Tumors also have the propensity to lose expression of CAR-targeted antigens, and thus many groups are developing bi-specific and tri-specific CAR T cells in order to capture a greater diversity of tumor cells. This is well-described in the context of B-cell malignancies, where multi-specific CAR T cells against CD19, CD20 and CD22 are in clinical development. Solid tumors and the solid tumor microenvironment are an even greater challenge to overcome with considerably more tumor heterogeneity. New, more advanced methods, of targeting immune effector cells are thus in great need.

SUMMARY

[0005] Provided herein are chimeric antigen receptor (CAR) bridging proteins that re-direct mono-specific CAR-T cells to alternative or multiple target antigens. For example, fusion proteins and antibody-conjugates are provided, which, on the one end, engage a CAR and, on the other, a target antigen of choice. Therefore, in contrast to creating multi-specific CARs, the bridging protein provided herein re-direct single-variant CAR-T cells toward diverse antigens via multi-specific bridge proteins. Single or multiple bridge proteins can be infused either sequentially or together as a moiety for a simultaneous multi-targeted approach.

[0006] In ~~some embodiments~~one aspect, the present disclosure provides chimeric antigen receptor (CAR) bridging proteins comprising (1) an antigen-binding domain and (2) a CAR-binding domain, that comprises at least a portion of an HIV-1 gp120 protein. In some ~~aspect~~examples, the CAR-binding domain is chemically conjugated to the antigen-binding domain. In some ~~aspect~~examples, the CAR bridging proteins further comprise an antibody Fc domain. In some ~~aspect~~examples, the Fc domain is positioned between the CAR-binding domain and the antigen-binding domain. In some ~~aspect~~examples, the CAR-binding domain is positioned between the antigen-binding domain and the Fc domain. In some ~~aspect~~examples, the CAR bridging proteins further comprise a linker sequence between the antigen binding domain and the CAR-binding domain. In some ~~aspect~~examples, the CAR-binding domain comprises the sequence provided in SEQ ID NO: 6. In some ~~aspect~~examples, the Fc domain comprises a human Fc domain sequence. In other ~~aspect~~examples, the Fc domain comprises a human heavy chain Fc domain sequence. In still other ~~aspect~~examples, the Fc domain comprises CH2 and CH3 regions of a human heavy chain Fc domain sequence. In yet other ~~aspect~~examples, the Fc domain comprises substitutions relative to the wild-type human heavy chain Fc domain sequence which prevent binding to FcgR receptors. In other ~~aspect~~examples, the Fc

domain comprises a sequence that is at least 85%, at least 90%, at least 95%, or 100% identical to the sequence provided by SEQ ID NO: 4.

[0007] In some ~~aspect~~examples, the antigen-binding domain binds to a tumor antigen or a viral antigen. In some ~~aspect~~examples, the antigen-binding domain comprises a peptide that interacts with an antigen of interest. In some ~~aspect~~examples, the antigen-binding domain comprises an antigen-binding portion of an antibody that recognizes the antigen of interest. In some ~~aspect~~examples, the antigen-binding domain comprises at least a portion of a ligand that interacts with the antigen of interest. In some ~~aspect~~examples, the antigen-binding domain is capable of binding to CD19, CD20, or CD22. In other ~~aspect~~examples, the antigen-binding domain is capable of binding to a coronavirus spike protein. In further ~~aspect~~examples, the coronavirus spike protein is a SARS-CoV-1 or SARS-CoV-2 spike protein. In some ~~aspect~~examples, the antigen-binding domain comprises at least a portion of an ACE2 extracellular domain. In further ~~aspect~~examples, the portion of an ACE2 extracellular domain is the ACE2t domain. In still further ~~aspect~~examples, the ACE2t domain comprises a sequence that is at least 85%, at least 90%, at least 95%, or 100% identical to the sequence of SEQ ID NO: 2.

[0008] In some ~~aspect~~examples, the CAR bridging proteins further comprise at least one linker sequence between the CAR-binding domain, Fc domain, and/or antigen-binding domain. In some ~~aspect~~examples, the CAR bridging protein comprises a linker sequence between each of the CAR-binding domain, Fc domain, and/or antigen-binding domains. In some ~~aspect~~examples, the linker sequence comprises the sequence of GGGS (SEQ ID NO: 7). In some ~~aspect~~examples, the linker sequence comprises a sequence provided by SEQ ID NO: 8. In some ~~aspect~~examples, the CAR bridging protein forms a homodimer.

