Each year, of the approximately 49,000 patients that will develop RCC, a little over 40,000 of those will be diagnosed with ccRCC in the US (American Cancer Society: Cancer Facts and Figures final (2008). While some newer therapeutics have been approved for RCC over the last 4 years, the 5 year survival rate for patients with metastatic RCC remains dismal at 10-20% (National Caner Institute. SEER cancer statistics fact sheet: cancer of the kidney and renal pelvis -- accessed 2008) and significant unmet medical need remains. The projected yearly number of newly diagnosed ccRCC patients (U.S.) that are expected to express CD27L is approximately 36,000. There are an estimated 64,000 ccRCC patients currently with active disease.

Of the B-cell malignancies reported to aberrantly express CD27L, the B-NHL subsets of diffuse large cell B-cell lymphoma (DLBCL) and follicular lymphoma (FL) show the highest incidence of expression ranging from 33% for FL to 71% for DLBCL as assessed by IHC on frozen sections using a validated antibody (Lens et al., *Brit. J. Hematol.* 106, 491-503 (1999). 50-89 % of B-CLL tumors also express CD27L as assessed by IHC on frozen tumor sections or by flow cytometry on circulating tumor cells (Ranheim et al., *Blood* 85, 3556-3565 (1965); Trentin et al., *Cancer Res.* 57, 4940-4947 (1997)).

Of the 127,000 patients in the US currently with active B-NHL, approximately 50% of these patients present with the DLBCL (intermediate grade) sub-type (Morton et al., *Blood* 107, 265-276 (2002)). Despite Rituxan plus cyclophosphamide, adriamycin, vincristine, prednisone (CHOP) standard of care therapy for DLBCL patients, almost 50% relapse. Therefore an unmet medical need remains in this disease as well.

SUMMARY

The disclosure provides anti-CD27L antigen binding proteins, e.g., antibodies and functional fragments thereof. The anti-CD27L antigen binding proteins are particularly useful in methods of treating diseases and disorders associated with aberrant cell proliferation, e.g., cancer, and/or with inflammation.

In one aspect, the present disclosure refers to a CD27L antigen binding protein comprising a light chain variable domain and a heavy chain variable domain, wherein

a) the light chain variable domain comprises the amino acid sequence SEQ ID NO: 66 but has an R24K-S26G mutation, and the heavy chain variable domain comprises the amino acid sequence SEQ ID NO: 20 but has an N31S-I34M mutation;
b) the light chain variable domain comprises the amino acid sequence SEQ ID NO: 66 but has an R24K-S26G mutation, and the heavy chain variable domain comprises the amino acid sequence SEQ ID NO: 20; c) the light chain variable domain comprises the amino acid sequence SEQ ID NO: 66 but has an L55I-Y58F mutation, and the heavy chain variable domain comprises the amino acid sequence SEQ ID NO: 20; d) the light chain variable domain comprises the amino acid sequence SEQ ID NO: 66 but has a Q95N-T96S mutation, and the heavy chain variable domain comprises the amino acid sequence SEQ ID NO: 20 but has an N31S-I34M mutation; or e) the light chain variable domain comprises the amino acid sequence SEQ ID NO: 66 but has a Q95N-T96S mutation, and the heavy chain variable domain comprises the amino acid sequence SEQ ID NO: 20.

In another aspect, the present disclosure refers to a composition comprising a CD27L antigen binding protein as described herein, wherein the average number of DM1 molecules per CD27L antigen binding protein is between 1 and 10, preferably between 3 and 7, preferably between 4 and 6, or 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, or 6.0. In another aspect, the present disclosure refers to an isolated nucleic acid encoding a polypeptide, said polypeptide comprising: a) a light chain variable domain comprising an LCDR1 having the amino acid sequence set forth in SEQ ID NO: 74; an LCDR2 having the amino acid sequence set forth in SEQ ID NO: 82; and an LCDR3 having the amino acid sequence set forth in SEQ ID NO: 90; and a heavy chain variable domain comprising an HCDR1 having the amino acid sequence set forth in SEQ ID NO: 28; an HCDR2 having the amino acid sequence set forth in SEQ ID NO: 36; and an HCDR3 having the amino acid sequence set forth in SEQ ID NO: 44; b) light chain variable domain comprising the amino acid sequence SEQ ID NO: 66 but having an R24K-S26G mutation or a Q95N-T96S mutation; and a heavy chain variable domain

