

Without being bound by theory it is believed that a CD3 affinity that is significantly less than the affinity of mOKT3 is preferred in a bispecific T-cell engager format. It is preferred that the bispecific antibody binds to CD3 with an affinity that is less than the affinity of binding to the tumor antigen. Without being bound to theory it is believed that this difference in affinity permits preferential opsonization of the tumor cells by the bispecific antibody, thereby labelling them for destruction by immune effector cells including NK and/or T cells present in the vicinity.

The inventors observed that results obtained with the 3056 antibody exhibited batch to batch variation. This surprised the inventors as the variability was not an issue with the antibody 15C3, which has the same VH-sequence as antibody 3056 but a different light chain (described in WO2005/118635).

It is an object of the invention to provide a variant of antibody 3056 with essentially the same CD3 binding properties in kind, not necessarily in amount, with improved characteristics.

SUMMARY

In one example, the present disclosure provides an antibody that binds human CD3 which antibody comprises a heavy chain and light chain wherein said heavy chain comprises a variable region that comprises the amino acid sequence:

QVQLV QSGGG VVQPG RSLRL SCVASG FTFSS YGMHW VRQAP GKGLE
WVAAI WYX₁X₂R KQDYA DSVKG RFTIS RDNSK NTLYL QMNSL RAEDT
AVYYC TRGTG YNWFD PWGQG TLVTV SS

with 0-10, preferably 0-5 amino acid insertions, deletions, substitutions, additions or a combination thereof at one or more positions other than the position indicated by X₁X₂;

wherein

- $X_1 = N$ and $X_2 = A$;
- $X_1 = N$ and $X_2 = T$;
- $X_1 = S$ and $X_2 = G$;
- 5 $X_1 = H$ and $X_2 = G$;
- $X_1 = D$ and $X_2 = G$; or
- $X_1 = H$ and $X_2 = A$.

In one aspect, the present disclosure refers to an antibody that binds human
 10 CD3 which antibody comprises a heavy chain and light chain wherein said
 heavy chain comprises a variable region that comprises the amino acid
 sequence:

QVQLV QSGGG VVQPG RSLRL SCVAS GFTFS SYGMH WVRQA PGKGL EWVAA
 IWYX₁X₂RKQDY ADSVK GRFTI SRDNS KNTLY LQMNS LRAED TAVYY
 15 CTRGT GYNWF DPWGQ GTLVT VSS

with 0-10, preferably 0-5 amino acid insertions, deletions, substitutions,
 additions or a combination thereof at one or more positions other than the
 position indicated by X_1X_2 and leaving H35, Y102, N103, and W104
 unchanged;

20 wherein

- $X_1 = N$ and $X_2 = A$;
- $X_1 = N$ and $X_2 = T$;
- $X_1 = H$ and $X_2 = G$; or
- $X_1 = H$ and $X_2 = A$.

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In another aspect, the present disclosure refers to an antibody that binds
 human CD3 which antibody comprises a heavy chain and light chain
 wherein said heavy chain comprises a variable region that comprises the
 amino acid sequence:

QVQLV QSGGG VVQPG RSLRL SCVAS GFTFS SYGMH WVRQA PGKGL
 EWVAA IWYX₁X₂ RKQDY ADSVK GRFTI SRDNS KNTLY LQMNS
 LRAED TAVYY CTRGT GYNWF DPWGQ GTLVT VSS

with 0-5 amino acid insertions, deletions, substitutions, additions or a
 5 combination thereof at one or more positions other than the position
 indicated by X₁X₂ and leaving H35, Y102, N103, and W104 unchanged ;
 wherein

X₁ = D and X₂ = G,

and wherein said light chain comprises a common light chain variable
 10 region.

The disclosure further provides a nucleic acid molecule that
 encodes an amino acid sequence:

QVQLV QSGGG VVQPG RSLRL SCVASG FTFSS YGMHW VRQAP GKGLE
 WVA AI WYX₁X₂R KQDYA DSVKG RFTIS RDNSK NTLYL QMNSL RAEDT
 15 AVYYC TRGTG YNWFD PWGQG TLVTV SS

with 0-10, preferably 0-5 amino acid insertions, deletions, substitutions,
 additions or a combination thereof at one or more positions other than the
 position indicated by X₁X₂;
 wherein

20 X₁ = N and X₂ = A;

X₁ = N and X₂ = T;

X₁ = S and X₂ = G;

X₁ = H and X₂ = G;

X₁ = D and X₂ = G; or

25 X₁ = H and X₂ = A.

The combination X₁ and X₂ in an antibody as described herein is
 preferably X₁ = N and X₂ = A.

The disclosure further provides a cell that expresses the antibody
 30 and/or comprises the nucleic acid molecule.

An antibody of the disclosure is, unless otherwise specifically specified, preferably a bispecific antibody. The bispecific antibody preferably binds at least human CD3. In addition, the bispecific antibody preferably binds at least a surface molecule that is preferentially expressed on human tumor cells. In a preferred example, the bispecific antibody binds to BCMA, CD19, CD20, CD30, CD33, CD38, CD44, CD123, CD138, CEA, CLEC12A, CS-1, EGFR, EGFRvIII, EPCAM, DLL3, LGR5, MSLN, FOLR1, FOLR3, HER2, HM1.24, MCSP, or PSMA. In a more preferred example, the bispecific antibody binds to CLEC12A.

The disclosure further provides a pharmaceutical composition comprising an antibody according to the disclosure.