[0009] In ~~other embodiments~~one aspect, the present disclosure provides chimeric antigen receptor (CAR) bridging proteins comprising a CAR-binding domain and an antigen-binding domain; optionally wherein~~. In some aspects,~~ the CAR-binding domain is chemically conjugated to the antigen-binding domain; or the antigen-binding domain is chemically conjugated to the CAR-binding domain. In some ~~aspect~~examples, the CAR bridging proteins further comprising an antibody Fc domain. In some ~~aspect~~examples, the Fc domain is positioned between the CAR-binding domain and the antigen-binding domain. In other ~~aspect~~examples, the CAR-binding domain is positioned between the antigen-binding domain and the Fc domain. In some ~~aspect~~examples, the CAR-binding domain comprises a peptide that interacts with the extracellular portion of a CAR. In some ~~aspect~~examples, the CAR-binding domain comprises the antigen-binding portion of an antibody that recognizes the extracellular portion of a CAR. In some ~~aspect~~examples, the CAR-binding domain

comprises at least a portion of a ligand that interacts with the extracellular portion of a CAR. In some ~~aspect~~examples, the CAR-binding domain comprises at least a portion of an HIV-1 gp120 protein. In further ~~aspect~~examples, the CAR-binding domain comprises the sequence provided in SEQ ID NO: 6. In certain ~~aspect~~examples, the CAR-binding domain consists essentially of the sequence provided in SEQ ID NO: 6. In certain ~~aspect~~examples, the CAR-binding domain consists of the sequence provided in SEQ ID NO: 6.

[0010] In some ~~aspect~~examples, the Fc domain comprises a human Fc domain sequence. In some ~~aspect~~examples, the Fc domain comprises a human heavy chain Fc domain sequence. In some ~~aspect~~examples, the Fc domain comprises CH2 and CH3 regions of a human heavy chain Fc domain sequence. In some ~~aspect~~examples, the Fc domain comprises substitutions relative to the wild-type human heavy chain Fc domain sequence which prevent binding to FcgR receptors. In some ~~aspect~~examples, the Fc domain comprises a sequence that is at least 85%, at least 90%, at least 95%, or 100% identical to the sequence provided by SEQ ID NO: 4. In some ~~aspect~~examples, the antigen-binding domain binds to a tumor antigen or a viral antigen. In some ~~aspect~~examples, the antigen-binding domain comprises a peptide that interacts with an antigen of interest. In some ~~aspect~~examples, the antigen-binding domain comprises an antigen-binding portion of an antibody that recognizes the antigen of interest. In some ~~aspect~~examples, the antigen-binding domain comprises at least a portion of a ligand that interacts with the antigen of interest. In some ~~aspect~~examples, the antigen-binding domain is capable of binding to CD19, CD20, or CD22. In some ~~aspect~~examples, the antigen-binding domain is capable of binding to a coronavirus spike protein. In further ~~aspect~~examples, the coronavirus spike protein is a SARS-CoV-1 or SARS-CoV-2 spike protein.

[0011] In some ~~aspect~~examples, the antigen-binding domain comprises at least a portion of an ACE2 extracellular domain. In some ~~aspect~~examples, the portion of an ACE2 extracellular domain is the ACE2t domain. In further ~~aspect~~examples, the ACE2t domain comprises a sequence that is at least 85%, at least 90%, at least 95%, or 100% identical to the sequence of SEQ ID NO: 2. In some ~~aspect~~examples, the CAR bridging proteins further comprise at least one linker sequence between the CAR-binding domain, Fc domain, and/or antigen-binding domain. In some ~~aspect~~examples, the CAR bridging protein comprises a linker sequence between the CAR-binding domain and the antigen-binding domain, and optionally, the Fc domain. In some ~~aspect~~examples, the linker sequence comprises the sequence of GGGS (SEQ ID NO: 7). In some ~~aspect~~examples, the linker sequence

comprises a sequence provided by SEQ ID NO: 8. In some ~~aspect~~examples, the CAR bridging protein forms a homodimer.

