particular, LAT1/CD98 overexpression appears to be required for tumor metastasis in patients with colon cancer. (Kaira et al., Cancer Sci. 99: 2380-2386, 2008).

[0005] The expression pattern and functions of CD98 and LAT1 suggest these proteins as promising targets for treatment of a variety of human cancers. Inhibitors of LAT1 activity have demonstrated antitumor activity in a number of cancer types, including non-small cell lung cancers (Imai et al., supra), colon cancer cells (Oda et al., Cancer Sci. 101: 173-179, 2010), oral cancer cells (Kim et al., Biol. Pharm. Bull. 33: 1117-1121, 2010), and breast cancer cells (Shennan and Thomson, Oncol. Rep. 20: 885-889, 2008). LAT1 has also been suggested as a target for treatment of ovarian cancer (Fan et al, supra).

[0006] A murine monoclonal antibody to CD98, identified as HBJ127, was found to inhibit lymphocyte proliferation (Yagita and Hashimoto, J. Immunol. 136: 2062-2068, 1986) and to inhibit the growth of bladder tumor and lymphoma cells (Yagita et al., Cancer Res. 46: 1478-1489, 1986). The epitope for the HJ127 antibody was found to be residues $_{442}$AFS$_{444}$ of human CD98 (Itoh et al., 2007). A different murine monoclonal antibody to CD98 was shown to significantly inhibit tumor cell growth in vitro for glioma, prostate and colon cancer cells (Papetti and Herman, Am. J. Pathol. 159: 165-178, 2001). Additional monoclonal antibodies to human CD98 have been disclosed in U.S. Publication No. 20100143367. These monoclonal antibodies bind to epitopes within amino acid regions 372-530 or 104-371 of CD98. Five of these antibodies were found to inhibit amino acid uptake in a bladder cancer cell, and three of these antibodies were shown to suppress tumor growth in a mouse model.

[0007] As disclosed herein, analysis of fresh primary acute myelogenous leukemia (AML) tumor samples from patients using surface tagged antigen profiling (sTAg) of the cell surface proteome identified the transmembrane protein CD98 as being present at high density on the surface of AML tumor cells. CD98 is therefore a target for the treatment of AML, for example, by using binding agents such as antibodies which specifically bind to CD98. Binding agents specific for CD98, such as anti-CD98 antibodies, were also shown in various *in vivo* xengraft models to have utility in treating not only AML but various cancers, such as sarcoma, lymphoma, non-small cell lung cancer (NSCLC) and colorectal cancer.

[0008] The invention provides antibodies to CD98 that are useful in the diagnosis and treatment of various types of human cancers.

SUMMARY

[0009] Using in-solution labeling of intact AML tumor cell surfaces, followed by high-resolution, solution-based liquid chromatography coupled tandem mass spectrometry (LC-MS/MS), CD98 was identified as being present at high density on the surface of a majority of AML cell subtypes as compared to normal cells including developing blood cells. Thus, the invention provides anti-CD98 antibodies and ~~methods of using the such antibodies~~their uses in the treatment of AML and other cancers, including but not limited to lymphoma, sarcoma, non-small cell lung cancer and colorectal cancer.

[0010] In an embodiment, the invention provides an isolated antibody or a functional fragment thereof that specifically binds to human CD98, wherein the antibody or functional fragment binds to an epitope comprising residues A377, D397, I398, G400 and A401 of human CD98. In some embodiments, the epitope further comprises residues D374 and L378 of human CD98. In some embodiments, the epitope further comprises residues P379 and G380 of human CD98. In some embodiments, the epitope further comprises residues F395 and P396 of human CD98. In some embodiments, the epitope further comprises residues Q381, P382 and P399 of human CD98. In some embodiments, the epitope further comprises any one or more additional residues selected from the group consisting of D374, L378, P379, G380, Q381, P382, F395, P396 and P399 of human CD98.

[0011] In an embodiment, the invention provides an isolated antibody or a functional fragment thereof that specifically binds to human CD98, wherein the antibody binds to an epitope comprising residues P379, G380, D397 and I398 of human CD98. In some embodiments, the epitope further comprises residues F395 and P396 of human CD98. In some embodiments, the epitope further comprises residues Q381, P382, P399, G400 and A401 of human CD98. In some embodiments, the epitope further comprises residues D374, A377 and L378 of human CD98. In some embodiments, the epitope further comprises any one or more additional residues selected from the group consisting of D374, A377, L378, Q381, P382, F395, P396, P399, G400 and A401 of human CD98.

