be used in a screening assay to identify candidate or test compounds or agents (e.g., proteins, peptides, peptidomimetics, peptoids, small molecules or other drugs) that have a modulatory effect on the bio-signature of a specific cell-of-origin exosome. Compounds identified via such screening assays may be useful, for example, for modulating, e.g., inhibiting, ameliorating, treating, or preventing conditions or diseases.

[0305] For example, a bio-signature for an exosome can be obtained from a patient who is undergoing successful treatment for a particular cancer. Cells from a cancer patient not being treated with the same drug can be cultured and exosomes from the cultures obtained for determining bio-signatures. The cells can be treated with test compounds and the bio-signature of the exosomes from the cultures can be compared to the bio-signature of the exosomes obtained from the patient undergoing successful treatment. The test compounds that results in exosome bio-signatures that are similar to those of the patient undergoing successful treatment can be selected for further studies.

[0306] The bio-signature of a specific cell-of-origin exosome can also be used to monitor the influence of an agent (e.g., drug compounds) on the bio-signature in clinical trials. Monitoring an exosome bio-signature can also be used in a method of assessing the efficacy of a test compound, such as a test compound for inhibiting cancer cells.

[0307] An exosome bio-signature can also be used to determine the effectiveness of a particular therapeutic intervention (pharmaceutical or non-pharmaceutical) and to alter the intervention to 1) reduce the risk of developing adverse outcomes, 2) enhance the effectiveness of the intervention or 3) identify resistant states. Thus, in addition to diagnosing or confirming the presence of or risk for developing a disease, condition or a syndrome, the methods and compositions disclosed herein also provide a system for optimizing the treatment of a subject having such a disease, condition or syndrome. For example, a therapy-related approach to treating a disease, condition or syndrome by integrating diagnostics and therapeutics to improve the real-time treatment of a subject can be determined by identifying the bio-signature of an exosome.

[0308] Tests that identify an exosome bio-signature can be used to identify which patients are most suited to a particular therapy, and provide feedback on how well a drug is working, so as to optimize treatment regimens. For example, in pregnancy-induced hypertension and associated conditions, therapy-related diagnostics can flexibly monitor changes in important parameters (e.g., cytokine and/or growth factor levels) over time, to optimize treatment.

[0309] Within the clinical trial setting of investigational agents as defined by the FDA, MDA, EMA, USDA, and EMEA, therapy-related diagnostics as determined by a bio-signature disclosed herein, can provide key information to optimize trial design, monitor efficacy, and enhance drug safety. For instance, for trial design, therapy-related diagnostics can be used for patient stratification, determination of patient eligibility (inclusion/exclusion), creation of homogeneous treatment groups, and selection of patient samples that are optimized to a matched case control cohort. Such therapy-related diagnostic can therefore provide the means for patient efficacy enrichment, thereby minimizing the number of individuals needed for trial recruitment. For example, for efficacy, therapy-related diagnostics are useful for monitoring therapy and assessing efficacy criteria. Alternatively, for safety, therapy-related diagnostics can be used to prevent adverse drug reactions or avoid medication error and monitor compliance with the therapeutic regimen.

[0310] Therefore, an exosomal bio-signature can be used to monitor drug efficacy, determine response or resistance to a given drug, and thereby enhance drug safety. For example, in colon cancer, exosomes are typically shed from colon cancer cells and can be isolated from the peripheral blood and used to isolate one or more biomarkers (e.g., KRAS mRNA). In the case of mRNA biomarkers, the mRNA can be reverse transcribed into cDNA and sequenced (e.g., by Sanger sequencing) to determine if there are mutations present that confer resistance to a drug (e.g., cetuximab or panitumimab).

[0311] In another example, exosomes that are specifically shed from lung cancer cells are isolated from a biological sample and used to isolate a lung cancer biomarker, e.g., EGFR mRNA. The EGFR mRNA is processed to cDNA and sequenced to determine if there are EGFR mutations present that show resistance or response to specific drugs or treatments for lung cancer.

[0312] One or more exosome bio-signatures can be grouped so that information obtained about the set of bio-signatures in a particular group provides a reasonable basis for making a clinically relevant decision, such as but not limited to a diagnosis, prognosis, or management of treatment, such as treatment selection.

[0313] As with most diagnostic markers, it is often desirable to use the fewest number of markers sufficient to make a correct medical judgment. This prevents a delay in treatment pending further analysis as well inappropriate use of time and resources.

[0314] Also disclosed herein are methods of conducting retrospective analysis on samples (e.g., serum and tissue biobanks) for the purpose of correlating qualitative and quantitative properties, such as exosome bio-signatures, with clinical outcomes in terms of disease state, disease stage, progression, prognosis; therapeutic efficacy or selection; or physiological conditions. Furthermore, methods and compositions disclosed herein are utilized for conducting prospective analysis on a sample (e.g., serum and/or tissue collected from individuals in a clinical trial) for the purpose of correlating qualitative and quantitative exosome bio-signatures with clinical outcomes in terms of disease state, disease stage, progression, prognosis; therapeutic efficacy or selection; or physiological conditions can also be performed. As used herein, exosome bio-signatures can be to cell-of-origin specific exosomes. Furthermore, bio-signatures can be determined based on an exosome surface marker profile and/or exosome contents (e.g., biomarkers).

[0315] An exosome bio-signature can comprise at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 40, 50, 75, or 100 characteristics. A bio-signature with more than one exosomal characteristic, such as at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 40, 50, 75, or 100 characteristics, may provide higher sensitivity, specificity, or both, in determining a phenotype. For example, assessing a plurality of exosomal characteristics can provide increased sensitivity, specificity, or both, as compared to assessing less than a plurality of exosomal characteristics.

[0316] A bio-signature comprising more than one exosomal characteristic can be used to characterize a phenotype with at least 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, or 70% sensitivity, such as with at least 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, or 87% sensitivity. For example, the phenotype can be characterized with at least 87.1, 87.2, 87.3, 87.4, 87.5, 87.6, 87.7, 87.8, 87.9, 88.0, or 89% sensitivity, such as at least 90% sensitivity. The phenotype can be characterized with at least 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% sensitivity.

[0317] The bio-signature can be used to characterize a phenotype of a subject with at least 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, or 97% specificity, such as with at least 97.1, 97.2, 97.3, 97.4, 97.5, 97.6, 97.7, 97.8, 97.8, 97.9, 98.0, 98.1, 98.2, 98.3, 98.4, 98.5, 98.6, 98.7, 98.8, 98.9, 99.0, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, 99.9 or 100% specificity.

[0318] The phenotype can also be characterized using a bio-signature with at least 70% sensitivity and at least 80, 90, 95, 99, or 100% specificity; at least 75% sensitivity and at least 80, 90, 95, 99, or 100% specificity; at least 80% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 85% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 86% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 87% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 88% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 89% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 90% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 95% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 99% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; or at least 100% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity.

[0319] Furthermore, the confidence level for determining the specificity, sensitivity, or both, may be with at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% confidence.

Bio-Signatures: Exosomal Biomarkers

[0320] An exosome bio-signature can comprise one or more biomarkers. An exosomal biomarker can be any component present in an exosome or on the exosome, such as any nucleic acid (e.g. RNA or DNA); protein, peptide, polypeptide, antigen, lipid, carbohydrate, or proteoglycan.

[0321] The bio-signature can include the presence or absence, expression level, mutational state, genetic variant state, or any modification (such as epigentic modification, post-translation modification) of a biomarker (e.g. any one or more biomarker listed in FIGS. **1**, **3-60**). The expression level of a biomarker can be compared to a control or reference, to determine the overexpression or underexpression (or upregulation or downregulation) of a biomarker in a sample. The control or reference level can be the amount of a biomarker, such as a miRNA in a control sample, such as a sample from a subject that does not have or exhibit the condition or disease, and further described below.

[0322] The nucleic acid can be any RNA or DNA species. For example, the biomarker can be mRNA, miRNA, small nucleolar RNAs (snoRNA), small nuclear RNAs (snRNA), ribosomal RNAs (rRNA), heterogeneous nuclear RNA (hnRNA), ribosomal RNAS (rRNA), siRNA, transfer RNAs (tRNA), or shRNA. The DNA can be double-stranded DNA, single stranded DNA, complementary DNA, or noncoding DNA.

[0323] In addition, the biomarker can be a polypeptide, peptides or protein, such as the modification state, truncations, mutations, expression level (such as overexpression or underexpression as compared to a reference level), and post-translational modifications, such as described above.

[0324] An exosome bio-signature may include a number of the same type of biomarkers (e.g., two different mRNAs, each corresponding to a different gene) or one or more of different types of biomarkers (e.g. mRNAs, miRNAs, proteins, peptides, ligands, and antigens).

[0325] One or more exosome bio-signatures can comprise at least one biomarker selected from those listed in FIGS. **1**, **3-60**. A specific cell-of-origin bio-signature may include one or more biomarkers. FIGS. **3-58** depict tables which lists a number of disease or condition specific biomarkers that can be derived and analyzed from an exosome. The biomarker can also beCD24, midkine, hepcidin, TMPRSS2-ERG, PCA-3, PSA, EGFR, EGFRvIII, BRAF variant, MET, cKit, PDGFR, Wnt, beta-catenin, K-ras, H-ras, N-ras, Raf, N-myc, c-myc, IGFR, PI3K, Akt, BRCA1, BRCA2, PTEN, VEGFR-2, VEGFR-1, Tie-2, TEM-1, CD276, HER-2, HER-3, or HER-4. The biomarker can also be annexin V, CD63, Rab-5b, or caveolin, or a miRNA, such as let-7a; miR-15b; miR-16; miR-19b; miR-21; miR-26a; miR-27a; miR-92; miR-93; miR-320 or miR-20. The biomarker can also be of any gene or fragment thereof as disclosed in PCT Publication No. WO2009/100029, such as those listed in Tables 3-15.

[0326] Other biomarkers useful for assessment in methods and compositions disclosed herein can include those associated with conditions or physiological states as disclosed in Rajendran et al., *Proc Natl Acad Sci USA* 2006; 103:11172-11177, Taylor et al., *Gynecol Oncol* 2008; 110:13-21, Zhou et al., *Kidney Int* 2008; 74:613-621, Buning et al., *Immunology* 2008, Prado et al. *J Immunol* 2008; 181:1519-1525, Vella et al. (2008) *Vet Immunol Immunopathol* 124(3-4): 385-93, Gould et al. (2003). *Proc Natl Acad Sci USA* 100(19): 10592-7, Fang et al. (2007). *PLoS Biol* 5(6): e158, Chen, B. J. and R. A. Lamb (2008). *Virology* 372(2): 221-32, Bhatnagar, S, and J. S. Schorey (2007). *J Biol Chem* 282(35): 25779-89, Bhatnagar et al. (2007) *Blood* 110(9): 3234-44, Yuyama, et al. (2008). *J Neurochem* 105(1): 217-24, Gomes et al. (2007). *Neurosci Lett.* 428(1): 43-6, Nagahama et al. (2003). *Autoimmunity* 36(3): 125-31, Taylor, D. D., S. Akyol, et al. (2006). *J Immunol* 176(3): 1534-42, Peche, et al. (2006). *Am J Transplant* 6(7): 1541-50, lero, M., M. Valenti, et al. (2008). *Cell Death and Differentiation* 15: 80-88, Gesierich, S., I. Berezoversuskiy, et al. (2006), *Cancer Res* 66(14): 7083-94, Clayton, A., A. Turkes, et al. (2004). *Faseb J* 18(9): 977-9, Skriner., K. Adolph, et al. (2006). *Arthritis Rheum* 54(12): 3809-14, Brouwer, R., G. J. Pruijn, et al. (2001). *Arthritis Res* 3(2): 102-6, Kim, S. H., N. Bianco, et al. (2006). *Mol Ther* 13(2): 289-300, Evans, C. H., S. C. Ghivizzani, et al. (2000). *Clin Orthop Relat Res* (379 Suppl): S300-7, Zhang, H. G., C. Liu, et al. (2006). *J Immunol* 176(12): 7385-93, Van Niel, G., J. Mallegol, et al. (2004). *Gut* 52: 1690-1697, Fiasse, R. and O. Dewit (2007). *Expert Opinion on Therapeutic Patents* 17(12): 1423-1441(19).

[0327] A biomarker that can be derived and analyzed from an exosome includes, but is not limited to, the presence or absence, expression level, mutations (for example genetic mutations, such as deletions, translocations, duplications, nucleotide or amino acid substitutions, and the like) of miRNA (miR) and miRNA*nonsense (miR*), and other RNAs (including, but not limited to, mRNA, preRNA, preRNA, hnRNA, snRNA, siRNA, shRNA), DNA, proteins, peptides, and ligands. Any epigenetic modulation or copy number variation of a biomarker can also be analyzed. A miRNA biomarker includes not only its miRNA and microRNA*nonsense, but its precursor molecules: pri-microRNAs (pri-miRs) and pre-microRNAs (pre-miRs) are also included as biomarkers. The sequence of a miRNA can be obtained from publicly available databases such as http://www.mirbase.org/, http://www.microrna.org/, or any others available.

[0328] The one or more biomarkers analyzed from an exosome can be indicative of a particular tissue or cell of origin, disease, or physiological state, as further described below. Furthermore, the presence, absence or expression level of one or more of the biomarkers described herein can be correlated to a phenotype of a subject, including a disease, condition, prognosis or drug efficacy. The specific biomarker and bio-signature set forth below constitute non-inclusive examples for each of the diseases, condition comparisons, conditions, and/or physiological states. Furthermore, the one or more biomarker assessed for a phenotype can be a cell-of-origin specific exosome, such as those described above.

[0329] The one or more miRNAs used to characterize a phenotype may be selected from those disclosed in PCT Publication No. WO2009/036236. For example, one or more miRNAs listed in Tables I-VI (FIGS. **6-11**) can be used to characterize colon adenocarcinoma, colorectal cancer, prostate cancer, lung cancer, breast cancer, b-cell lymphoma, pancreatic cancer, diffuse large BCL cancer, CLL, bladder cancer, renal cancer, hypoxia-tumor, uterine leiomyomas, ovarian cancer, hepatitis C virus-associated hepatocellular carcinoma, ALL, Alzheimer's disease, myelofibrosis, myelofibrosis, polycythemia vera, thrombocythemia, HIV, or HIV-I latency, as further described herein.

[0330] The one or more miRNAs can be detected in plasma exosomes. The one or more miRNAs can be miR-223, miR-484, miR-191, miR-146a, miR-016, miR-026a, miR-222, miR-024, miR-126, and miR-32. One or more miRNAs can also be detected in PBMC. The one or more miRNAs can be miR-223, miR-150, miR-146b, miR-016, miR-484, miR-146a, miR-191, miR-026a, miR-019b, or miR-020a. The one or more miRNAs can be used to characterize a particular disease or condition. For example, for the disease bladder cancer, one or more miRNAs can be detected, such as miR-223, miR-26b, miR-221, miR-103-1, miR-185, miR-23b, miR-203, miR-17-5p, miR-23a, miR-205 or any combination thereof. The one or more miRNAs may be upregulated or overexpressed.

[0331] In some embodiments, the one or more miRNAs is used to characterize hypoxia-tumor. The one or more miRNA may be miR-23, miR-24, miR-26, miR-27, miR-103, miR-107, miR-181, miR-210, or miR-213, and may be upregulated. One or more miRNAs can also be used to characterize uterine leiomyomas. For example, the one or more miRNAs used to characterize a uterine leiomyoma may be a let-7 family member, miR-21, miR-23b, miR-29b, or miR-197. The miRNA can be upregulated.

[0332] Myelofibrosis can also be characterized by one or more miRNAs, such as miR-190, which can be upregulated; miR-31, miR-150 and miR-95, which can be downregulated, or any combination thereof. Furthermore, myelofibrosis, polycythemia vera or thrombocythemia can also be characterized by detecting one or more miRNAs, such as, but not limited to, miR-34a, miR-342, miR-326, miR-105, miR-149, miR-147, or any combination thereof. The one or more miRNAs may be down-regulated.

[0333] Other examples of phenotypes that can be characterized by assessing an exosome for one or more biomarkers are further described herein.

[0334] The one or more biomarkers can be detected by a probe. A probe can comprise of an oligonucleotide, such as DNA or RNA, an aptamer, monoclonal antibody, polyclonal antibody, Fabs, Fab', single chain antibody, synthetic antibody, peptoid, zDNA, peptide nucleic acid (PNA), locked nucleic acid (LNA), lectin, synthetic or naturally occurring chemical compound (including but not limited to a drug or labeling reagent), dendrimer, or any combination thereof. The probe can be directly detected, for example by being directly labeled, or be indirectly detected, such as through a labeing reagent. The probe can selectively hybridize to a biomarker. For example, a probe that is an oligonucleotide can selectively hybridize to a miRNA biomarker.

[0335] Breast Cancer

[0336] Breast cancer specific biomarkers can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNA, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **3**.

[0337] One or more breast cancer specific biomarker can be assessed to provide a breast cancer specific exosome bio-signature. For example, the bio-signature can comprise one or more overexpressed miRs, including but not limited to, miR-21, miR-155, miR-206, miR-122a, miR-210, miR-21, miR-21, miR-155, miR-206, miR-122a, miR-210, or miR-21, or any combination thereof.

[0338] The bio-signature can also comprise one or more underexpressed miRs such as, but not limited to, let-7, miR-10b, miR-125a, miR-125b, miR-145, miR-143, miR-145, miR-16, let-7, let-7, let-7, miR-10b, miR-125a, miR-125b, or miR-145, or any combination thereof.

[0339] The mRNAs that may be analyzed can include, but are not limited to, ER, PR, HER2, MUC1, or EGFR, or any combination thereof. Mutations including, but not limited to, those related to KRAS, B-Raf, or CYP2D6, or any combination thereof can also be used as specific biomarkers from exosomes for breast cancer. In addition, a protein, ligand, or peptide that can be used as biomarkers from exosomes that are specific to breast cancer includes, but are not limited to, hsp70, MART-1, TRP, HER2, hsp70, MART-1, TRP, HER2, ER, PR, Class III b-tubulin, or VEGFA, or any combination thereof. Furthermore the snoRNA that can be used as an exosomal biomarker for breast cancer include, but are not limited to, GAS5. The gene fusion ETV6-NTRK3 can also be used a biomarker for breast cancer.

[0340] Also provided herein is an isolated exosome comprising one or more breast cancer specific biomarkers, such as ETV6-NTRK3, or biomarkers listed in FIG. **3** and in FIG. **1** for breast cancer. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more breast cancer specific biomarkers, such as ETV6-NTRK3, or biomarkers listed in FIG. **3** and in FIG. **1** for breast cancer. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for breast cancer specific exosomes or exosomes comprising one or more breast cancer specific biomarkers, such as ETV6-NTRK3, or biomarkers listed in FIG. **3** and in FIG. **1** for breast cancer.

[0341] One or more breast cancer specific biomarkers, such as ETV6-NTRK3, or biomarkers listed in FIG. **3** and in FIG. **1** for breast cancer can also be detected by one or more systems disclosed herein, for characterizing a breast cancer. For example, a detection system can comprise one or more probes to detect one or more breast cancer specific biomarkers, such as ETV6-NTRK3, or biomarkers listed in FIG. **3** and in FIG. **1** for breast cancer, of one or more exosomes of a biological sample.

[0342] Ovarian Cancer

[0343] Ovarian cancer specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **4**, and can be used to create a ovarian cancer specific exosome bio-signature. For example, the bio-signature can comprise one or more overexpressed miRs, such as, but not limited to, miR-200a, miR-141, miR-200c, miR-200b, miR-21, miR-141, miR-200a, miR-200b, miR-200c, miR-203, miR-205, miR-214, miR-199", or miR-215, or any combination thereof. The bio-signature can also comprise one or more underexpressed miRs such as, but not limited to, miR-199a, miR-140, miR-145, miR-100, miR-let-7 cluster, or miR-125b-1, or any combination thereof. The one or more mRNAs that may be analyzed can include, but are not limited to, ERCC1, ER, TOPO1, TOP2A, AR, PTEN, HER2/neu, CD24 or EGFR, or any combination thereof.

[0344] A biomarker mutation for ovarian cancer that can be assessed in an exosome includes, but is not limited to, a mutation of KRAS, mutation of B-Raf, or any combination of mutations specific for ovarian cancer. The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, VEGFA, VEGFR2, or HER2, or any combination thereof. Furthermore, an exosome isolated or assayed can be ovarian cancer cell specific, or derived from ovarian cancer cells.

[0345] Also provided herein is an isolated exosome comprising one or more ovarian cancer specific biomarkers, such as CD24, those listed in FIG. **4** and in FIG. **1** for ovarian cancer. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more ovarian cancer specific biomarkers, such as CD24, those listed in FIG. **4** and in FIG. **1** for ovarian cancer. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for ovarian cancer specific exosomes or exosomes comprising one or more ovarian cancer specific biomarkers, such as CD24, those listed in FIG. **4** and in FIG. **1** for ovarian cancer.

[0346] One or more ovarian cancer specific biomarkers, such as CD24, those listed in FIG. **4** and in FIG. **1** for ovarian cancer can also be detected by one or more systems disclosed herein, for characterizing an ovarian cancer. For example, a detection system can comprise one or more probes to detect one or more ovarian cancer specific biomarkers, such as CD24, those listed in FIG. **4** and in FIG. **1** for ovarian cancer, of one or more exosomes of a biological sample.

[0347] Lung Cancer

[0348] Lung cancer specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **5**, and can be used to create a lung cancer specific exosome bio-signature.

[0349] The bio-signature can comprise one or more overexpressed miRs, such as, but not limited to, miR-21, miR-205, miR-221 (protective), let-7a (protective), miR-137 (risky), miR-372 (risky), or miR-122a (risky), or any combination thereof. The bio-signature can comprise one or more upregulated or overexpressed miRNAs, such as miR-17-92, miR-19a, miR-21, miR-92, miR-155, miR-191, miR-205 or miR-210; one or more downregulated or underexpressed miRNAs, such as miR-let-7, or any combination thereof.

[0350] The one or more mRNAs that may be analyzed can include, but are not limited to, EGFR, PTEN, RRM1, RRM2, ABCB1, ABCG2, LRP, VEGFR2, VEGFR3, class III b-tubulin, or any combination thereof.

[0351] A biomarker mutation for lung cancer that can be assessed in an exosome includes, but is not limited to, a mutation of EGFR, KRAS, B-Raf, UGT1A1, or any combination of mutations specific for lung cancer. The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, KRAS, hENT1, or any combination thereof.

[0352] The biomarker can also be midkine (MK or MDK). Furthermore, an exosome isolated or assayed can be lung cancer cell specific, or derived from lung cancer cells.

[0353] Also provided herein is an isolated exosome comprising one or more lung cancer specific biomarkers, such as RLF-MYCL1, TGF-ALK, or CD74-ROS1, or those listed in FIG. **5** and in FIG. **1** for lung cancer. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more lung cancer specific biomarkers, such as RLF-MYCL1, TGF-ALK, or CD74-ROS1, or those listed in FIG. **5** and in FIG. **1** for lung cancer. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for lung cancer specific exosomes or exosomes comprising one or more lung cancer specific biomarkers, such as RLF-MYCL1, TGF-ALK, or CD74-ROS1, or those listed in FIG. **5** and in FIG. **1** for lung cancer.

[0354] One or more lung cancer specific biomarkers, such as RLF-MYCL1, TGF-ALK, or CD74-ROS1, or those listed in FIG. **5** and in FIG. **1** for lung cancer can also be detected by one or more systems disclosed herein, for characterizing a lung cancer. For example, a detection system can comprise one or more probes to detect one or more lung cancer specific biomarkers, such as RLF-MYCL1, TGF-ALK, or CD74-ROS1, or those listed in FIG. **5** and in FIG. **1** for lung cancer, of one or more exosomes of a biological sample.

[0355] Colon Cancer

[0356] Colon cancer specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **6**, and can be used to create a colon cancer specific exosome bio-signature. For example, the bio-signature can comprise one or more overexpressed miRs, such as, but not limited to, miR-24-1, miR-29b-2, miR-20a, miR-10a, miR-32, miR-203, miR-106a, miR-17-5p, miR-30c, miR-223, miR-126, miR-128b, miR-21, miR-24-2, miR-99b, miR-155, miR-213, miR-150, miR-107, miR-191, miR-221, miR-20a, miR-510, miR-92, miR-513, miR-19a, miR-21, miR-20, miR-183, miR-96, miR-135b, miR-31, miR-21, miR-92, miR-222, miR-181b, miR-210, miR-20a, miR-106a, miR-93, miR-335, miR-338, miR-133b, miR-346, miR-106b, miR-153a, miR-219, miR-34a, miR-99b, miR-185, miR-223, miR-211, miR-135a, miR-127, miR-203, miR-212, miR-95, or miR-17-5p, or any combination thereof. The bio-signature can also comprise one or more underexpressed miRs such as miR-143, miR-145, miR-143, miR-126, miR-34b, miR-34c, let-7, miR-9-3, miR-34a, miR-145, miR-455, miR-484, miR-101, miR-145, miR-133b, miR-129, miR-124a, miR-30-3p, miR-328, miR-106a, miR-17-5p, miR-342, miR-192, miR-1, miR-34b, miR-215, miR-192, miR-301, miR-324-5p, miR-30a-3p, miR-34c, miR-331, or miR-148b, or any combination thereof.

[0357] The one or more biomarker can be an upregulated or overexpressed miRNA, such as miR-20a, miR-21, miR-106a, miR-181b or miR-203, for characterizing a colon adenocarcinoma. The one or more biomarker can be used to characterize a colorectal cancer, such as an upregulated or overexpressed miRNA selected from the group consisting of: miR-19a, miR-21, miR-127, miR-31, miR-96, miR-135b and miR-183, a downregulated or underexpressed miRNA, such as miR-30c, miR-133a, mir143, miR-133b or miR-145, or any combination thereof.

[0358] The one or more mRNAs that may be analyzed can include, but are not limited to, EFNB1, ERCC1, HER2, VEGF, or EGFR, or any combination thereof. A biomarker mutation for colon cancer that can be assessed in an exosome includes, but is not limited to, a mutation of EGFR, KRAS, VEGFA, B-Raf, APC, or p53, or any combination of mutations specific for colon cancer. The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, AFRs, Rabs, ADAM10, CD44, NG2, ephrin-B1, MIF, b-catenin, Junction, plakoglobin, glalectin-4, RACK1, tetrspanin-8, FasL, TRAIL, A33, CEA, EGFR, dipeptidase 1, hsc-70, tetraspanins, ESCRT, TS, PTEN, or TOPO1, or any combination thereof. Furthermore, an exosome isolated or assayed can be colon cancer cell specific, or derived from colon cancer cells.

[0359] Also provided herein is an isolated exosome comprising one or more colon cancer specific biomarkers, such as listed in FIG. **6** and in FIG. **1** for colon cancer. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more colon cancer specific biomarkers, such as listed in FIG. **6** and in FIG. **1** for colon cancer. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for colon cancer specific exosomes or exosomes comprising one or more colon cancer specific biomarkers, such as listed in FIG. **6** and in FIG. **1** for colon cancer.

[0360] One or more colon cancer specific biomarkers, such as listed in FIG. **6** and in FIG. **1** for colon cancer can also be detected by one or more systems disclosed herein, for characterizing a colon cancer. For example, a detection system can comprise one or more probes to detect one or more colon cancer specific biomarkers, such as listed in FIG. **6** and in FIG. **1** for colon cancer, of one or more exosomes of a biological sample.

[0361] Adenoma Versus Hyperplastic Polyp

[0362] Adenoma versus hyperplastic polyp specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, or any combination thereof, such as listed in FIG. **7**, and can be used to create an adenoma versus hyperplastic polyp specific exosome bio-signature. For example, the one or more mRNAs that may be analyzed can include, but are not limited to, ABCA8, KIAA1199, GCG, MAMDC2, C2orf32, 229670_at, IGF1, PCDH7, PRDX6, PCNA, COX2, or MUC6, or any combination thereof.

[0363] A biomarker mutation to distinguish for adenoma versus hyperplastic polyp that can be assessed in an exosome includes, but is not limited to, a mutation of KRAS, mutation of B-Raf, or any combination of mutations specific for distinguishing between adenoma versus hyperplastic polyp. The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, hTERT.

[0364] Also provided herein is an isolated exosome comprising one or more specific biomarkers for distinguishing between an adenoma and a hyperplastic polyp, such as listed in FIG. **7**. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more specific biomarkers for distinguishing between an adenoma and a hyperplastic polyp, such as listed in FIG. **7**. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for having one or more specific biomarkers for distinguishing between an adenoma and a hyperplastic polyp, such as listed in FIG. **7**.

[0365] One or more specific biomarkers for distinguishing between an adenoma and a hyperplastic polyp, such as listed in FIG. **7** can also be detected by one or more systems disclosed herein, for distinguishing between an adenoma and a hyperplastic polyp. For example, a detection system can comprise one or more probes to detect one or more specific biomarkers for distinguishing between an adenoma and a hyperplastic polyp, such as listed in FIG. **7**, of one or more exosomes of a biological sample.

[0366] Irritable Bowel Disease (IBD)

[0367] IBD versus normal biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **8**, and can be used to create a IBD versus normal specific exosome bio-signature. For example, the one or more mRNAs that may be analyzed can include, but are not limited to, REG1A, MMP3, or any combination thereof.

[0368] Also provided herein is an isolated exosome comprising one or more specific biomarkers for distinguishing between IBD and a normal sample, such as listed in FIG. **8**. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more specific biomarkers for distinguishing between IBD and a normal sample, such as listed in FIG. **8**. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for having one or more specific biomarkers for distinguishing between IBD and a normal sample, such as listed in FIG. **8**.

[0369] One or more specific biomarkers for distinguishing between IBD and a normal sample, such as listed in FIG. **8** can also be detected by one or more systems disclosed herein, for distinguishing between IBD and a normal sample. For example, a detection system can comprise one or more probes to detect one or more specific biomarkers for distinguishing between IBD and a normal sample, such as listed in FIG. **8**, of one or more exosomes of a biological sample.

[0370] Adenoma Versus Colorectal Cancer (CRC)

[0371] Adenoma versus CRC specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **9**, and can be used to create a Adenoma versus CRC specific exosome bio-signature. For example, the one or more mRNAs that may be analyzed can include, but are not limited to, GREM1, DDR2, GUCY1A3, TNS1, ADAMTS1, FBLN1, FLJ38028, RDX, FAM129A, ASPN, FRMD6, MCC, RBMS1, SNA12, MEIS1, DOCK10, PLEKHC1, FAM126A, TBC1D9, VWF, DCN, ROBO1, MSRB3, LATS2, MEF2C, IGFBP3, GNB4, RCN3, AKAP12, RFTN1, 226834_at, COL5A1, GNG2, NR3C1*, SPARCL1, MAB21L2, AXIN2, 236894_at, AEBP1, AP1S2, C10orf56, LPHN2, AKT3, FRMD6, COL15A1, CRYAB, COL14A1, LOC286167, QKI, WWTR1, GNG11, PAPPA, or ELDT1, or any combination thereof.

[0372] Also provided herein is an isolated exosome comprising one or more specific biomarkers for distinguishing between an adenoma and a CRC, such as listed in FIG. **9**. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more specific biomarkers for distinguishing between an adenoma and a CRC, such as listed in FIG. **9**. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for having one or more specific biomarkers for distinguishing between an adenoma and a CRC, such as listed in FIG. **9**.

[0373] One or more specific biomarkers for distinguishing between an adenoma and a CRC, such as listed in FIG. **9** can also be detected by one or more systems disclosed herein, for distinguishing between an adenoma and a CRC. For example, a detection system can comprise one or more probes to detect one or more specific biomarkers for distinguishing between an adenoma and a CRC, such as listed in FIG. **9**, of one or more exosomes of a biological sample.

[0374] IBD Versus CRC

[0375] IBD versus CRC specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **10**, and can be used to create a IBD versus CRC specific exosome bio-signature. For example, the one or more mRNAs that may be analyzed can include, but are not limited to, 227458_at, INDO, CXCL9, CCR2, CD38, RARRES3, CXCL10, FAM26F, TNIP3, NOS2A, CCRL1, TLR8, IL18BP, FCRL5, SAMD9L, ECGF1, TNFSF13B, GBPS, or GBP1, or any combination thereof.

[0376] Also provided herein is an isolated exosome comprising one or more specific biomarkers for distinguishing between IBD and a CRC, such as listed in FIG. **10**. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more specific biomarkers for distinguishing between IBD and a CRC, such as listed in FIG. **10**. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for having one or more specific biomarkers for distinguishing between IBD and a CRC, such as listed in FIG. **10**.

[0377] One or more specific biomarkers for distinguishing between IBD and a CRC, such as listed in FIG. **10** can also be detected by one or more systems disclosed herein, for distinguishing between IBD and a CRC. For example, a detection system can comprise one or more probes to detect one or more specific biomarkers for distinguishing between IBD and a CRC, such as listed in FIG. **10**, of one or more exosomes of a biological sample.

[0378] CRC Dukes B Versus Dukes C-D

[0379] CRC Dukes B versus Dukes C-D specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **11**, and can be used to create a CRC D-B versus C-D specific exosome bio-signature. For example, the one or more mRNAs that may be analyzed can include, but are not limited to, TMEM37*, IL33, CA4, CCDC58, CLIC6, VERSUSNL1, ESPN, APCDD1, C13orf18, CYP4X1, ATP2A3, LOC646627, MUPCDH, ANPEP, C1orf115, HSD3B2, GBA3, GABRB2, GYLTL1B, LYZ, SPC25, CDKN2B, FAM89A, MOGAT2, SEMA6D, 229376_at, TSPAN5, IL6R, or SLC26A2, or any combination thereof.

[0380] Also provided herein is an isolated exosome comprising one or more specific biomarkers for distinguishing between CRC Dukes B and a CRC Dukes C-D, such as listed in FIG. **11**. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more specific biomarkers for distinguishing between CRC Dukes B and a CRC Dukes C-D, such as listed in FIG. **11**. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for having one or more specific biomarkers for distinguishing between CRC Dukes B and a CRC Dukes C-D, such as listed in FIG. **11**.

[0381] One or more specific biomarkers for distinguishing between CRC Dukes B and a CRC Dukes C-D, such as listed in FIG. **11** can also be detected by one or more systems disclosed herein, for distinguishing between CRC Dukes B and a CRC Dukes C-D. For example, a detection system can comprise one or more probes to detect one or more specific biomarkers for distinguishing between CRC Dukes B and a CRC Dukes C-D, such as listed in FIG. **11**, of one or more exosomes of a biological sample.

[0382] Adenoma with Low Grade Dysplasia Versus Adenoma with High Grade Dysplasia

[0383] Adenoma with low grade dysplasia versus adenoma with high grade dysplasia specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **12**, and can be used to create an adenoma low grade dysplasia versus adenoma high grade dysplasia specific exosome bio-signature. For example, the one or mRNAs that may be analyzed can include, but are not limited to, SI, DMBT1, CFI*, AQP1, APOD, TNFRSF17, CXCL10, CTSE, IGHA1, SLC9A3, SLC7A1, BATF2, SOCS1, DOCK2, NOS2A, HK2, CXCL2, IL15RA, POU2AF1, CLEC3B, ANI3BP, MGC13057, LCK*, C4BPA, HOXC6, GOLT1A, C2orf32, IL10RA, 240856_at, SOCS3, MEIS3P1, HIPK1, GLS, CPLX1, 236045_x_at, GALC, AMN, CCDC69, CCL28, CPA3, TRIB2, HMGA2, PLCL2, NR3C1, EIF5A, LARP4, RP5-1022P6.2, PHLDB2, FKBP1B, INDO, CLDN8, CNTN3, PBEF1, SLC16A9, CDC25B, TPSB2, PBEF1, ID4, GJB5, CHN2, LIMCH1, or CXCL9, or any combination thereof.