[0012] In ~~still other embodiments~~one aspect, the present disclosure provides nucleic acid molecules encoding a CAR bridging protein of the present disclosure, wherein ~~. In some aspects,~~ the sequence encoding the CAR bridging protein is operatively linked to an expression control sequence; or~~. In some aspects,~~ the nucleic acid molecules are further defined as an expression vector, such as wherein~~. In some aspects,~~ the expression vector is an episomal vector; or~~. In other aspects,~~ the expression vector is a viral vector; optionally wherein~~. In further aspects,~~ the viral vector is an adenovirus, adeno-associated virus, retrovirus or lentivirus vector.

[0013] In ~~yet other embodiments~~one aspect, the present disclosure provides pharmaceutical compositions comprising a CAR bridging protein of the present disclosure in a pharmaceutically acceptable carrier, optionally further comprising ~~. In some aspects, the pharmaceutical compositions further comprise~~ a population of immune effector cells comprising a CAR polypeptide that the CAR-binding domain of the CAR bridging protein binds. In another aspect, the present disclosure provides a use of a pharmaceutical composition comprising a CAR bridging protein of the present disclosure in the manufacture of a medicament for treating a subject in need thereof, wherein an effective amount of the CAR bridging protein is to be administered to the subject; such as wherein the subject has previously been administered a population of immune effector cells comprising a CAR polypeptide that the CAR-binding domain of the CAR bridging protein binds; an effective amount of a population of immune effector cells is to be administered to the subject, wherein the population of immune effector cells comprises a CAR polypeptide that the CAR-binding domain of the CAR bridging protein binds; optionally wherein the cells are allogeneic, autologous or HLA matched to the subject; or the subject has a cancer.

[0014] In further ~~embodiment~~examples, the present disclosure provides methods of treating a subject in need thereof, the method comprising administering to the subject an effective amount of a CAR bridging protein of the present disclosure. In some ~~aspect~~examples, the subject has previously been administered a population of immune effector cells comprising a CAR polypeptide that the CAR-binding domain of the CAR bridging protein binds. In some ~~aspect~~examples, the methods further comprise administering to the subject an effective amount of a population of immune effector cells comprising a CAR polypeptide that the CAR-binding domain of the CAR bridging protein binds. In some ~~aspect~~examples, the cells are allogeneic to the subject. In some ~~aspect~~examples, the cells are autologous to the subject. In some ~~aspect~~examples, the cells are HLA matched to the subject. In some ~~aspect~~examples, the subject has a coronavirus infection. In some ~~aspect~~examples, the subject has a SAR-CoV infection. In some ~~aspect~~examples, the subject has a SAR-CoV-2 infection. In some ~~aspect~~examples, the subject has COVID-19. In some ~~aspect~~examples, the CAR bridging protein comprises (i) an antigen-binding domain that is at least 85%, at least 90%, at least 95%, or 100% identical to the sequence of SEQ ID NO: 2; and (ii) a CAR-binding domain that is comprises the sequence provided in SEQ ID NO: 6, and wherein the CAR polypeptide comprises a CD4 domain as its antigen-binding domain. In some ~~aspect~~examples, the subject has a cancer. In some ~~aspect~~examples, the CAR bridging protein comprises an antigen-binding domain that is capable of binding to CD19, CD20, or CD22.

[0015] In still further ~~embodiment~~examples, the present disclosure provides chimeric antigen receptor (CAR) bridging proteins comprising a CAR-binding domain and an antigen-binding domain. In some ~~aspect~~examples, the antigen-binding domain is chemically conjugated to the CAR-binding domain. In some ~~aspect~~examples, the antigen-binding domain and the CAR-binding domain are comprised in a fusion protein. In some ~~aspect~~examples, the CAR bridging protein further comprises an antibody Fc domain. In some ~~aspect~~examples, the Fc domain is positioned between the CAR-binding domain and the antigen-binding domain. In other ~~aspect~~examples, the CAR-binding domain is positioned between the antigen-binding domain and the Fc domain. In some ~~aspect~~examples, the CAR-binding domain comprises a peptide that interacts with the extracellular portion of a CAR. In some ~~aspect~~examples, the CAR-binding domain comprises the antigen-binding portion of an antibody that recognizes the extracellular portion of a CAR. In some ~~aspect~~examples, the CAR-binding domain comprises at least a portion of a ligand that interacts with the extracellular portion of a CAR. In some ~~aspect~~examples, the CAR-binding domain binds to a portion of the CAR that is specific for the target of the CAR. In some ~~aspect~~examples, the CAR comprises scFv and wherein the CAR-binding domain binds to a variable region of the scFv. In some ~~aspect~~examples, the CAR-binding domain comprises an antibody or an antigen binding fragment thereof. In some ~~aspect~~examples, the CAR-binding domain comprises scFv.

