a cancer therapeutic. Therefore, there is a need for new antibodies against the 5T4 antigen and for corresponding antibody-drug conjugates for cancer therapy. To determine the suitability of these antibodies and corresponding ADCs in a preclinical setting, such antibodies should be cross-reactive for the 5T4 antigen of non-human animal species relevant for the preclinical development of a drug candidate.

SUMMARY

The present disclosure describes antibodies against the human 5T4 oncofoetal antigen and corresponding ADCs that are suitable for testing in clinical trials. Suitable antibodies and corresponding ADCs in a preclinical setting should be cross-reactive for the 5T4 antigen of non-human animal species relevant for preclinical development of a drug candidate.

Preferably, the antibodies are cross-reactive for humans and cynomolgus monkeys and exhibit an affinity for human 5T4 antigen (hu 5T4) which is in the same order of magnitude as their affinity for cynomolgus monkey 5T4 antigen (cyno 5T4).

The disclosure further describes the use of the antibodies and corresponding ADCs in the treatment of solid tumours and haematological malignancies.

In one aspect, the present invention refers to an anti-5T4 antibody comprising heavy chain (HC) and light chain (LC) variable region (VR) complementarity determining regions (CDRs) selected from the group consisting of:

a. CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:1 and CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:2;

b. CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:5 and CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:6; and

CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:11 and CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:12;

wherein the antibody comprises at least one engineered cysteine at one or more positions of said antibody selected from heavy chain framework region positions 40, 41 and 89 according to Kabat numbering and light chain framework region positions 40 and 41 according to Kabat numbering.

In another aspect, the present invention refers to an antibody-drug conjugate comprising the antibody as disclosed herein.

In yet another aspect, the present invention refers to a pharmaceutical composition comprising the antibody as disclosed herein or the antibody-drug conjugate as disclosed herein and one or more pharmaceutically acceptable excipients, preferably in the form of a lyophilized powder.

CLAIMS

1. A humanized anti-5T4 antibody comprising heavy chain (HC) and light chain (LC) variable region (VR) complementarity determining regions (CDRs) selected from the group consisting of:

a. CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:1 and CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:2;

b. CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:5 and CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:6; and
CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:11 and CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:12;

wherein the antibody comprises at least one engineered cysteine at one or more positions of said antibody selected from heavy chain framework region positions 40, 41 and 89 according to Kabat numbering and light chain framework region positions 40 and 41 according to Kabat numbering.

2. The humanized antibody according to claim 1, comprising

a. CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:1 and CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:2 and HCVR amino acid sequence of SEQ ID NO:35 and LCVR amino acid sequence of SEQ ID NO:45;

b. CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:1 and CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:2 and HCVR amino acid sequence of SEQ ID NO:36 and LCVR amino acid sequence of SEQ ID NO:45;

c. CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:1 and CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:2 and HCVR amino acid sequence of SEQ ID NO:37 and LCVR amino acid sequence of SEQ ID NO:44;

d. CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:1 and CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:2 and HCVR amino acid sequence of SEQ ID NO:37 and LCVR amino acid sequence of SEQ ID NO:46;

e. CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:11 and CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:12; and HCVR amino acid sequence of SEQ ID NO:40 and LCVR amino acid sequence of SEQ ID NO:51;

f. CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:11 and CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:12; and HCVR amino acid sequence of SEQ ID NO:41 and LCVR amino acid sequence of SEQ ID NO:51;

g. CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:11 and CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:12; and HCVR amino acid sequence of SEQ ID NO:42 and LCVR amino acid sequence of SEQ ID NO:49;

h. CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:11 and CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:12; and HCVR amino acid sequence of SEQ ID NO:43 and LCVR amino acid sequence of SEQ ID NO:50;

i. CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:5 and CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:6; and HCVR amino acid sequence of SEQ ID NO:38 and LCVR amino acid sequence of SEQ ID NO:47;

j. CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:5 and CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:6; and HCVR amino acid