[0384] Also provided herein is an isolated exosome comprising one or more specific biomarkers for distinguishing between adenoma with low grade dysplasia and adenoma with high grade dysplasia, such as listed in FIG. **12**. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more specific biomarkers for distinguishing between adenoma with low grade dysplasia and adenoma with high grade dysplasia, such as listed in FIG. **12**. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for having one or more specific biomarkers for distinguishing between adenoma with low grade dysplasia and adenoma with high grade dysplasia, such as listed in FIG. **12**.

[0385] One or more specific biomarkers for distinguishing between adenoma with low grade dysplasia and adenoma with high grade dysplasia, such as listed in FIG. **12** can also be detected by one or more systems disclosed herein, for distinguishing between adenoma with low grade dysplasia and adenoma with high grade dysplasia. For example, a detection system can comprise one or more probes to detect one or more specific biomarkers for distinguishing between adenoma with low grade dysplasia and adenoma with high grade dysplasia, such as listed in FIG. **12**, of one or more exosomes of a biological sample.

[0386] Ulcerative Colitis (UC) Versus Crohn's Disease (CD)

[0387] Ulcerative colitis (UC) versus Crohn's disease (CD) specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **13**, and can be used to create a UC versus CD specific exosome bio-signature. For example, the one or more mRNAs that may be analyzed can include, but are not limited to, IFITM1, IFITM3, STAT1, STAT3, TAP1, PSME2, PSMB8, HNF4G, KLF5, AQP8, APT2B1, SLC16A, MFAP4, CCNG2, SLC44A4, DDAH1, TOB1, 231152_at, MKNK1, CEACAM7*, 1562836_at, CDC42SE2, PSD3, 231169_at, IGL@*, GSN, GPM6B, CDV3*, PDPK1, ANP32E, ADAM9, CDH1, NLRP2, 215777_at, OSBPL1, VNN1, RABGAP1L, PHACTR2, ASH1L, 213710_s_at, CDH1, NLRP2, 215777_at, OSBPL1, VNN1, RABGAP1L, PHACTR2, ASH1, 213710_s_at, ZNF3, FUT2, IGHA1, EDEM1, GPR171, 229713_at, LOC643187, FLVCR1, SNAP23*, ETNK1, LOC728411, POSTN, MUC12, HOXA5, SIGLEC1, LARP5, PIGR, SPTBN1, UFM1, C6orf62, WDR90, ALDH1A3, F2RL1, IGHV1-69, DUOX2, RAB5A, or CP, or any combination thereof can also be used as specific biomarkers from exosomes for UC versus CD.

[0388] A biomarker mutation for distinguishing UC versus CD that can be assessed in an exosome includes, but is not limited to, a mutation of CARD15, or any combination of mutations specific for distinguishing UC versus CD. The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, (P)ASCA.

[0389] Also provided herein is an isolated exosome comprising one or more specific biomarkers for distinguishing between UC and CD, such as listed in FIG. **13**. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more specific biomarkers for distinguishing between UC and CD, such as listed in FIG. **13**. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for having one or more specific biomarkers for distinguishing between UC and CD, such as listed in FIG. **13**.

[0390] One or more specific biomarkers for distinguishing between UC and CD, such as listed in FIG. **13** can also be detected by one or more systems disclosed herein, for distinguishing between UC and CD. For example, a detection system can comprise one or more probes to detect one or more specific biomarkers for distinguishing between UC and CD, such as listed in FIG. **13**, of one or more exosomes of a biological sample.

[0391] Hyperplastic Polyp

[0392] Hyperplastic polyp versus normal specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **14**, and can be used to create a hyperplastic polyp versus normal specific exosome bio-signature. For example, the one or more mRNAs that may be analyzed can include, but are not limited to, SLC6A14, ARHGEF10, ALS2, IL1RN, SPRy4, PTGER3, TRIM29, SERPINB5, 1560327 at, ZAK, BAG4, TRIB3, TTL, FOXQ1, or any combination.

[0393] Also provided herein is an isolated exosome comprising one or more hyperplastic polyp specific biomarkers, such as listed in FIG. **14**. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more hyperplastic polyp specific biomarkers, such as listed in FIG. **14**. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for hyperplastic polyp specific exosomes or exosomes comprising one or more hyperplastic polyp specific biomarkers, such as listed in FIG. **14**.

[0394] One or more hyperplastic polyp specific biomarkers, such as listed in FIG. **14** can also be detected by one or more systems disclosed herein, for characterizing a hyperplastic polyp. For example, a detection system can comprise one or more probes to detect one or more listed in FIG. **14**. One or more hyperplastic specific biomarkers, such as listed in FIG. **14**, of one or more exosomes of a biological sample.

[0395] Adenoma with Low Grade Dysplasia Versus Normal

[0396] Adenoma with low grade dysplasia versus normal specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **15**, and can be used to create an adenoma low grade dysplasia versus normal specific exosome bio-signature. For example, the RNAs that may be analyzed can include, but are not limited to, UGT2A3, KLK11, KIAA1199, FOXQ1, CLDN8, ABCA8, or PYY, or any combination thereof and can be used as specific biomarkers from exosomes for Adenoma low grade dysplasia versus normal. Furthermore, the snoRNA that can be used as an exosomal biomarker for adenoma low grade dysplasia versus normal can include, but is not limited to, GAS5.

[0397] Also provided herein is an isolated exosome comprising one or more specific biomarkers for distinguishing between adenoma with low grade dysplasia and normal, such as listed in FIG. **15**. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more specific biomarkers for distinguishing between adenoma with low grade dysplasia and normal, such as listed in FIG. **15**. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for having one or more specific biomarkers for distinguishing between adenoma with low grade dysplasia and normal, such as listed in FIG. **15**.

[0398] One or more specific biomarkers for distinguishing between adenoma with low grade dysplasia and normal, such as listed in FIG. **15** can also be detected by one or more systems disclosed herein, for distinguishing between adenoma with low grade dysplasia and normal. For example, a detection system can comprise one or more probes to detect one or more specific biomarkers for distinguishing between adenoma with low grade dysplasia and normal, such as listed in FIG. **15**, of one or more exosomes of a biological sample.

[0399] Adenoma Versus Normal

[0400] Adenoma versus normal specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **16**, and can be used to create an Adenoma versus normal specific exosome bio-signature. For example, the one or more mRNAs that may be analyzed can include, but are not limited to, KIAA1199, FOXQ1, or CA7, or any combination thereof. The protein, ligand, or peptide that can be used as a biomarker from exosomes that is specific to adenoma versus. normal can include, but is not limited to, Clusterin.

[0401] Also provided herein is an isolated exosome comprising one or more specific biomarkers for distinguishing between adenoma and normal, such as listed in FIG. **16**. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more specific biomarkers for distinguishing between adenoma and normal, such as listed in FIG. **16**. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for having one or more specific biomarkers for distinguishing between adenoma and normal, such as listed in FIG. **16**.

[0402] One or more specific biomarkers for distinguishing between adenoma and normal, such as listed in FIG. **16** can also be detected by one or more systems disclosed herein, for distinguishing between adenoma and normal. For example, a detection system can comprise one or more probes to detect one or more specific biomarkers for distinguishing between adenoma and normal, such as listed in FIG. **16**, of one or more exosomes of a biological sample.

[0403] CRC Versus Normal

[0404] CRC versus normal specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **17**, and can be used to create a CRC versus normal specific exosome bio-signature. For example, the one or mRNAs that may be analyzed can include, but are not limited to, VWF, IL8, CHI3L1, S100A8, GREM1, or ODC, or any combination thereof and can be used as specific biomarkers from exosomes for CRC versus normal.

[0405] A biomarker mutation for CRC versus normal that can be assessed in an exosome includes, but is not limited to, a mutation of KRAS, BRAF, APC, MSH2, or MLH1, or any combination of mutations specific for distinguishing between CRC versus normal. The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, cytokeratin 13, calcineurin, CHK1, clathrin light chain, phospho-ERK, phospho-PTK2, or MDM2, or any combination thereof.

[0406] Also provided herein is an isolated exosome comprising one or more specific biomarkers for distinguishing between CRC and normal, such as listed in FIG. **17**. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more specific biomarkers for distinguishing between CRC and normal, such as listed in FIG. **17**. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for having one or more specific biomarkers for distinguishing between CRC and normal, such as listed in FIG. **17**.

[0407] One or more specific biomarkers for distinguishing between CRC and normal, such as listed in FIG. **17** can also be detected by one or more systems disclosed herein, for distinguishing between CRC and normal. For example, a detection system can comprise one or more probes to detect one or more specific biomarkers for distinguishing between CRC and normal, such as listed in FIG. **17**, of one or more exosomes of a biological sample.

[0408] Benign Prostatic Hyperplasia (BPH)

[0409] Benign prostatic hyperplasia (BPH) specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **18**, and can be used to create a BPH specific exosome bio-signature. The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, intact fibronectin.

[0410] Also provided herein is an isolated exosome comprising one or more BPH specific biomarkers, such as listed in FIG. **18** and in FIG. **1** for BPH. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more BPH specific biomarkers, such as listed in FIG. **18** and in FIG. **1** for BPH. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for BPH specific exosomes or exosomes comprising one or more BPH specific biomarkers, such as listed in FIG. **18** and in FIG. **1** for BPH.

[0411] One or more BPH specific biomarkers, such as listed in FIG. **18** and in FIG. **1** for BPH, can also be detected by one or more systems disclosed herein, for characterizing a BPH. For example, a detection system can comprise one or more probes to detect one more BPH specific biomarkers, such as listed in FIG. **18** and in FIG. **1** for BPH, of one or more exosomes of a biological sample.

[0412] Prostate Cancer

[0413] Prostate cancer specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **19**, and can be used to create a prostate cancer specific exosome bio-signature. For example, a bio-signature for prostate cancer can comprise miR-9, miR-21, miR-141, miR-370, miR-200b, miR-210, miR-155, or miR-196a. In some embodiments, the bio-signature can comprise one or more overexpressed miRs, such as, but not limited to, miR-202, miR-210, miR-296, miR-320, miR-370, miR-373, miR-498, miR-503, miR-184, miR-198, miR-302c, miR-345, miR-491, miR-513, miR-32, miR-182, miR-31, miR-26a-1/2, miR-200c, miR-375, miR-196a-1/2, miR-370, miR-425, miR-425, miR-194-1/2, miR-181a-1/2, miR-34b, let-71, miR-188, miR-25, miR-106b, miR-449, miR-99b, miR-93, miR-92-1/2, miR-125a, or miR-141, or any combination thereof.

[0414] The bio-signature can also comprise one or more underexpressed miRs such as, but not limited to, let-7a, let-7b, let-7c, let-7d, let-7g, miR-16, miR-23a, miR-23b, miR-26a, miR-92, miR-99a, miR-103, miR-125a, miR-125b, miR-143, miR-145, miR-195, miR-199, miR-221, miR-222, miR-497, let-7f, miR-19b, miR-22, miR-26b, miR-27a, miR-27b, miR-29a, miR-29b, miR-30_5p, miR-30c, miR-100, miR-141, miR-148a, miR-205, miR-520h, miR-494, miR-

490, miR-133a-1, miR-1-2, miR-218-2, miR-220, miR-128a, miR-221, miR-499, miR-329, miR-340, miR-345, miR-410, miR-126, miR-205, miR-7-1/2, miR-145, miR-34a, miR-487, or let-7b, or any combination thereof. The bio-signature can comprise upregulated or overexpressed miR-21, down-regulated or underexpressed miR-15a, miR-16-1, miR-143 or miR-145, or any combination thereof.

[0415] The one or more mRNAs that may be analyzed can include, but are not limited to, AR, PCA3, or any combination thereof and can be used as specific biomarkers from exosomes for prostate cancer.

[0416] The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, FASLG or TNFSF10 or any combination thereof. Furthermore, an exosome isolated or assayed can be prostate cancer cell specific, or derived from prostate cancer cells. Furthermore, the snoRNA that can be used as an exosomal biomarker for prostate cancer can include, but is not limited to, U50. Examples of prostate cancer bio-signatures are further described below.

[0417] Also provided herein is an isolated exosome comprising one or more prostate cancer specific biomarkers, such as ACSL3-ETV1, C15ORF21-ETV1, FLJ35294-ETV1, HERV-ETV1, TMPRSS2-ERG, TMPRSS2-ETV1/4/5, TMPRSS2-ETV4/5, SLC5A3-ERG, SLC5A3-ETV1, SLC5A3-ETV5 or KLK2-ETV4, or those listed in FIGS. **19**, **60** and in FIG. **1** for prostate cancer. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more prostate cancer specific biomarkers such as ACSL3-ETV1, C15ORF21-ETV1, FLJ35294-ETV1, HERV-ETV1, TMPRSS2-ERG, TMPRSS2-ETV1/4/5, TMPRSS2-ETV4/5, SLC5A3-ERG, SLC5A3-ETV1, SLC5A3-ETV5 or KLK2-ETV4, or those listed in FIGS. **19**, **60** and in FIG. **1** for prostate cancer. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for prostate cancer specific exosomes or exosomes comprising one or more prostate cancer specific biomarkers, such as ACSL3-ETV1, C15ORF21-ETV1, FLJ35294-ETV1, HERV-ETV1, TMPRSS2-ERG, TMPRSS2-ETV1/4/5, TMPRSS2-ETV4/5, SLC5A3-ERG, SLC5A3-ETV1, SLC5A3-ETV5 or KLK2-ETV4, or those listed in FIGS. **19**, **60** and in FIG. **1** for prostate cancer.

[0418] One or more prostate cancer specific biomarkers, such as ACSL3-ETV1, C15ORF21-ETV1, FLJ35294-ETV1, HERV-ETV1, TMPRSS2-ERG, TMPRSS2-ETV1/4/5, TMPRSS2-ETV4/5, SLC5A3-ERG, SLC5A3-ETV1, SLC5A3-ETV5 or KLK2-ETV4, or those listed in FIGS. **19**, **60** and in FIG. **1** for prostate cancer can also be detected by one or more systems disclosed herein, for characterizing a prostate cancer. For example, a detection system can comprise one or more probes to detect one or more prostate cancer specific biomarkers, such as ACSL3-ETV1, C15ORF21-ETV1, FLJ35294-ETV1, HERV-ETV1, TMPRSS2-ERG, TMPRSS2-ETV1/4/5, TMPRSS2-ETV4/5, SLC5A3-ERG, SLC5A3-ETV1, SLC5A3-ETV5 or KLK2-ETV4, or those listed in FIGS. **19**, **60** and in FIG. **1** for prostate cancer, of one or more exosomes of a biological sample.

[0419] Melanoma

[0420] Melanoma specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **20**, and can be used to create a melanoma specific exosome bio-signature. For example, the bio-signature can comprise one or more over-expressed miRs, such as, but not limited to, miR-19a, miR-144, miR-200c, miR-211, miR-324-5p, miR-331, or miR-374, or any combination thereof. The bio-signature can also comprise one or more underexpressed miRs such as, but not limited to, miR-9, miR-15a, miR-17-3p, miR-23b, miR-27a, miR-28, miR-29b, miR-30b, miR-31, miR-34b, miR-34c, miR-95, miR-96, miR-100, miR-104, miR-105, miR-106a, miR-107, miR-122a, miR-124a, miR-125b, miR-127, miR-128a, miR-128b, miR-129, miR-135a, miR-135b, miR-137, miR-138, miR-139, miR-140, miR-141, miR-149, miR-154, miR-154#3, miR-181a, miR-182, miR-183, miR-184, miR-185, miR-189, miR-190, miR-199, miR-199b, miR-200a, miR-200b, miR-204, miR-213, miR-215, miR-216, miR-219, miR-222, miR-224, miR-299, miR-302a, miR-302b, miR-302c, miR-302d, miR-323, miR-325, let-7a, let-7b, let-7d, let-7e, or let-7g, or any combination thereof.

[0421] The one or more mRNAs that may be analyzed can include, but are not limited to, MUM-1, beta-catenin, or Nop/5/Sik, or any combination thereof and can be used as specific biomarkers from exosomes for melanoma.

[0422] A biomarker mutation for melanoma that can be assessed in an exosome includes, but is not limited to, a mutation of CDK4 or any combination of mutations specific for melanoma. The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, DUSP-1, Alix, hsp70, Gib2, Gia, moesin, GAPDH, malate dehydrogenase, p120 catenin, PGRL, syntaxin-binding protein 1 & 2, septin-2, or WD-repeat containing protein 1, or any combination thereof. The snoRNA that can be used as an exosomal biomarker for melanoma include, but are not limited to, H/ACA (U1071), SNORA11D, or any combination thereof. Furthermore, an exosome isolated or assayed can be melanoma cell specific, or derived from melanoma cells.

[0423] Also provided herein is an isolated exosome comprising one or more melanoma specific biomarkers, such as listed in FIG. **20** and in FIG. **1** for melanoma. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more melanoma specific biomarkers, such as listed in FIG. **20** and in FIG. **1** for melanoma. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for melanoma specific exosomes or exosomes comprising one or more melanoma specific biomarkers, such as listed in FIG. **20** and in FIG. **1** for melanoma.

[0424] One or more melanoma specific biomarkers, such as listed in FIG. **20** and in FIG. **1** for melanoma can also be detected by one or more systems disclosed herein, for characterizing a melanoma. For example, a detection system can comprise one or more probes to detect one or more cancer specific biomarkers, such as listed in FIG. **20** and in FIG. **1** for melanoma, of one or more exosomes of a biological sample.

[0425] Pancreatic Cancer

[0426] Pancreatic cancer specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **21**, and can be used to create a pancreatic cancer specific exosome bio-signature. For example, the bio-signature can comprise one or more overexpressed miRs, such as, but not limited to, miR-221, miR-181a, miR-155, miR-210, miR-213, miR-181b, miR-222, miR-181b-2, miR-21, miR-181b-1, miR-220, miR-181d, miR-223, miR-100-1/2, miR-125a, miR-143, miR-10a, miR-146, miR-99, miR-100, miR-199a-1, miR-10b, miR-199a-2, miR-221, miR-181a, miR-155, miR-210, miR-213, miR-181b, miR-222, miR-181b-2, miR-21, miR-181b-1, miR-181c, miR-220, miR-181d, miR-223, miR-100-1/2, miR-125a, miR-143, miR-10a, miR-146, miR-99, miR-100, miR-199a-1, miR-10b, miR-199a-2, miR-107, miR-103, miR-103-2, miR-125b-1, miR-205, miR-23a, miR-221, miR-424, miR-301, miR-100, miR-376a, miR-125b-1, miR-21, miR-16-1, miR-181a, miR-181c, miR-92, miR-15, miR-155, let-7f-1, miR-212, miR-107, miR-024-1/2, miR-18a, miR-31, miR-93, miR-224, or let-7d, or any combination thereof.

[0427] The bio-signature can also comprise one or more underexpressed miRs such as, but not limited to, miR-148a, miR-148b, miR-375, miR-345, miR-142, miR-133a, miR-216, miR-217 or miR-139, or any combination thereof. The one or more mRNAs that may be analyzed can include, but are not limited to, PSCA, Mesothelin, or Osteopontin, or any combination thereof and can be used as specific biomarkers from exosomes for pancreatic cancer.

[0428] A biomarker mutation for pancreatic cancer that can be assessed in an exosome includes, but is not limited to, a mutation of KRAS, CTNNLB1, AKT, NCOA3, or B-RAF, or any combination of mutations specific for pancreatic cancer. The biomarker can also be BRCA2, PALB2, or p16. Furthermore, an exosome isolated or assayed can be pancreatic cancer cell specific, or derived from pancreatic cancer cells.

[0429] Also provided herein is an isolated exosome comprising one or more pancreatic cancer specific biomarkers, such as listed in FIG. **21**. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more pancreatic cancer specific biomarkers, such as listed in FIG. **21**. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for pancreatic cancer specific exosomes or exosomes comprising one or more pancreatic cancer specific biomarkers, such as listed in FIG. **21**.

[0430] One or more pancreatic cancer specific biomarkers, such as listed in FIG. **21**, can also be detected by one or more systems disclosed herein, for characterizing a pancreatic cancer. For example, a detection system can comprise one or more probes to detect one or more pancreatic cancer specific biomarkers, such as listed in FIG. **21**, of one or more exosomes of a biological sample.

[0431] Brain Cancer

[0432] Brain cancer (including, but not limited to, gliomas, glioblastomas, meinigiomas, acoustic neuroma/schwannomas, medulloblastoma) specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **22**, and can be used to create a brain cancer specific exosome bio-signature. For example, the bio-signature can comprise one or more overexpressed miRs, such as, but not limited to miR-21, miR-10b, miR-130a, miR-221, miR-125b-1, miR-125b-2, miR-9-2, miR-21, miR-25, or miR-123, or any combination thereof.

[0433] The bio-signature can also comprise one or more underexpressed miRs such as, but not limited to, miR-128a, miR-181c, miR-181a, or miR-181b, or any combination thereof. The one or more mRNAs that may be analyzed include, but are not limited to, MGMT, which can be used as specific biomarker from exosomes for brain cancer. The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, EGFR.

[0434] Also provided herein is an isolated exosome comprising one or more brain cancer specific biomarkers, such as GOPC-ROS1, or those listed in FIG. **22** and in FIG. **1** for brain cancer. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more brain cancer specific biomarkers, such as GOPC-ROS1, or those listed in FIG. **22** and in FIG. **1** for brain cancer. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for brain cancer specific exosomes or exosomes comprising one or more brain cancer specific biomarkers, such as GOPC-ROS1, or those listed in FIG. **22**. and in FIG. **1** for brain cancer.

[0435] One or more brain cancer specific biomarkers, such as listed in FIG. **22** and in FIG. **1** for brain cancer, can also be detected by one or more systems disclosed herein, for characterizing a brain cancer. For example, a detection system can comprise one or more probes to detect one or more brain cancer specific biomarkers, such as GOPC-ROS1, or those listed in FIG. **22** and in FIG. **1** for brain cancer, of one or more exosomes of a biological sample.

[0436] Psoriasis

[0437] Psoriasis specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **23**, and can be used to create a psoriasis specific exosome bio-signature. For example, the bio-signature can comprise one or more overexpressed miRs, such as, but not limited to, miR-146b, miR-20a, miR-146a, miR-31, miR-200a, miR-17-5p, miR-30e-5p, miR-141, miR-203, miR-142-3p, miR-21, or miR-106a, or any combination thereof. The bio-signature can also comprise one or more underexpressed miRs such a, but not limited to, miR-125b, miR-99b, miR-122a, miR-197, miR-100, miR-381, miR-518b, miR-524, let-7e, miR-30c, miR-365, miR-133b, miR-10a, miR-133a, miR-22, miR-326, or miR-215, or any combination thereof.

[0438] The one or more mRNAs that may be analyzed can include, but are not limited to, IL-20, VEGFR-1, VEGFR-2, VEGFR-3, or EGR1, or any combination thereof and can be used as specific biomarkers from exosomes for psoriasis. A biomarker mutation for psoriasis that can be assessed in an exosome includes, but is not limited to, a mutation of MGST2, or any combination of mutations specific for psoriasis.

[0439] Also provided herein is an isolated exosome comprising one or more psoriasis specific biomarkers, such as listed in FIG. **23** and in FIG. **1** for psoriasis. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more psoriasis specific biomarkers, such as listed in FIG. **23** and in FIG. **1** for psoriasis. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for psoriasis specific exosomes or exosomes comprising one or more psoriasis specific biomarkers, such as listed in FIG. **23** and in FIG. **1** for psoriasis.

[0440] One or more psoriasis specific biomarkers, such as listed in FIG. **23** and in FIG. **1** for psoriasis, can also be detected by one or more systems disclosed herein, for characterizing psoriasis. For example, a detection system can comprise one or more probes to detect one or more psoriasis specific biomarkers, such as listed in FIG. **23** and in FIG. **1** for psoriasis, of one or more exosomes of a biological sample.

[0441] Cardiovascular Disease (CVD)

[0442] CVD specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **24**, and can be used to create a CVD specific exosome bio-signature. For example, the bio-signature can comprise one or more overexpressed miRs, such as, but not limited to, miR-195, miR-208, miR-214, let-7b, let-7c, let-7e, miR-15b, miR-23a, miR-24, miR-27a, miR-27b, miR-93, miR-99b, miR-100, miR-103, miR-125b, miR-140, miR-145, miR-181a, miR-191, miR-195, miR-199a, miR-320, miR-342, miR-451, or miR-499, or any combination thereof.

[0443] The bio-signature can also comprise one or more underexpressed miRs such as, but not limited to, miR-1, miR-10a, miR-17-5p, miR-19a, miR-19b, miR-20a, miR-20b, miR-26b, miR-28, miR-30e-5p, miR-101, miR-106a, miR-126, miR-222, miR-374, miR-422b, or miR-423, or any combination thereof. The mRNAs that may be analyzed can include, but are not limited to, MRP14, CD69, or any combination thereof and can be used as specific biomarkers from exosomes for CVD.

[0444] A biomarker mutation for CVD that can be assessed in an exosome includes, but is not limited to, a mutation of MYH7, SCN5A, or CHRM2, or any combination of mutations specific for CVD.

[0445] The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, CK-MB, cTnI (cardiac troponin), CRP, BPN, IL-6, MCSF, CD40, CD40L, or any combination thereof. Furthermore, an exosome isolated or assayed can be a CVD cell specific, or derived from cardiac cells.

[0446] Also provided herein is an isolated exosome comprising one or more CVD specific biomarkers, such as listed in FIG. **24** and in FIG. **1** for CVD. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more CVD specific biomarkers, such as listed in FIG. **24** and in FIG. **1** for CVD. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for CVD specific exosomes or exosomes comprising one or more CVD specific biomarkers, such as listed in FIG. **24** and in FIG. **1** for CVD.

[0447] One or more CVD specific biomarkers, such as listed in FIG. **24** and in FIG. **1** for CVD, can also be detected by one or more system's disclosed herein, for characterizing a CVD. For example, a detection system can comprise one or more probes to detect one or more CVD specific biomarkers, such as listed in FIG. **24** and in FIG. **1** for CVD, of one or more exosomes of a biological sample.

[0448] Blood Cancers

[0449] Hematological malignancies specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **25**, and can be used to create a hematological malignancies specific exosome bio-signature. For example, the one or more mRNAs that may be analyzed can include, but are not limited to, HOX11, TAL1, LY1, LMO1, or LMO2, or any combination thereof and can be used as specific biomarkers from exosomes for hematological malignancies.

[0450] A biomarker mutation for a blood cancer that can be assessed in an exosome includes, but is not limited to, a mutation of c-kit, PDGFR, or ABL, or any combination of mutations specific for hematological malignancies.

[0451] Also provided herein is an isolated exosome comprising one or more blood cancer specific biomarkers, such as listed in FIG. **25** and in FIG. **1** for blood cancer. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more blood cancer specific biomarkers, such as listed in FIG. **25** and in FIG. **1** for blood cancer. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for blood cancer specific exosomes or exosomes comprising one or more blood cancer specific biomarkers, such as listed in FIG. **25** and in FIG. **1** for blood cancer.

[0452] One or more blood cancer specific biomarkers, such as listed in FIG. **25** and in FIG. **1** for blood cancer, can also be detected by one or more systems disclosed herein, for characterizing a blood cancer. For example, a detection system can comprise one or more probes to detect one or more blood cancer specific biomarkers, such as listed in FIG. **25** and in FIG. **1** for blood cancer, of one or more exosomes of a biological sample.

[0453] The one or more blood cancer specific biomarkers can also be a gene fusion selected from the group consisting of: TTL-ETV6, CDK6-MLL, CDK6-TLX3, ETV6-FLT3, ETV6-RUNX1, ETV6-TTL, MLL-AFF1, MLL-AFF3, MLL-AFF4, MLL-GAS7, TCBA1-ETV6, TCF3-PBX1 or TCF3-TFPT, for acute lymphocytic leukemia (ALL); BCL11B-TLX3, IL2-TNFRFS17, NUP214-ABL1, NUP98-CCDC28A, TAL1-STIL, or ETV6-ABL2, for T-cell acute lymphocytic leukemia (T-ALL); ATIC-ALK, KIAA1618-ALK, MSN-ALK, MYH9-ALK, NPM1-ALK, TGF-ALK or TPM3-ALK, for anaplastic large cell lymphoma (ALCL); BCR-ABL1, BCR-JAK2, ETV6-EVI1, ETV6-MN1 or ETV6-TCBA1, for chronic myelogenous leukemia (CML); CBFB-MYH11, CHIC2-ETV6, ETV6-ABL1, ETV6-ABL2, ETV6-ARNT, ETV6-CDX2, ETV6-HLXB9, ETV6-PER1, MEF2D-DAZAP1, AML-AFF1, MLL-ARHGAP26, MLL-ARHGEF12, MLL-CASC5, MLL-CBL, MLL-CREBBP, MLL-DAB21P, MLL-ELL, MLL-EP300, MLL-EPS15, MLL-FNBP1, MLL-FOXO3A, MLL-GMPS, MLL-GPHN, MLL-MLLT1, MLL-MLLT11, MLL-MLLT3, MLL-MLLT6, MLL-MYO1F, MLL-PICALM, MLL-SEPT2, MLL-SEPT6, MLL-SORBS2, MYST3-SORBS2, MYST-CREBBP, NPM1-MLF1, NUP98-HOXA13, PRDM16-EVI1, RABEP1-PDGFRB, RUNX1-EVI1, RUNX1-MDS1, RUNX1-RPL22, RUNX1-RUNX1T1, RUNX1-SH3D19, RUNX1-USP42, RUNX1-YTHDF2, RUNX1-ZNF687, or TAF15-ZNF-384, for AML; CCND1-FSTL3, for chronic lymphocytic leukemia (CLL); and FLIP1-PDGFRA, FLT3-

ETV6, KIAA1509-PDGFRA, PDE4DIP-PDGFRB, NIN-PDGFRB, TP53BP1-PDGFRB, or TPM3-PDGFRB, for hyper eosinophilia/chronic eosinophilia.

[0454] The one or more biomarkers for CLL can also include one or more of the following upregulated or overexpressed miRNAs, such as miR-23b, miR-24-1, miR-146, miR-155, miR-195, miR-221, miR-331, miR-29a, miR-195, miR-34a, or miR-29c; one or more of the following downregulated or underexpressed miRs, such as miR-15a, miR-16-1, miR-29 or miR-223, or any combination thereof.

[0455] The one or more biomarkers for ALL can also include one or more of the following upregulated or overexpressed miRNAs, such as miR-128b, miR-204, miR-218, miR-331, miR-181b-1, miR-17-92; or any combination thereof.

[0456] B-Cell Chronic Lymphocytic Leukemia (B-CLL)

[0457] B-CLL specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **26**, and can be used to create a B-CLL specific exosome bio-signature. For example, the bio-signature can comprise one or more overexpressed miRs, such as, but not limited to, miR-183-prec, miR-190, miR-24-1-prec, miR-33, miR-19a, miR-140, miR-123, miR-10b, miR-15b-prec, miR-92-1, miR-188, miR-154, miR-217, miR-101, miR-141-prec, miR-153-prec, miR-196-2, miR-134, miR-141, miR-132, miR-192, or miR-181b-prec, or any combination thereof.

[0458] The bio-signature can also comprise one or more underexpressed miRs such as, but not limited to, miR-213, miR-220, or any combination thereof. The one or more mRNAs that may be analyzed can include, but are not limited to, ZAP70, AdipoR1, or any combination thereof and can be used as specific biomarkers from exosomes for B-CLL. A biomarker mutation for B-CLL that can be assessed in an exosome includes, but is not limited to, a mutation of IGHV, P53, ATM, or any combination of mutations specific for B-CLL.

[0459] Also provided herein is an isolated exosome comprising one or more B-CLL specific biomarkers, such as BCL3-MYC, MYC-BTG1, BCL7A-MYC, BRWD3-ARHGAP20 or BTG1-MYC, or those listed in FIG. **26**. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more B-CLL specific biomarkers, such as BCL3-MYC, MYC-BTG1, BCL7A-MYC, BRWD3-ARHGAP20 or BTG1-MYC, or those listed in FIG. **26**. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for B-CLL specific exosomes or exosomes comprising one or more B-CLL specific biomarkers, such as BCL3-MYC, MYC-BTG1, BCL7A-MYC, BRWD3-ARHGAP20 or BTG1-MYC, or those listed in FIG. **26**.

[0460] One or more B-CLL specific biomarkers, such as BCL3-MYC, MYC-BTG1, BCL7A-MYC, BRWD3-ARHGAP20 or BTG1-MYC, or those listed in FIG. **26**, can also be detected by one or more systems disclosed herein, for characterizing a B-CLL. For example, a detection system can comprise one or more probes to detect one or more B-CLL specific biomarkers, such as BCL3-MYC, MYC-BTG1, BCL7A-MYC, BRWD3-ARHGAP20 or BTG1-MYC, or those listed in FIG. **26**, of one or more exosomes of a biological sample.

[0461] B-Cell Lymphoma

[0462] B-cell lymphome specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **27**, and can be used to create a B-cell lymphoma specific exosome bio-signature. For example, the bio-signature can comprise one or more overexpressed miRs, such as, but not limited to, miR-17-92 polycistron, miR-155, miR-210, or miR-21, miR-19a, miR-92, miR-142 miR-155, miR-221 miR-17-92, miR-21, miR-191, miR-205, or any combination thereof. Furthermore the snoRNA that can be used as an exosomal biomarker for B-cell lymphoma can include, but is not limited to, U50.

[0463] Also provided herein is an isolated exosome comprising one or more B-cell lymphoma specific biomarkers, such as listed in FIG. **27**. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more B-cell lymphoma specific biomarkers, such as listed in FIG. **27**. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for B-cell lymphoma specific exosomes or exosomes comprising one or more B-cell lymphoma specific biomarkers, such as listed in FIG. **27**.

[0464] One or more B-cell lymphoma specific biomarkers, such as listed in FIG. **27**, can also be detected by one or more systems disclosed herein, for characterizing a B-cell lymphoma. For example, a detection system can comprise one or more probes to detect one or more B-cell lymphoma specific biomarkers, such as listed in FIG. **27**, of one or more exosomes of a biological sample.

[0465] Diffuse Large B-Cell Lymphoma (DLBCL)

[0466] DLBCL specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **28**, and can be used to create a DLBCL specific exosome bio-signature. For example, the bio-signature can comprise one or more overexpressed miRs, such as, but not limited to, miR-17-92, miR-155, miR-210, or miR-21, or any combination thereof. The one or more mRNAs that may be analyzed can include, but are not limited to, A-myb, LMO2, JNK3, CD10, bcl-6, Cyclin D2, IRF4, Flip, or CD44, or any combination thereof and can be used as specific biomarkers from exosomes for DLBCL.

[0467] Also provided herein is an isolated exosome comprising one or more DLBCL specific biomarkers, such as CITTA-BCL6, CLTC-ALK, IL21R-BCL6, PIM1-BCL6, TFCR-BCL6, IKZF1-BCL6 or SEC31A-ALK, or those listed in FIG. **28**. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more DLBCL specific biomarkers, such as CITTA-BCL6, CLTC-ALK, IL21R-BCL6, PIM1-BCL6, TFCR-BCL6, IKZF1-BCL6 or SEC31A-ALK, or those listed in FIG. **28**. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for DLBCL specific exosomes or exosomes comprising one or more DLBCL specific biomarkers, such as CITTA-BCL6, CLTC-ALK, IL21R-BCL6, PIM1-BCL6, TFCR-BCL6, IKZF1-BCL6 or SEC31A-ALK, or those listed in FIG. **28**.

[0468] One or more DLBCL specific biomarkers, such as CITTA-BCL6, CLTC-ALK, IL21R-BCL6, PIM1-BCL6, TFCR-BCL6, IKZF1-BCL6 or SEC31A-ALK, or those listed in FIG. **28**, can also be detected by one or more systems disclosed herein, for characterizing a DLBCL. For example, a detection system can comprise one or more probes to detect one or more DLBCL specific biomarkers, such as CITTA-BCL6, CLTC-ALK, IL21R-BCL6, PIM 1-BCL6, TFCR-BCL6, IKZF1-BCL6 or SEC31A-ALK, or those listed in FIG. **28**, of one or more exosomes of a biological sample.