[0016] In some ~~aspect~~examples, the CAR-binding domain comprises at least a portion of an HIV-1 gp120 protein. In some ~~aspect~~examples, the CAR-binding domain comprises the sequence provided in SEQ ID NO: 6. In some ~~aspect~~examples, the CAR is a CD19 specific CAR and the CAR binding domain binds to the CD19-specific CAR. In some ~~aspect~~examples, the CAR binding domain comprises an antibody or an antigen binding fragment thereof. In some ~~aspect~~examples, the CAR binding domain comprises a scFv. In some ~~aspect~~examples, the CAR-binding domain comprises at least a portion of a CD19 protein. In some ~~aspect~~examples, the Fc domain comprises a human Fc domain sequence. In some ~~aspect~~examples, the Fc domain comprises a human heavy chain Fc domain sequence. In some ~~aspect~~examples, the Fc domain comprises CH2 and CH3 regions of a human heavy chain Fc domain sequence. In some ~~aspect~~examples, the Fc domain comprises substitutions relative to the wild-type human heavy chain Fc domain sequence which prevent binding to FcgR receptors. In some ~~aspect~~examples, the Fc domain comprises a sequence that is at least 85%, at least 90%, at least 95%, or 100% identical to the sequence provided by SEQ ID NO: 4. In some ~~aspect~~examples, the antigen-binding domain binds to a tumor antigen or a viral antigen.

[0017] In some ~~aspect~~examples, the antigen-binding domain comprises a peptide that interacts with an antigen of interest. In some ~~aspect~~examples, the antigen-binding domain comprises an antigen-binding portion of an antibody that recognizes the antigen of interest. In some ~~aspect~~examples, the antigen-binding domain comprises at least a portion of a ligand that interacts with the antigen of interest. In some ~~aspect~~examples, the antigen-binding domain binds to CD19, CD20, or CD22. In some ~~aspect~~examples, the antigen-binding domain is capable of binding to a coronavirus spike protein. In some ~~aspect~~examples, the coronavirus spike protein is a SARS-CoV-1 or SARS-CoV-2 spike protein. In some ~~aspect~~examples, the antigen-binding domain comprises at least a portion of an ACE2 extracellular domain. In some ~~aspect~~examples, the portion of an ACE2 extracellular domain is the ACE2t domain. In some ~~aspect~~examples, the ACE2t domain comprises a sequence that is at least 85%, at least 90%, at least 95%, or 100% identical to the sequence of SEQ ID NO: 2. In some ~~aspect~~examples, the CAR bridging protein further comprises at least one linker sequence between the CAR-binding domain, Fc domain, and/or antigen-binding domain. In some ~~aspect~~examples, the CAR bridging protein comprises a linker sequence between the CAR-binding domain and the antigen-binding domain, and optionally, the Fc domain. In some ~~aspect~~examples, the linker sequence comprises the sequence of GGGS (SEQ ID NO: 7). In some ~~aspect~~examples, the linker sequence comprises a sequence provided by SEQ ID NO: 8. In some ~~aspect~~examples, the CAR bridging protein forms a homodimer.

[0018] In yet other ~~embodiment~~examples, the present disclosure provides nucleic acid molecule encoding a CAR bridging protein of the present disclosure. In some ~~aspect~~examples, the sequence encoding the CAR bridging protein is operatively linked to an expression control sequence. In other ~~aspect~~examples, the CAR bridging protein is further defined as an expression vector. In some ~~aspect~~examples, the expression vector is an episomal vector. In other ~~aspect~~examples, the expression vector is a viral vector. In some ~~aspect~~examples, the viral vector is an adenovirus, adeno-associated virus, retrovirus or lentivirus vector.