Further provided is an antibody according to the disclosure that further comprises a label, preferably a label for in vivo imaging.

The disclosure also provides a method for the treatment of a subject having a tumor or at risk of having a tumor comprising administering to the subject a bispecific antibody according to the disclosure. Also provided is a bispecific antibody according to the disclosure for use in the treatment of a subject having a tumor or at risk of a tumor. Further provided is the use of an antibody of the disclosure for the preparation of a medicament for the treatment of a subject having a tumor or at risk of a tumor. In a preferred example the tumor is a CLEC12A positive tumor.

In another aspect, the present disclosure refers to the antibody as disclosed herein for use in the treatment of a subject in need thereof.

DETAILED DESCRIPTION OF THE INVENTION

An antibody of the invention is preferably a bispecific antibody. The bispecific antibody preferably binds at least human CD3. In addition, the bispecific antibody preferably binds at least a surface molecule that is expressed on human tumor cells. In a preferred embodiment the bispecific antibody binds to BCMA, CD19, CD20, CD30, CD33, CD38, CD44, CD123, CD138, CEA, CLEC12A,

Claims

1. An antibody that binds human CD3 which antibody comprises a heavy chain and light chain wherein said heavy chain comprises a variable region that comprises the amino acid sequence:

QVQLV QSGGG VVQPG RSLRL SCVAS GFTFS SYGMH WVRQA PGKGL EWVAA
IWX₁X₂RKQDY ADSVK GRFTI SRDNS KNTLY LQMNS LRAED TAVYY CTRGT
GYNWF DPWGQ GTLVT VSS

with 0-10, preferably 0-5 amino acid insertions, deletions, substitutions, additions or a combination thereof at one or more positions other than the position indicated by X₁X₂ and leaving H35, Y102, N103, and W104 unchanged; wherein

X₁ = N and X₂ = A;

X₁ = N and X₂ = T;

X₁ = H and X₂ = G; or

X₁ = H and X₂ = A.

2. The antibody of claim 1, wherein said light chain comprises a common light chain variable region.

3. An antibody that binds human CD3 which antibody comprises a heavy chain and light chain wherein said heavy chain comprises a variable region that comprises the amino acid sequence:

QVQLV QSGGG VVQPG RSLRL SCVAS GFTFS SYGMH WVRQA PGKGL
EWVAA IWX₁X₂ RKQDY ADSVK GRFTI SRDNS KNTLY LQMNS LRAED
TAVYY CTRGT GYNWF DPWGQ GTLVT VSS

with 0-5 amino acid insertions, deletions, substitutions, additions or a combination thereof at one or more positions other than the position indicated by X₁X₂ and leaving H35, Y102, N103, and W104 unchanged ; wherein

X1 = D and X2 = G,

and wherein said light chain comprises a common light chain variable region.

4. The antibody of claim 2 or 3, wherein said common light chain variable region comprises an O12 / IgV κ 1-39 light chain variable region.

5. The antibody of claim 4, wherein said light chain variable region is a germline O12 / IgV κ 1-39*01 variable region.

6. The antibody of claim 5, wherein the light chain variable region comprises a kappa light chain IgV κ 1-39*01/IGJ κ 1*01 or IgV κ 1-39*01/IGJ κ 5*01.

7. The antibody of claim 6, wherein the light chain variable region comprises a germline kappa light chain IgV κ 1-39*01/IGJ κ 1*01 or IgV κ 1-39*01/IGJ κ 5*01.

8. The antibody of any one of claims 14, wherein said light chain variable region comprises the amino acid sequence

DIQMT QSPSS LSASV GDRVT ITCRA SQSIS SYLNW YQQKP GKAPK LLIYA
ASSLQ SGVPS RFSGS GSGTD FTLTI SSLQP EDFAT YYCQQ SYSTP PTFGQ
GTKVE IK or DIQMT QSPSS LSASV GDRVT ITCRA SQSIS SYLNW YQQKP
GKAPK LLIYA ASSLQ SGVPS RFSGS GSGTD FTLTI SSLQP EDFAT YYCQQ
SYSTP PITFG QGTRL EIK with 0-5 amino acid insertions, deletions,
substitutions, additions or a combination thereof.

9. The antibody of any one of claims 1-8, which is a bispecific antibody.

10. The bispecific antibody of claim 9, comprising a H/L chain combination of any one of claims 1-8, and a H/L chain combination that binds a tumor-antigen.

11. The bispecific antibody of claim 10, wherein said H/L chain combination that binds a tumor-antigen binds CLEC12A.
12. The antibody or bispecific antibody of claims 1-11, which is a human or humanized antibody.
13. The bispecific antibody of any one of claims 9-12, comprising two different immunoglobulin heavy chains with compatible heterodimerization domains.
14. The bispecific antibody of claim 13, wherein said compatible heterodimerization domains are compatible immunoglobulin heavy chain CH3 heterodimerization domains.
15. The bispecific antibody of any one of claims 9-14, wherein said bispecific antibody is an IgG antibody with a mutant CH2 and/or lower hinge domain such that interaction of the bispecific IgG antibody to a Fc-gamma receptor is reduced.
16. The bispecific antibody of claim 15, wherein the mutant CH2 and/or lower hinge domain comprise an amino substitution at position 235 and/or 236, preferably an L235G and/or G236R substitution.
17. The bispecific antibody of any one of claims 9-16, comprising a common light chain.
18. The antibody of any one of claims 1-17, for use in the treatment of a subject in need thereof.