[0469] Burkitt's Lymphoma

[0470] Burkitt's lymphoma specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **29**, and can be used to create a Burkitt's lymphoma specific exosome bio-signature. For example, the bio-signature can also comprise one or more underexpressed miRs such as, but not limited to, pri-miR-155, or any combination thereof. The one or more mRNAs that may be analyzed can include, but are not limited to, MYC, TERT, NS, NP, MAZ, RCF3, BYSL, IDE3, CDC7, TCL1A, AUTS2, MYBL1, BMP7, ITPR3, CDC2, BACK2, TTK, MME, ALOX5, or TOP1, or any combination thereof and can be used as specific biomarkers from exosomes for Burkitt's lymphoma. The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, BCL6, KI-67, or any combination thereof.

[0471] Also provided herein is an isolated exosome comprising one or more Burkitt's lymphoma specific biomarkers, such as IGH-MYC, LCP1-BCL6, or those listed in FIG. **29**. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more Burkitt's lymphoma specific biomarkers, such as IGH-MYC, LCP1-BCL6, or those listed in FIG. **29**. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for Burkitt's lymphoma specific exosomes or exosomes comprising one or more Burkitt's lymphoma specific biomarkers, such as IGH-MYC, LCP1-BCL6, or those listed in FIG. **29**.

[0472] One or more Burkitt's lymphoma specific biomarkers, such as IGH-MYC, LCP1-BCL6, or those listed in FIG. **29**, can also be detected by one or more systems disclosed herein, for characterizing a Burkitt's lymphoma. For example, a detection system can comprise one or more probes to detect one or more Burkitt's lymphoma specific biomarkers, such as IGH-MYC, LCP1-BCL6, or those listed in FIG. **29**, of one or more exosomes of a biological sample.

[0473] Hepatocellular Carcinoma

[0474] Hepatocellular carcinoma specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **30** and can be used to create a hepatocellular carcinoma specific exosome bio-signature. For example, the bio-signature can comprise one or more overexpressed miRs, such as, but not limited to, miR-221. The bio-signature can also comprise one or more underexpressed miRs such as, but not limited to, let-7a-1, let-7a-2, let-7a-3, let-7b, let-7c, let-7d, let-7e, let-7f-2, let-fg, miR-122a, miR-124a-2, miR-130a, miR-132, miR-136, miR-141, miR-142, miR-143, miR-145, miR-146, miR-150, miR-155(BIC), miR-181a-1, miR-181a-2, miR-181c, miR-195, miR-199a-1-5p, miR-199a-2-5p, miR-199b, miR-200b, miR-214, miR-223, or pre-miR-594, or any combination thereof. The one or more mRNAs that may be analyzed can include, but are not limited to, FAT10.

[0475] The one or more biomarkers of a bio-signature can also be used to characterize hepatitis C virus-associated hepatocellular carcinoma. The one or more biomarkers can be a miRNA, such as an overexpressed or underexpressed miRNA. For example, the upregulated or overexpressed miRNA can be miR-122, miR-100, or miR-10a and the downregulated miRNA can be miR-198 or miR-145.

[0476] Also provided herein is an isolated exosome comprising one or more hepatocellular carcinoma specific biomarkers, such as listed in FIG. **30** and in FIG. **1** for hepatocellular carcinoma. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more hepatocellular carcinoma specific biomarkers, such as listed in FIG. **30** and in FIG. **1** for hepatocellular carcinoma. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for hepatocellular carcinoma specific exosomes or exosomes comprising one or more hepatocellular carcinoma specific biomarkers, such as listed in FIG. **30** and in FIG. **1** for hepatocellular carcinoma.

[0477] One or more hepatocellular carcinoma specific biomarkers, such as listed in FIG. **30** and in FIG. **1** for hepatocellular carcinoma, can also be detected by one or more systems disclosed herein, for characterizing a hepatocellular carcinoma. For example, a detection system can comprise one or more probes to detect one or more hepatocellular carcinoma specific biomarkers, such as listed in FIG. **30** and in FIG. **1** for hepatocellular carcinoma, of one or more exosomes of a biological sample.

[0478] Cervical Cancer

[0479] Cervical cancer specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **31**, and can be used to create a cervical cancer specific exosome bio-signature. For example, the one or more mRNAs that may be analyzed can include, but are not limited to, HPV E6, HPV E7, or p53, or any combination thereof and can be used as specific biomarkers from exosomes for cervical cancer.

[0480] Also provided herein is an isolated exosome comprising one or more cervical cancer specific biomarkers, such as listed in FIG. **31** and in FIG. **1** for cervical cancer. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more cervical cancer specific biomarkers, such as listed in FIG. **31** and in FIG. **1** for cervical cancer. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for cervical cancer specific exosomes or exosomes comprising one or more cervical cancer specific biomarkers, such as listed in FIG. **31** and in FIG. **1** for cervical cancer.

[0481] One or more cervical cancer specific biomarkers, such as listed in FIG. **31** and in FIG. **1** for cervical cancer, can also be detected by one or more systems disclosed herein, for characterizing a cervical cancer. For example, a detection system can comprise one or more probes to detect one or more cervical cancer specific biomarkers, such as listed in FIG. **31** and in FIG. **1** for cervical cancer, of one or more exosomes of a biological sample.

[0482] Endometrial Cancer

[0483] Endometrial cancer specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **32** and can be used to create a endometrial cancer specific exosome bio-signature. For example, the bio-signature can comprise one or more overexpressed miRs, such as, but not limited to, miR-185, miR-106a, miR-181a, miR-210, miR-423, miR-103, miR-107, or let-7c, or any combination thereof. The bio-signature can also comprise one or more underexpressed miRs such as, but not limited to, miR-71, miR-221, miR-193, miR-152, or miR-30c, or any combination thereof.

[0484] A biomarker mutation for endometrial cancer that can be assessed in an exosome includes, but is not limited to, a mutation of PTEN, K-RAS, B-catenin, p53, Her2/neu, or any combination of mutations specific for endometrial cancer. The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, NLRP7, AlphaV Beta6 integrin, or any combination thereof.

[0485] Also provided herein is an isolated exosome comprising one or more endometrial cancer specific biomarkers, such as listed in FIG. **32** and in FIG. **1** for endometrial cancer. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more endometrial cancer specific biomarkers, such as listed in FIG. **32** and in FIG. **1** for endometrial cancer. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for endometrial cancer specific exosomes or exosomes comprising one or more endometrial cancer specific biomarkers, such as listed in FIG. **32** and in FIG. **1** for endometrial cancer.

[0486] One or more endometrial cancer specific biomarkers, such as listed in FIG. **32** and in FIG. **1** for endometrial cancer, can also be detected by one or more systems disclosed herein, for characterizing a endometrial cancer. For example, a detection system can comprise one or more probes to detect one or more endometrial cancer specific biomarkers, such as listed in FIG. **32** and in FIG. **1** for endometrial cancer, of one or more exosomes of a biological sample.

[0487] Head and Neck Cancer

[0488] Head and neck cancer specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **33**, and can be used to create a head and neck cancer specific exosome bio-signature. For example, the bio-signature can comprise one or more overexpressed miRs, such as, but not limited to, miR-21, let-7, miR-18, miR-29c, miR-142-3p, miR-155, miR-146b, miR-205, or miR-21, or any combination thereof. The bio-signature can also comprise one or more underexpressed miRs such as, but not limited to, miR-494. The one or more mRNAs that may be analyzed include, but are not limited to, HPV E6, HPV E7, p53, IL-8, SAT, H3FA3, or EGFR, or any combination thereof and can be used as specific biomarkers from exosomes for head and neck cancer.

[0489] A biomarker mutation for head and neck cancer that can be assessed in an exosome includes, but is not limited to, a mutation of GSTM1, GSTT1, GSTP1, OGG1, XRCC1, XPD, RAD51, EGFR, p53, or any combination of mutations specific for head and neck cancer. The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, EGFR, EphB4, or EphB2, or any combination thereof.

[0490] Also provided herein is an isolated exosome comprising one or more head and neck cancer specific biomarkers, such as CHCHD7-PLAG1, CTNNB1-PLAG1, FHIT-HMGA2, HMGA2-NFIB, LIFR-PLAG1, or TCEA1-PLAG1, or those listed in FIG. **33** and in FIG. **1** for head and neck cancer. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more head and neck cancer specific biomarkers, such as CHCHD7-PLAG1, CTNNB1-PLAG1, FHIT-HMGA2, HMGA2-NFIB, LIFR-PLAG1, or TCEA1-PLAG1, or those listed in FIG. **33** and in FIG. **1** for head and neck cancer. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for head and neck cancer specific exosomes or exosomes comprising one or more head and neck cancer specific biomarkers, such as CHCHD7-PLAG1, CTNNB1-PLAG1, FHIT-HMGA2, HMGA2-NFIB, LIFR-PLAG1, or TCEA1-PLAG1, or those listed in FIG. **33** and in FIG. **1** for head and neck cancer.

[0491] One or more head and neck cancer specific biomarkers, such as listed in FIG. **33** and in FIG. **1** for head and neck cancer, can also be detected by one or more systems disclosed herein, for characterizing a head and neck cancer. For example, a detection system can comprise one or more probes to detect one or more head and neck cancer specific biomarkers, such as CHCHD7-PLAG1, CTNNB1-PLAG1, FHIT-HMGA2, HMGA2-NFIB, LIFR-PLAG1, or TCEA1-PLAG1, or those listed in FIG. **33** and in FIG. **1** for head and neck cancer, of one or more exosomes of a biological sample.

[0492] Inflammatory Bowel Disease (IBD)

[0493] IBD specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **34**, and can be used to create a IBD specific exosome bio-signature. The one or more mRNAs that may be analyzed can include, but are not limited to, Trypsinogen IV, SERT, or any combination thereof and can be used as specific biomarkers from exosomes for IBD.

[0494] A biomarker mutation for IBD that can be assessed in an exosome can include, but is not limited to, a mutation of CARD15 or any combination of mutations specific for IBD. The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, II-16, II-1beta, II-12, TNF-alpha, interferon gamma, 11-6, Rantes, MCP-1, Resistin, or 5-HT, or any combination thereof.

[0495] Also provided herein is an isolated exosome comprising one or more IBD specific biomarkers, such as listed in FIG. **34** and in FIG. **1** for IBD. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more IBD specific biomarkers, such as listed in FIG. **34** and in FIG. **1** for IBD. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for IBD specific exosomes or exosomes comprising one or more IBD specific biomarkers, such as listed in FIG. **34** and in FIG. **1** for IBD.

[0496] One or more IBD specific biomarkers, such as listed in FIG. **34** and in FIG. **1** for IBD, can also be detected by one or more systems disclosed herein, for characterizing a IBD. For example, a detection system can comprise one or more probes to detect one or more IBD specific biomarkers, such as listed in FIG. **34** and in FIG. **1** for IBD, of one or more exosomes of a biological sample.

[0497] Diabetes

[0498] Diabetes specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **35**, and can be used to create a diabetes specific exosome bio-signature. For example, the one or more mRNAs that may be analyzed can include, but are not limited to, 11-8, CTSS, ITGB2, HLA-DRA, CD53, PLAG27, or MMP9, or any combination thereof and can be used as specific biomarkers from exosomes for diabetes. The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, RBP4.

[0499] Also provided herein is an isolated exosome comprising one or more diabetes specific biomarkers, such as listed in FIG. **35** and in FIG. **1** for diabetes. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more diabetes specific biomarkers, such as listed in FIG. **35** and in FIG. **1** for diabetes. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for diabetes specific exosomes or exosomes comprising one or more diabetes specific biomarkers, such as listed in FIG. **35** and in FIG. **1** for diabetes.

[0500] One or more diabetes specific biomarkers, such as listed in FIG. **35** and in FIG. **1** for diabetes, can also be detected by one or more systems disclosed herein, for characterizing a diabetes. For example, a detection system can comprise one or more probes to detect one or more diabetes specific biomarkers, such as listed in FIG. **35** and in FIG. **1** for diabetes, of one or more exosomes of a biological sample.

[0501] Barrett's Esophagus

[0502] Barrett's Esophagus specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **36**, and can be used to create a Barrett's Esophagus specific exosome bio-signature. For example, the bio-signature can comprise one or more overexpressed miRs, such as, but not limited to, miR-21, miR-143, miR-145, miR-194, or miR-215, or any combination thereof. The one or more mRNAs that may be analyzed include, but are not limited to, S100A2, S100A4, or any combination thereof and can be used as specific biomarkers from exosomes for Barrett's Esophagus.

[0503] A biomarker mutation for Barrett's Esophagus that can be assessed in an exosome includes, but is not limited to, a mutation of p53 or any combination of mutations specific for Barrett's Esophagus. The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, p53, MUC1, MUC2, or any combination thereof.

[0504] Also provided herein is an isolated exosome comprising one or more Barrett's Esophagus specific biomarkers, such as listed in FIG. **36** and in FIG. **1** for Barrett's Esophagus. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more Barrett's Esophagus specific biomarkers, such as listed in FIG. **36** and in FIG. **1** for Barrett's Esophagus. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for Barrett's Esophagus specific exosomes or exosomes comprising one or more Barrett's Esophagus specific biomarkers, such as listed in FIG. **36** and in FIG. **1** for Barrett's Esophagus.

[0505] One or more Barrett's Esophagus specific biomarkers, such as listed in FIG. **36** and in FIG. **1** for Barrett's Esophagus, can also be detected by one or more systems disclosed herein, for characterizing a Barrett's Esophagus. For example, a detection system can comprise one or more probes to detect one or more Barrett's Esophagus specific biomarkers, such as listed in FIG. **36** and in FIG. **1** for Barrett's Esophagus, of one or more exosomes of a biological sample.

[0506] Fibromyalgia

[0507] Fibromyalgia specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **37**, and can be used to create a fibromyalgia specific exosome bio-signature. The one or more mRNAs that may be analyzed can include, but are not limited to, NR2D which can be used as a specific biomarker from exosomes for fibromyalgia.

[0508] Also provided herein is an isolated exosome comprising one or more fibromyalgia specific biomarkers, such as listed in FIG. **37** and in FIG. **1** for fibromyalgia. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more fibromyalgia specific biomarkers, such as listed in FIG. **37** and in FIG. **1** for fibromyalgia. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for fibromyalgia specific exosomes or exosomes comprising one or more fibromyalgia specific biomarkers, such as listed in FIG. **37** and in FIG. **1** for fibromyalgia.

[0509] Stroke

[0510] Stroke specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **38**, and can be used to create a stroke specific exosome bio-signature. For example, the one or more mRNAs that may be analyzed can include, but are not limited to, MMP9, S100-P, S100A12, SI00A9, coag factor V, ArginaseI, CA-IV, monocarboxylic acid transporter, ets-2, EIF2alpha, cytoskeleton associated protein 4, N-formylpeptide receptor, Ribonuclease2, N-acetylneuraminate pyruvate lyase, BCL-6, or Glycogen phosphorylase, or any combination thereof and can be used as specific biomarkers from exosomes for stroke.

[0511] Also provided herein is an isolated exosome comprising one or more stroke specific biomarkers, such as listed in FIG. **38** and in FIG. **1** for stroke. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more stroke specific biomarkers, such as listed in FIG. **38** and in FIG. **1** for stroke. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for stroke specific exosomes or exosomes comprising one or more stroke specific biomarkers, such as listed in FIG. **38** and in FIG. **1** for stroke.

[0512] One or more stroke specific biomarkers, such as listed in FIG. **38** and in FIG. **1** for stroke, can also be detected by one or more systems disclosed herein, for characterizing a stroke. For example, a detection system can comprise one or more probes to detect one or more stroke specific biomarkers, such as listed in FIG. **38** and in FIG. **1** for stroke, of one or more exosomes of a biological sample.

[0513] Multiple Sclerosis (MS)

[0514] MS specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **39**, and can be used to create a MS specific exosome bio-signature. For example, the one or more mRNAs that may be analyzed can include, but are not limited to, IL-6, IL-17, PAR-3, IL-17, T1/ST2, JunD, 5-LO, LTA4H, MBP, PLP, or alpha-beta crystallin, or any combination thereof and can be used as specific biomarkers from exosomes for MS.

[0515] Also provided herein is an isolated exosome comprising one or more MS specific biomarkers, such as listed in FIG. **39** and in FIG. **1** for MS. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more MS specific biomarkers, such as listed in FIG. **39** and in FIG. **1** for MS. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for MS specific exosomes or exosomes comprising one or more MS specific biomarkers, such as listed in FIG. **39** and in FIG. **1** for MS.

[0516] One or more MS specific biomarkers, such as listed in FIG. **39** and in FIG. **1** for MS, can also be detected by one or more systems disclosed herein, for characterizing a MS. For example, a detection system can comprise one or more probes to detect one or more MS specific biomarkers, such as listed in FIG. **39** and in FIG. **1** for MS, of one or more exosomes of a biological sample.

[0517] Parkinson's Disease

[0518] Parkinson's disease specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **40**, and can be used to create a Parkinson's disease specific exosome bio-signature. For example, the bio-signature can include, but is not limited to, one or more underexpressed miRs such as miR-133b. The one or more mRNAs that may be analyzed can include, but are not limited to Nurr1, BDNF, TrkB, gstm1, or 5100 beta, or any combination thereof and can be used as specific biomarkers from exosomes for Parkinson's disease.

[0519] A biomarker mutation for Parkinson's disease that can be assessed in an exosome includes, but is not limited to, a mutation of FGF20, alpha-synuclein, FGF20, NDUFV2, FGF2, CALB1, B2M, or any combination of mutations specific for Parkinson's disease. The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, apo-H, Ceruloplasmin, BDNF, IL-8, Beta2-microglobulin, apoAII, tau, ABeta1-42, DJ-1, or any combination thereof.

[0520] Also provided herein is an isolated exosome comprising one or more Parkinson's disease specific biomarkers, such as listed in FIG. **40** and in FIG. **1** for Parkinson's disease A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more Parkinson's disease specific biomarkers, such as listed in FIG. **40** and in FIG. **1** for Parkinson's disease. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for Parkinson's disease specific exosomes or exosomes comprising one or more Parkinson's disease specific biomarkers, such as listed in FIG. **40** and in FIG. **1** for Parkinson's disease.

[0521] One or more Parkinson's disease specific biomarkers, such as listed in FIG. **40** and in FIG. **1** for Parkinson's disease, can also be detected by one or more systems disclosed herein, for characterizing a Parkinson's disease. For example, a detection system can comprise one or more probes to detect one or more Parkinson's disease specific biomarkers, such as listed in FIG. **40** and in FIG. **1** for Parkinson's disease, of one or more exosomes of a biological sample.

[0522] Rheumatic Disease

[0523] Rheumatic disease specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **41**, and can be used to create a rheumatic disease specific exosome bio-signature. For example, the bio-signature can also comprise one or more underexpressed miRs such as, but not limited to, miR-146a, miR-155, miR-132, miR-16, or miR-181, or any combination thereof. The one or more mRNAs that may be analyzed can include, but are not limited to, HOXD10, HOXD11, HOXD13, CCL8, LIM homeobox2, or CENP-E, or any combination thereof and can be used as specific biomarkers from exosomes for rheumatic disease. The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, TNFα.

[0524] Also provided herein is an isolated exosome comprising one or more rheumatic disease specific biomarkers, such as listed in FIG. **41** and in FIG. **1** for rheumatic disease. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more rheumatic disease specific biomarkers, such as listed in FIG. **41** and in FIG. **1** for rheumatic disease. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for rheumatic disease specific exosomes or exosomes comprising one or more rheumatic disease specific biomarkers, such as listed in FIG. **41** and in FIG. **1** for rheumatic disease.

[0525] One or more rheumatic disease specific biomarkers, such as listed in FIG. **41** and in FIG. **1** for rheumatic disease, can also be detected by one or more systems disclosed herein, for characterizing a rheumatic disease. For example, a detection system can comprise one or more probes to detect one or more rheumatic disease specific biomarkers, such as listed in FIG. **41** and in FIG. **1** for rheumatic disease, of one or more exosomes of a biological sample.

[0526] Alzheimer's Disease

[0527] Alzheimer's disease specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **42**, and can be used to create a Alzheimers disease specific exosome bio-signature. For example, the bio-signature can also comprise one or more underexpressed miRs such as miR-107, miR-29a, miR-29b-1, or miR-9, or any combination thereof. The bio-signature can also comprise one or more overexpressed miRs such as miR-128 or any combination thereof.

[0528] The one or more mRNAs that may be analyzed can include, but are not limited to, HIF-1α, BACE1, Reelin, CHRNA7, or 3Rtau/4Rtau, or any combination thereof and can be used as specific biomarkers from exosomes for Alzheimer's disease.

[0529] A biomarker mutation for Alzheimer's disease that can be assessed in an exosome includes, but is not limited to, a mutation of APP, presenilin1, presenilin2, APOE4, or any combination of mutations specific for Alzheimer's disease. The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, BACE1, Reelin, Cystatin C, Truncated Cystatin C, Amyloid Beta, C3a, t-Tau, Complement factor H, or alpha-2-macroglobulin, or any combination thereof.

[0530] Also provided herein is an isolated exosome comprising one or more Alzheimer's disease specific biomarkers, such as listed in FIG. **42** and in FIG. **1** for Alzheimer's disease. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more Alzheimer's disease specific biomarkers, such as listed in FIG. **42** and in FIG. **1** for Alzheimer's disease. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for Alzheimer's disease specific exosomes or exosomes comprising one or more Alzheimer's disease specific biomarkers, such as listed in FIG. **42** and in FIG. **1** for Alzheimer's disease.

[0531] One or more Alzheimer's disease specific biomarkers, such as listed in FIG. **42** and in FIG. **1** for Alzheimer's disease, can also be detected by one or more systems disclosed herein, for characterizing a Alzheimer's disease. For example, a detection system can comprise one or more probes to detect one or more Alzheimer's disease specific biomarkers, such as listed in FIG. **42** and in FIG. **1** for Alzheimer's disease, of one or more exosomes of a biological sample.

[0532] Prion Disease

[0533] Prion specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **43**, and can be used to create a prion specific exosome bio-signature. For example, the one or more mRNAs that may be analyzed can include, but are not limited to, Amyloid B4, App, IL-1R1, or SOD1, or any combination thereof and can be used as specific biomarkers from exosomes for a prion. The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, PrP(c), 14-3-3, NSE, S-100, Tau, AQP-4, or any combination thereof.

[0534] Also provided herein is an isolated exosome comprising one or more prion disease specific biomarkers, such as listed in FIG. **43** and in FIG. **1** for prion disease. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more prion disease specific biomarkers, such as listed in FIG. **43** and in FIG. **1** for prion disease. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for prion disease specific exosomes or exosomes comprising one or more prion disease specific biomarkers, such as listed in FIG. **43** and in FIG. **1** for prion disease.

[0535] One or more prion disease specific biomarkers, such as listed in FIG. **43** and in FIG. **1** for prion disease, can also be detected by one or more systems disclosed herein, for characterizing a prion disease. For example, a detection system can comprise one or more probes to detect one or more prion disease specific biomarkers, such as listed in FIG. **43** and in FIG. **1** for prion disease, of one or more exosomes of a biological sample.

[0536] Sepsis

[0537] Sepsis specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **44**, and can be used to create a sepsis specific exosome bio-signature. For example, the one or more mRNAs that may be analyzed can include, but are not limited to, 15-Hydroxy-PG dehydrogenase (up), LAIR1 (up), NFKB1A (up), TLR2, PGLYPR1, TLR4, MD2, TLR5, IFNAR2, IRAK2, IRAK3, IRAK4, PI3K, PI3KCB, MAP2K6, MAPK14, NFKB1A, NFKB1, IL1R1, MAP2K1IP1, MKNK1, FAS, CASP4, GADD45B, SOCS3, TNFSF10, TNFSF13B, OSM, HGF, or IL18R1, or any combination thereof and can be used as specific biomarkers from exosomes for sepsis.

[0538] Also provided herein is an isolated exosome comprising one or more sepsis specific biomarkers, such as listed in FIG. **44**. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more sepsis specific biomarkers, such as listed in FIG. **44**. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for sepsis specific exosomes or exosomes comprising one or more sepsis specific biomarkers, such as listed in FIG. **44**.

[0539] One or more sepsis specific biomarkers, such as listed in FIG. **44**, can also be detected by one or more systems disclosed herein, for characterizing a sepsis. For example, a detection system can comprise one or more probes to detect one or more sepsis specific biomarkers, such as listed in FIG. **44**, of one or more exosomes of a biological sample.

[0540] Chronic Neuropathic Pain

[0541] Chronic neuropathic pain (CNP) specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **45**, and can be used to create a CNP specific exosome bio-signature. For example, the one or more mRNAs that may be analyzed can include, but are not limited to, ICAM-1 (rodent), CGRP (rodent), TIMP-1 (rodent), CLR-1 (rodent), HSP-27 (rodent), FABP (rodent), or apolipoprotein D (rodent), or any combination thereof and can be used as specific biomarkers from exosomes for CNP. The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, chemokines, chemokine receptors (CCR2/4), or any combination thereof.

[0542] Also provided herein is an isolated exosome comprising one or more chronic neuropathic pain specific biomarkers, such as listed in FIG. **45** and in FIG. **1** for chronic neuropathic pain. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more chronic neuropathic pain specific biomarkers, such as listed in FIG. **45** and in FIG. **1** for chronic neuropathic pain. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for chronic neuropathic pain specific exosomes or exosomes comprising one or more chronic neuropathic pain specific biomarkers, such as listed in FIG. **45** and in FIG. **1** for chronic neuropathic pain.

[0543] One or more chronic neuropathic pain specific biomarkers, such as listed in FIG. **45** and in FIG. **1** for chronic neuropathic pain, can also be detected by one or more systems disclosed herein, for characterizing a chronic neuropathic pain. For example, a detection system can comprise one or more probes to detect one or more chronic neuropathic pain specific biomarkers, such as listed in FIG. **45** and in FIG. **1** for chronic neuropathic pain, of one or more exosomes of a biological sample.

[0544] Peripheral Neuropathic Pain

[0545] Peripheral neuropathic pain (PNP) specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **46**, and can be used to create a PNP specific exosome bio-signature. For example, the protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, OX42, ED9, or any combination thereof.

[0546] Also provided herein is an isolated exosome comprising one or more peripheral neuropathic pain specific biomarkers, such as listed in FIG. **46** and in FIG. **1** for peripheral neuropathic pain. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more peripheral neuropathic pain specific biomarkers, such as listed in FIG. **46** and in FIG. **1** for peripheral neuropathic pain. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for peripheral neuropathic pain specific exosomes or exosomes comprising one or more peripheral neuropathic pain specific biomarkers, such as listed in FIG. **46** and in FIG. **1** for peripheral neuropathic pain.

[0547] One or more peripheral neuropathic pain specific biomarkers, such as listed in FIG. **46** and in FIG. **1** for peripheral neuropathic pain, can also be detected by one or more systems disclosed herein, for characterizing a peripheral neuropathic pain. For example, a detection system can comprise one or more probes to detect one or more peripheral neuropathic pain specific biomarkers, such as listed in FIG. **46** and in FIG. **1** for peripheral neuropathic pain, of one or more exosomes of a biological sample.

[0548] Schizophrenia

[0549] Schizophrenia specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **47**, and can be used to create a schizophrenia specific exosome bio-signature. For example, the bio-signature can comprise one or more overexpressed miRs, such as, but not limited to, miR-181b. The bio-signature can also comprise one or more underexpressed miRs such as, but not limited to, miR-7, miR-24, miR-26b, miR-29b, miR-30b, miR-30e, miR-92, or miR-195, or any combination thereof.

[0550] The one or more mRNAs that may be analyzed can include, but are not limited to, IFITM3, SERPINA3, GLS, or ALDH7A1BASP1, or any combination thereof and can be used as specific biomarkers from exosomes for schizophrenia. A biomarker mutation for schizophrenia that can be assessed in an exosome includes, but is not limited to, a mutation of to DISC1, dysbindin, neuregulin-1, seratonin 2a receptor, NURR1, or any combination of mutations specific for schizophrenia.

[0551] The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, ATP5B, ATP5H, ATP6V1B, DNM1, NDUFV2, NSF, PDHB, or any combination thereof.

[0552] Also provided herein is an isolated exosome comprising one or more schizophrenia specific biomarkers, such as listed in FIG. **47** and in FIG. **1** for schizophrenia. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more schizophrenia specific biomarkers, such as listed in FIG. **47** and in FIG. **1** for schizophrenia. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for schizophrenia specific exosomes or exosomes comprising one or more schizophrenia specific biomarkers, such as listed in FIG. **47** and in FIG. **1** for schizophrenia.

[0553] One or more schizophrenia specific biomarkers, such as listed in FIG. **47** and in FIG. **1** for schizophrenia, can also be detected by one or more systems disclosed herein, for characterizing a schizophrenia. For example, a detection system can comprise one or more probes to detect one or more schizophrenia specific biomarkers, such as listed in FIG. **47** and in FIG. **1** for schizophrenia, of one or more exosomes of a biological sample.

[0554] Bipolar Disease

[0555] Bipolar disease specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **48**, and can be used to create a bipolar disease specific exosome bio-signature. For example, the one or more mRNAs that may be analyzed can include, but are not limited to, FGF2, ALDH7A1, AGXT2L1, AQP4, or PCNT2, or any combination thereof and can be used as specific biomarkers from exosomes for bipolar disease. A biomarker mutation for bipolar disease that can be assessed in an exosome includes, but is not limited to, a mutation of Dysbindin, DAOA/G30, DISC1, neuregulin-1, or any combination of mutations specific for bipolar disease.

[0556] Also provided herein is an isolated exosome comprising one or more bipolar disease specific biomarkers, such as listed in FIG. **48**. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more bipolar disease specific biomarkers, such as listed in FIG. **48**. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for bipolar disease specific exosomes or exosomes comprising one or more bipolar disease specific biomarkers, such as listed in FIG. **48**.

[0557] One or more bipolar disease specific biomarkers, such as listed in FIG. **48**, can also be detected by one or more systems disclosed herein, for characterizing a bipolar disease. For example, a detection system can comprise one or more probes to detect one or more bipolar disease specific biomarkers, such as listed in FIG. **48**, of one or more exosomes of a biological sample.

[0558] Depression

[0559] Depression specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **49**, and can be used to create a depression specific exosome bio-signature. For example, the one or more mRNAs that may be analyzed can include, but are not limited to, FGFR1, FGFR2, FGFR3, or AQP4, or any combination thereof can also be used as specific biomarkers from exosomes for depression.

[0560] Also provided herein is an isolated exosome comprising one or more depression specific biomarkers, such as listed in FIG. **49**. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more depression specific biomarkers, such as listed in FIG. **49**. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for depression specific exosomes or exosomes comprising one or more depression specific biomarkers, such as listed in FIG. **49**.

[0561] One or more depression specific biomarkers, such as listed in FIG. **49**, can also be detected by one or more systems disclosed herein, for characterizing a depression. For example, a detection system can comprise one or more probes to detect one or more depression specific biomarkers, such as listed in FIG. **49**, of one or more exosomes of a biological sample.

[0562] Gastrointestinal Stromal Tumor (GIST)

[0563] GIST specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **50**, and can be used to create a GIST specific exosome bio-signature. For example, the one or more mRNAs that may be analyzed can include, but are not limited to, DOG-1, PKC-theta, KIT, GPR20, PRKCQ, KCNK3, KCNH2, SCG2, TNFRSF6B, or CD34, or any combination thereof and can be used as specific biomarkers from exosomes for GIST.

[0564] A biomarker mutation for GIST that can be assessed in an exosome includes, but is not limited to, a mutation of PKC-theta or any combination of mutations specific for GIST. The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, PDGFRA, c-kit, or any combination thereof.

[0565] Also provided herein is an isolated exosome comprising one or more GIST specific biomarkers, such as listed in FIG. **50** and in FIG. **1** for GIST. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more GIST specific biomarkers, such as listed in FIG. **50** and in FIG. **1** for GIST. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for GIST specific exosomes or exosomes comprising one or more GIST specific biomarkers, such as listed in FIG. **50** and in FIG. **1** for GIST.

[0566] One or more GIST specific biomarkers, such as listed in FIG. **50** and in FIG. **1** for GIST, can also be detected by one or more systems disclosed herein, for characterizing a GIST. For example, a detection system can comprise one or more probes to detect one or more GIST specific biomarkers, such as listed in FIG. **50** and in FIG. **1** for GIST, of one or more exosomes of a biological sample.

[0567] Renal Cell Carcinoma

[0568] Renal cell carcinoma specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **51**, and can be used to create a renal cell carcinoma specific exosome bio-signature. For example, the bio-signature can also comprise one or more underexpressed miRs such as, but not limited to, miR-141, miR-200c, or any combination thereof. The one or more upregulated or overexpressed miRNA can be miR-28, miR-185, miR-27, miR-let-7f-2, or any combination thereof.

[0569] The one or more mRNAs that may be analyzed can include, but are not limited to, laminin receptor 1, betaig-h3, Galectin-1, a-2 Macroglobulin, Adipophilin, Angiopoietin 2, Caldesmon 1, Class II MHC-associated invariant chain (CD74), Collagen IV-al, Complement component, Complement component 3, Cytochrome P450, subfamily IIJ polypeptide 2, Delta sleep-inducing peptide, Fc g receptor 111a (CD16), HLA-B, HLA-DRa, HLA-DRb, HLA-SB, IFN-induced transmembrane protein 3, IFN-induced transmembrane protein 1, or Lysyl Oxidase, or any combination thereof and can be used as specific biomarkers from exosomes for renal cell carcinoma.

[0570] A biomarker mutation for renal cell carcinoma that can be assessed in an exosome includes, but is not limited to, a mutation of VHL or any combination of mutations specific renal cell carcinoma.

[0571] The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, IF1 alpha, VEGF, PDGFRA, or any combination thereof.

[0572] Also provided herein is an isolated exosome comprising one or more RCC specific biomarkers, such as ALPHA-TFEB, NONO-TFE3, PRCC-TFE3, SFPQ-TFE3, CLTC-TFE3, or MALAT1-TFEB, or those listed in FIG. **51** and in FIG. **1** for RCC. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more RCC specific biomarkers, such as ALPHA-TFEB, NONO-TFE3, PRCC-TFE3, SFPQ-TFE3, CLTC-TFE3, or MALAT1-TFE, or those listed in FIG. **51** and in FIG. **1** for RCC. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for RCC specific exosomes or exosomes comprising one or more RCC specific biomarkers, such as ALPHA-TFEB, NONO-TFE3, PRCC-TFE3, SFPQ-TFE3, CLTC-TFE3, or MALAT1-TFE, or those listed in FIG. **51** and in FIG. **1** for RCC.

[0573] One or more RCC specific biomarkers, such as ALPHA-TFEB, NONO-TFE3, PRCC-TFE3, SFPQ-TFE3, CLTC-TFE3, or MALAT1-TFE, or those listed in FIG. **51** and in FIG. **1** for RCC, can also be detected by one or more systems disclosed herein, for characterizing a RCC. For example, a detection system can comprise one or more probes to detect one or more RCC specific biomarkers, such as ALPHA-TFEB, NONO-TFE3, PRCC-TFE3, SFPQ-TFE3, CLTC-TFE3, or MALAT1-TFE, or those listed in FIG. **51** and in FIG. **1** for RCC, of one or more exosomes of a biological sample.

[0574] Cirrhosis

[0575] Cirrhosis specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **52**, and can be used to create a cirrhosis specific exosome bio-signature. The one or more mRNAs that may be analyzed include, but are not limited to, NLT, which can be used as aspecific biomarker from exosomes for cirrhosis.

[0576] The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, NLT, HBsAG, AST, YKL-40, Hyaluronic acid, TIMP-1, alpha 2 macroglobulin, a-1-antitrypsin P1Z allele, haptoglobin, or acid phosphatase ACP AC, or any combination thereof.

[0577] Also provided herein is an isolated exosome comprising one or more cirrhosis specific biomarkers, such as those listed in FIG. **52** and in FIG. **1** for cirrhosis. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more cirrhosis specific biomarkers, such as those listed in FIG. **52** and in FIG. **1** for cirrhosis. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for cirrhosis specific exosomes or exosomes comprising one or more cirrhosis specific biomarkers, such as those listed in FIG. **52** and in FIG. **1** for cirrhosis.