sequence of SEQ ID NO:39 and LCVR amino acid sequence of SEQ ID NO:47; and

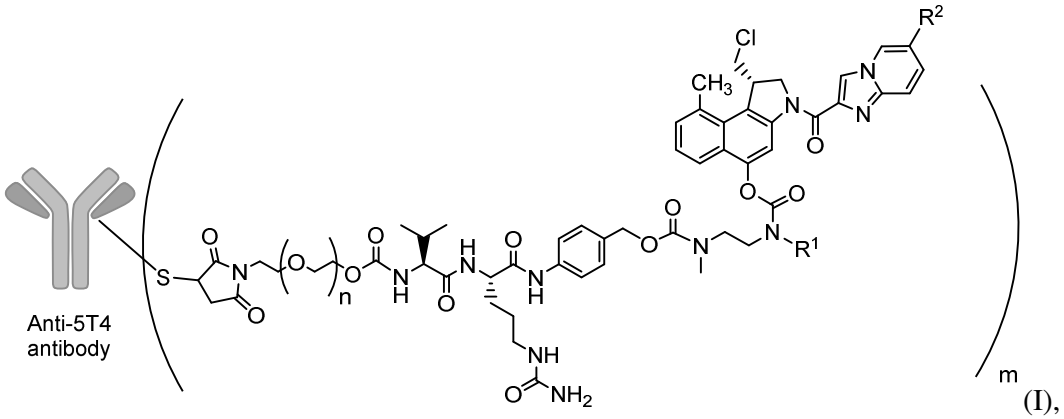
k. CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:5 and CDR1, CDR2 and CDR3 amino acid sequences of SEQ ID NO:6; and HCVR amino acid sequence of SEQ ID NO:39 and LCVR amino acid sequence of SEQ ID NO:48;

wherein the HCVR amino acid sequence comprises at least one engineered cysteine at one or more positions selected from heavy chain framework region positions 40, 41 and 89 according to Kabat numbering and/or the LCVR amino acid sequence comprises at least one engineered cysteine at one or more positions selected from light chain framework region positions 40 and 41 according to Kabat numbering.

3. The antibody according to claim 1 or claim 2 wherein the at least one engineered cysteine is present at one or more positions of said antibody selected from heavy chain framework region positions 40 and 41, and light chain framework region positions 40 and 41, preferably selected from heavy chain framework region position 41 and light chain framework region positions 40 and 41, more preferably the at least one engineered cysteine is present at heavy chain framework region position 41.

4. An antibody-drug conjugate comprising the antibody according to any one of claims 1 to 3, wherein a linker drug is site-specifically conjugated to the antibody through the at least one engineered cysteine.

5. The antibody-drug conjugate according to claim 4 of formula (I)



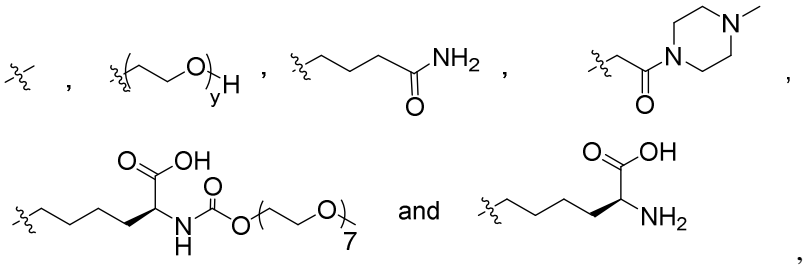
(I),

wherein

n is 0-3,

m represents an average DAR of from 1 to 6,

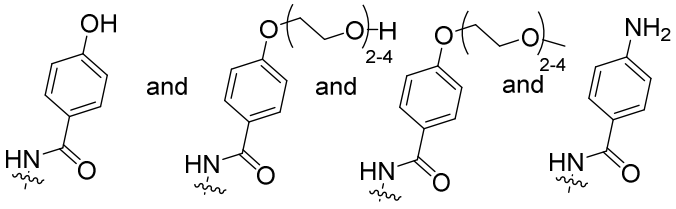
R^1 is selected from



,

y is 1-16, and

R^2 is selected from



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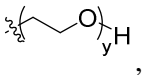
6. The antibody-drug conjugate according to claim 5, wherein

