BRIEF SUMMARY

[0006] Provided herein is a compound comprising a CLPTM1L-targeting agent selected from the group consisting of an antibody, a peptide, an aptamer, or a fragment thereof. In one aspect, provided herein is a CLPTM1L-targeting agent, wherein the CLPTM1L-targeting agent is a monoclonal antibody specific for an epitope of a CLPTM1L polypeptide, wherein the epitope consists of an amino acid sequence of SEQ ID NO:6 or SEQ ID NO:10. The CLPTM1L-targeting agent can be a monoclonal antibody specific for at least a portion of a CLPTM1L polypeptide. The CLPTM1L polypeptide can have the amino acid sequence set forth in SEQ ID NO: 2 or a portion thereof. The monoclonal antibody can be specific to peptide having an amino acid sequence selected from the group consisting of SEQ ID NO:4-25. The monoclonal antibody can be a monoclonal anti-CLPTM1L clone selected from the group consisting of 6-1, 6-2, 10-1, 10-2, and 10-3. The monoclonal antibody can be specific to a CLPTM1L polypeptide having one or more of the mutations set forth in Table 2. In some cases, the CLPTM1L-targeting agent is a peptide having an amino acid sequence selected from the group consisting of SEQ ID NO:4-25.

[0007] In another aspect, provided herein is a pharmaceutical composition comprising the agent provided herein and a pharmaceutically acceptable carrier.

[0008] Provided herein is an agent according to a compound or composition provided herein for use as a medicament. In one aspect, provided herein is an agent as described above for use as a medicament. In another aspect, provided is use of such an agent in the manufacture of a medicament for the treatment of a tumor, a cancer, or a preneoplastic lesion associated with CLPTM1L protein dysfunction.

[0009] Provided herein is an article of manufacture comprising a pharmaceutical composition of the disclosure and instructions for administration to a human subject. In one aspect, provided herein is an article of manufacture comprising: (a) the pharmaceutical composition as described above, and (b) an insert providing instructions for treating a solid tumor in a human subject.

[0010] In one aspect, provided herein is use of a compound comprising a CLPTM1L-targeting agent in the manufacture of a medicament for treating or preventing a tumor in a subject in need thereof, wherein the CLPTM1L-targeting agent is a monoclonal antibody specific for an epitope of a CLPTM1L polypeptide, wherein the epitope consists of an amino acid sequence of SEQ ID NO:6 or SEQ ID NO:10, whereby the tumor is treated or prevented in the subject. Also provided herein is a method for treating or preventing a tumor pre- in a subject. The use or method typically comprises administering a therapeutically effective amount of a compound comprising a CLPTM1L-targeting agent to a subject in need thereof, whereby the tumor is treated or prevented in the subject. In some cases, the CLPTM1L-targeting agent is selected from the group consisting of an antibody, a peptide, and aptamer, or a fragment thereof. The CLPTM1L-targeting agent can be a monoclonal antibody specific for at least a portion of a CLPTM1L polypeptide. The CLPTM1L polypeptide can have the amino acid sequence set forth in SEQ ID NO:2 or a portion thereof. The monoclonal antibody can be specific to a peptide having an amino acid sequence selected from the group consisting of SEQ ID NO:4-25. The monoclonal antibody can be specific to a CLPTM1L polypeptide having one or more of the mutations set forth in Table 2. The CLPTM1L-targeting agent can be a peptide having an amino acid sequence selected from the group consisting of SEQ ID NO:4-25.

[0011] In some cases, the tumor is a solid tumor selected from the group consisting of glioblastoma, sarcoma, carcinoma, and lymphoma. In some cases, the tumor is associated with

a cancer or pre-neoplastic lesion selected from the group consisting of lung cancer, pancreatic cancer, prostate cancer, skin cancer, bladder cancer, kidney cancer, ovarian cancer, colon cancer, colorectal cancer, breast cancer, cervical cancer, brain cancer, esophageal cancer, and stomach cancer, or a pre-neoplastic lesion thereof. The tumor can be associated with lung cancer or a pre-neoplastic lesion thereof. The tumor can exhibit resistance to a chemotherapeutic agent. The chemotherapeutic agent can be selected from the group consisting of cisplatin and gemcitabine. In some cases, the compound is administered with a pharmaceutically acceptable carrier.