[0578] One or more cirrhosis specific biomarkers, such as those listed in FIG. **52** and in FIG. **1** for cirrhosis, can also be detected by one or more systems disclosed herein, for characterizing cirrhosis. For example, a detection system can comprise one or more probes to detect one or more cirrhosis specific biomarkers, such as those listed in FIG. **52** and in FIG. **1** for cirrhosis, of one or more exosomes of a biological sample.

[0579] Esophageal Cancer

[0580] Esophageal cancer specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **53**, and can be used to create a esophageal cancer specific exosome bio-signature. For example, the bio-signature can comprise one or more overexpressed miRs, such as, but not limited to, miR-192, miR-194, miR-21, miR-200c, miR-93, miR-342, miR-152, miR-93, miR-25, miR-424, or miR-151, or any combination thereof. The bio-signature can also comprise one or more underexpressed miRs such as, but not limited to, miR-27b, miR-205, miR-203, miR-342, let-7c, miR-125b, miR-100, miR-152, miR-192, miR-194, miR-27b, miR-205, miR-203, miR-200c, miR-99a, miR-29c, miR-140, miR-103, or miR-107, or any combination thereof. The one or more mRNAs that may be analyzed include, but are not limited to, MTHFR and can be used as specific biomarkers from exosomes for esophageal cancer.

[0581] Also provided herein is an isolated exosome comprising one or more esophageal cancer specific biomarkers, such as listed in FIG. **53** and in FIG. **1** for esophageal cancer. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more esophageal cancer specific biomarkers, such as listed in FIG. **53** and in FIG. **1** for esophageal cancer. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for esophageal cancer specific exosomes or exosomes comprising one or more esophageal cancer specific biomarkers, such as listed in FIG. **53** and in FIG. **1** for esophageal cancer.

[0582] One or more esophageal cancer specific biomarkers, such as listed in FIG. **53** and in FIG. **1** for esophageal cancer, can also be detected by one or more systems disclosed herein, for characterizing a esophageal cancer. For example, a detection system can comprise one or more probes to detect one or more esophageal cancer specific biomarkers, such as listed in FIG. **53** and in FIG. **1** for esophageal cancer, of one or more exosomes of a biological sample.

[0583] Gastric Cancer

[0584] Gastric cancer specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **54**, and can be used to create a gastric cancer specific exosome bio-signature. For example, the bio-signature can comprise one or more overexpressed miRs, such as, but not limited to, miR-106a, miR-21, miR-191, miR-223, miR-24-1, miR-24-2, miR-107, miR-92-2, miR-214, miR-25, or miR-221, or any combination thereof. The bio-signature can also comprise one or more underexpressed miRs such as, but not limited to, let-7a.

[0585] The one or more mRNAs that may be analyzed include, but are not limited to, RRM2, EphA4, or survivin, or any combination thereof and can be used as specific biomarkers from exosomes for gastric cancer. A biomarker mutation for gastric cancer that can be assessed in an exosome includes, but is not limited to, a mutation of APC or any combination of mutations specific for gastric cancer. The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to EphA4.

[0586] Also provided herein is an isolated exosome comprising one or more gastric cancer specific biomarkers, such as listed in FIG. **54**. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more gastric cancer specific biomarkers, such as listed in FIG. **54**. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for gastric cancer specific exosomes or exosomes comprising one or more gastric cancer specific biomarkers, such as listed in FIG. **54**.

[0587] One or more gastric cancer specific biomarkers, such as listed in FIG. **54**, can also be detected by one or more systems disclosed herein, for characterizing a gastric cancer. For example, a detection system can comprise one or more probes to detect one or more gastric cancer specific biomarkers, such as listed in FIG. **54**, of one or more exosomes of a biological sample.

[0588] Autism

[0589] Autism specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **55**, and can be used to create an autism specific exosome bio-signature. For example, the bio-signature can comprise one or more overexpressed miRs, such as, but not limited to, miR-484, miR-21, miR-212, miR-23a, miR-598, miR-95, miR-129, miR-431, miR-7, miR-15a, miR-27a, miR-15b, miR-148b, miR-132, or miR-128, or any combination thereof. The bio-signature can also comprise one or more underexpressed miRs such as, but not limited to, miR-93, miR-106a, miR-539, miR-652, miR-550, miR-432, miR-193b, miR-181d, miR-146b, miR-140, miR-381, miR-320a, or miR-106b, or any combination thereof. The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, GM1, GD1a, GD1b, or GT1b, or any combination thereof.

[0590] Also provided herein is an isolated exosome comprising one or more autism specific biomarkers, such as listed in FIG. **55** and in FIG. **1** for autism. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more autism specific biomarkers, such as listed in FIG. **55** and in FIG. **1** for autism. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for autism specific exosomes or exosomes comprising one or more autism specific biomarkers, such as listed in FIG. **55** and in FIG. **1** for autism.

[0591] One or more autism specific biomarkers, such as listed in FIG. **55** and in FIG. **1** for autism, can also be detected by one or more systems disclosed herein, for characterizing a autism. For example, a detection system can comprise one or more probes to detect one or more autism specific biomarkers, such as listed in FIG. **55** and in FIG. **1** for autism, of one or more exosomes of a biological sample.

[0592] Organ Rejection

[0593] Organ rejection specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **56**, and can be used to create an organ rejection specific exosome bio-signature. For example, the bio-signature can comprise one or more overexpressed miRs, such as, but not limited to, miR-658, miR-125a, miR-320, miR-381, miR-628, miR-602, miR-629, or miR-125a, or any combination thereof. The bio-signature can also comprise one or more underexpressed miRs such as, but not limited to, miR-324-3p, miR-611, miR-654, miR-330_MM1, miR-524, miR-17-3p_MM1, miR-483, miR-663, miR-5,6-5p, miR-326, miR-197_MM2, or miR-346, or any combination thereof. The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, matix metalloprotein-9, proteinase 3, or HNP, or any combinations thereof. The biomarker can be a member of the matrix metalloproteinases.

[0594] Also provided herein is an isolated exosome comprising one or more organ rejection specific biomarkers, such as listed in FIG. **56**. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more organ rejection specific biomarkers, such as listed in FIG. **56**. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for organ rejection specific exosomes or exosomes comprising one or more organ rejection specific biomarkers, such as listed in FIG. **56**.

[0595] One or more organ rejection specific biomarkers, such as listed in FIG. **56**, can also be detected by one or more systems disclosed herein, for characterizing a organ rejection. For example, a detection system can comprise one or more probes to detect one or more organ rejection specific biomarkers, such as listed in FIG. **56**, of one or more exosomes of a biological sample.

[0596] Methicillin-Resistant *Staphylococcus aureus*

[0597] Methicillin-resistant *Staphylococcus aureus* specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **57**, and can be used to create a methicillin-resistant *Staphylococcus aureus* specific exosome bio-signature.

[0598] The one or more mRNAs that may be analyzed include, but are not limited to, TSST-1 which can be used as a specific biomarker from exosomes for methicillin-resistant *Staphylococcus aureus*. A biomarker mutation for methicillin-resistant *Staphylococcus aureus* that can be assessed in an exosome includes, but is not limited to, a mutation of mecA, Protein A SNPs, or any combination of mutations specific for methicillin-resistant *Staphylococcus aureus*. The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, ETA, ETB, TSST-1, or leukocidins, or any combination thereof.

[0599] Also provided herein is an isolated exosome comprising one or more methicillin-resistant *Staphylococcus aureus* specific biomarkers, such as listed in FIG. **57**. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more methicillin-resistant *Staphylococcus aureus* specific biomarkers, such as listed in FIG. **57**. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for methicillin-resistant *Staphylococcus aureus* specific exosomes or exosomes comprising one or more methicillin-resistant *Staphylococcus aureus* specific biomarkers, such as listed in FIG. **57**.

[0600] One or more methicillin-resistant *Staphylococcus aureus* specific biomarkers, such as listed in FIG. **57**, can also be detected by one or more systems disclosed herein, for characterizing a methicillin-resistant *Staphylococcus aureus*. For example, a detection system can comprise one or more probes to detect one or more methicillin-resistant *Staphylococcus aureus* specific biomarkers, such as listed in FIG. **57**, of one or more exosomes of a biological sample.

[0601] Vulnerable Plaque

[0602] Vulnerable plaque specific biomarkers from exosomes can include one or more (for example, 2, 3, 4, 5, 6, 7, 8, or more) overexpressed miRs, underexpressed miRs, mRNAs, genetic mutations, proteins, ligands, peptides, snoRNA, or any combination thereof, such as listed in FIG. **58**, and can be used to create a vulnerable plaque specific exosome bio-signature. The protein, ligand, or peptide that can be assessed in an exosome can include, but is not limited to, IL-6, MMP-9, PAPP-A, D-dimer, fibrinogen, Lp-PLA2, SCD40L, Il-18, oxLDL, GPx-1, MCP-1, P1GF, or CRP, or any combination thereof.

[0603] Also provided herein is an isolated exosome comprising one or more vulnerable plaque specific biomarkers, such as listed in FIG. **58** and in FIG. **1** for vulnerable plaque. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more vulnerable plaque specific biomarkers, such as listed in FIG. **58** and in FIG. **1** for vulnerable plaque. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for vulnerable plaque specific exosomes or exosomes comprising one or more vulnerable plaque specific biomarkers, such as listed in FIG. **58** and in FIG. **1** for vulnerable plaque.

[0604] One or more vulnerable plaque specific biomarkers, such as listed in FIG. **58** and in FIG. **1** for vulnerable plaque, can also be detected by one or more systems disclosed herein, for characterizing a vulnerable plaque. For example, a detection system can comprise one or more probes to detect one or more vulnerable plaque specific biomarkers, such as listed in FIG. **58** and in FIG. **1** for vulnerable plaque, of one or more exosomes of a biological sample.

[0605] Autoimmune Disease

[0606] Also provided herein is an isolated exosome comprising one or more autoimmune disease specific biomarkers, such as listed in FIG. **1** for autoimmune disease. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more autoimmune disease specific biomarkers, such as listed in FIG. **1** for autoimmune disease. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for autoimmune disease specific exosomes or exosomes comprising one or more autoimmune disease specific biomarkers, such as listed in FIG. **1** for autoimmune disease.

[0607] One or more autoimmune disease specific biomarkers, such as listed in FIG. **1** for autoimmune disease, can also be detected by one or more systems disclosed herein, for characterizing a autoimmune disease. For example, a detection system can comprise one or more probes to detect one or more autoimmune disease specific biomarkers, such as listed in FIG. **1** for autoimmune disease, of one or more exosomes of a biological sample.

[0608] Tuberculosis (TB)

[0609] Also provided herein is an isolated exosome comprising one or more TB disease specific biomarkers, such as listed in FIG. **1** for TB disease. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more TB disease specific biomarkers, such as listed in FIG. **1** for TB disease. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for TB disease specific exosomes or exosomes comprising one or more TB disease specific biomarkers, such as listed in FIG. **1** for TB disease.

[0610] One or more TB disease specific biomarkers, such as listed in FIG. **1** for TB disease, can also be detected by one or more systems disclosed herein, for characterizing a TB disease. For example, a detection system can comprise one or more probes to detect one or more TB disease specific biomarkers, such as listed in FIG. **1** for TB disease, of one or more exosomes of a biological sample.

[0611] HIV

[0612] Also provided herein is an isolated exosome comprising one or more HIV disease specific biomarkers, such as listed in FIG. **1** for HIV disease. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more HIV disease specific biomarkers, such as listed in FIG. **1** for HIV disease. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for HIV disease specific exosomes or exosomes comprising one or more HIV disease specific biomarkers, such as listed in FIG. **1** for HIV disease.

[0613] One or more HIV disease specific biomarkers, such as listed in FIG. **1** for HIV disease, can also be detected by one or more systems disclosed herein, for characterizing a HIV disease. For example, a detection system can comprise one or more probes to detect one or more HIV disease specific biomarkers, such as listed in FIG. **1** for HIV disease, of one or more exosomes of a biological sample.

[0614] The one or more biomarker can also be a miRNA, such as an upregulated or overexpressed miRNA. The upregulated miRNA can be miR-29a, miR-29b, miR-149, miR-378 or miR-324-5p. One or more biomarkers can also be used to characterize HIV-1 latency, such as by assessing one or more miRNAs. The miRNA can be miR-28, miR-125b, miR-150, miR-223 and miR-382, and upregulated.

[0615] Asthma

[0616] Also provided herein is an isolated exosome comprising one or more asthma disease specific biomarkers, such as listed in FIG. **1** for asthma disease. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more asthma disease specific biomarkers, such as listed in FIG. **1** for asthma disease. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for asthma disease specific exosomes or exosomes comprising one or more asthma disease specific biomarkers, such as listed in FIG. **1** for asthma disease.

[0617] One or more asthma disease specific biomarkers, such as listed in FIG. **1** for asthma disease, can also be detected by one or more systems disclosed herein, for characterizing a asthma disease. For example, a detection system can comprise one or more probes to detect one or more asthma disease specific biomarkers, such as listed in FIG. **1** for asthma disease, of one or more exosomes of a biological sample.

[0618] Lupus

[0619] Also provided herein is an isolated exosome comprising one or more lupus disease specific biomarkers, such as listed in FIG. **1** for lupus disease. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more lupus disease specific biomarkers, such as listed in FIG. **1** for lupus disease. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for lupus disease specific exosomes or exosomes comprising one or more lupus disease specific biomarkers, such as listed in FIG. **1** for lupus disease.

[0620] One or more lupus disease specific biomarkers, such as listed in FIG. **1** for lupus disease, can also be detected by one or more systems disclosed herein, for characterizing a lupus disease. For example, a detection system can comprise one or more probes to detect one or more lupus disease specific biomarkers, such as listed in FIG. **1** for lupus disease, of one or more exosomes of a biological sample.

[0621] Influenza

[0622] Also provided herein is an isolated exosome comprising one or more influenza disease specific biomarkers, such as listed in FIG. **1** for influenza disease. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more influenza disease specific biomarkers, such as listed in FIG. **1** for influenza disease. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for influenza disease specific exosomes or exosomes comprising one or more influenza disease specific biomarkers, such as listed in FIG. **1** for influenza disease.

[0623] One or more influenza disease specific biomarkers, such as listed in FIG. **1** for influenza disease, can also be detected by one or more systems disclosed herein, for characterizing a influenza disease. For example, a detection system can comprise one or more probes to detect one or more influenza disease specific biomarkers, such as listed in FIG. **1** for influenza disease, of one or more exosomes of a biological sample.

[0624] Thyroid Cancer

[0625] Also provided herein is an isolated exosome comprising one or more thyroid cancer specific biomarkers, such as AKAP-BRAF, CCDC6-RET, ERC1-RETM, GOLGA5-RET, HOOK3-RET, HRH4-RET, KTN1-RET, NCOA4-RET, PCM1-RET, PRKARA1A-RET, RFG-RET, RFG9-RET, Ria-RET, TGF-NTRK1, TPM3-NTRK1, TPM3-TPR, TPR-MET, TPR-NTRK1, TRIM24-RET, TRIM27-RET or TRIM33-RET, characteristic of papillary thyroid carcinoma; or PAX8-PPARy, characteristic of follicular thyroid cancer. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more thyroid cancer specific biomarkers, such as listed in FIG. **1** for thyroid cancer. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for thyroid cancer specific exosomes or exosomes comprising one or more thyroid cancer specific biomarkers, such as listed in FIG. **1** for thyroid cancer.

[0626] One or more thyroid cancer specific biomarkers, such as listed in FIG. **1** for thyroid cancer, can also be detected by one or more systems disclosed herein, for characterizing a thyroid cancer. For example, a detection system can comprise one or more probes to detect one or more thyroid cancer specific biomarkers, such as listed in FIG. **1** for thyroid cancer, of one or more exosomes of a biological sample.

[0627] Gene Fusions

[0628] The one or more biomarkers assessed of an exosome can be a gene fusion, such as one or more listed in FIG. **59**. A fusion gene is a hybrid gene created by the juxtaposition of two previously separate genes. This can occur by chromosomal translocation or inversion, deletion or via trans-splicing. The resulting fusion gene can cause abnormal temporal and spatial expression of genes, such as leading to abnormal expression of cell growth factors, angiogenesis factors, tumor promoters or other factors contributing to the neoplastic transformation of the cell and the creation of a tumor. Such fusion genes can be oncogenic due to the juxtaposition of: 1) a strong promoter region of one gene next to the coding region of a cell growth factor, tumor promoter or other gene promoting oncogenesis leading to elevated gene expression, or 2) due to the fusion of coding regions of two different genes, giving rise to a chimeric gene and thus a chimeric protein with abnormal activity.

[0629] An example of a fusion gene is BCR-ABL, a characteristic molecular aberration in ~90% of chronic myelogenous leukemia (CML) and in a subset of acute leukemias (Kurzrock et al., *Annals of Internal Medicine* 2003; 138(10): 819-830). The BCR-ABL results from a translocation between chromosomes 9 and 22. The translocation brings together the 5' region of the BCR gene and the 3' region of ABL1, generating a chimeric BCR-ABL1 gene, which encodes a protein with constitutively active tyrosine kinase activity (Mittleman et al., Nature *Reviews Cancer* 2007; 7(4): 233-245). The aberrant tyrosine kinase activity leads to de-regulated cell signaling, cell growth and cell survival, apoptosis resistance and growth factor independence, all of which contribute to the pathophysiology of leukemia (Kurzrock et al., *Annals of Internal Medicine* 2003; 138(10):819-830).

[0630] Another fusion gene is IGH-MYC, a defining feature of ~80% of Burkitt's lymphoma (Ferry et al. *Oncologist* 2006; 11(4):375-83). The causal event for this is a translocation between chromosomes 8 and 14, bringing the c-Myc oncogene adjacent to the strong promoter of the immunoglobin heavy chain gene, causing c-myc overexpression (Mittleman et al., *Nature Reviews Cancer* 2007; 7(4):233-245). The c-myc rearrangement is a pivotal event in lymphomagenesis as it results in a perpetually proliferative state. It has wide ranging effects on progression through the cell cycle, cellular differentiation, apoptosis, and cell adhesion (Ferry et al. *Oncologist* 2006; 11(4):375-83).

[0631] A number of recurrent fusion genes have been catalogued in the Mittleman database (http://cgap.nci.nih.gov/Chromosomes/Mitelman) and can be assess in an exosome and used to characterize a phenotype. The gene fusion can be used to characterize a hematological malignancy or epithelial tumor. For example, TMPRSS2-ERG, TMPRSS2-ETV and SLC45A3-ELK4 fusions can be detected and used to characterize prostate cancer; and ETV6-NTRK3 and ODZ4-NRG 1 for breast cancer.

[0632] Furthermore, assessing the presence or absence, or expression level of a fusion gene can be used to diagnosis a phenotype such as a cancer as well as a monitoring a therapeutic response to selecting a treatment. For example, the presence of the BCR-ABL fusion gene is a characteristic not only for the diagnosis of CML, but is also the target of the Novartis drug Imatinib mesylate (Gleevec), a receptor tyrosine kinase inhibitor, for the treatment of CML. Imatinib treatment has led to molecular responses (disappearance of BCR-ABL+blood cells) and improved progression-free survival in BCR-ABL+CML patients (Kantarjian et al., *Clinical Cancer Research* 2007; 13(4):1089-1097).

[0633] Assessing an exosome for the presence, absence, or expression level of a gene fusion can be of a heterogeneous population of exosomes. Alternatively, the exosome can be derived from a specific cell type, such as cell-or-origin specific exosomes, as described above.

[0634] Breast Cancer

[0635] To characterize a breast cancer, an exosome can be assessed for one or more breast cancer specific fusions, including, but not limited to, ETV6-NTRK3. The exosome can be derived from breast cancer cells.

[0636] Lung Cancer

[0637] To characterize a lung cancer, an exosome can be assessed for one or more lung cancer specific fusions, including, but not limited to, RLF-MYCL1, TGF-ALK, or CD74-ROS1. The exosome can be derived from lung cancer cells.

[0638] Prostate Cancer

[0639] To characterize a prostate cancer, an exosome can be assessed for one or more prostate cancer specific fusions, including, but not limited to, ACSL3-ETV1, C15ORF21-ETV1, FLJ35294-ETV1, HERV-ETV1, TMPRSS2-ERG, TMPRSS2-ETV1/4/5, TMPRSS2-ETV4/5, SLC5A3-ERG, SLC5A3-ETV1, SLC5A3-ETV5 or KLK2-ETV4. The exosome can be derived from prostate cancer cells.

[0640] Brain Cancer

[0641] To characterize a brain cancer, an exosome can be assessed for one or more brain cancer specific fusions, including, but not limited to, GOPC-ROS1. The exosome can be derived from brain cancer cells.

[0642] Head and Neck Cancer

[0643] To characterize ahead and neck cancer, an exosome can be assessed for one or more head and neck cancer specific fusions, including, but not limited to, CHCHD7-PLAG1, CTNNB1-PLAG1, FHIT-HMGA2, HMGA2-NFIB, LIFR-PLAG1, or TCEA1-PLAG1. The exosome can be derived from head and neck cancer cells.

[0644] Renal Cell Carcinoma (RCC)

[0645] To characterize a RCC, an exosome can be assessed for one or more RCC specific fusions, including, but not limited to, ALPHA-TFEB, NONO-TFE3, PRCC-TFE3, SFPQ-TFE3, CLTC-TFE3, or MALAT1-TFEB. The exosome can be derived from RCC cells.

[0646] Thyroid Cancer

[0647] To characterize a thyroid cancer, an exosome can be assessed for one or more thyroid cancer specific fusions, including, but not limited to, AKAP9-BRAF, CCDC6-RET, ERC1-RETM, GOLGA5-RET, HOOK3-RET, HRH4-RET, KTN1-RET, NCOA4-RET, PCM1-RET, PRKARA1A-RET, RFG-RET, RFG9-RET, R1a—RET, TGF-NTRK1, TPM3-NTRK1, TPM3-TPR, TPR-MET, TPR-NTRK1, TRIM24-RET, TRIM27-RET or TRIM33-RET, characteristic of papillary thyroid carcinoma; or PAX8-PPARy, characteristic of follicular thyroid cancer. The exosome can be derived from thyroid cancer cells.

[0648] Blood Cancers

[0649] To characterize a blood cancer, an exosome can be assessed for one or more blood cancer specific fusions, including, but not limited to, TTL-ETV6, CDK6-MLL, CDK6-TLX3, ETV6-FLT3, ETV6-RUNX1, ETV6-TTL, MLL-AFF1, MLL-AFF3, MLL-AFF4, MLL-GAS7, TCBA1-ETV6, TCF3-PBX1 or TCF3-TFPT, characteristic of acute lymphocytic leukemia (ALL); BCL11B-TLX3, IL2-TNFRFS17, NUP214-ABL1, NUP98-CCDC28A, TALI-STIL, or ETV6-ABL2, characteristic of T-cell acute lymphocytic leukemia (T-ALL); ATIC-ALK, KIAA1618-ALK, MSN-ALK, MYH9-ALK, NPM1-ALK, TGF-ALK or TPM3-ALK, characteristic of anaplastic large cell lymphoma (ALCL); BCR-ABL1, BCR-JAK2, ETV6-EVI1, ETV6-MN1 or ETV6-TCBA1, characteristic of chronic myelogenous leukemia (CML); CBFB-MYH11, CHIC2-ETV6, ETV6-ABL1, ETV6-ABL2, ETV6-ARNT, ETV6-CDX2, ETV6-HLXB9, ETV6-PER1, MEF2D-DAZAP1, AML-AFF1, MLL-ARHGAP26, MLL-ARHGEF12, MLL-CASC5, MLL-CBL, MLL-CREBBP, MLL-DAB21P, MLL-ELL, MLL-EP300, MLL-EPS15, MLL-FNBP1, MLL-FOXO3A, MLL-GMPS, MLL-GPHN, MLL-MLLT1, MLL-MLLT11, MLL-MLLT3, MLL-MLLT6, MLL-MYO1F, MLL-PICALM, MLL-SEPT2, MLL-SEPT6, MLL-SORBS2, MYST3-SORBS2, MYST-CREBBP, NPM1-MLF1, NUP98-HOXA13, PRDM16-EVI1, RABEP1-PDGFRB, RUNX1-EVI1, RUNX1-MDS1, RUNX1-RPL22, RUNX1-RUNX1T1, RUNX1-SH3D19, RUNX1-USP42, RUNX1-YTHDF2, RUNX1-ZNF687, or TAF15-ZNF-384, characteristic of AML; CCND1-FSTL3, characteristic of chronic lymphocytic leukemia (CLL); BCL3-MYC, MYC-BTG1, BCL7A-MYC, BRWD3-ARHGAP20 or BTG1-MYC, characteristic of B-cell chronic lymphocytic leukemia (B-CLL); CITTA-BCL6, CLTC-ALK, IL21R-BCL6, PIM1-BCL6, TFCR-BCL6, IKZF1-BCL6 or SEC31A-ALK, characteristic of diffuse large B-cell lymphomas (DLBCL); FLIP1-PDGFRA, FLT3-ETV6, KIAA1509-PDGFRA, PDE4DIP-PDGFRB, NIN-PDGFRB, TP53BP1-PDGFRB, or TPM3-PDGFRB, characteristic of hyper eosinophilia/chronic eosinophilia; IGH-MYC or LCP1-BCL6, characteristic of Burkitt's lymphoma. The exosome can be derived from blood cancer cells.

[0650] Also provided herein is an isolated exosome comprising one or more gene fusions as disclosed herein, such as listed in FIG. **59**. A composition comprising the isolated exosome is also provided. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more gene fusions, such as listed in FIG. **59**. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for exosomes comprising one or more gene fusions, such as listed in FIG. **59**.

[0651] Also provided herein is a detection system for detecting one or more gene fusions, such as gene fusions listed in FIG. **59**. For example, a detection system can comprise one or more probes to detect one or more gene fusions listed in FIG. **59**. Detection of the one or more gene fusions can be used to characterize a cancer.

[0652] Gene-Associated mRNA Biomarkers

[0653] The one or more biomarkers assessed can also include one or more genes selected from the group consisting of PFKFB3, RHAMM (HMMR), cDNA FLJ42103, ASPM, CENPF, NCAPG, Androgen Receptor, EGFR, HSP90, SPARC, DNMT3B, GART, MGMT, SSTR3, and TOP2B. The microRNA that interacts with the one or more genes can also be a biomarker (see for example, FIG. **60**). Furthermore, the one or more biomarkers can be used to characterize prostate cancer.

[0654] Also provided herein is an isolated exosome comprising one or more one or more biomarkers consisting of PFKFB3, RHAMM (HMMR), cDNA FLJ42103, ASPM, CENPF, NCAPG, Androgen Receptor, EGFR, HSP90, SPARC, DNMT3B, GART, MGMT, SSTR3, and TOP2B; or the microRNA that interacts with the one or more genes (see for example, FIG. **60**). Also provided is a composition comprising the isolated exosome. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more biomarkers consisting of PFKFB3, RHAMM (HMMR), cDNA FLJ42103, ASPM, CENPF, NCAPG, Androgen Receptor, EGFR, HSP90, SPARC, DNMT3B, GART, MGMT, SSTR3, and TOP2B; or the microRNA that interacts with the one or more genes, such as listed in FIG. **60**. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for exosomes comprising one or more biomarkers consisting of PFKFB3, RHAMM (HMMR), cDNA FLJ42103, ASPM, CENPF, NCAPG, Androgen Receptor, EGFR, HSP90, SPARC, DNMT3B, GART, MGMT, SSTR3, and TOP2B; or the microRNA that interacts with the one or more genes, such as listed in FIG. **60**.

[0655] One or more prostate cancer specific biomarkers, such as listed in FIG. **60** can also be detected by one or more systems disclosed herein. For example, a detection system can comprise one or more probes to detect one or more prostate cancer specific biomarkers, such as listed in FIG. **60**, of one or more exosomes of a biological sample.

[0656] The miRNA that interacts with PFKFB3 can be miR-513a-3p, miR-128, miR-488, miR-539, miR-658, miR-524-5p, miR-1258, miR-150, miR-216b, miR-377, miR-135a, miR-26a, miR-548a-5p, miR-26b, miR-520d-5p, miR-224, miR-1297, miR-1197, miR-182, miR-452, miR-509-3-5p, miR-548m, miR-625, miR-509-5p, miR-1266, miR-135b, miR-190b, miR-496, miR-616, miR-621, miR-650, miR-105, miR-19a, miR-346, miR-620, miR-637, miR-651, miR-1283, miR-590-3p, miR-942, miR-1185, miR-577, miR-602, miR-1305, miR-220c, miR-1270, miR-1282, miR-432, miR-491-5p, miR-548n, miR-765, miR-768-3p or miR-924, and can be used as a biomarker.

[0657] Also provided herein is an isolated exosome comprising one or more one or more miRNA that interacts with PFKFB3. Also provided is a composition comprising the isolated exosome. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more biomarkers consisting of miRNA that interacts with PFKFB3. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for exosomes comprising one or more miRNA that interacts with PFKFB3. Furthermore, the one or more miRNA that interacts with PFKFB3 can also be detected by one or more systems disclosed herein. For example, a detection system can comprise one or more probes to detect one or more one or more miRNA that interacts with PFKFB3 of one or more exosomes of a biological sample.

[0658] The miRNA that interacts with RHAMM can be miR-936, miR-656, miR-105, miR-361-5p, miR-194, miR-374a, miR-590-3p, miR-186, miR-769-5p, miR-892a, miR-380, miR-875-3p, miR-208a, miR-208b, miR-586, miR-125a-3p, miR-630, miR-374b, miR-411, miR-629, miR-1286, miR-1185, miR-16, miR-200b, miR-671-5p, miR-95, miR-421, miR-496, miR-633, miR-1243, miR-127-5p, miR-143, miR-15b, miR-200c, miR-24 or miR-34c-3p.

[0659] Also provided herein is an isolated exosome comprising one or more one or more miRNA that interacts with RHAMM. Also provided is a composition comprising the isolated exosome. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more biomarkers consisting of miRNA that interacts with RHAMM. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for exosomes comprising one or more miRNA that interacts with RHAMM. Furthermore, the one or more miRNA that interacts with RHAMM can also be detected by one or more systems disclosed herein. For example, a detection system can comprise one or more probes to detect one or more one or more miRNA that interacts with RHAMM of one or more exosomes of a biological sample.

[0660] The miRNA that interacts with CENPF can be miR-30c, miR-30b, miR-190, miR-508-3p, miR-384, miR-512-5p, miR-548p, miR-297, miR-520f, miR-376a, miR-1184, miR-577, miR-708, miR-205, miR-376b, miR-520g, miR-520h, miR-519d, miR-596, miR-768-3p, miR-340, miR-620, miR-539, miR-567, miR-671-5p, miR-1183, miR-129-3p, miR-636, miR-106a, miR-1301, miR-17, miR-20a, miR-570, miR-656, miR-1263, miR-1324, miR-142-5p, miR-28-5p, miR-302b, miR-452, miR-520d-3p, miR-548o, miR-892b, miR-302d, miR-875-3p, miR-106b, miR-1266, miR-1323, miR-20b, miR-221, miR-520e, miR-664, miR-920, miR-922, miR-93, miR-1228, miR-1271, miR-30e, miR-483-3p, miR-509-3-5p, miR-515-3p, miR-519e, miR-520b, miR-520c-3p or miR-582-3p.

[0661] Also provided herein is an isolated exosome comprising one or more one or more miRNA that interacts with CENPF. Also provided is a composition comprising the isolated exosome. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more biomarkers consisting of miRNA that interacts with CENPF. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for exosomes comprising one or more miRNA that interacts with CENPF. Furthermore, the one or more miRNA that interacts with CENPF can also be detected by one or more systems disclosed herein. For example, a detection system can comprise one or more probes to detect one or more one or more miRNA that interacts with CENPF of one or more exosomes of a biological sample.

[0662] The miRNA that interacts with NCAPG can be miR-876-5p, miR-1260, miR-1246, miR-548c-3p, miR-1224-3p, miR-619, miR-605, miR-490-5p, miR-186, miR-448, miR-129-5p, miR-188-3p, miR-516b, miR-342-3p, miR-1270, miR-548k, miR-654-3p, miR-1290, miR-656, miR-34b, miR-520g, miR-1231, miR-1289, miR-1229, miR-23a, miR-23b, miR-616 or miR-620.

[0663] Also provided herein is an isolated exosome comprising one or more one or more miRNA that interacts with NCAPG. Also provided is a composition comprising the isolated exosome. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more biomarkers consisting of miRNA that interacts with NCAPG. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for exosomes comprising one or more miRNA that interacts with NCAPG. Furthermore, the one or more miRNA that interacts with NCAPG can also be detected by one or more systems disclosed herein. For example, a detection system can comprise one or more probes to detect one or more one or more miRNA that interacts with NCAPG of one or more exosomes of a biological sample.

[0664] The miRNA that interacts with Androgen Receptor can be miR-124a, miR-130a, miR-130b, miR-143, miR-149, miR-194, miR-29b, miR-29c, miR-301, miR-30a-5p, miR-30d, miR-30e-5p, miR-337, miR-342, miR-368, miR-488, miR-493-5p, miR-506, miR-512-5p, miR-644, miR-768-5p or miR-801.

[0665] The miRNA that interacts with EGFR can be miR-105, miR-128a, miR-128b, miR-140, miR-141, miR-146a, miR-146b, miR-27a, miR-27b, miR-302a, miR-302d, miR-370, miR-548c, miR-574, miR-587 or miR-7.

[0666] Also provided herein is an isolated exosome comprising one or more one or more miRNA that interacts with AR. Also provided is a composition comprising the isolated exosome. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more biomarkers consisting of miRNA that interacts with AR. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for exosomes comprising one or more miRNA that interacts with AR. Furthermore, the one or more miRNA that interacts with AR can also be detected by one or more systems disclosed herein. For example, a detection system can comprise one or more probes to detect one or more one or more miRNA that interacts with AR of one or more exosomes of a biological sample.

[0667] The miRNA that interacts with HSP90 can be miR-1, miR-513a-3p, miR-548d-3p, miR-642, miR-206, miR-450b-3p, miR-152, miR-148a, miR-148b, miR-188-3p, miR-23a, miR-23b, miR-578, miR-653, miR-1206, miR-192, miR-215, miR-181b, miR-181d, miR-223, miR-613, miR-769-3p, miR-99a, miR-100, miR-454, miR-548n, miR-640, miR-99b, miR-150, miR-181a, miR-181c, miR-522, miR-624, miR-130a, miR-130b, miR-146, miR-148a, miR-148b, miR-152, miR-181a, miR-181b, miR-181c, miR-204, miR-206, miR-211, miR-212, miR-215, miR-223, miR-23a, miR-23b, miR-301, miR-31, miR-325, miR-363, miR-566, miR-9 or miR-99b.

[0668] Also provided herein is an isolated exosome comprising one or more one or more miRNA that interacts with HSP90. Also provided is a composition comprising the isolated exosome. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more biomarkers consisting of miRNA that interacts with HSP90. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for exosomes comprising one or more miRNA that interacts with HSP90. Furthermore, the one or more miRNA that interacts with HSP90 can also be detected by one or more systems disclosed herein. For example, a detection system can comprise one or more probes to detect one or more one or more miRNA that interacts with HSP90 of one or more exosomes of a biological sample.

[0669] The miRNA that interacts with SPARC can be miR-768-5p, miR-203, miR-196a, miR-569, miR-187, miR-641, miR-1275, miR-432, miR-622, miR-296-3p, miR-646, miR-196b, miR-499-5p, miR-590-5p, miR-495, miR-625, miR-1244, miR-512-5p, miR-1206, miR-1303, miR-186, miR-302d, miR-494, miR-562, miR-573, miR-10a, miR-203, miR-204, miR-211, miR-29, miR-29b, miR-29c, miR-339, miR-433, miR-452, miR-515-5p, miR-517a, miR-517b, miR-517c, miR-592 or miR-96.