[0012] In some embodiments, the invention provides an isolated antibody or a functional fragment thereof, wherein the antibody or functional fragment binds to an epitope comprising residues D374, A377, L378, P379, G380, Q381, P382, F395, P396, D397, I398, P399, G400 and A401 of human CD98.

[0013] In some embodiments, the invention provides an isolated antibody or a functional fragment thereof that specifically binds to human CD98, wherein the antibody or functional fragment binds to an epitope comprised within amino acid residues 369-405 of human CD98. In some embodiments, the invention provides an isolated antibody or a functional fragment thereof that specifically binds to human CD98, wherein the antibody or functional fragment binds to an epitope consisting of amino acid residues 369-405 of human CD98.

[0014] In some embodiments, the monoclonal antibody of the invention is a humanized, human or chimeric antibody. In some embodiments, the antibody functional fragment of the invention is an Fab, F(ab')2, Fv or scFv fragment.

[0015] In an ~~embodiment~~example, ~~the invention provides~~disclosed herein is an isolated antibody or a functional fragment thereof comprising all three heavy chain complementarity determining regions (CDRs) from a heavy chain variable domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 8, SEQ ID NO: 12, SEQ ID NO: 31, and SEQ ID NO: 35, and/or all three light chain CDRs from a light chain variable domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 6, SEQ ID NO: 10, SEQ ID NO: 14, SEQ ID NO: 33, and SEQ ID NO: 37.

[0016] In an ~~embodiment~~example, the ~~invention~~disclosure provides an isolated antibody or a functional fragment thereof comprising all three heavy chain CDRs from a heavy chain variable domain having an amino acid

sequence selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 8, SEQ ID NO: 12, SEQ ID NO: 31, and SEQ ID NO: 35, and all three light chain CDRs from a light chain variable domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 6, SEQ ID NO: 10, SEQ ID NO: 14, SEQ ID NO: 33, and SEQ ID NO: 37. In some ~~embodiments~~examples, the antibody or functional fragment thereof comprises all heavy and light chain complementarity determining regions (CDRs) from: (a) the antibody designated 8-34B; (b) the antibody designated 18-2A 2.2; (c) the antibody designated 18-2A 7.1; (d) the antibody designated 1-47C; or (e) the antibody designated 1-115A. In some ~~embodiments~~examples, the antibody or functional fragment thereof comprises all heavy and light chain CDRs from the antibody designated 8-34B. In some ~~embodiments~~examples, the antibody or functional fragment thereof comprises all all heavy and light chain CDRs from the antibody designated 18-2A 2.2. In some ~~embodiments~~examples, the antibody or functional fragment thereof comprises all all heavy and light chain CDRs from the antibody designated 18-2A 7.1. In some ~~embodiments~~examples, the antibody or functional fragment thereof comprises all all heavy and light chain CDRs from the antibody designated 1-47C. In some ~~embodiments~~examples, the antibody or functional fragment thereof comprises all all heavy and light chain CDRs from the antibody designated 1-115A.

[0017] In some ~~embodiments~~examples, the antibody comprises a heavy chain variable domain sequence selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 8, SEQ ID NO: 12, SEQ ID NO. 31, and SEQ ID NO: 35. In some ~~embodiments~~examples, the antibody comprises a light chain variable domain sequence consisting of SEQ ID NO: 6, SEQ ID NO: 10, SEQ ID NO: 14, SEQ ID NO: 33, and SEQ ID NO: 37. In some ~~embodiments~~examples, the antibody comprises a heavy chain variable domain sequence selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 8, SEQ ID NO: 12, SEQ ID NO: 31, and SEQ ID NO: 35, and further comprises a light chain variable domain sequence consisting of SEQ ID NO: 6, SEQ ID NO: 10, SEQ ID NO: 14, SEQ ID NO: 33, and SEQ ID NO: 37.

