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 OF THE INVENTION

In one aspect, the present invention 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 WYX$_1$X$_2$R 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 X_1X_2;

wherein

X_1 = N and X_2 = A;

X_1 = N and X_2 = T;

X_1 = S and X_2 = G;

X_1 = H and X_2 = G;

X_1 = D and X_2 = G; or

X_1 = H and X_2 = A.

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

QVQLV QSGGG VVQPG RSLRL SCVASG FTFSS YGMHW VRQAP GKGLE WVAAI WYX$_1$X$_2$R 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 X_1X_2;

wherein

X_1 = N and X_2 = A;

X_1 = N and X_2 = T;

X_1 = S and X_2 = G;

X_1 = H and X_2 = G;

X_1 = D and X_2 = G; or

X_1 = H and X_2 = A.

The combination X_1 and X_2 in an antibody as described herein is preferably X_1 = N and X_2 = A.

The disclosure further provides a cell that expresses the antibody 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.

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,