[0012] In yet another aspect, provided herein is use of a compound comprising a CLPTM1L-targeting agent in the manufacture of a medicament for treating or preventing a tumor, a cancer, or a preneoplastic lesion associated with CLPTM1L protein dysfunction, wherein the medicament is to be administered to a cell, tissue, or organ of a subject at risk of, diagnosed as having, or exhibiting a symptom of the tumor, a cancer, or a preneoplastic lesion, wherein the CLPTM1L-targeting agent is a monoclonal antibody specific for an epitope of a CLPTM1L polypeptide, wherein the epitope consists of an amino acid sequence of SEQ ID NO:6 or SEQ ID NO:10. Also provided herein is a method of treating or preventing a disease or condition associated with over-expression or inappropriate expression of a nucleic acid sequence encoding CLPTM1L in a subject. The use or method typically comprises administering a compound comprising a CLPTM1L-targeting agent to a cell, tissue, or organ of a subject at risk of, diagnosed as having, or exhibiting a symptom of the disease or condition. The disease or condition can be a cancer, tumor, (*e.g.*, solid tumor) or a pre-neoplastic lesion. The tumor, cancer, or pre-neoplastic lesion can be selected from the group consisting of lung cancer, pancreatic cancer, glioblastoma, prostate cancer, skin cancer, bladder cancer, kidney cancer, ovarian cancer, colon cancer, colorectal cancer, breast cancer, cervical cancer, brain cancer, esophageal cancer, stomach cancer, lymphoma, chronic leukemia, and acute leukemia. The tumor can exhibit resistance to a chemotherapeutic agent. The chemotherapeutic agent can be selected from the group consisting of cisplatin and gemcitabine. The CLPTM1L-targeting agent can be selected from the group consisting of an antibody, a peptide, and aptamer, or a fragment thereof. The CLPTM1L-targeting agent can be a monoclonal antibody specific for at least a portion of a CLPTM1L polypeptide. The CLPTM1L polypeptide can have the amino acid sequence set forth in SEQ ID NO: 2 or a portion thereof. In some cases, the monoclonal antibody is specific to a peptide having an amino acid sequence selected from the group consisting of SEQ ID NO:4-25. The monoclonal antibody can be specific to a CLPTM1L polypeptide having one or more of the mutations set forth in Table 2. The CLPTM1L-targeting agent can be a peptide having an amino acid sequence selected from the group consisting of SEQ ID NO:4-25. The compound can be administered with a pharmaceutically acceptable carrier.

[0013] These and other features, aspects, and advantages of the present disclosure will become better understood from the description that follows. In the description, reference is made to the accompanying drawings, which form a part hereof and in which there is shown by way of illustration, not limitation, embodiments of the disclosure. The description of preferred

embodiments is not intended to limit the disclosure to cover all modifications, equivalents and alternatives. Reference should therefore be made to the claims recited herein for interpreting the scope of the disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] The present invention will be better understood and features, aspects and advantages other than those set forth above will become apparent when consideration is given to the following detailed description thereof. The detailed description makes reference to the following drawings, wherein:

[0015] FIG. 1 presents structural data demonstrating the presence of two separate globular domains separated by a small disordered region (amino acid residues 142-162) within the larger extracellular region.

[0016] FIG. 2 presents (A) a summary of CLPTM1L predicted structure including orientation of the human sequence of CLPTM1L within the plasma membrane, two extracellular globular domains (ECR1 and ECR2), the interstitial disordered region, transmembrane regions, and identified glycosylated cell surface peptides (in blue) and predicted sites N-glycosylation sites (green). Monoclonal antibodies generated against CLPTM1L peptides targeting each ECR are indicated in parentheses. Image was generated using the Protter application (Omasits *et al.*, *Bioinformatics* 30(6):884-6 (2014)). (B) A splicing variant of CLPTM1L, lacking extracellular region 1 and some transmembrane domains changing the predicted structure. The expression pattern of this isoform is not known.

[0017] FIG. 3 depicts selection of epitopes to raise monoclonal antibodies specific for human CLPTM1L protein. The focus region for monoclonal antibody design included the ordered regions of the predicted extracellular domain. Glycosylation sites were excluded.