[0018] In an ~~embodiment~~example, the antibody comprises the heavy chain variable domain sequence of SEQ ID NO: 4 and the light chain variable domain sequence of SEQ ID NO: 6. In an ~~embodiment~~example, the antibody comprises the heavy chain variable domain sequence of SEQ ID NO: 8 and the light chain variable domain sequence of SEQ ID NO: 10. In an ~~embodiment~~example, the antibody comprises the heavy chain variable domain sequence of SEQ ID NO: 12 and the light chain variable domain sequence of SEQ ID NO: 14. In an ~~embodiment~~example, the antibody comprises the heavy chain variable domain sequence of SEQ ID NO: 31 and the light chain variable domain sequence of SEQ ID NO: 33. In an ~~embodiment~~example, the antibody comprises the heavy chain variable domain sequence of SEQ ID NO: 35 and the light chain variable domain sequence of SEQ ID NO: 37.

[0019] In an ~~embodiment~~example, the ~~invention~~disclosure provides humanized antibodies. In some ~~embodiments~~examples, the humanized antibody comprises a heavy chain variable domain sequence selected from SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 22, and SEQ ID NO: 23. In some ~~embodiments~~examples, the humanized antibody comprises a light chain variable domain sequence selected from SEQ ID NO:15, SEQ ID NO: 16, SEQ ID NO: 20, and SEQ ID NO: 21. In some ~~embodiments~~examples, the humanized antibody comprises a heavy chain variable domain sequence selected from SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 22, and SEQ ID NO: 23, and further comprises a light

chain variable domain sequence selected from SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 20, and SEQ ID NO: 21. In some ~~embodiments~~examples, the humanized antibody comprises a light chain variable domain sequence selected from SEQ ID NO: 15 and SEQ ID NO: 16, and a heavy chain variable domain sequence selected from SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19. In an ~~embodiment~~example, the humanized antibody comprises the light chain variable domain sequence of SEQ ID NO: 15 and the heavy chain variable domain sequence of SEQ ID NO: 18.

[0020] In an embodiment, the humanized antibody comprises the light chain variable domain sequence of SEQ ID NO: 20 and the heavy chain variable domain sequence of SEQ ID NO: 22. In an embodiment, the humanized antibody comprises the light chain variable domain sequence of SEQ ID NO: 21 and the heavy chain variable domain sequence of SEQ ID NO: 23. In an ~~embodiment~~example, the humanized antibody comprises the light chain variable domain sequence of SEQ ID NO: 20 and the heavy chain variable domain sequence of SEQ ID NO: 23. In an embodiment, the humanized antibody comprises the light chain variable domain sequence of SEQ ID NO: 21 and the heavy chain variable domain sequence of SEQ ID NO: 22. In an ~~embodiment~~example, the ~~invention~~disclosure provides an antibody that bind to the same epitope as a humanized antibody comprising the light ~~chain~~ variable domain sequence of SEQ ID NO: 21 and the heavy chain variable domain sequence of SEQ ID NO: 22. In an alternative ~~embodiment~~example, the ~~invention~~disclosure comprises a binding agent that binds to essentially the same epitope as an antibody from bin 1 or bins 3-7 as shown in Fig. 1.

[0021] In a further embodiment, the invention comprises a binding agent that binds to essentially the same epitope as any of the antibodies disclosed above. In some embodiments, the binding agent inhibits the growth of a tumor expressing CD98. In some embodiments, the binding agent is an antibody or a functional fragment thereof. In other embodiments, the binding agent is an anticalin, an adnectin, an affibody, a DARPin, a fynomer, an affitin, an affilin, an avimer, a cysteine-rich knottin peptide, or an engineered Kunitz-type inhibitor.

[0022] In one embodiment, the invention provides a binding agent capable of binding to CD98, wherein any one of the antibodies disclosed above displaces the binding agent in a competitive binding assay. In some embodiments, the binding agent is an antibody, or a functional fragment thereof. In another embodiment, the invention provides a binding agent capable of binding to CD98, wherein the binding agent displaces any one of the antibodies disclosed above in a competitive binding assay. In some embodiments, the binding agent is an antibody, or a functional fragment thereof.

