In a first aspect, the present invention is directed to 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: 12, 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: 14.

In a second aspect, the present invention is directed to a binding agent which is any one of an antibody, 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, that binds to essentially the same epitope as an antibody of the present invention.

In a third aspect, the present invention is directed to a binding agent capable of binding to CD98 which is an antibody or a functional fragment thereof, wherein the antibody of the present invention displaces the binding agent in a competitive binding assay, or wherein the binding agent displaces the antibody of the present invention in a competitive binding assay.

In a fourth aspect, the present invention is directed to a vector comprising a polynucleotide encoding the antibody or fragment thereof of the present invention.

In a fifth aspect, the present invention is directed to a pharmaceutical composition that comprises the antibody or functional fragment of the present invention and a pharmaceutically acceptable carrier.

In a sixth aspect, the present invention is directed to use of an antibody or functional fragment of the present invention in the manufacture of a medicament for inhibiting growth of cancer cells that express CD98.

In a seventh aspect, the present invention is directed to a use of a pharmaceutical composition of the present invention in the manufacture of a medicament for treating a cancer in a subject

In an eight aspect, the present invention is directed to an *in vitro* method of detecting the presence of CD98 in a biological sample, comprising contacting the biological sample with an antibody of the present invention under conditions permissive for binding of the antibody to CD98, and detecting whether a complex is formed between the antibody and CD98.

In a ninth aspect, the present invention is directed to a method of diagnosing a cancer associated with increased expression of CD98, comprising contacting a test cell *in vitro* with an antibody of the present invention; 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.

In a tenth aspect, the present invention is directed to an antibody or functional fragment of the present invention for use in inhibiting the growth of cancer cells that express CD98.

In an eleventh aspect, the present invention is directed to a pharmaceutical composition that comprises the antibody or functional fragment of the present invention and a pharmaceutically acceptable carrier, for use in treating cancer in a subject.

[0010] In an ~~embodiment~~example, the ~~invention~~disclosure 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, 1398, G400 and A401 of human CD98. In some ~~embodiments~~examples, the epitope further comprises residues D374 and L378 of human CD98. In some ~~embodiments~~examples, the epitope further comprises residues P379 and G380 of human CD98. In some ~~embodiments~~examples, the epitope further comprises residues F395 and P396 of human CD98. In some ~~embodiments~~examples, the epitope further comprises residues Q381, P382 and P399 of human CD98. In some ~~embodiments~~examples, the epitope further comprises any one or more additional residues selected from the group consisting ofD374, L378, P379, G380, Q381, P382, F395, P396 and P399 of human CD98.

[0011] In an ~~embodiment~~example, the ~~invention~~disclosure 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~~examples, the epitope further comprises residues F395 and P396 of human CD98. In some ~~embodiments~~examples, the epitope further comprises residues Q381, P382, P399, G400 and A401 of human CD98. In some ~~embodiments~~examples, the epitope further comprises residues D374, A377 and L378 of human CD98. In some ~~embodiments~~examples, 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~~examples, the ~~invention~~disclosure 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, 1398, P399, G400 and A401 of human CD98.

[0013] In some ~~embodiments~~examples, the ~~invention~~disclosure 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~~examples, the ~~invention~~disclosure 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~~examples, the monoclonal antibody of the ~~invention~~disclosure is a humanized, human or chimeric antibody. In some ~~embodiments~~examples, the antibody functional fragment of the invention is an Fab, F(ab')2, Fv or scFv fragment.

[0015] In an example, 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 JD 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 example, the 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

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 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 and SEQ ID NO: 19. In an 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~~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: 22. In an ~~embodiment~~example, 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 example, the humanized antibody comprises the light chain variable domain sequence of SEQ ID NO: 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: 21 and the heavy chain variable domain sequence of SEQ ID NO: 22. In an example, the 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 example, the 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~~example, the ~~invention~~disclosure comprises a binding agent that binds to 20 essentially the same epitope as any of the antibodies disclosed above. In some ~~embodiments~~examples, the binding agent inhibits the growth of a tumor expressing CD98. In some ~~embodiments~~examples, the binding agent is an antibody or a functional fragment thereof. In other ~~embodiments~~examples, 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~~example, the ~~invention~~disclosure 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~~examples, the binding agent is an antibody, or a functional fragment thereof. In another ~~embodiment~~example, the ~~invention~~disclosure 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~~examples, the binding agent is an antibody, or a functional fragment thereof.

[0023] In some examples, the 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 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 1D NO: 20, SEQ ID NO: 21, SEQ ID NO: 33, and SEQ ID NO: 37. In some example, 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 lD 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 lD NO: 10, SEQ ID NO: 14, SEQ ID NO: 15, SEQ lD NO: 16, SEQ lD NO: 20, SEQ ID NO: 21, SEQ ID NO: 33, and SEQ ID NO: 37.