[0019] In other ~~embodiment~~examples, the present disclosure provides pharmaceutical compositions comprising a CAR bridging protein of the present disclosure in a pharmaceutically acceptable carrier. In some ~~aspect~~examples, the pharmaceutical compositions further comprise a population of immune effector cells comprising a CAR polypeptide that the CAR-binding domain of the CAR bridging protein binds.

[0020] In still other ~~embodiment~~examples, the present disclosure provides methods of treating a subject in need thereof, the method comprising administering to the subject an effective

amount of a CAR bridging protein of the present disclosure. In some ~~aspect~~examples, the subject has previously been administered a population of immune effector cells comprising a CAR polypeptide that the CAR-binding domain of the CAR bridging protein binds. In some ~~aspect~~examples, the methods further comprise administering to the subject an effective amount of a population of immune effector cells comprising a CAR polypeptide that the CAR-binding domain of the CAR bridging protein binds. In some ~~aspect~~examples, the cells are allogeneic to the subject. In some ~~aspect~~examples, the cells are autologous to the subject. In some ~~aspect~~examples, the cells are HLA matched to the subject. In some ~~aspect~~examples, the subject has a coronavirus infection. In some ~~aspect~~examples, the subject has a SAR-CoV infection. In other ~~aspect~~examples, the subject has a SAR-CoV-2 infection. In still other ~~aspect~~examples, the subject has COVID-19. In some ~~aspect~~examples, the CAR bridging protein comprises (i) an antigen-binding domain that is at least 85%, at least 90%, at least 95%, or 100% identical to the sequence of SEQ ID NO: 2; and (ii) a CAR-binding domain that is comprises the sequence provided in SEQ ID NO: 6, and wherein the CAR polypeptide comprises a CD4 domain as its antigen-binding domain. In certain ~~aspect~~examples, the CAR-binding domain consists essentially of the sequence provided in SEQ ID NO: 6. In certain ~~aspect~~examples, the CAR-binding domain consists of the sequence provided in SEQ ID NO: 6. In some ~~aspect~~examples, the subject has a cancer. In some ~~aspect~~examples, the CAR bridging protein comprises an antigen-binding domain that is capable of binding to CD19, CD20, or CD22. In some ~~aspect~~examples, the CAR-binding domain of the CAR bridging protein comprises at least a portion of a CD19 protein.

[0021] Other objects, features and advantages of the present ~~invention~~disclosure will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating preferred ~~embodiment~~examples of the ~~invention~~disclosure, are given by way of illustration only, since various changes and modifications within the spirit and scope of the ~~invention~~disclosure will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

WHAT IS CLAIMED IS:

1. A chimeric antigen receptor (CAR) bridging protein comprising (1) an antigen-binding domain and (2) a CAR-binding domain, that comprises at least a portion of an HIV-1 gp120 protein.

2. The CAR bridging protein of claim 1, wherein:
(a) the CAR-binding domain is chemically conjugated to the antigen-binding domain.;
~~3. The CAR bridging protein of claim 1, wherein~~ (b) the antigen-binding domain is chemically conjugated to the CAR-binding domain.; or
~~4. The CAR bridging protein of claim 1, wherein~~ (c) the antigen-binding domain and the CAR-binding domain are comprised in a fusion protein.

~~5. The CAR bridging protein of claim 4,~~; optionally further comprising an antibody Fc domain. , such as wherein
~~6. The CAR bridging protein of claim 5, wherein~~ (i) the Fc domain is positioned between the CAR-binding domain and the antigen-binding domain.;
~~7. The CAR bridging protein of claim 5, wherein~~ (ii) the CAR-binding domain is positioned between the antigen-binding domain and the Fc domain.; or
~~8. The CAR bridging protein of claim 5, wherein~~ (iii) the Fc domain comprises a human Fc domain sequence.; optionally wherein
~~9. The CAR bridging protein of claim 8, wherein~~ (1) the Fc domain comprises a human heavy chain Fc domain sequence.;
~~10. The CAR bridging protein of claim 8, wherein~~ (2) the Fc domain comprises CH2 and CH3 regions of a human heavy chain Fc domain sequence.;
~~11. The CAR bridging protein of claim 8, wherein~~(3) the Fc domain comprises substitutions relative to the wild-type human heavy chain Fc domain sequence which prevent binding to FcgR receptors.; or
~~12. The CAR bridging protein of claim 8,~~ (4) wherein the Fc domain comprises a sequence that is at least 85%, at least 90%, at least 95%, or 100% identical to the sequence provided by SEQ ID NO: 4.
~~13.~~