[0023] In some ~~embodiments~~examples, the ~~invention~~disclosure provides an antibody that binds to CD98, wherein the antibody comprises a heavy chain variable domain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to an amino acid sequence selected from SEQ ID NO: 4, SEQ ID NO: 8, SEQ ID NO: 12, SEQ ID NO: 17, SEQ ID NO: 18; SEQ ID NO: 19, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 31, and SEQ ID NO; 35. In some ~~embodiments~~examples, the antibody comprises a light chain variable domain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to an amino acid sequence selected from the

group consisting of SEQ ID NO: 6, SEQ ID NO: 10, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 33, and SEQ ID NO: 37. In some ~~embodiments~~examples, the antibody comprises a heavy chain variable domain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to an amino acid sequence selected from SEQ ID NO: 4, SEQ ID NO: 8, SEQ ID NO: 12, SEQ ID NO: 17, SEQ ID NO: 18; SEQ ID NO: 19, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 31, and SEQ ID NO: 35, and the antibody further comprises a light chain variable domain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO: 6, SEQ ID NO: 10, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 33, and SEQ ID NO: 37.

[0024] In some ~~embodiments~~examples, the ~~invention~~disclosure provides an antibody that is a variant of any of the above antibodies having one or more amino acid substitutions, deletions, insertions or modifications, and which retains a biological function of an antibody. In some ~~embodiments~~examples, the ~~invention~~disclosure provides an antibody that binds to CD98 expressed on the cell surface and inhibits the growth of the cell. In some ~~embodiments~~examples, the anti-CD98 antibody binds to CD98 expressed on the cell surface and inhibits cell proliferation. In some ~~embodiments~~examples, the anti-CD98 antibody binds to CD98 expressed to the cell surface and induces cell death. In some ~~embodiments~~examples, the ~~invention~~disclosure provides an antibody that is a variant of any one of the above antibodies having improvements in one or more of a property such as binding affinity, specificity, thermostability, expression level, effector function, glycosylation, reduced immunogenicity, or solubility as compared to the unmodified antibody.

[0025] In some ~~embodiments~~examples, the ~~invention~~disclosure provides any one of the above antibodies or functional fragments, wherein theantibody or fragment is conjugated to a cytotoxic agent. In various ~~embodiments~~examples, the cytotoxic agent is selected from a chemotherapeutic agent, a drug, a growth inhibitory agent, a toxic, or a radioactive isotope. In some ~~embodiments~~examples, the ~~invention~~disclosure provides any one of the above antibodies or functional fragments, wherein theantibody or fragment is conjugated to a detectable marker. In various ~~embodiments~~examples, the detectable marker is selected from a radioisotope, a metal chelator, an enzyme, a fluorescent compound, a bioluminescent compound and a chemiluminescent compound.

[0026] In an embodiment, the invention provides a hybridoma that produces a monoclonal antibody of the invention. In an embodiment, the invention provides a transgenic animal that produces a monoclonal antibody of the invention.

[0027] In some ~~embodiments~~examples, a polynucleotide encoding any one of the above antibodies is provided. In an embodiment, a vector comprising the polynucleotide is provided. In an embodiment, a host cell comprising the vector is provided. In an ~~embodiment~~example, the host cell is prokaryotic. In an ~~embodiment~~example, the host cell is an E. coli cell. In another ~~embodiment~~example, the host cell is eukaryotic. In an ~~embodiment~~example, the host cell is a Chinese Hamster Ovary (CHO) cell. In an ~~embodiment~~example, a method of making an anti-CD98 antibody is provided, wherein the method comprises culturing the host cell under

conditions suitable for expression of the polynucleotide encoding the antibody, and isolating the antibody.

[0028] In one embodiment, the invention provides a pharmaceutical composition comprising any of the above antibodies or functional fragments thereof, antibody conjugates, or binding agents of the invention.

[0028a] In a further example, the invention provides the use of an antibody or functional fragment as defined above in the manufacture of a medicament for inhibiting growth of cancer cells that express CD98.

[0028b] In a further example, the invention provides the use of a pharmaceutical composition as defined above in the manufacture of a medicament for treating a cancer in a subject.

[0028c] In a further example, the invention provides an *in vitro* method of detecting the presence of CD98 in a biological sample, comprising contacting the biological sample with an antibody as defined above under conditions permissive for binding of the antibody to CD98, and detecting whether a complex is formed between the antibody and CD98.