[0024] In some examples, the 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 the antibody. In some examples, the disclosure provides an antibody that binds to CD98 expressed on the cell surface and inhibits the growth of the cell. In some examples, the anti-CD98 antibody binds to CD98 expressed on the cell surface and inhibits cell proliferation. In some examples, the anti-CD98 antibody binds to CD98 expressed on the cell surface and induces cell death. In some examples, the 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 examples, the disclosure provides any one of the above antibodies or functional fragments, wherein theantibody or fragment is conjugated to a cytotoxic agent. In various examples, the cytotoxic agent is selected from a chemotherapeutic agent, a drug, a growth inhibitory agent, a toxin, or a radioactive isotope. In some examples, the disclosure provides any one of the above antibodies or functional fragments, wherein the antibody or fragment is conjugated to a detectable marker. In various 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~~example, the ~~invention~~disclosure provides a hybridoma that produces a monoclonal antibody of the invention. In an ~~embodiment~~example, the ~~invention~~disclsoure provides a transgenic animal that produces a monoclonal antibody of the invention.

[0027] In some examples, a polynucleotide encoding any of the above antibodies is provided. In an ~~embodiment~~example, a vector comprising the polynucleotide is provided. In an ~~embodiment~~example, a host cell comprising the vector is provided. In an ~~embodiment~~example, the host cell is prokaryotic. In an example, the host cell is an E. coli cell. In another example, the host cell is eukaryotic. In an example, the host cell is a Chinese Hamster Ovary (CHO) cell. In an 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~~example, the ~~invention~~disclosure provides a pharmaceutical composition comprising any of the above antibodies or functional fragments thereof, antibody conjugates, or binding agents of the ~~invention~~disclosure.

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

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

[0029] In an example, the disclosure provides a method for treating a cancer in a subject comprising administering 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 examples, the cancer is selected from bladder, breast, colon, rectal, gastric, esophageal, lung, larynx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, melanoma, glioma, lymphoma or leukemia, or a metastasis of any ofthese cancers. In some embodiments, the cancer is acute myeloid leukemia. In some examples, the subject has relapsed or refractory acute myeloid leukemia. In some examples, the cancer is associated with increased expression of CD98 on the surface of a cell.

[0030] In some 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.

[0031] In an 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 examples, the biological sample is from a mammal having or suspected of having a cancer of cells or tissues including, but not limited to,

30 bladder, breast, colon, rectal, gastric, esophageal, lung, larynx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, melanoma, glioma, lymphoma or leukemia, or a metastasis of any of these cancers.

[0032] In an example, a method of diagnosing a cancer associated with increased expression of CD98 is provided, the method comprising contacting a test cell with any ofthe above antibodies; determining the level of expression of CD98 by detecting binding of the antibody to CD98;

35 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 examples, the test cell is a cell from a patient suspected of having a cancer selected from bladder, breast, colon,

rectal, esophageal, lung, larynx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, glioma, lymphoma or leukemia, or a metastasis of any of these cancers. In an 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 examples, the test cell is a cancer cell and the control cell is a normal cell of the same tissue type.

[0033] In an example, the 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 examples, the cells are from a cancer is selected from bladder, breast, colon, rectal, gastric, esophageal, lung, larynx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, melanoma, glioma, lymphoma or leukemia, or a metastasis of any of these cancers.

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

[0035] In an example, the 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 examples, the cancer is selected from bladder, breast, colon, rectal, gastric, esophageal, lung, larynx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, melanoma, glioma, lymphoma or leukemia, or a metastasis of any of these cancers. In some examples, the cancer is acute myeloid leukemia. In some examples, the subject has relapsed or refractory acute myeloid leukemia. In some examples, the cancer is associated with increased expression of CD98 on the surface of a cell. In some 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~~example, the ~~invention~~disclosure 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~~examples, the cancer is selected from bladder, breast, colon, rectal, gastric, esophageal, lung, larynx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, melanoma, glioma, lymphoma or leukemia, or a metastasis 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 examples, the cancer is associated with increased expression of CD98 on the surface of a cell. In some 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 example, the 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 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 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, larynx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, melanoma, glioma, lymphoma or leukemia, or a metastasis of any of these cancers.

[0038] In an example, the 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 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 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, larynx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, melanoma, glioma, lymphoma or leukemia, or a metastasis of any of these cancers.

[0039] In an example, the 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 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 examples, the test cell is a cell from a patient suspected of having a cancer selected from bladder, breast, colon, rectal, esophageal, lung, larynx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, glioma, lymphoma or leukemia, or a metastasis of any of these cancers. In an 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 examples, the test cell is a cancer cell and the control cell is a normal cell of the same tissue type.