[0018] FIG. 4 demonstrates CLPTM1L localization. (A) Western blotting of cell surface and whole cell protein lysates for CLPTM1L, transmembrane receptor EGFR and nuclear protein Cyclin D1.Monoclonal antibodies 6-1, 10-2, and 10-3 were used for western blotting. (B) Immunofluorescent staining of non-permeablized A549 lung tumor cells using DAPI dye to stain cell nuclei and polyclonal antibody to the predicted extracellular N-terminus of human CLPTM1L followed by a secondary FITC conjugated antibody to detect CLPTM1L. A non-specific antibody was used as a control. Staining indicates punctuate plasma membrane localization of the protein. (C) Western blotting for CLPTM1L in H838 cells with monoclonal antibodies. (D) Immunofluorescent staining of non-permeabilized A549 cells with monoclonal CLPTM1L

CLAIMS

We claim:

1. A CLPTM1L-targeting agent, wherein the CLPTM1L-targeting agent is a monoclonal antibody specific for an epitope of a CLPTM1L polypeptide, wherein the epitope consists of an amino acid sequence of SEQ ID NO:6 or SEQ ID NO:10.

2. The agent of claim 1, wherein the monoclonal antibody is a monoclonal anti-CLPTM1L clone selected from the group consisting of 6-1, 6-2, 10-1, 10-2, and 10-3.

3. A pharmaceutical composition comprising the agent according to claim 1 or 2 and a pharmaceutically acceptable carrier.

4. The agent according to claim 1 or 2 for use as a medicament.

5. Use of the agent according to claim 1 or 2 in the manufacture of a medicament for the treatment of a tumor, a cancer, or a preneoplastic lesion associated with CLPTM1L protein dysfunction.

6. An article of manufacture comprising: (a) the pharmaceutical composition of claim 3, and (b) an insert providing instructions for treating a solid tumor in a human subject.

7. Use of a compound comprising a CLPTM1L-targeting agent in the manufacture of a medicament for treating or preventing a tumor in a subject in need thereof, wherein the CLPTM1L-targeting agent is a monoclonal antibody specific for an epitope of a CLPTM1L polypeptide, wherein the epitope consists of an amino acid sequence of SEQ ID NO:6 or SEQ ID NO:10, whereby the tumor is treated or prevented in the subject.

8. The use of claim 7, wherein the monoclonal antibody is a monoclonal anti-CLPTM1L clone selected from the group consisting of 6-1, 6-2, 10-1, 10-2, and 10-3.

9. The use of claim 7, wherein the tumor is a solid tumor selected from the group consisting of glioblastoma, sarcoma, carcinoma, and lymphoma.

10. The use of claim 7, wherein the tumor is associated with a cancer or pre-neoplastic lesion selected from the group consisting of lung cancer, pancreatic cancer, prostate cancer,

skin cancer, bladder cancer, kidney cancer, ovarian cancer, colon cancer, colorectal cancer, breast cancer, cervical cancer, brain cancer, esophageal cancer, and stomach cancer, or a pre-cancerous lesion thereof.

11. The use of claim 10, wherein the tumor is associated with lung cancer or pre-cancerous lesion thereof.

12. The use of claim 7, wherein the subject is a human.

13. The use of claim 7, wherein the tumor exhibits resistance to a chemotherapeutic agent.

14. The use of claim 13, wherein the chemotherapeutic agent is selected from the group consisting of cisplatin and gemcitabine.

15. The use of claim 7, wherein the compound is to be administered with a pharmaceutically acceptable carrier.

16. Use of a compound comprising a CLPTM1L-targeting agent in the manufacture of a medicament for treating or preventing a tumor, a cancer, or a preneoplastic lesion associated with CLPTM1L protein dysfunction, wherein the medicament is to be administered to a cell, tissue, or organ of a subject at risk of, diagnosed as having, or exhibiting a symptom of the tumor, a cancer, or a preneoplastic lesion, wherein the CLPTM1L-targeting agent is a monoclonal antibody specific for an epitope of a CLPTM1L polypeptide, wherein the epitope consists of an amino acid sequence of SEQ ID NO:6 or SEQ ID NO:10.

17. The use of claim 16, wherein the CLPTM1L protein dysfunction comprises one or more of pathogenic protein production, pathogenic protein modification, or pathogenic protein function.

18. The use of claim 16, wherein the tumor is a solid tumor selected from the group consisting of glioblastoma, sarcoma, carcinoma, and lymphoma.

19. The use of claim 18, wherein the tumor exhibits resistance to a chemotherapeutic agent.

20. The use of claim 19, wherein the chemotherapeutic agent is selected from the group consisting of cisplatin and gemcitabine.

21. The use of claim 16, wherein the monoclonal antibody is a monoclonal anti-CLPTM1L clone selected from the group consisting of 6-1, 6-2, 10-1, 10-2, and 10-3.

22. The use of claim 16, wherein the compound is to be administered with a pharmaceutically acceptable carrier.