[0028d] In a further example, the invention provides a method of diagnosing a cancer associated with increased expression of CD98, comprising contacting a test cell *in vitro* with an antibody as defined above; determining the level of expression of CD98 by detecting binding of the antibody to CD98; and comparing the level of expression of CD98 in the test cell with the level of expression of CD98 in a control cell, wherein a higher level of expression of CD98 in the test cell as compared to the control cell indicates the presence of a cancer associated with increased expression of CD98.

[0028e] In a further ~~embodiment~~example, the ~~invention~~disclosure provides a method of inhibiting growth of cancer cells that express CD98, the method comprising exposing the cells to any one or more of the above antibodies or functional fragment thereof, antibody conjugates, or binding agents ~~of the invention~~disclosed herein.

In various embodiments, the cancer cells are from a cancer selected from bladder, breast, colon, rectal, gastric, esophageal, lung, laryx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, melanoma, glioma, lymphoma or leukemia, or a metatasis of any of these cancers.

[0029] In an ~~embodiment~~example, the ~~invention~~disclosure provides a method for treating a cancer in a subject comprisingadministering to the subject a pharmaceutical composition comprising any of the above antibodies or functional fragments thereof, antibody conjugates, or binding agents of the invention. In various ~~embodiments~~examples, the cancer is selected from bladder, breast, colon, rectal, gastric, esophageal, lung laryx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, melanoma, glioma, lymphoma or leukemia, or a metatasis of any of these cancers. In some embodiments, the cancer is acute myeloid leukemia. In some ~~embodiments~~examples, the subject has relapsed or refractory acute myeloid leukemia. In some ~~embodiments~~examples, the cancer is associated with increased expression of CD98 on the surface of a cell.

[0030] In some ~~embodiments~~examples, the subject is administered one of more chemotherapeutic compound in combination with the antibody or functional fragment, wherein the chemotherapeutic compound is selected from bendamustine hydrochloride, cyclophosphamide, ifosfamide, fludurabine, cytarabine, gemcitabine, prednisone, prednisolone, methylprednisolone, paclitaxel, docetaxel, vinorelbine, vincristine, etoposide, irinotecan, anthracycline, adriamycin, cisplatin, carboplatin and rituximab.

[0031] In an ~~embodiment~~example, a method of detecting the presence of CD98 in a biological sample is provided, the method comprising contacting the biological sample with any of the above antibodies under conditions permissive for binding of the antibody to CD98, and detecting whether a complex is formed between the antibody and CD98. In some ~~embodiments~~examples, the biological sample is from a mammal having or suspected of having a cancer of cells or tissues including, but not limited to, bladder, breast, colon, rectal, gastric, esophageal, lung, laryx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, melanoma, glioma, lymphoma or leukemia, or a metatasis of any of these cancers.

[0032] In an ~~embodiment~~example, a method of diagnosing a cancer associated with increased expression of CD98 is provided, the method comprising contacting a test cell with any of the above antibodies; determining the level of expression of CD98 by detecting binding of the antibody to CD98; and comparing the level of expression of CD98 by the test cell with the level of expression of CD98 by a control cell, wherein a higher level of expression of CD98 by the test cell as compared to the control cell indicates the presence of a cancer associated with increased expression of CD98. In some ~~embodiments~~examples, the test cell is a cell from a patient suspected of having a cancer selected from bladder, breast, colon,

rectal, esophageal, lung, laryx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, glioma, lymphoma or leukemia,,or a metatasis of any of these cancers. In an ~~embodiment~~example, the method comprises determining the level of expression of CD98 on the surface of the test cell and comparing the level of expression of CD98 on the surface of the test cell with the level of expression of CD98 on the surface of the control cell. In some ~~embodiments~~examples, the test cell is a cancer cell and the control cell is a normal cell of the same tissue type.

[0033] In an ~~embodiment~~example, the ~~invention~~disclosure provides a use of any of the above antibodies or functional fragments in the in the manufacture of a medicament, wherein the medicament is for use in a method of inhibiting growth of cancer cells that express CD98. In various ~~embodiments~~examples, the cells are from a cancer is selected from bladder, breast, colon, rectal, gastric, esophageal, lung, laryx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, melanoma, glioma, lymphoma or leukemia, or a metatasis of any of these cancers.

[0034] In an ~~embodiment~~example, the ~~invention~~disclosure provides any of the above antibodies or functional fragments for use in inhibiting the growth of cancer cells that express CD98. In various ~~embodiments~~examples, the cells are from a cancer is selected from bladder, breast, colon, rectal, gastric, esophageal, lung, laryx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, melanoma, glioma, lymphoma or leukemia, or a metatasis of any of these cancers.