3. The CAR bridging protein of claim 1, wherein:
(a) the CAR bridging protein further ~~comprising~~comprises a linker sequence between the antigen binding domain and the CAR-binding domain.; or
~~14. The CAR bridging protein of claim 1, wherein~~ (b) the CAR-binding domain comprises the sequence provided in SEQ ID NO: 6.; such as~~The CAR bridging protein of any one of claims 1-14,~~ wherein:
(i) the antigen-binding domain binds to a tumor antigen or a viral antigen.;
~~16. The CAR bridging protein of any one of claims 1-15, wherein~~ (ii) the antigen-binding domain comprises a peptide that interacts with an antigen of interest.;

17. The CAR bridging protein of any one of claims 1-16, wherein (iii) the antigen-binding domain comprises an antigen-binding portion of an antibody that recognizes the antigen of interest.; or

18. The CAR bridging protein of any one of claims 1-17, wherein (iv) the antigen-binding domain comprises at least a portion of a ligand that interacts with the antigen of interest.

19.

4. The CAR bridging protein of any one of claims 1-183, wherein:

(a) the antigen-binding domain is capable of binding to CD19, CD20, or CD22.

20. The CAR bridging protein of any one of claims 1-18, wherein the antigen-binding domain is capable of binding , or to a coronavirus spike protein.;

21. The CAR bridging protein of claim 20, wherein (b) the coronavirus spike protein is a SARS-CoV-1 or SARS-CoV-2 spike protein.

22. The CAR bridging protein of any one of claims 1-21,; such as wherein the antigen-binding domain comprises at least a portion of an ACE2 extracellular domain.; or

23. The CAR bridging protein of claim 22, wherein (c) the portion of an ACE2 extracellular domain is the ACE2t domain.

24. The CAR bridging protein of claim 23,; such as wherein the ACE2t domain comprises a sequence that is at least 85%, at least 90%, at least 95%, or 100% identical to the sequence of SEQ ID NO: 2.

25.

5. The CAR bridging protein of any one of claims 1-244, further comprising at least one linker sequence between the CAR-binding domain, Fc domain, and/or antigen-binding domain.; optionally wherein:

26. The CAR bridging protein of claim 25, wherein(a) the CAR bridging protein comprises a linker sequence between each of the CAR-binding domain, Fc domain, and/or antigen-binding domains.;

27. The CAR bridging protein of claim 25 or 26, wherein (b) the linker sequence comprises the sequence of GGGS.; or

28. The CAR bridging protein of any one of claims 25-27, wherein (c) the linker sequence comprises a sequence provided by SEQ ID NO: 6.

29.

6. The CAR bridging protein of any one of claims 1-285, wherein the CAR bridging protein forms a homodimer.

30.

7. A chimeric antigen receptor (CAR) bridging protein comprising a CAR-binding domain and an antigen-binding domain.; optionally wherein:

31. The CAR bridging protein of claim 30, wherein(a) the CAR-binding domain is chemically conjugated to the antigen-binding domain.; or

32. The CAR bridging protein of claim 30, wherein(b) the antigen-binding domain is chemically conjugated to the CAR-binding domain.

33.

8. The CAR bridging protein of claim 1, wherein the antigen-binding domain and the CAR-binding domain are comprised in a fusion protein.

34.

9. The CAR bridging protein of claim ~~30~~7, further comprising an antibody Fc domain~~.~~

~~35. The CAR bridging protein of claim 34,~~; optionally wherein:

(a) the Fc domain is positioned between the CAR-binding domain and the antigen-binding domain~~.~~; or

~~36. The CAR bridging protein of claim 34, wherein~~ (b) the CAR-binding domain is positioned between the antigen-binding domain and the Fc domain.

~~37.~~

10. The CAR bridging protein of any one of claims ~~30-36~~7-9, wherein the CAR-binding domain comprises a peptide that interacts with the extracellular portion of a CAR~~.~~; optionally wherein:

~~38. The CAR bridging protein of any one of claims 30-37, wherein~~ (a) the CAR-binding domain comprises the antigen-binding portion of an antibody that recognizes the extracellular portion of a CAR~~.~~; or

~~39. The CAR bridging protein of any one of claims 30-37, wherein~~ (b) the CAR-binding domain comprises at least a portion of a ligand that interacts with the extracellular portion of a CAR.