[0040] In an example, the 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 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 examples, the test cell is a cell from a patient suspected of having a cancer selected from bladder, breast, colon, rectal, esophageal, lung, larynx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, glioma, lymphoma or leukemia,or a metastasis of any of these cancers. In an 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 examples, the test cell is a cancer cell and the control cell is a normal cell of the same tissue type.

[0041] In another example of the 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.

WHAT IS CLAIMED IS:

1. 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: 12, 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: 14.

2. The antibody of claim 1, wherein 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.

3. A binding agent which is any one of an antibody, 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, that binds to essentially the same epitope as an antibody of any one of claims 1 or 2.

4. The binding agent of claim 3, wherein the binding agent inhibits the growth of a tumor expressing CD98.

5. A binding agent capable of binding to CD98 which is an antibody or a functional fragment thereof, wherein the antibody of any one of claims 1 or 2 displaces the binding agent in a competitive binding assay, or wherein the binding agent displaces the antibody of any one of claims 1 or 2 in a competitive binding assay.

6. The antibody or functional fragment of any one of claims 1-3 and 5, wherein the antibody or fragment is conjugated to a cytotoxic agent.

7. The antibody or functional fragment of claim 6, wherein the cytotoxic agent is selected from a chemotherapeutic agent, a drug, a growth inhibitory agent, a toxin, or a radioactive isotope.

8. The antibody or functional fragment of any one of claims 1-3 and 5, wherein the antibody or fragment is conjugated to a detectable marker.

9. The antibody or functional fragment of claim 8, wherein the detectable marker is selected from a radioisotope, a metal chelator, an enzyme, a fluorescent compound, a bioluminescent compound and a chemiluminescent compound.

10. A vector comprising a polynucleotide encoding the antibody or fragment thereof of any one of claims 1-3 and 5.

11. A pharmaceutical composition that comprises the antibody or functional fragment of any one of claims 1-3 and 5, and a pharmaceutically acceptable carrier.

12. Use of an antibody or functional fragment of any one of claims 1-3 and 5 in the manufacture of a medicament for inhibiting growth of cancer cells that express CD98.

13. The use of claim 12, wherein the cancer cells are from a cancer selected from bladder, breast, colon, rectal, gastric, esophageal, lung, larynx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, melanoma, glioma, lymphoma or leukemia, or a metastasis of any of these cancers.

14. The use of claim 13, wherein the cancer cells are from acute myeloid leukemia.

15. Use of a pharmaceutical composition of claim 11 in the manufacture of a medicament for treating a cancer in a subject.

16. The use of claim 15, wherein the cancer is selected from bladder, breast, colon, rectal, gastric, esophageal, lung, larynx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, melanoma, glioma, lymphoma or leukemia, or a metastasis of any of these cancers.

17. The use of claim 16, wherein the cancer is acute myeloid leukemia.

18. The use of claim 15, wherein the subject has relapsed or refractory acute myeloid leukemia.

19. The use of claim 15, 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.

20. The use of claim 15 wherein the cancer is associated with increased expression of

CD98 on the surface of a cell.

21. 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 1-3 and 5 under conditions permissive for binding of the antibody to CD98, and detecting whether a complex is formed between the antibody and CD98.

22. The method of claim 21, wherein the biological sample is from a mammal having or suspected of having a cancer selected from bladder, breast, colon, rectal, gastric, esophageal, lung, larynx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, melanoma, glioma, lymphoma or leukemia, or a metastasis of any of these cancers.

23. 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 1-3 and 5; 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.

24. The method of claim 23 wherein the test cell is from a patient suspected of having a cancer selected from bladder, breast, colon, rectal, gastric, esophageal, lung, larynx, kidney, oral, ovarian, or prostate cancer, or a sarcoma, melanoma, glioma, lymphoma or leukemia, or a metastasis of any of these cancers.

25. The method of claim 24 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.

26. The method of claim 25 wherein the test cell is a cancer cell and the control cell is a normal cell of the same tissue type.

27. An antibody or functional fragment of any one of claims 1-3 and 5 for use in inhibiting the growth of cancer cells that express CD98.

28. A pharmaceutical composition that comprises the antibody or functional fragment

of any one of claims 1-3 and 5, and a pharmaceutically acceptable carrier, for use in treating cancer in a subject.

WHAT IS CLAIMED IS:

1. 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.

2. The isolated antibody or functional fragment of claim 1, wherein said epitope further comprises residues D374 and L378 of human CD98.

3. The isolated antibody or functional fragment of claim 2, wherein said epitope further comprises residues P379 and G380 of human CD98.

