

immunotherapy agents have been evaluated in advanced pancreatic cancer with limited success. Pancreatic tumors are characterized by desmoplasia and immunosuppressive immune infiltrates which drives this lack of response. New therapies with the potential to overcome this immunosuppressive environment and extend survival are needed.

Bispecific antibody constructs comprising one domain that binds to CD3 on a T cell and one domain that binds to a protein expressed on a target cell directly connect T cells to target cells to induce T cell redirected lysis. This mechanism of action is distinct from chemotherapy, targeted therapy and other immunotherapy in that it can work with any CD3-positive T cell, independent of a costimulatory activating signal (Klinger et al., Immunol Reviews 2016). The expression of CLDN18.2 on the cell surface of gastric cancer, gastroesophageal cancer and pancreatic cancer provides a basis for targeting these tumor types with a CLDN18.2 x CD3 antibody construct. Furthermore, a CLDN18.2 x CD3 antibody construct has the potential to target additional tumor types that express CLDN18.2, including mucinous ovarian cancer, colorectal cancer and non-small cell lung cancer.

Summary

In one aspect, the present disclosure provides an antibody construct comprising a first domain which binds Claudin 18.2 (CLDN18.2), and a second domain which binds human CD3, wherein the first domain comprises a VH region comprising CDR-H1, CDR-H2 and CDR-H3 and a VL region comprising CDR-L1, CDR-L2 and CDR-L3 selected from the group consisting of: a) CDR-H1 as depicted in SEQ ID NO: 121, CDR-H2 as depicted in SEQ ID NO: 122, and CDR-H3 as depicted in SEQ ID NO: 123, CDR-L1 as depicted in SEQ ID NO: 124, CDR-L2 as depicted in SEQ ID NO: 125 and CDR-L3 as depicted in SEQ ID NO: 126; and b) CDR-H1 as depicted in SEQ ID NO: 133, CDR-H2 as depicted in SEQ ID NO: 134, and CDR-H3 as depicted in SEQ ID NO: 135, and CDR-L1 as depicted in SEQ ID NO: 136, CDR-L2 as depicted in SEQ ID NO: 137 and CDR-L3 as depicted in SEQ ID NO: 138.

In another aspect, the present disclosure provides a polynucleotide encoding the antibody construct of the disclosure.

In another aspect, the present disclosure provides a vector comprising the polynucleotide of the disclosure.

In another aspect, the present disclosure provides a host cell transformed or transfected with the polynucleotide of the disclosure.

In another aspect, the present disclosure provides a process for producing an antibody construct, said process comprising culturing the host cell of the disclosure under conditions allowing the expression of said antibody construct and recovering the produced antibody construct from the culture.

In another aspect, the present disclosure provides a composition comprising the antibody construct of the disclosure and a carrier, stabilizer, excipient, diluent, solubilizer, surfactant, emulsifier, preservative and/or adjuvant.

In another aspect, the present disclosure provides a use of the antibody construct of the disclosure in the manufacture of a medicament for treating or ameliorating a CLDN18.2-expressing disease or neoplasm.

In another aspect, the present disclosure provides a kit comprising the antibody construct of the disclosure and a recipient.

Detailed description of the invention

Thus, in one aspect, the present invention provides an antibody construct comprising a first domain which binds to CLDN18.2 on the surface of a target cell and a second domain which binds to CD3 on the surface of a T cell.

It is also envisaged that:

(1) the first domain of the antibody construct of the invention binds to the first extracellular loop (loop 1) of CLDN18.2;

(2) the first domain of the antibody construct of the invention binds to the same epitope of CLDN18.2 as an antibody or antibody construct comprising a domain which binds to CLDN18.2 on the surface of a target cell and which comprises:

a) a VH region comprising CDR-H1 as depicted in SEQ ID NO: 121, CDR-H2 as depicted in SEQ ID NO: 122, and CDR-H3 as depicted in SEQ ID NO: 123, and a VL region comprising CDR-L1 as depicted in SEQ ID NO: 124, CDR-L2 as depicted in SEQ ID NO: 125 and CDR-L3 as depicted in SEQ ID NO: 126;

b) a VH region comprising CDR-H1 as depicted in SEQ ID NO: 133, CDR-H2 as depicted in SEQ ID NO: 134, and CDR-H3 as depicted in SEQ ID NO: 135, and a VL region comprising CDR-L1