~~40.~~

11. The CAR bridging protein of any one of claims ~~30-37~~7-10, wherein the CAR-binding domain binds to a portion of the CAR that is specific for the target of the CAR~~.~~; optionally wherein

~~41. The CAR bridging protein of claim 40, wherein~~ (a) the CAR comprises scFv ~~and~~; such as wherein the CAR-binding domain binds to a variable region of the scFv~~.~~;

~~42. The CAR bridging protein of any one of claims 30-37, wherein~~ (b) the CAR-binding domain comprises an antibody or an antigen binding fragment thereof~~.~~

~~43. The CAR bridging protein of claim 42,~~; such as wherein the CAR-binding domain comprises scFv~~.~~; or

~~44. The CAR bridging protein of any one of claims 30-37, wherein~~(c) the CAR-binding domain comprises at least a portion of an HIV-1 ~~gp120 protein.~~

~~45. The CAR bridging protein of claim 44,~~gp120protein; such as wherein the CAR-binding domain comprises the sequence provided in SEQ ID NO: 6.

~~46.~~

~~The CAR bridging protein of any one of claims 30-37, wherein the CAR is a CD19 specific CAR and the CAR binding domain binds to the CD19-specific CAR.~~;

~~47. The CAR bridging protein of claim 46, wherein the CAR binding domain comprises an antibody or an antigen binding fragment thereof.~~

~~48. The CAR bridging protein of claim 47, wherein the CAR binding domain comprises a scFv.~~

~~49. The CAR bridging protein of claim 46, wherein the CAR-binding domain comprises at least a portion of a CD19 protein.~~

~~50.~~ 12. The CAR bridging protein of any one of claims ~~34-49~~9-11, wherein:

(a) the Fc domain comprises a human Fc domain sequence~~.~~;

~~51. The CAR bridging protein of any one of claims 34-50, wherein~~ (b) the Fc domain comprises a human heavy chain Fc domain sequence~~.~~;

52. The CAR bridging protein of any one of claims 34-51, wherein (c) the Fc domain comprises CH2 and CH3 regions of a human heavy chain Fc domain sequence.;
53. The CAR bridging protein of any one of claims 34-52, wherein (d) the Fc domain comprises substitutions relative to the wild-type human heavy chain Fc domain sequence which prevent binding to FcgR receptors.; or
54. The CAR bridging protein of any one of claims 34-53, wherein (e) the Fc domain comprises a sequence that is at least 85%, at least 90%, at least 95%, or 100% identical to the sequence provided by SEQ ID NO: 4.
55.

13. The CAR bridging protein of claim 307, wherein the antigen-binding domain binds to a tumor antigen or a viral antigen.

56. The CAR bridging protein of any one of claims 30-55,; optionally wherein:
(a) the antigen-binding domain comprises a peptide that interacts with an antigen of interest.; or
57. The CAR bridging protein of any one of claims 30-56, wherein (b) the antigen-binding domain comprises an antigen-binding portion of an antibody that recognizes the antigen of interest.

14.58. The CAR bridging protein of any one of claims 30-577-13, wherein:
(a) the antigen-binding domain comprises at least a portion of a ligand that interacts with the antigen of interest.
59. The CAR bridging protein of any one of claims 30-58, wherein (b) the antigen-binding domain binds to CD19, CD20, or CD22.;
60. The CAR bridging protein of any one of claims 30-58, wherein(c) the antigen-binding domain is capable of binding to a coronavirus spike protein.

61. The CAR bridging protein of claim 60,; such as wherein the coronavirus spike protein is a SARS-CoV-1 or SARS-CoV-2 spike protein.; or
62. The CAR bridging protein of any one of claims 30-61, wherein (d) the antigen-binding domain comprises at least a portion of an ACE2 extracellular domain.; such as wherein:
63. The CAR bridging protein of claim 62, wherein (i) the portion of an ACE2 extracellular domain is the ACE2t domain.; or
64. The CAR bridging protein of claim 63, wherein (ii) the ACE2t domain comprises a sequence that is at least 85%, at least 90%, at least 95%, or 100% identical to the sequence of SEQ ID NO: 2.
65.