n is 0-1,

m represents an average DAR of from 1.5 to 2,

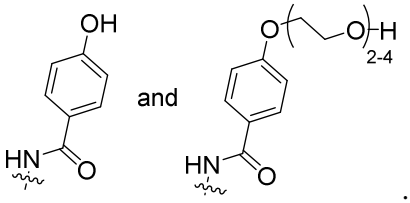
R^1 is



,

y is 1-4, and

R^2 is selected from



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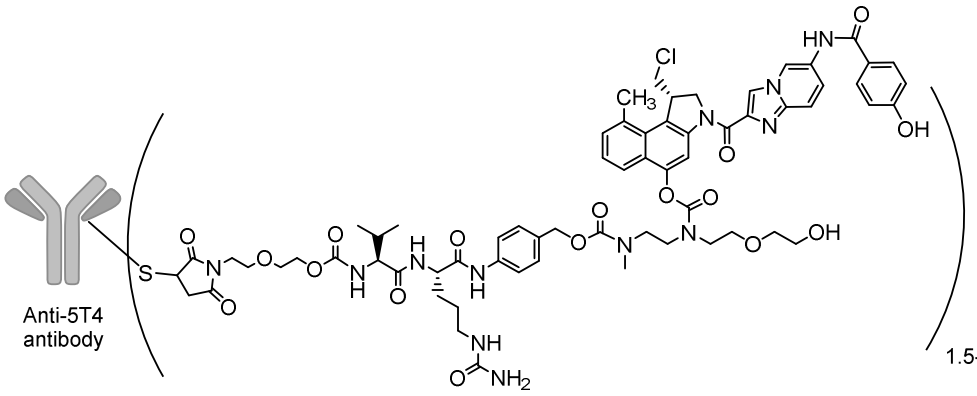
7. The antibody-drug conjugate according to any one of claims 4 to 6 of formula (II)



(II).

8. The antibody-drug conjugate according to any one of claims 4 to 7, wherein the antibody comprises HCVR and LCVR selected from the group consisting of:

a. HCVR amino acid sequence of SEQ ID NO:61 and LCVR amino acid sequence of SEQ ID NO:51;

b. HCVR amino acid sequence of SEQ ID NO:62 and LCVR amino acid sequence of SEQ ID NO:51;

c. HCVR amino acid sequence of SEQ ID NO:63 and LCVR amino acid sequence of SEQ ID NO:49;

d. HCVR amino acid sequence of SEQ ID NO:64 and LCVR amino acid sequence of SEQ ID NO:50;

e. HCVR amino acid sequence of SEQ ID NO:59 and LCVR amino acid sequence of SEQ ID NO:47; and

f. HCVR amino acid sequence of SEQ ID NO:60 and LCVR amino acid sequence of SEQ ID NO:48;

wherein the linker drug is site-specifically conjugated to the antibody through the engineered cysteine at heavy chain framework region position 41.

9. A pharmaceutical composition comprising the antibody according to any one of claims 1 to 3 or the antibody-drug conjugate according to any one of claims 4 to 8 and one or more pharmaceutically acceptable excipients, preferably in the form of a lyophilized powder.

10. The antibody according to any one of claims 1 to 3, the antibody-drug conjugate according to any one of claims 4 to 8 or the pharmaceutical composition according to claim 9 for use as a medicament.

11. Use of the antibody according to any one of claims 1 to 3, the antibody-drug conjugate according to any one of claims 4 to 8 or the pharmaceutical composition according to claim 9 in the manufacture of a medicament for treating human solid tumours and haematological malignancies.

12. The use according to claim 11, wherein the human solid tumours are selected from the group consisting of breast cancer, gastric cancer, colorectal cancer, ovarian cancer, lung cancer, and mesothelioma.