Claims

1. An antibody construct comprising a first domain which binds Claudin 18.2 (CLDN18.2), and a second domain which binds human CD3, wherein the first domain comprises a VH region comprising CDR-H1, CDR-H2 and CDR-H3 and a VL region comprising CDR-L1, CDR-L2 and CDR-L3 selected from the group consisting of:
 - a) CDR-H1 as depicted in SEQ ID NO: 121, CDR-H2 as depicted in SEQ ID NO: 122, and CDR-H3 as depicted in SEQ ID NO: 123, CDR-L1 as depicted in SEQ ID NO: 124, CDR-L2 as depicted in SEQ ID NO: 125 and CDR-L3 as depicted in SEQ ID NO: 126; and
 - b) CDR-H1 as depicted in SEQ ID NO: 133, CDR-H2 as depicted in SEQ ID NO: 134, and CDR-H3 as depicted in SEQ ID NO: 135, and CDR-L1 as depicted in SEQ ID NO: 136, CDR-L2 as depicted in SEQ ID NO: 137 and CDR-L3 as depicted in SEQ ID NO: 138.
2. The antibody construct according to claim 1, wherein the first domain comprises a VH region having an amino acid sequence as depicted in SEQ ID NO: 127 or SEQ ID NO: 139.
3. The antibody construct according to claim 1, wherein the first domain comprises a VL region having an amino acid sequence as depicted in SEQ ID NO: 128 or SEQ ID NO: 140.
4. The antibody construct according to claim 1, wherein the first domain comprises a VH region and a VL region having an amino acid sequence as depicted in SEQ ID NOs: 127 and 128 or SEQ ID NOs: 139 and 140.
5. The antibody construct according to claim 1, wherein the first domain comprises a polypeptide having an amino acid sequence as depicted in SEQ ID NO: 129 or SEQ ID NO: 141.
6. The antibody construct according to claim 1, comprising or consisting of a polypeptide having an amino acid sequence of SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 143, or SEQ ID NO: 144.
7. A polynucleotide encoding the antibody construct of claim 1.
8. A vector comprising the polynucleotide of claim 7.

9. A host cell transformed or transfected with the polynucleotide of claim 7.
10. A process for producing an antibody construct, said process comprising culturing the host cell of claim 9 under conditions allowing the expression of said antibody construct and recovering the produced antibody construct from the culture.
11. A composition comprising the antibody construct of claim 1 and a carrier, stabilizer, excipient, diluent, solubilizer, surfactant, emulsifier, preservative and/or adjuvant.
12. Use of the antibody construct of claim 1 in the manufacture of a medicament for treating or ameliorating a CLDN18.2-expressing disease or neoplasm.
13. The use of claim 12, wherein the disease or neoplasm is gastrointestinal cancer, ovarian cancer or lung cancer.
14. The use of claim 13, wherein the gastrointestinal cancer is gastric cancer, esophageal cancer, gastroesophageal cancer, pancreatic cancer, or colorectal cancer.
15. A kit comprising the antibody construct of claim 1 and a recipient.
16. The antibody construct according to claim 1, wherein the second domain binds to human CD3 epsilon and to *Callithrix jacchus* or *Saimiri sciureus* CD3 epsilon.
17. The antibody construct according to claim 1, wherein
 - a) the antibody construct is a single chain antibody construct;
 - b) the first domain is in the format of an scFv;
 - c) the second domain is in the format of an scFv;
 - d) the first and the second domain are connected via a linker; and/or
 - e) the antibody construct further comprises a domain providing an extended serum half-life.
18. The antibody construct according to claim 1, wherein the first domain does not bind or does not significantly bind to CLDN18.1, CLDN1, CLDN2, CLDN3, CLDN4, CLDN6, and/or CLDN9.