[0670] Also provided herein is an isolated exosome comprising one or more one or more miRNA that interacts with SPARC. Also provided is a composition comprising the isolated exosome. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more biomarkers consisting of miRNA that interacts with SPARC. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for exosomes comprising one or more miRNA that interacts with SPARC. Furthermore, the one or more miRNA that interacts with SPARC can also be detected by one or more systems disclosed herein. For example, a detection system can comprise one or more probes to detect one or more one or more miRNA that interacts with SPARC of one or more exosomes of a biological sample.

[0671] The miRNA that interacts with DNMT3B can be miR-618, miR-1253, miR-765, miR-561, miR-330-5p, miR-326, miR-188, miR-203, miR-221, miR-222, miR-26a, miR-26b, miR-29a, miR-29b, miR-29c, miR-370, miR-379, miR-429, miR-519e, miR-598, miR-618 or miR-635.

[0672] Also provided herein is an isolated exosome comprising one or more one or more miRNA that interacts with DNMT3B. Also provided is a composition comprising the isolated exosome. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more biomarkers consisting of miRNA that interacts with DNMT3B. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for exosomes comprising one or more miRNA that interacts with DNMT3B. Furthermore, the one or more miRNA that interacts with DNMT3B can also be detected by one or more systems disclosed herein. For example, a detection system can comprise one or more probes to detect one or more one or more miRNA that interacts with DNMT3B of one or more exosomes of a biological sample.

[0673] The miRNA that interacts with GART can be miR-101, miR-141, miR-144, miR-182, miR-189, miR-199a, miR-199b, miR-200a, miR-200b, miR-202, miR-203, miR-223, miR-329, miR-383, miR-429, miR-433, miR-485-5p, miR-493-5p, miR-499, miR-519a, miR-519b, miR-519c, miR-569, miR-591, miR-607, miR-627, miR-635, miR-636 or miR-659.

[0674] Also provided herein is an isolated exosome comprising one or more one or more miRNA that interacts with GART. Also provided is a composition comprising the isolated exosome. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more biomarkers consisting of miRNA that interacts with GART. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for exosomes comprising one or more miRNA that interacts with GART. Furthermore, the one or more miRNA that interacts with GART can also be detected by one or more systems disclosed herein. For example, a detection system can comprise one or more probes to detect one or more one or more miRNA that interacts with GART of one or more exosomes of a biological sample.

[0675] The miRNA that interacts with MGMT can be miR-122a, miR-142-3p, miR-17-3p, miR-181a, miR-181b, miR-181c, miR-181d, miR-199b, miR-200a, miR-217, miR-302b, miR-32, miR-324-3p, miR-34a, miR-371, miR-425-5p, miR-496, miR-514, miR-515-3p, miR-516-3p, miR-574, miR-597, miR-603, miR-653, miR-655, miR-92, miR-92b or miR-99a.

[0676] Also provided herein is an isolated exosome comprising one or more one or more miRNA that interacts with MGMT. Also provided is a composition comprising the isolated exosome. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more biomarkers consisting of miRNA that interacts with MGMT. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for exosomes comprising one or more miRNA that interacts with MGMT. Furthermore, the one or more miRNA that interacts with MGMT can also be detected by one or more systems disclosed herein. For example, a detection system can comprise one or more probes to detect one or more one or more miRNA that interacts with MGMT of one or more exosomes of a biological sample.

[0677] The miRNA that interacts with SSTR3 can be miR-125a, miR-125b, miR-133a, miR-133b, miR-136, miR-150, miR-21, miR-380-5p, miR-504, miR-550, miR-671, miR-766 or miR-767-3p.

[0678] Also provided herein is an isolated exosome comprising one or more one or more miRNA that interacts with SSTR3. Also provided is a composition comprising the isolated exosome. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more biomarkers consisting of miRNA that interacts with SSTR3. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for exosomes comprising one or more miRNA that interacts with SSTR3. Furthermore, the one or more miRNA that interacts with SSTR3 can also be detected by one or more systems disclosed herein. For example, a detection system can comprise one or more probes to detect one or more one or more miRNA that interacts with SSTR3 of one or more exosomes of a biological sample.

[0679] The miRNA that interacts with TOP2B can be miR-548f, miR-548a-3p, miR-548g, miR-513a-3p, miR-548c-3p, miR-101, miR-653, miR-548d-3p, miR-575, miR-297, miR-576-3p, miR-548b-3p, miR-624, miR-548n, miR-758, miR-1253, miR-1324, miR-23b, miR-320a, miR-320b, miR-1183, miR-1244, miR-23a, miR-451, miR-568, miR-1276, miR-548e, miR-590-3p, miR-1, miR-101, miR-126, miR-129, miR-136, miR-140, miR-141, miR-144, miR-147, miR-149, miR-18, miR-181b, miR-181c, miR-182, miR-184, miR-186, miR-189, miR-191, miR-19a, miR-19b, miR-200a, miR-206, miR-210, miR-218, miR-223, miR-23a, miR-23b, miR-24, miR-27a, miR-302, miR-30a, miR-31, miR-320, miR-323, miR-362, miR-374, miR-383, miR-409-3p, miR-451, miR-489, miR-493-3p, miR-514, miR-542-3p, miR-544, miR-548a, miR-548b, miR-548c, miR-548d, miR-559, miR-568, miR-575, miR-579, miR-585, miR-591, miR-598, miR-613, miR-649, miR-651, miR-758, miR-768-3p or miR-9.

[0680] Also provided herein is an isolated exosome comprising one or more one or more miRNA that interacts with TOP2B. Also provided is a composition comprising the isolated exosome. Accordingly, in some embodiments, the composition comprises a population of exosomes comprising one or more biomarkers consisting of miRNA that interacts with TOP2B. The composition can comprise a substantially enriched population of exosomes, wherein the population of exosomes is substantially homogeneous for exosomes comprising one or more miRNA that interacts with TOP2B. Furthermore, the one or more miRNA that interacts with TOP2B can also be detected by one or more systems disclosed herein. For example, a detection system can comprise one or more probes to detect one or more one or more miRNA that interacts with TOP2B of one or more exosomes of a biological sample.

Bio-Signatures: Biomarker Detection

[0681] Bio-signatures can be detected qualitatively or quantitatively. Exosome levels may be characterized as described above. Analysis of exosomes can comprise detecting the level of exosomes in combination with determining the biomarkers of the exosomes. Determining the level or amount of exosome can be performed in conjunction with determining the biomarkers of the exosome. Alternatively, determining the amount of exosome may be performed prior to or subsequent to determining the biomarkers of the exosomes. Methods for analyzing biomarkers of tissues or cells can be used to analyze the biomarkers associated with or contained in exosomes.

[0682] For example, biomarkers can be detected by microarray analysis, PCR (including PCR-based methods such as RT-PCR, qPCR and the like), hybridization with allele-specific probes, enzymatic mutation detection, ligation chain reaction (LCR), oligonucleotide ligation assay (OLA), flow-cytometric heteroduplex analysis, chemical cleavage of mismatches, mass spectrometry, nucleic acid sequencing, single strand conformation polymorphism (SSCP), denaturing gradient gel electrophoresis (DGGE), temperature gradient gel electrophoresis (TGGE), restriction fragment polymorphisms, serial analysis of gene expression (SAGE), or any combinations thereof. The biomarker, such as a nucleic acid, can be amplified prior to detection. Biomarkers can also be detected by immunoblot, immunoprecipitation, ELISA, RIA, flow cytometry, or electron microscopy.

[0683] One method of detecting biomarkers can include purifying or isolating a heterogeneous exosome population from a biological sample, as described above, and performing a sandwich assay. An exosome in the population can be captured with a primary antibody, such as an antibody bound to a substrate, for example an array, well, or particle. The captured or bound exosome can be detected with a detection antibody. For example, the detection antibody can be for an antigen of the exosome. The detection antibody can be directly labeled and detected. Alternatively, an enzyme linked secondary antibody can react with the detection antibody. A detection reagent or detection substrate is added and the reaction can be detected, such as described in PCT Publication No. WO2009092386. The primary antibody can be an anti-Rab 5b antibody and the detection antibody anti-CD63 or anti-caveolin-1. Alternatively, the capture antibody can be an antibody to CD9, PSCA, TNFR, CD63, B7H3, MFG-E8, EpCam, Rab, CD81, STEAP, PCSA, PSMA, or 5T4. The detection antibody can be an antibody to CD63, CD9, CD81, B7H3, or EpCam.

[0684] In some embodiments, the capture agent binds or targets EpCam, and the one or more biomarkers detected on the exosome is CD9, CD63, or both CD9 and CD63. In other embodiments, the capture agent targets PCSA, and the one or more biomarkers detected on the captured exosome is B7H3, PSMA, or both B7H3 and PSMA. In yet other embodiments, the capture agent targets CD63 and the one or more biomarkers detected on the exosome is CD81, CD83, CD9, CD63, or any combination thereof. The different capture agent and biomarker combinations can be used to characterize a phenotype, such as prostate cancer or colon cancer. For example, capturing one or more exosomes can be performed with a capture agent targeting EpCam and detection of CD9 and CD63; a capture agent targeting PCSA and detection of B7H3 and PSMA; or a capture agent of CD63 and detection of CD81; can be used to characterize prostate cancer. A capture agent targeting CD63 and detection of CD63, or a capture agent targeting CD9 and detecting CD63, can be used to characterize colon cancer.

[0685] Other methods can include the use of a planar substrate such as an array (i.e., biochip or microarray), with immobilized molecules as capture agents, which can facilitate the detection of a particular bio-signature of exosomes. The arrays can be provided as part of a kit for assaying exosomes. Molecules that identify the biomarkers described above and shown in FIG. **3-60**, as well as antigens in FIG. **1** can be included in a custom array for detection and diagnosis of diseases including presymtomatic diseases. Arrays comprising biomolecules that specifically identify selected biomarkers can be used to develop a database of information using data provided in the present specification. Additional biomolecules that identify bio-signatures which lead to improved cross-validated error rates in multivariate prediction models (e.g., logistic regression, discriminant analysis, or regression tree models) can be included in a custom array.

[0686] Customized array(s) provide an opportunity to study the biology of a disease, condition or syndrome and profile exosomes that are shed in defined physiological states. Standard p values of significance (0.05) can be chosen to exclude or include additional specific biomolecules on the microarray that identify particular biomarkers.

[0687] A planar array can generally contain addressable locations (e.g., pads, addresses, or micro-locations) of biomolecules in an array format. The size of the array will depend on the composition and end use of the array. Arrays containing from about 2 different molecules to many thousands can be made. Generally, the array can comprise from two to as many as 100,000 or more molecules, depending on the end use of the array and the method of manufacture. A microarray can generally comprise at least one biomolecule that identifies or captures a biomarker present in a bio-signature of specific cell-of-origin exosomes. In some embodiments, the compositions of the invention may not be in an array format; that is, for some embodiments, compositions comprising a single biomolecule may be made as well. In addition, in some arrays, multiple substrates may be used, either of different or identical compositions. Thus, for example, large planar arrays may comprise a plurality of smaller substrates.

[0688] An array of the present invention encompasses any means for detecting a biomarker. For example, microarrays can be biochips that provide high-density immobilized arrays of recognition molecules (e.g., antibodies), where biomarker binding is monitored indirectly (e.g., via fluorescence). In addition, an array can be of a format that involves the capture of proteins by biochemical or intermolecular interaction, coupled with direct detection by mass spectrometry (MS).

[0689] Arrays and microarrays that can be used to detect the biomarkers of a bio-signature of exosomes can be made according to the methods described in U.S. Pat. Nos. 6,329,209; 6,365,418; 6,406,921; 6,475,808; and 6,475,809, and U.S. patent application Ser. No. 10/884,269, each of which is herein incorporated by reference in its entirety. New arrays, to detect specific selections of sets of biomarkers described herein can also be made using the methods described in these patents. Furthermore, commercially available microarrays, such as for protein or nucleic acid detection can also be used, such as from Affymetrix (Santa Clara, Calif.), Illumina (San Diego, Calif.), Agilent (Santa Clara, Calif.), Exiqon (Denmark), or Invitrogen (Carlsbad, Calif.).

[0690] In many embodiments, immobilized molecules, or molecules to be immobilized, are proteins or peptides. One or more types of proteins may be immobilized on a surface. In certain embodiments, the proteins are immobilized using methods and materials that minimize the denaturing of the proteins, that minimize alterations in the activity of the proteins, or that minimize interactions between the protein and the surface on which they are immobilized.

[0691] Surfaces useful may be of any desired shape (form) and size. Non-limiting examples of surfaces include chips, continuous surfaces, curved surfaces, flexible surfaces, films, plates, sheets, tubes, or the like. Surfaces can have areas ranging from approximately a square micron to approximately 500 cm^2. The area, length, and width of surfaces according to the present invention may be varied according to the requirements of the assay to be performed. Considerations may include, for example, ease of handling, limitations of the material(s) of which the surface is formed, requirements of detection systems, requirements of deposition systems (e.g., arrayers), or the like.

[0692] In certain embodiments, it is desirable to employ a physical means for separating groups or arrays of binding islands or immobilized biomolecules: such physical separation facilitates exposure of different groups or arrays to different solutions of interest. Therefore, in certain embodiments, arrays are situated within microwell plates having any number of wells. In such embodiments, the bottoms of the wells may serve as surfaces for the formation of arrays, or arrays may be formed on other surfaces and then placed into wells. In certain embodiments, such as where a surface without wells is used, binding islands may be formed or molecules may be immobilized on a surface and a gasket having holes spatially arranged so that they correspond to the islands or biomolecules may be placed on the surface. Such a gasket is preferably liquid tight. A gasket may be placed on a surface at any time during the process of making the array and may be removed if separation of groups or arrays is no longer necessary.

[0693] The immobilized molecules can bind to exosomes present in a biological sample overlying the immobilized molecules. Alternatively, the immobilized molecules modify or are modified by molecules present in exosomes overlying the immobilized molecules.

[0694] Modifications or binding of molecules in solution or immobilized on an array may be detected using detection techniques known in the art. Examples of such techniques include immunological techniques such as competitive binding assays and sandwich assays; fluorescence detection using instruments such as confocal scanners, confocal microscopes, or CCD-based systems and techniques such as fluorescence, fluorescence polarization (FP), fluorescence resonant energy transfer (FRET), total internal reflection fluorescence (TIRF), fluorescence correlation spectroscopy (FCS); colorimetric/spectrometric techniques; surface plasmon resonance, by which changes in mass of materials adsorbed at surfaces may be measured; techniques using radioisotopes, including conventional radioisotope binding and scintillation proximity assays (SPA); mass spectroscopy, such as matrix-assisted laser desorption/ionization mass spectroscopy (MALDI) and MALDI-time of flight (TOF) mass spectroscopy; ellipsometry, which is an optical method of measuring thickness of protein films; quartz crystal microbalance (QCM), a very sensitive method for measuring mass of materials adsorbing to surfaces; scanning probe microscopies, such as AFM and SEM; and techniques such as electrochemical, impedance, acoustic, microwave, and IR/Raman detection. See, e.g., Mere L, et al., "*Miniaturized FRET assays and microfluidics: key components for ultra-high-throughput screening,*" Drug Discovery Today 4(8):363-369 (1999), and references cited therein; Lakowicz J R, *Principles of Fluorescence Spectroscopy, 2nd Edition*, Plenum Press (1999), or Jain K K: *Integrative Omics, Pharmacoproteomics, and Human Body Fluids. In: Thongboonkerd V, ed., ed. Proteomics of Human Body Fluids: Principles, Methods and Applications. Volume* 1: Totowa, N.J.: Humana Press, 2007, each of which is herein incorporated by reference in its entirety.

[0695] Microarray technology can be combined with mass spectroscopy (MS) analysis and other tools. Electrospray interface to a mass spectrometer can be integrated with a capillary in microfluidics devices. For example, one commercially available system contains eTag reporters that are fluorescent labels with unique and well-defined electrophoretic mobilities; each label is coupled to biological or chemical probes via cleavable linkages. The distinct mobility address of each eTag reporter allows mixtures of these tags to be rapidly deconvoluted and quantitated by capillary electrophoresis. This system allows concurrent gene expression, protein expression, and protein function analyses from the same sample Jain K K: *Integrative Omics, Pharmacoproteomics, and Human Body Fluids. In: Thongboonkerd V, ed., ed. Proteomics of Human Body Fluids Principles, Methods and Applications. Volume* 1: Totowa, N.J.: Humana Press, 2007, which is herein incorporated by reference in its entirety.

[0696] These biochips can include components for microfluidic or nanofluidic assays. Microfluidic devices can be used for isolating exosomes, such as described herein, in combination with analyzing the exosomes, such as determining bio-signatures. Such systems miniaturize and compartmentalize processes that allow for capturing of exosomes, detection of exosomal biomarkers, and other processes. The microfluidic devices can utilize detection reagents in at least one aspect of the system, and such detection reagents may be used to detect one or more biomarkers of exosomes. For example, the device can detect biomarkers on the isolated exosomes or bound exosomes. One or more biomarkers of a sample of isolated exosomes can be detected through the use of a microfluidic device. For example, various probes, antibodies, proteins, or other binding agents can be used to detect a biomarker. The detection agents may be immobilized in different compartments of the microfluidic device or be entered into a hybridization or detection reaction through various channels of the device.

[0697] An exosome in a microfluidic device may be lysed and the contents, such as proteins or nucleic acids, such as DNA or RNA (such as miRNA, mRNA) can be detected within a microfluidic device. The nucleic acid may be amplified prior to detection, or directly detected, within the microfluidic device. Thus microfluidic systems can also be used for multiplexing detection of various biomarkers.

[0698] Novel nanofabrication techniques are opening up the possibilities for biosensing applications that rely on fabrication of high-density, precision arrays, e.g., nucleotide-based chips and protein arrays otherwise know as heterogeneous nanoarrays. Nanofluidics allows a further reduction in the quantity of fluid analyte in a microchip to nanoliter levels, and the chips used here are referred to as nanochips. (See, e.g., Unger M et al., *Biotechniques* 1999; 27(5):1008-14, Kartalov E P et al., *Biotechniques* 2006; 40(1):85-90, each of which are herein incorporated by reference in their entireties.) Commercially available nanochips currently provide simple one step assays such as total cholesterol, total protein or glucose assays that can be run by combining sample and reagents, mixing and monitoring of the reaction. Gel-free analytical approaches based on liquid chromatography (LC) and nanoLC separations (Cutillas et al. *Proteomics,* 2005; 5:101-112 and Cutillas et al., *Mol Cell Proteomics* 2005; 4:1038-1051, each of which is herein incorporated by reference in its entirety) can be used in combination with the nanochips.

[0699] Arrays suitable for identifying a disease, condition or a syndrome or physiological status may be included in kits. Such kits may also include, as non-limiting examples, reagents useful for preparing molecules for immobilization onto binding islands or areas of an array, reagents useful for detecting binding of exosomes or exosomal components to immobilized molecules, and instructions for use.

[0700] Further provided herein is a rapid detection device that facilitates the detection of a particular bio-signature of exosomes in a biological sample. The device can integrate biological sample preparation with polymerase chain reaction (PCR) on a chip. The device can facilitate the detection of a particular bio-signature of exosomes in a biological sample, and an example is provided as described in Pipper et al., *Angewandte Chemie,* 47(21), p. 3900-3904 (2008), which is herein incorporated by reference in its entirety. The bio-signatures of the exosomes can be incorporated using micro-/nano-electrochemical system (MEMS/NEMS) sensors and oral fluid for diagnostic applications as described in Li et al., *Adv Dent Res* 18(1): 3-5 (2005), which is herein incorporated by reference in its entirety.

[0701] As an alternative to planar arrays, assays using particles, such as bead based assays as described herein, can be used in combination with flow cytometry. Multiparametric assays or other high throughput detection assays using bead coatings with cognate ligands and reporter molecules with specific activities consistent with high sensitivity automation can be used. In bead based assay systems, the binding agents, such as an antibody for exosomes, can be immobilized on addressable microspheres. Each binding agent for each individual binding assay is coupled to a distinct type of microsphere (i.e., microbead) and the assay reaction takes place on the surface of the microspheres, such as depicted in FIG. **64**A. A binding agent for an exosome, such as a capture antibody is coupled to a bead. Dyed microspheres with discrete fluorescence intensities are loaded separately with their appropriate binding agent or capture probes. The different bead sets carrying different binding agents can be pooled as necessary to generate custom bead arrays. Bead arrays are then incubated with the sample in a single reaction vessel to perform the assay. Examples of microfluidic devices that may be used, or adapted for use with exosomes, include but are not limited to those described herein.

[0702] Product formation of the biomarker with their immobilized capture molecules or binding agents can be detected with a fluorescence based reporter system (see for example, FIG. **64**A). The biomarker can either be labeled directly by a fluorophore or detected by a second fluorescently labeled capture biomolecule. The signal intensities derived from captured biomarkers are measured in a flow cytometer. The flow cytometer first identifies each microsphere by its individual color code. For example, distinct beads can be dyed with discrete fluorescence intensities such that each bead with a different intensity has a different binding agent. The beads can be labeled or dyed with at least 2 different labels or dyes. In some embodiments, the beads are labeled with at least 3, 4, 5, 6, 7, 8, 9, or 10 different labels. The beads with more than one label or dye can also have various ratios and combinations of the labels or dyes. The beads can be labeled or dyed externally or may have intrinsic fluorescence or signaling labels.

[0703] The amount of captured biomarkers on each individual bead can be measured by the second color fluorescence specific for the bound target. This allows multiplexed quantitation of multiple targets from a single sample within the same experiment. Sensitivity, reliability and accuracy are compared, or can be improved to standard microtiter ELISA procedures. An advantage of bead-based systems is the individual coupling of the capture biomolecule, or binding agent for an exosome, to distinct microspheres, which provides multiplexing. For example, as depicted in FIG. **64**B, a combination of 5 different biomarkers to be detected (detected by antibodies to antigens such as CD63, CD9, CD81, B7H3, and EpCam) and 20 biomarkers for which to capture the exosome (using capture antibodies, such as antibodies to CD9, PSCA, TNFR, CD63, B7H3, MFG-E8, EpCam, Rab, CD81, STEAP, PCSA, PSMA, and 5T4) can result in 100 combinations to be detected. Thus, captured exosomes can be detected using detection agents, such as antibodies. The detection agents can be labeled directly or indirectly, such as described above.

[0704] Multiplexing of at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 50, 75 or 100 different biomarkers may be performed. For example, an assay of a heterogeneous population of exosomes can be performed with a plurality of particles that are differentially labeled. There can be at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 50, 75 or 100 differentially labeled particles. The particles may be externally labeled, such as with a tag, or they may be intrinsically labeled. Each differentially labeled particle can be coupled to a capture agent, such as a binding agent, for an exosome, resulting in capture of an exosome. Biomarkers of the captured exosomes can then be detected by a plurality of binding agents. The binding agent can be directly labeled and thus, detected. Alternatively, the binding agent is labeled by a secondary agent. For example, the binding agent may be an antibody for a biomarker on the exosome. The binding agent is linked to biotin. A secondary agent comprises streptavidin linked to a reporter and can be added to detect the biomarker. In some embodiments, the captured exosomes are assayed for at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 50, 75 or 100 different biomarkers. For example, as depicted in FIG. **70**, multiple detectors, i.e. detection of multiple biomarkers of a captured exosome, can increase the signal obtained, permitted increased sensitivity, specificity or both, and the use of smaller amounts of samples.

[0705] ELISA based methods, so sandwich assay can also be used to detect biomarkers on an exosome. A binding agent or capture agent can be bound to a well, for example an antibody to an exosomal antigen. Biomarkers on the captured exosome can be detected based on the methods described herein.

[0706] Peptide or protein biomakers can be analyzed by mass spectrometry or flow cytometry. Proteomic analysis of exosomes may also be carried out on exosomes by immunocytochemical staining, Western blotting, electrophoresis, chromatography or x-ray crystallography in accordance with procedures well known in the art. In other embodiments, the protein bio-signatures of exosomes may be analyzed using 2 D differential gel electrophoresis as described in, Chromy et al. *J Proteome Res,* 2004; 3:1120-1127, which is herein incorporated by reference in its entirety, or with liquid chromatography mass spectrometry as described in Zhang et al. *Mol Cell Proteomics,* 2005; 4:144-155, which is herein incorporated by reference in its entirety. Exosomes may be subjected to activity-based protein profiling described for example, in Berger et al., *Am J Pharmacogenomics,* 2004; 4:371-381, which is in incorporated by reference in its entirety. In other embodiments, exosomes may be profiled using nanospray liquid chromatography-tandem mass spectrometry as described in Pisitkun et al., *Proc Natl Acad Sci USA,* 2004; 101:13368-13373, which is herein incorporated by reference in its entirety. In another embodiment, the exosomes may be profiled using tandem mass spectrometry (MS) such as liquid chromatography/MS/MS (LC-MS/MS) using for example a LTQ and LTQ-FT ion trap mass spectrometer. Protein identification can be determined and relative quantitation can be assessed by comparing spectral counts as described in Smalley et al., *J Proteome Res,* 2008; 7:2088-2096, which is herein incorporated by reference in its entirety.

[0707] Protein expression of exosomes can also be identified, such as following the isolation of cell-of-origin specific exosomes, such exosomes can be resuspended in buffer, centrifuged at 100×g for example, for 3 minutes using a cytocentrifuge on adhesive slides in preparation for immunocytochemical staining. The cytospins can be air-dried overnight and stored at—80° C. until staining. Slides can then be fixed and blocked with serum-free blocking reagent. The slides can then be incubated with a specific antibody to detect the expression of a protein of interest. In some embodiments, the exosomes are not purified, isolated or concentrated prior to protein expression analysis.

[0708] Exosomes, such as isolated cell-of-origin specific exosomes can be characterized by analysis of metabolite markers or metabolites, which can also form a bio-signature for exosomes. Various metabolite-oriented approaches have been described such as metabolite target analyses, metabolite profiling, or metabolic fingerprinting, see for example, Denkert et al., *Molecular Cancer* 2008; 7: 4598-4617, Ellis et al., *Analyst* 2006; 8: 875-885, Kuhn et al., *Clinical Cancer Research* 2007; 24: 7401-7406, Fiehn O., *Comp Funct Genomics* 2001; 2:155-168, Fancy et al., *Rapid Commun Mass Spectrom* 20(15): 2271-80 (2006), Lindon et al., *Pharm Res,* 23(6): 1075-88 (2006), Holmes et al., *Anal Chem.* 2007 Apr. 1; 79(7):2629-40. Epub 2007 February 27. *Erratum in: Anal Chem.* 2008 Aug. 1; 80(15):6142-3, Stanley et al., *Anal Biochem.* 2005 Aug. 15; 343(2):195-202., *Lehtimäki et al., J Biol. Chem.* 2003 Nov. 14; 278(46):45915-23, each of which is herein incorporated by reference in its entirety.

[0709] Peptides from exosomes can be analyzed by systems described in Jain K K: *Integrative Omics, Pharmacoproteomics, and Human Body Fluids. In: Thongboonkerd V. ed., ed. Proteomics of Human Body Fluids: Principles, Methods and Applications. Volume* 1: Totowa, N.J.: Humana Press, c2007., 2007, which is herein incorporated by reference in its entirety. This system can generate sensitive molecular fingerprints of proteins present in a body fluid as well as in exosomes. Commercial applications which include the use of chromatography/mass spectroscopy and reference libraries of all stable metabolites in the human body, for example Paradigm Genetic's Human Metabolome Project, may be used to determine the metabolite bio-signature of exosomes, such as isolated cell-of-origin specific exosomes. Other methods for analyzing a metabolic profile can include methods and devices described in U.S. Pat. No. 6,683,455 (Metabometrix), U.S. Patent Application Publication Nos. 20070003965 and 20070004044 (Biocrates Life Science), each of which is herein incorporated by reference in its entirety. Other proteomic profiling techniques are described in Kennedy, *Toxicol Lett* 120:379-384 (2001), Berven et al., *Curr Pharm Biotechnol* 7(3): 147-58 (2006), Conrads et al., *Expert Rev Proteomics* 2(5): 693-703, Decramer et al., *World J Urol* 25(5): 457-65 (2007), Decramer et al., *Mol Cell Proteomics* 7(10): 1850-62 (2008), Decramer et al., *Contrib Nephrol,* 160: 127-41 (2008), Diamandis, *J Proteome Res* 5(9): 2079-82 (2006), Immler et al., *Proteomics* 6(10): 2947-58 (2006), Khan et al., *J Proteome Res* 5(10): 2824-38 (2006), Kumar et al., *Biomarkers* 11(5): 385-405 (2006), Noble et al., *Breast Cancer Res Treat* 104(2): 191-6 (2007), Omenn, *Dis Markers* 20(3): 131-4 (2004), Powell et al., *Expert Rev Proteomics* 3(1): 63-74 (2006), Rai et al., *Arch Pathol Lab Med,* 126(12): 1518-26 (2002), Ramstrom et al., *Proteomics,* 3(2): 184-90 (2003), Tammen et al., *Breast Cancer Res Treat,* 79(1): 83-93 (2003), Theodorescu et al., *Lancet Oncol,* 7(3): 230-40 (2006), or Zurbig et al., *Electrophoresis,* 27(11): 2111-25 (2006).

[0710] For analysis of mRNAs, miRNAs or other small RNAs, the total RNA can be first isolated from exosomes using any other known methods for isolating nucleic acids such as methods described in U.S. Patent Application Publication No. 2008132694, which is herein incorporated by reference in its entirety. These include, but are not limited to, kits for performing membrane based RNA purification, which are commercially available. Generally, kits are available for the small-scale (30 mg or less) preparation of RNA from cells and tissues, for the medium scale (250 mg tissue) preparation of RNA from cells and tissues, and for the large scale (1 g maximum) preparation of RNA from cells and tissues. Other commercially available kits for effective isolation of small RNA-containing total RNA are available.

[0711] Alternatively, RNA can be isolated using the method described in U.S. Pat. No. 7,267,950, which is herein incorporated by reference in its entirety. U.S. Pat. No. 7,267,950 describes a method of extracting RNA from biological systems (cells, cell fragments, organelles, tissues, organs, or organisms) in which a solution containing RNA is contacted with a substrate to which RNA can bind and RNA is withdrawn from the substrate by applying negative pressure. Alternatively, RNA may be isolated using the method described in U.S. Patent Application No. 20050059024, which is herein incorporated by reference in its entirety, which describes the isolation of small RNA molecules. Other methods are described in U.S. Patent Application No. 20050208510, 20050277121, 20070238118, each of which is incorporated by reference in its entirety.

[0712] In one embodiment, mRNA expression analysis can be carried out on mRNAs from exosomes isolated from a sample. In some embodiments, the exosomes are cell-of-origin specific exosomes. Expression patterns generated from these exosomes can be indicative of a given disease state, disease stage, therapy related signature, or physiological condition. Once the total RNA has been isolated, cDNA can be synthesized and either qRT-PCR assays (e.g. Applied Biosystem's Taqman® assays) for specific mRNA targets can be performed according to manufacturer's protocol, or an expression microarray can be performed to look at highly multiplexed sets of expression markers in one experiment. Methods for establishing gene expression profiles include determining the amount of RNA that is produced by a gene that can code for a protein or peptide. This is accomplished by quantitative reverse transcriptase PCR (qRT-PCR), competitive RT-PCR, real time RT-PCR, differential display RT-PCR, Northern Blot analysis or other related tests. While it is possible to conduct these techniques using individual PCR reactions, it is also possible to amplify complementary DNA (cDNA) or complementary RNA (cRNA) produced from mRNA and analyze it via microarray.

[0713] The level of a miRNA product in a sample can be measured using any technique that is suitable for detecting mRNA expression levels in a biological sample, including but not limited to Northern blot analysis, RT-PCR, qRT-PCR, in situ hybridization or microarray analysis. For example, using gene specific primers and target cDNA, qRT-PCR enables sensitive and quantitative miRNA measurements of either a small number of target miRNAs (via singleplex and multiplex analysis) or the platform can be adopted to conduct high throughput measurements using 96-well or 384-well plate formats. See for example, Ross J S et al, *Oncologist.* 2008 May; 13(5):477-93, which is herein incorporated by reference in its entirety. A number of different array configurations and methods for microarray production are known to those of skill in the art and are described in U.S. patents such as: U.S. Pat. Nos. 5,445,934; 5,532,128; 5,556,752; 5,242,974; 5,384,261; 5,405,783; 5,412,087; 5,424,186; 5,429,807; 5,436,327; 5,472,672; 5,527,681; 5,529,756; 5,545,531; 5,554,501; 5,561,071; 5,571,639; 5,593,839; 5,599,695; 5,624,711; 5,658,734; or 5,700,637; each of which is herein incorporated by reference in its entirety. Other methods of profiling miRNAs are described in Taylor et al., *Gynecol Oncol.* 2008 July; 110(1):13-21, Gilad et al, *PLoS ONE.* 2008 Sep. 5; 3(9):

e3148, Lee et al., *Annu Rev Pathol.* 2008 September 25 and Mitchell et al, *Proc Natl Acad Sci USA.* 2008 Jul. 29; 105(30): 10513-8, Shen R et al, *BMC Genomics.* 2004 Dec. 14; 5(1): 94, Mina L et al, *Breast Cancer Res Treat.* 2007 June; 103 (2):197-208, Zhang L et al, *Proc Natl Acad Sci USA.* 2008 May 13; 105(19):7004-9, Ross J S et al, *Oncologist.* 2008 May; 13(5):477-93, Schetter A J et al, *JAMA.* 2008 Jan. 30; 299(4):425-36, Staudt L M, *N Engl J Med* 2003; 348:1777-85, Mulligan G et al, *Blood.* 2007 Apr. 15; 109(8):3177-88. Epub 2006 Dec. 21, McLendon R et al, *Nature.* 2008 Oct. 23; 455(7216):1061-8, and U.S. Pat. Nos. 5,538,848, 5,723,591, 5,876,930, 6,030,787, 6,258,569, and 5,804,375, each of which is herein incorporated by reference.

[0714] Microarray technology allows for the measurement of the steady-state mRNA or miRNA levels of thousands of transcripts or miRNAs simultaneously thereby presenting a powerful tool for identifying effects such as the onset, arrest, or modulation of uncontrolled cell proliferation. Two microarray technologies, such as cDNA arrays and oligonucleotide arrays can be used. The product of these analyses are typically measurements of the intensity of the signal received from a labeled probe used to detect a cDNA sequence from the sample that hybridizes to a nucleic acid sequence at a known location on the microarray. Typically, the intensity of the signal is proportional to the quantity of cDNA, and thus mRNA or miRNA, expressed in the sample cells. A large number of such techniques are available and useful. Methods for determining gene expression can be found in U.S. Pat. No. 6,271,002 to Linsley, et al.; U.S. Pat. No. 6,218,122 to Friend, et al.; U.S. Pat. No. 6,218,114 to Peck et al.; or U.S. Pat. No. 6,004,755 to Wang, et al., each of which is herein incorporated by reference in its entirety.

[0715] Analysis of the expression levels is conducted by comparing such intensities. This can be performed by generating a ratio matrix of the expression intensities of genes in a test sample versus those in a control sample. The control sample may be used as a reference, and different references to account for age, ethnicity and sex may be used. Different references can be used for different conditions or diseases, as well as different stages of diseases or conditions, as well as for determining therapeutic efficacy.

[0716] For instance, the gene expression intensities of mRNA or miRNAs isolated from exosomes derived from a diseased tissue can be compared with the expression intensities generated from exosomes isolated from normal tissue of the same type (e.g., diseased breast tissue sample versus. normal breast tissue sample). A ratio of these expression intensities indicates the fold-change in gene expression between the test and control samples. Alternatively, if exosomes are not normally present in from normal tissues (e.g. breast) then absolute quantitation methods, as is known in the art, can be used to define the number of miRNA molecules present without the requirement of miRNA or mRNA isolated from exosomes derived from normal tissue.