CLAIMS

What is claimed is:

1. A CD27L antigen binding protein comprising

a light chain variable domain and a heavy chain variable domain, wherein

a) the light chain variable domain comprises the amino acid sequence SEQ ID NO: 66 but has an R24K-S26G mutation, and the heavy chain variable domain comprises the amino acid sequence SEQ ID NO: 20 but has an N31S-I34M mutation;

b) the light chain variable domain comprises the amino acid sequence SEQ ID NO: 66 but has an R24K-S26G mutation, and the heavy chain variable domain comprises the amino acid sequence SEQ ID NO: 20;

c) the light chain variable domain comprises the amino acid sequence SEQ ID NO: 66 but has an L55I-Y58F mutation, and the heavy chain variable domain comprises the amino acid sequence SEQ ID NO: 20;

d) the light chain variable domain comprises the amino acid sequence SEQ ID NO: 66 but has a Q95N-T96S mutation, and the heavy chain variable domain comprises the amino acid sequence SEQ ID NO: 20 but has an N31S-I34M mutation; or

e) the light chain variable domain comprises the amino acid sequence SEQ ID NO: 66 but has a Q95N-T96S mutation, and the heavy chain variable domain comprises the amino acid sequence SEQ ID NO: 20.

2. The CD27L antigen binding protein of claim 1, wherein the antigen binding protein specifically binds human CD27L with an affinity of less than or equal to 2×10^{-11} M.

3. The CD27L antigen binding protein of any of claims 1 to 2, wherein the antigen binding protein inhibits binding of CD27L to CD27.

4. The CD27L antigen binding protein of any of claims 1 to 3, wherein the antigen binding protein is an antibody, preferably a human antibody.

5. The CD27L antigen binding protein of any of claims 1-4, wherein the CD27L antigen binding protein is a bispecific antibody.

6. The CD27L antigen binding protein of claim 5, wherein the bispecific antibody binds CD27L and a human effector cell antigen which is CD3.

7. The CD27L antigen binding protein of any one of claims 1-6, wherein the CD27L antigen binding protein is an antibody fragment.

8. The CD27L antigen binding protein of claim 7, wherein the antibody fragment is selected from the group consisting of F(ab), Fab fragments consisting of VL, VH, CL and CH1 domains, F(ab'), F(ab')2, Fv, Fv fragments consisting of the VL and VH domains of a single antibody, dAb fragments, single chain Fv molecules (scFv), bispecific single chain Fv dimers, diabodies and triabodies.

9. The CD27L antigen binding protein of any of claims 1-8, wherein the CD27L antigen binding protein is conjugated to a chemotherapeutic agent preferably via a linker, wherein the linker preferably is a non-cleavable linker, preferably comprising MCC.

10. The CD27L antigen binding protein of claim 9, wherein the chemotherapeutic agent is conjugated to one or more lysines contained with a polypeptide of the CD27L antigen binding protein.

11. The CD27L antigen binding protein of claim 9 or 10, wherein the chemotherapeutic agent is DM1.

12. A composition comprising a CD27L antigen binding protein of claim 11, wherein the average number of DM1 molecules per CD27L antigen binding protein is between 1 and 10, preferably between 3 and 7, preferably between 4 and 6, or 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, or 6.0.

13. The composition of claim 12, wherein the composition is a pharmaceutical composition comprising a therapeutically effective amount of the CD27L antigen binding protein, preferably wherein the pharmaceutical composition is lyophilized.