15. The CAR bridging protein of any one of claims 34-649-14, wherein:
(a) the CAR bridging protein further comprisingcomprises at least one linker sequence between the CAR-binding domain, Fc domain, and/or antigen-binding domain.; or
66. The CAR bridging protein of any one of claims 34-65, wherein the (b) CAR bridging protein comprises a linker sequence between the CAR-binding domain and the antigen-binding domain, and optionally, the Fc domain.; such as wherein:
67. The CAR bridging protein of claim 65 or 66, wherein (i) the linker sequence comprises the sequence of GGGS.; or

68. The CAR bridging protein of any one of claims 65-67, wherein (ii) the linker sequence comprises a sequence provided by SEQ ID NO: 6.

69.

16. The CAR bridging protein of any one of claims 30-687-15, wherein the CAR bridging protein forms a homodimer.

70.

17. A nucleic acid molecule encoding a CAR bridging protein in accordance with any one of claims 1-1669., wherein;

71. The nucleic acid molecule of claim 70, wherein a) the sequence encoding the CAR bridging protein is operatively linked to an expression control sequence.; or

72. Theb) the nucleic acid molecule of claim 70,is further defined as an expression vector.

73. The nucleic acid molecule of claim 72,; such as wherein:

(i) the expression vector is an episomal vector.; or

74. The nucleic acid molecule of claim 72, wherein(ii) the expression vector is a viral vector.

75. The nucleic acid molecule of claim 74,; optionally wherein the viral vector is an adenovirus, adeno-associated virus, retrovirus or lentivirus vector.

76.

18. A pharmaceutical composition comprising a CAR bridging protein in accordance with any one of claims 1-1669 in a pharmaceutically acceptable carrier.

77. The pharmaceutical composition of claim 76, in a pharmaceutically acceptable carrier, optionally further comprising a population of immune effector cells comprising a CAR polypeptide that the CAR-binding domain of the CAR bridging protein binds.

7819. –Use of a pharmaceutical composition comprising a CAR bridging protein in accordance with any one of claims 1-16 in the manufacture of a medicament for A method of treating a subject in need thereof, wherein themethod comprising administering to the subject an effective amount of athe CAR bridging protein is to be administered to the subject in accordance with any one of claims 1-69.; such as wherein:

79. The method of claim 78, wherein(i) the subject has previously been administered a population of immune effector cells comprising a CAR polypeptide that the CAR-binding domain of the CAR bridging protein binds.;

80. The(ii) method of claim 78, further comprising administering to the subject an effective amount of a population of immune effector cells is to be administered to the subject, wherein the population of immune effector cells comprises ing a CAR polypeptide that the CAR-binding domain of the CAR bridging protein binds; optionally wherein the cells are allogeneic, autologous or HLA matched to the subject; or

81. The method of claim 80, wherein the cells are allogeneic to the subject.

82. The method of claim 80, wherein the cells are autologous to the subject.

~~83. The method of claim 80, wherein the cells are HLA matched to the subject.~~

~~84. The method of any one of claims 78-83, wherein the subject has a coronavirus infection.~~

~~85. The method of any one of claims 78-84, wherein the subject has a SAR-CoV infection.~~

~~86. The method of any one of claims 78-84, wherein the subject has a SAR-CoV-2 infection.~~

~~87. The method of any one of claims 78-84, wherein the subject has COVID-19.~~

~~88. The method of claim 86 or 87, wherein the CAR bridging protein comprises (i) an antigen-binding domain that is at least 85%, at least 90%, at least 95%, or 100% identical to the sequence of SEQ ID NO: 2; and (ii) a CAR-binding domain that is comprises the sequence provided in SEQ ID NO: 6, and wherein the CAR polypeptide comprises a CD4 domain as its antigen-binding domain.~~

~~89. The method of any one of claims 78-83, wherein~~ (iii) the subject has a cancer.

~~90. The method of claim 89, wherein the CAR bridging protein comprises an antigen-binding domain that is capable of binding to CD19, CD20, or CD22.~~

~~91. The method of claim 78, wherein the CAR binding domain of the CAR bridging protein comprises at least a portion of a CD19 protein.~~