[0035] In an ~~embodiment~~example, the ~~invention~~disclosure provides a use of a pharmaceutical composition comprising any of the above antibodies or functional fragments in the manufacture of a medicament, wherein the medicament is for use in a method of treating cancer in a subject. In various ~~embodiments~~examples, the cancer is selected from bladder, breast, colon, rectal, gastric, esophageal, lung, laryx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, melanoma, glioma, lymphoma or leukemia, or a metatasis of any of these cancers. In some ~~embodiments~~examples, the cancer is acute myeloid leukemia. In some ~~embodiments~~examples the subject has relapsed or refractory acute myeloid leukemia. In some ~~embodiments~~examples, the cancer is associated with increased expression of CD98 on the surface of a cell. In some ~~embodiments~~examples, the subject is administered one or more chemotherapeutic compound in combination with the antibody or functional fragment, wherein the chemotherapeutic compound is selected from bendamustine hydrochloride, cyclophosphamide, ifosfamide, fludurabine, cytarabine, gemcitabine, prednisone, prednisolone, methylprednisolone, paclitaxel, docetaxel, vinorelbine, vincristine, etoposide, irinotecan, anthracycline, adriamycin, cisplatin, carboplatin and rituximab.

[0036] In an embodiment, the invention provides a pharmaceutical composition comprising any of the above antibodies or functional fragments and a pharmaceutically acceptable carrier, for use in treating cancer in a subject. In various embodiments, the cancer is selected from bladder, breast, colon, rectal, gastric, esophageal, lung, laryx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, melanoma, glioma, lymphoma or leukemia, or a metatasis of any of these cancers. In some embodiments, the cancer is acute myeloid leukemia. In some embodiments, the subject has relapsed or refractory acute myeloid leukemia. In some ~~embodiments~~examples, the cancer is associated with increased expression of CD98 on the surface of a cell. In some ~~embodiments~~examples, the subject is administered one or more chemotherapeutic

compound in combination with the antibody or functional fragment, wherein the chemotherapeutic compound is selected from bendamustine hydrochloride, cyclophosphamide, ifosfamide, fludurabine, cytarabine, gemcitabine, prednisone, prednisolone, methylprednisolone, paclitaxel, docetaxel, vinorelbine, vincristine, etoposide, irinotecan, anthracycline, adriamycin, cisplatin, carboplatin and rituximab.

[0037] In an ~~embodiment~~example, the ~~invention~~disclosure provides the use of any of the above antibodies or functional fragments in the manufacture of a medicament, wherein the medicament is for use in a method for detecting the presence of of CD98 in a biological sample. In some ~~embodiments~~examples, the method comprisescontacting the biological sample with any of the above antibodies under conditions permissive for binding of the antibody to CD98, and detecting whether a complex is formed between the antibody and CD98. In some ~~embodiments~~examples, the biological sample is from a mammal having or suspected of having a cancer of cells or tissues including, but not limited to, bladder, breast, colon, rectal, gastric, esophageal, lung, laryx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, melanoma, glioma, lymphoma or leukemia, or a metatasis of any of these cancers.

[0038] In an ~~embodiment~~example, the ~~invention~~disclosure provides any of the above antibodies or functional fragments for use in a method of detecting the presence of CD98 in a biological sample. In some ~~embodiments~~examples, the method comprisescontacting the biological sample with any of the above antibodies under conditions permissive for binding of the antibody to CD98, and detecting whether a complex is formed between the antibody and CD98. In some ~~embodiments~~examples, the biological sample is from a mammal having or suspected of having a cancer of cells or tissues including, but not limited to, bladder, breast, colon, rectal, gastric, esophageal, lung, laryx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, melanoma, glioma, lymphoma or leukemia, or a metatasis of any of these cancers.