4. The isolated antibody or functional fragment of claim 3, wherein said epitope further comprises residues F395 and P396 of human CD98.

5. The isolated antibody or functional fragment of claim 3, wherein said epitope further comprises residues Q381, P382 and P399 of human CD98.

6. The isolated antibody or functional fragment of claim 1, wherein said 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.

7. 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.

8. The isolated antibody or functional fragment of claim 7, wherein said epitope further comprises residues F395 and P396 of human CD98.

9. The isolated antibody or functional fragment of claim 8, wherein said epitope further comprises residues Q381, P382, P399, G400 and A401 of human CD98.

10. The isolated antibody or functional fragment of claim 8, wherein said epitope further comprises residues D374, A377 and L378 of human CD98.

11. The isolated antibody or functional fragment of claim 7, wherein said 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.

12. The isolated antibody or a functional fragment according to claim 1, 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.

13. 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.

14. 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.

15. The antibody or functional fragment of claim 1, wherein the antibody is a monoclonal antibody.

16. The antibody or functional fragment of claim 15, wherein the monoclonal antibody is a humanized, human or chimeric antibody.

17. The antibody or functional fragment of claim 1, wherein the fragment is an Fab, F(ab')2, Fv or Sfv fragment.

18. 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: 8 and SEQ ID NO: 12, 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: 10 and SEQ ID NO: 14.

19. 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: 8 and SEQ ID NO: 12, 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: 10 and SEQ ID NO: 14.

20. The antibody of claim 19, wherein the antibody comprises a heavy chain variable domain sequence selected from the group consisting of SEQ ID NO: 8 and SEQ ID NO: 12.

21. The antibody of claim 19, wherein the antibody comprises a light chain variable domain sequence consisting of SEQ ID NO: 10 and SEQ ID NO: 14.

22. Then antibody of claim 20, wherein the antibody further comprises a light chain variable domain sequence consisting of SEQ ID NO: 10 and SEQ ID NO: 14.

23. The antibody of claim 22, wherein 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.

24. The antibody of claim 22, wherein 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.

25. The humanized antibody of claim 16, wherein the antibody comprises a heavy chain variable domain sequence selected from SEQ ID NO:22 and SEQ ID NO:23.

26. The humanized antibody of claim 16, wherein the antibody comprises a light chain variable domain sequence selected from SEQ ID NO:20 and SEQ ID NO:21.

27. The humanized antibody of claim 25, further comprising a light chain variable domain sequence selected from SEQ ID NO:20 and SEQ ID NO:21.

28. The humanized antibody of claim 27,wherein the 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.

29. The humanized antibody of claim 27,wherein the 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.

30. The humanized antibody of claim 27,wherein the 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.

31. An antibody that binds to essentially the same epitope as an antibody of claim 30.

32. A binding agent that binds to essentially the same epitope as an antibody of any one of claims 1-31.

33. The binding agent of claim 32, wherein the binding agent inhibits the growth of a tumor expressing CD98.

34. The binding agent of claim 32, which is an antibody or a functional fragment thereof.

35. The binding agent of claim 32, which 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.

36. A binding agent capable of binding to CD98, wherein the antibody of any one of claims 1-31 displaces the binding agent in a competitive binding assay.

37. A binding agent capable of binding to CD98, wherein the binding agent displaces the antibody of any one of claims 1-31 in a competitive binding assay.

38. The binding agent of claim 36, wherein the binding agent is an antibody, or a functional fragment thereof.

39. The binding agent of claim 37, wherein the binding agent is an antibody, or a functional fragment thereof.

40. The antibody or functional fragment of any one of claims 1-31, 34, and 38-39, wherein the antibody or fragment is conjugated to a cytotoxic agent.

41. The antibody or functional fragment of claim 40, wherein the cytotoxic agent is selected from a chemotherapeutic agent, a drug, a growth inhibitory agent, a toxin, or a radioactive isotope.

42. The antibody or functional fragment of any one of claims 1-31, 34, and 38-39, wherein the antibody or fragment is conjugated to a detectable marker.

43. The antibody or functional fragment of claim 40, wherein the detectable marker is selected from a radioisotope, a metal chelator, an enzyme, a fluorescent compound, a bioluminescent compound and a chemiluminescent compound.

44. A transgenic animal that produces the monoclonal antibody of claim 15.

45. A hybridoma that produces the monoclonal antibody of claim 15.

46. A vector comprising a polynucleotide encoding the antibody or fragment thereof of any one of claims 1-31, 34, and 38-39.

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 inhibiting growth of cancer cells that express CD98.

49. The 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 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 for treating a cancer in a subject.

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

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

55. The 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 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. 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.

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.