[0717] Gene expression profiles can also be displayed in a number of ways. The most common method is to arrange raw fluorescence intensities or ratio matrix into a graphical dendogram where columns indicate test samples and rows indicate genes. The data is arranged so genes that have similar expression profiles are proximal to each other. The expression ratio for each gene is visualized as a color. For example, a ratio less than one (indicating down-regulation) may appear in the blue portion of the spectrum while a ratio greater than one (indicating up-regulation) may appear as a color in the red portion of the spectrum. Commercially available computer software programs are available to display such data.

[0718] mRNAs or miRNAs that are considered differentially expressed can be either over expressed or under expressed in patients with a disease relative to disease free individuals. Over and under expression are relative terms meaning that a detectable difference (beyond the contribution of noise in the system used to measure it) is found in the amount of expression of the mRNAs or miRNAs relative to some baseline. In this case, the baseline is the measured mRNA/miRNA expression of a non-diseased individual. The mRNA/miRNA of interest in the diseased cells can then be either over or under expressed relative to the baseline level using the same measurement method. Diseased, in this context, refers to an alteration of the state of a body that interrupts or disturbs, or has the potential to disturb, proper performance of bodily functions as occurs with the uncontrolled proliferation of cells. Someone is diagnosed with a disease when some aspect of that person's genotype or phenotype is consistent with the presence of the disease. However, the act of conducting a diagnosis or prognosis includes the determination of disease/status issues such as determining the likelihood of relapse or metastasis and therapy monitoring. In therapy monitoring, clinical judgments are made regarding the effect of a given course of therapy by comparing the expression of genes over time to determine whether the mRNA/miRNA expression profiles have changed or are changing to patterns more consistent with normal tissue.

[0719] Levels of over and under expression are distinguished based on fold changes of the intensity measurements of hybridized microarray probes. A 2× difference is preferred for making such distinctions or a p-value less than 0.05. That is, before an mRNA/miRNA is said to be differentially expressed in diseased/relapsing versus normal/non-relapsing cells, the diseased cell is found to yield at least 2 times more, or 2 times less intensity than the normal cells. The greater the fold difference, the more preferred is use of the gene as a diagnostic or prognostic tool. mRNA/miRNAs selected for the expression profiles of the instant invention have expression levels that result in the generation of a signal that is distinguishable from those of the normal or non-modulated genes by an amount that exceeds background using clinical laboratory instrumentation.

[0720] Statistical values can be used to confidently distinguish modulated from non-modulated mRNA/miRNA and noise. Statistical tests find the mRNA/miRNA most significantly different between diverse groups of samples. The Student's t-test is an example of a robust statistical test that can be used to find significant differences between two groups. The lower the p-value, the more compelling the evidence that the gene is showing a difference between the different groups. Nevertheless, since microarrays measure more than one mRNA/miRNA at a time, tens of thousands of statistical tests may be performed at one time. Because of this, one is unlikely to see small p-values just by chance and adjustments for this using a Sidak correction as well as a randomization/permutation experiment can be made. A p-value less than 0.05 by the t-test is evidence that the gene is significantly different. More compelling evidence is a p-value less then 0.05 after the Sidak correction is factored in. For a large number of samples in each group, a p-value less than 0.05 after the randomization/permutation test is the most compelling evidence of a significant difference.

[0721] In one embodiment, a method of generating a posterior probability score to enable diagnostic, prognostic, therapy-related, or physiological state specific bio-signature scores can be arrived at by obtaining mRNA or miRNA (biomarker) expression data from a statistically significant number of patient exosomes, such as cell-of-origin specific exosomes; applying linear discrimination analysis to the data to obtain selected biomarkers; and applying weighted expression levels to the selected biomarkers with discriminate function factor to obtain a prediction model that can be applied as a posterior probability score. Other analytical tools can also be used to answer the same question such as, logistic regression and neural network approaches.

[0722] For instance, the following can be used for linear discriminant analysis:

[0723] where,

$I(p_s i_d)$=The log base 2 intensity of the probe set enclosed in parenthesis. $d(cp)$=The discriminant function for the disease positive class $d(C_N)$=The discriminant function for the disease negative class

$P(_{CP})$=The posterior p-value for the disease positive class

$P(_{CN})$=The posterior p-value for the disease negative class

[0724] Numerous other well-known methods of pattern recognition are available. The following references provide some examples: Weighted Voting: Golub et al. (1999); Support Vector Machines: Su et al. (2001); and Ramaswamy et al. (2001); K-nearest Neighbors: Ramaswamy (2001); and Correlation Coefficients: van 't Veer et al. (2002), all of which are herein incorporated by reference in their entireties.

[0725] Bio-signature portfolios, further described below, can be established such that the combination of biomarkers in the portfolio exhibit improved sensitivity and specificity relative to individual biomarkers or randomly selected combinations of biomarkers. In one embodiment, the sensitivity of the bio-signature portfolio can be reflected in the fold differences, for example, exhibited by a transcript's expression in the diseased state relative to the normal state. Specificity can be reflected in statistical measurements of the correlation of the signaling of transcript expression with the condition of interest. For example, standard deviation can be a used as such a measurement. In considering a group of biomarkers for inclusion in a bio-signature portfolio, a small standard deviation in expression measurements correlates with greater specificity. Other measurements of variation such as correlation coefficients can also be used in this capacity.

[0726] Another parameter that can be used to select mRNA/miRNA that generate a signal that is greater than that of the non-modulated mRNA/miRNA or noise is the use of a measurement of absolute signal difference. The signal generated by the modulated mRNA/miRNA expression is at least 20% different than those of the normal or non-modulated gene (on an absolute basis). It is even more preferred that such mRNA/miRNA produce expression patterns that are at least 30% different than those of normal or non-modulated mRNA/miRNA.

[0727] MiRNA can also be detected and measured by amplification from a biological sample and measured using methods described in U.S. Pat. No. 7,250,496, U.S. Application Publication Nos. 20070292878, 20070042380 or 20050222399 and references cited therein, each of which is herein incorporated by reference in its entirety.

[0728] Peptide nucleic acids (PNAs) which are a new class of synthetic nucleic acid analogs in which the phosphate-sugar polynucleotide backbone is replaced by a flexible pseudo-peptide polymer may be utilized in analysis of bio-signatures of exosomes. PNAs are capable of hybridizing with high affinity and specificity to complementary RNA and DNA sequences and are highly resistant to degradation by nucleases and proteinases. Peptide nucleic acids (PNAs) are an attractive new class of probes with applications in cytogenetics for the rapid in situ identification of human chromosomes and the detection of copy number variation (CNV). Multicolor peptide nucleic acid-fluorescence in situ hybridization (PNA-FISH) protocols have been described for the identification of several human CNV-related disorders and infectious diseases. PNAs can also be utilized as molecular diagnostic tools to non-invasively measure oncogene mRNAs with tumor targeted radionuclide-PNA-peptide chimeras. Methods of using PNAs are described further in Pellestor F et al., *Curr Pharm Des.* 2008; 14(24):2439-44, Tian X et al, *Ann N Y Acad. Sci.* 2005 November, 1059:106-44, Paulasova P and Pellestor F, *Annales de Génétique,* 47 (2004) 349-358, Stender H. *Expert Rev Mol. Diagn.* 2003 September; 3(5): 649-55. *Review*, Vigneault et al., *Nature Methods,* 5(9), 777±779 (2008), each reference is herein incorporated by reference in its entirety. These methods can be used to screen the genetic materials isolated from exosomes. When applying these techniques to cell-of-origin specific exosomes they can be used to identify a given molecular signal that directly pertains to the cell of origin.

[0729] In addition, mutational analysis may be carried out for mRNAs and DNA that are identified from the exosomes. For mutational analysis of targets or biomarkers that are of RNA origin, the RNA (mRNA, miRNA or other) can be reverse transcribed into cDNA and subsequently sequenced or assayed for known SNPs (by Taqman SNP assays, for example), or single nucleotide mutations, as well as using sequencing to look for insertions or deletions to determine mutations present in the cell-of-origin. Muliplexed ligation dependent probe amplification (MLPA) could alternatively be used for the purpose of identifying CNV in small and specific areas of interest. For example, once the total RNA has been obtained from isolated colon cancer-specific exosomes, cDNA can be synthesized and primers specific for exons 2 and 3 of the KRAS gene can be used to amplify these two exons containing codons 12, 13 and 61 of the KRAS gene. The same primers used for PCR amplification can be used for Big Dye Terminator sequence analysis on the ABI 3730 to identify mutations in exons 2 and 3 of KRAS. Mutations in these codons are known to confer resistance to drugs such as Cetuximab and Panitumimab. Methods of conducting mutational analysis are described in Maheswaran S et al., Jul. 2, 2008 (10.1056/NEJMoa0800668) and Orita, M et al, *PNAS* 1989, (86): 2766-70, each of which is herein incorporated by reference in its entirety. Other methods of conducting mutational analysis can include miRNA sequencing. Applications for identifying and profiling miRNAs can be done by cloning techniques and the use of capillary DNA sequencing or "next-generation" sequencing technologies. The new sequencing technologies currently available allow the identification of low-abundance miRNAs or those exhibiting modest expression differences between samples, which may not be detected by hybridization-based methods. Such new sequencing technologies include the massively parallel signature sequencing (MPSS) methodology described in Nakano et al. 2006, *Nucleic Acids Res.* 2006; 34:D731D735. doi: 10.1093/nar/gkj077, the Roche/454 platform described in Margulies et al. 2005, *Nature.* 2005; 437:376 380 or the Illumina sequencing platform described in Berezikov et al. *Nat. Genet.* 2006b; 38:1375-1377, each of which is incorporated by reference in its entirety.

[0730] Additional methods to determine bio-signatures include assaying biomarkers by allele-specific PCR which include specific primers to amplify and discriminate between two alleles of a gene simultaneously, single-strand conformation polymorphism (SSCP) which involves the electrophoretic separation of single-stranded nucleic acids based on subtle differences in sequence and DNA and RNA aptamers. DNA and RNA aptamers are short oligonucleotide sequences that can be selected from random pools based on their ability to bind a particular molecule with high affinity. Methods of using aptamers are described in Ulrich H et al, *Comb Chem High Throughput Screen.* 2006 September; 9(8):619-32, Ferreira C S et al, *Anal Bioanal Chem.* 2008 February; 390(4): 1039-50, Ferreira C S et al, *Tumour Biol.* 2006; 27(6):289-301, each of which is herein incorporated by reference in its entirety.

[0731] Exosome biomarkers can also be detected using fluorescence in situ hybridization (FISH). Methods of using FISH to detect and localize specific DNA sequences, localize specific mRNAs within tissue samples or identify chromosomal abnormalities are described in Shaffer D R et al, *Clin Cancer Res.* 2007 Apr. 1; 13(7):2023-9, Cappuzo F et al, *Journal of Thoracic Oncology, Volume* 2, Number 5, May 2007, Moroni M et al., *Lancet Oncol.* 2005 May; 6(5):279-86, each of which is herein incorporated by reference in its entirety.

Bio-Signature: Binding Agents

[0732] Bio-signatures of exosomes can comprise binding agents for exosomes. The binding agent can be DNA, RNA, aptamers, monoclonal antibodies, polyclonal antibodies, Fabs, Fab', single chain antibodies, synthetic antibodies, aptamers (DNA/RNA), peptoids, zDNA, peptide nucleic acids (PNAs), locked nucleic acids (LNAs), lectins, synthetic or naturally occurring chemical compounds (including but not limited to drugs, labeling reagents).

[0733] Binding agents can used to isolate exosomes by binding to exosomal components, as described above. The binding agents can be used to detect the exosomes, such as for detecting cell-of-origin specific exosomes. A binding agent or multiple binding agents can themselves form a binding agent profile that provides a bio-signature for an exosome. One or more binding agents can be selected from FIG. **2**. For example, if an exosome population is detected or isolated using two, three or four binding agents in a differential detection or isolation of an exosome from a heterogeneous population of exosomes, the particular binding agent profile for the exosome population provides a bio-signature for the particular exosome population.

[0734] As an illustrative example, an exosome for analysis for lung cancer can be detected with one or more binding agents including, but not limited to, SCLC specific aptamer HCA 12, SCLC specific aptamer HCC03, SCLC specific aptamer HCH07, SCLC specific aptamer HCH01, A-p50 aptamer (NF-KB), Cetuximab, Panitumumab, Bevacizumab, L19 Ab, F16 Ab, anti-CD45 (anti-ICAM-1, aka UV3), or L2G7 Ab (anti-HGF), or any combination thereof.

[0735] An exosome for analysis for colon cancer can be detected with one or more binding agents including, but not limited to, angiopoietin 2 specific aptamer, beta-catenin aptamer, TCF1 aptamer, anti-Derlin1 ab, anti-RAGE, mAbgb3.1, Galectin-3, Cetuximab, Panitumumab, Matuzumab, Bevacizumab, or Mac-2, or any combination thereof.

[0736] An exosome for analysis for adenoma versus colorectal cancer (CRC) can be detected with one or more binding agents including, but not limited to, Complement C3, histidine-rich glycoprotein, kininogen-1, or Galectin-3, or any combination thereof.

[0737] An exosome for analysis for adenoma with low grade hyperplasia versus adenoma with high grade hyperplasia can be detected with a binding agent such as, but not limited to, Galectin-3 or any combination of binding agents specific for this comparison.

[0738] An exosome for analysis for CRC versus normal state can be detected with one or more binding agents including, but not limited to, anti-ODC mAb, anti-CEA mAb, or Mac-2, or any combination thereof.

[0739] An exosome for analysis for prostate cancer can be detected with one or more binding agents including, but not limited to, PSA, PSMA, TMPRSS2, mAB 5D4, XPSM-A9, XPSM-A 10, Galectin-3, E-selectin, Galectin-1, or E4 (IgG2a kappa), or any combination thereof.

[0740] An exosome for analysis for melanoma can be detected with one or more binding agents including, but not limited to, Tremelimumab (anti-CTLA4), Ipilimumumab (anti-CTLA4), CTLA-4 aptamers, STAT-3 peptide aptamers, Galectin-1, Galectin-3, or PNA, or any combination thereof.

[0741] An exosome for analysis for pancreatic cancer can be detected with one or more binding agents including, but not limited to, H38-15 (anti-HGF) aptamer, H38-21(anti-HGF) aptamer, Matuzumab, Cetuximanb, or Bevacizumab, or any combination thereof.

[0742] An exosome for analysis for brain cancer can be detected with one or more binding agents including, but not limited to, aptamer III.1 (pigpen) and/or TTA1 (Tenascin-C) aptamer, or any combination thereof.

[0743] An exosome for analysis for psoriasis can be detected with one or more binding agents including, but not limited to, E-selectin, ICAM-1, VLA-4, VCAM-1, alphaE-beta7, or any combination thereof.

[0744] An exosome for analysis for cardiovascular disease (CVD) can be detected with one or more binding agents including, but not limited to, RB007 (factor 1×A aptamer), ARC1779 (anti VWF) aptamer, or LOX1, or any combination thereof.

[0745] An exosome for analysis for hematological malignancies can be detected with one or more binding agents including, but not limited to, anti-CD20 and/or anti-CD52, or any combination thereof.

[0746] An exosome for analysis for B-cell chronic lymphocytic leukemias can be detected with one or more binding agents including, but not limited to, Rituximab, Alemtuzumab, Apt48 (BCL6), R0-60, or D-R15-8, or any combination thereof.

[0747] An exosome for analysis for B-cell lymphoma can be detected with one or more binding agents including, but not limited to, Ibritumomab, Tositumomab, Anti-CD20 Antibodies, Alemtuzumab, Galiximab, Anti-CD40 Antibodies, Epratuzumab, Lumiliximab, Hu1D10, Galectin-3, or Apt48, or any combination thereof.

[0748] An exosome for analysis for Burkitt's lymphoma can be detected with one or more binding agents including, but not limited to, TD05 aptamer, IgM mAB (38-13), or any combination thereof.

[0749] An exosome for analysis for cervical cancer can be detected with one or more binding agents including, but not limited to, Galectin-9 and/or HPVE7 aptamer, or any combination thereof.

[0750] An exosome for analysis for endometrial cancer can be detected with one or more binding agents including, but not limited to, Galectin-1 or any combinations of binding agents specific for endometrial cancer.

[0751] An exosome for analysis for head and neck cancer can be detected with one or more binding agents including, but not limited to, (111)In-cMAb U36, anti-LOXL4, U36, BIWA-1, BIWA-2, BIWA-4, or BIWA-8, or any combination thereof.

[0752] An exosome for analysis for IBD can be detected with one or more binding agents including, but not limited to, ACCA (anti-glycan Ab), ALCA(anti-glycan Ab), or AMCA (anti-glycan Ab), or any combination thereof.

[0753] An exosome for analysis for diabetes can be detected with one or more binding agents including, but not limited to, RBP4 aptamer or any combination of binding agents specific for diabetes.

[0754] An exosome for analysis for fibromyalgia can be detected with one or more binding agents including, but not limited to, L-selectin or any combination of binding agents specific for fibromyalgia.

[0755] An exosome for analysis for multiple sclerosis (MS) can be detected with one or more binding agents including, but not limited to, Natalizumab (Tysabri) or any combination of binding agents specific for MS.

[0756] In addition, An exosome for analysis for rheumatic disease can be detected with one or more binding agents including, but not limited to, Rituximab (anti-CD20 Ab) and/or Keliximab (anti-CD4 Ab), or any combination of binding agents specific for rheumatic disease.

[0757] An exosome for analysis for Alzheimer disease can be detected with one or more binding agents including, but not limited to, TH14-BACE1 aptapers, S10-BACE1 aptapers, anti-Abeta, Bapineuzumab (AAB-001)-Elan, LY2062430 (anti-amyloid beta Ab)-Eli Lilly, or BACE1-Anti sense, or any combination thereof.

[0758] An exosome for analysis for Prion specific diseases can be detected with one or more binding agents including, but not limited to, rhuPrP(c) aptamer, DP7 aptamer, Thioaptamer 97, SAF-93 aptamer, 15B3 (anti-PrPSc Ab), monoclonal anti PrPSc antibody P1:1, 1.5D7, 1.6F4 Abs, mab 14D3, mab 4F2, mab 8G8, or mab 12F10, or any combination thereof.

[0759] An exosome for analysis for sepsis can be detected with one or more binding agents including, but not limited to, HA-1A mAb, E-5 mAb, TNF-alpha MAb, Afelimomab, or E-selectin, or any combination thereof.

[0760] An exosome for analysis for schizophrenia can be detected with one or more binding agents including, but not limited to, L-selectin and/or N-CAM, or any combination of binding agents specific for schizophrenia.

[0761] An exosome for analysis for depression can be detected with one or more binding agents including, but not limited to, GPIb or any combination of binding agents specific for depression.

[0762] An exosome for analysis for GIST can be detected with one or more binding agents including, but not limited to, ANTI-DOG1 Ab or any combination of binding agents specific for GIST.

[0763] An exosome for analysis for esophageal cancer can be detected with one or more binding agents including, but not limited to, CaSR binding agent or any combination of binding agents specific for esophageal cancer.

[0764] An exosome for analysis for gastric cancer can be detected with one or more binding agents including, but not limited to, Calpain nCL-2 binding agent and/or drebrin binding agent, or any combination of binding agents specific for gastric cancer.

[0765] An exosome for analysis for COPD can be detected with one or more binding agents including, but not limited to, CXCR3 binding agent, CCR5 binding agent, or CXCR6 binding agent, or any combination of binding agents specific for COPD.

[0766] An exosome for analysis for asthma can be detected with one or more binding agents including, but not limited to, VIP binding agent, PACAP binding agent, CGRP binding agent, NT3 binding agent, YKL-40 binding agent, S-nitrosothiols, SCCA2 binding agent, PAI binding agent, amphiregulin binding agent, or Periostin binding agent, or any combination of binding agents specific for asthma.

[0767] An exosome for analysis for vulnerable plaque can be detected with one or more binding agents including, but not limited to, Gd-DTPA-g-mimRGD (Alpha v Beta 3 integrin binding peptide), or MMP-9 binding agent, or any combination of binding agents specific for vulnerable plaque.

[0768] An exosome for analysis for ovarian cancer can be detected with one or more binding agents including, but not limited to, (90) Y-muHMFG1 binding agent and/or OC125 (anti-CA125 antibody), or any combination of binding agents specific for ovarian cancer.

[0769] The binding agent can be for a general exosome marker, or "housekeeping protein" or antigen, such as CD9, CD63, or CD81. For example, the binding agent can be an antibody for CD9, CD63, or CD81. The binding agent can also be for other exosomal proteins, such as for prostate specific exosomes, or cancer specific exosomes, such as PCSA, PSMA, EpCam, B7H3, or STEAP. For example, the binding agent can be an antibody for PCSA, PSMA, EpCam, B7H3, or STEAP.

[0770] Furthermore, additional cellular binding partners or binding agents may be identified by any conventional methods known in the art, or as described herein, and may additionally be used as a diagnostic, prognostic or therapy-related marker.

Bio-Signatures: Prostate Cancer, Colon Cancer and Ovarian Cancer

[0771] Prostate Cancer

[0772] An exosome bio-signature can be used to characterize prostate cancer. As described above, a bio-signature for prostate cancer can comprise a binding agent associated with prostate cancer (for example, as shown in FIG. **2**), and one or more additional biomarkers, such as shown in FIG. **19**. For example, a bio-signature for prostate cancer can comprise a binding agent to PSA, PSMA, TMPRSS2, mAB 5D4, XPSM-A9, XPSM-A10, Galectin-3, E-selectin, Galectin-1, E4 (IgG2a kappa), or any combination thereof, with one or more additional biomarkers, such as one or more miRNA, one or more DNA, one or more additional peptide, protein, or antigen associated with prostate cancer, such as, but not limited to, those shown in FIG. **19**.

[0773] A bio-signature for prostate cancer can comprise an antigen associated with prostate cancer (for example, as shown in FIG. **1**), and one or more additional biomarkers, such as shown in FIG. **19**. A bio-signature for prostate cancer can comprise one or more antigens associated with prostate cancer, such as, but not limited to, KIA1, intact fibronectin, PSA, TMPRSS2, FASLG, TNFSF10, PSMA, NGEP, IL-7R1, CSCR4, CysLT1R, TRPM8, Kv1.3, TRPV6, TRPM8, PSGR, MISIIR, or any combination thereof. The bio-signature for prostate cancer can comprise one or more of the aforementioned antigens and one or more additional biomarkers, such as, but not limited to miRNA, mRNA, DNA, or any combination thereof.

[0774] A bio-signature for prostate cancer can also comprise one or more antigens associated with prostate cancer, such as, but not limited to, KIA1, intact fibronectin, PSA, TMPRSS2, FASLG, TNFSF10, PSMA, NGEP, IL-7R1, CSCR4, CysLT1R, TRPM8, Kv1.3, TRPV6, TRPM8, PSGR, MISIIR, or any combination thereof, and one or more miRNA biomarkers, such as, but not limited to, miR-202, miR-210, miR-296, miR-320, miR-370, miR-373, miR-498, miR-503, miR-184, miR-198, miR-302c, miR-345, miR-491, miR-513, miR-32, miR-182, miR-31, miR-26a-1/2, miR-200c, miR-375, miR-196a-1/2, miR-370, miR-425, miR-425, miR-194-1/2, miR-181a-1/2, miR-34b, let-71, miR-188, miR-25, miR-106b, miR-449, miR-99b, miR-93, miR-92-1/2, miR-125a, miR-141, let-7a, let-7b, let-7c, let-7d, let-7g, miR-16, miR-23a, miR-23b, miR-26a, miR-92, miR-99a, miR-103, miR-125a, miR-125b, miR-143, miR-145, miR-195, miR-199, miR-221, miR-222, miR-497, let-7f, miR-19b, miR-22, miR-26b, miR-27a, miR-27b, miR-29a, miR-29b, miR-30_5p, miR-30c, miR-100, miR-141, miR-148a, miR-205, miR-520h, miR-494, miR-490, miR-133a-1, miR-1-2, miR-218-2, miR-220, miR-128a, miR-221, miR-499, miR-329, miR-340, miR-345, miR-410, miR-126, miR-205, miR-7-1/2, miR-145, miR-34a, miR-487, or let-7b, or any combination thereof.

[0775] Furthermore, the miRNA for a prostate cancer bio-signature can be a miRNA that interacts with PFKFB3, RHAMM (HMMR), cDNA FLJ42103, ASPM, CENPF, NCAPG, Androgen Receptor, EGFR, HSP90, SPARC, DNMT3B, GART, MGMT, SSTR3, TOP2B, or any combination thereof, such as those described herein and depicted in FIG. **60**. The miRNA can also be miR-9, miR-629, miR-141, miR-671-3p, miR-491, miR-182, miR-125a-3p, miR-324-5p, miR-148B, miR-222, or any combination thereof.

[0776] The bio-signature for prostate cancer can comprise one or more antigens associated with prostate cancer, such as, but not limited to, KIA1, intact fibronectin, PSA, TMPRSS2, FASLG, TNFSF10, PSMA, NGEP, IL-7R1, CSCR4, CysLT1R, TRPM8, Kv1.3, TRPV6, TRPM8, PSGR, MISIIR, or any combination thereof, and one or more additional biomarkers such as, but not limited to, the aforementioned miRNAs, mRNAs (such as, but not limited to, AR or PCA3), snoRNA (such as, but not limited to, U50) or any combination thereof.

[0777] The bio-signature can also comprise one or more gene fusions, such as ACSL3-ETV 1, C15ORF21-ETV1, FLJ35294-ETV1, HERV-ETV 1, TMPRSS2-ERG, TMPRSS2-ETV 1/4/5, TMPRSS2-ETV4/5, SLC5A3-ERG, SLC5A3-ETV1, SLC5A3-ETV5 or KLK2-ETV4.

[0778] An exosome can be isolated and assayed for one or more miRNA and one or more antigens associated with prostate cancer to provide a diagnostic, prognostic or theranostic profile, such as the stage of the cancer, the efficacy of the cancer, or other characteristics of the cancer. Alternatively, the exosome can be directly assayed from a sample, such that the exosomes are not purified or concentrated prior to assaying for one or more miRNA or antigens associated with prostate cancer.

[0779] As depicted in FIG. **68**, a prostate cancer bio-signature can comprise assaying EpCam, CD63, CD81, CD9, or any combination thereof, of an exosome. The prostate cancer bio-signature can comprise detection of EpCam, CD9, CD63, CD81, PCSA or any combination thereof. For example, the prostate cancer bio-signature can comprise EpCam, CD9, CD63 and CD81 or PCSA, CD9, CD63 and CD81 (see for example, FIG. **70**A). The prostate cancer bio-signature can also comprise PCSA, PSMA, B7H3, or any combination thereof (see for example, FIG. **70**B).

[0780] Furthermore, assessing a plurality of biomarkers can provide increased sensitivity, specificity, or signal intensity, as compared to assessing less than a plurality of biomarkers. For example, assessing PSMA and B7H3 can provide increased sensitivity in detection as compared to assessing PSMA or B7H3 alone. Assessing CD9 and CD63 can provide increased sensitivity in detection as compared to assessing CD or CD63 alone.

[0781] Prostate cancer can also be characterized based on meeting at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 criteria. For example, a number of different criteria can be used: 1) if the amount of exosomes in a sample from a subject is higher than a reference value; 2) if the amount of prostate cell derived exosomes is higher than a reference value; and 3) if the amount of exosomes with one or more cancer specific biomarkers is higher than a reference value, the subject is diagnosed with prostate cancer. The method can further include a quality control measure, such that the subject is diagnosed with prostate cancer if the determination of the other criteria

[0782] The prostate cancer can be characterizing using one or more processes disclosed herein with at least 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, or 70% sensitivity. The prostate cancer can be characterized with at least 80, 81, 82, 83, 84, 85, 86, or 87% sensitivity. For example, the prostate cancer can be characterized with at least 87.1, 87.2, 87.3, 87.4, 87.5, 87.6, 87.7, 87.8, 87.9, 88.0, or 89% sensitivity, such as with at least 90% sensitivity, such as at least 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% sensitivity.

[0783] The prostate cancer of a subject can also be characterized with at least 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, or 97% specificity, such as with at least 97.1, 97.2, 97.3, 97.4, 97.5, 97.6, 97.7, 97.8, 97.8, 97.9, 98.0, 98.1, 98.2, 98.3, 98.4, 98.5, 98.6, 98.7, 98.8, 98.9, 99.0, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, 99.9 or 100% specificity.

[0784] The prostate cancer can also be characterized with at least 70% sensitivity and at least 80, 90, 95, 99, or 100% specificity; at least 80% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 85% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 86% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 87% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 88% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 89% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 90% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 95% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 99% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; or at least 100% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity.

[0785] Furthermore, the confidence level for determining the specificity, sensitivity, or both, may be with at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% confidence.

[0786] Colon Cancer

[0787] A colon cancer bio-signature can comprise any one or more antigens for colon cancer as listed in FIG. **1**, any one or more binding agents associated with isolating an exosome for characterizing colon cancer (for example, as shown in FIG. **2**), any one or more additional biomarkers, such as shown in FIG. **6**.

[0788] The bio-signature can comprise one or more miRNA selected from the group consisting of miR-24-1, miR-29b-2, miR-20a, miR-10a, miR-32, miR-203, miR-106a, miR-17-5p, miR-30c, miR-223, miR-126, miR-128b, miR-21, miR-24-2, miR-99b, miR-155, miR-213, miR-150, miR-107, miR-191, miR-221, miR-20a, miR-510, miR-92, miR-513, miR-19a, miR-21, miR-20, miR-183, miR-96, miR-135b, miR-31, miR-21, miR-92, miR-222, miR-181b, miR-210, miR-20a, miR-106a, miR-93, miR-335, miR-338, miR-133b, miR-346, miR-106b, miR-153a, miR-219, miR-34a, miR-99b, miR-185, miR-223, miR-211, miR-135a, miR-127, miR-203, miR-212, miR-95, or miR-17-5p, or any combination thereof. The bio-signature can also comprise one or more underexpressed miRs such as miR-143, miR-145, miR-143, miR-126, miR-34b, miR-34c, let-7, miR-9-3, miR-34a, miR-145, miR-455, miR-484, miR-101, miR-145, miR-133b, miR-129, miR-124a, miR-30-3p, miR-328, miR-106a, miR-17-5p, miR-342, miR-192, miR-1, miR-34b, miR-215, miR-192, miR-301, miR-324-5p, miR-30a-3p, miR-34c, miR-331, and miR-148b.

[0789] The bio-signature can comprise assessing one or more genes, such as EFNB1, ERCC1, HER2, VEGF, and EGFR. A biomarker mutation for colon cancer that can be assessed in an exosome can also include one or more mutations of EGFR, KRAS, VEGFA, B-Raf, APC, or p53. The bio-signature can also comprise one or more proteins, ligands, or peptides that can be assessed of an exosome such as AFRs, Rabs, ADAM10, CD44, NG2, ephrin-B1, MIF, b-catenin, Junction, plakoglobin, glalectin-4, RACK1, tetrspanin-8, FasL, TRAIL, A33, CEA, EGFR, dipeptidase 1, hsc-70, tetraspanins, ESCRT, TS, PTEN, or TOPO1

[0790] An exosome can be isolated and assayed for to provide a diagnostic, prognostic or theranostic profile, such as the stage of the cancer, the efficacy of the cancer, or other characteristics of the cancer. Alternatively, the exosome can be directly assayed from a sample, such that the exosomes are not purified or concentrated prior to assaying for a bio-signature associated with colon cancer.

[0791] As depicted in FIG. **69**, a colon cancer signature can comprise detection of EpCam, CD63, CD81, CD9, CD66, or any combination thereof, of an exosome. Furthermore, a colon cancer-bio-signature for various stages of cancer can comprise CD63, CD9, EpCam, or any combination thereof (see for example, FIGS. **71** and **72**). For example, the bio-signature can comprise CD9 and EpCam.

[0792] The colon cancer can be characterizing using one or more processes disclosed herein with at least 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, or 70% sensitivity. The colon cancer can be characterized with at least 80, 81, 82, 83, 84, 85, 86, or 87% sensitivity. For example, the colon cancer can be characterized with at least 87.1, 87.2, 87.3, 87.4, 87.5, 87.6, 87.7, 87.8, 87.9, 88.0, or 89% sensitivity, such as with at least 90% sensitivity, such as at least 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% sensitivity.

[0793] The colon cancer of a subject can also be characterized with at least 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, or 97% specificity, such as with at least 97.1, 97.2, 97.3, 97.4, 97.5, 97.6, 97.7, 97.8, 97.8, 97.9, 98.0, 98.1, 98.2, 98.3, 98.4, 98.5, 98.6, 98.7, 98.8, 98.9, 99.0, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, 99.9 or 100% specificity.

[0794] The colon cancer can also be characterized with at least 70% sensitivity and at least 80, 90, 95, 99, or 100%) specificity; at least 80% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 85% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 86% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 87% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 88% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 89% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 90% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 95% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; at least 99% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity; or at least 100% sensitivity and at least 80, 85, 90, 95, 99, or 100% specificity.

[0795] Furthermore, the confidence level for determining the specificity, sensitivity, or both, may be with at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% confidence.

[0796] Ovarian Cancer

[0797] A bio-signature for characterizing ovarian cancer can comprise an antigen associated with ovarian cancer (for example, as shown in FIG. **1**), and one or more additional biomarkers, such as shown in FIG. **4**.

[0798] In one embodiment, a bio-signature for ovarian cancer can comprise one or more antigens associated with ovarian cancer, such as, but not limited to, CD24, CA125, VEGF1, VEGFR2, HER2, MISIIR, or any combination thereof. The bio-signature for ovarian cancer can comprise one or more of the aforementioned antigens and one or more additional biomarker, such as, but not limited to miRNA, mRNA, DNA, or any combination thereof. The bio-signature for ovarian cancer can comprise one or more antigens associated with ovarian cancer, such as, but not limited to, CD24, CA125, VEGF I, VEGFR2, HER2, MISIIR; or any combination thereof, with one or more miRNA biomarkers, such as, but not limited to, miR-200a, miR-141, miR-200c, miR-200b, miR-21, miR-141, miR-200a, miR-200b, miR-200c, miR-203, miR-205, miR-214, miR-215, miR-199a, miR-140, miR-145, miR-125b-1, or any combination thereof.

[0799] A bio-signature for ovarian cancer can comprise one or more antigens associated with ovarian cancer, such as, but not limited to, CD24, CA125, VEGF1, VEGFR2, HER2, MISIIR, or any combination thereof, with one or more miRNA biomarkers (such as the aforementioned miRNA), mRNAs (such as, but not limited to, ERCC1, ER, TOPO1, TOP2A, AR, PTEN, HER2/neu, EGFR), mutations (including, but not limited to, those relating to KRAS and/or B-Raf) or any combination thereof.

[0800] An exosome can be isolated and assayed for one or more miRNA and one or more antigens associated with ovarian cancer to provide a diagnostic, prognostic or theranostic profile. Alternatively, the exosome can be directly assayed from a sample, such that the exosomes are not purified or concentrated prior to assaying for one or more miRNA or antigens associated with ovarian cancer.

Bio-Signatures: Assessing Organ Transplant Rejection and Autoimmune Conditions

[0801] An exosome can also be used for determining phenotypes such as organ distress and/or organ transplant rejection. As used herein organ transplant includes partial organ or tissue transplant. The presence, absence or levels of one or more biomarkers present in exosomes is assessed to monitor organ rejection or success. The level, or amount, of exosomes in the sample can also be used to assess organ rejection or success. The assessment can be determined with at least 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% specificity, sensitivity, or both. For example, the assessment can be determined with at least 97.5, 97.6, 97.7, 97.8, 97.8, 97.9, 98.0, 98.1, 98.2, 98.3, 98.4, 98.5, 98.6, 98.7, 98.8, 98.9, 99.0, 99.1, 998.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, 99.9% sensitivity, specificity, or both

[0802] The exosome can be purified or concentrated prior to analysis. Alternatively, the level, or amount, of exosomes can be directly assayed from a sample, without prior purification or concentration. The exosome quantitated can be a cell-of-origin specific exosome. For example, a cell or tissue-specific exosome can be isolated using one or more binding agents specific for a particular organ. The cell-of-origin specific exosome can be assessed for one or more molecular features, such as one or more biomarkers associated with organ distress or organ transplant rejection. The presence, absence or levels of one or more biomarkers present in an isolated cell-of-origin specific exosome can be assessed to monitor organ rejection or success.