[0039] In an ~~embodiment~~example, the ~~invention~~disclosure provides the use of any of the above antibodies or functional fragments in the manufacture of a medicament, wherein the medicament is for use in a method of diagnosing a cancer associated with increased expression of CD98. In some ~~embodiments~~examples, the method comprises contacting a test cell with any of the above antibodies; determining the level of expression of CD98 by detecting binding of the antibody to CD98; and comparing the level of expression of CD98 by the test cell with the level of expression of CD98 by a control cell, wherein a higher level of expression of CD98 by the test cell as compared to the control cell indicates the presence of a cancer associated with increased expression of CD98. In some ~~embodiments~~examples, the test cell is a cell from a patient suspected of having a cancer selected from bladder, breast, colon, rectal, esophageal, lung, laryx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, glioma, lymphoma or leukemia,, or a metatasis of any of these cancers. In an ~~embodiment~~example, the method comprises determining the level of expression of CD98 on the surface of the test cell and comparing the level of expression of CD98 on the surface of the test cell with the level of expression of CD98 on the surface of the control cell. In some ~~embodiments~~examples, the test cell is a cancer cell and the control cell is a normal cell of the same tissue type.

[0040] In an ~~embodiment~~example, the ~~invention~~disclosure provides any of the above antibodies or functional fragments for use in a method of diagnosing a cancer associated with increased expression of CD98. In

some ~~embodiments~~examples, the method comprises contacting a test cell with any of the above antibodies; determining the level of expression of CD98 by detecting binding of the antibody to CD98; and comparing the level of expression of CD98 by the test cell with the level of expression of CD98 by a control cell, wherein a higher level of expression of CD98 by the test cell as compared to the control cell indicates the presence of a cancer associated with increased expression of CD98. In some ~~embodiments~~examples, the test cell is a cell from a patient suspected of having a cancer selected from bladder, breast, colon, rectal, esophageal, lung, laryx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, glioma, lymphoma or leukemia,or a metatasis of any of these cancers. In an ~~embodiment~~example, the method comprises determining the level of expression of CD98 on the surface of the test cell and comparing the level of expression of CD98 on the surface of the test cell with the level of expression of CD98 on the surface of the control cell. In some ~~embodiments~~examples, the test cell is a cancer cell and the control cell is a normal cell of the same tissue type.

[0041] In another ~~embodiment~~example of the ~~invention~~disclosure, an article of manufacture, or "kit", containing materials useful for the treatment of the disorders described above is provided. The article of manufacture comprises a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, blister pack, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds an antibody or an antibody-drug conjugate (ADC) composition which is effective for treating the condition, and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is an antibdy or ADC. The label or package insert indicates that the composition is used for treating the condition of choice, such as cancer. Alternatively, or additionally, the article of manufacture may further comprise a second (or third) container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

BRIEF DESCRIPTION OF THE FIGURES

[0042] Fig. 1 shows the protein expression level of CD98 that was identified and quantified by sTAg analysis in the AML, CLL, CRC specimens and relevant normal controls. Lines indicate the mean of % normalized spectral abundance factor (NSAF) in positive samples.

[0043] Fig. 2 is a graph showing the results of epitope binning for 39 anti-CD98 antibodies.

[0044] Fig. 3 shows the binding properties of chimeric anti-CD98 monoclonal antibodies 8-34B, 18-2A 2.1, 18-2A 2.2, and 18-2A 2.7. Fig. 3A is a graph showing the results of epitope binning for chimeric anti-CD98 monoclonal antibodies. The four reference antibodies are as in Fig. 1. "Isotype" is a control antibody of the same isotype that does not bind CD98. Fig. 3B shows the Kd of chimeric anti-CD98 monoclonal antibodies as determined by FACS analysis with colon cancer cell line DLD1. Fig.

47. A pharmaceutical composition that comprises the antibody or functional fragment of any one of claims 1-31, 34, and 38-43, and a pharmaceutically acceptable carrier.

48. Use of an antibody or functional fragment of any one of claims 1-31, 34, and 38-43 in the manufacture of a medicament for ~~A method of~~ inhibiting growth of cancer cells that express CD98~~, the method comprising exposing the cells to the antibody or functional fragment of any one of claims 1-31, 34, and 38-43~~.

49. The ~~method~~ use of claim 48, wherein the cancer cells are from a cancer selected from bladder, breast, colon, rectal, gastric, esophageal, lung, laryx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, melanoma, glioma, lymphoma or leukemia, or a metatasis of any of these cancers.