14. An isolated nucleic acid encoding a polypeptide, said polypeptide comprising:

a) a light chain variable domain comprising an LCDR1 having the amino acid sequence set forth in SEQ ID NO: 74; an LCDR2 having the amino acid sequence set forth in SEQ ID NO: 82; and an LCDR3 having the amino acid sequence set forth in SEQ ID NO: 90; and a heavy chain variable domain comprising an HCDR1 having the amino acid sequence set forth in SEQ ID NO: 28; an HCDR2 having the amino acid sequence set forth in SEQ ID NO: 36; and an HCDR3 having the amino acid sequence set forth in SEQ ID NO: 44;

b) a light chain variable domain comprising the amino acid sequence SEQ ID NO: 66 but having an R24K-S26G mutation or a Q95N-T96S mutation; and a heavy chain variable domain comprising the amino acid sequence SEQ ID NO: 20 but having an N31S-I34M mutation; or

c) a light chain variable domain comprising the amino acid sequence SEQ ID NO: 66 but having an L55I-Y58F mutation; and a heavy chain variable domain comprising the amino acid sequence SEQ ID NO: 20.

15. The isolated nucleic acid of claim 14, wherein

a) the isolated nucleic acid comprises a nucleotide sequence which is at least 80% identical, preferably at least 90% identical, preferably at least 95% identical to the nucleotide sequence set forth in SEQ ID NO:51, or comprises the nucleotide sequence set forth in SEQ ID NO:51; or

b) the isolated nucleic acid comprises a nucleotide sequence which is at least 80% identical, preferably at least 90% identical, preferably at least 95% identical to

the nucleotide sequence set forth in SEQ ID NO:5; or comprises the nucleotide sequence set forth in SEQ ID NO:5.

16. An expression vector comprising the isolated nucleic acid of claim 14 or 15.

17. A recombinant host cell comprising an isolated nucleic acid of claim 14 or 15 operably linked to a promoter, or comprising an expression vector of claim 16.

18. A method of making a CD27L antibody drug conjugate, said method comprising the steps of:

(i) a) providing a CD27L antigen binding protein of any one of claims 1-8

b) conjugating the CD27L antigen binding protein to a linker; and

c) conjugating a drug to said linker;

wherein the linker preferably comprises MCC; the drug preferably comprises DM1; or the linker preferably comprises MCC and the drug preferably comprises DM1; or

(ii) a) providing a CD27L antigen binding protein of any one of claims 1-8; and

b) conjugating a linker covalently bound to a drug to said CD27L antigen binding protein.

19. Use of the CD27L antigen binding protein of any one of claims 1-8 conjugated to DM1 by an MCC linker, in the manufacture of a medicament for treating cancer.

20. The use as in claim 19, wherein the CD27L antigen binding protein is comprised in a pharmaceutical composition.

21. The use as in claim 20, wherein the antibody comprises enhanced effector function.

22. The use as in claim 21, wherein
the average number of DM1 molecules per antibody is between 1 and 10, preferably between 3 and 7, preferably between 4 and 6, or is 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, or 6.0.

23. The use as in any of claims 20-22, wherein a sample from the patient, preferably a blood sample or a biopsy, is to be tested for CD27L expression, preferably for CD27L mRNA expression or for CD27L protein expression.

24. The use as in any one of claims 20-23, wherein the cancer is renal cell carcinomas (RCC), clear cell RCC, head and neck cancer, glioblastoma, breast cancer, brain tumor, nasopharangeal carcinoma, non-Hodgkin's lymphoma (NHL), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), Burkitt's lymphoma, anaplastic large-cell lymphomas (ALCL), multiple myeloma, cutaneous T-cell lymphomas, nodular small cleaved-cell lymphomas, lymphocytic lymphomas, peripheral T-cell lymphomas, Lennert's lymphomas, immunoblastic lymphoma, T-cell leukemia/lymphomas (ATLL), adult T-cell leukemia (T-ALL), entroblastic/centrocytic (cb/cc) follicular lymphoma cancer, diffuse large cell lymphoma of B lineage, angioimmunoblastic lymphadenopathy (AILD)-like T cell lymphoma, HIV associated body cavity based lymphoma, embryonal carcinoma, undifferentiated carcinoma of the rhino-pharynx, Castleman's disease, Kaposi's Sarcoma, multiple myeloma, Waldenstrom's macroglobulinemia or other B-cell lymphoma.