[0803] One or more exosomes can be analyzed for the assessment, detection or diagnosis of the rejection of a tissue or organ transplant by a subject. The tissue or organ transplant rejection can be hyperacute, acute, or chronic rejection. The exosome can also be analyzed for the assessment, detection or diagnosis of graft versus host disease in a subject. The subject can be the recipient of an autogenic, allogenic or xenogenic tissue or organ transplant.

[0804] The exosome can also be analyzed to detect the rejection of a tissue or organ transplant. The exosome may be produced by the tissue or organ transplant. Such tissues or organs include, but are not limited to, a heart, lung, pancreas, kidney, eye, cornea, muscle, bone marrow, skin, cartilage, bone, appendages, hair, face, tendon, stomach, intestine, vein, artery, differentiated cells, partially differentiated cells or stem cells.

[0805] The exosome can comprise at least one biomarker which is used to assess, diagnose or determine the probability or occurrence of rejection of a tissue or organ transplant by a subject. A biomarker can also be used to assess, diagnose or detect graft versus host disease in a subject. The biomarker can be a protein, a polysaccharide, a fatty acid or a nucleic acid (such as DNA or RNA). The biomarker can be associated with the rejection of a specific tissue or organ or systemic organ failure. More than one biomarker can be analyzed, for example, one or more proteins marker can be analyzed in combination with one or more nucleic acid markers. The biomarker may be an intracellular or extracellular marker.

[0806] The exosome can also be analyzed for at least one marker for the assessment, detection or diagnosis of cell apoptosis or necrosis associated with, or the causation of, rejection of a tissue or organ transplant by a subject.

[0807] The presence of a biomarker can be indicative of the rejection of a tissue or an organ by a subject, wherein the biomarker includes, but is not limited to, CD40, CD40 ligand, N-acetylmuramoyl-L-alanine amidase precursor, adiponectin, AMBP protein precursor, C4b-binding protein a-chain precursor, ceruloplasmin precursor, complement C3 precursor, complement component C9 precursor, complement factor D precursor, alpha 1-B-glycoprotein, beta2-glycoprotein I precursor, heparin cofactor II precursor, Immunoglobulin mu chain C region protein, Leucine-rich alpha2-glycoprotein precursor, pigment epithelium-derived factor precursor, plasma retinol-binding protein precursor, translation initiation factor 3 subunit 10, ribosomal protein L7, beta-transducin, 1-TRAF, or lysyl-tRNA synthetase.

[0808] Rejection of a kidney by a subject can also be detected by analyzing exosomes for the presence of beta-transducin. Rejection of transplanted tissue can also be detected by isolating a cell-of-origin specific exosome from CD40-expressing cells and detecting for the increase of Bcl-2 or TNFalpha.

[0809] Rejection of a liver transplant by a subject can be detected by analyzing the exosomes for the presence of an F1 antigen marker. The F1 antigen is, without being bound to theory, specific to liver to and can be used to detect an increase in liver cell-of-origin specific exosomes. This increase can be used as an early indication of organ distress/rejection.

[0810] Bronchiolitis obliterans due to bone marrow and/or lung transplantation or other causes, or graft atherosclerosis/graft phlebosclerosis can also be diagnosed by the analysis of an exosome.

[0811] An exosome can also be analyzed for the detection, diagnosis or assessment of an autoimmune or other immunological reaction-related phenotypes in a subject. Examples of such a disorder include, but are not limited to, systemic lupus erythematosus (SLE), discoid lupus, lupus nephritis, sarcoidosis, inflammatory arthritis, including juvenile arthritis, rheumatoid arthritis, psoriatic arthritis, Reiter's syndrome, ankylosing spondylitis, and gouty arthritis, multiple sclerosis, hyper IgE syndrome, polyarteritis nodosa, primary biliary cirrhosis, inflammatory bowel disease, Crohn's disease, celiac's disease (gluten-sensitive enteropathy), autoimmune hepatitis, pernicious anemia, autoimmune hemolytic anemia, psoriasis, scleroderma, myasthenia gravis, autoimmune thrombocytopenic purpura, autoimmune thyroiditis, Grave's disease, Hasimoto's thyroiditis, immune complex disease, chronic fatigue immune dysfunction syndrome (CFIDS), polymyositis and dermatomyositis, cryoglobulinemia, thrombolysis, cardiomyopathy, pemphigus vulgaris, pulmonary interstitial fibrosis, asthma, Churg-Strauss syndrome (allergic granulomatosis), atopic dermatitis, allergic and irritant contact dermatitis, urtecaria, IgE-mediated allergy, atherosclerosis, vasculitis, idiopathic inflammatory myopathies, hemolytic disease, Alzheimer's disease, chronic inflammatory demyelinating polyneuropathy and AIDs.

[0812] One or more biomarkers from the exosome can be used to assess, diagnose or determine the probability of the occurrence of an autoimmune or other immunological reaction-related disorder in a subject. The biomarker can be a protein, a polysaccharide, a fatty acid or a nucleic acid (such as DNA or RNA). The biomarker can be associated with a specific autoimmune disorder, a systemic autoimmune disorder, or other immunological reaction-related disorder. More than one biomarker can be analyzed. For example one or more protein markers can be analyzed in combination with one or more nucleic acid markers. The biomarker can be an intracellular or extracellular marker. The biomarker can also be used to detect, diagnose or assess inflammation.

[0813] Analysis of an exosome from subjects can be used identify subjects with inflammation associated with asthma, sarcoidosis, emphysema, cystic fibrosis, idiopathic pulmonary fibrosis, chronic bronchitis, allergic rhinitis and allergic diseases of the lung such as hypersensitivity pneumonitis, eosinophilic pneumonia, as well as pulmonary fibrosis resulting from collagen, vascular, and autoimmune diseases such as rheumatoid arthritis.

Exosome Compositions

[0814] Also provided herein is an isolated exosome with a particular bio-signature. The isolated exosome can comprise one or more biomarkers or bio-signatures specific for specific cell type, or for characterizing a phenotype, such as described above. For example, the isolated exosome can comprise one or more biomarkers, such as CD63, EpCam, CD81, CD9, PCSA, PSMA, B7H3, TNFR, MFG-E8, Rab, STEAP, 5T4, or CD59. The isolated exosome can have the one or more biomarkers on its surface of within the exosome. The isolated exosome can also comprise one or more miRNAs, such as miR-9, miR-629, miR-141, miR-671-3p, miR-491, miR-182, miR-125a-3p, miR-324-5p, miR-148B, or miR-222. An isolated exosome can comprise a biomarker such as CD66, and further comprise one or more biomarkers selected from the group consisting of: EpCam, CD63, or CD9. An isolated exosome can also comprise a fusion gene or protein, such as TMRSSG2:ERG.

[0815] An isolated exosome can also comprise one or more biomarkers, wherein the expression level of the one or more biomarkers is higher, lower, or the same for an isolated exosome as compared to an isolated exosome derived from a normal cell (ie. a cell derived from a subject without a phenotype of interest). For example, an isolated exosome can comprise one or more biomarkers selected from the group consisting of: B7H3, PSCA, MFG-E8, Rab, STEAP, PSMA, PCSA, 5T4, miR-9, miR-629, miR-141, miR-671-3p, miR-491, miR-182, miR-125a-3p, miR-324-5p, miR-148b, and miR-222, wherein the expression level of the one or more biomarkers is higher for an isolated exosome as compared to an isolated exosome derived from a normal cell. The isolated exosome can comprise at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 18, or 19 of the biomarkers selected from the group. The isolated exosome can further comprising one or more biomarkers selected from the group consisting of: EpCam, CD63, CD59, CD81, or CD9.

[0816] An isolated exosome can comprise the biomarkers PCSA, EpCam, CD63, and CD8; the biomarkers PCSA, EpCam, B7H3 and PSMA. An isolated exosome can comprise the biomarkers miR-9, miR-629, miR-141, miR-671-3p, miR-491, miR-182, miR-125a-3p, miR-324-5p, miR-148b, and miR-222.

[0817] A composition comprising an isolated exosome is also provided herein. The composition can comprise one or more isolated exosomes. For example, the composition can comprise a plurality of exosomes, or one or more populations of exosomes.

[0818] The composition can be substantially enriched for exosomes. For example, the composition can be substantially absent of cellular debris, cells, or non-exosomal proteins, peptides, or nucleic acids (such as biological molecules not contained within the exosomes). The cellular debris, cells, or non-exosomal proteins, peptides, or nucleic acids, can be present in a biological sample along with exosomes. A composition can be substantially absent of cellular debris, cells, or non-exosomal proteins, peptides, or nucleic acids (such as biological molecules not contained within the exosomes), can be obtained by any method disclosed herein, such as through the use of one or more binding agents or capture agents for one or more exosomes. The exosomes can comprise at least 30, 40, 50, 60, 70, 80, 90, 95 or 99% of the total composition, by weight or by mass. The exosomes of the composition can be a heterogeneous or homogeneous population of exosomes. For example, a homogeneous population of exosomes comprises exosomes that are homogeneous as to one or more properties or characteristics. For example, the one or more characteristics can be selected from a group consisting of: one or more of the same biomarkers, a substantially similar or identical bio-signature, derived from the same cell type, exosomes of a particular size, and a combination thereof.

[0819] Thus, in some embodiments, the composition comprises a substantially enriched population of exosomes. The composition can be enriched for a population of exosomes that are at least 30, 40, 50, 60, 70, 80, 90, 95 or 99% homogeneous as to one or more properties or characteristics. For example, the one or more characteristics can be selected from a group consisting of: one or more of the same biomarkers, a substantially similar or identical bio-signature, derived from the same cell type, exosomes of a particular size, and a combination thereof. For example, the population of exosomes can be homogeneous by all having a particular bio-signature, having the same biomarker, having the same biomarker combination, or derived from the same cell type. In some embodiments, the composition comprises a substantially homogeneous population of exosomes, such as a population with a specific bio-signature, derived from a specific cell, or both.

[0820] The population of exosome can comprise one or more of the same biomarkers. The biomarker can be any component present in an exosome or on the exosome, such as any nucleic acid (e.g. RNA or DNA), protein, peptide, polypeptide, antigen, lipid, carbohydrate, or proteoglycan. For example, each exosome in a population can comprise the same or identical one or more biomarkers. In some embodiments, each exosome in the population comprises the same 1, 2, 3, 4, 5, 6, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 50, 75 or 100 biomarkers. The one or more biomarkers can be selected from FIGS. **1**, **3**-**60**.

[0821] The exosome population comprising the same or identical biomarker can refer to each exosome in the population having the same presence or absence, expression level, mutational state, or modification of the biomarker. For example, an enriched population of exosome can comprise exosomes, wherein each exosome has the same biomarker present, the same biomarker absent, the same expression level of a biomarker, the same modification of a biomarker, or the same mutation of a biomarker. The same expression level of a biomarker can refer to a quantitative or qualitive measurement, such as the exosomes in the population underexpress, overexpress, or have the same expression level of a biomarker as compared to a reference level. Alternatively, the same expression level of a biomarker can be a numerical value representing the expression of a biomarker that is similar for each exosome in a population. For example the copy number of a miRNA, the amount of protein, or the level of mRNA of each exosome can be quantitatively similar for each exosome in a population, such that the numerical amount of each exosome is ±1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, or 20% from the amount in each other exosome in the population, as such variations are appropriate.

[0822] In some embodiments, the composition comprises a substantially enriched population of exosomes, wherein the exosomes in the enriched population has a substantially similar or identical bio-signature. The bio-signature can comprise one or more exosomal characteristic such as the level or amount of exosomes, temporal evaluation of the variation in exosomal half-life, circulating exosomal half-life or exosomal metabolic half-life, or the activity of an exosome. The bio-signature can also comprise the presence or absence, expression level, mutational state, or modification of a biomarker, such as those described herein.

[0823] The bio-signature of each exosome in the population can be at least 30, 40, 50, 60, 70, 80, 90, 95, or 99% identical. In some embodiments, the bio-signature of each exosome is 100% identical. The bio-signature of each exosome in the enriched population can have the same 1, 2, 3, 4, 5, 6, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 50, 75 or 100 exosomal characteristics. For example, a bio-signature of an exosome in an enriched population can be the presence of a first biomarker, the presence of a second biomarker, and the underexpression of a third biomarker. Another exosome in the same population can be 100% identical, having the same first and second biomarkers present and underexpression of the third biomarker. Alternatively, an exosome in the same population can have the same first and second biomarkers, but not have underexpression of the third biomarker.

[0824] In some embodiments, the composition comprises a substantially enriched population of exosomes, wherein the exosomes are derived from the same cell type. For example, the exosomes can all be derived from cells of a specific tissue, cells from a specific tumor of interest or a diseased tissue of interest, circulating tumor cells, or cells of maternal or fetal origin. The exosomes can all be derived from tumor cells. The exosomes can all be derived from lung, pancreas, stomach, intestine, bladder, kidney, ovary, testis, skin, colorectal, breast, prostate, brain, esophagus, liver, placenta, or fetal cells.

[0825] The composition comprising a substantially enriched population of exosomes can also comprise exosomes are of a particular size. For example, the exosomes can all a diameter of greater than about 10, 20, or 30 nm. They can all have a diameter of about 30-1000 nm, about 30-800 nm, about 30-200 nm, or about 30-100 nm. In some embodiments, the exosomes can all have a diameter of less than about 10,000 nm, 1000 nm, 800 nm, 500 nm, 200 nm, 100 nm or 50 nm.

[0826] The population of exosomes homogeneous for one or more characteristics can comprises at least about 30, 40, 50, 60, 70, 80, 90, 95, or 99% of the total exosome population of the composition. In some embodiments, a composition comprising a substantially enriched population of exosomes comprises at least 2, 3, 4, 5, 10, 20, 25, 50, 100, 250, 500, or 1000 times the concentration of an exosome as compared to a concentration of the exosome in a biological sample from which the composition was derived. In yet other embodiments, the composition can further comprise a second enriched population of exosomes, wherein the population of exosomes is at least 30% homogeneous as to one or more characteristics, as described herein.

[0827] Multiplex analysis can be used to obtain a composition substantially enriched for more than one population of exosomes, such as at least 2, 3, 4, 5, 6, 7, 8, 9, 10 exosome populations. Each substantially enriched exosome population can comprise at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 46, 47, 48, or 49% of the composition, by weight or by mass. In some embodiments, the substantially enriched exosome populations comprises at least about 30, 40, 50, 60, 70, 80, 90, 95, or 99% of the composition, by weight or by mass.

[0828] A substantially enriched population of exosomes can be obtained by using one or more methods, processes, or systems as disclosed herein. For example, isolation of a population of exosomes from a sample can be performed by using one or more binding agents for one or more biomarkers of an exosome, such as using two or more binding agents that target two or more biomarkers of an exosome. One or more capture agents can be used to obtain a substantially enriched population of exosomes. One or more detection agents can be used to identify a substantially enriched population of exosomes.

[0829] In one embodiment, a population of exosomes with a particular bio-signature is obtained by using one or more binding agents for the biomarkers of the bio-signature. The exosomes can be isolated resulting in a composition comprising a substantially enriched population of exosomes with the particular bio-signature. In another embodiment, a population of exosomes with a particular bio-signature of interest can be obtained by using one or more binding agents for biomarkers that are not a component of the bio-signature of interest. Thus, the binding agents can be used to remove the exosomes that do not have the bio-signature of interest and the resulting composition is substantially enriched for the population of exosomes with the particular bio-signature of interest. The resulting composition can be substantially absent of the exosomes comprising a biomarker for the binding agent.

Detection System and Kits

[0830] Also provided is a detection system configured to determine one or more bio-signatures for an exosome. The detection system can be used to detect a heterogeneous population of exosomes or one or more homogeneous population of exosomes. The detection system can be configured to detect a plurality of exosomes, wherein at least a subset of said plurality of exosomes comprises a different bio-signature from another subset of said plurality of exosomes. The detection system detect at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, or 100 different subsets of exosomes, wherein each subset of exosomes comprises a different bio-signature. For example, a detection system, such as using one or more methods, processes, and compositions disclosed herein, can be used to detect at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, or 100 different populations of exosomes.

[0831] The detection system can be configured to assess at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 1000, 2500, 5000, 7500, 10,000, 100,000, 150,000, 200,000, 250,000, 300,000, 350,000, 400,000, 450,000, 500,000, 750,000, or 1,000,000 different biomarkers for one or more exosomes. In some embodiments, the one or more biomarkers are selected from FIGS. **1**, **3-60**, or as disclosed herein. The detection system can be configured to assess a specific population of exosomes, such as exosomes from a specific cell-of-origin, or to assess a plurality of specific populations of exosomes, wherein each population of exosomes has a specific bio-signature.

[0832] The detection system can be a low density detection system or a high density detection system. For example, a low density detection system can detect up to 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 different exosome populations, whereas a high density detection system can detect at least about 15, 20, 25, 50, or 100 different exosome populations In another embodiment, a low density detection system can detect up to about 100, 200, 300, 400, or 500 different biomarkers, whereas a high density detection system can detect at least about 750, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9,000, 10,000, 15,000, 20,000, 25,000, 50,000, or 100,000 different biomarkers. In yet another embodiment, a low density detection system can detect up to about 100, 200, 300, 400, or 500 different bio-signatures or biomarker combinations, whereas a high density detection system can detect at least about 750, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9,000, 10,000, 15,000, 20,000, 25,000, 50,000, or 100,000 bio-signatures or biomarker combinations.

[0833] The detection system can comprise a probe that selectively hybridizes to an exosome. The detection system can comprise a plurality of probes to detect an exosome. In some embodiments, a plurality of probes is used to detect the amount of exosomes in a heterogeneous population of exosomes. In yet other embodiments, a plurality of probes is used to detect a homogeneous population of exosomes. A plurality of probes can be used to isolate or detect at least two different subsets of exosomes, wherein each subset of exosomes comprises a different bio-signature.

[0834] A detection system, such as using one or more methods, processes, and compositions disclosed herein, can comprise a plurality of probes configured to detect, or isolate, such as using one or more methods, processes, and compositions disclosed herein at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, or 100 different subsets of exosomes, wherein each subset of exosomes comprises a different bio-signature.

[0835] For example, a detection system can comprise a plurality of probes configured to detect at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, or 100 different populations of exosomes. The detection system can comprise a plurality of probes configured to selectively hybridize to at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 1000, 2500, 5000, 7500, 10,000, 100,000, 150,000, 200,000, 250,000, 300,000, 350,000, 400,000, 450,000, 500, 000, 750,000, or 1,000,000 different biomarkers for one or more exosomes. In some embodiments, the one or more biomarkers are selected from FIGS. **1**, **3-60**, or as disclosed herein. The plurality of probes can be configured to assess a specific population of exosomes, such as exosomes from a specific cell-of-origin, or to assess a plurality of specific populations of exosomes, wherein each population of exosomes has a specific bio-signature.

[0836] The detection system can be a low density detection system or a high density detection system comprising probes to detect exosomes. For example, a low density detection system can comprise probes to detect up to 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 different exosome populations, whereas a high density detection system can comprise probes to detect at least about 15, 20, 25, 50, or 100 different exosome populations In another embodiment, a low density detection system can comprise probes to detect up to about 100, 200, 300, 400, or 500 different biomarkers, whereas a high density detection system can comprise probes to detect at least about 750, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9,000, 10,000, 15,000, 20,000, 25,000, 50,000, or 100,000 different biomarkers. In yet another embodiment, a low density detection system can comprise probes to detect up to about 100, 200, 300, 400, or 500 different bio-signatures or biomarker combinations, whereas a high density detection system can comprise probes to detect at least about 750, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9,000, 10,000, 15,000, 20,000, 25,000, 50,000, or 100,000 bio-signatures or biomarker combinations.

[0837] The probes can be specific for detecting a specific exosome population, for example an exosome with a particular bio-signature, and as described above. A plurality of probes for detecting prostate specific exosomes is also provided. A plurality of probes can comprise probes for detecting one or more of the following biomarkers: CD9, PSCA, TNFR, CD63, MFG-E8, EpCAM, Rab, CD81, STEAP, PCSA, 5T4, EpCAM, PSMA, CD59, CD66, CD24 and B7H3. A plurality of probes for detecting Bcl-XL, ERCC1, Keratin 15, CD81/TAPA-1, CD9, Epithelial,Specific Antigen (ESA), and Mast Cell Chymase can also be provided. A plurality of probes for detecting one or more miRNAs of an exosome can comprise probes for detecting one or more of the following miRNAs: miR-9, miR-629, miR-141, miR-671-3p, miR-491, miR-182, miR-125a-3p, miR-324-5p, miR-148b, and miR-222,

[0838] The probes may be attached to a solid substrate, such as an array or bead. Alternatively, the probes are not attached. The detection system may be an array based system, a sequencing system, a PCR-based system, or a bead-based system, such as described above. For example, the detection system can be a microfluidic device as described above.

[0839] The detection system may be part of a kit. Alternatively, the kit may comprise the one or more probe sets, or plurality of probes, as described herein. The kit may comprise probes for detecting an isolated exosome, a plurality of exosomes, such as exosomes in a heterogeneous population. The kit may comprise probes for detecting a homogeneous population of exosomes. For example, the kit may comprise probes for detecting a population of specific cell-of-origin exosomes, or exosomes with the same specific bio-signature.

Portfolios

[0840] Portfolios of multiplexed markers to guide clinical decisions and disease detection and management can be established such that the combination of bio-signatures in the portfolio exhibit improved sensitivity and specificity relative to individual bio-signatures or randomly selected combinations of bio-signatures. In the context of the instant invention, the sensitivity of the portfolio can be reflected in the fold differences exhibited by a bio-signature's expression in the diseased state relative to the normal state. Specificity can be reflected in statistical measurements of the correlation of the signaling of gene expression, for example, with the condition of interest (e.g. standard deviation can be a used as such a measurement). In considering a group of bio-signature for inclusion in a portfolio, a small standard deviation in measurements correlates with greater specificity. Other measurements of variation such as correlation coefficients can also be used in this capacity.

[0841] When combining biomakers or bio-signatures in this invention In Vitro Diagnostic Multivariate Index Assays (IVDMIAs) guidelines and regulations may apply. IVDMIAs can apply to bio-signatures as defined as a set of 2 or more markers composed of any combination of genes, gene alterations, mutations, amplifications, deletions, polymorphisms or methylations, or proteins, peptides, polypeptides or RNA molecules, miRNAs, mRNAs, snoRNAs, hnRNAs or RNA that can be grouped so that information obtained about the set of bio-signatures in the group provides a sound basis for making a clinically relevant judgment such as a diagnosis, prognosis, or treatment choice. These sets of bio-signatures make up various portfolios of the invention. As with most diagnostic markers, it is often desirable to use the fewest number of markers sufficient to make a correct medical judgment. This prevents a delay in treatment pending further analysis as well inappropriate use of time and resources. Preferably, portfolios are established such that the combination of bio-signatures in the portfolio exhibit improved sensitivity and specificity relative to individual bio-signatures or randomly selected combinations of bio-signatures. In the context of the instant invention, the sensitivity of the portfolio can be reflected in the fold differences exhibited by a bio-signature's expression in the diseased state relative to the normal state. Specificity can be reflected in statistical measurements of the correlation of the signaling of gene expression, for example, with the condition of interest. In considering a group of markers in a bio-signature for inclusion in a portfolio, standard deviations, variances, co-variances, correlation coefficients, weighted averages, arithmetic sums, means, multiplicative values, weighted or balanced values or any mathematical manipulation of the values of 2 or more markers that can together be used to calculate a value or score that taken as a whole can be shown to produce greater sensitivity, specificity, negative predictive value, positive predictive value or accuracy can also be used in this capacity and are within the scope of this invention.

[0842] In another embodiment pattern recognition methods can be used. One example involves comparing biomarker expression profiles for various biomarkers (or bio-signature portfolios) to ascribe diagnoses. The expression profiles of each of the biomarker comprising the bio-signature portfolio are fixed in a medium such as a computer readable medium.

[0843] In one example, a table can be established into which the range of signals (e.g., intensity measurements) indicative of disease or physiological state is input. Actual patient data can then be compared to the values in the table to determine whether the patient samples are normal, benign, diseased, or represent a specific physiological state. In a more sophisticated embodiment, patterns of the expression signals (e.g., fluorescent intensity) are recorded digitally or graphically. In the example of RNA expression patterns from the biomarker portfolios used in conjunction with patient samples are then compared to the expression patterns. Pattern comparison software can then be used to determine whether the patient samples have a pattern indicative of the disease, a given prognosis, a pattern that indicates likeliness to respond to therapy, or a pattern that is indicative of a particular physiological state. The expression profiles of the samples are then compared to the portfolio of a control cell. If the sample expression patterns are consistent with the expression pattern (s) for disease, prognosis, or therapy-related response then (in the absence of countervailing medical considerations) the patient is diagnosed as meeting the conditions that relate to these various circumstances. If the sample expression patterns are consistent with the expression pattern derived from the normal/control exosome population then the patient is diagnosed negative for these conditions.

[0844] In another exemplary embodiment, a method for establishing biomarker expression portfolios is through the use of optimization algorithms such as the mean variance algorithm widely used in establishing stock portfolios. This method is described in detail in the U.S. Application Publication No. 20030194734, incorporated herein by reference. Alternatively, measured DNA alterations, changes in mRNA, protein, or metabolites to phenotypic readouts of efficacy and toxicity may be modeled and analyzed using algorithms, systems and methods described in U.S. Pat. Nos. 7,089,168, 7,415,359 and U.S. Application Publication Nos. 20080208784, 20040243354, or 20040088116, each of which is herein incorporated by reference in its entirety.

[0845] An exemplary process of bio-signature portfolio selection and characterization of an unknown is summarized as follows:

[0846] 1. Choose baseline class.

[0847] 2. Calculate mean, and standard deviation of each biomarker for baseline class samples.

[0848] 3. Calculate (X*Standard Deviation+Mean) for each biomarker. This is the baseline reading from which all other samples will be compared. X is a stringency variable with higher values of X being more stringent than lower.

[0849] 4. Calculate ratio between each Experimental sample versus baseline reading calculated in step 3.

[0850] 5. Transform ratios such that ratios less than 1 are negative (eg. using Log base 10). (Under expressed biomarkers now correctly have negative values necessary for MV optimization).

[0851] 6. These transformed ratios are used as inputs in place of the asset returns that are normally used in the software application.

[0852] 7. The software will plot the efficient frontier and return an optimized portfolio at any point along the efficient frontier.

[0853] 8. Choose a desired return or variance on the efficient frontier.

[0854] 9. Calculate the Portfolio's Value for each sample by summing the multiples of each gene's intensity value by the weight generated by the portfolio selection algorithm.

[0855] 10. Calculate a boundary value by adding the mean Bio-signature Portfolio Value for Baseline groups to the multiple of Y and the Standard Deviation of the Baseline's Bio-signature Portfolio Values. Values greater than this boundary value shall be classified as the Experimental Class.

[0856] 11. Optionally one can reiterate this process until best prediction.

[0857] The process of selecting a bio-signature portfolio can also include the application of heuristic rules. Preferably, such rules are formulated based on biology and an understanding of the technology used to produce clinical results. More preferably, they are applied to output from the optimization method. For example, the mean variance method of bio-signature portfolio selection can be applied to microarray data for a number of biomarkers differentially expressed in subjects with a specific disease. Output from the method would be an optimized set of biomarkers that could include those that are expressed in exosomes as well as in diseased tissue. If samples used in the testing method are obtained from exosomes and certain biomarkers differentially expressed in instances of disease or physiological state could also be differentially expressed in exosomes, then a heuristic rule can be applied in which a bio-signature portfolio is selected from the efficient frontier excluding those that are differentially expressed in exosomes. Of course, the rule can be applied prior to the formation of the efficient frontier by, for example, applying the rule during data pre-selection.

[0858] Other statistical, mathematical and computational algorithms for the analysis of linear and non-linear feature subspaces, feature extraction and signal deconvolution in large scale datasets to identify exosome-derived multiplex analyte profiles for diagnosis, prognosis and therapy selection and/or characterization of define physiological states can be done using any combination of unsupervised analysis methods, including but not limited to: principal component analysis (PCA) and linear and non-linear independent component analysis (ICA); blind source separation, nongaussinity analysis, natural gradient maximum likelihood estimation; joint-approximate diagonalization; eigenmatrices; Gaussian radical basis function, kernel and polynominal kernel analysis sequential floating forward selection.

Computer Systems

[0859] An exosome can be assayed for molecular features, for example, by determining an amount, presence or absence of one or more biomarkers such as listed FIGS. **1**, **3-60**. The data generated can be used to produce a bio-signature, which can be stored and analyzed by a computer system, such as shown in FIG. **62**. The assaying or correlating of the bio-signature with one or more phenotypes can also be performed by computer systems, such as by using computer executable logic.

[0860] A computer system, such as shown in FIG. **62**, can be used to transmit data and results following analysis. Accordingly, FIG. **62** is a block diagram showing a representative example logic device through which results from exosome analysis can be reported or generated. FIG. **62** shows a computer system (or digital device) **800** to receive and store data generated from exosome analysis, analyze the data to generate one or more bio-signatures, and produce a report of the one or more bio-signatures. The computer system can also perform comparisons and analyses of bio-signatures generated, and transmit the results. Alternatively, the computer system can receive raw data of exosome analysis, such as through transmission of the data over a network, and perform the analysis.

[0861] The computer system **800** may be understood as a logical apparatus that can read instructions from media **811** and/or network port **805**, which can optionally be connected to server **809** having fixed media **812**. The system shown in FIG. **62** includes CPU **801**, disk drives **803**, optional input devices such as keyboard **815** and/or mouse **816** and optional monitor **807**. Data communication can be achieved through the indicated communication medium to a server **809** at a local or a remote location. The communication medium can include any means of transmitting and/or receiving data. For example, the communication medium can be a network connection, a wireless connection or an Internet connection. Such a connection can provide for communication over the World Wide Web. It is envisioned that data relating to the present invention can be transmitted over such networks or connections for reception and/or review by a party **822**. The receiving party **822** can be but is not limited to an individual, a health care provider or a health care manager. In one embodiment, a computer-readable medium includes a medium suitable for transmission of a result of an analysis of a biological sample, such as exosome bio-signatures. The medium can include a result regarding an exosome bio-signature of a subject, wherein such a result is derived using the methods described herein.

Ex vivo Harvesting of Exosomes

[0862] Exosomes for analysis and determination of a phenotype can also be from ex vivo harvesting. Cells can be cultured and that exosomes released from cells of interest in culture either result spontaneously or can be stimulated to release exosomes into the medium. (see for example, Zitvogel, et al./998. *Nat. Med.* 4: 594-600; Chaput, et al. 2004. *J. Immunol.* 172: 2137-214631: 2892-2900; Escudier, et al. 2005. *J. Transl. Med.* 3: 10; Morse, et al. 2005, *J. Transl. Med.* 3: 9; Peche, et al. 2006. *Am. J. Transplant.* 6: 1541-1550; Kim, et al. 2005. *J. Immunol.* 174: 6440-6448, all of which are herein incorporated by reference in their entireties). Cell lines or tissue samples can be grown to 80% confluence before being cultured in fresh DMEM for 72 h. Subsequent exosome production can be stimulated (see, for example, heat shock treatment of melanoma cells as described by Dressel, et al. 2003. *Cancer Res.* 63: 8212-8220, which is herein incorporated by reference in its entirety). The supernatant can then be harvested and exosomes prepared as described herein.

[0863] Exosomes produced ex vivo can, in one example, be cultured from a cell-of-origin or cell line of interest, exosomes can be isolated from the cell culture medium and subsequently labeled with a magnetic label, a fluorescent moiety, a radioisotope, an enzyme, a chemiluminescent probe, a metal particle, a non-metal colloidal particle, a polymeric dye particle, a pigment molecule, a pigment particle, an electrochemically active species, semiconductor nanocrystal or other nanoparticles including quantum dots or gold particles to be reintroduced in vivo as a label for imaging analysis. Ex vivo cultured exosomes can alternatively be used to identify novel bio-signatures by setting up culturing conditions for a given cell-of-origin with characteristics of interest, for example a culture of lung cancer cells or cell line with a known EGFR mutation that confers resistant to or susceptibility to gefitinib, then exposing the cell culture to gefitinib, isolating exosomes that arise from the culture and subsequently analyzing them on a discovery array to look for novel antigens or binding agents expressed on the outside of exosomes that could be used as a bio-signature to capture this species of exosome. Additionally, it would be possible to isolate any other biomarkers or bio-signatures found within these exosomes for discovery of novel signatures (including but not limited to nucleic acids, proteins, lipids, or combinations thereof) that may have clinical diagnostic, prognostic or therapy related implication.

[0864] Cells of interest can also be first isolated and cultured from tissues of interest. For example, human hair follicles in the growing phase, anagen, can be plucked individually from a patient's scalp using sterile equipment and plasticware, taking care not to damage the follicle. Each sample can be transferred to a Petri dish containing sterile PBS for tissue culture. Isolated human anagen hair follicles can be carefully transferred to an individual well of a 24-well plate containing 1 ml of William's E medium. Follicles can be maintained free-floating at 37° C. in an atmosphere of 5% CO_2 and 95% air in a humidified incubator. Medium can be changed every 3 days, taking care not to damage the follicles. Cells can then be collected and spun down from the media. Exosomes may then be isolated using antigens or cellular binding partners that are specific to such cell-of-origin specific exosomes using methods as previously described. Biomarkers and bio-signatures can then be isolated and characterized by methods known to those skilled in the art.

[0865] Cells of interest may also be cultured under microgravity or zero-gravity conditions or under a free-fall environment. For example, NASA's bioreactor technology will allow such cells to be grown at much faster rate and in much greater quantities. Exosomes may then be isolated using antigens or cellular binding partners that are specific to such cell-of-origin specific exosomes using methods as previously described.

[0866] Rotating wall vessels or RWVersus are a class of bioreactors developed by and for NASA that are designed to grow suspension cultures of cells in a quiescent environment that simulates microgravity can also be used. (see for example, U.S. Pat. Nos. 5,026,650; 5,153,131; 5,153,133; 5,437,998; 5,665,594; 5,702,941; 7,351,584, 5,523,228, 5,104,802, 6,117,674, Schwarz, R P, et al., *J. Tiss. Cult. Meth.* 14:51-58, 1992; Martin et al., *Trends in biotechnology* 2004; 22; 80-86, Li et al., *Biochemical Engineering Journal* 2004; 18; 97-104, Ashammakhi et al., *Journal Nanoscience Nanotechnology* 2006; 9-10: 2693-2711, Zhang et al., *International Journal of Medicine* 2007; 4: 623-638, Cowger, N L, et al., *Biotechnol. Bioeng* 64:14-26, 1999, Spaulding, G F, et al., *J. Cell. Biochem.* 51:249-251, 1993, Goodwin, T J, et al., *Proc. Soc. Exp. Biol. Med.* 202:181-192, 1993; Freed, L E et al., *In Vitro Cell. Dev. Biol.* 33:381-385, 1997, Clejan, S. et al, *Biotechnol. Bioeng.* 50:587-597, 1996). Khaoustov, V I, et al., *In Vitro Cell. Dev. Biol.* 35:501-509. 1999, each of which is herein incorporated by reference in its entirety).

[0867] Alternatively, cells of interest or cell-of-origin specific exosomes that have been isolated may be cultured in a stationary phase plug-flow bioreactor as generally described in U.S. Pat. No. 6,911,201, and U.S. Application Publication Nos. 20050181504, 20050180958, 20050176143 and 20050176137, each of which is herein incorporated by reference in its entirety. Alternatively, cells of interest or cell-origin specific exosomes may also be isolated and cultured as generally described in U.S. Pat. No. 5,486,359.