50. The ~~method~~ use of claim 49, wherein the cancer cells are from acute myeloid leukemia.

51. Use of a pharmaceutical composition of claim 47 in the manufacture of a medicament ~~A method~~ for treating a cancer in a subject ~~comprising administering to the subject the pharmaceutical composition of claim 47~~.

52. The ~~method~~ use of claim 51, wherein the cancer is selected from bladder, breast, colon, rectal, gastric, esophageal, lung, laryx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, melanoma, glioma, lymphoma or leukemia, or a metatasis of any of these cancers.

53. The ~~method~~ use of claim 52, wherein the cancer is acute myeloid leukemia.

54. The ~~method~~ use of claim 51, wherein the subject has relapsed or refractory acute myeloid leukemia.

55. The ~~method~~ use of claim 51, wherein the subject is to be administered one or more chemotherapeutic compound in combination with the antibody or functional fragment, wherein the chemotherapeutic compound is selected from bendamustine hydrochloride, cyclophosphamide, ifosfamide, fludurabine, cytarabine, gemcitabine, prednisone, prednisolone, methylprednisolone, paclitaxel, docetaxel, vinorelbine, vincristine, etoposide, irinotecan, anthracycline, adriamycin, cisplatin, carboplatin and rituximab.

56. The ~~method~~ use of claim 51 wherein the cancer is associated with increased expression of CD98 on the surface of a cell.

57. An *in vitro* method of detecting the presence of CD98 in a biological sample, comprising contacting the biological sample with an antibody of any one of claims 1-31, 34, and 38-43 under

conditions permissive for binding of the antibody to CD98, and detecting whether a complex is formed between the antibody and CD98.

58. The method of claim 57, wherein the biological sample is from a mammal having or suspected of having a cancer selected from bladder, breast, colon, rectal, gastric, esophageal, lung, laryx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, melanoma, glioma, lymphoma or leukemia, or a metatasis of any of these cancers.

59. A method of diagnosing a cancer associated with increased expression of CD98, comprising contacting a test cell *in vitro* with an antibody of any one of claims 1-31, 34, and 38-43; determining the level of expression of CD98 by detecting binding of the antibody to CD98; and comparing the level of expression of CD98 in the test cell with the level of expression of CD98 in a control cell, wherein a higher level of expression of CD98 in the test cell as compared to the control cell indicates the presence of a cancer associated with increased expression of CD98.

60. The method of claim 59 wherein the test cell is from a patient suspected of having a cancer selected from bladder, breast, colon, rectal, gastric, esophageal, lung, laryx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, melanoma, glioma, lymphoma or leukemia, or a metatasis of any of these cancers.

61. The method of claim 60 wherein the method comprises determining the level of expression of CD98 on the surface of the test cell and comparing the level of expression of CD98 on the surface of the test cell with the level of expression of CD98 on the surface of the control cell.

62. The method of claim 61 wherein the test cell is a cancer cell and the control cell is a normal cell of the same tissue type.

~~63. Use of the antibody or functional fragment of any one of claims 1-31, 34, and 38-43 in the manufacture of a medicament, wherein the medicament is for use in a method of inhibiting growth of cancer cells that express CD98.~~

~~64~~63. An antibody or functional fragment of any one of claims 1-31, 34, and 38-43 for use in inhibiting the growth of cancer cells that express CD98.

~~65. Use of the pharmaceutical composition of claim 47 in the manufacture of a medicament, wherein the medicament is for use in a method of treating cancer in a subject.~~

~~66~~64. A pharmaceutical composition that comprises the antibody or functional fragment of any one of claims 1-31, 34, and 38-43, and a pharmaceutically acceptable carrier, for use in treating cancer in a subject.

~~67. Use of an antibody or functional fragment of any one of claims 1-31, 34, and 38-43 in the manufacture of a medicament, wherein the medicament is for use in a method for detecting the presence of CD98 in a biological sample.~~

~~68. An antibody or functional fragment of any one of claims 1-31, 34, and 38-43 for use in a method of detecting the presence of CD98 in a biological sample.~~

~~69. Use of an antibody or functional fragment of any one of claims 1-31, 34, and 38-43 in the manufacture of a medicament, wherein the medicament is for use in a method of diagnosing a cancer associated with increased expression of CD98.~~

~~70. An antibody or functional fragment of any one of claims 1-31, 34, and 38-43 for use in a method of diagnosing a cancer associated with increased expression of CD98.~~