[0868] One embodiment can include the steps of providing a tissue specimen containing cells of interest or cell-origin specific exosomes, adding cells or exosomes from the tissue specimen to a medium which allows, when cultured, for the selective adherence of only the cells of interest or cell-origin specific exosomes to a substrate surface, culturing the specimen-medium mixture, and removing the non-adherent matter from the substrate surface is generally described in U.S. Pat. No. 5,486,359, which is herein incorporated by reference in its entirety.

Exosomes as Imaging Tools

[0869] In other embodiments, exosomes can be used as imaging tools. Labeled circulating tumor cells (CTCs) can be noninvasively visualized in vivo as they flow through the peripheral vasculature (He, W et al. (2007) *PNAS* 104(28) 11760-11765). The method can involve i.v. injection of a tumor-specific fluorescent ligand followed by multiphoton fluorescence imaging of superficial blood vessels to quantitate the flowing CTCs. Studies in mice with metastatic tumors demonstrated that CTCs can be quantitated weeks before metastatic disease is detected by other means. Similar methods could be used and applied to circulating cell-of-origin specific exosomes as well. The decision to administer chemotherapy after tumor resection usually depends on an oncologist's assessment of the presence of microscopic metastatic disease. Although computed tomography, MRI, tissue/sentinel lymph node biopsy or serum cancer marker analysis can each detect some level of residual disease, the presence of circulating tumor derived exosomes can correlate most sensitively with cancer progression and metastasis. Noninvasive imaging of these exosomes in real time as they flow through the peripheral vasculature could improve detection sensitivity by enabling analysis of significantly larger blood volumes (potentially the entire blood volume of the patient). Exosomes isolated from bodily fluid, purified, labeled and then reintroduced into the system can be used for identification of early tumors not yet visible by traditional imaging methods (e.g. early breast tumors or early ovarian tumor cells). Labeled exosomes can also be used as a signal to identify tumors of metastatic potential.

[0870] In one embodiment, exosomes can be labeled by peptide/antigen targeting to label the exosomes either in vivo or in vitro and then reintroduce in the circulatory system for the purposes of diagnostic imaging. Suitable labels may include those that may be detected by intravital flow cytometry, X-radiography, NMR, PET/SPECT or MRI. For X-radiographic techniques, suitable labels include any radioisotope that emits detectable radiation but that is not overtly harmful to the patient, such as barium or cesium, for example. Suitable labels for NMR or MRI generally include those with a detectable characteristic spin, such as deuterium. Suitable imaging systems may be used to detect the labeled exosomes in the circulatory system.

[0871] The labeled exosomes can be administered by arterial or venous injection, and can be formulated as a sterile, pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred formulation for intravenous injection should contain, in addition to the labeled exosomes, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle. An effective amount of labeled exosomes can be an amount sufficient to yield an acceptable image using equipment which is available for clinical use. An effective amount of the labeled exosomes may be administered in more than one injection. Effective amounts of the labeled exosomes will vary according to factors such as the degree of susceptibility of the individual, the age, sex, and weight of the individual, idiosyncratic responses of the individual, the dosimetry. Effective amounts of the labeled exosomes will also vary according to instrument and film-related factors.

[0872] In a further embodiment, intravital flow cytometry can be used to noninvasively count labeled exosomes in vivo as they flow through the peripheral vasculature. The method can include i.v. injection of a tumor-specific fluorescent ligand followed by multiphoton fluorescence imaging of superficial blood vessels to quantitate the flowing exosomes. Intravital flow cytometry for detection of exosomes circumvents sampling limitations and renders quantitation of rare events statistically significant by enabling analysis of the majority of a patient's blood volume (≈5 liters).

[0873] Many human carcinomas overexpress a receptor for the vitamin folic acid (>90% of ovarian and endometrial cancers, 86% of kidney cancers, 78% of nonsmall cell lung cancers, etc). Alternatively, normal tissues either lack measurable folate receptors (FR) or express FR at a site that is inaccessible to parenterally administered drugs. Because FR-expressing cancer masses can be selectively labeled in vivo by injection of either radioactive or fluorescent folate conjugates that bind FR with nanomolar affinity it is possible for single exosomes to bind sufficient numbers of folate conjugates to allow their detection in vivo as they pass through a patient's peripheral vasculature. To increase signal-to-background ratios, a tumor-specific probe is used that rapidly clear circulation if left uncaptured by exosomes. For this purpose, folate-dye conjugates (e.g. folate-AlexaFluor 488) conjugates can be used because tumor-specific antibodies were found to promote phagocytic clearance of the exosomes to which they bound, thereby causing significant underestimation of exosomes counts. To further ensure that the cells labeled with folate-AlexaFluor 488 are indeed malignant, monoclonal anti-human antibodies can be used (e.g. CA125 for ovarian cancer) plus an appropriate secondary antibody conjugated to rhodamine-X.

[0874] In another embodiment, exosomes can be labeled in vivo by intravenously introducing a labeling agent that specifically targets the exosome for downstream imaging applications similar to those described above.

Reimbursement Codes

[0875] In one embodiment, the use of exosomes as diagnostic, therapy-related or prognostic markers in the identification of disease, disease stage, progression or therapy can be assigned specific U.S. Medicare reimbursement codes. In one embodiment, the isolation and the use of cell-of-origin specific exosomes are used. The reimbursement code may be a code developed under the National Council for Prescription Drug Programs Professional Pharmacy Services (NCPDP/PPS code). A reimbursement code can be a diagnosis code utilized or recognized by an insurance company, for example. The diagnostic code is assignable based upon a reimbursement requirement by a third party. Alternatively, the diagnostic code is assignable based upon a need to analyze the utilization of medical resources. A set of diagnosis codes can conform to and/or be compatible with, for example, ICD (International Classification of Diseases) codes, 9th Edition, Clinical Modification, (ICD-9-CM), Volumes 1, 2 and 3; ICD-10, which is maintained and distributed by the U.S. Health and Human Services department; HCPCS (Health Care Financing Administration Common Procedure Coding System); NDC (National Drug Codes); CPT-4 (Current Procedural Terminology); Fourth Edition CDPN (Code on Dental Procedures and Nomenclature); SNOMED-RT "Systematicized Nomenclature of Medicine, Reference Terminology" by the College of American Pathologists; UMLS (Unified Medical Language System), by the National Library of Medicine; LOINC Logical Observation Identifiers, Names, and Codes; Regenstrief Institute and the Logical Observation Identifiers Names and Codes (LOINC®) Committee; Clinical Terms also known as "Read Codes"; DIN Drug Identification Numbers; Reimbursement Classifications including DRGs (Diagnosis Related Groups); CDT Current Dental Terminology; NIC (Nursing intervention codes); or Commercial Vocabulary Services (such as Health-Language by HealthLanguage Inc.), each of which is incorporated by reference in its entirety.

[0876] In one embodiment, each of the isolation methods for exosomes described herein can be assigned a specific reimbursement code. For example, each of the isolation methods of cell-of-origin specific exosomes described herein can be assigned a specific reimbursement code. In another embodiment, the specific bio-signature(s) obtained from the analysis of exosomes can be assigned a specific reimbursement code. In yet another embodiment, the specific bio-signature(s) obtained from the analysis of cell-of-origin specific exosomes can be assigned a specific reimbursement code. Alternatively, kits for the detection of a particular bio-signature of exosomes in a biological sample can be assigned to a specific reimbursement code. Alternatively, kits for the detection of a particular bio-signature of specific cell-of-origin exosomes in a biological sample can be assigned to a specific reimbursement code.

[0877] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

EXAMPLES

Example 1

Purification of Exosomes from Prostate Cancer Cell Lines

[0878] Prostate cancer cell lines are cultured for 3-4 days in culture media containing 20% FBS (fetal bovine serum) and 1% P/S/G. The cells are then pre-spun for 10 minutes at 400×g at 4° C. The supernatant is kept and centrifuged for 20 minutes at 2000×g at 4. The supernatant containing exosomes can be concentrated using a Millipore Centricon Plus-70 (Cat # UFC710008 Fisher).

[0879] The Centricon is pre washed with 30 mls of PBS at 1000×g for 3 minutes at room temperature. Next, 15-70 mls of the pre-spun cell culture supernatant is poured into the Concentrate Cup and is centrifuged in a Swing Bucket Adapter (Fisher Cat #75-008-144) for 30 minutes at 1000×g at room temperature.

[0880] The flow through in the Collection Cup is poured off. The volume in the Concentrate Cup is brought back up to 60 mls with any additional supernatant. The Concentrate Cup is centrifuged for 30 minutes at 1000×g at room temperature until all of the cell supernatant is concentrated.

[0881] The Concentrate Cup is washed by adding 70 m-1s of PBS and centrifuged for 30-60 minutes at 1000×g until approximately 2 mls remains. The exosomes are removed from the filter by inverting the concentrate into the small sample cup and centrifuge for 1 minute at 4° C. The volume is brought up to 25 mls with PBS. The exosomes are now concentrated and are added to a 30% Sucrose Cushion.

[0882] To make a cushion, 4 mls of Tris/30% Sucrose/D2O solution (30 g protease-free sucrose, 2.4 g Tris base, 50 ml D2O, adjust pH to 7.4 with ION NCL drops, adjust volume to 100 mls with D2O, sterilize by passing thru a 0.22-um filter) is loaded to the bottom of a 30 ml V bottom thin walled Ultracentrifuge tube. The diluted 25 mls of concentrated exosomes is gently added above the sucrose cushion without disturbing the interface and is centrifuged for 75 minutes at 100,000×g at 4° C. The ~25 mls above the sucrose cushion is carefully removed with a 10 ml pipet and the ~3.5 mls of exosome is collected with a fine tip transfer pipet (SAMCO 233) and transferred to a fresh ultracentrifuge tube, where 30 mls PBS is added. The tube is centrifuged for 70 minutes at 100,000×g at 4° C. The supernatant is poured off carefully. The pellet is resuspended in 200 ul PBS and can be stored at 4° C. or used for assays. A BCA assay (1:2) can be used to determine protein content and Western blotting or electron micrography can be used to determine exosome purification.

Example 2

Purification of Exosomes from VCaP and 22Rv1

[0883] Exosomes from Vertebral-Cancer of the Prostate (VCaP) and 22Rv1, a human prostate carcinoma cell line, derived from a human prostatic carcinoma xenograft (CWR22R) were collected by ultracentrifugation by first diluting plasma with an equal volume of PBS (1 ml). The diluted fluid was transferred to a 15 ml falcon tube and centrifuged 30 minutes at 2000×g 4° C. The supernatant (~2 mls) was transferred to an ultracentrifuge tube 5.0 ml PA thinwall tube (Sorvall #03127) and centrifuged at 12,000×g, 4° C. for 45 minutes.

[0884] The supernatant (~2 mls) was transferred to a new 5.0 ml ultracentrifuge tubes and filled to maximum volume with addition of 2.5 mls PBS and centrifuged for 90 minutes at 110,000×g, 4° C. The supernatant was poured off without disturbing the pellet and the pellet resuspended with 1 ml PBS. The tube was filled to maximum volume with addition of 4.5 ml of PBS and centrifuged at 110,000×g, 4° C. for 70 minutes.

[0885] The supernatant was poured off without disturbing the pellet and an additional 1 ml of PBS was added to wash the pellet. The volume was increased to maximum volume with the addition of 4.5 mls of PBS and centrifuged at 110,000×g for 70 minutes at 4° C. The supernatant was removed with P-1000 pipette until ~100 μl of PBS was in the bottom of the tube. The ~90 μl remaining was removed with P-200 pipette and the pellet collected with the ~10 μl of PBS remaining by gently pipetting using a P-20 pipette into the microcentrifuge tube. The residual pellet was washed from the bottom of a dry tube with an additional 5 μl of fresh PBS and collected into microcentrifuge tube and suspended in phosphate buffered saline (PBS) to a concentration of 500 μg/ml.

Example 3

Plasma Collection and Exosome Purification

[0886] Blood is collected via standard veinpuncture in a 7 ml K2-EDTA tube. The sample is spun at 400 g for 10 minutes in a 4° C. centrifuge to separate plasma from blood cells (SORVALL Legend RT+ centrifuge). The supernatant (plasma) is transferred by careful pipetting to 15 ml Falcon centrifuge tubes. The plasma is spun at 2,000 g for 20 minutes and the supernatant is collected.

[0887] For storage, approximately 1 ml of the plasma (supernatant) is aliquoted to a cryovials, placed in dry ice to freeze them and stored in −80° C. Before exosome purification, if samples were stored at −80° C., samples are thawed in a cold water bath for 5 minutes. The samples are mixed end over end by hand to dissipate insoluble material.

[0888] In a first prespin, the plasma is diluted with an equal volume of PBS (example, approximately 2 ml of plasma is diluted with 2 ml of PBS). The diluted fluid is transferred to a 15 ml Falcon tube and centrifuged for 30 minutes at 2000×g at 4° C.

[0889] For a second prespin, the supernatant (approximately 4 mls) is carefully transferred to a 50 ml Falcon tube and centrifuged at 12,000×g at 4° C. for 45 minutes in a Sorval.

[0890] In the isolation step, the supernatant (approximately 2 mls) is carefully transferred to a 5.0 ml ultracentrifuge PA thinwall tube (Sorvall #03127) using a P1000 pipette and filled to maximum volume with an additional 0.5 mls of PBS. The tube is centrifuged for 90 minutes at 110,000×g at 4° C.

[0891] In the first wash, the supernatant is poured off without disturbing the pellet. The pellet is resuspended or washed with 1 ml PBS and the tube is filled to maximum volume with an additional 4.5 ml of PBS. The tube is centrifuged at 110,000×g at 4° C. for 70 minutes. A second wash is performed by repeating the same steps.

[0892] The exosomes are collected by removing the supernatant with P-1000 pipette until approximately 100 μl of PBS is in the bottom of the tube. Approximately 90 μl 1 of the PBS is removed and discarded with P-200 pipette. The pellet and remaining PBS is collected by gentle pipetting using a P-20 pipette. The residual pellet is washed from the bottom of the dry tube with an additional 5 μl of fresh PBS and collected into a microcentrifuge tube.

Example 4

Analysis of Exosomes Using Antibody-Coupled Microspheres and Directly Conjugated Antibodies

[0893] This example demonstrates the use of particles coupled to an antibody, where the antibody captures the exosomes (see for example, FIG. **64**A). An antibody, the detector antibody, is directly coupled to a label, and is used to detect a biomarker on the captured exosome.

[0894] First, an antibody-coupled microsphere set is selected (Luminex, Austin, Tex.). The microsphere set can comprise various antibodies, and thus allows multiplexing. The microspheres are resuspended by vortex and sonication for approximately 20 seconds. A Working Microsphere Mixture is prepared by diluting the coupled microsphere stocks to a final concentration of 100 microspheres of each set/μL in Startblock (Pierce (37538)). (Note: 50 μL of Working Microsphere Mixture is required for each well.) Either PBS-1% BSA or PBS-BN(PBS, 1% BSA, 0.05% Azide, pH 7.4) may be used as Assay Buffer.

[0895] A 1.2 μm Millipore filter plate is pre-wet with 100 μl/well of PBS-1% BSA (Sigma (P3688-10PAK+0.05% NaAzide (S8032))) and aspirated by vacuum manifold. An aliquot of 50 μl of the Working Microsphere Mixture is dispensed into the appropriate wells of the filter plate (Millipore Multiscreen HTS (MSBVN1250)). A 50 μl aliquot of standard or sample is dispensed into to the appropriate wells. The filter plate is covered and incubated for 60 minutes at room temperature on a plate shaker. The plate is covered with a sealer, placed on the orbital shaker and set to 900 for 15-30 seconds to re-suspend the beads. Following that the speed is set to 550 for the duration of the incubation.

[0896] The supernatant is aspirated by vacuum manifold (less than 5 inches Hg in all aspiration steps). Each well is washed twice with 100 μl of PBS-1% BSA (Sigma (P3688-10PAK+0.05% NaAzide (S8032))) and is aspirated by vacuum manifold. The microspheres are resuspended in 50 μL of PBS-1% BSA (Sigma (P3688-10PAK+0.05% NaAzide (S8032))). The PE conjugated detection antibody is diluted to 4 μg/mL (or appropriate concentration) in PBS-1% BSA (Sigma (P3688-10PAK+0.05% NaAzide (S8032))). (Note: 50 μL of diluted detection antibody is required for each reaction.) A 50 μl aliquot of the diluted detection antibody is added to each well. The filter plate is covered and incubated for 60 minutes at room temperature on a plate shaker. The filter plate is covered with a sealer, placed on the orbital shaker and set to 900 for 15-30 seconds to re-suspend the beads. Following that the speed is set to 550 for the duration of the incubation. The supernatant is aspirated by vacuum manifold. The wells are washed twice with 100 μl of PBS-1% BSA (Sigma (P3688-10PAK+0.05% NaAzide (S8032))) and aspirated by vacuum manifold. The microspheres are resuspended in 100 μl of PBS-1'% BSA (Sigma (P3688-10PAK+0.05% NaAzide (S8032))). The microspheres are analyzed on a Luminex analyzer according to the system manual.

Example 5

Analysis of Exosomes Using Antibody-Coupled Microspheres and Biotinylated Antibody

[0897] This example demonstrates the use of particles coupled to an antibody, where the antibody captures the exosomes. An antibody, the detector antibody, is biotinylated. A label coupled to streptavidin is used to detect the biomarker.

[0898] First, the appropriate antibody-coupled microsphere set is selected (Luminex, Austin, Tex.). The microspheres are resuspended by vortex and sonication for approximately 20 seconds. A Working Microsphere Mixture is prepared by diluting the coupled microsphere stocks to a final concentration of 50 microspheres of each set/μL in Startblock (Pierce (37538)). (Note: 50 μl of Working Microsphere Mixture is required for each well.) Beads in Start Block should be blocked for 30 minutes and no more than 1 hour.

[0899] A 1.2 μm Millipore filter plate is pre-wet with 100 μl/well of PBS-1% BSA+Azide (PBS-BN)((Sigma (P3688-10PAK+0.05% NaAzide (S8032))) and is aspirated by vacuum manifold. A 50 μl aliquot of the Working Microsphere Mixture is dispensed into the appropriate wells of the filter plate (Millipore Multiscreen HTS (MSBVN1250)). A 50 μl aliquot of standard or sample is dispensed to the appropriate wells. The filter plate is covered with a seal and is incubated for 60 minutes at room temperature on a plate shaker. The covered filter plate is placed on the orbital shaker and set to 900 for 15-30 seconds to re-suspend the beads. Following that, the speed is set to 550 for the duration of the incubation.

[0900] The supernatant is aspirated by a vacuum manifold (less than 5 inches Hg in all aspiration steps). Aspiration can be done with the Pall vacuum manifold. The valve is place in the full off position when the plate is placed on the manifold. To aspirate slowly, the valve is opened to draw the fluid from the wells, which takes approximately 3 seconds for the 100 μl of sample and beads to be fully aspirated from the well. Once all of the sample is drained, the purge button on the manifold is pressed to release residual vacuum pressure from the plate.

[0901] Each well is washed twice with 100 μl of PBS-1% BSA+Azide (PBS-BN)(Sigma (P3688-10PAK+0.05% NaAzide (S8032))) and is aspirates by vacuum manifold. The microspheres are resuspended in 50 μl of PBS-1% BSA+Azide (PBS-BN)((Sigma (P3688-10PAK+0.05% NaAzide (S8032)))

[0902] The biotinylated detection antibody is diluted to 4 μg/mL in PBS-1% BSA+Azide (PBS-BN)((Sigma (P3688-10PAK+0.05% NaAzide (S8032))). (Note: 50 μl of diluted detection antibody is required for each reaction.) A 50 μl aliquot of the diluted detection antibody is added to each well.

[0903] The filter plate is covered with a sealer and is incubated for 60 minutes at room temperature on a plate shaker. The plate is placed on the orbital shaker and set to 900 for 15-30 seconds to re-suspend the beads. Following that, the speed is set to 550 for the duration of the incubation.

[0904] The supernatant is aspirated by vacuum manifold. Aspiration can be done with the Pall vacuum manifold. The valve is place in the full off position when the plate is placed on the manifold. To aspirate slowly, the valve is opened to draw the fluid from the wells, which takes approximately 3 seconds for the 100 ul of sample and beads to be fully aspirated from the well. Once all of the sample is drained, the purge button on the manifold is pressed to release residual vacuum pressure from the plate.

[0905] Each well is washed twice with 100 μl of PBS-1% BSA+Azide (PBS-BN)((Sigma (P3688-10PAK+0.05% NaAzide (S8032))) and is aspirated by vacuum manifold. The microspheres are resuspended in 50 μl of PBS-1% BSA (Sigma (P3688-10PAK+0.05% NaAzide (S8032))).

[0906] The streptavidin-R-phycoerythrin reporter (Molecular Probes 1 mg/ml) is diluted to 4 μg/mL in PBS-1% BSA+Azide (PBS-BN)(. (Note: 50 μl of diluted streptavidin-R-phycoerythrin is required for each reaction.) A 50 μl aliquot of the diluted streptavidin-R-phycoerythrin is added to each well.

[0907] The filter plate is covered with a sealer and is incubated for 60 minutes at room temperature on a plate shaker. The plate is placed on the orbital shaker and set to 900 for 15-30 seconds to re-suspend the beads. Following that, the speed is set to 550 for the duration of the incubation.

[0908] The supernatant is aspirated by vacuum manifold. Aspiration can be done with the Pall vacuum manifold. The valve is place in the full off position when the plate is placed on the manifold. To aspirate slowly, the valve is opened to draw the fluid from the wells, which takes approximately 3 seconds for the 100 ul of sample and beads to be fully aspirated from the well. Once all of the sample is drained, the purge button on the manifold is pressed to release residual vacuum pressure from the plate.

[0909] Each well is washed twice with 100 μl of PBS-1% BSA+Azide (PBS-BN)((Sigma (P3688-10PAK+0.05% NaAzide (S8032))) and is aspirated by vacuum manifold. The microspheres are resuspended in 100 μl of PBS-1% BSA+Azide (PBS-BN)((Sigma (P3688-10PAK+0.05% NaAzide (S8032))) and analyzed on the Luminex analyzer according to the system manual.

Example 6

Determining Bio-Signatures for Prostate Cancer Using Multiplexing

[0910] The exosomes samples obtained using methods as described in Example 1-3 are used in multiplexing assays as described in Examples 4 and 5. The detection antibodies used are CD63, CD9, CD81, B7H3 and EpCam. The capture antibodies used are CD9, PSCA, TNFR, CD63 2X, B7H3, MFG-E8, EpCam 2×, CD63, Rab, CD81, SETAP, PCSA, PSMA, 5T4, Rab IgG (control) and IgG (control), resulting in 100 combinations to be screened (FIG. **64**B).

[0911] Ten prostate cancer patients and 12 normal control patients were screened. The results are depicted in FIG. **68** and FIG. **70**A. FIG. **70**B depicts the results of using PCSA capture antibodies (FIG. **70**B, left graph) or EpCam capture antibodies (FIG. **70**B, right graph), and detection using one or more detector antibodies. The sensitivity and specificity of the different combinations is depicted in FIG. **73**.

Example 7

Determining Bio-Signatures for Colon Cancer Using Multiplexing

[0912] The exosomes samples obtained using methods as described in Example 3 is used in multiplexing assays as described in Examples 4 and 5. The detection antibodies used are CD63, CD9, CD81, B7H3 and EpCam. The capture antibodies used are CD9, PSCA, TNFR, CD63 2X, B7H3, MFG-E8, EpCam 2X, CD63, Rab, CD81, STEAP, PCSA, PSMA, 5T4, Rab IgG (control) and IgG (control), resulting in 100 combinations to be screened.

[0913] The results are depicted in FIGS. **69**, **71**, and **72**. The sensitivity of the different combinations is depicted in FIG. **74**.

Example 9

Capture of Exosomes Using Magnetic Beads

[0914] Exosomes isolated as described in Example 2 are used. Approximately 40 ul of the exosomes are incubated with approximately 5 ug (~50 μl) of EpCam antibody coated Dynal beads (Invitrogen, Carlsbad, Calif.) and 50 μl of Starting Block. The exosomes and beads are incubated with shaking for 2 hours at 45° C. in a shaking incubator. The tube containing the Dynal beads is placed on the magnetic separator for 1 minute and the supernatant removed. The beads are washed twice and the supernatant removed each time. Wash beads twice, discarding the supernatant each time.

Example 10

Detection of TMPRSS2:ERG in Exosomes

[0915] The RNA from the bead-bound exosomes of Example 9 was isolated using the Qiagen miRneasy™ kit, (Cat. No. 217061), according to the manufacturer's instructions.

[0916] The exosomes are homogenized in QIAzol™ Lysis Reagent (Cat. No. 79306). After addition of chloroform, the homogenate is separated into aqueous and organic phases by centrifugation. RNA partitions to the upper, aqueous phase, while DNA partitions to the interphase and proteins to the lower, organic phase or the interphase. The upper, aqueous phase is extracted, and ethanol is added to provide appropriate binding conditions for all RNA molecules from 18 nucleotides (nt) upwards. The sample is then applied to the RNeasy™ Mini spin column, where the total RNA binds to the membrane and phenol and other contaminants are efficiently washed away. High quality RNA is then eluted in RNase-free water.

[0917] RNA from the VCAP bead captured exosomes was measured with the Taqman TMPRSS:ERG fusion transcript assay (Kirsten D. Mertz et al. *Neoplasia*. 2007 March; 9(3): 200-206.). RNA from the 22Rv1 bead captured exosomes was measured with the Taqman SPINK1 transcript assay (Scott A. Tomlin et al. *Cancer Cell* 2008 June 13(6):519-528). The GAPDH transcript (control transcript) was also measured for both sets of exosomal RNA.

[0918] Higher CT values indicate lower transcript expression. One change in cycle threshold (CT) is equivalent to a 2 fold change, 3 CT difference to a 4 fold change, and so forth, which can be calculated with the following: $2^{\wedge CT1-CT2}$. This experiment shows a difference in CT of the expression of the fusion transcript TMPRSS:ERG and the equivalent captured with the IgG2 negative control bead (FIG. **75**). The same comparison of the SPINK1 transcript in 22RV1 exosomes shows a CT difference of 6.14 for a fold change of 70.5 (FIG. **75**C).

Example 11

MicroRNA Profiles in Exosomes

[0919] Exosomes were collected by ultracentrifugation from 22Rv1, LNCaP, Vcap and normal plasma (pooled from 16 donors) as described in Examples 1 and 2. RNA was extracted using the Exiqon miR isolation kit (Cat. No. 300110, 300111). Equals amounts of exosomes (30 μg) were used as determined by BCA assay.

[0920] Equal volumes (5 μl) were put into a reverse-transcription reaction for microRNA. The reverse-transcriptase reactions were diluted in 81 μl of nuclease-free water and then 9 μl of this solution was added to each individual miR assay. MiR-629 was found to only be expressed in PCa (prostate cancer) exosomes and was virtually undetectable in normal plasma exosomes. MiR-9 was found to be highly overexpressed (~704 fold increase over normal as measured by copy number) in all PCa cell lines, and has very low expression in normal plasma exosomes. The top ten differentially expressed miRNAs are depicted in FIG. **76**.

Example 12

MicroRNA Profiles of Magentic EpCam-Captured Exosomes

[0921] The bead-bound exosomes of Example 9 was placed in QIAzol™ Lysis Reagent (Cat. #79306). An aliquot of 125 fmol of *c. elegans* miR-39 was added. The RNA from the exosomes was isolated using the Qiagen miRneasy™ kit, (Cat. #217061), according to the manufacturer's instructions, and eluted in 30 ul RNAse free water.

[0922] 10 μl of the purified RNA was placed into a pre-amplification reaction for miR-9, miR-141 and miR-629 using a Veriti 96-well thermocycler. A 1:5 dilution of the pre-amplification solution was used to set up a qRT-PCR reaction for miR9 (ABI 4373285), miR-141 (ABI 4373137) and miR-629 (ABI 4380969) as well as *c. elegans* miR-39 (ABI 4373455). The results were normalized to the *c. elegans* results for each sample.

Example 13

MicroRNA Profiles of CD9-Captured Exosomes

[0923] The CD9 coated Dynal beads (Invitrogen, Carlsbad, Calif.) were used instead of EpCam coated beads as in Example 12. Exosomes from prostate cancer patients, LNCaP, or normal purified exomes were incubated with the CD9 coated beads and the RNA isolated as described in

Example 12. The expression of miR-21 and miR-141 was detected by qRT-PCR and the results depicted in FIGS. **77** and **78**.

Example 14

Reference Values for Prostate Cancer

[0924] Fourteen stage 3 prostate cancer subjects, eleven benign prostate hyperplasia (BPH) samples, and 15 normal samples were tested. Exosome samples were obtained using methods as described in Example 3 and used in multiplexing assays, such as described in Examples 4 and 5. The samples were analyzed to determine four criteria 1) if the sample has overexpressed exosomes, 2) if the sample has overexpressed prostate exosomes, 3) if the sample has overexpressed cancer exosomes, and 4) if the sample is reliable. If the sample met all four criteria, the categorization of the sample as positive for prostate cancer had varying sensitivities and specificities, depending on the different bio-signatures present for a sample as described below (Cancer-1, Cancer-2, and Cancer-3, FIG. **79**). The four criteria were as follows:

Exosome Overexpression

[0925] The mean fluorescence intensities (MFIs) for a sample in three assays were averaged to determine a value for the sample. Each assay used a different capture antibody. The first used a CD9 capture antibody, the second a CD81 capture antibody, and the third a CD63 antibody. The same combination of detection antibodies was used for each assay, antibodies for CD9, CD81, and CD63. If the average value obtained for the three assays was greater than 3000, the sample was categorized as having overexpressed exosomes (FIG. **79**, Exosome).

[0926] Prostate Exosome Overexpression

[0927] The MFIs for a sample in two assays were averaged to determine a value for the sample. Each assay used a different capture antibody. The first used a PCSA capture antibody and the second used a PSMA capture antibody. The same combination of detection antibodies was used for each assay, antibodies for CD9, CD81, and CD63. If the average value obtained for the two assays was greater than 100, the sample was categorized as having prostate exosomes overexpressed (FIG. **79**, Prostate).

[0928] Cancer Exosome Overexpression

[0929] Three different cancer bio-signatures were used to determine if cancer exosomes were overexpressed in a sample. The first, Cancer-1, used an EpCam capture antibody and detection antibodies for CD81, CD9, and CD63. The second, Cancer-2, used a CD9 capture antibody with detection antibodies for EpCam and B7H3. If the MFI value of a sample for any two of the three cancer bio-signatures was above a reference value, the sample was categorized as having overexpressed cancer (see FIG. **79**, Cancer-1, Cancer-2, Cancer-3).

[0930] Reliability of Sample

[0931] Two quality control measures, QC-1 and QC-2, were determined for each sample. If the sample met one of them; the sample was categorized as reliable.

[0932] For QC-1, the sum of all the MFIs of 7 assays was determined. Each of the 7 assays used detection antibodies for CD59 and PSMA. The capture antibody used for each assay was CD63, CD81, PCSA, PSMA, STEAP, B7H3, and EpCam. If the sum was greater than 4000, the sample was not reliable and not included.

[0933] For QC-2, the sum of all the MFIs of 5 assays was determined. Each of the 5 assays used detection antibodies for CD9, CD81 and CD63. The capture antibody used for each assay was PCSA, PSMA, STEAP, B7H3, and EpCam. If the sum was greater than 8000, the sample was not reliable and not included.

[0934] The sensitivity and specificity for samples with BPH and without BPH samples after a sample met the criteria as described herein, are shown in FIG. **79**.

[0935] It will also be understood that the foregoing description is of exemplary embodiments of the invention and that the invention is not limited to the specific forms shown or described herein. Various modifications may be made in the design, arrangement, and type of elements disclosed herein, as well as the steps of utilizing the invention without departing from the scope of the invention as expressed in the appended claims.

What is claimed is:

1. A method for determining a theranosis in a subject comprising:

(a) assessing a bio-signature for a microvesicle present in a biological sample from a subject suffering a disorder, wherein said assessing comprises assaying two or more polypeptides associated with said microvesicle; and

(b) determining whether said subject may respond to a selected treatment based on said assessing in (a), thereby determining a theranosis for said subject.

2. The method of claim **1**, wherein said disorder is a cancer, an autoimmune disorder or a cardiac disorder.

3. The method of claim **2**, wherein said cancer is lung cancer, breast cancer, or colon cancer.

4. The method of claim **1**, wherein said assessing comprises contacting said sample with at least three antibodies specific for three different analytes.

5. The method of claim **1**, wherein said microvesicle is assessed with respect to at least one nucleic acid.

6. The method of claim **5**, wherein said nucleic acid is DNA, mRNA, microRNA, snoRNA, snRNA, rRNAs, tRNAs, siRNA, hnRNA, or shRNA.

7. The method of claim **5**, wherein said nucleic acid is one or more of miR-21, miR-205, miR-92, miR-147 or miR-574.

8. The method of claim **1**, wherein said assessing comprises multiplexed analysis of said microvesicle surface biomarkers.

9. The method of claim **8**, wherein said assessing comprises identifying at least one nucleic acid, peptide, protein, lipid, antigen, carbohydrate, proteoglycan or a combination thereof.

10. The method of claim **1**, wherein said determining comprises obtaining a measure for an amount of said microvesicle.

11. The method of claim **8**, wherein said assessing further comprises multiplexed analysis of a plurality of nucleic acids in said microvesicle.

12. The method of claim **11**, wherein said plurality comprises at least one microRNA in FIGS. **3-6**, **19-24**, **26-30**, **32**, **33**, **36**, **40-42**, **47**, **51**, **53-57**, and **60**.

13. The method of claim **6**, wherein said microRNA is selected from miR-21, miR-205, miR-92, miR-147 or miR-574.

14. The method of claim **1**, wherein said disorder is lung cancer.

15. The method of claim **14**, wherein said bio-signature comprises at least one microRNA selected from miR-21, miR-205, miR-92, miR-147 or miR-574.

16. A method for determining biomarkers of a disorder in a subject comprising:

(a) assessing a bio-signature for a microvesicle present in a biological sample from a subject suffering a disorder, wherein said assessing comprises assaying two or more polypeptides associated with said microvesicle;

(b) determining whether one or more biomarkers are present in said microvesicle;

(c) comparing said one or more biomarkers in said sample to a reference; and

(d) determining biomarkers of said disorder based on said comparison.

17. The method of claim **16**, wherein said disorder is a cancer, an autoimmune disorder or a cardiac disorder.

18. The method of claim **17**, wherein said cancer is lung cancer, breast cancer, or colon cancer

19. The method of claim **16**, wherein said assessing comprises contacting said sample with at least three antibodies specific for three different analytes.

20. The method of claim **16**, wherein said one or biomarker is a nucleic acid, peptide, protein, lipid, antigen, carbohydrate, proteoglycan or a combination thereof.

21. The method of claim **20**, wherein said nucleic acid is DNA, mRNA, microRNA, snoRNA, snRNA, rRNAs, tRNAs, siRNA, hnRNA, or shRNA.

22. The method of claim **20**, wherein the nucleic acid is one or more of miR-21, miR-205, miR-92, miR-147 or miR-574.

23. The method of claim **16**, wherein said assessing comprises multiplexed analysis of surface markers of said microvesicle.

24. The method of claim **20**, wherein said one or more biomarker comprises at least one polypeptide and at least one nucleic acid.

25. The method of claim **16**, wherein said determining comprises obtaining a measure for an amount of said microvesicle.

26. The method of claim **23**, wherein said assessing further comprises multiplexed analysis of a plurality of nucleic acids in said microvesicle.

27. The method of claim **26**, wherein said plurality comprises at least one microRNA in FIGS. **3-6**, **19-24**, **26-30**, **32**, **33**, **36**, **40-42**, **47**, **51**, **53-57**, and **60**.

28. The method of claim **27**, wherein said microRNA is selected from miR-21, miR-205, miR-92, miR-147 or miR-574.

29. The method of claim **16**, wherein said disorder is lung cancer.

30. The method of claim **29**, wherein said bio-signature comprises at least one microRNA selected from miR-21, miR-205, miR-92, miR-147 or miR-574.

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